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Abstracts of the 2018 Meeting of Argentine Society for Research in Neurosciences

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The Argentine Society for Research in Neurosciences (SAN) held its XXXIII Annual meeting in the Argentine Pavilion (Pabellón Argentina) at the National University of Córdoba, city of Córdoba, Argentina, on October 24 and 26 of this year. The 2018 meeting took place especially under the framework of the centenary of the Córdoba University Reform of 1918.

SAN 2018 meeting had a great call with about 400 attendees among researchers, scholars, PhD students, and guests from different centers and universities of Argentina and abroad from other 11 countries of Latin America (Brazil, Uruguay, Chile, México, and Colombia), North America (USA and Canada), and Europe (Denmark, Switzerland, Ireland, and Spain). The scientific program included a total of 4 Plenary Lectures, 10 Symposia, 10 Youth Investigator Lectures, 14 Oral Communications, and 287 Posters, covering a great variety of areas in the field of neurosciences.

It is noteworthy that two of the Plenary Lectures were placed in honors of the pioneers of neurochemistry and neurobiology in Argentina, Drs. Ranwel Caputto and Eduardo De Robertis. This year the Ranwel Caputto Lecture was delivered by Prof. Charles Gilbert of Rockefeller University (USA) and De Robertis Lecture by Prof. Claudio Cuello of McGill University (Montreal, Canada). The opening lecture was delivered by Prof. Annie Andrieux (Grenoble, France), and the forth plenary lecture by Prof. Steven Fliesler of Buffalo University (USA).

As pre-meeting activities, on October 22 and 23, two specific courses were held: (a) A workshop tribute to the memory of Prof. Ricardo Miledi, pioneer in the study of synaptic transmission and ion channels, held at the Mercedes and Martin Ferreyra Institute (INIMEC CONICET, Córdoba), in which 77 undergrads and PhD students participated, as well as (b) a course entitled "Neurobiology of drug addiction," held at the School of Chemical Sciences (UNC, CONICET), which had 65 attendees and invited speakers from all around the world. In addition, on October 23, we organized a day of communication of neurosciences, open to the public, and held at the conference room of Pabellón Argentina of the National University of Córdoba.

Remarkably, all the activities organized, including the Symposia and the Young Investigator Lectures, covered a number of diverse disciplines in the field of neurosciences with the participation of outstanding invited speakers from Argentina and other countries.

Moreover, a very friendly atmosphere for discussion and data presentation was generated during the poster and oral communication sessions with the participation of 176 PhD students, 61 undergrads, and 27 postdocs.

Lecture Abstracts

Wednesday, 24: 11:00–12:00 Opening Lecture/Room A

Tubulin Tyrosination-Detyrosination Cycle: Key Role in Neuronal Functions

Annie Andrieux[1,2], C. Aillaud[1], C. Bosc[1], L. Peris[1], L. Lafanechère[3], E. Denarier[1,2], C. Boscheron[1,2], M. Bogyo[4], K. Rogowski[5], Y. Wehland[6,†], D. Job[1] and M. J. Moutin[1]

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Microtubules are cytoskeletal polymers of α/β tubulin heterodimers, centrally involved in cell division, motility, and morphogenesis. In the de/tyrosination cycle of tubulin, the C-terminal tyrosine of α-tubulin is removed by a carboxy peptidase (TCP),

and re-added by the enzyme tubulin tyrosine ligase. This cycle, which is unique to tubulin and mostly conserved throughout evolution, has a vital role *in vivo* (Erck et al., 2005, PNAS). Although the detyrosination reaction was first described 40 years ago (Hallak et al., 1977), the molecular identity of TCP has long remained unknown. We have now successfully identified vasohibin/SVBP complexes as TCP enzymes (Aillaud et al., 2017). Based on data obtained in yeast, neurons, and mouse models, we will present results demonstrating the crucial role of the tubulin de/tyrosination cycle in neuronal physiology. The impact of abnormal tubulin tyrosination levels on neuronal functions during neurodevelopment and neurodegenerative processes will also be presented.

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Wednesday, 24: 19:30–20:30 Ranwel Caputto Lecture/Room A

Visual Cortical Dynamics

Charles Gilbert[1]

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Vision is an active and dynamic process. The strategy our brain uses to parse scenes and recognize objects depends on experience. Our interpretation of visual scenes requires an interaction between internal representations of object properties acquired through experience and the immediate information coming from the retina. These internal representations enable the brain's analysis of scenes to be subject to top-down influences of attention, expectation, perceptual tasks, perceptual learning, working memory, and motor commands. At the level of brain circuitry, this process involves an interaction between long-range and intrinsic cortical connections and enables neurons to assume different functional states according to the task being executed. Each cortical area represents an association field, whereby bits of information are dynamically linked via a plexus of long-range horizontal connections. Although each neuron receives 10^5 inputs from other neurons, neurons are capable of selecting a small subset of task-relevant inputs and suppressing the influence of task-irrelevant inputs. The circuitry of the adult cortex therefore is under a continual long-term process of modification as we assimilate new information and short-term dynamics as we analyze the constituents of visual scenes. These mechanisms are common to all regions of the brain and when disrupted may account for visual and behavioral disorders.

Thursday, 25: 11:00–12:00 Plenary Lecture/ Room A

Retinal Degenerations: The Isoprenoid Connection

Steven J. Fliesler[1]

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The mevalonate pathway generates a number of biologically important isoprenoid products, including sterols (e.g., cholesterol), steroid hormones, bile acids, dolichol and its derivatives, isoprenylpyrophosphates, and biogenically related compounds. Cholesterol—quantitatively the dominant product of the pathway—is a ubiquitous component of the membranes of almost all eukaryotic cells and tissues as well as of blood-borne lipoproteins. However, although cholesterol is essential for the viability and normal function of higher eukaryotes, an overabundance of cholesterol has been associated with human disease, including Alzheimer's disease and age-related macular degeneration. Similarly, a paucity of cholesterol also can be deleterious, even lethal. Hence, defective cholesterol biosynthesis can lead to disruption of cellular and systemic physiology, resulting in profound pathologies. Using a rat model that mimics one such human recessive disease (Smith-Lemli-Opitz syndrome [SLOS]), it has been shown that blocking the last step in cholesterol synthesis causes a progressive and irreversible retinal degeneration. Studies in our lab indicate that the molecular mechanism underlying this degeneration is not simply due to cholesterol deficiency; rather, it is complex, involving marked lipidomic, proteomic, and genomic changes, including lipid and protein oxidation. Hence, providing exogenous cholesterol alone (the current standard of care for SLOS patients) is not an effective therapeutic strategy. We hypothesized that combined antioxidant-cholesterol supplementation should prevent or markedly reduce the severity of the retinal degeneration in the SLOS rat model. This prediction has been validated, providing the necessary proof-of-principle to guide an evidence-based clinical trial for developing an improved therapeutic intervention for SLOS and related diseases.

Friday, 26: 19:30–20:30 De Robertis Lecture/ Room A

Unraveling a Novel NGF Metabolic Pathway and Its Deregulation in Alzheimer's Pathology

A. Claudio Cuello[1]
[1]Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada

We have revealed a novel brain metabolic pathway responsible for the activity-dependent release of pro-nerve growth factor (NGF) from cortical cells, its conversion to mature NGF (mNGF), and subsequent degradation by metalloproteases (Bruno and Cuello), a pathway validated pharmacologically (Allard et al.). Both Alzheimer's disease (AD) and Down syndrome (DS) exhibit a marked atrophy of the NGF-dependent Basal Forebrain (BF) cholinergic system. Applying the NGF pathway paradigm in AD and DS human brain, we demonstrated that in both conditions a marked pathway deregulation (Bruno et al.; Iulita et al.) indicating a trophic factor deprivation of NGF-dependent BF neurons given the failure of proNGF conversion to mNGF and aggravated mNGF degradation. In brief, that higher levels of the NGF precursor (proNGF) in AD are not "good news" but rather an indication of the trophic factor failure to sustain the BF cholinergic phenotype.

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Symposium Abstracts

October 24—8:30–10:30 hr

ISN International Society for Neurochemistry

Neurobiology of Drug Addiction Symposium

Chairs: Liliana M. Cancela[1] **and Marcelo Rubinstein**[2]
[1]IFEC-CONICET. Departamento de Farmacología, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Cordoba, Argentina
[2]Instituto de Investigaciones en Ingeniería Genética y Biología Molecular "Dr. Héctor N. Torres"/ Facultad de Ciencias Exactas y Naturales (UBA), CABA, Argentina

A hallmark of drug addiction is the uncontrollable desire to consume drugs at the expense of severe negative consequences. Moreover, addicts that successfully refrain from drug use have a high vulnerability to relapse even after months or years of abstinence. The current understanding of drug-induced neuroplasticity within the mesocorticolimbic brain system that contributes to the development of addiction and the persistence of relapse to drug seeking is one of the most prominent challenges in neurobiology of drug addiction. The long-lived behavioral abnormalities associated with addiction are thought to arise from pathological plasticity not only in dopaminergic but also in glutamatergic neurotransmission. Identification of drug-induced neuroplasticity is crucial to understand how molecular and cellular adaptations contribute to the end stage of addiction, which from a clinical perspective, is a time point where pharmacotherapy may be most effectively employed. The neural mechanisms underlying drug compulsive disorder and reward learning will be included. The newest molecular, behavioral, and electrophysiological advances as well as therapeutic strategies will be proposed for drug addiction.

8:30–9:00 Verónica Álvarez (USA)

Dissecting the Roles of Dopamine D2 Receptors in the Basal Ganglia and Motivated Behaviors

Dopamine actions in the nucleus accumbens are responsible for generating most of the behaviors triggered by stimulant drugs such as cocaine. This is in large part known because

antagonists for the two main types of dopamine receptors expressed in the accumbens, D1 and D2 receptors, can block the behavioral response to cocaine. Dopamine D1 receptors are mainly expressed in the direct-pathway projection neurons of the striatum. D2 receptors, however, are expressed on the indirect-pathway projection neurons as well as on cholinergic interneurons and the synaptic terminals of glutamate inputs and dopamine inputs to the striatum. Veronica Alvarez will present data from multiple studies in which her laboratory and that of Dr. Rubinstein used genetic tools to dissect out the specific contributions of the dopamine D2 receptors expressed in different cell types in driving motivated behaviors from the response to stimulant drugs to alcohol-induced sedation and stimulation.

9:00–9:30 Bruno Averbeck (USA)

Neural Systems Underlying Reinforcement Learning

To survive, animals must find food, avoid harm and reproduce. Learning is critical to solving these problems as environments often change, and animals have to adapt to these changes. Reinforcement learning (RL) is the behavioral process of learning from the outcomes of decisions to make better choices in the future. The neural systems underlying these processes are, therefore, critical for adapting to changes in the environment. However, when these systems are driven too far, they also underlie disorders including addiction and acquired forms of anxiety like posttraumatic stress disorder. The standard model of RL focuses on dopamine and its role in the striatum. Specifically, this model suggests that the activity of dopamine neurons, which codes errors in the prediction of rewards, drives plasticity on frontal-cortical synaptic inputs to the striatum. Through this process, striatal medium spiny neurons represent and track the values of choices. However, recent work by our lab has shown that the amygdala also plays an important role in RL. Specifically, when animals have to learn the values of visual images, the amygdala and ventral striatum play important roles. However, when animals have to learn the values of actions, the dorsal striatum is important. In addition, the amygdala can rapidly update value estimates, whereas the striatum adapts more slowly. The slower striatal learning is, however, less sensitive to noise.

9:30–10:00 Martine Cador (France)

Opiate Withdrawal Memories: Behavior and Neural Network

Compulsive drug-seeking behavior and its renewal in former drug addicts are promoted by several situations among which reactivation of drug withdrawal memories plays a crucial role. Opiate abuse induces a strong dependence, which is characterized by the appearance of a withdrawal syndrome upon drug use cessation and in abstinent individuals; withdrawal-associated aversive memories are hypothesized to motivate drug seeking and relapse. In rats, it was shown that re-activation of affective memories associated with the withdrawal state induced a negative emotional state influencing motivated behaviors and leading to drug seeking. In term of neuronal substrates, several structures of the mesolimbic corticostriatal circuit are reactivated by the simple re-exposure to environmental stimuli previously associated with naloxone-precipitated opiate withdrawal in dependent rats suggesting that the processing of withdrawal memories is underpinned by activity changes within these interconnected limbic structures. I will present behavioral, anatomical, and *in vivo* gamma oscillation recordings, showing that among these structures, the nucleus accumbens, the basolateral amygdala, and the hippocampus are of crucial interest in processing salience and valence of withdrawal-associated memories.

10:00–10:30 Peter W. Kalivas (USA)

Using the Neurobiology of Willpower to Treat Drug Addiction

All treatments for drug addiction are replacement therapies, such as methadone for opioids or varenicline for tobacco, that do not directly treat the changes in the brain produced by chronic drug use. The brain pathology produced by chronic drug use is located in neuro-circuitry controlling decision-making, which accounts for why drug addicts make poor choices in life that cause increasing drug use and addiction. We have identified this pathology and found ways to reverse the pathology in rodent models of addiction. Some of these therapeutic approaches have successfully moved into clinical trials.

Wednesday 24: 15:30–17:30 Symposium II/ Room A

Emerging Mechanisms in Neuronal Signaling: From Cell Biology to Pathogenesis

Chairs: Gabriela Salvador[1] and Mauricio Martín[2]
[1]INIBIBB-UNS-CONICET, Bahía Blanca, Argentina
[2]CONICET-INIMEC-UNC, Córdoba, Argentina

Abstract not available

C-Fos, a Moonlighting Protein: What We Know About Its Lipid Activator Capacity in the Nervous System

Beatriz L. Caputto[1], Cesar G. Prucca[1] and Lucía Rodríguez-Berdini[1]

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It is expected that the synthesis of lipids, the quantitatively most important molecular species of cell membranes, be synchronized with the cell's diverse functional states. In cells actively involved in proliferation or in plasma membrane extension, processes that demand massive membrane biogenesis and lipid synthesis rates must be higher than those in cells that are neither dividing nor actively growing. However, the nature of the regulatory events underlying such processes is still poorly understood. In the past years, we have shown that the protein c-Fos is actively involved in these regulatory events. The content of c-Fos, a member of the activator protein (AP)-1 family of inducible transcription factors, is tightly regulated in cells: c-Fos is at the limit of detection in quiescent cells, whereas its expression is rapidly and only transiently induced when cells are stimulated to re-enter growth. It has been hypothesized that this c-Fos-AP-1 activity transmits short-termed, growth-promoting cellular signals into longer lasting changes by regulating the expression of growth-related genes. We established that c-Fos is capable of regulating growth not only by its AP-1 activity but also by its capacity to act as a cytoplasmic activator of lipid synthesis in normal and pathological cell processes that demand high rates of membrane biogenesis. Such is the case in light-stimulated retina ganglion and photoreceptor cells, in growing NIH 3T3 cells, in differentiating PC12 cells and primary rat hippocampal neurons, and in tumors of the nervous system. Specifically blocking c-Fos expression or in c-fos −/− mice, proliferation and growth of normal and tumor cells are slowed/halted without substantial changes in their AP-1 content. At present, we are examining *in vivo*, putative c-Fos deletion mutants that do not affect its AP-1 activity but act as negative dominants of its lipid synthetizing activity in the hope to limit the unrestricted proliferation and growth of these central nervous system tumor cells.

Specific Phospholipids Regulate the Acquisition of Neuronal and Astroglial Identities in Post-Mitotic Cells

Aneley Montaner[1], Consuelo Perez[1] and Claudia Banchio[1]

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Up to now, the known mechanisms underpinning cell-fate specification act on neural progenitors, affecting their commitment to generate neuron or glial cells. Here, we show that particular phospholipids supplemented in the culture media modify the commitment of post-mitotic neural cells *in vitro*. Phosphatidylcholine (PtdCho)-enriched media enhances neuronal differentiation at the expense of astroglial and unspecified cells. Conversely, phosphatidylethanolamine (PtdEtn) enhances astroglial differentiation and accelerates astrocyte maturation. The ability of phospholipids to modify the fate of post-mitotic cells depends on its presence during a narrow time-window during cell differentiation, and it is mediated by the selective activation of particular signaling pathways. While PtdCho-mediated effect on neuronal differentiation depends on cAMP-dependent kinase/calcium responsive element binding protein, PtdEtn stimulates astrogliogenesis through the activation of the MEK/ERK signaling pathway. Collectively, our results provide an additional degree of plasticity in neural cell specification and further support the notion that cell differentiation is a reversible phenomenon. They also contribute to our understanding of neuronal and glial lineage specification in the central nervous system, opening up new avenues to retrieve neurogenic capacity in the brain.

Fatty Acids Participation in Neuronal Differentiation of SH-SY5Y Cells

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Fatty acids (FAs) are classically associated with structural and metabolic roles, as they can be stored as triglycerides, degraded by oxidation, or used in phospholipids' synthesis, the main components of biological membranes. Recently, it has been shown that these lipids also exhibit regulatory functions in different cell types, and the neuronal tissue should not be strange to this role. For example, the central nervous system is enriched in poly-unsaturated FAs, such as arachidonic acid, which participates in the regulation of membrane fluidity, axonal growth, development, and

inflammatory response. Alterations in lipid metabolism have been associated with cognitive problems and neurodegenerative diseases, but the molecular mechanism behind these effects remains elusive. These "lipokines" bind to specific receptors triggering second messenger's systems and regulating gene expression. Four plasma membranes, G protein-coupled receptors that recognize free FAs were identified since 2005, commonly known as FFARs. But their roles in neuronal tissues are yet not fully understood. Our aim is to characterize the mechanisms by which different FAs modulate the differentiation of SHSY5Y cells *in vitro*, a broadly used model system for studies of neurodegenerative diseases such as Parkinson's disease. We evaluated the effect of supplementation with FAs, monitoring Akt expression and phosphorylation levels; Ca^{+2} release and neurite outgrowth. Our results support a positive role for FAs acting through FFARs in neuronal differentiation, although further studies considering other receptors like PPARs or FABPs should also be considered for a wider understanding of FAs' neuronal effects. Characterization of lipid receptors in the nervous system will provide a framework for a better understanding of their roles in neurophysiology and, potentially, new targets for drug design against aging and neurodegenerative processes.

Role of Isoprenoids in Autophagy and Prion-Like Spread of Amyloid Beta Pathology

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The development of disease-modifying therapies for Alzheimer's disease (AD) is hampered by the poor understanding of early pathogenic mechanisms that lead to it. Brain accumulation of beta amyloid peptides ($A\beta$) drive AD pathogenesis. In addition, $A\beta$ may be transmitted from cell to cell in a "prion-like" spread that contributes to AD progression. We discovered that $A\beta_{42}$ inhibits cholesterol and isoprenoids (farnesylpyrophosphate and geranylgeranylpyrophosphate [GGPP]) synthesis, reducing protein prenylation in neurons exposed to $A\beta_{42}$ and in TgCRND8 mouse brains. Autophagy relies heavily on prenylated proteins such as Rabs. Autophagy is altered in AD and reversing autophagy dysfunction improves pathophysiology and rescues memory performance in TgCRND8 mice. We showed that autophagic flux is blocked in neurons treated with $A\beta_{42}$ and in TgCRND8 mouse brain. Autophagy dysfunction is caused by inhibition of prenylation because GGPP normalizes autophagic flux in cultured cells and *in vivo*. Rab7 is required for autophagy progression. Rab7 localization to autophagosomes is reduced in $A\beta_{42}$-treated neurons, and GGPP corrects Rab7 prenylation and subcellular localization. When autophagy is compromised, cells may resource to protein secretion to alleviate stress, although this also may favor "prion-like" spreading. $A\beta$ is released in extracellular vesicles (EVs). Autophagy blockade may increase EVs secretion. We isolated EVs from N2a cells and $N2aAPP^{swe}$ cells by ultracentrifugation and density gradient and characterized them using light scattering asymmetric flow field fractionation electron microscopy and image flow cytometry. Using trypsin protection assays, we have determined that the majority of $A\beta$ is located at the EVs surface but around $\sim$25% is present inside EVs. Our studies identify the reduction of protein prenylation as a key mechanism of autophagy dysfunction and prion-like spread in AD and will provide evidence of treatments *in vivo* with disease-modifying value.

Wednesday 24: 15:30–17:30
Symposium III/Room B

Chronic Pain: Basic Research and Translational Perspectives

Chair: Susana González[1]

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Abstract not available

Role of 2-Pore Domain Potassium Channels in Spontaneous Pathological Pain

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Pathological pain affects one of the five adults worldwide and is often refractory to traditional therapies. Patients affected by this condition exhibit debilitating sensory abnormalities including spontaneous pain, hyperlagesia, allodynia, and paresthesias. Changes in nociceptor excitability are essential for the initiation and maintenance of this pain. As neuronal excitability is highly dependent on the resting membrane potential (Em), we focused on two-pore domain potassium channels (K2Ps) whom are main contributors to Em in primary afferent neurons. We studied systematically 12 of the known 15 functional K2P channels in a model of cutaneous inflammation and found that they exhibit a complex pattern

of expression at the mRNA level. We then focused on two K2P channels, TREK2 and THIK1. We characterized the expression pattern for these channels and examined their role in pathological pain. We found that they were both expressed by subpopulations of nociceptors and that down-regulating their expression *in vivo* resulted in exacerbated spontaneous pain in rats also in a model of cutaneous inflammation. Importantly, TREK2 appears to limit spontaneous pain by hyperpolarizing a subpopulation of IB4-binding C-nociceptors, while THIK1 seems to play a role in both peptidergic and non-peptidergic nociceptors. Taken together, our findings put selective activation of K2P channels as a new potential target to treat spontaneous pain.

Role of Pannexin 1 in the Chronic Pain: A Preclinical Study

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Pannexin 1 (panx1) is a large-pore membrane channel expressed in many tissues of mammals, including neurons and glial cells. Panx1 channels are highly permeable to calcium and adenosine triphosphatase (ATP); on the other hand, they can be opened by ATP and glutamate, two crucial molecules for acute and chronic pain signaling in the spinal cord dorsal horn, thus suggesting that panx1 could be a key component for the generation of central sensitization during persistent pain. In this study, we examined the effect of three panx1 blockers, namely, 10panx peptide, carbenoxolone, and probenecid, on C-reflex wind-up activity and mechanical nociceptive behavior in a spared nerve injury neuropathic rat model involving sural nerve transection. In addition, the expression of panx1 protein in the dorsal horn of the ipsilateral lumbar spinal cord was measured in sural nerve-transected and sham-operated control rats. Sural nerve transection resulted in a lower threshold for C-reflex activation by electric stimulation of the injured hindpaw, together with persistent mechanical hypersensitivity to pressure stimuli applied to the paw. Intrathecal administration of the panx1 blockers significantly depressed the spinal C-reflex wind-up activity in both neuropathic and sham control rats and decreased mechanical hyperalgesia in neuropathic rats without affecting the nociceptive threshold in sham animals. Western blotting showed that panx1 was similarly expressed in the dorsal horn of lumbar spinal cord from neuropathic and sham rats. These results constitute the first evidence that panx1 channels play a significant role in the mechanisms underlying central sensitization in neuropathic pain.

IMT504 for the Treatment of Chronic Pain: Preclinical Observations and Translational Perspective

Pablo R. Brumovsky[1]
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Chronic pain, which can be inflammatory or neuropathic in nature, affects millions of people around the world. Unfortunately, an important number of patients do not see a proper solution to their problem, in part due to the fact that most drugs currently available to treat pain have limited efficacy or exert serious adverse effects. Such scenario reinforces the need of further research and the identification of new analgesic drugs that could help chronic pain patients. IMT504 is an oligodeoxynucleotide (ODN) with immunomodulatory and tissue repair properties, as shown in various human disease animal models. Recently, we showed that IMT504 prevents or abolishes the progress of pain in rats with sciatic nerve crush, a self-limiting neuropathy that exposes the injured animal to up to 21 days of pain. In this conference, results demonstrating the efficacy of IMT504 for the control of chronic inflammatory or neuropathic pain will be presented. The results suggest the potential of this ODN in diverse chronic pain conditions, in turn prompting the translation to humans suffering pain. Such potential will be elaborated by presenting the steps taken thus far in relation to the validation of IMT504 as a therapeutic agent for the treatment of inflammatory or neuropathic pain in humans, through the development of a Phase I to Phase II clinical trial.

Neuroactive Steroids and Central Neuropathic Pain

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Neuropathic pain develops in nearly 70% of patients with spinal cord injury. These patients, already burdened with the disability of paralysis, emotional trauma, and spasticity, must contend with severe unrelenting pain that is refractory to conventional treatment. The precise mechanisms underlying neuropathic pain after spinal injury remain elusive. However, central sensitization involving the hyperexcitability of dorsal horn neurons in the pain pathway is known to be mediated by N-methyl-D-aspartate receptor (NMDAR), and the activation of glial cells,

with the subsequent release of pro-nociceptive mediators, also play a crucial role. Previous work from our laboratory and others has shown that progesterone, a neuroactive steroid, exerts neuroprotective and promyelinating actions in the injured spinal cord. Furthermore, we have recently reported that this steroid may offer a promising perspective in pain modulation. In this work, we used a recognized model of central neuropathic pain to study the effects of progesterone on the expression of NMDAR subunits and protein kinase C (PKC), key players in the process of central sensitization at the spinal level. Injured animals receiving vehicle showed well-established mechanical and thermal allodynia (pain elicited by innocuous stimuli) and a significant increase in the spinal expression of all the NMDAR subunits and PKC. Interestingly, animals receiving progesterone did not develop mechanical allodynia and showed reduced sensitivity to cold stimulation. In these animals, the expression of NMDAR subunits and PKC remained similar to control levels. In addition, progesterone was also able to reduce glial cell activation and the production of pro-inflammatory cytokines, which strongly contribute to the pathology of central neuropathic syndromes. Our current investigations add new data to further stimulate the study of neuroactive steroids-based therapies and may open new avenues to prevent chronic pain after central injuries.

Thursday, 25: 08:30–10:30
Symposium IV/Room A

Oligodendrocytes: Its Role in Myelination and Remyelination

Chairs: Juana Pasquini[1] and Jorge Correale[2]
[1]Dept Química Biológica, IQUIFIB, Facultad de Farmacia y Bioquímica, UBA-CONICET, Buenos Aires, Argentina
[2]Instituto de Investigaciones Neurológicas Dr Raúl Carrea, FLENI, Buenos Aires, Argentina

Abstract not available

Signaling Mechanisms Regulating CNS Myelination

Wendy B. Macklin[1], Kathryn Bercury[1], Hannah Hathaway[1] and Teresa Wood[1]
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The mammalian target of rapamycin (mTOR) signaling pathway is a ubiquitous signal integrator for numerous growth and survival factors, guidance cues, and differentiation drivers. In the central nervous system (CNS), it impacts the development of neurons and glia. Oligodendrocyte differentiation and myelination are tightly regulated, and we have shown that Akt and mTOR are important regulators of CNS myelination *in vivo*. mTOR functions through two distinct complexes, mTOR complex 1 (mTORC1) and mTORC2, by binding to either Raptor or Rictor, respectively. In order to establish whether both mTORC1 and mTORC2 have unique functions during CNS myelination, we conditionally ablated either Raptor or Rictor in the oligodendrocyte lineage *in vivo*. Initial studies deleted proteins from oligodendrocytes using the 2′,3′-cyclic nucleotide phosphohydrolase (CNP) promoter. In CNP-Cre X Raptor fl/fl mice (RaptorcKO mice), myelination in the spinal cord was dramatically impaired. By contrast, when Rictor (mTORC2) was comparably deleted, it has far less impact on myelination. However, in recent studies, we deleted Rictor selectively in oligodendrocyte progenitor cells using the platelet-derived growth factor receptor alpha promoter (PDGFRα-Cre). Interestingly, a significant reduction of myelination was seen in PDGFRα-Cre X Rictorfl/fl(RictorcKO) mice. Unexpectedly, this dysmyelination was seen in corpus callosum rather than in spinal cord. These studies suggest that there are regional effects of mTOR signaling in oligodendrocytes and that mTORC1 and mTORC2 are both important for myelination. These studies also indicate that the specific promoter used for deletion may change the impact of the deletion and that there may be compensation for loss of mTOR signaling depending on when the deletion occurs during the differentiation of the cells.

This study was supported by NIH R37 NS082203.

NG2-Glia: Old Friends or New Strangers? Implications and Roles in the Adult Brain

Leda Dimou[1]
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Glial cells in the adult brain are very diverse, and some of them represent the stem and progenitor cells of the central nervous system (CNS). My talk will focus on the adult oligodendrocyte progenitor cells, also known as NG2-glia, in the intact and injured mouse brain. The widespread interest in this glial cell population raises from their unique properties, as adult NG2-glia represent the only proliferating cell type in the adult brain parenchyma outside the neurogenic niches and continuously generate—in a region-specific manner—mature, myelinating oligodendrocytes. However, their functions in the adult CNS and the mechanisms regulating their behavior under both physiological and pathological conditions are still not resolved. Additionally, it is still widely unknown whether NG2-glia comprise a homogeneous or heterogeneous population. Interestingly, NG2-glia were found to build postsynapses for neurons and axons,

with still unraveled roles. To tackle these questions, we use various tools such as novel transgenic mouse lines, transplantation experiments, conditional depletion of proliferating NG2-glia, proteomic and transcriptomic analysis, as well as *in vivo* live imaging of these cells in the adult mouse cerebral cortex. By these techniques, we were able to reveal new insights into the functional role of NG2-glia in the intact and injured brain.

Dialogue Between Oligodendrocytes and Axons in the Process of Neurodegeneration and Neuroprotection

Jorge Correale[1]

[1]Instituto de Investigaciones Neurológicas Dr Raúl Carrea, FLENI, Buenos Aires, Argentina

Results from immunological, genetic, and histopathology studies have demonstrated that multiple sclerosis is not only an inflammatory disease but also a neurodegenerative condition. Growing knowledge indicates that oligodendroglial dysfunction can contribute to neuropathology in classical neurodegenerative diseases and their respective mouse models. The study of oligodendrocyte (OGD)-dependent axonal function and survival represents a new aspect of central nervous system (CNS) neurodegenerative pathophysiology. Although myelin is traditionally viewed as an inert insulating structure, it has become clear that myelin is metabolically active, allowing the movement of macromolecules into the periaxonal space, with important functional impact on axonal nutrition and neuronal survival. Disruption of oligodendroglial proteins participating in various cellular functions may interfere, directly or indirectly, with efficient metabolic coupling between OGDs and axons, ultimately altering axon integrity and function. Several studies have demonstrated that lactate is critical for neuronal energy supply during increased activity and that interfering with its pathway will result in neurodegeneration. As astrocytes are essentially the only cells containing glycogen in the adult CNS, glycogen metabolism followed by glycolysis provides a source of lactate to other cells. Studies combining both astrocytes and OGDs have demonstrated that astrocytes transfer energy metabolites directly to OGDs, which in turn support the metabolism of neurons and axons. Connections between astrocytes and myelinating cells occur via gap junctions formed by connexins (Cx) in the plasma membranes of two adjacent cells; Cx form channels that allow the exchange of small molecules between connected cells. Although most of the alternative energy transported from astrocytes consists in lactate, ketone bodies and pyruvate can also be produced by astrocytes and thus contribute to neuron energy supplies. Overall, the role of OGDs in supporting axons at a metabolic level is of obvious relevance to various myelin diseases. The close link in the axon-myelin unit makes them cellular partners and further contributes to the understanding of how pathological alterations can spread across white and gray matter boundaries.

Experimental Demyelination Models: Effects of Apotransferrin Administration

Juana Pasquini[1], **Vanesa Mattera**[1] **and Jorge Correale**[1]

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Previous results from our laboratory showed the pro-differentiating effect of apotransferrin (aTf; intracranially injected) on oligodendroglial cells both *in vivo* and *in vitro*. In addition, the remyelinating effect of aTf was demonstrated in two different models of demyelination such as cuprizone intoxication and hypoxia–ischemia (H/I) and in an iron-deficiency model of hypomyelination. In H/I, we observed that the intranasal administration of human aTf provides neuroprotection to the brain. Treatment with aTf reduces white matter damage, neuronal loss, and astrogliosis in different brain areas, increasing the proliferation of oligodendroglial precursor cells in the subventricular zone. All these data induced us to develop a less invasive technique to deliver aTf to the CNS. Exosomes were isolated from human and mouse plasma as well as from neuroblastoma (N2a) and oligodendroglioma (OLN-93) cell lines and astrocyte primary cultures. Exosome characterization was conducted by Western blot, dynamic light scattering, and scanning electron microscopy, all of which showed that the nanoparticles had been isolated in pure conditions and without integrity modifications and were thus able to be loaded with aTf. The presence of Tf receptor was also detected in all the extracellular vesicles studied as well as their ability to bind aTf. Obtaining exosomes with a clearly defined active therapeutic cargo such as Tf and with a surface marker to ensure the targeting of recipient cells may constitute a promising approach to nanomedicine.

Thursday, 25: 16:00–18:00
Symposium V/Room A

Move On! Neural Circuits Underlying Sensorimotor Transformations

Chairs: Violeta Medan[1] and Martín Carbo Tano[1]
[1]IFIByNE, CONICET, Buenos Aires, Argentina
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Abstract not available

Spinal Circuits for Somatosensation and Movement

Martyn Goulding[1]
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Animals use a variety of sensory modalities to interact with and explore the environment in which they move. Of particular importance is the somatosensory system, which monitors the internal and external state of the body during movement. Very little is currently known about how somatosensory information is processed and gated by the spinal cord. Using a sophisticated suite of genetic tools, we have begun to functionally dissect the cutaneous arm of the somatosensory system, which plays a central role in generating many of the protective and affective behaviors animals display. Our studies have led to the identification of a number of excitatory and inhibitory cell types that play key roles in processing and gating noxious and innocuous mechanosensory stimuli. This knowledge is now being used to determine how sensory afferent feedback interfaces with the spinal motor system to control movement and generate stimulus-specific motor reflexes.

Brainstem Circuits for the Control of Locomotion

María Soledad Espósito[1]
[1]Silvia Arber Lab, Friedrich Miescher Institute for Biomedical Research, Basel, Suiza

The ability to move between places is an essential animal behavior that fascinated researchers since the beginning of neuroscience. Today, we know that spinal cord circuits control the basic locomotor pattern determined by intra- and inter-limb coordination; however, supraspinal commands are indispensable in order to initiate locomotion. Classical experiments based on electrical microstimulation identified brain regions with the ability to elicit locomotion, but in most cases, the coexistence of functionally different neuronal subpopulations may have led to controversial results. In my talk, I will describe recent findings on the cellular and functional organization of brainstem motor centers in which specific neuronal subpopulations control opposing aspects of motor behavior such as locomotion or immobility.

Neuronal Networks for Motor Control

Lidia Szczupak[1]
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Neural networks that control animal movement are, on one hand, hierarchically organized and, on the other hand, highly distributed. The study of such networks requires the implementation of experimental strategies that allow simultaneous recordings at multiple levels within the nervous system to evaluate how these levels interact to generate a coherent behavioral output. The nervous system of leeches presents unique advantages for the understanding on how motor control networks function. Leeches display robust locomotive and defensive behaviors. The simplicity of the organism structure is reflected in the relative simplicity of its nervous system formed by a chain of identical ganglia flanked by two brains, one in the head and the other in the tail. Neurons in each ganglion are not type representative units, but they play well-defined functions that are complementary shared with as few as one other neuron to very few other neurons. The study of how the crawling motor pattern is organized in the leech nervous system had shed light on the role played by motoneurons in motor control. Previously conceived as mere output units, motoneurons shape the crawling motor pattern via recurrent inhibitory circuits and through the interaction with the central pattern generator. Thus, in addition to well-known proprioceptive feedback mechanism, the output of motoneurons participates in the pattern generation. The results obtained throughout the analysis of the crawling network do not contradict the hierarchical nature of motor networks but shed light on how the processing of feedforward and feedback signals is essential to shape a behavioral output.

Neural Mechanisms of Leg Proprioception and Motor Control in *Drosophila*

Jhon Tuthill[1]
[1]University of Washington, Seattle, WA, USA

Animals rely on an internal sense of body position and movement to effectively control motor behavior. This sense of

proprioception is mediated by diverse populations of internal mechanosensory neurons distributed throughout the body. My laboratory is trying to understand how proprioceptive stimuli are detected by sensory neurons, integrated and transformed in central circuits, and used to guide motor output. We approach these questions using genetic tools, *in vivo* two-photon imaging, and patch-clamp electrophysiology in *Drosophila*. We recently found that the axons of fly leg proprioceptors are organized into distinct functional projections that contain topographic representations of specific kinematic features: one group of axons encodes tibia position, another encodes movement direction, and a third encodes bidirectional movement and vibration frequency. Whole-cell recordings from downstream neurons reveal that position, movement, and directional information remain segregated in central circuits. These feedback signals then converge upon motor neurons that control leg muscles. Overall, our findings reveal how a low-dimensional stimulus—the angle of a single leg joint—is encoded by a diverse population of mechanosensory neurons. Specific proprioceptive parameters are initially processed by parallel pathways but are ultimately integrated to influence motor output. This architecture may help to maximize information transmission, processing speed, and robustness, which are critical for feedback control of the limbs during adaptive locomotion.

Thursday, 25: 16:00–18:00
Symposium VI/Room B

INTERNATIONAL BRAIN IBRO RESEARCH ORGANIZATION

Astroglial Heterogeneity: An Opportunity for Neuroprotection and Regeneration?

Chair: Elaine Del-Bel[1,2]

[1]Department of MFPB-Physiology, FORP, University of São Paulo, Brazil
[2]Center for Interdisciplinary Research on Applied Neurosciences (NAPNA), São Paulo, Brazil

Abstract not available

Cellular Targets of Tyrosine Kinase Inhibitors in Amyotrophic Lateral Sclerosis

Luis Barbeito[1]

[1]Instituto Pasteur de Montevideo, Uruguay

Inhibitors of type III tyrosine kinase have demonstrated therapeutic benefit in oncologic, inflammatory, and fibrotic diseases. We have previously shown evidence that post-paralysis survival of SOD1G93A rats can be significantly extended by the masitinib, a drug currently in Phase 3 clinical trials for amyotrophic lateral sclerosis (ALS). Masitinib is unique among many other ALS-developmental drugs because it exerts protection in SOD1G93A rats when treatment starts after overt paralysis onset, potentially reproducing the clinical setting in ALS patients. Masitinib targets a highly selective profile of tyrosine kinases including CSF1R, KIT, PDGF-R, Fyn, and Lyn. Through inhibition of CSF1R, masitinib strongly reduces gliosis and the emergence of aberrant glial cells in the ventral horn of symptomatic SOD1G93A rats. In the fast-fatigable muscle extensor digitorum longus, post-paralysis treatment with masitinib significantly decreases c-Kit-expressing mast cells that accumulate close to denervated motor plates. Masitinib treatment starting after paralysis onset dramatically reduces the number of degranulating mast cells and delays neuromuscular junction denervation, as compared with vehicle-treated rats. In the sciatic nerve of symptomatic SOD1G93A rats, a subset of reactive Schwann cells expresses CSF1 and IL-34, which stimulate macrophage proliferation and activation through CSF1R. Additionally, a subset of invading macrophages express stem cell factor, which promotes the proliferation and differentiation of mast cell precursors through activation of c-Kit. Furthermore, a sub-set of chymase+ macrophages accumulate and pack together with neutrophils, likely exacerbating the focal nerve pathology. Treatment with masitinib for 15 days from paralysis onset prevents the appearance of mast cell/neutrophil aggregates and reduces the number of non-phagocytic macrophages. Remarkably, the treatment also significantly decreases axonal pathology and demyelination, as compared to vehicle-treated rats. These findings further strengthen the rationale for treating ALS with tyrosine kinase inhibitors, in particular masitinib, and indicate novel pathogenic pathways in the central and peripheral nervous systems involving inflammatory cells, the emergence of which is likely associated with paralysis progression.

Astrocyte Transforming Growth Factor Beta 1 Protects Synapses Against Aβ Oligomers in Alzheimer's Disease Model

Flávia C. A. Gomes[1]

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Alzheimer's disease (AD) is characterized by progressive cognitive decline, increasingly attributed to neuronal dysfunction induced by amyloid-β oligomers (AβOs). Although

the impact of AβOs on neurons has been extensively studied, only recently have the possible effects of AβOs on astrocytes begun to be investigated. Given the key roles of astrocytes in synapse formation, plasticity, and function, we sought to investigate the impact of AβOs on astrocytes and to determine whether this impact is related to the deleterious actions of AβOs on synapses. We found that AβOs interact with astrocytes, cause astrocyte activation, and trigger abnormal generation of reactive oxygen species, which is accompanied by impairment of astrocyte neuroprotective potential *in vitro*. We further show that both murine and human astrocyte conditioned media increase synapse density, reduce AβOs binding, and prevent AβO-induced synapse loss in cultured hippocampal neurons. Both a neutralizing anti-transforming growth factor-β1 (TGF-β1) antibody and siRNA-mediated knockdown of TGF-β1 previously identified as an important synaptogenic factor secreted by astrocytes, abrogated the protective action of astrocyte conditioned media against AβO-induced synapse loss. Notably, TGF-β1 prevented hippocampal dendritic spine loss and memory impairment in mice that received an intracerebroventricular infusion of AβOs. Results suggest that astrocyte-derived TGF-β1 is part of an endogenous mechanism that protects synapses against AβOs. By demonstrating that AβOs decrease astrocyte ability to protect synapses, our results unravel a new mechanism underlying the synaptotoxic action of AβOs in AD.

Astrocytes as Active Players of the Innate Immune System: Another Layer of Astroglial Heterogeneity?

Alberto Javier Ramos[1]
[1]Laboratorio de Neuropatología Molecular, Instituto de Biología Celular y Neurociencia "Prof. E. De Robertis," CONICET, Facultad de Medicina, Universidad de Buenos Aires, Argentina

Reactive gliosis involving activation and proliferation of astrocytes and microglia is a widespread but largely complex and graded glial response to brain injury. Astroglial population has a previously underestimated high heterogeneity with cells differing in their morphology, gene expression profile, and response to injury. Over the last years, we have been studying whether astrocytes may behave as facultative innate immunity cells after central nervous system injury. Classical innate immunity activation in the absence of infection relies on the damage-associated molecular patterns (DAMP) release by dying cells. DAMPs behave as ligands of the pattern recognition receptors, such as Toll-like receptor, RAGE, and others. Using a combination of mathematical modeling, *in vitro* and *in vivo* experimentation, we have been able to show that astrocytes essentially behave as facultative cells of the innate immunity response that classically follows brain damage. While classical innate immunity pathways such as those involving RAGE, Toll-like receptor 4/nuclear factor-κB, and TREM-2 are activated by released DAMPs, astrocytes are also key players in determining the interaction with local and peripheral professional immune cells. Moreover, detailed histological studies and *ex vivo* culture experiments have shown that only a subset of astrocytes seems to have the immune and neuroinflammatory role in experimental focal brain lesions and they can be specifically targeted by dendrimeric nanoparticles. This additional layer of neurobiological complexity can also be explored for therapeutic purposes oriented toward controlling neuroinflammation in the injured brain.

Are Neuroinflammation and Astrocytes Key Elements in L-DOPA-Induced Dyskinesia in Parkinson's Disease?

Elaine Del-Bel[1,2]
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Inflammation in Parkinson's disease (PD) is a new concept that has gained ground due to the potential of mitigating dopaminergic neuron death by decreasing inflammation. The solution to this question is likely to be complex. We propose here that the significance of inflammation in PD may go beyond the nigral cell death. The pathological process that underlies PD requires years to reach its full extent. A growing body of evidence has been accumulated on the presence of multiple inflammatory signs in the brain of PD patients even in very late stages of the disease. Because neuron–microglia–astrocyte interactions play a major role in the plasticity of neuronal response to l-DOPA in post-synaptic neurons, we focused this review on our recent results of l-DOPA-induced dyskinesia in rodents correlating it to significant findings regarding glial cells and neuroinflammation. We showed that in the rat model of PD/l-DOPA-induced dyskinesia, there was an increased expression of inflammatory markers, such as the enzymes COX2 in neurons and iNOS in glial cells, in the dopamine-denervated striatum. The gliosis commonly seem in PD was associated with modifications in astrocytes and microglia that occur after chronic treatment with l-DOPA. Either as a cause, consequence, or promoter of progression of neuronal degeneration, inflammation plays a role in PD. The key aims of current PD research ought to be to elucidate (a) the time sequence in which the inflammatory factors act in PD patient brain and (b) the mechanisms by which

neuroinflammatory response contributes to the collateral effects of l-DOPA treatment.

Friday, 26: 08:30–10:30
Symposium VII/Room A

Synaptic Drive and Neuromodulatory Circuits in Cognitive and Emotional Processes

Chairs: Joaquin Piriz[1] and Mariano Soiza Reilly[2]
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[2]IFIBYNE, UBA-CONICET, Buenos Aires, Argentina

Abstract not available

Experience-Dependent Synaptic Plasticity in the Lateral Habenula

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In everyday life, proper behavioral responses when foreseeing an unpleasant event are necessary for survival. Neurons in the lateral portion of the epithalamic nucleus habenula (LHb) are excited upon a negative event. Furthermore, after conditioning, LHb neurons show excitation when the conditioned stimulus is presented (Matsumoto and Hikosaka, 2007). However, whether synaptic adaptations occur within the LHb during learning, allowing anticipating an aversive stimulus, remains unknown. We hypothesized that, during the formation of an association between an external stimulus and the successive administration of a punishment, plasticity at excitatory synapses occurs in the LHb. To investigate this issue, we interrogated synaptic transmission onto LHb neurons in acute brain slices from animals at different stages of learning using an active avoidance paradigm (30 trials/day, 5 days). The animals learned to avoid a footshock preannounced by a tone already from the second and third sessions ("learners"). Control mice instead received the footshocks and the CS randomly, not contingently. Twenty-four hours after Training Session 2, we measured spontaneous excitatory post-synaptic currents (sEPSC) in acute brain slices containing the LHb. The frequency of sEPSCs, but not amplitude, was significantly increased in the LHb of learners, compared to control mice. Recording trains of EPSCs revealed similar paired-pulse ratios between learners and controls. We then measured AMPA and NMDA currents elicited by electrical stimulation within the LHb, observing a significant increase in AMPA/NMDA ratio in learners compared to controls. Furthermore, this AMPA/NMDA increase was observed when evoking EPSCs using uncaged glutamate in the proximity of dendrites. These data suggest that learning to predict an aversive stimulus engages post-synaptic strengthening at excitatory synapses in the LHb.

Reference

Matsumoto, M., & Hikosaka, O. (2007). Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature*, *447*(7148), 1111–1115.

Synaptic Tagging and Capture: From Synapses to Behavior

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It is shown that long-term potentiation (LTP) is the cellular basis of memory formation. However, since all but small fraction of memories are forgotten, LTP has been further divided into early LTP (e-LTP), the mechanism by which short-term memories are formed, and a more stable late LTP (L-LTP), by which long-term memories are formed. Remarkably, it has been shown that an e-LTP can be stabilized if it is preceded or followed by heterosynaptic L-LTP. According to synaptic tagging and capture (STC) hypothesis, e-LTP is stabilized by capturing proteins that are made by L-LTP induction. The model proposes that this mechanism underlies the formation of late associative memory, where the stability of a memory is not only defined by the stimuli that induce the change but also by events happening before and after these stimuli. As such, the model explicitly predicts that a short-term memory can be stabilized by inducing heterosynaptic L-LTP. A main project in our laboratory is to test this hypothesis. Specifically, we are testing two explicit predictions of STC model: (a) a short-term memory can be stabilized by induction of heterosynaptic LLTP and (b) this stabilization is caused by the protein synthesis feature of L-LTP. To do this, using optogenetics, we are engineering a short-term fear memory. Subsequently, we are examining if optogenetic delivery of L-LTP to a second pathway converging on the same population of neurons in the amygdala does stabilize the short-term fear memory. To be able to engineer natural memory by manipulating synaptic plasticity, we are developing a two-color optical activation system which permits selective manipulation of distinct neuronal populations with precise temporal and spatial resolution.

Cholinergic Mechanisms Shaping VTA Dopaminergic Maladaptations to Stress and Nicotine

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The stress response per se is beneficial; however, when responses are disproportionate or excessively long-lived, they become maladaptive. As such, traumatic experiences and social stress promote the onset of psychiatric disorders, including pathological anxiety, major depression, and inability to socially perform. Perhaps not surprisingly, nicotine dependence is two to three more common in psychiatric patients. The prevalence of this comorbidity and the complex interactions that occur between the two underlying disorders questions the strategy that consists to deal with each entity separately or consider only that one increase the vulnerability. We demonstrate that the interaction between stress (a major factor in depression etiology) and nicotine dependence occurs at the level of the ventral tegmental area (VTA). We show that chronic social stress increases activity of VTA dopamine neurons, causally resulting in depressive-like behaviors such as social aversion and anhedonia. Strikingly, mice that received nicotine in the drinking water are more sensitive to stress, and both behavioral and cellular maladaptations are triggered by a single defeat episode. Blocking ß2 or α7 nicotinic acetylcholine receptors prevents, respectively, the development and the expression of social stress-induced neuroadaptations. Using neuro-anatomical tracers and c-fos immunohistochemistry, we identify the laterodorsal tegmental nucleus (LDTg) as a source of cholinergic input to the VTA that is activated by stress. Patch-clamp recordings in LDTg-to-VTA cholinergic neurons revealed that this cell populations increases firing in response to chronic stress, consistent with increased cholinergic tone. We then used conditional expression of inhibitory DREADDs via viral stereotaxic injections in the LDTg. Silencing of LDTg cholinergic cells during stress was sufficient to prevent dopaminergic cellular maladaptations and depression-related behaviors. Our results pinpoints to a specific circuit dysregulation in relation to stress disorders, nicotine addiction, and depression.

Prefrontal Serotonin Transporter Shapes Cortico-Raphe Circuits and Long-Term Emotional Deficits of Early-Life Exposure to SSRIs

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Loss or reduced function of the serotonin transporter (Slc6a4/SERT) during early development has paradoxical long-term effects in adult life by increasing vulnerability to depression and anxiety. However, the basis for these developmental effects is not known. Here, we show that during an early postnatal period (P0–P10), Slc6a4/SERT is transiently expressed in a subset of Layers 5 to 6 pyramidal neurons of the prefrontal cortex (PFC). PFC-SERT+ neurons establish glutamatergic synapses with a number of subcortical targets, including 5-HT and GABA neurons in the dorsal raphe nucleus (DRN). PFC-to-DRN circuits develop postnatally, coinciding with the period of PFC Slc6a4/SERT expression. Complete or cortex-specific ablation of SERT increases the number of functional PFC glutamate synapses onto 5-HT and GABA DRN neurons. This PFC-to-DRN hyper-innervation is replicated by early postnatal exposure to the selective serotonin reuptake inhibitor (SSRI) fluoxetine from P2to P14, which also causes long-lasting emotional deficits and dampens the activation of the PFC in response to stress. Targeting the PFC-SERT+ neurons with pharmacogenetic tools, we show that chemogenetic inhibition of these neurons enhances the emotional deficits caused by early life exposure to SSRIs. Overall, our data identify specific PFC descending circuits that are targets of antidepressant drugs during the perinatal period. We demonstrate that developmental expression of SERT in a subset of PFC neurons controls synaptic maturation of PFC-to-DRN circuits and that maladaptive changes of these circuits, induced by early exposure to SSRIs, play a central role in behavioral responses to stress.

Friday, 26: 11:00–13:00
Symposium VIII/Room A

Cell Strategies in Degenerative and Regenerative Processes of the Nervous System

Chair: Luis E. Politi[1]

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Multipotent Cells as Mediators of Peripheral Nerve Regeneration

Patricia Setton[1]
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Demyelination is one of the hallmarks of the Wallerian degeneration (WD) process, and cell therapy is among the strategies under study to induce remyelination. Results from our group obtained in a reversible model of WD induced by the crush of the rat sciatic nerve demonstrated the spontaneous migration of endogenous or transplanted bone marrow mononuclear cells (BMMC) exclusively to the injured nerve. Once in the ipsilateral nerve, some BMMC colocalize with Schwann cell markers and nerve fiber markers. In this context, our group is currently digging into the regenerating effects of BMMC and adipose-derived mesenchymal stem cell transplant upon injury in terms of axon morphology and function, neuropathic pain amelioration, and the corresponding underlying mechanisms. In addition, studies underway are seeking to optimize cell recruitment to the lesion area through pharmacological and nanotechnological resources. So far, results hint at a beneficial role for multipotent cells in nerve injury and suggest they could be useful adjuvants to anti-inflammatory/analgesic drug treatments.

Restoring the Connectomes of Regenerated Retinal Bipolar Neurons Following a Tissue-Disrupting Retinal Lesion in Adult Zebrafish

Stenkamp Deborah[1], **T. E. McGinn**[1], **C. Galicia**[1] **and D. M. Mitchell**[1]
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We previously reported strikingly normal morphologies and functional connectivities of regenerated retinal bipolar neurons (BPs) in zebrafish retinas sampled 60 days after a ouabain-mediated lesion of inner retinal neurons (60 dpi; McGinn et al., 2018). Here, we report early steps in the birth of BPs and formation of their dendritic trees and axons in histologically regenerated retinas following retinal injury. Zebrafish were subjected to ouabain-mediated lesion that destroys inner retinal neurons and spares photoreceptors and Müller glia and were sampled at 13, 17, and 21 dpi, a time frame over which plexiform layers re-emerge, and which corresponds to the initial appearance and accumulation of two populations of BPs (PKCα+ and *nyx::mYFP*+). Sequential BrdU, then EdU, incorporation reveals that similar fractions of PKCα+ BPs and Hu+ amacrine/ganglion cells are generated at the same times, suggesting that the sequence of neuronal production during retinal regeneration may not strictly match that observed during embryonic development. The sparsely distributed *nyx::mYFP*+ BPs were examined for morphological detail by confocal microscopy, tracing, morphometric analyses, identification of cone synaptic contacts, and rendering/visualization. Apically projecting neurites (=dendrites) of regenerated BPs sampled at 13, 17, and 21 dpi are either truncated or display smaller dendritic trees when compared to controls. In cases where BP dendrites reach the outer plexiform layer (OPL), numbers of dendritic tips are similar to those of controls at all sampling times. Furthermore, by 13 to 17 dpi, BPs show patterns of photoreceptor connections that are statistically indistinguishable from controls, while those sampled at 21 dpi slightly favor contacts with double cone synaptic terminals over those of blue-sensitive cones. These findings suggest that dendrites of regenerated BPs that reach the OPL establish normal photoreceptor connectomes, albeit with some plasticity. Through 21 dpi, basally projecting neurites (=axons) of regenerated *nyx::mYFP*+ BPs traverse long distances, branch into inappropriate layers, or appear to abruptly terminate, making them difficult to trace. Collectively, these findings suggest that, after a lesion that destroys BPs and their postsynaptic partners, but spares their presynaptic inputs, maturation and pathfinding of regenerated BP axons are delayed compared to formation and maturation of their dendritic trees.

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3D Retinal Organoids: New Frontiers for Stem Cell-Based Clinical Applications

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Human-induced pluripotent stem cells (hiPSC) provide a unique tool for the development of *in vitro* models of retinal diseases as well as therapeutic strategies to regenerate the diseased retina. Recent progress in our ability to generate hiPSC-derived three-dimensional retinal tissue that closely mimics the *in vivo* retinal microenvironment and tissue organization opens new frontiers for their use in clinical applications. This talk will present and overview of the current-state-of-the art in retinal organoids, discuss the challenges and opportunities these systems present for clinical

applications, and describe new directions being pursued in the context of potential therapeutic approaches.

Friday, 26: 15:30–17:30
Symposium IX/Room A

Cellular and Molecular Mechanisms in Retina Degeneration

Chairs: Nora Rotstein[1] and Cecilia Sánchez[2]
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Abstract not available

Neuroprotection of Photoreceptors as a Therapeutic Strategy in Retinal Degeneration

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Retinitis pigmentosa (RP) is a degenerative disease leading to photoreceptor cell loss. Mouse models of RP, such as the rd10 mouse, have enhanced our understanding of the disease, allowing for development of potential therapeutics. Our group has demonstrated that the synthetic progesterone analogue "Norgestrel" is neuroprotective in two mouse models of retinal degeneration. We have elucidated several mechanisms by which Norgestrel protects photoreceptors, such as up-regulating growth factors and damping of glia cell activity. This presentation will outline the mechanism and action of Norgestrel's neuroprotective effects. Dams of post-natal day (P) 10 rd10 pups were given a Norgestrel-supplemented diet (80 mg/kg). Upon weaning, pups remained on Norgestrel. Tissue was harvested from P15 to P50 rd10 mice. Norgestrel-diet administration provided significant retinal protection to P40 in mice. Alterations in microglial activity coincided with significant protection, implicating microglial changes in Norgestrel-induced neuroprotection. Utilizing primary cultures of retinal microglia and 661W photoreceptor-like cells, we show that rd10 microglia drive neuronal cell death. We reveal a novel role of Norgestrel, acting directly on microglia to reduce pro-inflammatory activation and prevent cell death. Norgestrel effectively suppresses cytokine, chemokine, and danger-associated molecular pattern molecule expression in the rd10 retina. Remarkably, Norgestrel up-regulates fractalkine-CX3CR1 signaling 1,000-fold at the RNA level. Fractalkine-CX3CR1 signaling has been shown to protect neurons by regulating retinal microglial activation and migration. Ultimately, these results present Norgestrel as a promising treatment for RP.

Vascular and Nonvascular Alterations in Retinopathies: Toward a Change in the Therapeutic Strategy

Sánchez M. Cecilia[1], M. E. Ridano[1], P. V. Subirada[1], M. C. Paz[1], V. E. Lorenc[1,2], J. D. Luna[3], P. F. Barcelona[1] and M. V. Vaglienti[1]
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Neovascular retinopathies are leading causes of irreversible blindness. Although vascular endothelial growth factor (VEGF) inhibitors have been established as the mainstay of current treatment, clinical management of these diseases is still limited. As retinal impairment involves abnormal neovascularization and neuronal degeneration, we evaluated here the retinal functionality and the behavior of neuro-glial injury markers using the oxygen-induced retinopathy (OIR) model in mice treated or not with anti-VEGF mAb. Postnatal day 17 OIR mouse retinas showed the highest neovascular profile and exhibited neuro-glial alterations as well as retinal functional loss, which persisted until P26 OIR. Remarkably, although anti-VEGF treatment in P17 OIR improved retinal vascularization, neither non-vascular nor functional alterations were attenuated. These results suggest that, in addition to neovascularization, retinal neurodegeneration should also be considered an important pathogenic component of the disease highlights the importance of non-vascular alterations in proliferative retinopathies and the need of seeking new therapeutic agents targeting both neovascular and neurodegenerative processes to treat this multifactorial disease.

Molecular Mechanisms of PEDF Peptides in Retinal Degenerations

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The generation of retinoprotective peptides that activate specific and selective targets in the eye is of interest due to their high-potential therapeutic value in retinal dystrophies. The well-established actions of pigment epithelium-derived factor (PEDF) and its involvement in controlling retina homeostasis make this protein a prime candidate for future ocular therapeutic applications. PEDF exerts neurotrophic, neuroprotective, antiangiogenic, gliastatic, antioxidant, and antiangiogenic effects in the retina. It protects the retina from degeneration processes induced by cell death, pathological neovascularization, tumorigenesis, and inflammation. Studies on protein structure and function have demonstrated that the multiple actions of PEDF rely on specific epitopes distributed throughout the protein and interactions with several targets, including specific surface receptors, orphan receptors, or other proteins. Mapping of the biological active regions has made possible the isolation of individual and specific activities of this multifunctional protein. Protein fragmentation and chemical peptide synthesis have been employed in the design of small peptides that have retained independent activities of PEDF *in cellulo, ex vivo,* and *in vivo*. Peptides of 17 residues designed from the PEDF neurotrophic domain recapitulate the properties of its full-length protein of about 400 residues. They hinder photoreceptor cell death by binding the PEDF receptor and stimulating its phospholipase activity to liberate fatty acids from phospholipids, which in turn act on downstream signaling cascades. Our findings point out that the neurotrophic PEDF peptides act via the PEDF receptor on extrusion of intracellular calcium; attenuation of calpain activity; and regulation of Bcl2, Bax, and Aif for photoreceptor survival. The current knowledge of the molecular mechanisms of PEDF will be discussed.

This work was supported in part by the Intramural Research Program of the National Eye Institute, National Institutes of Health. Commercial disclosures: None.

Friday, 26: 15:30–17:30
Symposium X/Room B

Epilepsy From Bench to the Patients

Chairs: Jerónimo Auzmendi[1] and Alberto Lazarowski[2]

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[2]Clinical Biochemistry Department, FFyB, UBA, Buenos Aires, Argentina

Progressive P-Glycoprotein Overexpression and Its Relationship With SUDEP

Alberto Lazarowski[1]

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Sudden unexpected death in epilepsy (SUDEP) is the major cause of death in those patients suffering from refractory epilepsy (RE), with a 24-fold higher risk relative to the normal population. SUDEP risk increases with seizure frequency or seizure-duration as in RE and status epilepticus (SE). P-glycoprotein (P-gp), the product of the multidrug resistant *ABCB1-MDR-1* gene, is a detoxifying pump that extrudes drugs out of the cells and can confer pharmacoresistance to the expressing cells. Neurons and cardiomyocytes normally do not express P-gp; however, it is overexpressed in the brain of patients or in experimental models of RE and SE. P-gp was also detected after brain or cardiac hypoxia. We have previously demonstrated that repetitive pentylenetetrazole (PTZ)-induced seizures increase P-gp expression in the brain, which is associated with membrane depolarization in the hippocampus, and in the heart, which is associated with fatal SE. SE can produce hypoxic-ischemic altered cardiac rhythm and severe arrhythmias, and both are related with SUDEP. Our results suggest that the highly accumulated burden of convulsive stress results in a hypoxic heart insult, where P-gp expression may play a depolarizing role in cardiomyocyte membranes and in the development of the ECG changes, such as QT interval prolongation, that could be related with SUDEP. We postulate that this mechanism could explain, in part, the higher SUDEP risk in patients with RE or SE.

Epigenetic Changes Induced by Antiepileptic Drugs and Their Relevance in Epilepsy

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In the treatment of epilepsy, antiepileptic drugs (AEDs) represent a group of exogenous factors that can induce epigenetic modifications and alter the structure of chromatin. Epigenetic changes such as DNA methylation, histone modifications, and synthesis, as well as the function of non-coding RNAs (ncRNA), are part of the cellular environment of the brain with epilepsy. However, many of these changes can be induced by the sole administration of AEDs. Alterations in the chromatin structure induced by the AEDs can result in changes in the gene expression of various factors involved in the pathology of epilepsy both to the benefit of the disease and to the detriment of it. This presentation will focus on reviewing the epigenetic modifications induced by AEDs widely used in the clinic. It is important to consider that although AEDs are widely used to control epilepsy and other neurological diseases, their epigenetic effects are not considered. On the other hand, the knowledge of the epigenetic changes induced by AEDs represents new possibilities in the development or optimization of treatments for the patient with epilepsy.

Kainic Acid as a Preclinical Experimental Model for the Study of New Molecules for the Treatment of Epilepsy and Neurodegenerative Diseases

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Kainic acid (KA) is a non-degradable analog of glutamate, and a potent neurotoxin that acts through glutamate receptors, showing affinity for non-NMDA ionotropic receptors, specifically kainate receptors (KAR). In rodents, local or systemic administration of KA triggers a pattern of repetitive seizures for several hours, followed by a latency period, and a subsequent spontaneous onset of seizures (Ben-Ari, 1985). These seizures cause brain damage, often associated with the aberrant formation of new synapses, simultaneously with an increase in the density of kainate receptors, glial activation, deregulation of cellular homeostasis and a consequent loss of hippocampal neurons. These alterations are similar to those that develop in the most frequent epilepsy in adult humans, temporal lobe epilepsy (TLE) (Engel et al., 1989). In this way, the KA experimental model, in addition to reproducing the TLE, allows the understanding of neuronal death mechanisms present in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. In recent years, different studies have shown the participation of MAPK pathways in the mechanisms of neuronal death and inflammation, characteristic of neurodegenerative diseases (Chang and Karin 2001, Harper and Wilkie 2003). In particular, the JNK pathway has been broadly related to neurodegenerative disorders. Our studies have shown a reduction in neuronal death and absence of astrogliosis observed in the hippocampus of Jnk3 - / - and Jnk1 - / - mice after treatment with KA. The results obtained with Jnk1 - / - mice are novel, since the role of this isoform in neurodegenerative processes is demonstrated for the first time. In addition, these results have allowed us to demonstrate the efficacy of a molecule Licochalcone A (Lic-A) through the inhibition of JNK1, caused a reduction in the seizure pattern in rodents. In addition, it reduced the phosphorylation levels of JNK, as well as its activity. In addition, Lic-A prevents neuronal degeneration of the hippocampus, increases pro-survival antiapoptotic mechanisms, reduces pro-apoptotic biomarkers, and reduces cell stress and neuroinflammatory processes. Therefore, our results suggest that the inhibition of JNK1 by Lic-A has neuroprotective effects and that; it could be a potential new approach for the treatment of epileptic status and neurodegeneration.

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Identification of Epileptogenicity Markers From the Register of Individual Neurons in Patients Candidates to Epilepsy Surgery

Silvia Kochen[1]
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Epilepsy is the most frequent disease of neurological diseases. Patients who do not respond to pharmacological treatment (30%–40%) may benefit from surgical treatment. In some cases, for the identification of the epilepsy zone (EZ), the electrical activity must be recorded during the crisis of epilepsy with intracerebral macro- and microelectrodes (EEGi). The use of microelectrodes allows the registration of multiple neurons, as well as those of local field, simultaneously, with the registration of large neurons, participation in the different scales, more accurately identify the EZ and the new biomarkers. This line of research will affect the health of patients, the most selective surgery of the EZ with less risk of irreversible cognitive, or motor sequelae. On the other hand, it is a tool to better understand the dynamics of the neural network.

Young Investigator Lectures

Wednesday 24

YIL1. Studying Synaptic Transmission at the Level of Individual Synaptic Vesicles

L. Natali[1] **and R. Chanaday**[1]
[1]UT Southwestern Medical Center

Coupling of synaptic vesicle fusion and retrieval constitutes a core mechanism ensuring maintenance of presynaptic function. Recent studies have shown the coexistence of several endocytic pathways in neurons, with diverse kinetics and temperature dependencies. Using optical methods, we study the recycling of single and multiple synaptic vesicles in cultured hippocampal neurons, including their kinetics, calcium, and temperature dependence. Our goal is to understand the underlying molecular mechanisms coupling different modes of exocytosis to different endocytic routes.

YIL2. Dietary Restriction Promotes Tissue-Specific Reprogramming of Circadian Gene Expression

Victoria Acosta Rordiguez[1]
[1]UT Southwestern Medical Center, Dallas, TX, USA

Caloric restriction (CR) extends life span in many species, yet the mechanisms are unclear. Our previous studies showed that CR protocols involve a 2-h-temporal restricted (TR) feeding followed by 22 hr of fasting, all of which impact on health. Thus, it is unclear whether the timing, frequency, or amount of food intake is the critical factor that improves metabolic fitness. Here, we investigated how feeding conditions modulate the circadian (24 hr) profile of gene expression in the hypothalamus and three major metabolic tissues: liver, white, and brown adipose tissues. We developed an automated feeders to fed mice either during the day or the night, with or without 30% CR. We found complex tissue-specific circadian changes in mRNA expression induced by both timing and amount of food intake. While feeding time determined the circadian profile of core clock genes in the liver and WAT, it did not affect expression in the BAT and hypothalamus. Remarkably, despite the core clock machinery remaining unchanged, the profile of metabolic genes such as leptin followed feeding time in BAT. Thus, revealing misalignment within the BAT. Altogether, these results show that metabolic tissues integrate environmental (feeding and day/night cycles) and systemic signals in a tissue-specific manner. Integrating these tissue-specific signatures with metabolic outcomes may help elucidate the mechanism by which dietary restriction extends longevity, revealing a link between circadian clocks and healthy aging.

YIL3. Behavioral Plasticity and Action Selection in *Drosophila*

Ezequiel Axel Gorostiza[1]
[1]IFEC-CONICET-UNC, Cordoba, Argentina

Phototaxis is an iconic example for behaviors dominated by innate components or preferences. Such preferences likely reflect evolutionary adaptations to predictable situations, and the behaviors dominated by them have traditionally been conceptualized as hard-wired stimulus-response links.

Perhaps therefore, the century-old discovery of plasticity in *Drosophila phototaxis* has received little attention. Experiments performed by McEwen demonstrated that wing defects, caused by mutation or damage, profoundly affect phototaxis in walking *Drosophila* 1. The fact that manipulating an unrelated organ, such as wings, affects phototaxis contradicts the assumed hard-wired organization of this behavior, suggesting that it may not be a simple stereotypic and automatic response, but that it contains at least a certain element of flexibility. To explore this hypothesis in our laboratory, walking flies were tested for their light/dark preference in several different behavioral tests. Interestingly, light/dark preference tested in walking flies is dependent on various aspects of flight. If flying ability is temporarily compromise, photopreference reverses concomitantly. Neuronal activity in circuits expressing dopamine and octopamine, respectively, plays a differential role in photopreference, suggesting a potential involvement of these biogenic amines in this case of behavioral plasticity. We conclude that flies monitor their ability to fly and that flying ability exerts a fundamental effect on action selection in *Drosophila*. This work suggests that even behaviors which appear simple and hard-wired comprise a value-driven decision-making stage, negotiating the external situation with the animal's internal state before an action is selected.

YIL4. New Players in Cortical Development: Role of GDNF/GFRα1

Antonela Bonafina[1]
[1]IBCN-CONICET-UBA, Buenos Aires, Argentina

During development, neural stem cells and their derivative progenitor cells give rise to all the neurons of the nervous system. The transition of proliferative progenitor cells to fully differentiated neurons is controlled by intrinsic programs as well as extrinsic environmental cues such as neurotrophic factors. In this work, we studied the role of glial cell line-derived neurotrophic factor (GDNF) and its receptor, GFRα1, during the proliferation and differentiation of cortical neural precursors cells (CNPs) both in the developing cortex. We show that GDNF and GFRα1 are expressed in the mice neocortex during the period of cortical neurogenesis. We show that GDNF through its receptor GFRα1 inhibits self-renewal capacity of mouse CNPs induced by FGF2, promoting neuronal differentiation. While GDNF leads to decreased proliferation of cultured CNPs, selective ablation of GFRα1 in glutamatergic cortical precursors enhances its proliferation. Moreover, analysis of conditional GFRα1-knockout mice shows an increase in the number of cycling cells during cortical development. We also show that GDNF treatment of CNPs resulted in a marked increase in neuronal population and promoted morphological differentiation even in the presence of FGF2. Analysis of newborn conditional GFRα1-deficient mice shows a reduction in dendritic length in a subpopulation of cingulate cortical neurons *in vivo*. This result is in agreement with our previous findings indicating that the GDNF/GFRα1 complex plays a crucial role in the development of hippocampal dendritic arbors (a). Together, these results indicate that GDNF/GFRα1 signaling plays an essential role in regulating the proliferative condition and the differentiation of CNPs to cortical or hippocampal neurons. The evidence obtained gives new opportunities to study the function of GDNF in neurodevelopmental diseases characterized by cognitive deficits.

YIL5. Sex Hormone Effects in Brain Mitochondria: At the Crossroads of Neuroprotection and Aging

Sandra Zárate[1]
[1]INBIOMED (UBA-CONICET), Facultad de Medicina, Universidad de Buenos Aires, Argentina

Sex steroids have pleiotropic effects in the brain, preserving neural function and survival. Loss of ovarian hormones after menopause is often associated with synaptic and cognitive impairments and increased risk of neurodegeneration, processes also highly linked to mitochondria (MT) dysfunction. In this line, we study the role of ovarian hormones in the maintenance of a healthy neural function in the hippocampus, specially focusing on MT. To this aim, we use an animal model of surgical-induced menopause in Wistar rats. Our data show that hippocampal MT from ovariectomized (OVX) rats exhibit reduced active respiration and ATP production rates. This MT dysfunction is correlated with changes in its membrane lipid profile resulting in a higher peroxidizability index and lower cardiolipin content with altered fatty acid profile. Our results suggest that ovarian hormone loss induces an MT phenotype similar to an aging-related one in terms of higher susceptibility to membrane peroxidation together with impaired MT bioenergetic capacity. Also, we are currently studying the expression and function of Humanin (HN), a mitochondrial-derived peptide with cytoprotective, metabolic, and anti-inflammatory effects. Our data *in vivo* show that HN colocalizes with astrocyte markers and its expression decreases in the hippocampus of OVX rats. Also, there is a positive correlation between the expression of HN and glial fibrillary acidic protein, suggesting that ovarian hormone loss promotes functional and morphological changes in astrocyes, which could affect astroglial support to neuronal function and may represent an underlying mechanism for synaptic dysfunction. In fact, we show that HN prevents synapse loss in cultured hippocampal neurons exposed to glutamate. Also, our results in cultured

astrocytes show that ovarian hormones positively regulate HN expression and release. Our study could help find new therapeutic targets for interventions that may promote a healthier life span for post-menopausal women.

YIL6. Tell Me the Way You Live, I Will Tell the Way You Are: The Impact of Sensory and Motor Stimulation on the Epigenetic Control of Steroidogenic-Related Genes in the Rat Hippocampus

María Florencia Rosseti[1]
[1]ISAL-CONICET-UNL, Santa Fe, Argentina

Environmental enrichment (EE) promotes neuronal protection through various mechanisms of action. Neurosteroids are steroid hormones synthesized *de novo* from cholesterol or steroidal precursors in various brain regions and they have positive effects on neurogenesis, synaptic connectivity, and cognitive performance. We analyzed the effects of a short-term EE on the Mrna expression and DNA methylation state of steroidogenic enzymes in the hippocampus. For that, young adult (90-day-old) and middle-aged (360-day-old) female Wistar rats were exposed to sensory enrichment (SE) or motor enrichment (ME) during 10 days and compared to animals housed under standard conditions (SCs). SE was provided by an assortment of objects that included plastic tubes and toys; for ME, rodent wheels were provided. In young adult animals, both SE and ME increased the mRNA expression of P450(17α) and 3α-HSD enzymes and decreased the expression of P450arom. In addition, SE increased the transcription of 5αR-1. Interestingly, ME upregulated P450(11β)-2 gene expression in both young adult and middle-aged animals compared to SC. These results suggested that aged rats would require a more prolonged stimulus than young animals to observe a similar effect. We found hypomethylation at the 5αR-1 gene (Site d) produced by SE and at the 5αR1 (Site a) and 3α-HSD promoters produced by ME, in young adult rats. The fact that two different sites of the CpG Island 5αR-1 promoter altered their methylation patterns depending on the EE, suggest that these sites could be potential regulatory stimulus-specific sites. In middle-aged rats, ME decreased methylation levels at a cis-acting element Ad1 of the P450(11β)-2 promoter. Altogether, these results propose that sensory stimulation and motor stimulation differentially regulate the transcription of steroidogenic enzymes through epigenetic mechanisms associated with differential promoter methylation in the young and aged rat hippocampus.

Thursday 25

YIL7. Compartmentalization of Antagonistic Ca^{2+} Signals in Developing Cochlear Hair Cells

Marcelo Javier Moglie[1]
[1]INGEBI-CONICET, Buenos Aires, Argentina

The normal maturation of the auditory pathway relies on a critical developmental period characterized by the firing of sensory-independent action potentials by cochlear inner hair cells (IHCs). Spiking activity produces the influx of Ca^{2+} through voltage-gated channels which in turn triggers the synaptic release of glutamate onto dendrites of the auditory nerve, leading to the propagation of the spontaneous activity throughout the auditory system. On the other hand, IHCs are the postsynaptic target of efferent cholinergic neurons from the brainstem. At this synapse, Ca^{2+} entry through nicotinic $\alpha9\alpha10$ receptors is coupled to the activation of Ca^{2+}-dependent K+ channels to hyperpolarize the IHC. Thus, efferent Ca^{2+} influx is inhibitory, opposing the excitatory Ca^{2+} signal produced during IHC firing. The aim of our work was to investigate the mechanisms that allow segregation of excitatory versus inhibitory Ca^{2+} effects within the small and diffusionally compact IHCs. Electrophysiological recordings combined with swept-field confocal Ca^{2+} imaging experiments revealed the existence of multiple efferent Ca^{2+} entry hotspots, which were closely positioned to afferent Ca^{2+} entry sites within a single IHC. This finding was confirmed by IHC reconstructions at a nanometer scale using serial section electron micrographs (EMs), suggesting that efferent Ca^{2+} spread could invade afferent synapses. However, recordings from postsynaptic boutons of auditory nerve neurons showed that even high-frequency stimulation of efferent fibers failed to cross-activate and trigger the synaptic release of glutamate. Efficient compartmentalization of Ca^{2+} signals was accomplished by (a) sub-synaptic cisterns revealed in EM reconstructions, juxtaposed to cholinergic contacts; (b) a fast Ca^{2+} extrusion pathway mediated by sarcoendoplasmic reticulum calcium transport ATPase pumps; and (c) a very strong Ca^{2+} buffering in IHC cytoplasm. Thus, efferent fibers maintain its inhibitory signature and modulate spontaneous activity in the developing IHC.

YIL8. Revealing Expectancy Signals in the Barrel Cortex Using Repetitive Spatiotemporal Multi-Whisker Stimulations

Matías Goldin[1]
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The central nervous system (CNS) processes incoming sensory information in a way that reflects its preparedness for an expected input. Perception is therefore built by selective brain operations where the body state, its actions, and the sensory context are integrated to generate expectations. Neuronal signatures of those expectations and particularly to a violation of an expected stimulus have been recorded in animals and humans. Where are those signals generated? In the predictive coding Hypothesis 1, expectancy signals are generated in high cortical areas. However, it is debated if these signals are present in a primary sensory cortex. After a survey of the literature on expectancy signals in the CNS, I will present electrophysiological evidence for sensory responses in the primary somatosensory cortex (S1) related to expectation. We used the rat vibrissal system by applying highly predictable tactile inputs using a 24-whisker Stimulator 2. Multiple single-unit recordings, local field potentials, and current source density were obtained in the whisker region of S1 of anaesthetized rats. A stimulation pattern of successive whisker deflections (stimuli profile previously obtained 3,4) from the front to the back of the whisker pad was repeated many times during a training phase and truncated patterns, where the target whisker was missing, were presented at random times (with 5% chance) to follow the eventual buildup of expectancy signals. Our preliminary results show that the stimulus history can reconfigure the activity in the barrel cortex so that responses to truncated inputs resemble responses to the full pattern of stimulation. Ultimately, our project shall reveal how the brain compares sensory incoming information with inner representations of the world, an essential operation for identifying salient events.

YIL9. ERP Correlates of Recognition Semantic Memory After Active Versus Passive Memory Retrieval

Jorge Mario Andreau[1]
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Most of the event-related potential (ERP) studies of memory utilize recognition tasks (e.g., old/new item memory; Rugg and Doyle, 1994; Rugg et al., 1998; Curran et al., 2006). Recently, a cued memory recall task has been used to study associative memory retrieval. We introduced a modification to the latter and studied recognition memory process after an associative memory task. Twenty subjects were train to learn five pairs of arbitrary fractal images. We then evaluated semantic associative memory process through a delayed paired-association (DPA) task and a delayed match-to-sample (DMS) control task. Electroencephalography activity was recorded while subjects looked at a cue stimulus and, after 1 s delay, decided if the target stimulus matched the cue (DPA condition) or if it was identical to the cue (DMS condition). Therefore, they resembled traditional old/new studies except the memory trace was different not only between the two conditions (par/no pair and same/different) but also between the two tasks (DPA/DMS). Critically, in DPA, the recognition memory required active memory retrieval, while the recognition in DMS did not. When comparing the ERP activity between the two tasks, no familiarity effect was found (e.g., FN400 component; Curran et al., 2006) since all stimuli were equally familiar to the subjects. Interestingly, we found differences between 160 to 260 ms and 320 to 520 ms with a posterior topography. Those differences could be consider as a neural correlate of active associative long-term memory retrieval.

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YIL10. Neuroendocrine Regulation of Postprandial Dieresis in *Rhodnius prolixus*

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Given that hematophagous insects ingest large quantities of blood in a single meal, they should undergo a rapid postprandial diuresis to maintain the homeostasis. The diuresis is regulated by serotonin and neuropeptides, which modulate the secretory activity of the malpighian tubules and the fluid transport and peristaltic waves in the anterior midgut. Diuresis finishes 4 hr postbloodmeal (PBM), when anti-diuresis processes begin. CCHamide is a brain gut neuropeptide

precursor conserved in insect genomes. The physiological role of CCHamide has been studied in *Drosophila melanogaster* and *Bombyx mori*, where it modulates feeding behavior as an orexigenic factor. Here, we report that the neuropeptide RhoprCCHamide (RhoprCCHa) is involved in the regulation of the postprandial diuresis in *Rhodnius prolixus*, a triatomine insect which is a vector of Chagas disease. The expression of RhoprCCHa gene was downregulated by RNA interference in this insect, obtaining an 85% of gene silencing and we found a dual effect of RhoprCCHa in the diuresis. Our results point to an inhibition of immediate excretion (10–45 min PBM) and a stimulation of dieresis toward the end of the process (90–240 min PBM). Using *in vitro* approaches, we confirmed an effect of RhoprCCHa inhibiting the fluid transport by the anterior midgut stimulated with 5HT and an increasing in the secretion rate by stimulated malpighian tubules. The opposite role in different structures was not reported previously for any neuropeptidergic system in insects. It seems to reflect the necessity of a tight regulation of the volumes excreted in hematophagous, and thus avoiding defects in the diuresis that would endanger the homeostasis.

Oral Communications

Thursday 25: 14:30–15:30/Room C

OC1. Dopaminergic Neurodegeneration and Neuroinflammation: Modulation by IGF-I Gene Therapy

Macarena Lorena Herrera[1], Andrea Otamendi[1], Osvaldo Martín Basmadjian[1], Leandro Gabriel Champarini[1], Eugenia Falomir-Lockhart[2], Franco Juan-, Cruz Dolcetti[2], VIctor Alejandro Molina[1], María José Bellini[2] and Claudia Beatriz Hereñú[1]

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Abstract not available

OC2. Familiar Face Recognition in the Primate Brain

Sofia Landi[1] and Winrich Freiwald[1]

[1]Rockefeller University, New York, NY, USA

We have known for some time that there is a network of brain regions for face recognition. However, attempts at finding how and where face familiarity is encoded in the brain have proven inconclusive. We used functional magnetic resonance imaging (fMRI) in macaque monkeys to measure brain activity as they looked at pictures of other monkeys' faces that were familiar and unfamiliar to them. Activity in the entire face-processing system increased in response to the faces of long-term acquaintances. Additionally, these faces prompted the activation of two previously unknown face-selective areas. One is located in the perirhinal cortex (PR), a region that has been associated with declarative memory and the other one is embedded in a region involved in audio-visual integration and social knowledge: the temporal pole (TP). These two areas showed a nonlinear response as blurred faces became gradually visible, becoming abruptly active when the faces of familiar monkeys became recognizable. We are now exploring the electrophysiological properties of single-cell and neural populations in these areas. Preliminary results confirm our fMRI study: We found a high fraction of face-selective cells tuned to familiarity. Individual cells encoded specific familiar faces, and unfamiliar faces that were similar in shape or appearance failed to elicit the same neural responses. TP and PR emerge thus as special regions within the macaque face processing system that encode individual familiar faces.

OC3. Interoceptive Associations in Addiction to Smoked Cocaine

Laura Alethia de la Fuente[1], Lucas Sedeño[1], Sofia Schurmann[2], Camila Ellmann[2], Silvina Sonsogni[3], Laura Bellucio[3], Eduardo Canepa[3], Enzo Tagliazucchi[4], Teresa Torralva[2] and Agustin Ibañez[1]

[1]LPEN-INCyT, CABA, Argentina
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[4]COCUCO-UBA, CABA, Argentina

Contemporary neurocognitive models of drug addiction underscored the role of interoception. In these models, interoception is defined as the sensing and processing of body signals to serve a homeostatic function related to the onset and maintenance of addictive-behavior. In this

work, we assess the relation between interoception and smoked cocaine dependence with a multimodal and multidimensional approach. We use the heartbeat-detection (HBD) task and related heart evoked potential (HEP) recordings at baseline (interoceptive accuracy) and during learning. We combined this behavioral and electrophysiological data with structural and functional connectivity analysis of the main interoceptive hubs. Smoked cocaine dependent subjects presented ongoing psychophysiological measures of enhanced interoception accuracy (HBD and HEP); accompanied by structural and FC tuning of interoceptive networks. Our findings support both specialized effects of smoked cocaine on interoception, and also provide direct empirical evidence for drug models suggesting that hyper-interoception processing is a key aspect in addictions. Thus, multimodal assessment of interoception could serve as a potential domain to asses clinical and neurocognitive characterization of psychophysiological and underlaying neurophysiological adaptations in addiction.

OC4. Memory Deficits in Transgenic McGill-R-Thy1-APP Hemizygous Rats

Daniela Salas[1], Federico Filippin[1], Edgar Kornisiuk[1], Pilar Canal[1], Anna Di Tomas Lioro[1], Sonia Docarmo[2], A. Claudio Cuello[2], María Verónica Báez[1] and Diana Jerusalinsky[1]

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McGill-R-Thy1-APP Wistar transgenic (Tg) rats, with human APP under the Thy1.2 promoter, bearing the Swedish and Indiana mutations corresponding to familial Alzheimer's disease in homozygous condition, had been reported to show significant cognition deficits at 3 months of age. On the other hand, hemizygous Tg rats show a more subtle phenotype. In this work, 6- and 13-month-old hemizygous Tg males and their wild-type (WT) litter mates rats were individually left to freely explore an open field (OF) for 5 min and tested at 24 hr; the numbers of crosses in the floor were recorded. There were no differences between WT and Tg groups during the training and the number of crosses significantly decreased in the test compared with training. Rats were then trained in an inhibitory avoidance task (IA) of a mild electric foot shock and tested at 24 hr to evaluate long-term memory (LTM). Latency to go accross a door to get into a dark compartment where the rat will get the shock was recorded. There were no significant differences in training latencies between animal groups. Twenty-four hours later, test latencies were significantly higher than training latencies for WT rats, while there were no significant differences for Tg rats. Therefore, both Tg and WT rats are able to habituate to the OF, keeping LTM; on the other hand, WT animals learned and remembered the IA at 24 hr, while the Tg were not able to remember it, evidencing deficits in these sort of associative memory involving aversive and spatial components.

OC5. The Interplay Between Behavioral Pattern Completion and Pattern Separation for Retrieval in a Cue-Degraded Context

Magdalena Miranda[1], Facundo Morici[1], Dinka Piromalli Girado[1], Francisco Gallo[1], Weisstaub Noelia[1] and Pedro Bekinschtein[1]

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Because our environment is permanently evolving, it is crucial for episodic memory to remember our previous experiences despite environmental changes. Computational models have suggested the existence of a pattern completion process by which networks could retrieve entire memories from partial or degraded cues. The CA3 region of the hippocampus was proposed to mediate this computation by the plastic enhancement of the recurrent collateral connections of CA3 neurons that were active during learning. In this work, we manipulated the amount of cues available during retrieval (test phase) in a spontaneous object recognition task to investigate the function of CA3 NMDA receptors (NMDAR) for pattern completion. We show that pharmacological intervention of hippocampal CA3 NMDAR receptors impairs retrieval of the object location memory only when cues are degraded, while similar manipulations in the dentate gyrus have no effect. Moreover, while the context alone is enough to guide retrieval of the object memory under partial cues, antagonists of NMDAR in the test phase prevent this retrieval. These findings suggest that NMDAR in CA3 are necessary for the retrieval of spatial memories when the amount of environmental information is reduced, and that plastic changes in the dentate gyrus and CA3 are important to define if behavioral pattern separation or pattern completion occurs when exposed to a modified context.

OC6. Dissociating Reconsolidation and Extinction of Contextual Aversive Memory in Female Rats Using Midazolam Treatment and Reinstatement Paradigm: Influence of Reactivation Time Span

Jaqueline Maisa Franzen[1], Marcelo Giachero[1] and Leandro José Bertoglio[1]

[1]Department of Pharmacology, Federal University of Santa Catarina, Florianopolis, Santa Catarina, Brazil

Females (FEM) have particularities in contextual aversive memory (CAC). Reactivated aversive memories may follow alternative outcomes, which are dependent on duration of reactivation session. Although the time course of a CAC after retrieval has been well characterized in male rats, this temporal pattern is still unexplored in FEM. We aimed to investigate the passage from reconsolidation to extinction of memory combining CAC, different reactivation time span, midazolam, and a reinstatement procedure in FEM. Rats were trained and, on the following day, rats were exposed to different re-exposure times (1, 2, 5, 7, 10, or 30 min) that were followed by MDZ administration. Given that FEM showed a decrease in freezing expression with the increase in the number of re-exposures to the CAC, we used a reinstatement strategy that allowed dissociating the effect of MDZ on memory. Our findings showed that when the reactivation session lasted 2 to 5 min, memory returned to a labile state sensitive to disruption by MDZ and memory showed no reinstatement. When 30-min reactivation session was performed, memory was directed to extinction and MDZ was able to disrupt the retention of this process and memory showed reinstatement, but memory was insensitive to MDZ effect when reactivation session lasted 7 to 10 min. In summary, combining post-reactivation MDZ treatment with a reinstatement protocol, we managed to dissociate the mutually exclusive processes of reconsolidation and extinction in FEM rats.

Friday 26: 14:30–15:30/Room B

OC7. Temporal Mapping of Adult-Born Granule Cells Integration in Two Major Local Inhibitory Populations of the Hippocampus

Ayelen I. Groisman[1], Sung M. Yang[1] and Alejandro F. Schinder[1]

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Adult neurogenesis provides a continuous pool of new granule cells (GCs) that participate in information processing in the dentate gyrus of the hippocampus. We studied how GCs become integrated toward maturation into the preexisting circuit of the adult mouse dentate gyrus. We chose two major populations of GABAergic interneurons (INs) of the hippocampus: parvalbumin expressing cells (PV) and somatostatin expressing cells (SST). We combined optogenetics and acute slice electrophysiology to activate PV or SST and GCs, retrovirally labeled, at different stages of maturation and studied their connectivity in both directions, interneuron to GCs, and vice versa. We built a temporal map of synaptogenesis for each IN population and observed that connectivity between PV and GCs (input and output) reached maturation when GCs were $>$6 weeks old. For SST, the inhibitory postsynaptic current increased gradually with GCs development, while the GC output connectivity developed much later ($>$11 weeks) compared to PV. We found that PV synapses onto GCs were located perisomatically and contributed to both feedforward and feedback inhibitory loops within the granule cell layer. In contrast, SST contacted GCs in proximal and distal dendrites and contributed only to feedback inhibition. These data demonstrates that integration of new GCs within the preexistent dentate GABAergic network is specific of each IN population and that adult neurogenesis promotes a long-term plasticity for circuit remodeling.

OC8. The Varieties of the Psychedelic Experience: Association Between Reported Subjective Effects, Binding affinity profiles and Molecular Structures of 18 Psychoactive Compounds

Federico Zamberlan[1], Camila Sanz[2], Rocio Martinez Vivot[1], Carla Pallavicini[3], Fire Erowid[4], Earth Erowid[4] and Enzo Tagliazucchi[1]

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Classic psychedelics are substances of paramount cultural and neuroscientific importance. The observation of cross-tolerance and a series of empirical studies support partial agonism at the serotonin 5-HT2A receptor as a common mechanism for the action of psychedelics. The diversity of subjective effects elicited by different compounds has been attributed to the variables of "set" and "setting," to the binding affinities for other serotonin receptor subtypes, and to the heterogeneity of transduction pathways initiated

by conformational receptor states as they interact with different ligands ("functional selectivity"). Here, we evaluated the hypothesis that such variety is related to the binding affinity profiles for a range of different neurotransmitter and transporters including (but not limited to) serotonin receptors. Building on previous experimental binding affinity data in combination with natural language processing tools applied to a large repository of reports of psychedelic experiences (Erowid's Experience Vaults), we established that the similarity between the receptorome of 18 psychoactive compounds correlates with the closeness of their associated subjective effects. We also showed that the highest correlation could be achieved by considering a repertoire of receptors. Our methodological developments open the way to the systematic exploration of the relationship between the binding affinity profiles and subjective effects of other psychoactive compounds.

OC9. Leukocytes as Key Players in Optic Nerve Neuroinflammation

Marcos L. Aranda[1], Florencia Altschuler[1], María F. González Fleitas[1], Diego Guerrieri[2], Hernán H. Dieguez[1], Damián Dorfman[1] and Ruth E. Rosenstein[1]

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Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which leads to retinal ganglion cell (RGC) loss and a decrease in pupil light reflex (PLR) and visual evoked potentials (VEPs). Neuroinflammatory diseases are characterized by disruption of the blood–brain barrier (BBB) and increased leukocyte infiltration. The aim of the present work was to analyze the involvement of cell infiltration on visual damage induced by experimental ON. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. BBB integrity was analyzed through Evans blue perfusion on WT-GFPþ/WT chimeric rats. At 6 hr post-LPS injection, an increase in albumin-Evan's blue leakage and in optic nerve cellularity was observed. At 24 hr post-injection, e-GFP(+) cells (likely macrophages and neutrophils) were identify in LPS-injected optic nerves. Experimental ON induced an increase in the chemokine CCL2 immunoreactivity. The injection of Bindarit (a CCL2 inhibitor) and bone marrow depletion (by gamma irradiation) significantly prevented the effect of ON on PLR, VEP amplitude, and RGC number. In order to induce BBB breakdown, tissue plasminogen activator (tPA) was injected into the optic nerve. Tissue plasminogen activator microinjection mimicked the effect of ON on PLR and RGC number. These results indicate that BBB integrity loss and leukocyte recruitment play a key role in the visual damage induced by experimental ON.

OC10. Light-Regulation of Arylalkylamine-N-Acyltransferase and a New Potential Rol in Vertebrate Retina

Maximiliano Nicolas Rios[1] and Mario Eduardo Guido[1]

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A key regulatory step in melatonin synthesis is that at which serotonin is converted to N-acetyl-serotonin (NAS) by the enzyme arylalkylamine N-acetyltransferase (AANAT). AANAT is present in the retina and other regions, while NAS can activate the TrkB receptor to generate neuroprotective effects. In photoreceptor cells, AANAT activity peaks during the dark (D) and at subjective night, while activity is significantly decreased by light (L). By contrast, melatonin synthesis, AANAT expression, and activity are high during the subjective day or L phase in chicken retinal ganglion cells (RGCs). Here, we investigated the expression of AANAT and of nonvisual opsins in enriched embryonic RGC cultures exposed to different L conditions. Cultures expressed Opn4 (melanopsin), Opn3, and Opn5, which may confer intrinsic photosensitivity. Moreover, cultures exhibited blue L (BL) induction of AANAT immunoreactivity and mRNA as compared with D or red L treated cells. In addition, expression of this enzyme was significantly increased by adenylate cyclase activator forskolin (10 μM) in D. Interestingly, AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and this effect was reversible in darkness condition after L exposure; in addition, the nuclear importation of AANAT was blocked with protein synthesis inhibitor cycloheximide (50 μM) in BL. Results suggest that AANAT is a BL -induced enzyme in RGCs controlled by cAMP, likely playing important roles in inner retinal cells.

Friday 26: 14:30–15:30/Room C

OC11. Lrig2 Promotes Dendritic Complexity, Spine Morphogenesis, and Excitatory Synapse Formation in Hippocampal Neurons

Ana Paula De Vincenti[1], Fernando Cruz Alsina[1], Antonella Soledad Rios[1], Fernanda Ledda[1] and Gustavo Paratcha[1]

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Dendrite size and morphology are key determinants of the functional properties of neurons, and brain disorders are due primarily to structural abnormalities of dendrites and their connections. Distinct leucine-rich repeat (LRR) transmembrane proteins are highly expressed in the brain, especially in the hippocampus, where they play a critical role in the organization and function of neural circuits, regulating neurotrophin signaling, coordinating pre- and post-synaptic compartments during excitatory and inhibitory synapse formation and regulating synaptic plasticity. Recently, the LRR protein, Lrig1, has been described as an essential regulator of neurotrophin signaling and dendrite arborization of hippocampal neurons. However, the physiological contribution of Lrig2 for neuronal development remains to be determined. Taking advantage of the post-natal expression of Lrig2 by hippocampal developing neurons, we used gain and loss of function assays to examine how altered Lrig2 expression impacts dendrite morphology and synapse formation in search for specific LRR proteins involved in neurodevelopmental disorders. Here, we show that Lrig2 overexpression exacerbates dendrite complexity by promoting growth and branching, in a LRR domain-dependent manner. Our results also indicate that Lrig2 is expressed in pre- and post-synaptic fractions, where it controls the density of dendritic spines and increases the number of excitatory synaptic contacts in hippocampal neurons.

OC12. Role of Cytoplasmic c-Fos as an Activator of Lipid Synthesis During Neuronal Differentiation

Lucía Rodríguez Berdini[1], Gabriel Orlando Ferrero[2], Andrés Mauricio Cardozo Gizzi[1], Florentyna Bustos Plonka[1], Santiago Quiroga[1] and Beatriz Leonor Caputto[1]

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Cytoplasmic c-Fos activates phospholipid synthesis by associating with particular lipid synthesizing enzymes at the endoplasmic reticulum (ER). This activity of c-Fos supports the high rates of membrane genesis required for neuronal differentiation. In hippocampal cultures, blocking either c-Fos expression or its activity promotes an impairment in differentiation with no observable development of axonal processes. In addition, the expression of N-terminal deletion mutants of c-Fos capable of blocking only its cytoplasmic activity produces a similar effect. Moreover, using an in utero model to evaluate neuronal cortical migration, neurons electroporated with a shRNA targeting c-Fos fail to migrate and are mostly visualized in the ventricular/subventricular zones. Since we found c-Fos strongly co-localizing with ER markers in neuronal processes, we examined if its lipid synthesis activator capacity is exerted in neurons by examining CDP-diacylglycerol synthase (CDS), previously described as one of the enzymes activated by c-Fos, and CTP:phosphocholine cytidylyltransferase-β2 (CCTβ2), that is responsible for CDP-choline formation in the brain. A strong interaction between c-Fos and the enzymes was found by FRET experiments together with a marked increase in CDS enzymatic activity in the presence of recombinant c-Fos. These results support our hypothesis that c-Fos plays a main role in neuronal differentiation, and this might be achieved through phospholipid synthesis regulation.

OC13. Differences on the Effect of Proteins of the Same Tethering Complex on Neuronal Polarity

Florentyna Bustos Plonka[1] and Santiago Quiroga[1]
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The initial signals that determine polarity are largely unknown, placing the mechanisms underlying the axon formation under the scope of our investigation. Two interconnected process are essential for axon formation: the axonal biochemical specification and the rapid membrane outgrowth. The exocytic pathways that function to translocate membrane patches to plasma membrane undergoes by regulated nonsecretory exocytoses. It has been shown in hippocampal neurons that the axolemmal expansion occurs by the insertion of plasmmalemal precursor vesicles (PPVs) at the growth cone, a process regulated by IGF1. A previous physical interaction between the vesicle target and the membrane is necessary to fusion. This process is mediated by thethering complexes. The exocyst complex is a candidate for the regulation of fusion of PPVs of which the total composition is still unknown in neurons. It has been reported that IGF-1 triggers translocation to the plasma membrane of the exocyst component exo70 in the growth cone, being one of the steps at the complex formation. We determined that several proteins of the exocyst complex are present at hippocampal cultures in early stages of development. Moreover, two proteins of this complex have opposites effects on neuronal differentiation. The implication of silencing sec3 in hippocampal cultures and in utero electroporation develops abnormalities. In constrast, the effect of suppressing sec8 remains neuronal migration and polarity nonaffected.

OC14. Inter-Hemispheric Hypo-Connectivity and Regional Metabolic Hyper-Activity in an Experimental Model of Autism

Nonthué Uccelli[1], Martín Codagnone[1,2], Nadia Levanovich[3], Victoria Rosato Siri[4], Marianela Traetta[1,2], Leandro Urrutia[3], Germán Falasco[3], Juana Pasquini[4], Silvia Vázquez[3] and Analía Reinés[1,2]
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Autism spectrum disorders (ASD) are a group of neurodevelopmental disabilities characterized by alterations in brain connectivity and neuroinflammation. In accordance with the long-distance hypo-connectivity and local hyper-connectivity hypothesis, previous studies in our laboratory with the valproic acid (VPA) model demonstrate connectivity alterations and reactive gliosis in the prefrontal cortex and hippocampus of VPA rats. The aim of this work was to evaluate the brain metabolic activity and the structure of the corpus callosum (CC) in VPA animals. For this purpose, glial cells in the CC were studied at PND 36 by CC1, PDGFαR, GFAP and tomato lectin staining. Also, CC ultrastructure was assessed by electron microscopy (EM). Evaluated by positron emission tomography, glucose uptake was increased in local areas along the brain of VPA rats, while it was decreased when considered the whole forebrain. In the CC of VPA rats, the number of CC1+ cells diminished and number of PDGF+ cells increased, in the absence of astrogliosis or microgliosis. Concomitantly, EM showed less myelinated axons and aberrant myelin in the CC of VPA rats. To sum up, VPA animals exhibit hyper-metabolism in circumscribed brain areas along with global hypo-metabolism. Concurrently, CC myelination in VPA animals is disrupted, accompanied by an altered balance in the oligodendroglia lineage. Taking together, our findings support the local hyper-activity and long-distance hypo-connectivity hypothesis in ASD.

Poster Abstracts

Brain Awareness Week Activities

P1. UNQ-BAW the IV: The Last in the Line of Succession

Aiello Ignacio[1], Laura Lucía Trebucq[1], Carlos Sebastian Caldart[1] and Malena Lis Mul Fedele[1]
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The Brain Awareness Week at the University of Quilmes (UNQ) was carried out in two dates: June 9 and June 15. It was the fourth BAW event held on the south of the metropolitan area of Buenos Aires. On June 9, we offered the workshop "Neurosciences applied to Education," where four lectures were given to around 100 teachers, directives, and education students. The lectures were presented by specialists in the field: Dra. Juliana Leone (U. Di Tella), Dra. Cecilia Calero (U. Di Tella), Lic. Carolina Fracchia

(CEMIC), and Lic. Veronica Ramirez (CEMIC). On June 15, we organized a "Neuro-Fair" consisting on stands prepared by neuroscience research laboratories, covering topics such as memory, visual and auditory perception, biological rhythms, development of the nervous system, animal models, and brain anatomy, among others. The displays were specifically designed for a high-school level audience, aimed to inform as well as to promote scientific careers. Moreover, special talks were offered by recognized researchers as Dr. Rodrigo Laje, Dr. Santiago Plano featuring the illusionist/mentalist Maximiliano Giaconnia, Dr. Diego Golombek, and Dra. Maria Luz Gonzalez Gadea. We estimate that the event was visited by around 3,000 people.

The authors received financial support from the Argentinian Society for Research in Neuroscience (SAN) and the UNQ.

Brain Awareness Week Activities

P2. Musical Learning: Music and Sounds as Evocative of Memories and Emotions in Our Brain

Joana Asensio[1], Leandro Freites[1], Andrea Barauna[1], Cristina Croce[1], Samanta del Veliz[1], Sofía Masuelli[1], Elena Vasquez[1], Ismael Arias[2], Carla Garrido[3] and Karina Altamirano[1]

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Presenting author: Joana Asensio, joanaantonelaasensio@hotmail.com

Music has always represented an important part of every human culture, both past and present. It is a strong modulator of mood and social interactions. Nowadays advances in neuroscience enable researchers to quantitatively measure just how music affects the brain and neuronal networks. Individual sounds are capable of evoking different emotions and memories, depending on the context and the background of the hearer. We designed and developed our scientific communication project according to the guidelines for the Brain Awareness Week. Our goal was to introduce children between 8 and 10 years old to the exciting world of neurosciences. In order to carry on our purpose, we visited fourth and fifth grades in Valentín Bonetti and Saint Andrew's Schools in the city of Mendoza, Argentina. We designed workshops to explain how the brain is modified by its interaction with sounds and music. We also provided dynamic talks and games so that children could learn while playing them. In this way, we sought to explain the links between sounds stimuli and how our brain is able to interpret and respond to them. The children easily associated different sounds with emotions and memories they perceived; they also learnt that a numerical sequence was easier to remember with a background melody. They enthusiastically manipulated rat and cow fixed brains in order to learn brain anatomy. Fortunately, we received a positive feedback from the children who were really excited to receive us.

Brain Awareness Week Activities

P3. BAW 2018 in Misiones: Do We Know Our Brain? A Challenge of Senses

Gerardo Ariel Rosciszewski[1], Verónica Murta[1], María Vanesa Cadena[1], María Belén Cieri[1], Edgardo Gabriel Rosciszewski[2] and Alberto Javier Ramos[1]

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One of the most important challenges of the current scientists is to bring their knowledge, methods, procedures, and results to the society. Education is a main resource that students have to shape their future. So, it is fundamental to create bridges between science and education, through new forms of science divulgation. The objective of this BAW project was to improve students' knowledge about the brain functioning, brain protection, and also how to become neuroscientist in Argentina. For that purpose, during Brain Awareness Week (BAW) in March 2018, we visited three secondary schools located in Misiones province: Instituto Roque González (Posadas), Instituto Madre de la Misericordia (Posadas), and Escuela Provincial de Educación Técnica (E.P.E.T.) N° 50 (Leandro N. Alem). We developed the project through guide questions, group games, sense tests, and a final talk with a total of more than 200 students. We focused on the participation of the students: They were able to experience themselves and many questions arose during the talks, which were very dynamic and varied among the different schools. Children, together with the professors and school directors, enjoyed and took advantage of the opportunity of having neuroscientists in the schools. Teachers repeatedly thanked us for bringing our research and knowledge to very distant provinces like Misiones.

This work was supported by grants of SAN (BAW); Transportes Rio Uruguay; E.P.E.T. N° 50 and G. Rosciszewski family.

Brain Awareness Week Activities

P4. What Do You Have in Mind?

Paula Bonaccorso[1], Belén Mulle[1], Vanesa Bazzocchini[1], Vanina Bugueño[1] and Sebastián García[1]

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In the last decades, the study of the brain and the mind has become an important topic of science. Everyday we ask ourselves questions about we what do we have in mind. The main objective of our project is to answer those interrogants by explaining learning, emotions and memory, transfer public scientific knowledge, and promote interest and critical thinking. We are a multidisciplinary team of psychologists, biochemistries, biologists, and bioengineers. During the Brain Awareness Week (BAW, May 12–18, 2018), we perform talks, publications, and contests on our Facebook page (Qué tienes en Mente?). We published five weekly news and articles related to the topic and five neuroscientists joined our proposal to talk about their specialties. Finally, by making contests and giving the winners a book, we made understandable neuroscientific approaches and open dialogue spaces that produced integral e-learning. This project collaborated to stimulate and reinforce neuroscience divulgation.

Brain Awareness Week Activities

P5. Activities for the Brain Awareness Week Organized by the Institute of Neurosciences and Complex Systems

Silvia Kochen[1], Cecilia Forcato[1], Paula N. González[1], Mariana Vallejo[1], Malen Moyano[1], Mariana Benderky[1] and Silvia Oddo[1]

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During the Brain Awareness Week 2018—March 12 to 16—we organized several activities that took place at Hospital "El Cruce—Dr. Néstor Kirchner," Arturo Jauretche National University, and Florencio Varela Museum. Two workshops were held, one on "Healthy Aging," in which problems related to cognitive diseases prevention and treatment in older adults were tackled, and another on Mental Health and Neurosciences. The former was addressed to health and social development workers, and the latter to the general public. Various talks addressed to secondary schools teachers and students, university students, and the community were also delivered under the following titles: "Why do we feel pain?" "The internal clock that controls us," "What happens to our memories while we sleep?" "Why do we remember and forget?" Two movies were shown, followed by a talk-debate. At the end of the week an exhibition called "Everything you wanted to know about how your brain works and you were encouraged to ask . . . but was not enough" was organized. Around 300 people participated in the activities, which were also disseminated through institutional websites and social networks. Testing neural models for birdsong production and perception.

Brain Awareness Week Activities

P6. Getting in Contact With Schools: The Synapsis Between Students and Neuroscientists

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The brain is our most intriguing organ. An important function is to detect and interpret events taking place in the environment through senses and command a response. How are these processes seen from the eyes of children? As imagination is their powerful tool, we proposed to sail in the students' sea of marvellous theories. In this journey, we showed them though games what scientists already know. Framed around Brain Awareness Week 2018, an international campaign to educate general public and to support brain investigation, a group of researchers carried out the fourth edition of "Neuroscience of Senses visits the classrooms of fourth grade." This project, created and organised by Nicolás Unsain, was possible thanks to SAN financial support through its annual call for BAW projects. In addition,

CCT-CONICET Córdoba and the Ministry of Science and Technology of Córdoba provided school contact, scheduling, and transport. We visited 37 classrooms of 19 schools from Córdoba city and six nearby towns. Before the visit, teachers asked students to draw a neuroscientist, describe them, and write questions they would like to ask. In the visit, we displayed an interactive lecture mixed with exciting games. Students participated actively asking questions and discussing concepts acquired by their own experience. Finally, we took a microscopic sight of the brain with immunolabeled neurons and compared fixed caw and rat brains; activities that allowed children to discover the role of brain.

Cellular and Molecular Neurobiology

P7. Molecular Changes in GluN2A Knockdown of Mature Primary Neuronal Cultures

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NMDA receptors (NMDAR) are glutamatergic receptors involved in synaptic plasticity, learning, and memory processes as well as in several neuropathologies. NMDAR are composed by two GluN1 obligatory subunits and two regulatory subunits: GluN2 (A-D) or GluN3 (A-B). In cognitive-related brain structures, GluN2A and GluN2B are the most expressed regulatory subunits, that undergoes a tightly regulation at transcriptional and translational level. Whereas GluN2B expression is characteristic of immature synapses, GluN2A is present in mature and stable synapses. In order to better understand the role of GluN2A in synapsis, we transduced mature neuronal cultures with AAV-eGFP vectors: one codifying a specific shRNA anti GluN2A, AAV-sh2A, and the other carrying a shRNA scramble as control, AAV-shSc. As we verified that AAVsh2A knockdown GluN2A mRNA and protein levels (GluN2A KD), we analyzed the other NMDAR subunit expression in this cultures, as well as REST, a transcription factor that regulates GluN2A/GluN2B relationship. The GluN2A KD induced a decrease in REST levels without significant changes in GluN2B expression. On the other hand, GluN1 protein levels were significantly low in GluN2A KD cultures in spite of control mRNA levels. Furthermore, GluN1 splicing variants proportion was altered. These results suggest that GluN2A KD induce a rearrangement of NMDAR and REST expression similar to those observed in more immature states at neuronal differentiation.

Cellular and Molecular Neurobiology

P8. The Impact of DNA Methylation/ Demethylation Machinery on Hippocampus of Female Weaned Mice and Their Dams in a Protein Malnutrition Model

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The developing brain requires a specific sequence of molecular steps that must be finely regulated. Adverse environmental, like perinatal protein malnutrition, impacts brain development in mice leading to functional changes. Moreover, the gestation and post-partum period presents the mother with a wide hormonal, physiological, and metabolic changes that could be windows of susceptibility to all kinds of adverse factors. However, little is known about molecular mechanisms related with alterations describe above on malnourished weaned mice and their dams. CF1 dams received low protein diet (8% casein) or normal protein diet 2(0% casein) during gestation and lactation. After this period, dams and PD21 female mice was euthanized, and hippocampus was extracted to study RNA and protein expression. We observed a significant effect of nutritional condition on genes related with epigenetics mechanisms both in dams and weaned mice. We found an increase in DNMT3b and Gadd45b RNA expression in malnourished weaned mice, but there is no difference in DNMT3a and GR. Also, we evidence a greater expression of GR RNA and Gadd45b protein in dams who received low protein diet, but we do not observed difference on DNMT1 RNA and GR protein expression. We suggest that protein malnutrition during gestation and lactation alters the neurological development of female weaned mice and the anxiety and depressive-like behavior of dams through genes related with epigenetic mechanisms.

Cellular and Molecular Neurobiology

P9. Sphingosine Kinases and NPC1 Decrease Would Contribute to Altered Function in Old Hippocampal Neurons

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It is now recognized that sphingolipid metabolites regulate many cellular processes important for health and disease. One of the most important of these metabolites is sphingosine-1-phosphate produced by two sphingosine kinase isoenzymes, SPHK1 and SPHK2. Sphk1 and Sphk2 have been implicated in neuronal function and memory formation. In hippocampal neurons, SPHK1 participates in excitatory synaptic transmission and has profound effects on spatial learning. SPHK1 is activity-dependent recruited to presynaptic terminals and promotes neurotransmitter release. Decreased levels of SPHK1 have been also associated to sphingosine accumulation leading to defects in endocytic trafficking. In the nucleus, SPHK2 regulates transcription of memory genes by producing S1P, which acts as an endogenous inhibitor of histone deacetylases. Our results show that during aging, the levels of SPHK1 and SPHK2 are dramatically decreased in mouse hippocampus. According to these data, the accumulation of sphingosine was observed in hippocampal neurons aged *in vitro*. Furthermore, decreased expression of the Npc1 (Niemann Pick C1) gene, required for intracellular cholesterol redistribution and one of the SPHK2 targets, was found in the hippocampus of old mice. All these results suggest that defects of neuronal function during aging would be due, at least in part, to deficits in S1P signaling and endocytic defects mainly consequence of cholesterol accumulation in the endolisosomal compartment.

Cellular and Molecular Neurobiology

P10. Do Not Perturb Me While I Crawl

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Leeches crawl on solid surfaces by successive elongation and contraction of its body, anchored on the front and rear suckers. These movements would exert mechanical forces on the skin, innervated by three types of mechanosensory neurons. Because activation of the mechanoreceptors elicits a series of defensive behaviors, the mechanosensory signals could perturb the rhythmic displacement. Recordings of low threshold tactile (T) mechanosensory neurons in isolated midbody ganglia during dopamine-elicited fictive crawlings (crawling) show that T cells receive inhibitory signals in phase with the activation of the motoneurons that cause the contraction. The inhibition is probably due to the activation of a synaptically driven chloride conductance. Because the study was produced in the absence of the periphery, this inhibition must be originated by the nervous system, probably downstream of the central pattern generator. To confirm that inhibition of T cells is necessary to the smooth occurrence of crawling, we analyzed the effect of exciting these neurons during the contraction phase and during the elongation phase. The results show that activation of T cells interrupts the burst of the motoneuron that controls contraction but has no effect during elongation. We interpret that the circuit that controls crawling sends an efference copy to the sensory neurons to counteract the discharge caused by the mechanical forces exerted during contraction.

Cellular and Molecular Neurobiology

P11. Analysis of the Regulatory Mechanisms That Affect Gpm6a Expression Levels in the Hippocampus of Chronically Stressed Rats

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The neuronal membrane glycoprotein M6a (Gpm6a) is a member of myelin proteolipid protein (PLP/DM20) family that functions in the processes of neuronal remodeling and plasticity, such as neurite outgrowth, filopodium formation, and synaptogenesis. Pathological conditions have been linked to the alterations in Gpm6a expression levels or sequence. Downregulation of Gpm6a mRNA has been shown in the hippocampus of depressed suicide victims as well as in animal models of chronic stress. Regulatory mechanisms that affect Gpm6a expression levels during chronic stress exposure and in pathological conditions are not clearly understood. Different epigenetic mechanisms have been described to regulate Gpm6a mRNA levels: (a) direct post-transcriptional regulation by miR-133b or (b) by miR-124, as well as (c) transcriptional regulation through miR-124 and miR-9 mediated effect on Hdac5-regulated transcriptional factor Mef2c. Here, we use qPCR to demonstrate that in

the hippocampus of chronically stressed rats, the exposure to restraint stress decreases levels of Gpm6a mRNA as well as the expression levels of miR-133b, miR-124a but not miR-9-5p. Moreover, we detect altered levels of Hdac5 and Mef2c suggesting that chronic stress affects Gpm6a levels through miR-124 mediated effect on Hdac5 and Mef2c. Overexpression of miR-124 in cultured hippocampal neurons leads to increased neuronal arborization as assessed by Sholl analysis and increases Gpm6a protein levels.

Cellular and Molecular Neurobiology

P12. A Deeper View Into the Effects of Repetitive Traumatic Stress on Aging

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An attack or even the perception of a predator elicits a rapid "fight-or-flight" response to enhance the animal's chance of survival. In mammals, the acute fight-or-flight response leads to the release of catecholamines (CA). Perpetuated activation of this acute stress response, as is the case of patients suffering from post-traumatic stress disorder is associated with accelerated aging. Nevertheless, the molecular and cellular mechanisms that underlie this detrimental effect remain largely obscure. Taking advantage of its relative simple anatomy, genetics, high degree of conservation, and short life span, we introduced a model of the nematode *Caenorhabditis elegans*, to go deep into these mechanisms. *C. elegans* coordinates stress response by releasing the CA tyramine (TA), the structural and functional counterpart of adrenaline in mammals. We here determined that TA-deficient animals (tdc-1) exhibit increased healthspan and life span. On contrary, animals permanently exposed to acute stressors, have reduced lifespan and deteriorated general fitness. These detrimental effects are not observed in tdc-1 mutants suggesting that they depend on TA release. We are currently performing experiments in order to explore how neuronal architecture and function are affected by persistent activation of the fear-related response. This study was aimed to unravel how the stress response impacts on the structural, cellular and functional changes that normally occur with aging.

Cellular and Molecular Neurobiology

P13. Role of Aβ/APP Interaction in the Increase of APP and BACE 1 Convergence Induced by Aβ

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Abstract not available

Cellular and Molecular Neurobiology

P14. Neuronal Glycoprotein M6A as a Key Regulator of Synaptic Plasticity During Extra Uterine Brain Development

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Abstract not available

Cellular and Molecular Neurobiology

P15. IGF-1 Expression in the Cerebellum of the Developing Spontaneously Hypertensive Rat

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The spontaneously hypertensive rat (SHR) grows in a chronic hypoxic environment due to placental insufficiency. This situation resembles that of the IUGR, one of the major problems in perinatal medicine representing one of main causes of perinatal mortality and morbidity. Insulin-like

growth factor 1 (IGF-1) serves as a promoting factor for Purkinje cell postnatal survival and dendritic growth, and it stimulates repair mechanisms after hypoxic damage. An increase in IGF-1 levels has been associated with enhanced reactive astrocytosis. The refinement of neuronal circuits during postnatal (P) cerebellar development is critical to their subsequent function and abnormalities in this process can result in neurodevelopmental disorders, as shown by the SHR rats. We examined the expression of IGF-1 by RT-PCR in the cerebellum of SHR and of the normotensive counterparts of the WKY strain, at P7 and P14. We also measured GFAP immunofluorescence in the cerebellum white matter (WM) and corpus callosum (CC) of littermates. We found an increase IGF-1 expression in the WM of the SHR at P14 ($p < .01$ vs. WKY). In a preliminary assay we detected GFAP immunolabeling in WM and CC at P7 and P14 in both strains. This reactivity is apparently more intense in the SHR animals. These results indicate that the SHR brain may show signs of brain repair and remodeling as a consequence of an adverse gestational environment. SHR rat could be proposed as a valid animal model for studying IUGR.

Cellular and Molecular Neurobiology

P16. Molecular Mechanisms Associated With Impaired Peripheral Nerve Repair Mediated by Anti-Ganglioside Antibodies

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Abstract not available

Cellular and Molecular Neurobiology

P17. Neuroprotective Effect of *Yerba mate* (Ilex Paraguariensis) on Cultured Dopaminergic Neurons, From *In Vitro to Drosophila* Models of Parkinson's Disease

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Parkinson's disease (PD) is the second worldwide neurodegenerative disorder in prevalence. Its origin is unknown but its pathophysiological characteristic is the progressive degeneration of dopamine-releasing neurons (nDA) of the Substantia nigra pars compacta. Recently, a study conducted in Argentina revealed that the consumption of *Yerba mate* (YM) has an inverse association with the risk of developing PD. With the aim of demonstrating the putative neuroprotective properties of YM on nDA, we are undertaking experimental approaches both *in vitro* and *in vivo*. First, we studied the survival of mouse nDA on primary cultures treated with YM extract and found that YM provides higher neuroprotection over nDA than other known agents, such as caffeine. To delve into the basis of this neuroprotection, we have also tested some of the major compounds of the YM extract, such as chlorogenic acid and theobromine. Given these promising results, we hypothesized that the YM extract could also protect nDA *in vivo* from the degeneration caused by the expression of a-syn in a *Drosophila melanogaster* model of PD and improve the related locomotor deficit. To reach this goal, we have set up the administration of YM to these flies and produced preliminary behavioral and histological data. Our results demonstrate that YM protects nDA *in vitro* and set the grounds to study such effect on a simply, but very powerful, *in vivo* model of PD.

Cellular and Molecular Neurobiology

P18. Characterization of Functional Aspects of the Retina in a Mouse Model of Laser-Induced Choroidal Neovascularization

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Age-related macular degeneration (AMD) in its neovascular form is the leading cause of vision loss among adults above the age of 55 years. In the present study, we validate an established choroidal neovascularization (CNV) mice model, which resemble human neovascular AMD. Thus, this study was performed in this mouse model of CNV in order to characterize the neovascular process and its impact on the retinal functionality as well as the inflammatory profile. The CNV lesions were induced with four spots of argon green laser photocoagulation per eye on C57BL/6 mice. After 7 days of laser burn, we analyzed the retinal functionality by scotopic electroretinography. The a- and b-wave amplitude as well as the implicit time were evaluated. The results demonstrated that both, a- and b-wave amplitude, were decreased in the CNV mouse model. Then, the NV on choroid–RPE flatmounts was studied by isolectin B4 (IB4) staining. At the same time, different types of cells in the lesion area were characterized by specific cell markers: CD105 (ECs), NG2 (pericytes), F4/80 (microglia), and the inflammatory and pro-angiogenic profile were analyzed by qPCR. The lesion area showed an increased number of ECs, pericytes, and microglia, accompanied with high transcriptional levels of pro-inflammatory and pro-angiogenic factors. In conclusion, the functionality of cells localized in the outer and inner nuclear layers of retina was affected by the choroidal neovascularization process.

Cellular and Molecular Neurobiology

P19. Terminal Differentiation of Late-Born Spinal Cord Neurons

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Understanding the ontogenetic mechanisms that control cellular diversity is a central problem in developmental neurobiology. It still remains unclear how the timing of differentiation contributes to neuronal diversity, which are the properties of late-born neurons and how their identity is controlled. We have shown that CerebroSpinal Fluid-contacting Neurons (CSF-cNs), located in the spinal cord central canal, originate from unique late neurogenic events. We found that CSF-cNs robustly express Gata3 and Gata2 transcription factors, downstream of Ascl1. To determine their function, we performed loss of function experiments by generating Gata2/3 conditional mutant mice. We found that after Gata3 deletion, the dorsal group of CSF-cNs (CSF-cN') is missing, while the ventral subset (CSF-cN") remains unaffected. In Gata3/2 double mutants, we found a complete loss of CSF-cNs, suggesting that Gata2 acts redundantly with Gata3 during CSF-cN" differentiation. A close inspection on the temporal activation of Gata3 and Gata2 showed differences in the induction of these transcription factors during the development of both subpopulations. To better characterize CSF-cNs and their axonal topography, we performed mosaic genetic labeling using Ascl1CreER mice in combination with membrane-bound-YFP reporters. These experiments, in combination with retrograde fluorescent marking, indicate that CSF-cNs are rostrally projecting neurons.

Cellular and Molecular Neurobiology

P20. The Neddylation Pathway Regulates Axo-Dendritic Development by Controlling Cytoskeletal Dynamics

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Neuronal development is controlled by signaling cascades regulated by a myriad of posttranslational modifications. Although the role of ubiquitin has been well established in the maturation of nerve cells, the function of other members of the ubiquitin-like protein family remains poorly understood. Nedd8 is the UBL with the highest homology to Ub, and we demonstrated that Neddylation is highly abundant in the brain and is critical for synapse formation and maintenance. Blocking Neddylation with genetic and pharmacological tools reduced axonal and dendritic growth both in cell culture and in-utero electroporation approaches. These effects were partially reverted by Cyto-D and Taxol. These results suggest that cytoskeleton dynamics are involved in the effects of Nedd8 on axodendritic growth. To identify the structural details underlying the effects of Nedd8 we employed live-imaging, superresolution, and fluorescent microscopy. Neddylation blockade with MLN-4924 strongly reduced microtubular polymerization, induced ectopic lamellipodia formation, and increased the growth cone size in early neurons. In biochemical screenings, we have identified several neddylated targets that are regulators of cytoskeleton structure and function. We evaluated the function of neddylation on those targets performing molecular replacement strategies in primary neuronal cultures and in-utero electroporated mouse brains. The effect of neddylation on dendritic growth and arborization will be discussed.

Cellular and Molecular Neurobiology

P21. Low Led Light Exposure as a Model of Retinal Degeneration in Albino Rats

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Excessive exposure to artificial light (light pollution [LP]) can accelerate the course of certain genetic diseases, induce the death of rod cells, and promote circadian asynchrony, triggering the development of retinal degeneration (RD). Previously we developed an RD model by constant exposure of albino rats to low-intensity LED light (LL). This model is characterized by the death of rods, an increase in rhodopsin (Rho) phosphorylation and changes in the expression and localization of Opn4 and 5 in the internal retina. Based on this background, we decided to study the kinetic of rod cells death, so, we evaluated the levels of oxidative stress (OS), the composition of fatty acids in membranes, ERG responses, and whether Rho phosphorylation is a reversible mechanism. Our results show that the treatment with light produces a significant increase of OS levels after 4 days of LL. The changes in OS metabolites are followed by a significant reduction of docosahexaenoic acid, indicating the oxidation of membrane outer segment. Nevertheless, ERGs showed retinal activity completely abolished after LL3, suggesting an interruption of rods activity before OS. Finally, Rho phosphorylation was reversible if the animals were exposed to darkness for 48 hr after LL treatment. These results give evidence of a possible role of OS in the development of RD and the putative role of Rho phosphorylation/dephosphorylation. This model of constant light exposure may provide knowledge of LP effects.

Cellular and Molecular Neurobiology

P22. A Key Function for Microtubule-Associated-Protein 6 in Activity-Dependent Stabilization of Actin Filaments in Dendritic Spines

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Abstract not available

Cellular and Molecular Neurobiology

P23. Serotonin and Catecholamines Neuronal Circuits Regulate Opposing Behaviors in *Caenorhabditis elegans*

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Patients with anxiety disorders, such as post-traumatic stress disorders (PTSD) and panic attacks, exhibit high levels of catecholamines (CA), even in the absence of stress. Selective serotonin (5-HT) reuptake inhibitors (SSRIs), which increase the 5-HT level in the synaptic gap, are the most suitable drugs to treat these patients. This means 5-HT plays an important role in these disorders, but its relationship with CA is still unknown and difficult to study in the complex human nervous system. Given its simplicity and the highly conserved neurological pathways, *Caenorhabditis elegans* can be used to provide insights into the crosstalk between 5-TH and CA. When *C. elegans* encounters food, it releases 5-HT to inhibit locomotion. We exposed tdc-1 and tbh-1 null mutants (unable to synthetize the analogous of mammalian CA tyramine [TA] and octopamine [OA], respectively) to exogenous 5-HT and found that they are hypersensitive to paralysis. These results strongly suggest that 5-HT acts antagonistically to CA. In addition, we studied the hypersensitivity to exogenous 5-HT of mutants in TA and OA receptors. We observed that tyra-3, ser-3, and ser-6 null mutants do not recover completely from the serotonin-induced paralysis. We are now digging into the molecular and cellular underpinning of these antagonistic effects by analyzing mutants in 5-HT receptors. These opposite actions could be conserved in mammals and explain the efficiency of SSRIs in PTSD and panic attack treatments.

Cellular and Molecular Neurobiology

P24. Downregulation of Arginyltransferase (Ate1) Enhances Bortezomib-Induced Cell Death in Human Glioma Cells

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Abstract not available

Cellular and Molecular Neurobiology

P25. Role of Gata3 in the Development and Maintenance of Serotonergic Neuron Identity

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The serotonergic system, located in the Raphe's nuclei, controls different aspects of behavior and physiological processes. During embryonic development, serotonergic neurons are produced from progenitors in the most ventral domain of hindbrain, which also generate visceral motoneurons. Genetic studies have identified that the transcription factors Pet1, Lmx1b, and Gata3 are important for the proper assignment of serotonergic identity. By performing genetic tracings in young and adult mice in combination with expression analysis, we found that Gata2 and Gata3 expression is retained in mature serotonergic neurons. To assess the role of Gata3 in postnatal Raphe neurons, we generated inducible Gata3 conditional knockouts and found reduced expression of Pet1, Tph2, and Sert in the dorsal raphe nucleus. Moreover, we found a decrease in serotonin synthesis, which is accompanied with a loss of habituation in open-field tests, suggesting an anxiety-like phenotype. On the other hand, the deletion of Gata3 during advanced embryonic neuron maturation did not show altered expression of Pet1, Sert, and other genes related to serotonergic function. These results indicate that Gata transcription factors not only are important for serotonergic neurons specification but are also involved in maintaining serotonergic identity throughout life.

Cellular and Molecular Neurobiology

P26. Differences on the Effect of Proteins of the Same Tethering Complex on Neuronal Polarity

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The initial signals that determine polarity are largely unknown, placing the mechanisms underlying the axon formation under the scope of our investigation. Two interconnected processes are essential for axon formation: the axonal biochemical specification and the rapid membrane outgrowth. The exocytic pathways that function to

translocate membrane patches to plasma membrane undergo by regulated nonsecretory exocytoses. It has been shown in hippocampal neurons that the axolemmal expansion occurs by the insertion of plasmmalemal precursor vesicles (PPVs) at the growth cone, a process regulated by IGF1. A previous physical interaction between the vesicle target and the membrane is necessary to fusion. This process is mediated by thethering complexes. The exocyst complex is a candidate for the regulation of fusion of PPVs of which the total composition is still unknown in neurons. It has been reported that IGF-1 triggers translocation to the plasma membrane of the exocyst component exo70 in the growth cone, being one of the steps at the complex formation. We determined that several proteins of the exocyst complex are present at hippocampal cultures in early stages of development. Moreover, two proteins of this complex have opposite effects on neuronal differentiation. The implication of silencing sec3 in hippocampal cultures and in utero electroporation develops abnormalities. In contrast, the effect of suppressing sec8 remains neuronal migration and polarity nonaffected.

Cellular and Molecular Neurobiology

P27. TREM-1/TREM-2 Role in Reactive Astroglial Polarization to the Pro-Inflammatory Phenotype

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Reactive gliosis is a generic astroglial response to brain injury. Reactive astrocytes can further polarize into an A1 pro-inflammatory-neurodegenerative phenotype. We have recently described that TLR4/NFkB signaling facilitates astroglial conversion to the A1 phenotype (Rosciszewski et al., *Mol. Neurobiol*. 2017). Having in mind that TREM2/TREM1 and DAP12 participate in the fine-tuning of the inflammatory response by controlling TLR/NFκB signaling in immunocompetent cells, we here studied the expression of these receptors and DAP12 intracellular adaptor *in vivo* after brain ischemia and *in vitro* in glial cell cultures exposed to oxygen-glucose deprivation for 6 hr. Using an experimental model of brain ischemia in rats, we detected TREM2 and DAP12 expression in glial cells, with a peak between 3 and 7 DPI with a specific localization in the ischemic penumbra. *In vitro*, we observed that OGD exposure increases TREM2 expression in astrocytes and microglia; reduces TREM1 in both cell types; while DAP12 expression is not significantly altered by OGD. Finally, we performed co-culture experiments of ischemic explants (3 DPI) on primary glial cells. After 5 DIV, we observed that infiltrated cells from ischemic explants and mainly microglia expressed TREM2. Our results show that ischemia or OGD induces the expression of TREM1 and TREM2 in microglia but also in a subpopulation of reactive astrocytes and the DAP12 adaptor is available to signal in these cells.

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Reference

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Cellular and Molecular Neurobiology

P28. Expression of Aggressiveness Modulate Mesencephalic c-Fos Activation During a Social Interaction Test in Japanese Quail (*Coturnix coturnix*) Reared in Enriched or Plain Environments

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Abstract not available

Cellular and Molecular Neurobiology

P29. Characterization of the Antagonistic Actions of Histamine on Homomeric GABAAρ1 Receptors

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Abstract not available

Cellular and Molecular Neurobiology

P30. Are Transferrin Pro-Differentiating Effects on Neurons Mediated by Iron?

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Transferrin (Tf) is a glycoprotein best known for its role in iron delivery, although it has also been attributed trophic functions. Tf has been reported to favor the proliferation and differentiation of different cell types, and previous studies by our group have shown apoTransferrin to particularly accelerate the differentiation of oligodendrocytes *in vitro* as well as *in vivo* (Paez et al., 2005). In the present work, we aimed to determine the effects of apoTf treatment on neurons *in vitro*. For this purpose, we used two different systems: N2a cells, a neuroblastoma cell line which is frequently used to study the neuronal differentiation process, and primary cultures of cortical neurons. After examining the Tf–Tf receptor system in our models and verifying that both N2a and neurons are capable of internalizing Tf added to the culture medium, we assessed Tf effects on the degree of cell differentiation and whether these effects are linked to iron metabolism. We conducted morphological and immunocytochemical assays using primary antibodies as antigen markers of specific stages of lineage progression and established that Tf has pro-differentiation effects in these cell types.

Reference

Paez, P. M., et al. (2006) *J Neurosci Res*., *83*(4), 606–618.

Cellular and Molecular Neurobiology

P31. Alpha-MSH Modulates Hippocampal Neural Precursor Cell Proliferation and Differentiation

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Hippocampal neurogenesis is essential for learning and memory. Neural precursor cells (NPCs) in the subgranular zone of the hippocampal dentate gyrus proliferate and differentiate into either glial cells or dentate granule cells. Alpha-melanocyte-stimulating hormone (a-MSH) improves learning and memory, neuronal survival and plasticity in models of neuroinflammation, brain ischemia and Alzheimer's disease and is a mitogen for adult rat subventricular zone neural stem cells. Here, we studied the effect of [Nle4,D-Phe7]-a-MSH (NDP-MSH) on hippocampal NPC differentiation. Postnatal hippocampal NPCs were propagated *in vitro* as neurospheres. Cells were dispersed and cultured without growth factors. NDP-MSH was added on Days 0 and 3. After 6 days in culture, a large proportion of NPCs become quiescent, evidenced by loss of nuclear Ki-67 expression. Treatment with NDP-MSH prevents the exit from cell cycle, increasing the proportion of Ki-67+/Nestin+ cells (putative type 2 precursors) and promotes cell proliferation evidenced by BrdU incorporation. In turn, there is a decrease in the expression of neuroblast marker DCX and in the proportion of NS-1+ cells (oligodendrocytes) as well as GFAP+/Ki-67-cells (putative astrocytes or quiescent type 1 precursors). Additionally, NDP-MSH stimulates microglial phagocytosis of dead neurons. To conclude, NDP-MSH modulates the hippocampal neurogenic niche by regulating NPC fate while acting on local microglia to promote clearance of dead cells.

Cellular and Molecular Neurobiology

P32. MAG as a Therapeutic Target for Neurodegenerative Diseases Related to Glutamate Overload

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This research project analyzes the protective effect of oligodendrocytes (OLs) against glutamate (Glu) overload, focusing on their critical role as white matter modulators of extracellular glutamate. Our group has previously demonstrated that mAb-mediated crosslinking/activation of MAG triggers a phosphoinositides/PKC-dependent intracellular signaling which results in reduced oxidative stress and protection of OLs and nearby neurons against Glu overload.

Based on these previous findings, our current aims are to study the role of Ca^{2+}-dependent signaling pathways and to perform wide RNA sequencing on OLs under MAG activation. We seek to develop new therapeutic bioactive ligands of MAG derived from the structure of its axonal receptors. Also, to evaluate their efficacy in animal models displaying axonal damage secondary to Glu-mediated toxicity and to demonstrate its efficacy in modulating Glu levels in the CNS. We propose multiple approaches in order to characterize such pathways and to assess therapeutic effects: OL-enriched primary culture, cerebellar organotypic culture, myelinating oligodendrocyte-neuronal co-culture, gene expression analysis using RNA-seq and animal models of the human diseases such as multiple sclerosis and stroke. These studies can help to describe more precisely intracellular signaling pathways involved in axon–myelin interactions that provide stability and survival of both neurons and OLs. Moreover, they can contribute to the development of novel neuroprotective therapies in order to mitigate axonal damage secondary to demyelination as observed in multiple sclerosis.

Cellular and Molecular Neurobiology

P33. Studying Synaptic Transmission at the Level of Individual Synaptic Vesicles

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Abstract not available

Cellular and Molecular Neurobiology

P34. Altered Brain Global Translation in TDP-43 Transgenic Mice: Evidence From Polysome Profiling and SUNSET Method

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TDP-43 is a RNA-binding protein that participates in a plethora of functions, including mRNA metabolism, and it is a major component of inclusions observed in neurodegenerative diseases like frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). We aimed to deepen our understanding about the role of TDP-43 in the regulation of mRNA translation and protein metabolism, using two complementary approaches. To assess if TDP-43 regulates active translation, we performed subcellular fractionation of brain cortex by sucrose gradient centrifugation. The polysome profile of hTDP-43-expressing brains was significantly altered by a shift toward light fractions as compared to wild-type littermates, indicating a decrease in global mRNA translation. In brain slices, application of SUNSET method (which assesses ongoing translation by antibody detection of incorporated puromycin into newly synthetized proteins) indicating that hTDP-43 overexpression leads to decreased puromycin labeling. No puromycin-positive cells were observed in vehicle-incubated slices. Together, these results suggest that manipulating TDP-43 levels lead to changes in global translation and that the cytotoxic effects observed in FTD/ALS might be related to alterations in proteostasis by TDP-43. We are currently evaluating if TDP-43 regulates the unfolded protein response, a process that modifies global protein synthesis. These findings will contribute to understand the etiology of TDP-43 proteinopathies.

Cellular and Molecular Neurobiology

P35. Development of a Low-Cost 3D Printable Mouse Brain Matrix

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A Mouse Brain Matrix allows to slice a mouse brain into coronal or sagittal sections, enabling precise and reproducible removal of small brain regions for biological experiments. These matrices are commercially available but are expensive and designed for a defined species and age. Reproducibility is a hallmark of good science but usually involves high costs when designs and hardware are proprietary. Open science hardware allows for greater

reproducibility while improving accessibility when materials are low cost and easy to obtain, such as in 3D-printable designs. 3D printing is now within reach of many scientific laboratories allowing for rapid and inexpensive prototyping of custom laboratory equipment. We therefore aimed to produce a simple design that could be used to section brain tissue in a reliable and reproducible manner using freely available software and a consumer grade 3D printer. We have designed a matrix for adult mouse brains from an MRI scan processed with 3D modeling open source software: 3D Slicer, Meshlab, and OpenScad. Our matrix is specifically designed for the dissection of the dorsal and ventral hippocampus, prefrontal cortex, nucleus accumbens, and amygdala using ordinary razor blades and plastic micropipette tips. However, the design can be adapted to slice different regions or brain sizes and printed in any available material. The mouse brain matrix is freely available at https://www.thingiverse.com/thing:3077272

Cellular and Molecular Neurobiology

P36. Physical Interaction Between Dopamine Receptor Type-1 and CaV2.2 Channels Increases CaV2.2 Function

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Dopamine receptor type (D1R) co-localizes with voltage-gated calcium channel CaV2.2 in rat PFC neurons, and the sole expression of D1R increases CaV2.2 membrane expression in a heterologous expression system. It has been proposed that this effect of D1R on CaV2.2 distribution depends on a physical interaction between CaV2.2 channels and the loop-2 region of D1R, but the effect of this D1R-CaV2.2 complex on CaV2.2 function remains unclear. Here, we investigate how D1R expression impacts CaV2.2 function and whether the D1R-CaV2.2 complex plays a role. We recorded whole-cell calcium currents in transfected HEK293t cells and found that low D1R expression (D1R: CaV2.2 molar ratio of 0.1) increased both CaV2.2 current density (170% of control, $p = .0029$) and the number of functional CaV2.2 channels in the membrane (257% of control, $p = .0216$ as measured by ON gating currents). Next, we generated mammalian expression vectors containing the sequence for the loop-2 or loop-1 region of D1R, with an IRES-YFP tag to test for expression. Competitive expression of D1R loop-2 occluded the increase in CaV2.2 current caused by D1R expression, while competitive expression of D1R loop-1 did not, indicating that the gain in CaV2.2 function due to D1R expression relies on a physical interaction between D1R and CaV2.2. Thus, we demonstrate that the D1R-CaV2.2 complex impacts not only CaV2.2 distribution but also CaV2.2 function. Future experiments in PFC neurons will illuminate the physiological impact of these results.

Cellular and Molecular Neurobiology

P37. Toll-Like Receptors 2 and 4 in the Reactive Gliosis Propagation After Traumatic Brain Injury

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Astrocytes respond to CNS injury with a process named reactive gliosis. It is still unknown how reactive gliosis rapidly propagates reaching very distant regions in the CNS after a focal brain injury. It is proposed that damage proteins released by dying neurons acting on TLR/NFκB pathway could be involved in the reactive gliosis propagation. To address this question, we here performed a penetrating traumatic brain injury by stab wound in wild-type (WT), TLR4KO, and TLR2KO mice and used monolayer and 3D glial cells cultures. While stab-wounded WT animals showed a clear astrogliosis gradient at 3 to 7 to 14 days post-injury (DPI); TLR-deficient animals showed an exacerbated gradient of astrogliosis at 3 to 7 DPI. However, at 14 DPI, the TLR4KO animals showed a similar gradient to WT animals. At 3 to 7 DPI, microglial cells near to injury core showed an increased reactive phenotype in TLR-deficient animals compare to WT animals. *In vitro*, scratch wound produced a gradient of NFκB activation in astroglial cultures, and the LPS exposure increased this gradient. Astroglial 3D cultures injected with TLR agonists LPS and HMGB1 responded with re-orientation of their process to the injected site in a dose-dependent manner. These results show that reactive gliosis propagation is a complex phenomenon that involves both astrocytes and microglia and that absence of TLR2 or TLR4 does not preclude reactive gliosis propagation but affects it.

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Cellular and Molecular Neurobiology

P38. Age-Related Changes in Ang II Receptor's Immunolocalization and Expression in the Substantia Nigra

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Substantia nigra (SN) is the main source of dopamine and a critical area in Parkinson's disease (PD). Overstimulation of Ang II AT1 receptors could produce oxidative stress, which affect the sensitive area of the SN. Thus, we evaluated developmental changes in Ang II receptor's expression and localization in this area. Animals of P21, P100, and P365 days were used. For RNA extraction, the SN was dissected from slides obtained with a cryostat at the adequate level. RT-PCR assays allowed us to observe a decrease in the expression level of both AT1 and AT2 receptors with age. AT1 receptors decreased about 80% at P100, while AT2 receptors showed no significant difference between P21 and P100. Both receptors diminished at P365. Immunofluorescence staining of AT1 and AT2 receptors showed at P21 and P100 higher density of AT2 stained cells than AT1-labeled cells, with citoplasmatic and perinuclear localization. The number of stained cells diminishes at the stage P365. These results might account for the natural process encompassing aging. There are no previous reports regarding Ang II receptor localization in the SN by immunofluorescence at different ages. A new role has been proposed for Ang II AT2 receptors as neuroprotector, since its actions counteracts the damage cause by oxidative stress due to AT1 receptors. Our present results confirm the presence of both receptors during aging with a lower level of AT1 receptors and provide information of potential use for future treatments.

Cellular and Molecular Neurobiology

P39. A Model for Parkinson Disease: Administration of Rotenone by Using Microvesicles

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Parkinson's disease (PD) is one of the most frequent neurological diseases in elderness. Rotenone is an herbicide known to produce neurotoxic effects. Several methods of delivery have been explored, some of them with high mortality. Thus, we decided to administer rotenone by using microvesicles of a copolymer of PLGA. Microvesicles allow a slow delivery of the drug and thus a long treatment with a single dose administration. Resuspended microvesicles (25 μm) were administered by subcutaneous injection in a dose of 50 mg/kg. Rats were weighted every day, and no significant difference with control animals was observed during the whole treatment at the dose assayed. Animal's behavior was evaluated by using the bar test, grid test, and rearing test. Significant changes were observed on behavior tests after 5 weeks of treatment ($p < .01$) for the three test assayed. Latency in the behavior during the bar and grid test do correlate with catalepsy. Rigidity was tested with the rearing test. Physiological symptoms such as rigidity and immobility did appear after 5 weeks of treatment. An accurate experimental model of PD should reproduce the slow, progressive, and selective nigrostriatal dopaminergic degeneration seen in the disease. The lack of mortality in the treated group supports a good selection in the dose of rotenone applied. Although nigrostriatal degeneration can be confirmed by the specific staining, the behavioral results strongly suggest that animals developed PD.

Cellular and Molecular Neurobiology

P40. Ghrelin Receptor and Dopamine Receptor Type 2 Co-expression Modifies Each Receptor's Effects on Voltage Gated Calcium Channel CaV2.2

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Presynaptic CaV2.2 is activated by action potentials, and their calcium current induces neurotransmitter release. In this context, regulating CaV2.2 is critical, and one of the most important mechanisms for doing so is through G-protein coupled receptor (GPCR) activity. Two such GPCRs are the ghrelin receptor (GHSR) and the dopamine receptor type 2 (D2R). We have previously demonstrated that GHSR constitutive activity reduces CaV2.2 trafficking to the plasma membrane and that ghrelin-induced GHSR activity inhibits CaV2.2 currents. On the other hand, dopamine-mediated activation of D2R also inhibits CaV2.2 currents.

It has been recently shown that D2R and GHSR heterodimerize in hypothalamic neurons. Here, we explore how co-expression of GHSR and D2R modulates the effect that each GPCR has individually on CaV2.2. We found that GHSR-D2R co-expression increases the basal inhibition of CaV2.2 by GHSR constitutive activity, since less GHSR is needed to reduce CaV2.2 currents when D2R is co-transfected. By contrast, the acute inhibitory effect of ghrelin on CaV2.2 currents is unaffected by GHSR-D2R co-expression. Meanwhile, GHSR-D2R co-expression decreases inhibition of CaV2.2 by dopamine-evoked D2R activity (increase in EC50), since a higher dopamine concentration is needed to inhibit CaV2.2 currents when GHSR is co-transfected. This last effect depends on GHSR constitutive activity, since it is occluded by pre-incubation with Substance-P analog 1 μM, a GHSR inverse agonist.

Cellular and Molecular Neurobiology

P41. Lrig2 Promotes Dendritic Complexity, Spine Morphogenesis, and Excitatory Synapse Formation in Hippocampal Neurons

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Dendrite size and morphology are key determinants of the functional properties of neurons, and brain disorders are due primarily to structural abnormalities of dendrites and their connections. Distinct leucine-rich repeat (LRR) transmembrane proteins are highly expressed in the brain, especially in the hippocampus, where they play a critical role in the organization and function of neural circuits, regulating neurotrophin signaling, coordinating pre- and post-synaptic compartments during excitatory and inhibitory synapse formation, and regulating synaptic plasticity. Recently, the LRR protein, Lrig1, has been described as an essential regulator of neurotrophin signaling and dendrite arborization of hippocampal neurons. However, the physiological contribution of Lrig2 for neuronal development remains to be determined. Taking advantage of the post-natal expression of Lrig2 by hippocampal developing neurons, we used gain and loss of function assays to examine how altered Lrig2 expression impacts dendrite morphology and synapse formation in search for specific LRR proteins involved in neurodevelopmental disorders. Here, we show that Lrig2 overexpression exacerbates dendrite complexity by promoting growth and branching, in a LRR domain-dependent manner. Our results also indicate that Lrig2 is expressed in pre- and post-synaptic fractions, where it controls the density of dendritic spines and increases the number of excitatory synaptic contacts in hippocampal neurons.

Cellular and Molecular Neurobiology

P42. Alpha-Synuclein Aggregation and Toxicity: Structural Biology Meets Cell Biology

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Amyloid aggregation of alpha-synuclein (αS) in Parkinson's disease (PD) results in cellular toxicity and neuronal death. Several mutations in αS gene are associated with familial PD, supporting a central role for the protein in the development of the disease. However, the precise contribution of αS aggregates to neuronal impairment and death is not well understood. Previous work in our lab demonstrated that aromatic side chains of the N-terminal tyrosine residue at position 39 (Y39) of αS plays a critical role in its fibrillation pathway. In order to understand the key role of Y39 residue on αS aggregation and toxicity, we designed different point mutants of the protein. Through the combination of biophysics and cell-based assays, we demonstrated that replacement of Tyr by Ala or Leu at position 39 led to protein variants with different amyloidogenic potential. Interestingly, strong correlation was observed between the *in vitro* and in cell studies. Altogether, our data highlight the importance of combining structural and cell biology strategies and open new perspectives to elucidate the molecular basis behind the amyloid aggregation of the protein αS.

Cellular and Molecular Neurobiology

P43. IgGs From Sporadic Amyotrophic Lateral Sclerosis Patients Induce Neurodegeneration and Microglia Activation in Mouse-Isolated Spinal Cord Model

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Amyotrophic Lateral Sclerosis (ALS) has as a target upper and lower motoneurons. Our previous studies have demonstrated the pathological role of autoimmune mechanisms mediated by antibodies in sporadic ALS patients. In the present study, we tested the effect of IgG from a group of sporadic ALS patients on the mouse-isolated spinal cord preparation, which was incubated with different ALS and control sera for 6 hr. The purpose of the present study was to characterize (by immunohistochemistry) the localization of IgG in neurons and their role in microglia activation. Our results demonstrated significant IgG immunoreactivity in interneurons from dorsal and ventral spinal cord areas and motoneurons. Furthermore, after applying ALS sera, the number of ventral neurons was significantly decreased. On the contrary, while no changes in the number of microglia were observed, analysis of morphological parameters of microglial cells showed branche length to be significantly decreased following ALS serum incubation. Indeed, a significantly increase in CD68 staining, a marker for activated microglia, was observed that was consistent with post-transcriptional microglia activation, while no effect was observed in the CD68 mRNA analyzed by RT-PCR. These findings indicate the presence of a neuroinflammatory process in the pathological event induced by sporadic ALS sera and support the hypothesis of autoimmunity in the development of this neurodegenerative disease.

Cellular and Molecular Neurobiology

P44. Glial Metabotropic Glutamate Receptor Dysfunction in Alzheimer's: Implications for sAPPα-Mediated Aβ Clearance

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Astroglial metabotropic glutamate receptor (mGlu3R) promotes neuroprotective effects, such as releasing neurotrophin sAPPα and increasing Aβ uptake. We aimed to study whether mGlu3R alterations could be associated with AD progression in an AD mice model. Evidence for mechanisms involved in sAPPα-mediated Aβ elimination is provided here as well. mGlu3R protein levels remain stable during aging in non-transgenic (NTg) mice, whereas they progressively decrease with age in PDAPP-J20 (Tg) animals ($p < .05$). It is known that a truncated version of the receptor, called mGlu3Δ4R, acts as a negative modulator of mGlu3R. mGlu3Δ4R levels increase with age in NTg mice, and they are significantly elevated in 5-month-old Tg mice ($p < .001$). When analyzing mGlu3Δ4R/mGlu3R ratio, we found a significant increase in this ratio in 5-month-old Tg mice ($p < .05$). Also, we found decreased mGlu3R levels ($p < .01$) and increased mGlu3Δ4R/mGlu3R ratio ($p < .05$) in cultured astrocytes and neurons exposed to Aβ. On the other hand, sAPPα increases Aβ uptake in cultured astrocytes in a SRA-dependent manner. However, when—after 24 hr sAPPα incubation—medium was replaced by a mix of sAPPα/Aβ instead of Aβ alone, phagocytosis was inhibited ($p < .05$). Therefore, we postulate that Aβ clearance requires Aβ binding to sAPPα-SRA dimers at astrocyte surface. In conclusion, altered mGlu3Δ4R/mGlu3R ratio could constitute a novel early biomarker for AD and could lead to reduced sAPPα production by astrocytes and then to deficient Aβ elimination.

Cellular and Molecular Neurobiology

P45. Cholesterol Loss Triggered by Aging Stabilizes the Epigenetic Repressor CDYL in Old Hippocampal Neurons

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Aging is characterized by a progressive decline in cognitive capacities; however, it is unlikely that this decline arises from the altered expression or activity of a single factor. Over the past decade, accumulated evidence has indicated that one of the most dramatic changes that occur at the molecular level in the aging brain is the alteration of epigenetic mechanisms controlling gene expression. Epigenetic mechanisms regulate a plethora of brain functions including activity-dependent transcription of memory genes, synaptic plasticity, learning, and memory. Hippocampal aging is accompanied by the overexpression of the enzyme cholesterol-24-hydroxylase (CYP46) in cortex, cerebellum, and hippocampus. This enzyme converts cholesterol to 24-hydroxycholesterol, which is eliminated from the brain. As a consequence of CYP46 overexpression, cholesterol levels are reduced in old neuronal cells. We found that cholesterol loss impairs downstream signaling from NMDA receptors leading to nuclear accumulation of the transcriptional repressor CDYL. CDYL is part of a repressor complex, which includes REST and the H3K9 methyltransferase G9a, among others, and targets several genes related to memory formation such as the gene encoding the neurotrophin BDNF. Thus, we propose that altered synaptic activity in old neurons is promoted in part by cholesterol loss and leads to the formation of a transcriptional repressive structure at the promoter of memory genes.

Cellular and Molecular Neurobiology

P46. Mechanism of Calcium Release During Unfolded Protein Response

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Abstract not available

Cellular and Molecular Neurobiology

P47. Chemical Chaperone Reduces Endoplasmic Reticulum Stress in a GM2-Gangliosidosis Cell Model

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Abstract not available

Cellular and Molecular Neurobiology

P48. Tetraspanin Promotes NGF Signaling by Controlling TrkA Receptor Proteostasis

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A key question in developmental neurobiology is understanding how axons and dendrites from different neuronal populations develop to generate specific patterns of neuronal connectivity. This process is regulated by the interaction of extrinsic signals, such as neurotrophins (NTs), and intrinsic factors, such as endogenous regulators of their receptors. NTs are a group of secreted molecules that play a crucial role in the development and survival of neurons. They bind to tyrosine kinase receptors belonging to the

Trk family and promote the differentiation and survival of specific populations of neurons. The cooperation between NTs and other soluble factors are mechanisms that give specificity during the development of the nervous system. Recent studies also show the importance of intrinsic factors, which regulate the activity of these receptors and allow to broaden the repertoire of signals induced by NTs, conferring another level of regulation and control in the establishment of neuronal connectivity. In our work, we have identified members of the Tetraspanin superfamily that regulate the NGF-mediated TrkA signaling. We have shown that Tetraspanin is a specific intrinsic regulator of TrkA activation, its downstream signaling, and its effect on neuronal differentiation. We also provide a novel homeostatic mechanism to control biosynthetic trafficking and degradation of TrkA.

Cellular and Molecular Neurobiology

P49. Neuroprotective Effect of the Probiotic Bacterium *Bacillus subtilis* Against Parkinson's Disease in *Caenorhabditis elegans*

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Abstract not available

Cellular and Molecular Neurobiology

P50. The TM2-TM3 Loop of the α10 Subunit in the Potentiation of the Cholinergic Nicotinic Receptor α9α10 by Extracellular Calcium

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The α9α10 nicotinic acetylcholine receptor (nAChR) is expressed in cochlear hair cells. This nAChR mediates the inhibitory synapse between efferent fibers and outer hair cells. The inhibition results from calcium entry through the nAChR, in the presence of acetylcholine (ACh), followed by the activation of a Ca^{2+} dependent potassium current. This nAChR is composed of α9 and α10 subunits assembled into a pentameric cation-permeable ion channels. Each nAChR subunit comprises a large extracellular amino-terminal domain, four transmembrane domains (TM1–TM4), and a long cytoplasmic loop between TM3 and TM4. Expression of rat α9 and α10 nAChR subunits in *Xenopus laevis* oocytes yields functional α9 and α9α10 receptors but not α10 homomeric nAChRs. One of the functional differences between α9 and α9α10 nAChRs is their modulation by extracellular Ca^{2+}. α9 receptor responses to ACh are blocked by extracellular Ca^{2+}. In contrast, α9α10 responses are potentiated at sub-mM Ca^{2+} concentrations and blocked by higher concentrations of this ion. In order to determine the structural determinants responsible for these differences, we generated chimeric subunits, expressed them in Xenopus oocytes, and performed electrophysiological recordings under two electrode voltage clamps. Our results suggest that the TM2 to TM3 loop of the α10 subunit contains key structural determinants responsible for the potentiation of the α9α10 nAChR by extracellular Ca^{2+}.

Cellular and Molecular Neurobiology

P51. SOX-11 Regulates LINE-1 Retrotransposon Activity During Neuronal Differentiation

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Abstract not available

Cellular and Molecular Neurobiology

P52. Effects of the Val66Met Polymorphism on the BDNF Gene in Neuronal Development and Structure

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There is a single nucleotide polymorphism (SNP) in the BDNF gene (rs6265), which is associated with increased susceptibility to develop neuropsychiatric disorders in

human carriers. This SNP is present in ~25% of the world population and induces a substitution of a valine (Val) for a methionine (Met) in the BDNF prodomain (pBDNF), an abundant peptide in the central nervous system. pBDNF Met can trigger acute changes in 30 to 60 min to neuronal structure. However, the effects of pBDNF Val and Met for longer administrations periods, and in different stages of neuronal development, remain yet unknown. Thus, we studied the effects of both polymorphic variants of pBDNF on hippocampal neurons in culture at different stages of differentiation. In immature neurons, we did not detect alterations in the establishment of polarity nor in the development of dendrites and axons induced by either pBDNFs. On the other hand, in mature neurons, pBDNF Val and Met were able to significantly reduce the density of synaptic contacts. This is the first study to describe an effect of the Val variant of pBDNF (present in 75% of human population) on neuronal structure using a physiologically relevant dose. These results suggest that pBDNF is a modulator of synaptic contact density and that, together with mBDNF actions, might act as a regulator of precise circuit maturation.

Cellular and Molecular Neurobiology

P53. TGFb Effect During the Demyelination and Remyelination Process

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Adult neural progenitor cells (NPCs) from the subventricular zone (SVZ) can differentiate into oligodendrocytes, a key aspect during the remyelination process following a demyelinating event. We have demonstrated that TGFβ induces oligodendrocyte precursors cell (OPCs) proliferation through an increase in Jagged1 expression in astrocytes and oligodendrocyte maturation by direct action on OPCs. The current work studies the effect of TGFβ during demyelination through *in vitro* and *in vivo* experiments. SVZ NPCs obtained from control or 7-day cuprizone (CPZ)-treated rats were cultured in the presence of TGFβ or its vehicle for 4 days. Immunocytochemistry showed no changes in Nestin+, Nestin+/GFAP+, or GFAP+ populations in any of the experimental groups. Cultures obtained from demyelinated animals showed a higher proportion of PDGFRα+ cells than those obtained from control animals. The presence of TGFβ increased the proportion of PDGFRα+ cells in control cultures and showed a slight increase in cultures from demyelinated animals. Furthermore, preliminary results obtained from corpus callosum Western blot analyses of animals intracranially injected TGFβ showed an increase in MBP+ cells concomitantly with a decrease in PDGFRα+ cells both in control and CPZ-treated animals. These results indicate that TGFβ might contribute to OPC differentiation during demyelination. More experiments are needed to evaluate the real impact of TGFβ during the whole demyelination/remyelination process.

Cellular and Molecular Neurobiology

P54. Aβ Oligomers Detection by a Specific scFv Codified in an AAV Vector

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Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system that affects millions of people in the world. AD involves progressive lost in cognitive functions due to neuronal death in hippocampus and other related areas. AD was first characterized by the presence of amyloid plaques composed by Aβ peptides aggregates. Although it has been shown that neither Aβ peptides nor amyloid plaques were directly responsible for synaptic failures and neuronal death, it was suggested that soluble Aβ aggregates (from 4 to 50 monomers), the Aβ oligomers (AβOs), were the main toxins at early steps of this pathology. Moreover, elevated AβOs levels have been reported in AD rat models, even before neurodegeneration signs appear. In this context, we built an Adeno Associated Vector (AAV) for transiently expressing a single-chain variable fragment antibody (scFv) that specifically binds AβOs and bears a signal peptide to be secreted (AAV-scFv-NUSC1Glu). N2A y B104 cell lines were infected with AAV-scFv-NUSC1Glu, and the supernatant was then collected. First, we checked scFv expression at mRNA level, by PCR, and protein level by Western blot. Then, we attempted to detect synthetic AβOs levels by ELISA essays. We designed two different essays: A Direct ELISA and a Competitive one. Preliminary

results have shown that only the competition essay was useful to discriminate the tested AβOs levels.

Cellular and Molecular Neurobiology

P55. Iron Deficiency Strikes Again: Oligodendroglial and Astroglial Casualties

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Iron deficiency (ID) applied to developing rodents has proven to be an excellent model to understand the general myelination process and specific glial cell requirements. Previous work demonstrated that ID oligodendrocytes (OL) were mostly found in an immature stage, failing to attain complexity and a more mature morphology. In addition, ID astrocytes (AST) proliferated more than control ones and were more immature, much like OL. To further describe ID effects, we explore the hypothesis that low iron availability constrains OL maturation by impairing glial cell metabolic pathways. Pregnant mice were fed a control (C; 40 mg iron/kg diet) or an ID diet (4 mg iron/kg diet) from gestational Day 5; brain cortexes of P0-2 pups born to those mice were used for OL and AST primary cultures. ID metabolic signature was assessed using a Seahorse extracellular flux analyzer. Measurements of glycolysis and mitochondrial respiration showed a dysregulated pattern of proteins involved in the TCA and mitochondrial dysfunction following gestational ID; both ID OL and ID AST maximum respiration rate was lower than control ones. In addition, ID AST exhibited a lower basal glycolitic capacity than controls, which could be explained by a diminished of glycogen storage. These findings further prove that the regulation of cell metabolism may impact cell fate decisions and maturational status.

Cellular and Molecular Neurobiology

P56. Mild Stress Induced by Maternal Manipulation During Late Gestation and Infantile Ethanol Consumption Induce Changes in Pro-Dyn, Mu, and Kappa Opioid Mrna Expression

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Fetal ethanol experience generates learning and memories, capable of enhance ethanol consummatory behaviors during infancy. Opioid system seems to mediate alcohol reinforcement aspects. We proposed to study ethanol prenatal and infantile effects on opioid precursor peptides (POMC, Proenk, and Pro-DYN) and receptors (MOR, DOR, and KOR) mRNA expression, in hypothalamus. Pregnant rats received (GDs) 17–20, a daily intragastric (i.g.) administration with 2 g/kg ethanol or water, or remained undisturbed (unmanipulated group). An intake test was conducted at PDs 14–15. Three groups were performed: control (no intake test), water, and 5% ethanol. At the end of intake test, hypothalamus sections were obtained to perform qRT-PRC assessments. Alcohol intake was higher in animals whose dams received an i.g. manipulation, whenever water or alcohol. Prenatal manipulation possibly acts as a mild stressor capable of enhance consumption of alcohol, after birth. To test this alternative hypothesis, we regrouped prenatal manipulation in: unmanipulated and manipulated (pups from water and alcohol groups). qRT-PCR data, assessed only in unmanipulated group, demonstrated that ethanol intake experiences down-regulate the expression of Pro-Dyn mRNA and gradually up-regulate mRNA expression of MOR and KOR. Also, MOR mRNA expression was attenuated by prenatal i.g. manipulation, supporting the idea that possibly plays a role as a mild stressor.

Cellular and Molecular Neurobiology

P57. Leptin-Mediated Transcriptional Regulation of Pomc in Hypothalamic Neurons

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Although it is well accepted that the adipostatic hormone leptin activates Pomc expression in hypothalamic neurons, the mechanisms controlling this interaction remain unexplored. In the brain, leptin binds to the long form of the leptin receptor stimulating the intracellular phosphorylation of STAT3 which acts as a transcription factor of several genes by acting on STAT3 binding motifs. We have detected that the neuronal Pomc enhancer 1 (nPE1) contains two canonical STAT3 binding motifs (5′-TTCCNGGAA-3′), which are highly conserved in mammals. To challenge the hypothesis that these sites participate in leptin's induced Pomc expression, we generated mutant mice lacking both STAT3 sites from nPE1 using CRISPR/Cas9 technology. To maximize leptin's effect on hypothalamic Pomc expression, we previously reduced circulating leptin levels using two different experimental strategies. Our first approach was to study the effect of refeeding on mice previously fasted for 24 hr and analyze body weight variations and hypothalamic Pomc mRNA levels. Our preliminary results indicate a greater weight loss in mice lacking STAT3 sites after fasting and a more rapid regain of previous body weight. The second approach involves crossing nPE1(STAT3-less) mice with leptin-deficient (ob/ob) mice. Further progress of these experiments will give us the possibility to evaluate the implication of STAT3 binding sites in the regulation of hypothalamic expression of POMC induced by leptin.

Cellular and Molecular Neurobiology

P58. The Role of Sleep in the Consolidation of New Words in Temporal Lobe Epilepsy: Preliminary Results

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Abstract not available

Cellular and Molecular Neurobiology

P59. Impact of the Val66Met Polymorphism on the BDNF Gene on the Structure and Function of Dopaminergic Neurons

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A single nucleotide polymorphism (SNP) in the BDNF gene is present in more than 25% of the human population, and it results in a valine (Val) for methionine (Met) substitution (Val66Met) within its prodomain sequence. This SNP is associated with increased susceptibility to develop certain psychiatric and neurodegenerative disorders. Some of the associated diseases involve dopaminergic (DA) neuron dysfunction such as schizophrenia, addictions, and, in some populations, Parkinson's disease. It has been demonstrated that the Met variant of the BDNF prodomain affects hippocampal neuron structure, but its effects on DA neurons remain to be studied. We hypothesized that the Met variant of the BDNF prodomain affects DA neuron structure and function. Interestingly, we found that stimulation with the Met prodomain (but not the Val variant) induces superior cervical ganglion DA neuron death in culture. Moreover, mesencephalic DA neurons cultured from BDNF Met/Met knock-in mice displayed shorter processes as compared to the Val/Val littermates. Finally, BDNF Met/Met mice show increased spontaneous ipsilateral turns after the unilateral injection of the specific DA neurotoxin 6-hydroxydopamine, suggesting that DA neurons from this genotype are more susceptible to degenerate compared to Val/Val mice. Altogether, these results suggest a molecular explanation for the increased incidence of DA-related central nervous system disorders in Val66Met carriers.

Cellular and Molecular Neurobiology

P60. Cafeteria Diet Temporarily Affects Brain Reward Dopaminergic Pathway Through DNA Methylation Mechanisms

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We analyzed the short- and long-term effects of a highly palatable cafeteria diet (CAF) intake on the expression of key genes of the reward dopaminergic pathway of the brain (RW). Female rats were fed chow or CAF for 4(CAF4) or 11 (CAF11) weeks. Ventral Tegmental Area (VTA), Accumbens Nucleus Core (NAC) and Shell (NAS), and Ventral Pallidum (VP) were isolated by micropunching technique. For mRNA analysis, qPCR was performed. Digestion with methylation-sensitive restriction enzymes followed by qPCR was used for epigenetic studies. Serum leptin was assessed by RIA. CAF4 increased energy intake and adiposity. In VTA, CAF4 enhanced dopamine active transporter (DAT) and decreased both isoforms of glutamate decarboxylase (GAD), without altering tyrosine hydroxylase levels. CAF4 decreased dopamine receptor 2 mRNA in NAS and increased GAD2 levels in VP. The changes in DAT mRNA were related to a decrease in the methylation status of its promoter region. CAF11 further increased energy intake and adiposity, leading to hyperleptinemia, and increased mRNA of leptin receptor in VTA, without affecting the expression of any gene of the RW studied. Our results indicate that, in the short term, CAF deregulates the RW, at least in part via epigenetic changes, possibly reflecting a state of RW hyposensitivity, which might promote the excessive intake of palatable foods to compensate this status. This is reverted in the long term, when the hypercaloric intake could respond to an altered homeostatic control.

Cellular and Molecular Neurobiology

P61. The NFκB Alternative Pathway Is Activated by Antidepressant Drug Treatment

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Almost 30% of patients suffering from depression (MDD) remain resistant to the current medication and exist pressing need to discover new targets for antidepressant drug development. Our primary goal is to find new intracellular pathways regulated by antidepressants, which could be potential targets for drug development. We focused on kinases and phosphoproteins, which are well known for being drugable targets. As a first step, we carried out a protein array screening to reveal changes in the signalosome and phosphoproteome in the hippocampi of animals chronically treated with paroxetine. We extracted RNA from the same material and performed microarrays in order to compare mRNA and protein levels of the candidate molecules. We found strong changes in a number of interesting candidates including several members of the NF-κB pathway. We focused on this pathway and studied its role in emotional behavior and antidepressant action. To do that, we generated a conditional KO mouse line carrying a deletion of the NF-κB kinase IKK-α specifically in excitatory (glutamatergic) neurons of the forebrain. The effects of antidepressant drugs on different endophenotypes were analyzed on this mouse line at different levels, including adult neurogenesis, glial activation, depression-like behavior, and spine density of principal neurons of the hippocampus. These results point toward a relevant function of the NF-κB pathway on the mechanism of action of antidepressant drugs.

Cellular and Molecular Neurobiology

P62. Mesenchymal Stem Cells Therapy Reversed Hippocampal Atrophy, Neurodegeneration, Loss of Presynaptic Proteins, Reactive Microglia, and Behavior Impaired in a Rat Model of Sporadic Alzheimer's Disease

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Sporadic Alzheimer's disease (SAD) is a progressive neurodegenerative disorder with no efficient therapy. We are interested in developing therapeutic strategies to overcome the degenerative changes in SAD. In this context, we explored the neuroprotective effect of human mesenchymal stem cells (MSCs), using an SAD rat model by intracerebroventricular injection of streptozotocin (icv-STZ). Animals were divided into three experimental groups: Sham, STZ, and STZ+MSC. STZ and STZ+MSC received 3 mg/kg icv-STZ and, 24 days after, STZ+MSC received, every 18 days, 1 $\times$ 106 MSC in a tail vein. During the last 2 weeks until the end of the study (3 months post-icv-STZ), we performed different behavioral tests. Our results show that STZ-treated rats were behaviorally impaired, whereas the STZ+MSC group improved its spatial memory and decreased the anxiety. Immunohistochemistry in the stratum radiatum (SR) of the hippocampus revealed that neurons, astrocytes, and microglial cells were affected by STZ, and MSC therapy reversed the observed changes in neurons, microglial cells, and in the volume of the SR, previously atrophied by the STZ. Interestingly, Western blots of hippocampal lysates on presynaptic proteins (SYT1, SYT2, SYP, and SV2) and GABAergic neuron markers (GAD65/67) show that all these proteins levels decreased in the STZ group, whereas MSC therapy led to a recovery of SYT2, SV2, and GAD65 levels. We conclude that MSC therapy is a suitable biological tool in neurodegenerative disorders.

Cellular and Molecular Neurobiology

P63. On the Role of the γ2 Subunit in the Modulation of GABAA Receptors by Endogenous Redox Agents

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Abstract not available

Cellular and Molecular Neurobiology

P64. Approaching a Physiological Method for Studying Neuronal Activity-Regulated Gene Expression

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Abstract not available

Cellular and Molecular Neurobiology

P65. Glyphosate Exposure Impairs Neuronal Connectivity and Spatial Learning in Rats

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The developing nervous system is highly susceptible to damage caused by exposure to environmental contaminants. Glyphosate (gly) is the active ingredient of a number of broad-spectrum herbicide formulations, widely used all over the world to control weeds. Previous studies have demonstrated that gly induces neurotoxicity in mammals. Therefore, the cellular mechanism of this alteration needs to be determined. We evaluated hippocampus-dependent spatial learning by the Morris water maze test and found

that acquisition is impaired in rats exposed to gly during a critical period of synaptogenesis (first 3 postnatal weeks of life). These animals also showed alterations in the expression of synaptic proteins in the hippocampus such as PSD-95 and Synapsin I. To further analyze the effect of gly on neuronal connectivity, we used hippocampal cultured neurons to study the maturation of dendrite arbors in 17 days *in vitro* (DIV) control and treated neurons. We observed that gly exposure markedly decreased dendritic length and complexity in a dose-dependent manner. Then, we studied whether the herbicide impairs the development of dendritic spines in 17 and 20 DIV cultured neurons. Results showed that exposure to gly induce a decrease in spine density and maturation. Furthermore, we observed a defect in the number of synaptic clusters. In conclusion, these findings suggest that gly exposure alters neuronal connectivity both *in vivo* and *in vitro* impairing complex cognitive behavior.

Cellular and Molecular Neurobiology

P66. Stress Granules and Processing Bodies Oscillate in Mammalian Fibroblasts

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Stress granules (SGs) and processing bodies (PBs) are cytoplasmic membraneless organelles in which ribonucleoprotein complexes accumulates. SGs are formed by translational machinery components, like minor ribosomal subunits and translation initiation factors. SGs assemble when cells undergoes stress. PBs are formed by factors involved in mRNA translation inhibition and decay. It has been observed that several components of both SGs and PBs are rhythmically expressed, in a circadian fashion, thus we hypothesized that these foci oscillate. We show that the number and area of SGs induced by oxidative stress, as well as the PB number, exhibit daily oscillations in NIH3T3 cells. TIA-1, a protein with a prion-like domain that induces SG nucleation, is also expressed rhythmically. To test whether SG temporal changes were controlled by the transcriptional translational feedback loops (TTFLs) that form the molecular circadian clock, we analyzed SGs in wt and Bmal1−/− fibroblasts. Bmal1 is an essential and non-redundant component of TTFLs. Unexpectedly, we found oscillations in the number, area, and signal intensity of SGs in both genotypes. The period and phase of the oscillations were similar in both cell lines, but the amplitude was higher in Bmal1−/− cells, suggesting that the TTFLs modulate the strength of the response at different times. We thought that the SG rhythms could be generated by redox or translational rhythms that have been shown previously in Bmal1−/− cells.

Cellular and Molecular Neurobiology

P67. Role of Atypical GTPase RhoD During the Development of Neuronal Polarity

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Neurons are highly polarized cells typically extending a long thin axon and multiple short branched dendrites. These specialized compartments are developed through the coordination of cellular and molecular mechanisms in order to ensure the proper functioning of the nervous system and are highly regulated by several small Rho GTPases with their effectors controlling different aspects of neuronal morphology. Among others, these events include actin and microtubules cytoskeleton assembly and the addition of membrane in neuron specialized regions. Even though most of studies have been focused on classical Rho GTPases (RhoA, Rac1, and Cdc42), other less studied members of this family such as RhoD suggest to have unique effects on cytoskeleton and membrane dynamics. In this study, we have analyzed the role of RhoD during the development of axonal polarization and neurite extension. Our results reveal that the expression of RhoD active mutant in hippocampal neurons induces the generation of multiple axons and increase neuritic outgrowth and complexity. These results suggest that RhoD plays an important role during neuronal differentiation and neuritic outgrowth. In addition, we have designed a unimolecular activity RhoD biosensor based on resonance energy transfer to study the space–time dynamics of this Rho GTPase in cultured hippocampal neurons. Finally, we have evaluated how RhoD affects different dynamic parameters of microtubules cytoskeleton in fibroblast cells.

Cellular and Molecular Neurobiology

P68. Modifications of the Membrane-Associated Periodic Skeleton in Axons During Injury-Induced Axonal Degeneration

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Axonal fragmentation is a regulated process that depends on various signaling molecules, proteases, and other regulators to actively disintegrate the axonal compartment. In this work, we studied the change and possible role of the axonal membrane-associated periodic skeleton (MPS) during injury-induced degeneration. The injury model consisted on sensory neuron explants sections with a scalpel blade, producing axonal degeneration in the distal portion of the sectioned axons. The MPS is organized in periods of 190 nm, hence unobservable by diffraction-limited conventional fluorescence microscopy. Here, we used two different super-resolution techniques: Expansion Microscopy (ExM) and Stimulated Emission Depletion Nanoscopy (STED). We show that the MPS abundance and organization decays at an early time point after injury, well before the onset of axon fragmentation. In addition, pharmacological treatments that prevent axonal fragmentation, such as NAD+, also prevent early loss of the MPS. We further show evidence demonstrating the effect of dismantling the MPS with the actin depolymerization drug Latrunculin A on axonal fragmentation in control and injured axons. In summary, our work suggests that the MPS is necessary for stabilization of the axon compartment during injury-induced degeneration.

Cellular and Molecular Neurobiology

P69. Ghrelin Receptor Impairs Inhibitory Neurotransmission in Hippocampal Neurons in a Ghrelin Independent Manner

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Abstract not available

Cellular and Molecular Neurobiology

P70. Transferrin Transport Through the Endosomal–Exosomal Pathway in Oligodendrolioma Cell Line OLN-93

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Studies by our group have shown that apoTransferrin (aTF) has maturational effects on oligodendroglial precursor cells, which allows its use as a potential therapeutic agent in central nervous system demyelinating diseases. Exosomes are nanoparticles of 20 to 200 nm secreted by cells, which allow intercellular communication through long distances. In this context, the aim of our work is to analyze the effects of intranasally administered exosomes as Tf nanocarriers in a demyelination model. Given that some exosomes contain the Tf receptor (TfR), our interest is to find an easy and quick pathway of intracellular loading of aTf through its binding to the receptor. Oligodendroglioma cells OLN-93 were incubated for 30 min in the presence of human aTf, washed, and subsequently incubated for 24 hr in DMEMF12 without FCS. Western blot analyses were used to characterize the isolated exosomes with different exosome markers and also revealed the presence of the Tf-TfR complex. These results were corroborated using a special type of beads coated by exosomes to be detected by flow cytometry. Coated beads were treated with an anti-CD63 exosome marker and a fluorescent anti-Tf marker.

Cellular and Molecular Neurobiology

P71. Two Opposite Effects of Dopamine Receptor Type-1 Expression on CaV2.2 Calcium Currents

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Voltage-gated calcium channels type CaV2.2 co-localize with dopamine receptor type-1 (D1R) in prefrontal cortex (PFC) neurons, and CaV2.2 currents are modulated by dopamine-mediated activation of D1R. However, D1R is also known to display constitutive activity, and studies showed that the sole expression of D1R increases CaV2.2 surface expression. Thus, our aim is to study the role of D1R agonist-independent activity on CaV2.2 function. We transfected HEK293t cells with increasing D1R:CaV2.2 molar ratios and verified expression levels using YFP-tagged D1R. We recorded whole-cell calcium currents and found an increase in CaV2.2 current density at low D1R expression levels (170% of ctrl, $p = .0029$). Unexpectedly, at high D1R expression levels, CaV2.2 current density was reduced (61% of ctrl, $p = .0005$). To explore the role of D1R constitutive activity, we treated cells with haloperidol (D1R inverse agonist) and cholerotoxin (Gs protein inhibitor). We found that the increase in current at low D1R:CaV2.2 molar ratio depends on D1R constitutive activity, while the reduction of current at high D1R:CaV2.2 molar ratio does not. The latter may involve the formation of D1R complexes. In summary, we show two agonist-independent and opposite effects of D1R on CaV2.2 current, depending on D1R expression levels. Future experiments are required to understand the role of this effect on PFC neurons, where CaV2.2 has critical post-synaptic functions and where changes in D1R density are associated with cognitive deficits.

Cellular and Molecular Neurobiology

P72. EPHA3 and EPHA4 Regulate Ephexin1 and Rho Gtpases Activity During Axon Growth of Retinal Ganglion Cells

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Abstract not available

Cellular and Molecular Neurobiology

P73. Amygdala Stimulation Promotes Recovery of Behavioral Performance in a Spatial Memory Task and Increases GAP-43 and MAP-2 in the Hippocampus and Prefrontal Cortex of Male Rats

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The relationships between affective and cognitive processes are an important issue of present neuroscience. The amygdala, the hippocampus, and the prefrontal cortex appear as main players in these mechanisms. We have shown that post-training electrical stimulation of the basolateral amygdala (BLA) speeds the acquisition of a motor skill and produces a recovery in behavioral performance related to spatial memory in fimbria-fornix (FF) lesioned animals. BLA electrical stimulation rises BDNF RNA expression, BDNF protein levels, and arc RNA expression in the hippocampus. In the present paper, we have measured the levels of one presynaptic protein (GAP-43) and one post-synaptic protein (MAP-2) both involved in synaptogenesis to assess whether

structural neuroplastic mechanisms are involved in the memory enhancing effects of BLA stimulation. A single train of BLA stimulation produced in healthy animals an increase in the levels of GAP-43 and MAP-2 that lasted days in the hippocampus and the prefrontal cortex. In FF-lesioned rats, daily post-training stimulation of the BLA ameliorates the memory deficit of the animals and induces an increase in the level of both proteins. These results support the hypothesis that the effects of amygdala stimulation on memory recovery are sustained by an enhanced formation of new synapses.

Cellular and Molecular Neurobiology

P74. CircTulp4: A Circular RNA That Controls Excitatory Neurotransmission

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Abstract not available

Cellular and Molecular Neurobiology

P75. Role of the Types 1 and 2 Receptors for Angiotensin II in Inflammation-Induced Nociceptor Neuritogenesis

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Types 1 and 2 receptors for Ang II (AT1R/AT2R) may play a role in neuropathic pain. Albeit Ang II-induced neuritogenesis in primary sensory neurons has been offered as an explanation, the underlying mechanisms remain unknown. Our previous work showed that AT2R expressing neurons were C and A-δ nociceptors and that its expression increased in small neurons at CFA1, whereas at CFA4 increased only in medium neurons. Here, we examined the expression pattern of AT1R during cutaneous-induced inflammation. We used immunocytochemistry and selective AT1R and AT2R antagonists to examine their involvement in axonal growth and branching in normal and inflammatory conditions. We also tested *in vivo* neuritogenesis in IB4-nociceptors innervating the skin. *In vitro*, an inflammatory soup induced AT2R mRNA expression, while Ang II triggered TNF-α mRNA synthesis only when AT1R was blocked. Ang II promoted axonal growth and branching through both AT1R and AT2R. Their expressions correlated positively except when AT2R was inhibited. These suggest that the two receptors work together and are needed to sustain Ang II-mediated neuritogenesis. *In vivo*, AT1R expression did not change with inflammation in nociceptors, but it did in large neurons at CFA4. Four weeks treatment with antagonists against either AT1R or AT2R showed little impact on nociceptor neuritogenesis at skin level after inflammation. Thus, AT1R/AT2R seems to be required for the purported action of Ang II in the context of neuropathic pain.

Cellular and Molecular Neurobiology

P76. Pigmented Epithelium Derived Factor Prevents Apoptosis and Acts as a Neurotrophic Factor for Retinal Neurons

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PEDF has been shown to be cytoprotective on the R28 retinal progenitor cell line, but its effects on retinal neurons remain largely unknown. We investigated its effects in cultured photoreceptors and amacrine neurons. Pure neuronal cultures from 1-day-old rat retinas were grown in a serum-free, chemically defined media, and incubated at Day 2 with PEDF, small fragments from its neurotrophic (44-mer and 17-mer) or antiangiogenic (34-mer) domains, PEDF plus the blocking peptide P1, the PEDF-Receptor (PEDF-R) inhibitor, atglistatin; or vehicle (control) for 3 days. Apoptosis, cell death, opsin expression and axonal outgrowth were then analyzed. PEDF and the fragments from its neurotrophic domain prevented apoptosis, preserving mitochondrial functionality, and promoted both opsin localization in photoreceptor apical ends and neurite outgrowth, mainly in amacrine neurons. Retina neurons expressed PEDF-R, which showed a high degree of colocalization with membrane markers. Pre-treatment with either P1 or atglistatin

abolished PEDF effects whereas the fragment from PEDF antiangiogenic domain had no effect. In summary, this work suggests that PEDF is an effective survival factor for retinal photoreceptors during development *in vitro*. It also implies that PEDF plays different roles in neuronal differentiation, promoting the polarization and differentiation of photoreceptors and stimulating axonal outgrowth in amacrine neurons through the activation of its membrane receptor.

Cellular and Molecular Neurobiology

P77. Sex Differences in Gaba-Mediated Calcium Influx in Hypothalamic Neurons

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GABAA receptor (GABAAR) activation exerts trophic actions in immature neurons through depolarization of resting membrane potential gating the opening of voltage-dependent calcium channels. Previous results from our lab have shown gender-biased GABAAR responses in cultured hypothalamic neurons. These differences were found before brain masculinization by gonadal hormones. Considering these, in this work we evaluated the GABAAR-mediated Ca^{2+} entry in cultured neurons segregated by gonadal type. Hypothalamic cells were obtained from embryonic brains at E16 (both male and female), 2 days before the peak of testosterone production by the fetal testis, and cultured for 2 days. To measure calcium signals, neurons were loaded with the calcium indicator Cal-520, followed by a time-lapse recording on live cells using a spinning disk microscope. Our results show that there are more male than female neurons responding to GABAAR stimulation. Additionally, almost 50% of male neurons did not recover basal calcium level after stimulation, in contrast to only 20% observed in females. Moreover, although nifedipine blocks intracellular calcium entry equally, it was stronger in males. Together, these results highlight the influence of neural sex differences irrespectively of sexual hormone exposure.

Cellular and Molecular Neurobiology

P78. The Cuprizone Model Under Neurosphere's Scrutiny

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Cuprizone (CPZ) is a copper-chelating agent which induces demyelination in mice. Although its neurotoxic mechanism is still unknown, CPZ has been shown to produce astrogliosis, microglial activation, and loss of oligodendrocytes throughout the brain resulting in demyelination and neurotoxicity. Neural stem and progenitor cells (NSC/NPC) are able to generate all neural cell types and can be cultured as neurospheres (NS). NS can be maintained in a proliferative and undifferentiated state or alternatively be forced to differentiate into neurons, astrocytes or oligodendrocytes. In the present work, we used NS cultures to evaluate CPZ effects on NSC/NPC survival, proliferation, migration, and differentiation. Although NS generation was not affected when cultures were initiated in the presence of CPZ, we observed a slight decrease in NS size at higher CPZ concentrations. Migration was also affected in the presence of CPZ, which generated changes in migration patterns and an increase in the maximal migration distance reached by cells detached from NS. Treatment of dissociated NS during differentiation did not change mature oligodendrocyte, astrocyte or neuron proportions. However, CPZ treatment after cell differentiation produced a dose-dependent decrease in the number of MBP-positive cells. The detection of oligodendroglial precursor cells in these conditions suggests that CPZ has a deleterious effect on mature oligodendrocyte cells without affecting their precursors. Novelty improves or impairs LTM acting on the behavioral tagging process during reconsolidation.

Cellular and Molecular Neurobiology

P79. Protein Synthesis Regulation During the Behavioral Tagging Process in Memory Reconsolidation

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In the last years, we have shown that memory reconsolidation is achieved through a behavioral tagging process. In other words, that the event that triggers the reconsolidation induces the setting of a tag, that determines were to store an updated memory, and the synthesis of plasticity related proteins (PRPs) that once captured at the tagged sites will allow the reconsolidation to occur. Now we are focused in identifying the neurotransmitter systems and brain structures that regulate the synthesis of PRPs. Using the spatial object recognition (SOR) task, we show that the infusion of the D1/D5-dopaminergic receptor antagonist SCH23390, or the β-adrenergic receptor antagonist propranolol, 15 min before the reactivation of SOR memory induced long-term retrograde amnesia. Interestingly, the exploration of a novel OF 60 min before the reactivation session was able to rescue memory reconsolidation and prevent the amnestic effect of both antagonists. Now, we are combining the electrical stimulation of the ventral tegmental area (VTA) and the locus coeruleus (LC), with pharmacological interventions, to analyze if these structures are specifically recruited to regulate the synthesis of PRPs during SOR memory reconsolidation. At the moment, we show that D1/D5-dopaminergic and β-adrenergic receptors, in the hippocampus, are required to trigger the synthesis of PRPs during memory reconsolidation, and suggest that the VTA and the LC are the structures responsible of this regulation.

Cellular and Molecular Neurobiology

P80. Postgraduate Students Stress

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Abstract not available

Cellular and Molecular Neurobiology

P81. Ghrelin-Evoked GHSR Activity Impairs Low Voltage Activated Ca^{2+} Channel (CaV3) Currents in Hypothalamic Neurons

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CaV3 play a critical role in shaping burst firing and controlling pacemaker activity in neurons. Despite the importance of these channels, information regarding the mechanisms modulating CaV3 currents is scarce. In this context, we investigated the sensitivity of CaV3 currents to activation of GHSR, a receptor involved in energy balance and memory, among other central functions. We have previously showed that GHSR decreases CaV1 and CaV2 current in neurons, and that this inhibition impacts neurotransmission in areas where GHSR is physiologically relevant: the hypothalamus and the hippocampus. We performed whole cell patch clamp on hypothalamic neuronal primary cultures and found that ghrelin inhibits CaV3 currents. We next assayed this effect on CaV3 subtypes (CaV3.1-3) isolated in transfected HEK293T cells and found that CaV3.3 is the only CaV3 subtype inhibited by ghrelin in a Gq-dependent and G$\beta\gamma$-independent manner. For CaV3.3, we observed a 30% reduction in the number of channels available for opening, acceleration of the activation and inactivation kinetics, and no changes in voltage dependency parameters nor in the kinetics of deactivation or recovery from inactivation. Ghrelin application increases V1/2 of steady-state inactivation but does not affect steady-state activation, changing the window current size. Finally, we compile these parameters and run simulations on the program NEURON to model the putative impact of GHSR and CaV3.3 on neuron firing activity.

Cellular and Molecular Neurobiology

P82. Wnt7b Is Involved in Axon Differentiation and Elongation in Hippocampal Neurons

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The establishment of neuronal polarity and the development of axon and dendrites are essential for the formation of neuronal circuits. Wnt factors are secreted proteins functioning as neuronal modulators since are involved in neuronal differentiation, maturation and synapses. After Wnts bind to Frizzled (Fz) receptors, different signaling cascades can be activated: Wnt/β-catenin, planar cell polarity (PCP) and Wnt/Calcium pathways. Previously, we demonstrated that Wnt7b, through Fz7 receptor, regulates dendrite development and maturation. Now, we investigated the potential role of Wnt7b during early stages of neuronal development. Our findings showed that neuronal differentiation is altered after Wnt7b stimulation. The presence of Wnt7b stimulated axonal outgrowth and elongation compared to controls. Surprisingly, the function of Wn7b on neuronal differentiation did not seem to be mediated by Fz7 receptor, since the

expression of Fz7 did not affect axonal growth. Also, we found that Wnt7b effect was blocked when neurons were cultured in the presence of SFRP1 (the antagonist of Wnt), suggesting the specificity of Wnt effect on axonal growth. To go further, we examined the intracellular cascades triggered by Wnt7b. Pharmacological inhibition revealed that Wnt7b requires JNK activation to modulate the development of axon. More analyses are being performed in order to fully evaluate the Wnt7b function on early neuronal development.

Cellular and Molecular Neurobiology

P83. Regional Microgliosis in Transgenic Mice Expressing a Mislocalized Form of TDP-43: Implications for Neurodegenerative Disease Pathogenesis

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Activated microglia is a universal feature of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), two neurodegenerative disorders associated to mislocalization and aggregation of TAR DNA-binding protein 43 (TDP-43); however, its role in pathogenesis is not well understood. We generated and characterized transgenic (TG) mice conditionally overexpressing either nuclear (WT) or cytoplasmic (ΔNLS) forms of human TDP-43 in forebrain neurons. Recently, we showed that hTDP-43-WT mice display higher levels of microglial activation in hippocampal CA1 region and somatosensory cortex (SSC) respect to controls. In this study, we aimed to explore microgliosis in hTDP-43-ΔNLS mice. We analyzed microglial (Iba1+) staining in TG mice after 1 month of post-weaning induction in different brain regions. TG mice showed significant increases in total % Iba1+ area, microglial cell number and Iba+ cells with activated morphology (larger somatic area) in SSC and CA1 region compared to controls. In addition, there was a significant increase in mean Iba+ soma area in SSC, with borderline significance in CA1 region. Prefrontal cortex displayed no significant differences in any of the parameters analyzed. We are currently evaluating microgliosis in additional regions, including motor cortex and dentate gyrus, and also the status of astroglial response using GFAP staining. These results will help elucidate the role of gliosis in ALS, FTD, and other TDP-43 proteinopathies.

Cellular and Molecular Neurobiology

P84. Intracisternal Delivery of IGF-1 Mediated by a Recombinant Adenovector Is Neuroprotective for the Rat Spinal Cord Excitotoxic Damage Induced by KA

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Abstract not available

Cellular and Molecular Neurobiology

P85. Clonal Analysis of Stem/Progenitor Cells in Chicken Neural Retina

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Clonal cell analysis defines the potential of single cells, allowing to decode neural heterogeneity of cell lineages and their clonal relationships. We adapted the mouse genetic tracing strategy UbC-StarTrack to a chick model. UbC-StarTrack is based on transfection of genes encoding fluorescent reporter proteins, six in the cytoplasm and six in the nucleus, driven by an ubiquitous promoter in PiggyBac-based vectors. This method produces inheritable marks that enable long-term *in vivo* cell tracing and attributes a unique color-code to

single neural precursors, determining their differentiation potential and degree of dispersion. Once probed the accurate expression of these constructs in neurospheres obtained from dissociated cells of the chick retinal ciliary margin (CM) at 7 days of development (E7), UbC-StarTtrack mixture was co-electroporated into the retinal CM at E3.5. Labeled cell progenies were analyzed at different time points (2, 5, and 8 days postelectroporation). This allowed us to determine both, cell types originated from single cells and their clonal relationships within the retina. In conclusion: (a) UbC-StarTrack is valid in chicken model. (b) Cell clones formed columns extended between the inner and outer limitants of neural retina. (c) Cell clones displayed a large dispersion along the dorso-ventral axis but a limited dispersion by the anterior-posterior axis. (d) Different types of cells presented similar color combinations, revealing multipotency of some clones.

Cellular and Molecular Neurobiology

P86. NKX2.1 Controls the Differentiation of Hypothalamic Melanocortin Neurons and Regulates Arcuate Pomc Expression and Body Weight

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Abstract not available

Cellular and Molecular Neurobiology

P87. Intracellular Trafficking Defects Induced by α-Synuclein as a Pathogenic Mechanism for Parkinson's Disease

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of the substantia nigra. One of the hypotheses regarding the molecular mechanisms involved in the development of this disease postulates that defects in the intracellular protein and membrane trafficking is an initial event in the pathogenesis of this disorder. It is well known that increased expression of α-synuclein is associated with a higher incidence of PD. However, the underlying cellular and molecular mechanisms remain to be elucidated. We utilized a state-of-the-art system to synchronize the secretory pathway in order to study if α-synuclein is capable to affect the dynamics of vesicular transport between the endoplasmic reticulum (ER) and the Golgi apparatus, and the vesicle release from the latter. This system is based in fusion proteins that aggregates in the ER and can be synchronously released to the Golgi apparatus by a membrane permeable drug. Interestingly, we found that the expression of α-synuclein induces a delay in the proteins transport between the ER and the Golgi apparatus and also a delay in the vesicle exit from the Golgi apparatus toward the neuronal processes. These results suggest that the toxicity of α-synuclein may be due, at least in part, to the delay or blockage of the exocytic pathway.

Cellular and Molecular Neurobiology

P88. The Physiological Role of the GTPase Rab21 in Neuronal Migration and the Development of the Cerebral Cortex

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The development of the complex structure of the mammalian neocortex requires the proper migration of developing neurons from the ventricular zone containing neural progenitors to the cortical plate. The precise coordination of different cellular processes such as cytoskeleton dynamics, membrane trafficking and cell adhesion during migration is achieved by a variety of signaling pathways. GTPases play a central role in all these processes. In this context, the small GTPase Rab21 has been implicated in the regulation of cell adhesion dynamics by controlling the trafficking of endocytic vesicles containing adhesion molecules. Interestingly, Rab21 has been also implicated in neurite outgrowth. With the following project, we propose to study how Rab21 regulates sorting, traffic and endocytosis of adhesion proteins such as amyloid beta precursor protein (APP) and N-cadherin and elucidating its function in neuronal migration and the development of the cerebral cortex. These studies are important to better understand the mechanism governing the development of the cerebral cortex and the mechanisms that participate in neurodevelopmental pathologies such as autism spectrum disorders and cortical malformations.

Cellular and Molecular Neurobiology

P89. Posttranslational Modifications of α-Tubulin in Alzheimer's Disease: Focus on Tyrosination/Detyrosination Cycle

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Alzheimer disease (AD) is a neurodegenerative disease characterized by neurofibrillary tangles (NFTs) and senile plaques (SP) in brain. In early phases of AD, the exact role of SP and NFTs is still unclear and a contribution from other factors is expected to explain the synapse loss underlying the cognitive decline. Dendritic spines are dynamic structures regulating synaptic plasticity and cognitive abilities. Spine plasticity depends on actin and microtubule (MT) dynamics: the entrance of dynamic MTs into spines regulates their activity and morphology. Our team established causal link between MT dynamics and tubulin tyrosination: tyrosinated and detyrosinated tubulin are respectively present in dynamic and stable MTs. In the detyr/tyrosination cycle, the C-terminal tyrosine of α-tubulin is removed by recently identified carboxypeptidases (TCPs) and re-added by the ligase (TTL). The role of this cycle on synaptic plasticity modulation is still unknown. We investigated TTL levels and modified tubulins in control and AD brains. TTL level significantly decreases with AD progression and is highly correlated with increased levels of modified tubulins. TTL reduction leads to cognitive impairment in mice and reduced dendritic spine density in cultured neurons. Moreover, TTL over expression rescues spine density and protects spine loss induced by Aβ toxicity. Our results highlight the role of detyr/tyrosination cycle of tubulin in AD and refer TTL as a potential target for drug design.

Cellular and Molecular Neurobiology

P90. Roles of KIF5C on Neuronal Polarization and Neocortical Formation

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Three early signals of asymmetry have been described to occur in a single neurite of neurons in culture at Stage 2 of differentiation and shown to be essential for neuronal polarization: (a) accumulation of stable microtubules, (b) enrichment of the plasma membrane with activatable IGF-1r, and (c) polarized transport of the microtubular motor KIF5C. We have demonstrated that silencing of KIF5C expression prevents the polarized insertion of IGF-1r into the neuronal plasmalemma and neuronal polarization. Syntaxin 6 and VAMP4, necessary for the polarized insertion of the IGF-1r, are associated to vesicles carried by KIF5C and are transported preferentially to the neurite where KIF5C accumulates. We conclude that the enrichment of stable microtubules in the future axon enhances KIF5C mediated vesicular transport of syntaxin 6 and VAMP-4, which in turn mediate the polarized insertion of IGF-1r in the plasmalemma, a key step for neuronal polarization. These results prompted us to study the possible participation of KIF5C on neocortical formation. Using *in utero* electroporation, we have demonstrated that KIF5C is essential for early cortical neurons migration and, thus, neocortical formation. Neurons electroporated with a shRNA targeting KIF5C failed to migrate to the upper cortical layers and accumulated at the ventricular/subventricular zones. Further investigation will be necessary to study the regulation of dynamic changes in neuronal polarity during cortical neurons migration.

Cellular and Molecular Neurobiology

P91. Proteolipid Protein as a Marker of Olfactory Bulb Granule Cell Progenitors During Adult Neurogenesis

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The subventricular zone is a neurogenic niche that produces olfactory bulb interneurons throughout life. Stem cells that express glial fibrilary acidic protein (GFAP) generate transit amplifying progenitors that divide to produce neuroblasts, which in turn migrate to the olfactory bulb via the rostral migratory stream, mature, and integrate to the local circuit as granule and periglomerular neurons. Outside this neurogenic niche, neurogenesis of pyriform cortex pyramidal neurons has been shown to occur in the adult stage and involve progenitors expressing the oligodendrocyte marker proteolipid protein (PLP). Here, we ask whether PLP-expressing progenitors can generate new olfactory bulb interneurons. We used a tamoxifen-inducible PLP-Cre mouse line crossed with a Cre-reporter line (LSL-tdTomato) to label PLP-expressing cells and looked for labeled olfactory bulb interneurons at an early (1 week) and late (1 month) time points after induction. We found tdTomato-labeled spiny cells with a morphology compatible with olfactory bulb granule cells at the late but not at the early time point. We will: (a) test whether tdTomato-labeled cells at the late time point express characteristic markers of olfactory granule cells and (b) address whether tdTomato-labeled cells at the early time point are found in the subventricular zone and rostral migratory stream co-expressing markers characteristic of transit amplifying progenitors and neuroblasts of the olfactory bulb neuronal lineage.

Cellular and Molecular Neurobiology

P92. Platelets Bioenergetics Screening Reflects the Impact of Brain Aβ Plaque Accumulation in a Rat Model of Alzheimer

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Abstract not available

Cellular and Molecular Neurobiology

P93. Regulation of Cellular Sphingolipid Metabolism by Lipid-Protein Adducts and Genetic Variants Associated With Age-Related Macular Degeneration

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Abstract not available

Cellular and Molecular Neurobiology

P94. Light-Regulation of ArylalkylamineN-Acyltransferase and a New Potential Role in Vertebrate Retina

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A key regulatory step in melatonin synthesis is that at which serotonin is converted to N-acetyl-serotonin (NAS) by the enzyme Aralkylamine N-Acetyltransferase. AANAT is present in the retina and other regions while NAS can activate the TrkB receptor to generate neuroprotective effects. In photoreceptor cells, AANAT activity peaks during the dark (D) and at subjective night while activity is significantly decreased by light (L). By contrast, melatonin synthesis, AANAT expression, and activity are high during the subjective day or L phase in chicken retinal ganglion cells (RGCs). Here, we investigated the expression of AANAT and of non-visual opsins in enriched embryonic RGC cultures exposed to different L conditions. Cultures expressed Opn4 (melanopsin), Opn3, and Opn5 which may confer intrinsic photo sensitivity. Moreover, cultures exhibited blue L (BL) induction of AANAT immunoreactivity and mRNA as compared with D or red L treated cells. In addition, expression of this enzyme was significantly increased by adenylate cyclase activator forskolin (10 μM) in D. Interestingly, AANAT showed a localization change, from the cytoplasm to nucleus, increasing in BL, and this effect was reversible in darkness condition after L exposure; in addition, the nuclear importation of AANAT was blocked with protein synthesis inhibitor cycloheximide (50 μM) in BL. Results suggest that AANAT is a blue L-induced enzyme in RGCs controlled by cAMP, likely playing important roles in inner retinal cells.

Cellular and Molecular Neurobiology

P95. Pea3 Transcription Factors as Mediators of Nociception

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Sensory neurons of the dorsal root ganglion (DRG) are involved in the correct perception of external stimuli and require the appropriate peripheral target tissue innervation. The majority of DRG neurons, have a small-diameter soma, express the neurotrophin receptor TrkA during embryonic development, and project unmyelinated fibers to innervate the epidermis, depending on target-derived nerve growth factor (NGF). In mammals, peripheral neurotrophic signals have been shown to induce the expression of the Pea3 subfamily of ETS transcription factors, which comprise three members: Etv1, Etv4, and Etv5. Previous studies of our group showed that Etv4 and Etv5 are expressed by developing TrkA DRG neurons and are induced by peripheral NGF. Moreover, downregulation of Etv4 or Etv5 reduces DRG axonal growth in response to NGF *in vitro*. These results lead us to study TrkA sensory neuron population in the DRG *in vivo* and the target tissue innervation of peptidergic neurons. In the present study, we analyzed the *in vivo* role of Pea3 on the development of DRG, target innervation and its role in nociception. We investigated the consequence of disturbed Etv4 mediated signaling for pain sensation using different nociception assays such as the hot plate test, tail flick and formalin test. The results obtained by behavioral assays correlate with defects in target innervation observed in mutant mice. Our data indicate that Etv4 has a key role in sensing noxious nociceptive stimuli.

Cellular and Molecular Neurobiology

P96. HDAC3 Negatively Modulates Long-Term Memory Formation at Two Different Levels: Histone Deacetylation and NF-kB Inactivation

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Histone acetylation is a key process for gene expression during long-term memory consolidation. On the contrary, the activity of histone deacetylases (HDACs) diminishes transcriptional activity, thus functioning as negative modulators. Here, we study the effect of different HDACs inhibitors in long-term memory formation using the Novel Object Recognition task in mice. We found that RGFP966, an HDAC3 specific inhibitor, administered immediately after a week training session generates a memory that lasts 7 days. In contrast, class I HDAC inhibitor sodium butyrate, and HDAC6 specific inhibitor Tubastatin A failed to facilitate memory consolidation. As one of the target substrates of HDAC3 is the transcription factor NF-kB, we expect that the administration of RGFP966 will also produce an increase in the acetylated form of NF-kB. Acetyl-NF-kB is the active form of this transcription factor that is a key regulator of gene expression during memory consolidation. Thus, the inhibition of HDAC3 would be acting at two different levels: first increasing histone acetylation, that recruits transcriptional machinery; and second increasing the active form of one of the transcription factors required for gene expression. Ongoing experiments are in course to elucidate this last issue.

Cellular and Molecular Neurobiology

P97. Participation of Nuclear Receptors PPARγ and RXR in the Remyelination Process

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Demyelination in the CNS is a pathological process resulting from an insult on oligodendrocytes, while remyelination is a repair process by which oligodendroglial precursor cells restore myelin sheaths. Recent work has proven a significant increase in the mRNA of retinoid X receptor γ (RXRγ) during remyelination. RXRs are nuclear receptors forming complex with peroxisome proliferator activator proteins (PPARs), which regulate OL differentiation and maturation. Our aim is to study the joint activation of RXRγ and PPARγ by specific agonists 9 cis retinoic acid (RA) and pioglitazone (PIO), respectively, and their impact on remyelination through *in vitro* and *in vivo* experiments. NPC obtained from the SVZ were treated with RA, PIO, PIO+RA or their vehicle for 4 days. PIO treatment rendered a higher proportion of PDGFRα+/KI67+ cells. In contrast, RA cultures showed a higher proportion of MBP+ cells, with no significant differences in the PIO+RA condition regarding vehicle. For *in vivo* experiments, cuprizone-demyelinated mice were stereotaxically injected vehicle or PIO+RA, unilaterally into the corpus callosum (CC) and sacrificed 7 days after injection. Immunohistochemical and Western blot analyses of the CC rendered a decrease in the proportion of Iba-1+ and GFAP+ cells as a consequence of PIO+RA treatment, together with an increase in myelin deposition. These preliminary results hint at a pro-myelinating and anti-inflammatory effect of RXRγ and PPARγ activation, respectively.

Cellular and Molecular Neurobiology

P98. Role of Cytoplasmic c-Fos as an Activator of Lipid Synthesis During Neuronal Differentiation

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Cytoplasmic c-Fos activates phospholipid synthesis by associating with particular lipid synthesizing enzymes at the endoplasmic reticulum (ER). This activity of c-Fos supports the high rates of membrane genesis required for neuronal differentiation. In hippocampal cultures, blocking either c-Fos expression or its activity promotes an impairment in differentiation with no observable development of axonal processes. In addition, the expression of N-terminal deletion mutants of c-Fos capable of blocking only its cytoplasmic

activity produces a similar effect. Moreover, using an *in utero* model to evaluate neuronal cortical migration, neurons electroporated with a shRNA targeting c-Fos fail to migrate and are mostly visualized in the ventricular/subventricular zones. Since we found c-Fos strongly co-localizing with ER markers in neuronal processes, we examined if its lipid synthesis activator capacity is exerted in neurons by examining CDP-diacylglycerol synthase (CDS), previously described as one of the enzymes activated by c-Fos, and CTP:phosphocholine cytidylyltransferase-β2 (CCTβ2), that is responsible for CDP-choline formation in the brain. A strong interaction between c-Fos and the enzymes was found by FRET experiments together with a marked increase in CDS enzymatic activity in the presence of recombinant c-Fos. These results support our hypothesis that c-Fos plays a main role in neuronal differentiation and this might be achieved through phospholipid synthesis regulation.

Cellular and Molecular Neurobiology

P99. Analysis of the Key Functional Residues Within the C-Terminal Cytoplasmic Tail of Gpm6a Critical For Filopodium Outgrowth

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Gpm6a is a neuronal membrane glycoprotein with four transmembrane domains and the N- and C-terminal ends facing the cytoplasm. It functions in the processes of neuronal development, and its overexpression leads to the extensive formation of filopodia. However, the mechanism of action of Gpm6a is not clearly understood. Previously, we mapped the regulatory effect of Gpm6a in filopodium formation to its C- but not the N-terminal cytoplasmic end. Following alanine scanning mutagenesis of the C-terminal cytosolic end identified K250, K255, and E258 as the key functional residues. Subsequent bioinformatic analysis revealed that K250, K255, and E258 are predicted as part of sorting signals of transmembrane proteins. Here, we use flow cytometry analysis to show that total expression levels of truncation mutants do not differ from the wt Gpm6a, but the amount of both truncated proteins on cell surface is lower. Our colocalization assay shows that deletion of the C- but not the N-terminus diminishes the association of Gpm6a with clathrin implying involvement of clathrin-mediated trafficking events. Substitution of K250, K255, and E258 with alanine also diminishes the amount Gpm6a on cell surface and in case of K255 and E258 also leads to the lower amount of total expressed protein. Subsequent subcellular localization studies using confocal microscopy reveal that mutant forms of Gpm6a that fail to induce filopodia formation display preferential localization to Lamp1-positive structures.

Cellular and Molecular Neurobiology

P100. Experimental Febrile Seizures in Young Postnatal Rats Have a Long-Lasting Effect in Epileptic Threshold and Astroglial Morphology

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Retrospective studies in adult epilepsy patients show an initial precipitating injury, usually febrile seizures, during childhood between 6 months and 5 years of age. Using an animal model of hyperthermic seizures (HS), we here investigated the consequences of early HS young rats. Rat pups (10-11 postnatal, PND) were placed in a glass chamber, and their core temperature was raised and hyperthermia (39.5–42.5C) was maintained for 30 min. The seizures onset was monitored behaviorally and consisted of an acute sudden arrest of hyperthermia-induced tonic freeze postures and occasional oral automatism (biting and chewing) and often body flexion. Rats were then placed on a cool surface, monitored for 5 min before being returned to their mothers. At PND37-39 rats were exposed to repeated pilocarpine subconvulsive doses (10 mg/kg). We observed a significative reduction in the convulsive threshold in HS-exposed animals compared with controls. Another group of animals (PND35) was deeply anesthetized, fixed, and brains processed for immunohistochemistry. HS animals showed neuronal alterations with NeuN relocalization to the cytoplasm, moderate reactive gliosis with an atypical astrocytes distribution in the pyriform cortex and other brain structures. Our results suggest that HS exposure early in the postnatal brain development produce long-lasting effects in animals, which could be related to their future susceptibility to develop epilepsy.

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Cellular and Molecular Neurobiology

P101. Ceramide Induces the Death of Retina Photoreceptors Through Activation of Parthanatos

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Ceramide (Cer) has been proposed as a messenger in photoreceptor cell death in the retina. Here, we explored the pathways induced by C2-acetylsphingosine (C2-Cer), a cell permeable Cer, to elicit photoreceptor death. Treating pure retina neuronal cultures with 10 μM C2-Cer for 6 hr selectively induced photoreceptor death, decreasing mitochondrial membrane potential and increasing the formation of reactive oxygen species. Noteworthy, the amount of TUNEL-labeled cells and photoreceptors expressing cleaved-caspase 3 remained constant and pretreatment with a pan-caspase inhibitor did not prevent C2-Cer-induced death. C2-Cer provoked polyADP ribosyl polymerase-1 (PARP-1) overactivation. Increased polyADP ribose polymer (PAR) levels and induced the nuclear translocation of apoptosis inducing factor (AIF). Inhibiting PARP-1 decreased C2-Cer induced photoreceptor death and prevented AIF translocation. A calpain inhibitor reduced photoreceptor death whereas selective cathepsin inhibitors granted no protection. Combined pretreatment with a PARP-1 and a calpain inhibitor evidenced the same protection as each inhibitor by itself. Neither autophagy nor necroptosis were involved in C2-Cer-elicited death. These results suggest that C2-Cer induced photoreceptor death by a novel, caspase independent mechanism, involving activation of PARP-1, decline of mitochondrial membrane potential, calpain activation and AIF translocation, which are all biochemical features of parthanatos.

Cellular and Molecular Neurobiology

P102. SARA Participation as a Negative Regulator of the TGFβ Signaling Pathway in Neuronal Development

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Several events are necessary for proper neuronal development, such as cytoskeletal dynamics and endosomal trafficking. Smad Anchor for Receptor Activation (SARA) is a protein that binds to early endosomes; carrying out specific functions related to traffic but also participating in signaling such as TGFβ pathway. It has been described that SARA recruits Smad2/3 and, therefore, favors the activation of the pathway in epithelial cells. Moreover, it has been shown that TGFβ signaling specifies axon during neuronal development; however, SARA participation in this signaling pathway during the developmental process remains unknown. For this reason we proposed to analyze the role of SARA in the TGFβ signaling during neuronal development. Preliminary results in hippocampal neurons, through FRET Acceptor Photobleaching showed interaction between SARA and the TGFβ receptor. Also, performing loss and gain of function experiments, SARA suppression (through shRNA expression) generates both greater axonal growth and loss of axonal specification since neurons have more than one axon compared with the control. Interestingly, this same phenotype is obtained when we use a mutant form of SARA that prevents its binding to PP1c protein and therefore, the TβRI remains hyperphosphorylated, keeping the pathway activated. These results suggest that SARA participates in TGFβ pathway in neurons through the negative regulation, which seems to be a requirement for the correct neuronal development.

Cellular and Molecular Neurobiology

P103. Role of Electrical Activity in the Assembly of Sensory Circuits During the Development of the Nervous System

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Spontaneous electrical activity (SEA) expressed during early stages of development is required for the correct assembly and function of the nervous system. In the developing auditory system, SEA originates in the cochlea and is key for neuronal survival, maturation of auditory neurons, and refinement of tonotopic maps. In order to decipher the role of SEA in the development of sensory circuits, we used the *in vivo* Zebrafish (*Danio rerio*) lateral line system (LL). The LL is the sensory system that allows fishes and amphibians to detect water motion. It consists of clusters of mechanosensory hair cells, called neuromasts, which are innervated by afferent and efferent neurons and surrounded by non-sensory supporting cells. LL hair cells share structural, functional, and molecular similarities with the hair cells in the vertebrate inner ear. It has been reported that zebrafish LL afferent neurons exhibit SEA between 5 and 7 days post-fertilization. However, its role in the assembly of LL sensory circuits is still unknown. To answer this question, we silenced electrical activity by stochastic expression of inward rectifier K+ channels in single LL afferent neurons and analyzed the resulting phenotype under a confocal microscope. Suppression of SEA in single LL afferent neurons led to anomalous growth of axon arbors in the developing hindbrain and errors in neuromasts innervation. Our results provide an *in vivo* demonstration of the role of SEA in the correct assembly of the LL system.

Cellular and Molecular Neurobiology

P104. Trafficking of ASIC1a Channels Between Cellular Compartments: Role in Neuroinflammation

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Interleukin 6 (IL-6) is one of the main neuroinflammatory cytokines in the central nervous system (CNS). CNS IL-6 is upregulated when neuroinflammation occurs, determines changes in metabolic activity, and can result in acidosis. Changes in regional pH levels in the brain have been observed in a number of neurological and neurodegenerative disorders. ASIC (Acid sensing Ion) channels are sodium channels activated by tissue acidosis and thus become active in many pathological conditions. ASIC1 is the most abundant ASIC subunit in the mammalian CNS, permeate sodium and slightly calcium ions, and could contribute to intracellular calcium levels and neuronal injury in pathological conditions. We decided to analyze the role of IL-6 on ASIC1 channels. We established a method to analyze the presence of the channel in the different cellular compartments. Our preliminary results show that IL-6 determines the redistribution of ASIC1 channels to the plasma membrane of the cells and an increase in calcium currents via ASIC1. Also, we studied dissociated mouse hippocampal cultures. We incubated it with IL-6 and did immunocytochemistry of the samples to detect ASIC1 and used calcium-sensitive dyes and ASIC1 blockers to detect calcium currents posterior to ASIC activation. These results point at a mechanism by which neuroinflammation could contribute to neurodegeneration and ASIC1 as a potential target in these conditions and a method to analyze proteins in the different cell compartments.

Cellular and Molecular Neurobiology

P105. α-Synuclein Overexpression Triggers a Lipid Metabolic Switch: Lipid Droplets as an Early Marker of Neurodegeneration

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Pathological accumulation of α-synuclein (α-syn) is a hallmark of Parkinson's disease. α-syn is highly expressed in the brain and has the intriguing characteristic of interacting with lipids. However, little is known about its biological role. We demonstrated that α-syn overexpression downregulates neurofilament expression (NF) through the modulation of phosphatidic acid signaling (Conde et al., 2018). Here, we studied lipid metabolism in neuroblastoma cells either stably transfected with pcDNA3 vector (as a transfection control) or pcDNA-WT-α-syn (WT α-syn). WT α-syn neurons displayed an increase in triacylglycerides (TAG) and cholesterol content consequently with lipid droplet (LD) accumulation. α-syn overexpression also triggered SREBP-2 nuclear translocation coincidently with this lipid metabolic switch. Enhancers of α-syn aggregation (iron, manganese, and bortezomib) increased LD content. WT α-syn overexpression also induced Acyl-CoA synthetase activation which explained, at least in part, the increase in TAG, a rather unusual occurrence in healthy neurons. Pharmacological inhibition of TAG synthesis turned the neurons more vulnerable to the presence of WT α-syn. Additionally, NF recovery increased the expression of cleaved caspase 3. In conclusion, α-syn modulates neuronal lipid biology together with the loss of NF as part of a neuroprotective strategy.

Reference

Conde, M. A., Alza, N. P., Iglesias González, P. A., Scodelaro Bilbao, P. G., Sánchez Campos, S., Uranga, R. M., & Salvador, G. A. (2018). Phospholipase D1 downregulation by α-synuclein: Implications for neurodegeneration in Parkinson's disease. *Biochim Biophys Acta Mol Cell Biol Lipids*, *1863*(6), 639–650.

Cellular and Molecular Neurobiology

P106. Spleen Alterations and Increased Brain CD4+ Lymphocytes After Pilocarpine-Induced Status Epilepticus (SE)

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Epilepsy is one of the most frequent neurological diseases worldwide. A high percentage of patients with temporal lobe epilepsy (TLE) refer an initial precipitating event, such as febrile seizures, during childhood, followed by a silent latency period (LP), until the onset of the chronic seizures phase. In an experimental model of TLE, we have previously shown that neurodegeneration, reactive gliosis and macrophages brain infiltration occur during the LP and that early interventions limiting glial and immune activation during the LP increase epileptic threshold during the chronic phase (Rossi et al., 2013, 2017). We here studied the immune cells participation in the LP that follows pilocarpine-induced SE. Male Wistar rats were treated with lithium-pilocarpine (127 mg/kg /30 mg/kg) developing SE that were limited to 20 min by 20 mg/kg i.p. diazepam. After 3DPSE (days post-SE), blood and spleen smears stained with May-Grünwald Giemsa as well as splenocytes cultures of 3DPSE showed an increase in relative abundance of plasmocyte-like cells. Histological analysis of spleen sections showed increased cell density in the spleen white pulp and brain sections presented increased abundance of CD4+ lymphocytes in the choroid plexus as well as CD4+infiltrating cells in brain parenchyma. Our results suggest that peripheral immune system is probably responding to brain-derived clues released by the SE.

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Cellular and Molecular Neurobiology

P107. Impact of Early Overfeeding on the Transcriptional Regulation of Genes Associated With Food Intake Control

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Nutritional environment is critical during perinatal period and could impact in health in adult life. Litter size reduction is a good experimental model for the study of early overfeeding and obesity. Our aim was to analyze the effects of early overfeeding on the brain control of food intake in rats at postnatal day (PND) 21. Male offspring were divided in two experimental groups: small litter (SL, $n = 4$) or normal litter (NL, $n = 10$), from PND3 to PND21. On PND21, animals were sacrificed and the body weight and epididymal fat pad (EFP) were measured. Micropunch technique was used to isolate specific nuclei from rat brains. Energy intake control neuropeptides and mesolimbic dopaminergic related genes were measured by RT-PCR and their epigenetic control were analyzed ($N = 10$/group). Our results showed than the SL group had higher body and EFP weights than the NL group. Moreover, SL rats showed changes in the expression of: (a) anorexigenic and orexigenic neuropeptides on specific nuclei of the hypothalamus and (b) mesolimbic dopaminergic related genes in ventral tegmental area and nucleus accumbens. Changes in gene expression were related with the methylation status of their promoter regions, suggesting that the SL group developed an anorectic signal in different regions of the brain controlled by methylation-related mechanisms. Overfeeding during lactation triggered an epigenetic control of genes related with food intake, regulating the body energy balance in SL animals at weaning.

Cellular and Molecular Neurobiology

P108. Contribution of Neural Crest Derived Cells and GLAST+ Pericytes to Liver Fibrosis

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Little is known regarding the contribution of neural crest-derived cells (NCDCs) to the liver in health and disease. The aim of this work was to analyze the contribution of NCDCs and GLAST+ pericytes to the liver during fibrogenesis. Wnt1Cre2;R26RTom and GLASTCreERT (2);R26RTom mice were used. Two models of liver cirrhosis were applied: (a) chronic applications of thioacetamide and (b) bile duct ligation. Contribution of NCDCs to liver was analyzed. Wnt1Cre2;R26RTom animals showed a small number of NCDCs in the liver, corresponding to GFAP+ glia and hepatocyte-like cells (HLCs). GLASTCreERT (2);R26RTom contributed to small numbers of desmin-pericytes as well as HLCs, but not to GFAP+ glia; Tom+ HLCs were only found when tamoxifen (Tx) was injected at postnatal day (P)-2 and not at P60. Fibrogenesis was found to induce a significant increase in the incidence of glia, HLCs in Wnt1Cre2;R26RTom mice. A 2-week treatment with TAA was found to increase CD44+ GLAST+ Tom+ cell numbers in the peripheral blood of Wnt1Cre2;R26RTom mice and to decrease such stromal population within the bone marrow. Consistently, total and Tom+ CFU-F numbers were also reduced in the bone marrow of those animals. Glia cell numbers increase with fibrogenesis. In addition, stromal NCDCs get likely mobilized from the bone marrow during this process. Finally, NCDCs and GLAST+ pericytes likely contribute with myofibroblasts in the fibrotic liver.

Cellular and Molecular Neurobiology

P109. Kainate Excitotoxicity in the Spinal Cord of Female Young and Adult Rats

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Abstract not available

Cellular and Molecular Neurobiology

P110. Inhibition of SIRT-1 Reduces Brain Cholesterol Synthesis

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A reduction in the expression/activity of SIRT-1 has been observed during aging in different tissues. While SIRT-1 can regulate many cellular processes including metabolism, the particular role of SIRT-1 in brain cholesterol metabolism remains unknown. In an attempt to emulate SIRT-1 loss of function in the aging brain, we inhibit SIRT-1 in primary cortical cultures and C57BL/6 mice. Cortical cultures treated with 1 μM EX-527, a SIRT-1 cell-permeable specific inhibitor (IC50 = 98 nM), showed a significant reduction in the levels of cholesterol, without noticeable changes in the levels of oxysterols, the main cholesterol-derived metabolites. In order to better understand this effect, the expression of cholesterol-related genes was evaluated using quantitative RT-PCR. SIRT-1 inhibition induced a repression of three key genes related to cholesterol homeostasis: HMGCR (synthesis), CYP46A1 (catabolism), and Apo-E (transport).

Furthermore, C57BL/6 mice treated for 5 days with 10 mg/kg of EX-527 exhibited a similar reduction in the cholesterol content within the hippocampus. Lower levels of cholesterol upon treatment with EX-527 were also detected in synapses purified from mouse cortices. The reduced cholesterol levels *in vivo* were accompanied by repression of the transcription factor SREBP-2 and its target gene HMGCR. Altogether, these results suggest that SIRT-1 sustains cholesterol synthesis in the brain, and influences the synaptic cholesterol content.

Cellular and Molecular Neurobiology

P111. The Physiological Role of the GTPase Rab21 in Neuronal Migration and the Development of the Cerebral Cortex

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The development of the complex structure of the mammalian neocortex requires the proper migration of developing neurons from the ventricular zone containing neural progenitors to the cortical plate. The precise coordination of different cellular processes such as cytoskeleton dynamics, membrane trafficking, and cell adhesion during migration is achieved by a variety of signaling pathways. GTPases play a central role in all these processes. In this context, the small GTPase Rab21 has been implicated in the regulation of cell adhesion dynamics by controlling the trafficking of endocytic vesicles containing adhesion molecules. Interestingly, Rab21 has been also implicated in neurite outgrowth. With the following project, we propose to study how Rab21 regulates sorting, traffic and endocytosis of adhesion proteins such as amyloid beta precursor protein (APP) and N-cadherin and elucidating its function in neuronal migration and the development of the cerebral cortex. These studies are important to better understand the mechanism governing the development of the cerebral cortex and the mechanisms that participate in neurodevelopmental pathologies such as autism spectrum disorders and cortical malformations.

Cellular and Molecular Neurobiology

P112. Sex Differences in Gene Expression of X-Linked Histone Demethylase Kdm6a in Embryonic Hypothalamic Neurons

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Kdm6a and Kdm5c are histone demethylases that play an important role as epigenetic regulators of gene transcription by removing the di- and tri-methylation of Lys27 or Lys4 on histone H3 (H3K27me2/me3—H3K4me2/me3). Both demethylases are implicated in regulation of transcription during neuronal growth and differentiation, being possible to hypothesize that they may contribute to generate sex differences in brain since they are encoded by X-linked genes and escape X-chromosome inactivation. Using the Four Core Genotypes (FCG) mouse model, we first analyzed the expression of Kdm6a and Kdm5c genes by RT-qPCR in primary hypothalamic neuron cultures from E15. Only Kdm6a showed differences between genotypes, presenting higher levels of expression in XX than in XY neurons ($p < .05$), regardless of the embryo sex. Estradiol 10-10 M did not affect such expression pattern *in vitro*. When we measured Kdm6a mRNA in the ventromedial hypothalamic region of adults, we found only XX males presented higher levels than the other three genotypes. We next evaluated the effect of Kdm6a/b activity inhibitor GSK-J4 on the sexually dimorphic expression of neurogenin 3 (Ngn3), a gene involved in the neuritogenesis of cultured hypothalamic neurons. Our preliminary results showed that GSK-J4 diminishes Ngn3 expression only in male cultures. Further experiments are required to better understand the role of Kdm6a in generation of sex differences in growth and differentiation of hypothalamic neurons.

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Cellular and Molecular Neurobiology

P113. Peripheral Nerve Regeneration Promoted by Adipose-Derived Stem Cell Magneto Targeting

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Wallerian degeneration (WD) is an efficient animal experimental model in mimicking the impact of peripheral nerve lesion to shed light on possible regeneration strategies. AdSC transplant is a useful tool for regenerative therapies, while magneto targeting is a nanotechnological strategy to mobilize magnetic nanoparticle (MNP)-loaded cells to a specific tissue guided by an external magnetic field. In this context, the aim of the present work was to test whether AdSC-MNP magneto targeting can enhance the regenerative ability of AdSC upon rat sciatic nerve lesion. To this end, cultured AdSC were characterized for multipotent cell marker expression. MNP internalization was evaluated through transmission electron microscopy and vibrating sample magnetometry (VSM) experiments. Likewise, epifluorescence microscopy and VSM analyses were performed to evaluate the arrival of AdSC-MNP at the injured nerve. Finally, AdSC-MNP transplantation effects on nerve morphology and conduction were evaluated through immunofluorescence, Western blot, and electrophysiological experiments. Our results show that AdSC express CD105, CD90, and CD34 and can internalize 2 to 4 pg MNP/cell. We demonstrate AdSC-MNP to supersede AdSC arrival exclusively at the lesion site, exerting beneficial effects on nerve morphology and conduction. In short, our results prove that AdSC-MNP magneto targeting constitutes a valuable tool to enhance AdSC arrival at the lesion site and consequent nerve regeneration.

Cellular and Molecular Neurobiology

P114. Mechanisms of Neuronal Degeneration Induced by β-N-Methylamino-L-Alanine

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The non-proteic aminoacid β-N-Methylamino-L-Alanine (BMAA) is released by many cyanobacteria present in most dams and water resources around the world. Human chronic intake of this toxin has been linked with the development of Amyotrophic Lateral Sclerosis, Parkinson and Alzheimer Disease. We here investigated its effects on pure neuronal and mixed neuro-glial cells cultures, obtained from newborn rat retinas. Cultures were incubated with BMAA (400 nM) for 5 days. Apoptosis and cell death were evaluated by DAPI and Propidium Iodide (PI) staining; mitochondrial activity by Mitotracker labeling and cytoskeleton integrity and axonal outgrowth by immunocytochemical methods. In pure neuronal cultures, BMAA increased the percentage of apoptotic amacrine and photoreceptor neurons, from 22% to 45% and from 33% to 49%, in controls and BMAA-treated cultures, respectively. Noteworthy, functional mitochondria decreased significantly in amacrine neurons, and only slightly in photoreceptors. In addition, BMAA disrupted the organized assembly of tubulin in axons. In neuro-glial cultures, BMAA induced lamellipodia retraction and loss of mitochondrial membrane potential in glial cells, without increasing glial cell death. Noteworthy, glial cells partially prevented BMAA-induced neuronal death. This suggests that BMAA induces subcellular changes in both neurons and glial cells and markedly affects the viability of retinal neurons, confirming its threat to human health as a potential inducer of neurodegenerative damages.

Cellular and Molecular Neurobiology

P115. EphA3 Ectodomain and GDNF Regulate Axon Growth and Guidance of Retinal Ganglion Cells

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The Eph/ephrin system participates in the chicken retinotectal mapping. We showed that: Tectal EphA3 stimulates axon growth of nasal retinal ganglion cells (RGC) toward the caudal tectum preventing them from branching in the rostral tectum. Ephrin-A-mediated EphA4 forward signaling decreases axon growth of RGC whereas the tectal EphA3 produces the opposite effects by decreasing the EphA4 signaling by competing with EphA4 for ephrin-As binding. GDNF stimulates motor neurons axon growth binding to GFRalfa, RET functions as coreceptor of GFRalfa and binds to ephrin-A5. Thus, RET integrates the effects of GDNF on GFRalfa and of EphA4 through ephrin-A5. Our purpose was to study the individual and combinatorial effects of EphA3 and GDNF on axon growth and guidance. We cultured chicken embryo retinal explants exposed to control conditions, to EphA3 ectodomain (EphA3-Fc), to GDNF or to EphA3-Fc plus GDNF to evaluate their effects on axon growth and guidance using stripe assay. The results showed that: Decreased ephrin-A-mediated EphA4 forward signaling by EphA3-Fc increases nasal RGC axon growth and has an axon guidance effect. GDNF increases RGC axon growth and decreases EphA4-ephrin-A2 colocalization as EphA3-Fc does. EphA3-Fc plus GDNF increase axon growth more than EphA3-Fc and GDNF alone. This suggests that EphA3 and GDNF potentiate nasal RGC axon growth and that decrease of ephrin-A-mediated EphA4 signaling could participate in the effects of both of them.

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Cellular and Molecular Neurobiology

P116. Extracellular Galectin-3 Induces Accelerated Oligodendroglial Differentiation Through Changes in Actin Dynamics and Akt—mTOR Signaling Pathway

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Galectin-3 (Gal-3) is a chimeric protein structurally composed of unusual tandem repeats of proline and short glycine-rich segments fused onto a carbohydrate recognition domain. Our studies have previously shown that Gal-3 drives oligodendrocyte (OLG) differentiation. Cytoskeleton plays a key role in OLG maturation: early OLG process extension requires dynamic actin filament assembly, while subsequent myelin wrapping concurs with actin disassembly protein upregulation dependent on MBP expression. In this context, the present work aimed to elucidate the mechanism underlying recombinant Gal-3 (rGal-3)-mediated effect on OLG maturation, focusing on the actin cytoskeleton and Akt-mTOR signaling pathways. Our results showed rGal-3 to induce early actin filament assembly, accelerating the shift from polymerized to depolymerized actin between treatment day (TD) 3 and TD5. Significant increases in MBP, gelsolin, rac1, rac1-GTP, and β-catenin expression at TD5 were observed. Furthermore, Western blot studies revealed Akt signaling activation at TD1 and TD3, mTOR and mTOR substrates 4EBP1 and p70SK6x phosphorylation, and Erk 1/2 deactivation at all times evaluated. These results were strongly supported by assays using Erk 1/2, Akt, and mTOR inhibitors, which shows these pathways' key role in rGal-3-mediated effects. Altogether, these results indicate that rGal-3 accelerates OLG maturation by modulating signaling pathways and protein expression involved in actin cytoskeleton dynamics.

Cellular and Molecular Neurobiology

P117. Assessing the Neuronal Role in Hippocampal Hypoconnectivity in the VPA Model of Autism

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Autism spectrum disorders are characterized by impairments in social interaction and repetitive-stereotyped behaviors. Applying the VPA model, we reported in the hippocampus of juvenile VPA rats: a decrease in synaptophysin (SYN) along with an increased expression of the neural cell adhesion molecule (NCAM) and a decrease in its polysialylated form (PSA-NCAM). The aim of this study was to evaluate synapse formation and remodeling of primary hippocampal neurons from VPA or control male pups. Cytoskeletal and synaptic markers were evaluated by immunocytochemistry and WB. Neurons from VPA animals displayed a reduced dendritic tree (reduced MAP2 area), a reduced number of glutamatergic synapses (decreased vGLUT and PSD-95 puncta number) and NMDA receptor clusters (decreased NR1 puncta number and individual puncta area). These neurons exhibited reduced number of functional synapses (FM4-64 labeling) which contained smaller vesicular pools; total NCAM expression increased while PSA-NCAM decreased. While in neurons from control animals glutamate (5 μM, 3 min) induced an NMDA-dependent dendritic retraction and SYN puncta number reduction, neurons from VPA animals were only capable of dendritic retraction without any change in synapse number. Our results indicate that neurons from VPA animals form fewer glutamatergic synapses that exhibit a more adhesive and resistant profile to synaptic remodeling what would contribute to hippocampal hypoconnectivity and reduced synaptic plasticity.

Cellular and Molecular Neurobiology

P118. *Yerba mate* Tea and Parkinson's Disease. Neuroprotective Effect on Dopaminergic Neurons in an Animal Model

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Parkinson's disease (PD) is the second neurodegenerative disease with a wide range of prevalence worldwide. The neurodegenerative process primarily affects the dopaminergic neurons of the substantia nigra. Since the mechanisms that underlie this neuronal degeneration have not been fully clarified, currently there is no preventive therapy for PD. However, a case–control study in Argentina revealed that consumption of *Yerba mate* (YM) has an inverse association with the risk of developing PD. YM consumption is widely popular in the countries of the Río de la Plata. It has been shown to provide numerous health benefits, strongly related to its variety of bioactive phytochemicals. We propose to characterize the extract of YM and to evaluate if the consumption of YM provides a benefit on the survival of dopaminergic neurons in a mouse model of PD. The extract of YM was obtained by "cebada simulada" and the concentrations of the main bioactive components were quantified by HPLC. Wild-type mice received water or "mate" as their only source of fluid for 4 months before receiving an intrastriatal injection of 6-OHDA and continue 1 month with treatment. It was found that mice treated with YM have a density of dopaminergic remaining fibers in the striatum 12% higher than the control mice. Our results suggest that this neuroprotective effect could be beneficial to slow the evolution of the neurodegenerative process experienced by dopaminergic neurons in people suffering PD.

Cellular and Molecular Neurobiology

P119. High Plasticity of New Granule Cells in the Aging Hippocampus

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The aging brain displays a generalized decline in cognitive capacity and circuit plasticity, including a marked decrease in production of adult-born hippocampal neurons. In previous studies, we have shown that morphological development of new dentate granule cells (GCs) is affected by age. However, their functional properties and integration to the circuit along maturation remains unclear. We performed whole-cell recordings in an 8-month-old Ascl1 (CreERT2);CAG(floxStopTom) mice to measure intrinsic properties, firing behavior and afferent excitatory connectivity in adult-born GCs labeled with Tomato. We found that the functional properties and connectivity of these neurons also develop in a slow manner. Despite the delayed maturation, new GCs in aging mice display a remarkable potential for structural plasticity. Retrovirally labeled 3-week-old GCs in middle-aged mice are small, underdeveloped, and disconnected. Notably, enriched environment and voluntary exercise induced substantial dendritic growth and spine formation. To investigate whether these physiological stimuli could also modulate output connectivity, we analyzed axonal branching in the hilus and CA3-boutons morphology. We found that mice exposed to the running wheel for 21 days presented a higher number of axonal ramifications in the hilus and a 2-fold increase in the number of filopodia of CA3 boutons. These results indicate that not only does running accelerate input integration but also boosts output connectivity.

Cellular and Molecular Neurobiology

P120. GABAergic Proopiomelanocortin Neurons Regulate Energy Balance Through an Arcuate—Dorsomedial Hypothalamic Circuit

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Abstract not available

Cellular and Molecular Neurobiology

P121. Role of Retinoid X Receptors on Survival and Modulation of Inflammatory Response in a Mouse Model of Retinitis Pigmentosa

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Retinal neurodegenerative diseases, which have no effective treatments, share as a final common step the photoreceptor cells (PhR) death. Also inflammation has a role in these pathologies. Retinoid X receptors (RXR) have the capacity of modulate and integrate multiple cell functions; and their activation has shown beneficial clinical effects in animal models of chronic inflammatory diseases. In this work, we assessed whether this receptors might prevent PhR death and inflammation. Using rd1 mice, we analyze *in vivo* and *in vitro* the roles of RXR in retina degeneration. Here, we show, by qRT-PCR analysis, that the alpha isoform levels are decreased in rd1 mice retina respect to their wt counterparts, in concordance with our previous data obtained by immunohistochemistry from retina slices. Noteworthy, RXR activation modulated the mRNA levels of all three RXR isoforms in mixed neuroglial cultures from rd1 retina. Moreover, it also delayed the onset of PhR apoptosis, analyzed by TUNEL assay, and decreased Bax mRNA levels; also decreased GFAP expression of both mRNA and protein level, in Müller glial cells (MGC). Therefore, we evaluate whether RXR could regulate anti-inflammatory response in the retina. Our preliminary results suggest that RXR activation increased the transcription of IL-10 in rd1 mixed

neuroglial cultures. As a whole, the activation of RXR could promote survival of PhR either by direct action on them or by indirectly modulating the inflammatory response of MGC.

Cellular and Molecular Neurobiology

P122. Inter-Hemispheric Hypo-Connectivity and Regional Metabolic Hyper-Activity in an Experimental Model of Autism

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Autism spectrum disorders (ASD) are a group of neurodevelopmental disabilities characterized by alterations in brain connectivity and neuroinflammation. In accordance with the long-distance hypo-connectivity and local hyper-connectivity hypothesis, previous studies in our laboratory with the valproic acid (VPA) model demonstrate connectivity alterations and reactive gliosis in the prefrontal cortex and hippocampus of VPA rats. The aim of this work was to evaluate the brain metabolic activity and the structure of the corpus callosum (CC) in VPA animals. For this purpose, glial cells in the CC were studied at PND 36 by CC1, PDGFαR, GFAP, and tomato lectin staining. Also, CC ultrastructure was assessed by electron microscopy (EM). Evaluated by positron emission tomography, glucose uptake was increased in local areas along the brain of VPA rats, while it was decreased when considered the whole forebrain. In the CC of VPA rats, the number of CC1+ cells diminished and number of PDGF+ cells increased, in the absence of astrogliosis or microgliosis. Concomitantly, EM showed less myelinated axons and aberrant myelin in the CC of VPA rats. To sum up, VPA animals exhibit hyper-metabolism in circumscribed brain areas along with global hypo-metabolism. Concurrently, CC myelination in VPA animals is disrupted, accompanied by an altered balance in the oligodendroglia lineage. Taking together, our findings support the local hyper-activity and long-distance hypo-connectivity hypothesis in ASD.

Cellular and Molecular Neurobiology

P123. Neurorestorative and Protective Effects of Palmitoylethanolamide in Perinatal Asphyxia: An Analysis of the Rat Striatum

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Abstract not available

Cellular and Molecular Neurobiology

P124. A Defective Crosstalk Between Neurons and Müller Glial Cells Impairs Glial Stem Cell Regenerative Capacity in the rd Retina

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Müller glial cells (MGCs) are stem cells in the retina. Their regenerative capacity is high in lower vertebrates, but it is very low in mammals and cannot restore photoreceptor losses during retina degeneration, such as in retinitis pigmentosa or its animal model, the rd mice. Since rd retinas show no evidence of neuronal renewal, we hypothesize that, in addition to the low regenerative capacity of MGCs and the molecular abnormalities of rd photoreceptors, the rd MGCs may have alterations affecting even more deeply their stemness potential. We here investigated whether MGCs in rd retinas present abnormalities altering their regenerative capacity. We analyzed MGC in mixed neuroglial cultures and in slices obtained from newborn "rd" and normal (wt) retinas. We demonstrated that rd MGCs had alterations in stem cell markers compared to wt MGCs, showing reductions in Nestin and Sox2 expression and significantly decreasing their cell cycle. They also evidenced

significant morphological changes in their nuclei. We evaluated whether neuro-glial crosstalk might be responsible of these changes. Noteworthy, when we co-cultured rd MGCs with wt neurons, Nestin expression was restored in rd MGCs. Conversely, in co-cultures of wt MGCs with rd neurons, Nestin expression in MGCs decreased. These results suggest that the mutations in rd photoreceptors lead to a disruption in neuro-glial crosstalk, affecting the proliferative and regenerative capacities of rd MGCs.

Cellular and Molecular Neurobiology

P125. Dynamics of GABABR and Associated Proteins in the Postnatal Rat Cerebellum

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Before glutamatergic synapses are formed, GABA-mediated signaling is considered to drive cell differentiation in the developing central nervous system (CNS). GABA, a classical inhibitory neurotransmitter, can also depolarize immature cells. Although this shift is mediated by the ionotropic GABA A receptor (GABAAR), recent evidence suggests that the electrical properties of GABAARs can be modulated by the metabotropic GABA B receptor (GABABR). GABABRs are macromolecular complexes, formed by a G protein-coupled receptor and a large number of constituents that interact together and ultimately influence cell identity and behavior. The composition of these complexes exhibits wide spatiotemporal variations; however, the implications of such dynamism during development of the CNS are far from being understood. We have determined total protein expression of some constituents of GABABRs (GABABR1a; GABABR1b, GABABR2; KCTD12) in the developing cerebellum of postnatal rats at 5, 15, and 90 days after birth, by performing Western Blots. Our findings suggest that the expression levels of the core and auxiliary subunits of GABABRs vary ontogenetically. This dynamism was also observed at the mRNA levels by RT-PCR. In addition, multiple immunolabeling followed by confocal microscopy of cerebellar sections showed Purkinje cells as the most dynamic cell type in terms of subcellular localization of the different molecules studied here. Our data support a cell lineage-dependent GABABR regulation.

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Cellular and Molecular Neurobiology

P126. Neuron-Specific Expression of Drd2 Is Directed by Multiple Transcriptional Enhancers in the Mammalian Brain

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Abstract not available

Cellular and Molecular Neurobiology

P127. Inhibition of Colony-Stimulating Factor 1 Receptor Through BLZ945: Impact on Remyelination, Neurodegeneration and Behavior

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Cuprizone (CPZ)-induced demyelination is frequently used to study the de/remyelination processes as a multiple sclerosis (MS) model. Chronic CPZ induces oligodendrocyte loss, neuronal death, astrocytosis and microgliosis. Microglia (MG) participate in demyelination and neurodegeneration processes and are physiologically dependent on colony-stimulating factor 1 receptor (CSF-1R) signaling. The aim of this study is to evaluate the effects of BLZ945—a CSF-1R inhibitor which significantly reduces the number of MG—on remyelination and behavior in mice submitted to a chronic CPZ model. Mice were fed either control or CPZ (0.2% p/p) chow for 12 weeks, administered BLZ945 (200 mg/kg/day, oral gavage) or vehicle during 10 weeks (C, BLZ945, CPZ, and CPZ+BLZ945, respectively), and evaluated in the 12th week of CPZ treatment. Although other authors reported CPZ-induced changes in locomotion and

working memory, our preliminary results showed no significant differences across groups in open field, accelerated rotarod and locomotor activity behavior. In contrast, assays on MBP immunoreactivity and NeuN+, AβPP+, and Neurotrace+ cell number showed significant demyelination upon CPZ. In addition, a significant decrease was observed in neurodegeneration in CPZ+BLZ945 regarding CPZ mice. Positive results from these experiments could be transferred to the treatment of progressive forms of MS, an urgent and still unmet medical need.

Cellular and Molecular Neurobiology

P128. Post-Translational Incorporation of L-Dopa into the C-Terminus of A-Tubulin in Living Cells Affects Microtubule Dynamics and Mitochondrial Traffic

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Abstract not available

Chronobiology

P129. It's Time to Be Motivated: Circadian Modulation of Motivation for Food Rewards

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In mammals, the circadian clock is mainly synchronized by the light-dark (LD) cycle, and regulates several physiological, behavioral and molecular rhythms like activity-rest, feeding, and gene expression. Food intake is regulated by a homeostatic and a hedonic mechanism. Hedonic food consumption has strong effects in the central reward system stimulating striatal dopaminergic signaling pathways. In addition, evidence suggests that the dopamine D2 receptor (DRD2) plays an especially important role in this regulation. In this work, we present evidence that motivation for food reward (normal pellets) varies dramatically with the LD cycle in young (4 months old) but not in old-aged (over 1.5 years old) C57BL/6 mice. This variation is consistent with a daily oscillation in the striatal DRD2 content, both at mRNA and protein level, in young mice under LD but not constant light (LL) conditions. This variation in motivational behavior was also assayed under constant dark (DD) conditions, in order to evaluate the possibility of an endogenous rhythmicity. Finally, the effect of the circadian clock on motivation was also studied by using a palatable reward (chocolate) under a protocol without food restriction. Taken together, our results of daily rhythms in motivation and dopamine signaling may contribute to improve treatment related to psychiatric disorders or drugs of abuse. This knowledge would also be of great importance in order to plan behavioral experiments in animal models.

Chronobiology

P130. Dietary Restriction Promotes Tissue-Specific Reprogramming of Circadian Gene Expression

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Abstract not available

Chronobiology

P131. Deregulation of Cell Cycle and Immune Response in a Mice Model of Tumor Development Under Circadian Desynchronization

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Circadian disruption by shift work and jet-lag has been established as a health hazard both in humans and animal models. The aim of this study was to analyze the tumor growth in mice under chronic jet lag (CJL, 6 hr advances of the LD cycle every 2 days), using a melanoma model induced by a subcutaneous injection of the murine B16 cell line. We found an increased tumor growth rate and a decreased latency in comparison with mice maintained in a LD12:12 cycles. We also observed that circadian disruption induced the loss of clock genes Bmal1 and Cry1 rhythmic expression as well as the cell-cycle genes Cyclin E and B1 in liver, together with about 6-hr delay of their maximum levels. In the tumor, both clock genes and cyclins did not show a rhythmic expression pattern, but the mean levels of clock genes were decreased while Cyclin A2 levels were increased under the CJL conditions. Circadian disruption also abolished the rhythmic pattern of the cell-cycle inhibitor p21 both in liver and in tumor. Finally, we analyzed the immune response in spleen and tumor, and found that the daily pattern in the percentage of M1 (anti-tumoral) and M2 (pro-tumoral) macrophages and in the levels of pro-inflammatory cytokine were modified under the CJL conditions. In summary, we observed an increased tumoral growth rate together with a circadian deregulation in the mRNA levels of the cell cycle related molecules and in the immune response both in the tumor and in the peripheral tissue.

Chronobiology

P132. Differential Thermoregulatory and Inflammatory Patterns in the Circadian Response to LPS-Induced Septic Shock

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Septic shock is a lethal condition caused by a pathogen-induced chain of events. The same dose of lipopolysaccharide (LPS) inducing septic shock in mice generates survival at the night (ZT19), while it is lethal at the end of the day (ZT11). A similar effect was observed with cytokine Tumor Necrosis Factor-α (TNF-α) administration. In this study, we aim to characterize the circadian response to high doses of LPS in mice. We found higher hypothermia in mice treated with LPS at ZT11, than those at ZT19. Both hypothalamic preoptic and paraventricular nucleus activation was significantly higher after LPS administration at ZT11 (vs. ZT19). When we injected naïve animals at ZT11 or ZT19, with the serum of animals inoculated with LPS at ZT11, we observed the same daily pattern in thermal response. Increased serum levels of TNF-α were found in mice injected at ZT11, whereas Tnf-α mRNA expression was higher in the liver of animals treated at ZT19. Moreover, mice that lack the receptor 1 for TNF-α showed a greater survival and a lower hypothermia compared to WT mice injected at ZT11. The same thermal response appeared in mice subjected to circadian desynchronization, but the survival percentage of both groups was similar to that challenged at ZT11 in standard light conditions. These results suggest a circadian dependency of the central thermoregulatory and peripheral inflammatory response to septic-shock, being TNF-α signaling likely related to this circadian response.

Chronobiology

P133. Circadian Study of Antioxidant Defense System in the Hippocampus of Aged Rats Subjected to Caloric Restriction

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Oxidative stress plays a critical role in brain aging. Caloric restriction (CR) is the most accepted approach to slow the aging process and delay many age-related diseases. Previously, we showed circadian rhythms in the expression and activity of antioxidant enzymes in the hippocampus of young rats that were abolished in the old animals. In the present work, we investigated temporal patterns of catalase (CAT) and glutathione peroxidase (GPx) expression and activity, as well as Nrf2 mRNA levels, in the hippocampus of aged rats under CR. Holtzman male rats were fed with a diet reduced by 40% in calories during the last 3 months prior to the 22 months of age. The mRNA levels were determined by RT-PCR and the enzymatic activity were evaluated by kinetics assays in hippocampi isolated every 4 hr during a 24-hr period. Interestingly, we observed CR restored the circadian rhythmicity of all the studied parameters (Chronosfit: $p < .05$). In addition, CR accentuated the rhythms of the amplitudes and the mesor of both CAT and GPx (*t* test: $p < .05$ and $p < .05$, respectively), and the Nrf2 mesor (*t* test: $p < .05$). CR restores the 24-hr patterns of antioxidant defenses in aged animals. Restoration of temporal coordination could be one of the basis of CR efficiency and provide promising prospects against neurodegenerative diseases and cognitive decline.

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Chronobiology

P134. Daily Rhythms of Aβ-Degrading Enzymes in the Rat Hippocampus. Effect of an i.c.v. Injection of Amyloid Beta Peptide (1-42) Aggregates

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One of the main pathological features in the Alzheimer disease (AD) is the presence of senile plaques, primarily composed of Aβ peptide aggregates, in cortex and hippocampus. AD late onset, which constitutes 90% of cases, could be mainly attributable to deficiencies in the clearance of the Aß peptide. The objective of this work was to investigate the effects of an i.c.v. injection of Aβ (1-42) aggregates on the 24-hr rhythms of Aβ-degrading enzymes as well as Aβ, BMAL1 and RORα protein levels, in the rat hippocampus. Four-month-old male Holtzman rats were divided into two groups defined as: control (CO) and Aβ-injected (Aβ). Rats were maintained under 12-hr light:12-hr dark conditions and received water and food *ad libitum*. Tissues samples were isolated every 6 hr during a 24-hr period. NEP, ECE, and IDE mRNA levels were determined by RT-PCR and Aβ, BMAL1, and RORα protein levels were analyzed by immunoblotting. Interestingly, we found that expression of Aβ-degrading enzymes varies on a daily basis in the hippocampus and that an i.c.v. injection of Aβ aggregates phase shifted daily NEP and IDE expression and increased the mesor of ECE rhythms, as well as clock proteins (BMAL1 and RORα) daily rhythms. According to these results, we could suggest that the changes in the temporal patterns of enzymes involved in the clearance of Aβ, would precede the increase in the Aβ peptide levels and the deterioration of the endogenous clock function, observed in the Alzheimer's disease.

Chronobiology

P135. Combination Treatment With PPARγ Agonist Pioglitazone and Retinoic Acid Modifies Daily Patterns of Apo E in the Temporal Cortex of an Experimental Model of Alzheimer Disease

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Abstract Withdrawn

Chronobiology

P136. Exploring the Contribution of Evening Cells to the Circadian Pacemaker of *Drosophila*

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Abstract not available

Chronobiology

P137. A GABAA Receptor in Circadian and Arousal Neurons Regulates Sleep in *Drosophila melanogaster*

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Sleep is a complex and vital behavior regulated by both homeostatic and circadian mechanisms. The neural circuits involved in sleep homeostasis are not well described yet. However, it has been previously proposed that GABAergic inputs to the large lateral ventral neurons (lLNvs) of *Drosophila* may be responsible of informing those highly integrative arousal neurons about the sleep homeostat status. On the other hand, the current paradigm proposes that the main circadian pacemaker of the *Drosophila* brain, the small lateral ventral neurons (sLNvs) have only minor influence in the control of sleep behavior. Starting from this point, our aim is to describe the mechanisms of GABAergic inhibition in both sLNvs and lLNvs, their influence on sleep behavior and their role on the sleep homeostat. For this, we have performed specific genetic manipulations and quantified sleep behavior under basal and sleep deprivation conditions. Moreover, we have collected preliminary electrophysiological recordings to identify the extent of the role of the neurotransmitter GABA in the neuronal circuit studied, given that our final goal is to describe this network in detail. Our findings confirm that the lLNvs receive information about the sleep homeostat status via the GABAA receptor Rdl through a complex neuronal circuit. They also suggest that the sLNvs are involved not only in the control of the circadian sleep timing but also, through GABAergic inputs, can regulate the quantity and quality of sleep.

Chronobiology

P138. Effects of Pioglitazone-Retinoic Acid on Daily Rhythms of Oxidative Stress Parameters in an Experimental Model of Alzheimer Disease

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Alzheimer's disease (AD) is the main cause of dementia in the elderly. The pathological hallmarks of AD include senile plaques of amyloid-β (Aβ) aggregates and neurofibrillary tangles in brain. Elevated levels of Aβ causes an increase in intracellular reactive oxygen species associated to a deficient antioxidant defense system. The objectives of this study were: first, to analyze the effect of an i.c.v. injection of Aβ (1-42) on the 24-hr rhythms of oxidative stress parameters in the rat prefrontal cortex (PC); second, to evaluate the effect of pioglitazone-retinoic acid (Pio-RA) on those temporal patterns. Four-month old males Holtzman rats were used in this study. Groups were defined as: (a) control, (b) Aβ-injected, and (c) Aβ-injected treated with Pio-RA. PC samples were isolated every 4 hr during a 24-hr period. Lipid peroxidation and protein carbonyls levels were determined by colorimetric assays and ELISA, respectively. CAT

and GPx enzymatic activities were determined by kinetic assays and Aβ, BMAL1 proteins levels by immunoblotting. We found that injection of Aβ(1-42) modified the daily rhythms of lipid peroxidation, protein carbonyls, CAT and GPx enzymatic activities, Aβ and BMAL1 protein levels in the rat PC. The treatment of Pio-RA reestablished rhythmicity of those temporal patterns. These findings might constitute, at least in part, molecular and biochemical basis of restoration of circadian rhythmicity by the administration of Pio-AR in neurodegenerative disorders.

Chronobiology

P139. Circadian Control of Lipid and Redox Metabolisms in Proliferative Cancer Cells

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The circadian system comprising oscillators present in organs, tissues, and even in individual cells temporally controls the body physiology. Circadian rhythm disruption may cause higher cancer risk, but little is known about clock function in tumor cells. For this, we evaluated the circadian, redox, and metabolic state in glioblastoma T98G cell cultures under different proliferating conditions. In arrested cells, we observed functional and rhythmic clock oscillations in mRNAs for clock- (CGs) and glycerophospholipid (GPL) enzyme genes, and redox state/peroxiredoxin oxidation cycles. By contrast, in proliferating cells, circadian rhythms of gene expression were affected whereas metabolic rhythms persisted; moreover, rhythms in ROS levels were altered when Bmal1 expression was knocked down. Thus, the metabolic clock operates in proliferative tumor cells regardless the molecular clock. Here, we extended these studies to the human hepatoma cell line HepG2, to evaluate if this is a general phenomenon. We assessed the molecular clock work and its link with the lipid metabolism in HepG2 cells under proliferation. We analyzed the expression and protein content of CGs, clock controlled genes (CCGs) and enzymes involved in the GPL biosynthesis. We also studied the endogenous content and individual level of GPLs and lipid droplet content (number, size, and variation over time) and we found an active time-dependent control of gene expression and metabolism in proliferating HepG2 cells.

Chronobiology

P140. Synchronization of the Circadian Network: A New Role for the BMP Signaling Pathway

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Abstract Withdrawn

Chronobiology

P141. Studying the Selective Vulnerability of *Drosophila melanogaster* Clock Neurons to Huntingtin polyQ Elongation

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One of the hallmarks of polyglutamine (polyQ) diseases is the selective vulnerability of different neurons, in spite of ubiquitous expression of the pathogenic protein. The reasons behind this specificity underlying neurodegeneration are still an unsolved mystery. It has been reported that the two circadian clusters of lateral ventral neurons (LNv) of *Drosophila melanogaster* respond differently to the elongation of the polyQ tract of the huntingtin (Htt) protein. It has been shown that while HttpolyQ protein functionally ablates the small LNvs (sLNvs) subgroup, the large LNvs (lLNV) remain unaltered. Our goal is to explore this differential response of LNvs to the HttpolyQ. In order to do this, we are studying morphological phenotypes and the consequences over the behaviors these neurons command. Our preliminary results regarding the morphology of the LNvs under the expression of HttpolyQ in young flies fit well with the published literature. We have found that, in spite of being expressed in both neuronal types, sLNvs present protein accumulations of HttpolyQ and lLNvs do not. However, in aged flies lLNvs also show HttpolyQ protein aggregation, both in the somas and on their projections. These results suggest that, although the reported differential sensibility between the two neuronal groups exists, lLNvs are not immune to HttpolyQ protein aggregation. We will also show preliminary data regarding the effects of HttpolyQ expression in LNvs on the control of sleep behavior.

Chronobiology

P142. A Methodological Advance in the Study of the Circadian Behavior of Oviposition in *Drosophila melanogaster*

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Biological clocks allow organisms to anticipate changes in the environment to achieve adequate adaptation. In *Drosophila* spp., the periodic behavior of egg-laying or oviposition is one of several physiological processes regulated in circadian fashion. However, this rhythmic behavior is one of the less studied rhythms, perhaps due to the difficulties involved in monitoring and recording it. For example, the collection and counting of eggs is usually done manually, making the experiments particularly demanding and labor-intensive. This motivates us to develop an automated device for monitoring oviposition behavior in *Drosophila melanogaster.* Our device allows the simultaneous analysis of 21 flies individually and can be operated by a single person. In addition, since the sampling interval is controlled automatically, it is possible to test different time intervals to determine which is the most suitable to measure this rhythmic behavior. With this device we can detect rhythmic and arrhythmic phenotypes, with percentages of rhythmicity and periods similar to those obtained with the previous methodologies used to monitor this behavior. In addition, the number of rhythmic flies over the total (for genotypes considered rhythmic) is similar between manual versus semi-automatic methodologies, which supports the fact that the differences between the methodologies do not affect the results. Therefore, we developed a novel device for the study of oviposition behavior.

Chronobiology

P143. Chronopharmacological Study of the Novel Drug 1A for Glioblastoma Treatment

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Glioblastoma has a 90% mortality rate and had have no therapeutical improvements in the last 30 years, so research for novel drugs becomes critical. The efficacy of several drugs is modulated by the circadian system leading us to hypothesize that a chronopharmacological approach would improve the efficacy of glioma treatment. Our purpose was to study the effects of the drugs 1A (a Rac1 inhibitor) and Temozolomide (TMZ; current treatment of choice) when applied at different circadian times to LN229 glioblastoma cells. Because two of the main roles of Rac1 are related to cell proliferation and migration, we studied the effects of 1A and TMZ over these processes when applied at different circadian times. We found that the effectivity of 1A is rhythmic, showing a minimum inhibition of proliferation and migration when applied at CT3 after a serum shock; and a maximum of inhibition of both processes when applied at CT19. In primary murine astrocytes, 1A was not toxic in neither of the circadian times. The preliminary *in vivo* studies consisted on treating nude mice with 1A or control at ZT3 or 12. We found that the median survival of the mice treated at ZT3 was 82 days and at ZT12 was 78 days, whereas animals treated with control had a median survival of 58 days. Our *in vitro* results suggest that effects of these drugs are modulated by the circadian system. The novel drug 1A could be a viable candidate for chronomodulated therapies in the future.

Chronobiology

P144. Temporal Control of Tumor Formation and Growth in Nocturnal Mammals: Impact of the Circadian System

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Circadian rhythm disruption as a modern life consequence (shiftwork, jetlag, etc.) may lead to metabolic disorders or higher cancer risk. Cancer cells display aberrant proliferation with a very active metabolism to facilitate tumor growth and metastasis. However, little is known about the circadian clock function on tumor growth regulation. Here, we investigate the day/night differences in the growth of peripheral tumors of sciatic nerve after the inoculation of A530 glioma

cells isolated from NPcis (Trp53+/−; Nf1+/−) heterozygous mice, a human neurofibromatosis type I model. In A530 cultures, mRNA of clock and clock-controlled genes, levels of ROS and susceptibility to Bortezomib chemotherapy exhibited temporal fluctuations. When A530 cells were injected into the sciatic nerve of C57BL/6 mice during the morning or the night of a 12:12 hr L/D cycle, tumors growing on animals injected during the night showed a higher rate of growth as compared with those injected at day. Day/night differences were also found after subcutaneous inoculation of melanoma B16 cells in mice at day or night with higher values observed in males of night group. Lastly, when we examined the role of the molecular clock activator Bmal1 in tumor growth, a higher rate of tumor growth was found when Bmal1 expression was diminished by CRISPR/Cas9 in A530 cells compared with controls. Our observations strongly suggest that the tumor growth is subject to temporal control and mainly dependent on the host state.

Cognition, Behavior, and Memory

P145. Low Nutritional State Impairs Novel Object Recognition Memory in *Drosophila*

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Abstract not available

Cognition, Behavior, and Memory

P146. Ethanol-Related Breathing Disruptions in Rat Pups During the Brain Growth Spurt Period

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Abstract not available

Cognition, Behavior, and Memory

P147. Unidirectional Optomotor Responses in Two Distant Families of Estuarine Crabs

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When a rotational movement of the visual panorama occurs, animals, from invertebrates to humans, tend to stabilize the movement through compensatory movements of the eyes, head, or the whole body. This is known as optomotor response. In particular, unidirectional optomotor responses occur when animals stimulated monocularly with a horizontal optic flow show a unique effective direction of motion. This phenomenon has been reported in various species from mammals to birds, reptiles, amphibious, and flies. In all vertebrate reported cases, the preferred direction is always from the uncovered eye toward the covered eye (back-to-front direction [BTF] of movement in the ipsilateral receptive field). In contrast, the few reports in invertebrates (flies) show that the progressive (front-to-back, FTB) direction of motion induces a stronger optomotor response than the regressive direction. Here, we present the results of behavioral experiments aimed at exploring optomotor responses in two semiterrestrial crab species belonging to distant families: the varunid crab Neohelice granulata and the fiddler crab (Ocypodidae) Uca uruguayensis. We used different conditions of stimulation (binocular, monocular) and directions of stimulation (FTB, BTF) to shade light on the underlying circuit commanding this behavior. Results indicate that the circuitry underlying OR in crabs is very similarly organized to the one present in flies.

Cognition, Behavior, and Memory

P148. Differential Activity of Striatal Cholinergic Interneurons in Context That Propitiate Decision-Making/ Strategy Selection

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Assimilation of novel strategies into a consolidated action repertoire is critical for behavioral adaptation. This includes processes like decision-making, planning actions, and selection of strategies that require complex cortico-basal ganglia processing. The striatum is the main input nucleus to this

subcortical loop, and its activity is tightly controlled by local interneurons. In this regard, striatum cholinergic interneurons (SCIN) play a causal role in regulating behavioral flexibility, including reversal learning and goal-directed versus habitual response selection. We have previously shown that SCIN are necessary to switch between solving-problem strategies in order to optimize cost benefit ratios. However, it has not been studied whether a differential activation of SCIN exists when animals are required to select between competitive spatial strategies. Here, we aimed to study activity levels of SCIN under different degrees of spatial novelty and decision-making demands. For that, we subjected C57BL/6 wt mice to two mazes with increasing decision-making requirements (Y maze and dual solution cross maze) and evaluated SCIN activation, measured as rpS6 expression levels by IHC. Mice exposed to contexts that require decision-making situations present lower levels of SCIN activation compared to control littermates exposed to non-decision conditions. This result suggests that SCIN modify their activity patterns in contexts that propitiate decision-making/strategy selection.

Cognition, Behavior, and Memory

P149. Stress-induced Fear Memory Generalization: c-Fos Analysis in Amygdala and Hippocampus

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Abstract not available

Cognition, Behavior, and Memory

P150. Everyday Metaphors—Functional Anatomy

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Metaphors are omnipresent in everyday language as idiomatic expressions (IE). These are specific to the country or region they originate. There are hundreds of IE in a widely spoken language as Spanish. Neural correlates for literal and nonliteral language differ between each other, however there are not studies using stimuli in Spanish. The aim is to investigate the functional anatomy of Spanish IE in healthy participants. Twenty normal subjects, right-handed (10 women), underwent a paradigm-related fMRI session in a 3T scanner. Literal sentences or IE were displayed every 4 s in an event-related design. Participants had to pick one of four possible meanings via a key press. 213 whole brain volumes were acquired and analyzed using SPM12, computing a BOLD contrast image for each subject and comparing, by *t* tests, IE versus figurative language, as well as female versus male processing. Extensive clusters were activated in left F3/ F2, bilateral T1/T2, supramarginal gyrus, left insula, and pars triangularis bilaterally. Brain activation in males was lateralized leftwards, while women activated similar areas in both hemispheres. Spanish IE processing requires simultaneous activation of several areas in both hemispheres, as other forms of nonliteral language. These findings agree with previous reports about the functional anatomy of pragmatic language. Biological differences in IE processing between sexes were found.

Cognition, Behavior, and Memory

P151. Asymmetry and Gray Matter Content of Frontoparietal Operculum in Adults

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Anatomical structures with bilateral symmetry are characterized by the repetition of characters on both sides of the sagittal plane. They usually exhibit morphological differences between left and right sides. The causes of these asymmetries include genetic, functional, and developmental factors. In the human brain, numerous asymmetries have been described, mainly in size, although other morphological aspects have been less studied. The aim of this study is to identify anatomical asymmetries, in relation to the number and presence of accessory sulci, of the frontoparietal operculum. This region is formed by the portions of the frontal and parietal lobes and contains various areas related to language. We analyze a sample of 47 T1 magnetic resonance

images of the brain of healthy individuals of both sexes between 18 and 41 years old. The frontoparietal operculum was identified in parasagittal sections in each hemisphere and the following variables were registered: number of furrows in the anterior and posterior portions of the lateral sulcus; presence of accessory sulci (triangular and diagonal); continuous or discontinuous pattern of the precentral inferior and inferior frontal sulci; and the shape of the tip of the lateral sulcus (oblique up/down or horizontal). These variables were correlated with the content of gray matter of the gyri surrounding the lateral sulcus. The results obtained will allow us to characterize the normal asymmetry of the frontoparietal operculum.

Cognition, Behavior, and Memory

P152. Withdrawn Abstract

Cognition, Behavior, and Memory

P153. Dopamine D2 Receptors of the Central Amygdala Regulate Unconditioned Fear in Mice

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Abstract not available

Cognition, Behavior, and Memory

P154. Effect of IGF-1 Gene Therapy on the Formation of a Contextual Fear Memory Trace

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Basolateral amygdala complex plays an essential role in the generation of an emotional state caused by an aversive experience. Insulin growth factor like I (IGF-I) could modulate hippocampal circuits modifying cognitive functions, and possibly, the molecular mechanisms involved in some psychopathologies related to traumatic memories. The main objectives are (a) to promote and evaluate the expression of a memory trace through IGF-I gene therapy and (b) to evaluate if structural plastic changes in dorsal hippocampus, are responsible for the expression of this memory trace. Adult male Wistar rats were bilaterally infused into BLA with RAd-DS-Red, as a control virus and RAd-IGF-I, as therapeutic virus. Seven days later we performed a weak fear conditioning protocol (WFCP). Freezing behavior (FB) was assessed as a measure of retrieval and memory retention. At Day 15, we performed hot plate test to evaluate sensitivity damage. Rats were perfused and the brain fixed for dendritic spine analysis. A significantly increase in FB in the RAd-IGF-I group was observed after 7 days and maintained for 14 days postinjection. There was not sensitivity damage in both groups. Preliminary results for dendritic spine analysis indicate no significant differences in spine density. IGF-I gene therapy induces a significant expression of FB in a WFCP, with a possible promotor effect on the formation of a fear memory trace which prompt us to further studies under this experimental model.

Cognition, Behavior, and Memory

P155. The Probiotic Bacillus Subtilis Ameliorates the Progression of Alzheimer's Disease in the Model Organism *Caenorhabditis elegans*

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Abstract not available

Cognition, Behavior, and Memory

P156. Behavioral Changes Induced by Striatal Interneurons Ablation

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Corticostriatal dysfunction is involved in Parkinson's disease and Tourette syndrome (TS), among other neuropsychiatric disorders. There are studies showing a reduced number of multiple striatal interneurons (SIs) types in the brain of TS patients. In a previous study where we induced a selective ablation of striatal cholinergic interneurons in the mouse, we observed perseverative behaviors reminiscent of those observed in TS and related disorders, but we did not observe tics. In order to reproduce more closely the striatal changes observed in TS, we aimed to perform a combined ablation of striatal cholinergic and GABAergic interneurons by directing the expression of the human diphtheria toxin receptor to neurons that express Nkx2.1 before differentiating into different types of SIs. By administering diphtheria toxin (DT) into the striatum we obtained a selective ablation of Nkx2.1 positive interneurons. Mice treated with extensive SIs ablations developed unwilling and abnormal movements, alterations of locomotion and posture, and usually died during the first week after DT injection. Mice with restricted SIs ablations showed unwilling movements that did not progress and are being studied with a battery of behavioral tests. Altogether our data suggest a putative mechanism for the involuntary movements observed in patients with "benign hereditary chorea" caused by mutations of the Nkx2.1 gene and that tics in TS may be caused by combined dysfunction of multiple SIs types.

Cognition, Behavior, and Memory

P157. Temporal Dynamic of the Hippocampal Structural Plasticity Associated to Contextual Fear Memory: Influence of the Destabilization/ Reconsolidation Process

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Increasing experimental evidence indicates that fear memory reactivation induces a transient plastic state that presumably activates the neuronal circuit involved in the encoding of the long term fear memory. Under certain circumstances, such reactivation allows the incorporation and integration of new information to the original memory trace. Here, we evaluated whether fear memory reactivation impacts on the dendritic spines remodeling in CA1 region of the dorsal hippocampus associated with the formation of the contextual fear memory. In the same way, we tested whether stress exposure affects such dendritic spine remodeling. Thus, stressed and control animals were fear conditioned and sacrificed 24 hr postconditioning (preretrieval), 60 min postretrieval or 24 hr postretrieval. A higher dendritic spines density, particularly mature ones, were observed after fear encoding and later reduced to basal levels 60 min after fear reactivation, returning to higher levels 24 hr postretrieval. This temporal dynamic structural plasticity was prevented by pharmacologically blocking the destabilization/reconsolidation process in the basolateral amygdala complex or by a single stress exposure just before fear memory conditioning. Thus, the destabilization/reconsolidation process was evidenced by a change in the hippocampal structural plasticity immediately following reactivation, a plausible necessary step for the integration of new information.

Cognition, Behavior, and Memory

P158. Central Hypothermic Effects of Ethanol and Acetaldehyde in Newborn Rats Regulated Through Associative Learning Processes

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Different effects of ethanol (EtOH) during early ontogeny are modulated by the central accumulation of acetaldehyde (ACD). Newborns are sensitive to the reinforcing effects of ACD as well as to its depressant effects upon respiration. Both phenomena, studied in older organisms, have been linked with thermoregulatory disruptions caused by ACD. In this study, EtOH (100 mg%) or ACD (0.52 μM) were intracisternally administered during postnatal days (PDs) 2 and 4. Control pups received no explicit treatment (Untreated, UT) or were centrally administered with buffer (PB). Pups experienced the drug effects when exposed to EtOH odor. At PD6, pups were administered with PB with the sole exception of the UT group. Body temperatures and ultrasound emissions (USVs) under the presence of EtOH odor were recorded. In newborns, USVs are elicited by stress-related events. During PD2, significant levels of hypothermia were observed in PB, EtOH, and ACD groups. At PD4, only ACD pups showed heightened hypothermia. At test, pups preexposed to ACD again showed hypothermia despite being administered with buffer; an effect suggestive of a conditioned thermal response elicited by stimuli previously associated with ACD. USVs were not affected by prior treatments. Yet, temperature decrements were negatively correlated with USVs. The results show that central ACD recruits poikilothermic alterations in newborns which are associated with stimuli that later elicit isodirectional conditioned responses.

Cognition, Behavior, and Memory

P159. Use of c-Fos for Neuronal Activity Detection in Amphibian Medial Pallium During an Extra-Maze Cue Spatial Navigation Task

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Abstract not available

Cognition, Behavior, and Memory

P160. Systemic Administrations of Naloxone Before Reward Downshift or Reward Omission

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Opioid circuit is part of the mechanisms of physical pain regulation but it could also be implicated in the regulation of psychological pain, the emotional state observed after surprising reward devaluation (successive negative contrast, SNC paradigm) or omission (extinction paradigm). Two experiments are presented using intraperitoneal administration of Naloxone (2 mg/kg), an opioid antagonist. In Experiment 1, Long Evans rats were trained in an instrumental SNC. Animals received 12 runway preshift sessions reinforced with 32 micropellets, and 10 postshift sessions reinforced with four pellets. Their runway performance was compared with animals that always received four micropellets. Animals could be assigned to a 32-4 or 4-4 condition and a Saline or Naloxone condition. Injections took place before postshift Sessions 1 and 2. Downshifted animals in the saline condition exhibited a runway performance impairment in postshift Sessions 5 and 6, and a quick recovery. Animals in the Naloxone condition also exhibited performance impairment but did not showed recovery. In Experiment 2, two groups of animals received 12 runway acquisition trials and 10 extinction trials. In extinction Trials 1 and 2, a Saline or Naloxone injection was administrated. Both groups differed only in extinction Trial 3, where Naloxone group exhibited an increase in runway latency.

Both experiments suggest that blocking opioid receptors increases the effect of surprising reward devaluation and omission.

Cognition, Behavior, and Memory

P161. Withdrawn Abstract

Cognition, Behavior, and Memory

P162. Interoceptive Associations in Addiction to Smoked Cocaine

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Contemporary neurocognitive models of drug addiction underscored the role of interoception. In these models, interoception is defined as the sensing and processing of body signals to serve a homeostatic function related to the onset and maintenance of addictive-behavior. In this work, we assess the relation between interoception and smoked cocaine dependence with a multimodal and multidimensional approach. We use the Hearbeat-detection (HBD) task and related Heart Evoked Potential (HEP) recordings at baseline (interoceptive accuracy) and during learning. We combined this behavioral and electrophysiological data with structural and functional connectivity analysis of the main interoceptive hubs. Smoked cocaine dependent subjects presented ongoing psychophysiological measures of enhanced interoception accuracy (HBD and HEP); accompanied by structural and FC tuning of interoceptive networks. Our findings support both specialized effects of smoked cocaine on interoception and also provide direct empirical evidence for drug models suggesting that hyper-interoception processing is a key aspect in addictions. Thus, multimodal assessment of interoception could serve as a potential domain to asses clinical and neurocognitive characterization of psychophysiological and underlaying neurophysiological adaptations in addiction.

Cognition, Behavior, and Memory

P163. Role of the Lateral Habenula in a Rewarded Contextual Dependent Task

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The lateral habénula (LHb) is a diencephalic nucleus that plays critical functions in cognitive process. Increased activity of LHb neurons correlates with aversive stimuli presentation, whereas stimulation of LHb promotes avoidance behaviors. Concordantly, LHb projects to areas that control motivation, such as the ventral tegmental area and the rostromedial tegmental nucleus. Rewards, either negative or positive, are always given in a context. Increasing evidence supports a functional relation between the LHb and the hippocampus, a brain structure relevant for coding contextual information. In this scenario, our main goal is to study how the LHb processes information, and ultimately, how it functionally interacts with the hippocampus when animals perform a rewarded contextual dependent task. We implemented an arduino/Bonsai based system to analyze the behavior of rats as they look for a reward in our heart shaped-maze task. This system allows us to optogenetically stimulate in a specific part of the maze. Our preliminary results indicate that stimulation of the LHb makes the animal avoid the place where stimulation has occurred, either evaluated in a real time preference task or in our maze.

Cognition, Behavior, and Memory

P164. Retrosplenial Cortex Integrity Is Required During Acquisition for its Participation in an Object-Recognition Memory

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Several studies demonstrated that the retrosplenial cortex (RSC) is involved in navigation and contextual memory. Recently, we found that the RSC is also required for the processing of an object-recognition memory. We inactivated this structure with muscimol infusions performed at different time points of that task and found that memory was impaired when the RSC was inactivated during consolidation or retrieval. In this case, animals did not explore preferentially the novel object. In contrast, inactivating the RSC during acquisition did not interfere with recognition memory and animals explored preferentially the novel object. Taking into account these results, we evaluated whether inactivating the RSC during acquisition interferes with its recruitment in memory processing. Animals were subjected to a double-inactivation of the RSC, in order to affect both acquisition and consolidation or both acquisition and retrieval. We predicted that the first injection would disengage the RSC from memory processing, thus leaving consolidation and retrieval intact, despite the second injection targeting them. Our results showed that this was indeed the case as double-injected animals exhibited intact recognition memory. We thus propose that the RSC is recruited to process the object-recognition memory, only if it is active during the acquisition of that memory. On the contrary, when the RSC is not active during acquisition, other brain structures may take control of memory processing.

Cognition, Behavior, and Memory

P165. Dissociating Reconsolidation and Extinction of Contextual Aversive Memory in Female Rats Using Midazolam Treatment and Reinstatement Paradigm: Influence of Reactivation Time Span

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Abstract not available

Cognition, Behavior, and Memory

P166. Injection With Kainic Acid in Mice Decrease the Performance in Novel Object Recognition and Patter Separation Task

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Abstract not available

Cognition, Behavior, and Memory

P167. Dopamine Modulation of mPFC Activity in the Control of Retrieval Induced Forgetting

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Abstract not available

Cognition, Behavior, and Memory

P168. Withdrawn Abstract

Cognition, Behavior, and Memory

P169. Long-term Spatial Memory Consolidation During Sleep Along Developmental Neuronal Circuits Maturation

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Sleep following encoding favors the formation of episodic long-term memory. In particular, slow wave sleep appears to support hippocampus-dependent declarative memory consolidation. It has been proposed that this process is supported by the phase-locking of three cortical rhythms: neocortical slow oscillations, thalamic spindles, and hippocampal sharp wave-ripples sustaining hippocampal-neocortical long-term storage. During postnatal development, oscillations emerge in the network along with allocentric spatial abilities and sensorimotor repertoire. We are interested in the study of oscillation phase-locking related to memory consolidation during sleep, coupled with allocentric spatial emergence during development. To address this, Long Evans rats were repeatedly trained in a spatial memory task (OPR) during several postnatal days. Our data suggest that animals acquire the task at around P32, after several repetitions. Moreover, we predict that interregional connectivity will be enhanced during that period, reflected in enhanced synchrony in thalamocortical networks during sleep. According to this, we will implant multichannel electrodes in the cortex, thalamus, and hippocampus (CA1) for LFP recording during sleep. We hypothesize that early spatial memory reinforcement following sleep may improve the oscillation phase-locking and in consequence long-term storage.

Cognition, Behavior, and Memory

P170. Analysis of Hippocampal-Prefrontal Cortex Interaction During Spatial Exploratory Behavior

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The ventral hippocampus (vHP) is connected to medial prefrontal cortex (mPFC) by a monosynaptic unidirectional projection that is known to be altered in psychiatric disorders such as schizophrenia. The vHP-mPFC connection is thought to provide contextual information to the mPFC, and it plays a key role in the modulation of emotional behaviors such as fear and anxiety. However, it is still unknown how the interaction between the vHP and mPFC may allow the acquisition of relevant contextual information and regulate exploratory behaviors. It is well established that prominent theta oscillations emerge in the hippocampus during environmental exploration, and this rhythm impacts on mPFC activity. Our ongoing project focuses to understand the role of the vHP-mPFC interaction in mice performing exploratory behaviors. We aim to record simultaneously from the mPFC and vHP in mice performing a battery of exploratory tasks with different degrees of cognitive loads. We will analyze the correlation between vHP and mPFC activity and the phase locking of mPFC spikes to the hippocampal theta rhythm. We expect to find an increase in the vHP-mPFC interaction during stages of exploratory tasks where a high level of contextual information integration is required. This augmented vHP-mPFC interaction will be evidenced as an increase in the number of synchronized prefrontal units to the hippocampal theta rhythm and in the strength of this synchronization.

Cognition, Behavior, and Memory

P171. Hide If You Can't Fly? Behavioral Plasticity and Action Selection in *Drosophila*

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Abstract not available

Cognition, Behavior, and Memory

P172. Sexual Dimorphism in Aging Mice: Effect of IGF-1 Gene Therapy on Motor and Cognitive Performance

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Previously, we reported some therapeutic benefits of IGF-1 gene therapy administered in aging female rats. Here, we assessed the effects of gene therapy in the quantification of frailty through a clinical assessment of aging mice. The concept of frailty, which is a state of increased vulnerability to adverse health outcomes for people of the same age, was developed to explain the heterogeneity in clinical outcomes for older patients, so in this study we compared the relationship between frailty index scores, treatment and sexes. We performed Clinical Frailty Index (© Susan E. Howlett, 2013) and a set of behavioral tests in C57BL/6 mice of 74 weeks. We divided the animals in three experimental groups for each sex and administered i.m. PBS, RAd-DS-Red, or RAd-IGF-1. After 21 days, we re-quantify FIs scores and measured locomotor activity, strength, and cognitive performance. We observed a reduction of FIs in both sexes in the group administered with IGF-1 compared with the PBS group. However, there were no significant differences in the scores between sexes. Moreover, IGF-I gene therapy induced a significant improvement in strength performance in males compared with PBS group and in females compared with RAd-DS-Red group. These preliminary results have important implications in the design of therapeutic approaches geared to identify basic mechanisms of cellular dysfunction in aging into meaningful treatment.

Cognition, Behavior, and Memory

P173. Effect of Short- and Long-term High-Fat Diet on Contextual Fear Memory

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Abstract not available

Cognition, Behavior, and Memory

P174. Dopaminergic Neurodegeneration and Neuroinflammation: Modulation by IGF-I Gene Therapy

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Insulin-like growth factor 1 (IGF-1) is emerging as a powerful neuroprotective molecule since most brain disorders are accompanied by IGF-1 deficiency and/or resistance. IGF-1 has a wide variety of functions and its study could provide the basis to prevent the deleterious effects of neurodegeneration. The aim of this study is to explore the effects of IGF-1 gene therapy on different experimental models of neurodegeneration and neuroinflammation. Under an experimental model of Parkinson's disease, hippocampal IGF-1 gene therapy has important effects on neuronal activity that could explain, in part, the improvement in working memory dysfunction that we observed after 20 days of neurodegeneration in rats injected with 6-OHDA. ICV IGF-1 gene therapy induced a restorative effect in the hypothalamus of senile rats with DA dysfunction, and a significant

improvement in motor performance in aged rats. Besides, in a clinical assessment of frailty in female and male mice, we observed cognitive and motor improvements in the groups injected with IGF-I. Neuroinflammation comprises glial cells activation and the release of pro-inflammatory molecules, which is a normal response oriented to protect neural tissue. With regard to this, IGF-1 gene delivery to astrocytes *in vitro* reduces their inflammatory response to lipopolysaccharide. Besides, IGF-1 exerts neuroprotective actions in a traumatic brain injury, which triggers the activation of glial cells in the cortex. Our results provide a support to develop new therapeutic approaches.

Cognition, Behavior, and Memory

P175. Lateral Habenula and Formation of Fear Conditioning Memory

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The Lateral Habenula (LHb) is a small brain structure that forms part of the epithalamus, which codifies negative motivational value and has been related to major depression. We have previously shown that LHb activity determines temporal stability of aversive memories. Fear Conditioning (FC) is a well-established paradigm of associative learning mediated by well described neuronal circuits. In order to get an insight of the mechanisms by which LHb modulates temporal stability of aversive memories, we decided to test its function in FC.In our experiment, we inactivated LHb by local infusion of muscimol before training rats in FC. One week later we tested fear memory to context or tone. We found LHb inactivation disrupts both context and tone FC memory. Our results suggest LHb plays a general role in aversive and fear learning.

Cognition, Behavior, and Memory

P176. Mood Disorders in Animal Models of Neuropathic Pain

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Chronic pain is a debilitating neurological condition of high clinical relevance. The treatments currently available show limited efficacy. The transition to chronic pain fundamentally remodels neuronal circuits in the brain regions that mediate pain perception. In particular, in the long term, it is associated with exaggerated activation of the limbic system and a highly prevalent occurrence of mood disorders such as anxiety and depression. Although this brain plasticity was initially considered to be an epiphenomenon secondary to altered nociceptive signaling in the spinal cord, studies in both patients and animals suggest that it may actively contribute to the development of chronic pain symptoms. In order to seek for a suitable animal model to study long-term pathological mechanisms in the limbic system during pain chronicity, we addressed the behavioral profiles of two mice models of neuropathic pain: chronic constriction injury and spared-nerve injury. We established a timeline of the persistence of nociceptive sensitization and the emergence of mood-disorders associated symptoms. We tested the mechanical allodynia of the injured paw (Von Frey test) and the expression of anxiety (open field, elevated plus maze), depression (grooming behavior, sucrose preference), and cognitive-related (y-maze) impairments. Our preliminary results show that nerve injury induces a late onset ($\sim$4 weeks) of mood disorders that persist even after the nociceptive sensitization is reverted.

Cognition, Behavior, and Memory

P177. Does a Short Nap Reinforce Reactivated Memories in Humans?

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Abstract not available

Cognition, Behavior, and Memory

P178. Familiar Face Recognition in the Primate Brain

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Abstract not available

Cognition, Behavior, and Memory

P179. The Lack of c-Abl Improve Behavioral Performance in an Animal Model of Alzheimer's Disease

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c-Abl is a nonreceptor tyrosine kinase that plays a role in neuronal development, neurogenesis and synaptic plasticity. Increasing evidence suggests that the c-Abl play a role in the pathogenesis of Alzheimer's disease (AD). Our laboratory has shown that c-Abl is activated in both *in vitro* and *in vivo* AD models, and its activation is involved in synaptic loss and long-term potentiation inhibition induced by Aβ oligomers. Also, treatment with Imatinib, a c-Abl inhibitor, reduces neuronal loss, Aβ deposition and cognitive impairments in an AD mouse models. In the present study, we assess the effect of the genetic ablation of c-Abl in a transgenic AD mouse (APP/PSEN1) on behavioral performance and functional connectivity. Here, we use a new transgenic strain of AD that has a brain-specific genetic deletion of c-Abl (APP/PSEN1/Abl-KO). We evaluated the cognitive performance through two different behavioral tests: Novel Object Recognition (NOR) and Object-Location Memory (OLM). Also, we evaluated the functional connectivity in the hippocampal-prefrontal cortex axis, to establish a relationship between behavior and neuronal activity. We found that APP/PSEN1/Abl-KO mice recovered the ability to discriminate in the OLM test. However, NOR test didn't show differences between groups. Also, our data suggest that functional connectivity might be recovered in APP/PSEN1/Abl-KO mice. The present study contributes to the understanding of how c-Abl is involved in the pathogenesis of AD. The NFκB alternative pathway is activated by antidepressant drug treatment

Cognition, Behavior, and Memory

P180. Novel Spatiotemporal Perturbations in a Finger-Tapping Task

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Abstract not available

Cognition, Behavior, and Memory

P181. "Limbo" State of Memory: Identification and Characterization of a New Retrieval-Dependent Memory Process in the Crab Neohelice Granulata

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In aversive Pavlovian conditioning, contingent presentation of a neutral stimulus (conditioned stimulus, CS) and a negative outcome (unconditioned stimulus, US) results in the formation of a CS-US fear memory. Thus, the presentation of the CS alone triggers a conditioned response (CR). Fear memory persistence could be differentially affected by retrieval. Brief CS exposures trigger memory reconsolidation and CR maintenance, whereas exposure to a high number of CSs triggers extinction and CR inhibition. Both reconsolidation and extinction have been characterized at the molecular level, presenting specific mechanisms for each

process in vertebrates and invertebrates. Here, we tested the hypothesis that intermediate CS exposure sessions fail to engage either fear memory reconsolidation or extinction in crabs. Our results show that, whereas 1 or 40 CS presentations rendered the fear memory sensitive to the amnestic agent cycloheximide, 80 CSs failed to do so and were insufficient to trigger memory extinction. These results indicate that intermediate CS presentations leave the original memory in an insensitive or "limbo" state, characterized by the absence of behavioral effect of the amnestic agent cycloheximide. Considering that "limbo" has been also reported in rodents and humans, our results strongly suggest that it is an evolutionary conserved retrieval-dependent mechanism whose fundamental condition is the arrest of the memory labilization process initiated by the first CSs.

Cognition, Behavior, and Memory

P182. Cholinergic-Prediction Error Signaling in Aversive Learning: Towards a Better Understanding of Prediction Error on Memory Reconsolidation Processes

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Abstract not available

Cognition, Behavior, and Memory

P183. The Interplay Between Behavioral Pattern Completion and Pattern Separation for Retrieval in a Cue-Degraded Context

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Abstract not available

Cognition, Behavior, and Memory

P184. Enriched Environment as an Effective Strategy to Reverse Hippocampal-Related Behavioral and Molecular Changes After an Early Chronic Noise Exposure

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Abstract not available

Cognition, Behavior, and Memory

P185. Novelty Improves or Impairs LTM Acting on the Behavioral Tagging Process During Reconsolidation

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Prevailing theories propose that upon retrieval memories may be updated through a reconsolidation process. However, despite that daily-life remembering rarely occurs disassociated of other experiences, little is known about the rules that bound the fate of memory reconsolidation under these conditions. During the last years, we contributed to this problem by showing that the reconsolidation of different memories is achieved through a behavioral tagging (BT) process. Now, using the spatial object recognition (SOR) task in rats, we show when and how experiences occurring close to memory reactivation positively or negatively affect the reconsolidation. We demonstrate that a 2-min reactivation session is able to add new information to the trace through a BT process specifically during memory reconsolidation. We also show that the exploration of a novel OF close to the reactivation can improve the original memory, and the memory of the newly incorporated information, by providing further PRPs. Interestingly, the same experience occurring immediately after memory reactivation, interferes with the tag inducing retrograde and anterograde amnesia. In addition, we provide evidence of specific mechanisms

associated to the setting of the tag and the synthesis of PRPs. In summary, our results show how experiences associated to a reconsolidation process improve or impair memories and their update, depending on their effect over the reconsolidation tag and the availability of PRPs.

Cognition, Behavior, and Memory

P186. Somatostatin Containing Interneurons of Dentate Gyrus Participate in Discrimination of Similar Contexts Pattern Separation Mechanism

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Pattern separation is the process that ensures that similar memories will be stored in different way. For this process is important to keep a low excitability of granule cells, a principal neuron of dentate gyrus (DG). To understand the mechanism of pattern separation, we studied in transgenics mice the physiological and behavioral effect of optogenetic inhibition of somatostatin containing interneurons of dentate gyrus (SOM). In electrophysiological experiments we found that inhibition of SOM produces an increase in the firing rate of units that have longer duration and higher burst index, two characteristics of excitatory neurons of DG, within which are the granule cells. In behavioral experiments, we found that inhibition of SOM in encoding phase of the test affect the discrimination of two similar contextual configurations. According with our results, we propose that pattern separation mechanism involve activation of SOM, while memories are being encoded, ensuring low excitability of granule cell. For other hand, loss of SOM (which happens in epileptic and aged mice) would implicate problems in pattern separation mechanism.

Cognition, Behavior, and Memory

P187. Prefrontal Cortex Serotonin Type 2a Receptor Activity Mediates Retroactive Interference During Consolidation Phase

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Abstract not available

Cognition, Behavior, and Memory

P188. The Role of NREM Sleep in Memory Reconsolidation

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Cognition, Behavior, and Memory

P189. Mossy Fiber Plasticity of Adult Born Dentate Granule Cells Take Weeks to Mature In Vivo

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New granule cells (GCs) of the hippocampus are constantly incorporated during mammalian adulthood. *Ex vivo* studies showed that four-week-old GCs (young) are transiently

hyper-plastic, excitable and poorly coupled to feedback inhibitory loops. In agreement with this notion, young cells show enhanced synaptic plasticity on their main output, pyramidal cells in the CA3 region, visualized upon induction of long term potentiation in anesthetized mice. Our aim is to investigate output properties of developing adult-born GCs under physiological conditions on free-moving mice. We hypothesized that young GCs would be more likely to activate CA3 network than old GCs. We implanted arrays of optotrodes in transgenic adult mice and stimulated new GCs expressing channelrhodopsin-2 at different frequencies and variable laser intensities to stimulate GC cohorts trough their development, while simultaneously recording CA3 activity. We found that young GC activation evoke scarce spiking events in single cell recordings and small local field potential responses in CA3. Both spiking and field potentials increase substantially as GCs become mature. Interestingly, frequency facilitation of the postsynaptic response appeared by the fifth week and increased consistently until reaching neuronal maturation. This prolonged process of mossy fiber maturation may offer critical windows of network plasticity, which might be a crucial network property contributed by adult neurogenesis.

Cognition, Behavior, and Memory

P190. Thalamo-Cortical Information Transfer During Memory Expression

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In addition to bottom-up signaling, auditory cortex (ACx) receives top-down input involved in cognitive processes like memory and attention. Afferents carrying such feed-back information from higher-order areas preferentially target neocortical layer 1 (L1) where they may provide depolarization to the distal dendrites of lower layer pyramidal neurons or recruit local interneurons. One strong projection derives from higher-order thalamic nuclei (MGm/PIN). However its function as well as how it affects cortical processing remains unexplored. Using Calretinin (CR) as a marker for MGm/PIN combined with *in vivo* 2-photon calcium imaging, electrophysiology, optogenetics and auditory fear conditioning, we find that thalamic input to ACx contributes to encoding of stimuli that acquire behavioral relevance through associative learning. Associative learning induces plasticity of sound responses in the majority of individual thalamic synaptic boutons in L1 of ACx, which correlates with the strength of the memory trace. These signals are received by excitatory and inhibitory neurons across cortical layers and can in turn be locally modulated by presynaptic inhibition from defined L1 interneurons. Our results thus reveal that MGm/PIN afferents convey information on behavioral relevance to ACx, which can recruit dendritic signaling as well as inhibitory and disinhibitory circuits.

Cognition, Behavior, and Memory

P191. The Impact of Early Life Family Structure on Parental Care Behavior and Offspring Anxiety Response in C57BL/6 Mice

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Social attachment plays an important role in progeny development. Different social experiences during lactation and throughout life can affect offspring behavior. We aimed to analyze if mono- or biparental parenting, in C57BL/6 mice, may have a differential impact on adolescent behavior and on the parental care behavior during lactation. Mice were reared in a monoparental (MP, only mother) or biparental (BP, cohabitation of father-mother since copulation) condition until weaning (postnatal day, PD, 21). Litters from both parenting conditions were filmed during PDs 6, 9, and 12, and an ethogram was made taking into account the nest occupancy and the activity of the parents. At PDs 34 to 37 adolescent animals were evaluated in a modified version of the concentric square field. This test allows simultaneous measurement of different behavioral patterns. The observation of parental care behavior during lactation indicated that mothers MP spent less time in the nest, left the nest alone more time and displayed more self-directed behaviors than mothers BP. BP condition displayed more pup-directed behavior than MP. Analysis of adolescent behavior, indicated that MP subjects displayed more anxiogenic-like behaviors than BP mice. In conclusion, it seems that parenting by mother only implies that pups are more time unattended that, in turn increases anxiety responses during adolescence. Further research is being conducted aimed to analyze the neurobiology corresponding of this phenomenon.

Cognition, Behavior, and Memory

P192. Inhibition of Alpha 7 Nicotinic Receptors in the Prefrontal Cortex Impairs Cocaine-Induced Conditioned Place Preference

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Nicotinic acetylcholine receptors (nAChRs) in the prefrontal cortex (PFC) have critical roles in cognitive function including attention and memory and are key players in plasticity processes. Cocaine administration has been shown to induce plastic changes in PFC. However, whether nAChRs in the PFC are required for cocaine-associated memories and the underlying molecular mechanisms are still unknown. Conditioning place preference (CPP) is an animal model in which rats learn to associate the rewarding effects of a drug of abuse with the environmental context in which it is received. Here, we used behavioral pharmacology to assess the effect of intra-PFC methyllycaconitine, a specific antagonist of the α7 subtype of nAChRs, on the acquisition of cocaine-induced CPP in adult rats. We found that pharmacologic inhibition of α7 nAChRs in the PFC before conditioning impaired a 4-trial cocaine-induced CPP without altering acute locomotor response. We are now exploring the expression of molecular substrates for cocaine-associated memory on the mesolimbic circuit to shed light on signaling pathways related to our behavioral findings. In conclusion, our results suggest that α7 nAChRs in the PFC participate in the acquisition of cocaine CPP. Considering that drug seeking often depends on the association between drug-paired cues and the rewarding effects of the drug, α7 nAChRs in PFC could be considered as potential targets for the prevention of addictive behaviors.

Cognition, Behavior, and Memory

P193. Memory Retrieval at the Crossroads of mTORC1 Pathway and AMPA Receptors

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Recently we found that mTORC1 activity close in time to memory retrieval is required for normal expression of aversive and nonaversive long-term memories. Here we used inhibitory-avoidance task to evaluate the potential mechanisms by which mTORC1 signaling pathway participates in memory retrieval. As mTORC1 is necessary during consolidation to increase levels of GluA1-containing AMPA receptors (AMPAR) at the synapse, we assessed if a similar mechanism accounts for memory retrieval. Intrahippocampal infusion of GluA1 antisense but not GluA1 missense oligonucleotides 3 hr before testing impaired memory retention. The same result was observed upon delivery of GluA2 antisense oligonucleotides 3 hr before test, thus showing the necessity of GluA1 and GluA2 AMPAR subunits for memory retrieval. We next studied the role of GluA-subunit trafficking during memory recall and its relationship with mTORC1 pathway. We performed intrahippocampal infusion of GluA23ϒ, a peptide that selectively interferes with the endocytosis of GluA2-containing AMPAR, 30 min before rapamycin infusion, which inhibits mTORC1 signaling pathway. We found that GluA23ϒ prevented memory impairment caused by mTORC1 inactivation. Our work indicates that *de novo* GluA1 and GluA2 AMPAR subunits are required for memory retrieval and suggests that mTORC1 regulates AMPAR trafficking during retrieval.

Cognition, Behavior, and Memory

P194. Memory Reconsolidation Interference of an Implicit Aversive Memory in Humans

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Abstract not available

Cognition, Behavior, and Memory

P195. Positive Emotional Induction Interferes With the Reconsolidation of Negative Sad Autobiographical Memories, in Women Only

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Abstract not available

Cognition, Behavior, and Memory

P196. Analysis of Striatal Neural Activity During an Exploration/Exploitation Task in a Virtual Environment

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The correct balance between exploration of new territories and exploitation of known resources is key for an organism's survival. Studies suggest that the dorsomedial striatum is involved in decision-making and action selection. Our aim is to analyze the activity of striatal single units while head-fixed mice perform a virtual exploration/exploitation task. The task consists of a virtual linear track with short rewarded zones followed by longer unrewarded corridors. Mice are implanted with tetrodes and a metal plaque that is used for atraumatic head restraint. Mice run on a cylinder and the virtual environment is presented on two monitors in front of them. Running speed is detected using an optical mouse, and is used to control the speed at which animals navigate the virtual environment. Upon arrival to a rewarded zone, mice need to lick a spout a certain number of times to obtain a drop of water. Our results reveal that mice are able to learn the task in hand by running through the corridors towards the rewarded area and licking there to obtain a reward. As sessions progress, the animals' behavior becomes more organized restricting their licks to the rewarded zones. Our results also reveal a change in neuronal activity -by increases or decreases of firing rate- related to relevant events of the task such as entrance and exit from the rewarded areas or reward delivery. We also found a correlation between striatal firing rate and animals' speed.

Cognition, Behavior, and Memory

P197. Neuropeptide F and Mushroom Body Neurons Acutely Control Food-Seeking Behavior in Adult Fruit Flies

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How motivational drives shift from novelty-seeking behavior (NSB) to food-seeking behavior (FSB) is unclear. We recently have adapted the novel object recognition behavioral test to fruit flies. In this assay we found that fed flies show preference for novelty, whereas fasting impaired recognition memory, but not habituation or olfactory conditioning memory. We hypothesized that in hungry flies, hunger but not novelty drives the behavior. To analyze the relationship between NSB and FSB we began by developing a behavioral assay to examine and quantify FSB in the context of object recognition. Here we show that neuropeptide F and mushroom body (MB) neurons, but not insulin-like peptide release, acutely control FSB in adult fruit flies. First, we set the conditions where fasted flies strongly prefer an object loaded with food compared with an empty object. Then we examined the requirement of different neuronal components in FSB. Acute thermogenetic inhibition of the synaptic output of NPF neurons by Shits1 completely abolishes FSB in

fasted flies, in agreement with previous reports. In addition, acute thermogenetic inhibition of the synaptic output of all MB neurons also abolished FSB in fasted flies. More interesting, the inhibition of the synaptic output of all MB neurons in flies fed ad libitum promotes FSB, indicating that MB neurons constitutively inhibit FSB in fed flies. Ongoing experiments explore the role of NPF and MB neurons in NSB in fasted flies.

Cognition, Behavior, and Memory

P198. Acute Physical Activity Could Improve Spatial Pattern Separation in Humans

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To allow similar episodes to be distinguished in memory, the brain must form distinct representations of events. This process is called "pattern separation" and recently our group has shown that the brain-derived neurotrophic factor (BDNF) could be part of an essential mechanism underlying the consolidation of pattern-separated memories. Likewise, under conditions of physical activity, high levels of this factor have been reported, both in rodents and in humans. We specifically designed a task to assess spatial pattern separation in humans in a virtual reality environment, which consisted on testing the long-term memory of the position of two flags separated by different angles. The preliminary results of this study show that acute physical activity (25 min of fixed bicycle) could improve performance in this task using a small angle. It is a translational proposal that can certainly have an impact on the knowledge of the biological bases of human cognition and mental health.

Cognition, Behavior, and Memory

P199. Social Interaction and Memory are affected by Chronic Administration of Fluoxetine in 5-HT2AR Knockout Mice

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Fluoxetine (FLX) is a selective serotonin reuptake inhibitor (SSRI), well known for its antidepressant effects and for being widely prescribed in the treatment of different psychiatric disorders. Since the SSRI blockades the serotonin (5-HT) reuptake, the final effect of this drug is to increase the 5-HT permanence in the synaptic space. The Serotonin type 2A receptor (5-HT2AR) is one of the most expressed receptors in the postsynapses of the serotoninergic system. This receptor has been linked with the cognitive symptoms presented in some psychiatric disorders. Then, we intended to analyze if chronic administration of FLX presented cognitive effects and the possible role of 5-HT2AR in those effects. For this purpose, we administrated a chronic oral dose of fluoxetine (10 mg/kg) to Wild Type (WT) and 5-HT2AR knockout mice (KO). After 4 weeks of FLX administration, we performed a novel object recognition task and a social interaction test. The results showed that a 3 min training session is not enough to generate a long term NOR memory (24 hr delayed) independently of the genotype. Interestingly, FLX treatment allowed WT mice to solve the NOR test. However, we didn't see this effect in KO mice. Regarding social interaction, FLX improved the performance of the WT mice but not the KO. These results suggest that 5HT2A signaling might be involve in the effects of fluoxetine in memory and social interaction in mice.

Cognition, Behavior, and Memory

P200. Memory Deficits in Transgenic McGill-R-Thy1-APP Hemizygous Rats

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McGill-R-Thy1-APP Wistar transgenic (Tg) rats, with human APP under the Thy1.2 promoter, bearing the Swedish and Indiana mutations corresponding to familial AD in homozygous condition, had been reported to show significant cognition deficits at 3 months of age. On the other hand, hemizygous Tg rats show a more subtle phenotype. In this work, 6- and 13-month-old hemizygous Tg males and their WT litter mates rats were individually left to freely explore an open field (OF) for 5 min and tested at 24 hr; the numbers of crosses in the floor were recorded. There were no differences between WT and Tg groups during the training and the number of crosses significantly decreased in the test compared with training. Rats were then trained in an inhibitory avoidance task (IA) of a mild electric foot shock and tested at 24 hr to evaluate long-term memory (LTM). Latency to go across a door to get into a dark compartment where the rat will get the shock, was recorded. There were no significant differences in training latencies between animal groups. 24 hr later, test latencies were significantly higher than training latencies for WT rats, while there were no significant differences for Tg rats. Therefore, both Tg and WT rats are able to habituate to the OF, keeping LTM; on the other hand, WT animals learned and remembered the IA at 24 hr, while the Tg were not able to remember it, evidencing deficits in these sort of associative memory involving aversive and spatial components.

Cognition, Behavior, and Memory

P201. Reinforcing What Is Good: Appetitive Memory Strengthening Through Reconsolidation in the Crab Neohelice Granulata

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Information stored in the memories allows organisms to predict future events based on previous experiences. Thus it must persist even in the absence of the indicators used at the time of acquisition, and might be susceptible to changes in the environment. In this sense, the reconsolidation process opens the possibility to update memory in both strength and content. A recent work performed in rats has shown that brief memory reactivations events lead to memory enhancement as a result of reconsolidation, suggesting memory strengthening. However, this function has not been demonstrated in appetitive paradigms. In this study we were interested in addressing if an appetitive memory could be strengthened by this process in the crab Neohelice granulata. Animals received appetitive training and were re-exposed to the training context 24 hr later. Given the assumption that reconsolidation processes strengthen the original trace, the resulting memory should be more robust and less sensitive to the amnesic agent cicloheximide when administered minutes before reactivation. Preliminary results revealed that a single re-exposure to the training context triggers the reconsolidation process, and as a result, we observe memory enhancement. Future experiments will allow us to address the mechanisms of this modulation, such as if this strengthening as a consequence of reconsolidation implies plastic changes on the trace which can be revealed through neural correlates or epigenetic change.

Cognition, Behavior, and Memory

P202. Effect of Postnatal Mynocicline Treatment on a Two-Hit Model of Autism in Female Mice

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Autism spectrum disorders (ASD) are characterized by reduced sociability, diminished communicative skills and repetitive behaviors. Notably, the proportion between boys and girls diagnosed with ASD is 4:1 approx. This suggests a higher susceptibility in boys to develop ASD, or resilience in girls. To identify the biological mechanisms underlying this bias, we used a mouse model of ASD: the prenatal exposure to valproic acid (VPA). Remarkably, this model also presents a different phenotype in males and females, as females do not show the reduction in sociability observed in adult males. One important risk factor in ASD is immune system dysregulation. In fact, we found that prenatal exposure to VPA leads to alterations in microglia and astrocytes in females between postnatal day (PD) 21 and 35. Using a two-hit model, which consists in prenatal VPA exposure and a chronic treatment with LPS between PD 21 and 35, we found that female mice express a reduction in sociability. This evidence suggests that immune alterations during this postnatal period are critical to develop social alterations and may overcome the sex-dependent resilience. Minocycline is an antibiotic that crosses the blood–brain barrier and acts by reducing the microgliosis. We hypothesized that Minocycline

administration during the critical period mentioned above can revert the behavioral alterations observed in our two-hit model.

Cognition, Behavior, and Memory

P203. Layers IV and V Pyramidal Neurons of A29 Are Required for Disambiguate Emotionally Relevant Contexts

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Retrosplenial cortex (RSC) is divided in two anatomically distinct subregions: A29 and A30, but the functional role of each subunit in cognitive processing remains elusive. Systemic application of MK801 causes elimination of pyramidal neurons in layers IV and Va of A29 (A29MK801 neurons), without affecting A30 or other brain areas. Previously, we showed that selective loss of A29MK801 neurons did not affect freezing behavior but significantly impairs A30-activation and the retrieval of contextual fear memory (CFM). To dissect the functional role of A29MK801 neurons in CFM first we used open field and elevated plus maze tests and found that loss of A29MK801 neurons have no anxiolytic effect, suggesting these neurons are not required for risk assessment during CFM. Elimination of A29MK801 neurons did not impair contextual recognition as assessed by object in place tests or by an A-B-A design of contextual fear test. However, elimination of A29MK801 neurons completely abolishes retrieval of fear memory associated to preconditioned stimuli in higher-order conditioning. However, in a higher-order conditioning paradigm elimination of A29MK801neurons completely abolishes retrieval of fear memory associated to preconditioned stimuli. Altogether, our data suggest that A29MK801 neurons are critically required for the retrieval of complex contextual association memories with emotional relevance likely by impairing the activation of A30.

Cognition, Behavior, and Memory

P204. Role of Hippocampal Remapping in Contextual Memory

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The Hippocampus (HP) plays a central role in the encoding, consolidation and retrieval of episodic memories. Some hippocampal neurons, called place cells (PC), fire whenever an animal is at a certain location in the environment; however, only a subset of the PC fire in any given environment. When the environment changes, PC can change their activity (remapping). Accumulating evidence has suggested that the functions of PC, extend well beyond a specific role in mapping the physical space. It has been suggested that the hippocampal ability of storing and distinguishing between different situations and contexts, can be related with place cell's remapping.

Several studies have shown how the CA3, a hippocampal region, can either remap or not as consequence of the changes in contextual clues. Still, there is no study showing how this change in neural activity correlates with the behavioral response. In other words, It's still unknown whether when an animal recognizes a certain context as new, there is remapping in the activity of CA3 or not. The ongoing project takes advantage of a behavioral test that allowed us to discriminate if an animal recognizes a context as new, or as one they already knows. We carried out electrophysiological recordings in CA3 region of the HP while they were performing the task in order to correlate the remapping and the evocation of different contexts.

Cognition, Behavior, and Memory

P205. Ethanol-Induced Locomotion and Intake After Environmental Enrichment in the Offspring of Rats Selected for High or Low Ethanol Intake at Adolescence

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Animal models of genetic risk for alcohol use disorders include rat lines selected for high or low-ethanol consumption during adulthood or, as developed in our lab, during adolescence. The latter is the developmental stage in which the onset and escalation of ethanol intake takes place. Recent work suggested that environmental enrichment (EE) could reduce the problematic use of ethanol and other substances of abuse, although others indicated that EE could exacerbate ethanol intake when applied during adolescence. We assessed the effect of environmental enrichment rearing during adolescence upon ethanol-induced locomotion and intake, in two lines of rats, derived from mating "HIGH" or "LOW" ethanol-drinking F2 parents. From postnatal day 21 (DP 21) to 42, the animals—males and females—were reared under EE or standard conditions (SC). Ethanol-induced locomotion was evaluated

acutely and after nine administrations of ethanol (Experiment 1), and voluntary ethanol intake was measured across 3 weeks (Experiment 2). Ethanol-induced locomotion was lower in EE than in SC rats, regardless line (HIGH or LOW). After repeated administrations of the drug, this effect was observed only in male HIGH rats. In experiment 2, ethanol intake was significantly greater in HIGH versus LOW rats and, within females, in EE versus SC rats. These results are consistent with previous studies indicating that EE may have deleterious effects upon ethanol intake, when applied during adolescence.

Cognition, Behavior, and Memory

P206. Vocal Effort Modulates the Motor Planning

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Speech requires programming the sequence of vocal gestures that produce the sounds of words. Here we explored the timing of this program by asking our participants to pronounce, as quickly as possible, a sequence of consonant-consonant-vowel (CCV) structures appearing on screen. We measured the delay between visual presentation and voice onset. In the case of plosive consonants, produced by sharp and well defined movements of the vocal tract, we found that delays are positively correlated with the duration of the transition between consonants. We then used a battery of statistical tests and mathematical vocal models to show that delays reflect the motor planning of CCVs and transitions are proxy indicators of the vocal effort needed to produce them. These results support that the effort required to produce the sequence of movements of a vocal gesture modulates the onset of the motor plan.

Cognition, Behavior, and Memory

P207. Improvement of Declarative Memories in Older Adults Through the Reconsolidation Process

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Abstract not available

Cognition, Behavior, and Memory

P208. Spaced Learning and the Mechanisms That Optimize Memory Formation

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The superiority of spaced learning over the massed one is a fundamental fact in the formation of long-term memories (LTM). We studied the cellular processes and the temporal demands of this phenomenon, using weak spatial object recognition (wSOR) and weak inhibitory avoidance (wIA) learning tasks. We observed SOR-LTM promotion when two identical wSOR, which individually induced short-term memories but did not form LTM, were spaced by an inter trial interval (ITI) ranged between 15 min to 4 hr. The promoting effect was dependent on hippocampal protein synthesis and MAPKs activity. Also, two identical wIA training sessions spaced by 4 hr, promoted IA-LTM. In contrast, when we combined one wIA with a wSOR, neither of the two tasks formed LTMs. We discuss these results under the "behavioral tagging" hypothesis which postulate the existence of a tag induced by learning that utilize proteins to form LTM. We suggest that the neural contacts stimulated by the first training session are re-tagged by retraining. Moreover, after retraining, the intracellular mechanisms triggered by both sessions could be added, reaching the threshold for protein synthesis required for memory

consolidation. On the other hand, when animals are trained in two different and weak tasks, the processes triggered by them would not meet the spatial requirements necessary to form LTM.

Cognition, Behavior, and Memory

P209. Early Ethanol Intoxication Alters Enzymatic Catalase Activity and Generates Associative Respiratory Learning

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Ethanol (EtOH) during early ontogeny severely affects brain development, learning, memory and breathing plasticity. The catalase (CAT) system is the main metabolic pathway of EtOH oxidation to acetaldehyde in the brain; a metabolite that regulates different EtOH effects. We assessed whether EtOH experience may induce a differential activation of CAT while also evaluating respiratory plasticity. At postnatal days (PDs) 3, 5, and 7 Wistar rats were administrated via cisterna magna with EtOH (300 mg%) or phosphate buffer (PB) in association (Paired) or not (Unpaired) with EtOH odor (conditioned stimulus, CS). At PD9 all pups were administrated with PB and breathing frequencies were recorded by plethysmography under normoxia and hypoxia conditions with or without the CS. Pups later consumed a 5.5% EtOH solution and their brains were removed for determination of CAT activity. The intake test also provides exposure to the odor of the drug. When exposed to the CS, Paired-pups failed to hyperventilate during hypoxia; an effect that suggests a negative outcome of prior learning processes. A significant increase of CAT activity was observed in pups preexposed to central EtOH and this activation was more pronounced in Paired-pups. It appears that EtOH-related associative learning interferes with the capability of the organism to cope with the respiratory demands of a hypoxic event. Prior EtOH exposure was also found to cause an enzymatic induction of CAT modulated by a new toxic episode.

Cognition, Behavior, and Memory

P210. Effect of Systemic Administration of mGlu3R Agonist in a Model of Cerebral Ischemia

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Chronic cerebral hypoperfusion (CCH) resembles central changes in aging-related vascular dementias and Alzheimer's disease (AD). Our group has demonstrated, *in vitro*, that astroglial subtype 3 metabotropic glutamate receptors (mGlu3R) present protective actions against neurotoxic agents including Aβ. However, contradictory results were reported when mGlu3R ligands were administered *in vivo*. We examined the effect of the mGlu3R agonist, LY376298 (LY) 1 mg/kg i.p., in middle aged rats with CCH. Memory retention was evaluated using the aversive radial maze and NeuN and GFAP expression were determined by immunohistochemistry. All groups showed increased latency and number of reference memory after surgery ($p < .05$), while CCH+LY treatment aggravated it. We observed a decrease, although not significant, in NeuN expression in the hippocampus of the CCH+LY group compared to CCH. Moreover, GFAP expression showed an increase in CCH+LY hippocampus compared to CCH and sham groups. To conclude, our results suggest that the *in vivo* administration of a mGlu3R agonist potentiates the cognitive deficit in the CCH model, probably by inducing the activation of astrocytes and, consequently, decreasing neuronal survival.

Cognition, Behavior, and Memory

P211. Role of Sleep in the Organization of the Spatial Map During Episodic Memory Formation

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The development in the study of place cells discovered by O'Keefe (1971) has put the focus on the study of spatial representation of the environment in the processes and functions lead by the hippocampus. Among these functions, the hippocampus plays a preponderant role in the establishment of spatial memory, in which sleep is fundamental, suggesting a possible relationship between sleep and the establishment of spatial representations by place cells. In this line, there is a query if sleep participates in the consolidation and configuration of spatial representations. In this study we will evaluate the influence of sleep on the variations in the configuration of a spatial map given by changes in spatial context. Specifically, we will analyze the features of place cells recorded in hippocampal CA1 in terms of firing rate, place field location and spatial information during object in place recognition (OPR) test in conditions of Sleep or Sleep deprivation in the postlearning phase. Here we will present our preliminary results showing that postlearning sleep enhances performance in the OPR task and that this effect is related to specific changes in the patterns of configurations of the spatial representation leaded by place cells. The study of sleep's influence on spatial representations given by place cells in the hippocampus will allow us to understand the importance of this process in the performance of a cognitive function such as memory.

Reference

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Cognition, Behavior, and Memory

P212. Dorsal Hippocampal κ2 Opioid Receptors Activation Negatively Modulates Contextual Fear Memory Consolidation in Rats

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The κ opioid receptors (κORs) subtypes (κ1ORs and κ2ORs) are expressed in brain regions involved in fear memory consolidation, including the dorsal hippocampus (DH). The present study sought to investigate the contribution of DH κORs subtypes to contextual fear memory consolidation. Male Wistar rats were fear conditioned to context A (three shocks 1.0 mA, 3 s) and then received an intra-DH bilateral infusion of vehicle (VEH), a κ1OR agonist U-69593 (0.1, 0.3, 1.0 or 30.0 nmol) or a κ2OR agonist GR 89696 (0.1, 0.3, or 1.0 nmol/hemisphere). Tests sessions were performed on Days 1 and 8 after conditioning session (Tests A1 and A2, respectively). Freezing behavior was measured as an index of memory retention. Finally, animals had the DH dissected 90 min after fear conditioning and drugs infusion to BDNF analyzes by ELISA. In experiment 1, infusion of GR 89696 0.3 and 1.0 nmol immediately after conditioning session decreased the freezing time in both Tests A1 and A2 when compared with respective VEH groups (Test A1: VEH $= 80 \pm 4$, GR 89696 0.3 $= 51 \pm 6$ and GR 89696 1.0 $= 50 \pm 4$%; Test A2: VEH $= 74 \pm 3$, GR 89696 0.3 $= 40 \pm 7$ and GR 89696 1.0 $= 38 \pm 3$%). In experiment 2, U-69593 infusion had no effect on freezing time. Finally, in experiment 3, GR 89696 0.3 nmol decreased BDNF levels in DH (VEH $= 116 \pm 13$ vs. GR 89696 0.3 $= 65 \pm 11$ pg/mg of protein). Present results suggest that DH κ2ORs activation negatively modulates contextual fear memory consolidation, possibly via BDNF reduction.

Cognition, Behavior, and Memory

P213. Calrretinin+ Neurons Partially Compensate the Loss of Calbindin+ Neurons Caused by Perinatal Asphyxia in the Rat's Striatum

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The striatum is particularly vulnerable to perinatal asphyxia (PA). The main neuronal populations of the striatum are GABAergic median spiny neurons. A high portion of them also co-express calbindin (CB). At delivery time GABA has excitatory properties and excitotoxicity process could be mediated via GABAergic networks in case of pathological events. In previews works we found that PA generate a loss of calbindin neurons (around 50%) followed by an increase in other GABAergic subpopulations. The aim of the present work is to analyze the effect of PA over subpopulations of GABAergic neurons in the striatum and to assess the deep hypothermia therapeutic outcome. The uterus was removed by caesarean section and the fetuses

were exposed to hypoxia by immersion in water (19 min) at 37°C (PA). The hypothermic group was exposed to 10°C during 30 min after PA. Four experimental groups of three to four rats were formed. The immunolabeling of CB, Calretinin, Neun, and reelin was measured in adult rats by a skilled observer blind to treatment. Reelin+ cells that usually co-express Calretinin, showed no stain in the striatum besides subventricular zone. The PA group showed a significant decrease in CB+ neurons and a paradoxical increase in neurons estimated by Neun stain. Moreover, a specific subpopulation of GABaergic Calretinin + cells showed an increase caused by PA. Deep hypothermia reversed most of these alterations most likely by protecting calbindin neurons. The mechanism involved in this compensation is not clear. It is possible that Neun and Calretinin + cells filled the space left by Calbindin neurons. As well, an active mechanism to keep the homeostasis at excitation-inhibition balance is also plausible. Deep hypothermia could be a superlative option to reduce severe disability generated by the PA.

Cognition, Behavior, and Memory

P214. Effect of Attention on the Synchronization in a Paced Finger Tapping Task

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In the present work, we investigate the effects of attention and sensory feedback on synchronization to an auditory metronome where the subject must resynchronize after a tempo change. In most of these experiments subjects do not receive any specific indication about what to focus their attention to. We believe that this constitutes a source of uncontrolled variability that significantly affects performance in the task. Here, a group of subjects performs a paced finger tapping task without receiving any specific instruction about what they should focus their attention to (nonforced attention). A second, different group of subjects performs the task that forces them to focus their attention to the tempo change (forced attention). Both groups, in addition, perform the task in two conditions: with and without auditory feedback. We found that the group that tapped in the forced-attention condition showed a lower average asynchrony and a higher autocorrelation of the inter-tap intervals with respect to the group that tapped in the nonforced attention condition. Furthermore, the addition of feedback decreased the average asynchrony regardless of the attention condition. No significant effects of feedback or attention on resynchronization speed were found. These results suggest that the attentional factor has an effect on synchronization at least in the isochronous phase and that it must be taken into account in the experimental design.

Computational Neuroscience

P215. An Optimized Method to Acquire Single Cell Activity for Online Analysis of Screening Sessions in Humans

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The first requirement for the study of concept cells in the human medial temporal lobe is the finding of the stimuli eliciting responses from the neurons being recorded. To this end, a screening procedure is used, where a large set of stimuli is presented, and the recorded data is analyzed offline. During the analysis time, neurons might disappear from the recording, resulting in the loss of the responses that would be used in the upcoming experimental paradigms. Using the cbMEX interface of Blackrock Microsystems, we are able to employ the computational power of the acquisition system for a coarse spike detection and clustering, which is enough to determine whether or not a stimulus can elicit a response from a certain neuron. The strength of the response for each stimulus is automatically quantified, so the best ones can be selected for further tasks. In addition, this procedure allows us to initially present a larger number of stimuli in the same period of time (improving the chances of finding those related to a concept cell) and the possibility of stopping the screening after a few minutes once a certain amount of responses has been clearly found.

Computational Neuroscience

P216. Robotic Vehicles as a Tool to Study the Neural Basis of Locomotor Activity

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We used a robotic vehicle to study the neural basis of locomotor activity in the nematode *Caenorhabditis elegans*. Using a robot has a specific advantage over a biological model, since it is possible to access and have control over all the ingredients that governs its behavior. At the same time, it also allows for the implementation of a complex system that is subject in a natural way to the laws of physics in its interaction with a real environment. In particular, we implemented a numerical simulation of the neural system of the nematode *C. elegans* in a robotic vehicle. The environmental information is obtained by using a distance sensor that transmits information directly to sensory neurons, and locomotor activity is controlled by electric motors that are connected and receive information from the corresponding muscle output. We found that, as was observed experimentally in the *C. elegans* brain by Kato et al. (*Cell* 163, 656–669, 2015), a large proportion of the simulated neurons across the brain share information by engaging in coordinated, dynamical network activity. Also, as in the experiments by Kato et al., the simulation evolves on a smooth cyclical dynamics, where different segments, that correspond to the activities of different neuronal sub-populations, can be mapped to represent action sequences of the robot. Our results show the robustness of the brain dynamics of *C. elegans*, and also how robotics can contribute to the understanding of the neural basis of locomotor activity.

Reference

Kato, S., Kaplan, H. S., Schrödel, T., Skora, S., Lindsay, T. H., Yemini, E., Lockery, S., & Zimmer, M. (2015). Global brain dynamics embed the motor command sequence of Caenorhabditis elegans. *Cell*, *163*(3), 656–669.

Computational Neuroscience

P217. Mindfull Learning: Meditative State Classifier Using Random Forest

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Abstract not available

Computational Neuroscience

P218. Commonalities in Whole-Brain Functional Connectivity Associated With the Psychedelic State Determined Using Machine Learning Techniques Applied to fMRI Experiments

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Classic psychedelics (5-HT2A agonists) elicit profound transient modifications in the consciousness of the self and the environment. Other substances that modulate the level and quality of conscious content and are of potential therapeutic value are entactogen psychedelics such as MDMA and the dissociative ketamine (NMDA antagonist). Despite variability in the elicited subjective effects, these drugs share as a common motif the induction of a nonordinary or altered state of consciousness. We search for the commonalities and divergences between the changes in whole-brain activity elicited by two classic psychedelics: LSD & psilocybin; MDMA, ketamine and a control nonpsychedelic drug: Modafinil (dopaminergic stimulant). fMRI data acquired from different scanners was processed according to a unified standard. Then we computed the functional connectivity between all pairs of 90 neuroanatomical regions and trained a random forest classifier to identify them from their associated placebo condition. We investigated whether a classifier trained using data from one drug could generalize to detect the changes in brain activity associated with all other drugs, and mapped in anatomical space the network of functional connections associated with the successful generalization. Our results suggest that the shared effects of psychedelics can be quantitatively measured using fMRI, bringing us closer to dissect the varieties of the psychedelic state and their associated neural correlates.

Computational Neuroscience

P219. Metabolites Restriction and Connectivity Performance of Astrocytes Networks

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Within brain tissue, astrocytes (AST) represent by far the most abundant cell lineage. It has become widely accepted that AST are anything but the glue of the Central Nervous System and are associated, among others, with cognitive functions, information flow and processing, metabolic regulation and even the pathogenesis of certain neurodegenerative diseases. AST establish a very interesting cellular arrangement through specific and narrow junctions, GAP junctions, allowing a coordinated and dynamic function as a network. The present work explores how metabolite availability modulates connectivity levels of AST network combining a physiological approach with a biophysical one. Network connectivity was assessed in AST primary cultures by measuring fluorescence recovery after bleaching (FRAP technique) either in a medium with high glucose or a non-glucose one. In addition, we have designed a numerical model that mimics various dynamic aspects of AST networks. The model is a bidimensional cellular automaton where the first and second neighbor interaction has been set up in such a way that different hypotheses regarding the flow of information could be tested.

Computational Neuroscience

P220. Testing the Usability of a Cognitive Training Software for Measuring Executive Functions in Unsupervised Educational Interventions

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Mate Marote is an open source cognitive-training software aimed at children between 4 and 8 years old. It consists of a set of computerized games specifically tailored to train executive functions (EF): a class of processes critical for purposeful, goal-directed behavior, including working memory, planning, flexibility, and cognitive control. In previous studies, we showed that (a) less than 7 hr of training elicited transfer to some (but not all) facets of EF, (b) the academic performance of children living at risk was boosted by the intervention, and (c) the quality of play and behavioral patterns during the training phase in unsupervised interventions are comparable to the data collected in one-to-one supervised designs. In the present study we assessed whether the software can be used for measuring EF in unsupervised interventions. We show that children performance in the EF tests obtained in unsupervised, but controlled, school environments with their own teacher are comparable to the data collected in the testing phase of supervised designs, as expected. In this unsupervised experiment, the gameflow, the instructions, and the feedback were entirely provided by the software and their own teachers only had to ensure the correct login of each children. Our study suggests that testing the results of large scale educational interventions could be simple, under minimal, but appropriate, controlled conditions.

Motor Systems

P221. Testing Neural Models for Birdsong Production and Perception

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Songbirds are a well-established animal model to study the biomechanics and the neural circuits involved in vocal learning and production. The telencephalic nucleus HVC (proper name) is characterized by having selective neurons to the song of each bird. When the bird is asleep or anesthetized and a recording of its own song is reproduced, the neurons respond with a specific firing pattern, similar to the one generated during song production. Currently, there is a controversy over the neuronal coding of HVC. One view suggests that HVC encodes every detail of the song. It is proposed that the behavior is encoded by a firing chain in HVC. An alternative model suggests that song production occurs in a distributed manner along several nuclei of the song system and that HVC activity is related to specific motor instances. In this work we developed an extracellular neuronal registration system that allows the simultaneous acquisition of up to 64 recording channels, using commercial multi-electrodes (Neuronexus Tech. Inc). With this system we performed selectivity experiments in zebra finches (Taeniopygia guttata) to study the neural coding of HVC and, in particular, the scope of the two proposed models.

Motor Systems

P222. Effect of GABAergic Receptor Activity on Glutamate Release During Excitotoxic Damage in Mouse Spinal Cord Injury Model

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Acute spinal cord injury induces loss of motor, sensory, and autonomic functions through a process involving a primary injury and a secondary phase during which massive glutamate release occurs. This phenomenon implies dysregulation of the excitatory and inhibitory network balance. The present study on mouse organotypic spinal slices analyzed how pharmacological manipulation of GABA receptors might affect real-time glutamate release following 1 hr kainate application. We used a glutamate biosensor placed in the ventral horn area and monitored neuronal survival later. Furthermore, we studied if L-amino-4-phosphonobutyrate (L-AP4; 1 μM) could inhibit glutamate release. Glutamate release evoked by kainate was significantly reduced by the allosteric GABA modulator midazolam (10 nM) or the agonist THIP (10 μM), leading to neuroprotection. On the contrary, higher release was induced by bicuculline (20 μM), while no effect was observed with gabazine (20 μM). L-AP4, an agonist of group III mGluRs, largely depressed glutamate release and protected neurons. These findings indicate that pharmacological depression of glutamate release via enhancement of GABA receptor activity or inhibition of presynaptic release with mGluR activation were effective tools to counteract excitotoxic death in spinal networks. In view of the THIP activity, the present data imply a significant role for extrasynaptic GABA receptors in sparing spinal cord neurons from injury.

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Motor Systems

P223. Integration of Visual and Auditory Information in a Decision-Making Neuron

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One fundamental task of the nervous system is to make adaptive behavioral decisions based on multiple sources of sensory information. In this context, multimodal integration is the process by which different sensory components of an event are combined to form a single percept. Multimodal integration increases the probability of detecting a relevant event, especially when individual cues are weak or ambiguous. In fish, the circuit responsible for initiating the escape response is centered on the paired Mauthner cells (M-cell). These neurons are sensory integrators that receive both visual and auditory inputs and upon reaching firing threshold trigger the escape response. This relatively simple circuit provides a unique opportunity to dissect the mechanisms of multimodal integration at neuronal level. We performed *in vivo* intracellular recordings in M-cells of goldfish while the animals were stimulated with auditory or visual signals. Auditory signals were produced by a loudspeaker while visual signals consisted on trains of electrical stimulation of the optic tectum. We recorded M-cell responses to either unimodal stimuli or multimodal combinations of auditory and visual stimuli. Our results show that multimodal stimuli produce an enhancement of the M-cell response partly dependent of the delay between the auditory and visual stimuli. This underlines the importance of the temporal

coherence of individual components of a multimodal signal to be effectively integrated.

Motor Systems

P224. Subcellular Localization of Kv1.3 and Kv1.1 Potassium Channel Subunits in Striatal Cholinergic Interneurons of Mouse Models of Experimental Parkinsonism and L-DOPA-Induced Dyskinesia

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Parkinson's disease (PD) characterizes by a degeneration of mesencephalic dopaminergic neurons that innervate the striatum, a key nucleus for the selection of motor programs. In advanced stages of the disease only L-DOPA as a dopamine-replacement strategy allows an adequate performance in daily activities. However, the effectiveness of L-DOPA decreases and abnormal movements emerge (dyskinesia). Striatal cholinergic interneurons (SCIN) are key modulators of striatal circuits and are hyperexcitable in animal models of PD, owing to dysfunction of voltage-dependent potassium channels containing Kv1.3 and Kv1.1 subunits which is not due to a decrease in Kv1.3 protein expression. Enhanced SCIN activity was also linked to L-DOPA-induced dyskinesia (LID). Here, we address whether SCIN dysfunction in mouse models of PD (unilateral lesion of the medial forebrain bundle with 6-OHDA) and LID is associated with an impaired trafficking of Kv1 channel subunits to the plasma membrane. We use genetically modified mice that express a fluorescent membrane marker (channelrhodopsin-EYFP fusion protein) in SCIN (ChAT-Cre;LSL-ChR2-EYFP) and analyze the distribution of the Kv1.3 and Kv1.1 subunits in the plasma membrane and intracellular compartments of SCIN, using immunohistochemistry. Preliminary results show that the fraction of Kv1.3 and Kv1.1 immunolabeling localized to the plasma membrane of SCIN in parkinsonian and dyskinetic mice did not differ from what was observed in unlesioned mice.

Neural Circuit Physiology

P225. Effects of Static Magnetic Fields on Cortical Activity in a Rat Model of Epilepsy

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Epilepsy is one of the most common chronic neurological disorder. It is characterized by recurrent and spontaneous epileptic seizures caused by neuronal hyperexcitability. Currently, there is a demand for new clinical approaches to treat this disorder that do not respond to available pharmacological treatments. In that sense, Static Magnetic Field (SMF) reduces cortical activity in both, human and animal models. The aim of this work was to study the effect of SMF on epileptic cortical excitability. EEG was continuously recorded in eight anaesthetized rats, in which epilepsy was induced by the lithium-pilocarpine model. Rats were anaesthetized to get a stable slow wave activity showing up and down states. Animals were classified as "magnetic" (a NdFeB magnet was placed over the skull before pilocarpine injection), or "control" (a replica without magnetic properties was used). Between 15 and 30 min after a second injection of pilocarpine, EEG changes compatibles with epileptic seizures were clearly observable in the control animals: Down states duration was reduced and the power at 1-4 and 4-8Hz band was increased. Similar effects were visible in those animals with the real magnet but 1 to 2 hr later, indicating that SMF was able to slow down the appearance of abnormal cortical activity. These results reinforce the view that SMF is able to modulate cortical activity and open the door to future therapeutic use of SMF in epilepsy as a complement to current pharmacological treatments.

Neural Circuit Physiology

P226. Temporal Mapping of Adult-Born Granule Cells Integration in Two Major Local Inhibitory Populations of the Hippocampus

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Adult neurogenesis provides a continuous pool of new granule cells (GCs) that participate in information processing in the dentate gyrus of the hippocampus. We studied how GCs become integrated toward maturation into the preexisting circuit of the adult mouse dentate gyrus. We chose two major population of GABAergic interneurons (INs) of the hippocampus: Parvalbumin expressing cells (PV) and Somatostatin expressing cells (SST). We combined optogenetics and acute slice electrophysiology to activate PV or SST and GCs, retrovirally labeled, at different stages of maturation and studied their connectivity in both directions, interneuron to GCs and vice versa. We built a temporal map of synaptogenesis for each IN population and observed that connectivity between PV and GCs (input and output) reached maturation when GCs were >6 weeks old. For SST, the inhibitory postsynaptic current increased gradually with GCs development, while the GC output connectivity developed much later (>11 weeks) compared to PV. We found that PV synapses onto GCs were located perisomatically and contributed to both feedforward and feedback inhibitory loops within the granule cell layer. In contrast, SST contacted GCs in proximal and distal dendrites and contributed only to feedback inhibition. These data demonstrates that integration of new GCs within the preexistent dentate GABAergic network is specific of each IN population and that adult neurogenesis promotes a long-term plasticity for circuit remodeling.

Neural Circuit Physiology

P227. Network Dynamics of Nociceptive and Aversive Processing in the Anterior Cingulate Cortex

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The Anterior Cingulate Cortex (ACC) plays a central role in the evaluation of the affective aspects of pain and accumulating evidence indicates that the hyperactivity of the ACC is involved in the manifestation of the emotional distress that characterizes chronic pain (CP) conditions. However, little is known on how the functional organization of ACC microcircuits is affected during CP.Here we addressed how neuronal ensembles of the ACC process nociceptive information and how this microcircuit organization is affected in a mice model of neuropathic pain (NP). Using *in vivo* recording of spiking activity we have identified a subpopulation of neurons that are activated in response to noxious stimuli and show a preferential increase in spontaneous activity during NP. To gain insight on the organization of ACC "nociceptive" neuronal ensembles, we have monitored the activity of the same network of neurons on subsequent days during the transition to NP with two-photon calcium imaging. Our preliminary results show that noxious stimuli are codified by the activity of a discrete and partially stable assembly of ACC neurons. Interestingly, these neurons are also activated by other aversive but not noxious stimuli, suggesting that the representation of aversive events in ACC neuronal ensembles is not specific for nociception. Finally, we observed that this fine-tuned representation is degraded during NP resulting in a wide-spread neuronal representation of noxious events.

Neural Circuit Physiology

P228. What Happens in the Brain During Epileptogenesis? Analysis of Single-Unit Activity During Rapid Kindling

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Epilepsy is the fourth most common neurological disorder affecting people of all ages. This is why knowing what changes in the brain during epileptogenesis is of great

importance. The most widely accepted experimental model for mesial temporal lobe epilepsy is Kindling. Hippocampal Rapid Kindling (hRK) is a faster model that provides fully klindled animals in a shorter period of time, which is useful to get stable recordings of single-unit activity (SUA). Male Wistar rats were implanted with a bipolar macroelectrode in the CA1 region of right ventral hippocampus, through which they were kindled, and eight microwires were placed in the CA1 region of right dorsal hippocampus (rdH). SUA was recorded continuously during hRK protocol and analyzed during basal and ictal activity of rdH. Quantifying the neuron firing rate (FR) we found different patterns of SUA during epileptic seizures. Some neurons increase (nI) and others decrease (nD) their FR regarding their basal period, while many units did not change it (nNC). A tendency to increase ($p = .14$) and decrease ($p = .09$) the FR during the progression of hRK has been seen in nI and nD groups, respectively. Moreover, the nNC group did not show any tendency but a marked stability during the progression of hRK ($p = .93$). We also found an increase in the duration of seizures through the epileptogenesis progress ($p < .05$). Further SUA analysis may lead us to understand how these patterns are involved in epileptogenic networks.

Neural Circuit Physiology

P229. Neuronal Activity of the Dorsal Striatum Involved in the Timely Execution of Actions

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Corticostriatal circuits are involved in the selection and execution of sequences of movements in order to maximize the profit derived from them. With the aim of studying how actions are triggered at the right time in a self-initiated rewarded task, we used tetrodes to record the striatal activity. Briefly, after a minimum inter-trial interval (ITI), water-deprived rats must enter a nosepoke and, following a visual cue, emit an eight-licks sequence onto a tube to receive water. First, we found a modulation of the striatal activity that peaks right before the beginning of the trials. This activity is related to the waiting time and it differs between timely and premature nosepoke entries. Interestingly, such activity profile was also observed when the ITI was duplicated. In a third series of experiments, subjects had to enter the nosepoke in a restricted time window: if they entered prematurely or late, they received no reward. In this version of the task we found that the anticipatory activity was maximum when the animal entered the nosepoke within the rewarded time window. Considering that subjects must estimate the right time to perform a sequence of actions to obtain the reward, we hypothesize that this anticipatory neuronal activity codes for the reward expectancy associated to the time chosen for the initiation of the learned action and it is involved in its timely execution.

Neural Circuit Physiology

P230. Cholinergic Modulation Reorganizes Dentate Gyrus Microcircuits

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Neurogenesis in the adulthood continuously provides the dentate gyrus (DG) of the mouse hippocampus with pools of new granule cells (GCs) that integrate into the network. When afferent inputs arrive to the DG, immature neurons (4 weeks old-4wpiGC) respond with higher excitability, lower specificity, and a different ability to decode temporal information than mature GCs (matGC). These differences in processing are due to a difference in inhibitory circuits that mostly restrict matGC. In this work, we evaluated how the neuromodulator acetylcholine affects the processing of inputs in both matGC and 4wpiGC. Using pharmacologic and optogenetic tools combined with electrophysiological recordings, we observed that, upon cholinergic activation, matGCs increase their responses to afferent stimuli, whereas no changes were seen for 4wpiGC. At the synaptic level, we observed a reduction in the inhibitory component of the response, which was more prominent for matGC. This produced an increase in the excitation to inhibition balance that explains the differential activity pattern. Furthermore, upon a high-frequency stimulation protocol that is normally insufficient to produce potentiation, we could induce LTP if we pared it with optogenetic activation of cholinergic axons. We conclude that acetycholine can provide a temporal window of reduced inhibition in which the information processing and plasticity rules of GCs change, possibly adapting the encoding to the behavioral demands.

Neural Circuit Physiology

P231. Modulation of Piriform Cortex Neuronal Activity by Inputs From Basolateral Amygdala and Lateral Entorhinal Cortex

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Piriform cortex is the main region of the olfactory cortex where olfactory information is encoded. It receives sensory afferences from the olfactory bulb but also from other higher order brain regions such as the entorhinal cortex and the amygdala. Here, we study how the basolateral amygdala (BLA) and the lateral entorhinal cortex (LEC) are functionally connected to the posterior piriform cortex (pPC). We infected the BLA and the LEC with adeno-associated virus expressing channel rhodopsin (ChR2-AAV) under CamKIIa or parvalbumin promoters to activate either excitatory or inhibitory neurons, respectively. We recorded postsynaptic currents and spiking in different principal neurons of the pPC in response to photostimulation. We found that both excitatory and inhibitory long-range projections coming from the BLA synapse preferentially onto pyramidal neurons of the deep layers of pPC and do not contact semilunar neurons. Moreover, we discover that inputs from both BLA and LEC can modulate the spiking activity of pPC neurons evoked by electric stimulation of the afferent pathway. Deciphering the interaction between sensory "bottom-up" and "top-down" projections from higher brain areas will shed light on the understanding of how the brain could adaptively shape sensory cortical activity according to behavioral needs.

Neural Circuit Physiology

P232. Characterization of Beta Oscillation in the Primary Motor Cortex After Nigrostriatal Degeneration and During L-DOPA-Induced Dyskinesias in a Rodent Model of Parkinson's Disease

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Prolonged treatment with L-Dopa in Parkinson's disease (PD) often leads to the emergence of abnormal involuntary movements known as L-Dopa-induced dyskinesias (LIDs). Little is known about the oscillatory activity associated with LIDs, particularly in the motor cortex. On the other hand, recent studies have shown that motor symptoms of parkinsonian state correlate with the exacerbation of oscillations in the beta range (15–35 Hz) although the mechanisms which originate this activity remain unknown. Here, we sought to identify such alterations by recording local field potentials (LFPs) and single-unit activity in primary motor cortex of hemiparkinsonian mice before and after an L-DOPA treatment to induce LIDs, by means of high-density electrodes. We analyzed the oscillatory activity in the beta range and how the different cortical neuronal populations were related to this rhythm. We found that animals with lesion of nigrostriatal dopaminergic system present an increase in the number of beta events, with greater duration and power compared to sham animals. There is also a significant decrease in the firing rate prior to the beginning of beta events and a better entrainment of neuronal activity by the LFP around the middle of the events. After the L-DOPA priming, we found a similar but less pronounced pattern in LIDs "off" periods. Instead, during LIDs, there is a generalized decrease in cortical beta activity, with a reduction in the number of events, its duration, and power.

Neural Circuit Physiology

P233. The Onset of Sodium Appetite: Role of Oxitocinergic and Serotonergic Central Systems

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A temporal dissociation exists between sodium depletion (SD) and the appearance of sodium appetite (SA) 20 hr later; thus, an inhibitory modulation was postulated. Our previous studies demonstrated an inhibitory involvement of serotonergic (5HT) and oxytocinergic (OT) neurons on SA regulation. Our aim was to evaluate gene expression changes of different components of central OT and 5HT systems, during the delay of SA appearance after SD. Wistar rats were SD using furosemide combined with low-sodium diet, and 2 hr or 24 hr later the rats were decapitated. Specific brain areas: dorsal raphe nucleus

(DRN), subfornical organ (SFO), lateral parabrachial (LPBN), and anteroventral area of third ventricle plus supraoptic nucleus (AV3V+SON), were submitted to RT-PCR of oxytocin receptor (OTR), serotonin 2A receptor (5HT2A), tryptophan hydroxylase 2 (TPH2) and serotonin transporter (SERT). OTR mRNA expression significantly increased ($p = .045$) early at 2 hr after SD in the AV3V+SON in comparison to control and 24 hr-SD groups. In the DRN, the OTR mRNA expression followed the same tendency increasing 2 hr after SD and decreasing 24 hr later, in comparison to control and 2 hr SD groups; however, these differences did not reach significant levels ($p = .06$). Non-significant changes in the SERT and TPH2 mRNA expression were found in the DRN and the 5HT2A mRNA expression in the LPBN and SFO. In sum, our results suggest that OT circuits acting in nuclei previously involved in SA regulation may modulate SA appearance.

Neural Circuit Physiology

P234. Modulatory Effects of Histamine on Medial Prefrontal Cortical Neurons

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Histamine, in addition to its role as cytokine in the immune system, is an essential neuromodulator of wakefulness control. Studies show that it plays a selective role in attention, suggesting an action of histamine in brain areas involved in this cognitive process. To date, very little work has examined the cellular mechanisms by which histamine exerts this action. In this study, we examined the action of histamine in slices of the mouse medial prefrontal cortex, an area directly involved in attention control. In particular, we studied the effects of histamine on a population of neurons, parvalbumin (PV) GABAergic interneurons, involved in this function by whole-cell patch clamp recordings. Our results show that histamine selectively increases N-methyl-D-aspartate glutamatergic responses in PV neurons. On pyramidal cells, the main neuronal type in mPFC, the effect is more variable. Our recordings also show that the discharge pattern of PV interneurons is increased by HA with a frequency corresponding to a gamma rhythm. Histamine also induces a significant increase in the frequency of spontaneous synaptic excitatory activity in the PV interneurons. In addition, extracellular recordings show an increase in firing rate at theta frequency by histamine. These results suggest that histamine exerts an excitatory action on PV neurons of the prefrontal cortex that are selectively involved in attention processes.

Neural Circuit Physiology

P235. Multisensory Stimuli Encoding in the Hippocampus During a Non-Spatial Goal-Directed Task

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Abstract not available

Neurochemistry and Neuropharmacology

P236. Stress and Vulnerability to Develop Cocaine Self-Administration: Restoration of Glutamate Homeostasis in Nucleus Accumbens Core by Minocycline

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Abstract not available

Neurochemistry and Neuropharmacology

P237. Alcohol Neurotoxicity Effect in Spatial Memory. Omega 3 as a Protective Factor

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Abstract not available

Neurochemistry and Neuropharmacology

P238-Phosphorylation of Intracellular Tyrosines Modulates the Ionotropic Function of the α7 Nicotinic Receptor

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α7 is expressed in the brain and contributes to cognition, attention, and memory. It contains an extracellular domain with the agonist-binding sites; a transmembrane domain, which forms the ion pore; and an intracellular domain (ICD), which contains sites for modulation and intracellular signaling. The mechanisms by which the cell can regulate the ionotropic function of α7 remain unknown. We explored how intracellular phosphorylation affects α7 activity by patch clamp recordings in HEK cells expressing α7. Wild-type α7 channel activity elicited by ACh appears as brief isolated openings and as activation episodes containing a few brief openings in quick succession (bursts). Preincubation of cells expressing α7 with the inhibitor of Src family kinases (PP2) increased significantly the mean burst duration. The exposure of cells to PP2 during the course of the recording revealed a significant increase in the frequency of channel opening in addition to the increase of burst durations. To confirm that these changes were due to the inhibition of phosphorylation of α7-ICD, we introduced mutations at potential phosphorylation sites (Y386F and Y442F). The mutations prolonged burst durations, thus mimicking the effects of PP2. Also, the mutants were insensitive to PP2, confirming that Y386 and Y442 are responsible for its effects on α7 kinetics. Our results indicate that dephosphorylation positively modulates α7 channel activity in a way compatible with decreased desensitization.

Neurochemistry and Neuropharmacology

P239. Different Serotonin Type 3 Subunits Can Coassemble Into Heteromeric Receptors

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5-HT3 receptors are the only serotonin (5-HT) receptors that belong to the Cys-loop receptor family. They mediate fast excitatory transmission in central and peripheral nervous system. Five different subunits (A–E) have been identified in humans. The A subunit is able to form functional homomeric receptors (5-HT3A), and it can also combine with the B subunit to form heteromeric receptors (5-HT3AB). To evaluate the capability of the C, D, and E subunits to combine with the A subunit to form heteromeric receptors, we performed single-channel and macroscopic recordings. After expression of the A subunit, we recorded single-channel openings with an amplitude corresponding to the 5-HT3A receptor. However, when this subunit was expressed with one of the C to E subunits, opening events with different amplitudes were detected, thus confirming the expression of heteromeric receptors. From macroscopic currents, we determined that the EC50 values for 5-HT were statistically different when homomeric or heteromeric receptors were expressed. Taking together, our results demonstrate that all the 5-HT3 subunits can combine with the A subunit to form heteromeric receptors. *In silico* studies provided insights into the contribution of the different subunits to the 5-HT binding site. The functional characterization of different heteromeric 5-HT3 receptors will contribute to the development of selective therapies targeting this receptor family.

Neurochemistry and Neuropharmacology

P240. Differences in ALDH2 Activity in SH-SY5Y and HepG2 Cell Lines Exposed to Lead and Ethanol

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Several evidences demonstrate that the neurotoxicant lead (Pb) induces neurobehavioral alterations, including an altered response to drugs. We have previously reported that perinatally Pb-exposed rats showed elevated ethanol (EtOH) intake. It is known that EtOH metabolism determines its motivational properties. In fact, centrally formed acetaldehyde (ACD) promotes EtOH consumption, while peripheral ACD accumulation induces aversive effects. In both cases, aldehyde dehydrogenase (ALDH) is responsible for ACD oxidation to acetic acid. In the Pb-exposed rats, the elevated EtOH intake seems to be mediated by brain ACD accumulation, probably due to a reduced mitochondrial ALDH (ALDH2) activity and expression evidenced in these animals. In search of a mechanistic approach, *in vitro* experiments were performed in both SH-SY5Y and HepG2 cells, aimed to evaluate ALDH2 activity in a brain and liver like-environment. Both cell lines were exposed to Pb (5–200 μM), EtOH (100–200 mM) or Pb + EtOH (10 μM/200 mM) for 24 hr. The results resembled the *in vivo* data showing that Pb alone (5 μM and 10 μM) or in combination with EtOH inhibited ALDH2 activity only in the SH-SY5Y cells. On the contrast, no differences among groups emerged in the HepG2 cells, probably related to their low basal ALDH2 activity. Current studies are focalized in the assessment of ALDH2 expression and to explore the mechanisms that modulate ALDH2 function and ACD levels in each cell line in the presence of Pb and EtOH.

Neurochemistry and Neuropharmacology

P241. Context-Specific Increase of Glutamate Transmission in Cocaine-Conditioned Place Preference: An In Vivo Microdialysis Study

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The conditioned place preference (CPP) paradigm results suitable to evaluate the neurobiological changes induced by a cocaine-associated context in absence of the drug. Specifically, pharmacological evidence from our laboratory demonstrated the role of glutamatergic transmission within the nucleus accumbens (NAc) in different phases of cocaine-CPP. The aim of the present study was to evaluate *in vivo* changes in extracellular glutamate (GLU) levels in NAc as a result of cocaine conditioning and extinction. For this, a microdialysis assay was performed in male Wistar rats trained to acquire and then to extinguish cocaine-induced CPP. Animals were stereotaxically implanted with microdialysis probes, and then GLU dialysate samples were collected in the experimental room, first in the home cage to determine basal levels and then in the cocaine-paired or in the unpaired context. Dialysate samples were quantified by HPLC coupled with electrochemical detection. Results indicate that the enhancement of GLU is specific for the cocaine-paired context since animals evaluated before conditioning or in the unpaired context did not show such increase during re-exposure to the context. Furthermore, the increase of GLU was not either observed following extinction of cocaine-CPP. These findings support the idea that pairing cocaine with a specific context can modulate glutamate transmission in NAc influencing cocaine-seeking behavior and this can disappear after extinction of drug-CPP.

Neurochemistry and Neuropharmacology

P242. Effects of Acute Binge Ethanol Intoxication on Apoptosis in Hippocampus in Rats With Chronic Restraint Stress or Not

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Restraint stress (RS) induces substantial neurotoxicity in the hippocampus, yet most of the studies analyzing this phenomenon have employed protracted RS (i.e., $\approx$ 21 days). Binge ethanol administration can induce brain toxicity, analogous to that induced by stress, an effect that is affected by age. It could be postulated that ethanol intoxication may facilitate stress-induced neurotoxicity, perhaps to a greater extent in young versus old subjects. We analyzed if adolescents, adults, or aged rats exposed to five episodes of RS exhibit neurodegeneration in the hippocampus (CA1, CA2, CA3, and dentate gyrus [DG]) and whether this was modulated by a binge, yet brief (two administrations of 2.5 g/kg ethanol, separated by 120 min), ethanol administration. Compared to adult or aged rats, adolescents exhibited significantly greater RS-induced neurotoxicity in dorsal CA1 and CA2 and significantly greater ethanol-induced neurotoxicity dorsal CA2. Across ages, there was a synergistic effect between RS and ethanol at the dorsal and ventral CA1. A similar potentiation of RS by ethanol, yet restricted to adolescents, was found at ventral CA2. The study highlights the vulnerability of the developing brain to alcohol insult and stress exposure.

Neurochemistry and Neuropharmacology

P243. Pesticides, Toxic Aldehydes, and Parkinsonism

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Abstract not available

Neurochemistry and Neuropharmacology

P244. Validation of a Protocol for Oral Administration of PCPA, an Inhibitor of Serotonin Synthesis

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Adult hippocampal neurogenesis can be enhanced by factors depleting central serotonin (5-HT), like para-chlorophenylalanine (PCPA) that inhibits the 5-HT rate-limiting enzyme. Chronic PCPA intraperitoneal (i.p.) administration increases survival of newborn neurons, without affecting cell proliferation. Nevertheless, chronic i.p. injections affect animal welfare, as they are potentially painful. Thus, we designed and validated a protocol for PCPA oral administration. C57Bl/6J male mice received PCPA during 7 days via i.p. or by giving the drug inside jelly cubes. 5-HT levels decreased about 86.45% and 56.08% in the hippocampus of mice treated with oral and i.p PCPA, respectively, whereas in the prefrontal cortex, 5-HT levels decreased about 66.31% (oral) and 49.14% (i.p.). Behavioral tests, like the Forced Swimming test (FST), the Nestlet shredding test (NST), and the Marble Burying test (MBT) were performed. In the FST, mice received fluoxetine i.p. 30 min before the test. PCPA-treated mice spent significantly more time immobile than controls, revealing an effective reduction of 5-HT levels. While a tendency to significantly increased shredding was seen in the NST, no difference was observed in the MBT. In a second phase, mice received oral PCPA for 8 weeks, and survival of newborn cells was increased in the hippocampus of

hyposerotonergic mice. Therefore, neurochemical, behavioral, and neurogenic results allow us to validate the protocol for oral administration of PCPA.

Neurochemistry and Neuropharmacology

P245. Study of the Possible Interaction Between Wnt Canonical Pathway and Myelin Proteins in Cocaine-Induced Behavioral Sensitization

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Cocaine addiction is a chronic relapsing disorder mainly characterized by loss of control over drug seeking and taking. The transition between occasional use and addiction involves long-term neuroadaptations within the brain reward circuit. Among those neuroadaptations, we recently showed that Wnt/β-catenin pathway activity is modified in cocaine-induced behavioral sensitization. Other researchers have shown a relationship between cocaine and myelin composition as well as β-catenin and myelin genes expression. Our main goal was to evaluate whether Wnt/β-catenin pathway and myelin proteins are link to cocaine-induced behavioral sensitization. Thus, we submitted male Wistar rats to a sensitization paradigm (cocaine, 2 $\times$ 15 mg/kg i.p., 5 $\times$ 30 mg/kg i.p.), then they received seven injections of lithium chloride (LiCl, canonical pathway activator) or saline, and 2 weeks later a cocaine (15 mg/kg) or saline challenge. Locomotor activity was recorded on Days 1, 7, and 28 to measure sensitization. Animals were sacrificed, and their brains removed the day after the challenge to evaluate β-catenin and myelin basic protein levels. So far, our preliminary results showed that LiCl treatment during cocaine abstinence differentially impact on the behavioral response as well as on the protein levels depending on the previous development of sensitization. Ongoing studies are aimed to clarify the possible link between Wnt/β-catenin pathway activity, cocaine, and myelin proteins.

Neurochemistry and Neuropharmacology

P246. Chronic Benzodiazepine Exposure Regulates GABA-A Receptor Expression in Rat Cerebral Cortex

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Prolonged benzodiazepine exposure produces adaptive changes in GABA-A receptor structure and function that are associated with the development of tolerance. We have previously demonstrated that chronic benzodiazepine administration in rats results in tolerance to the sedative and anxiolytic effects which is accompanied with changes in the expression of GABA-A receptor alpha 1 subunit in the cerebral cortex. The aim of this work was to investigate the molecular mechanism of benzodiazepine tolerance in an *in vitro* model of primary neuronal cultures from rat cerebral cortex. The exposure of cultured neurons to diazepam for 48 hr produced a decrease in the interactions between GABA and benzodizepine-binding sites (40% uncoupling) which was prevented in the presence of nifedipine, an L-type voltage-gated calcium channel. Nifedipine also blocked the benzodiazepine-induced decrease in GABA-A receptor alpha 1 subunit mRNA levels. Results from calcium mobilization and nuclear run-on assays suggested that the mechanism of tolerance is mediated by repression of alpha 1 subunit gene expression induced by calcium influx through L-type voltage-gated calcium channels that would finally result in the uncoupling of GABA-A receptor allosteric interactions.

Neurochemistry and Neuropharmacology

P247. Restraint Stress-Induced Enhancement of Glutamate Transmission Within Nucleus Accumbens Core After Extinction of Cocaine-Conditioned Place Preference: An In Vivo Microdialysis Study

Andrea S. Guzman[1], Pia V. Euliarte[1], María P. Avalos[1], Marianela A. Sanchez[1], Leandro Oliveros[1], Daiana Rigoni[1], Flavia A. Bollati[1] and Liliana M. Cancela[1]

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Stress is considered an important factor that induces relapse in human addicts and in animal models of addiction. Findings from our lab demonstrated pharmacologically the role of glutamatergic transmission within core, and not shell, subcompartment of nucleus accumbens (NAc) in restraint stress-induced reinstatement of extinguished cocaine-conditioned place preference (CPP). The present *in vivo* microdialysis study aims to evaluate the effect of a single restraint stress session on extracellular levels of glutamate (GLU) in NAc Core during a re-exposure to the drug-paired context after extinction of cocaine-CPP. For this, male Wistar rats trained to acquire and then to extinguish cocaine-CPP were stereotaxically implanted with self-built microdialysis probes. The next day, GLU dialysate samples were collected in the experimental room, first in the home cage to determine basal levels and then in the cocaine-paired context after the exposure to restraint stress (30 min). Dialysate samples were quantified by HPLC coupled with electrochemical detection. Results indicate that animals submitted to restraint stress showed a significant increase in extracellular GLU levels in NAc Core during the first 15 min of re-exposure to cocaine-paired context, while the non-stress group did not show such increase. These findings are explained in the framework of a dysregulation of GLU homeostasis induced by stress and provide neurochemical basis to investigate mechanisms underpinning relapse.

Neurochemistry and Neuropharmacology

P248. GABAergic Disinhibition of the Anterior Thalamic Nucleus Partly Mimics Behavioral Responses Induced by MK-801. Regional Expression Pattern of FRA-2

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N-methyl-d-aspartate receptor (NMDA-R) antagonists (phencyclidine, ketamine, and MK-801) evoke its psychotomimetic action by selectively targeting GABAergic elements in cortical and thalamic circuits in rats, but the involvement of specific brain regions is under study. We reported that the anterior thalamic nucleus (ATN) is engaged in the psychotomimetic-like behaviors induced by MK-801 in rats, and these responses were mediated by ATN GABAergic disinhibition. It is still unknown if this action imply an increase in ATN neural activity and in its projection regions (hipoccampus [HPC], retrosplenial cortex [RS], and medial prefrontal cortex [mPFC]) and if a GABAA-R blockade by bicuculline (GABAA-R antagonist, 100 ng) application in ATN would totally or partially mimic the effect of MK-801 (0.2 mg/kg i.p.). We used the expression of FRA-2 as a neuronal activity marker. Dorsal (caudate-putamen [CPu]) and ventral striatum (nucleus accumbens, core and shell, NAcC, and NAcSh) were also analyzed. MK-801 significantly increased FRA-2-immunoreactivity (FRA-2-IR) in the ATN, mPFC (prelimbic area and PrL), and NAcSh. No changes were detected in RS, HPC (CA1 and dentate gyrus, DG), NAcC, and CPu. Intra-ATN bicuculline microinjection evoked a behavioral response similar to MK-801, yet of lower magnitude, which was associated to a different pattern of FRA-2 IR (e.g., increase in DG, and NAcSh, decrease in PrL). New insights about brain networks involved in positive symptoms of schizophrenia are provided.

Neurochemistry and Neuropharmacology

P249. In Search of the Serotonin Role in the Contrasting Synapse Remodeling Induced by Fluoxetine in Cortical and Hippocampal Neurons

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The antidepressant fluoxetine (FLX) is a specific serotonin (5HT) reuptake inhibitor (SSRI). We have previously showed that behavioral benefits induced by FLX in experimental depression occur concomitantly with hippocampal changes in synapse morphology and number. FLX has also shown to increase synapse number in the cerebral cortex of naive animals, an effect not shared by all SSRIs. The aim of this work was to study the *in vitro* profile of FLX-induced synapse remodeling in hippocampal and cortical neurons. To this aim, primary neuronal cultures obtained from embryonic (E18) and postnatal (P1-2) rats were exposed for 24 hr to FLX or 5HT. Immunostaining of the dendritic marker MAP-2 and the synaptic marker synaptophysin (SYN) were evaluated to

study dendritic and synapse remodeling, respectively. In cortical neurons (DIV7), FLX treatment (1μM) increased SYN puncta number and total puncta area without modifying the dentritic tree. This effect was mimicked by 5HT and blocked by ketanserin (5HT2R antagonist). In hippocampal neurons (DIV14), FLX treatment (0.1–1 μM) decreased SYN puncta number and total puncta area and induced dendritic retraction. 5HT treatment failed to mimic FLX effect in hippocampal neurons. Our results indicate that FLX-induced synapse remodeling depends on the neuronal phenotype and suggest that while FLX effect in cortical neurons is 5HT-mediated, it seems to involve a more complex mechanism in hippocampal neurons.

Neurochemistry and Neuropharmacology

P250. AT1 Receptors Are Essential Players in the Development of Amphetamine-Induced Inflammation in Prefrontal Cortex: Relevance for Neuroinflammatory Pathologies

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Amphetamine (Amph) is related to vascular damage, neuroinflammation, prefrontal cortex (PFC) hypo-function, and neuropsychiatric impairments. Angiotensin II, through AT1 receptors (AT1-R), mediates neuroinflammatory responses, promoting endothelial dysfunction, oxidative damage, and glial reactivity. The present work aimed to elucidate Amph-induced changes in the cell elements of brain's innate immune system within the PFC and to unmask AT1-R's role in its development. Attention deficit was evaluated as a functional assessment of PFC activity. Male Wistar rats (250 g) received AT1-R antagonist CV (3 mg/kg p.o., Days 1–5) and Amph (2.5 mg/kg i.p., Days 6–10). On Day 17, after behavioral tests, brains were processed for cresyl violet staining, GFAP, CD11b, and von Willebrand factor immunohistochemistry. Otherwise, animals exposed to Amph challenge (0.5 mg/kg i.p.) were evaluated for oxidative and cellular stresses in isolated brain micro-vessels. Two-way ANOVA and Bonferroni test were used. Amph promoted glial reactivity, apoptosis, and vascular network rearrangement in PFC and exacerbated MDA levels and HSP70 expression in response to an Amph challenge in brain micro-vessels. These alterations were observed concomitant with attention deficit. AT1-R blockade prevented the glial reactivity and vascular network rearrangement, the modified micro-vascular responses, and the attention deficit induced by Amph, highlighting AT1-R role in the development of Amph-induced neuroinflammation in PFC.

Neurochemistry and Neuropharmacology

P251. A New Old Tale: Dopamine Transporter Implications in an Attention-Deficit Hyperactivity Disorder Animal Model

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Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition characterized by atypical levels of inattention, hyperactivity, and impulsivity. We have shown that mice lacking the Cdk5 activator, p35 (p35KO), resemble ADHD characteristic phenotypes. P35KO mice show hyperactivity in novel contexts, less anxiety like behaviors and paradoxically response to amphetamine (AMPH). Furthermore, p35KO displays an increased dopamine (DA) synthesis and a decreased DA metabolism. Given that DA transporter (DAT) is the target of ADHD treatment drugs, and it is functional only when is exposed in surface, the aim of this work was to study total and superficial DAT expression in p35KO and WT striatal tissue and its modulation by AMPH treatment. Our results show no difference in total DAT levels between WT and p35KO mice. Nevertheless, using synaptosomal surface biotinylation technique, we show significant decreased DAT superficial levels in p35KO mice compared with WT. Besides, AMPH treatment (10 μM for 30 min) of WT synaptosomes induced a decrease in DAT superficial levels, but in p35KO, these expression levels remained unaltered. Taken together, our results suggest that the decreased DAT surface expression in p35KO mice correlates with an increased DA availability in synaptic cleft and therefore an increased locomotor activity. In these sense, our results are critical for the understanding of the mechanism underlying ADHD-like behavioral phenotypes.

Neurochemistry and Neuropharmacology

P252. Nano-Formulated Anandamide Decreases Neuroinflammatory Markers in Spontaneously Hypertensive Rats

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Essential hypertension is responsible for almost 95% of all cases of hypertension. Frequently of neurogenic origin, it is linked with an over-excitation of brainstem centers, sympathetic hyperactivation, and imbalance in the levels of pro- and anti-inflammatory cytokines. Spontaneously hypertensive rats (SHRs) is a validated model of hypertension plus several neurocognitive deficits. Since endocannabinoid anandamide (AEA) protects neurons from the inflammatory damage, and cannabinoid signaling decreases in brains of hypertensive animals, we applied a nano-formulated AEA in SHR. We used adult male rats ($n = 7$) of 250 to 300 g normotensive (WKY) and hypertensive (SHR), treated or not with nano-formulated AEA in polycaprolactone (AEA/PCL), at a weekly dose of 5 mg/kg IP, for 4 weeks. Regarding WKY, the SHR showed elevated inflammatory markers (IL-1, IL-6, FNTα, ultrasensitive PCR, and plasma Hsp70, $p < .05$) and oxidative stress markers (NADPH oxidase and nitrites). Protein expression of WT1, AT-1, and iNOS decreased after treatment, while Hsp70 increased within the cerebral cortex ($p < .01$). On the other hand, SHR treatment with AEA/PCL returned values to normal, including abnormal behaviors. These preliminary results suggest anti-inflammatory properties of nano-formulated anandamide, both peripherally and at the level of the central nervous system, specifically within the cerebral cortex.

Neurochemistry and Neuropharmacology

P253. Withdrawn Abstract

Neurochemistry and Neuropharmacology

P254. Allosteric Modulation of α7 Nicotinic Receptors by Flavonoids

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Plants have emerged as a valuable source for neuroprotective compounds like flavonoids. These polyphenolic compounds decrease neurotoxicity and the development of neurodegeneration. Potentiation of α7 nicotinic receptor, which is involved in cognition and memory, is a potential therapeutic strategy in neurodegenerative disorders. In particular, positive allosteric modulators (PAMs) are emerging as the best therapeutic tools. Some flavonoids have been reported as ligands for α7, but the molecular mechanisms underlying this interaction remain unknown. Our main goal is to unravel the molecular basis of flavonoid action at α7 by electrophysiological techniques. We analyzed the effects of prototypes of distinct classes of flavonoids: quercetin, genistein, and 7-dihydroxy-4-phenylcoumarin (neoflavonoid) on α7 activity. At the macroscopic level, the three compounds increased the peak current elicited by acetylcholine with minimal effects on desensitization, indicating that they behave as type I PAMs. At the single-channel level, they increased, with different efficacies, the duration of the open state. By analyzing the effects of flavonoids on mutant and chimeric α7 receptors, we found that they share the transmembrane structural determinants of potentiation known for other PAMs. We conclude that, in addition to the well-known effects as antioxidants, the unique properties of flavonoids as natural α7 PAMs make them candidate compounds for the treatment of neurodegenerative disorders.

Neurochemistry and Neuropharmacology

P255. Locomotor Sensitization and Gene Expression Induced by Coca Paste in Mice Nucleus Accumbens and Prefrontal Cortex

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Coca-paste (CP) is a smokable form of cocaine consumed in several South American countries. Its chronic consumption elicited a fast and strong dependence compared to cocaine, among other psychophysical alterations. CP is sold adulterated, being caffeine one of the most common psychoactive adulterant found in seized samples of the drug. In previous studies, we demonstrated that caffeine as an adulterant is able to enhance and facilitate CP locomotor sensitization. In order to investigate the underlying mechanisms of such potentiation, the aim of this study was to evaluate the gene expression in reward-circuit related areas (nucleo accumbens [NAc] and medial prefrontal cortex [mPFC]) after the expression of locomotor sensitization induced by caffeine-adulterated and non-adulterated CP. After 3 days of treatment and 5 days of abstinence, adult male mice were challenged to cocaine, caffeine-adulterated CP, and non-adulterated CP seized samples, and the motor activity was recorded. At the end of the behavioral test, mRNA levels of dopamine, adenosine, glutamate, and cannabinoids receptors subunits were quantified as well as CREB, CART, and synaptophysin mRNA levels. Only animals treated with caffeine-adulterated CP expressed locomotor sensitization, and this corresponded to specific changes in the mRNA levels in the NAc and PFC, associated to chronic stimulant induced neuroplasticity, despite the short treatment. Our results can help to understand the fast dependence induced by CP consumption.

Neurochemistry and Neuropharmacology

P256. Chronic Unpredictable Stress in *Drosophila* as a Preclinical Model for Psychopharmacology Research

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Exposition to chronic and unpredictable stress (CUS) plays a significant role in the psychiatric disorders onset. Frequent symptoms in humans include altered locomotion and anhedonia, which can be partially modeled in rodents as preclinical tests used for drug testing. However, frequent failure of predictive validity and animal welfare issues increase initiatives focused on 3Rs. *Drosophila* is a powerful organism for modeling human diseases mainly due to their phylogenetic relationship with rodents and their labor/cost-effective maintenance advantages. We aimed at using *Drosophila melanogaster* as an alternative preclinical model for stress and psychopharmacological research. Adult *D. melanogaster* were exposed to CUS with several stressors (random sequences of 24 hr isolation, 20 min heat shock, 5 min electric shock and 6 hr starvation between animals). Another group was treated with 10 mM fluoxetine, 5 mM diazepam (DIA), or vehicle during starvation stress. At the end of CUS, behavior in the open field (OF) and 2 mM sucrose preference (SP) were analyzed. Compared to control, stressed flies exhibited higher mobility, distance, and velocity as well as less time in OF boundaries. In contrast to control group, stressed flies exhibited less SP. No treatment prevented these behavioral disturbances; however, diazepam increased freezing time. Our CUS model contributes to the construction of a stress-related model meeting face validity where we reproduced some behavioral phenotypes in *Drosophila*.

Neurochemistry and Neuropharmacology

P257. Impact of Stress in the Vulnerability to Cocaine Addiction: Role of Cofilin in Nucleus Accumbens

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Animals models have demonstrated that exposure to stress predisposes to developing substance use disorders. We have previously shown that repeated stress alters the capacity of a subsequent cocaine injection to modulate dendritic spine morphology and actin dynamics. Our findings indicates that the pharmacological inhibition of actin polymerization in the nucleus accumbens (NA) prevents stress cross-sensitization with cocaine and influences actin cytoskeleton remodeling in the NA. Thus, the main goal of this project is to evaluate the impact of the actin cytoskeleton in the changes underling the facilitatory influence of cocaine after exposure to chronic stress in the acquisition of cocaine self-administration (SA). For this purpose, we have generated a lentivirus containing a short hairpin RNA (shRNA) specific to cofilin, to inhibit its expression in NA, and explore its function during the acquisition of cocaine SA. Thus, Sprague Dawley rats pre-exposed to chronic restraint stress will be administered intra-accumbens with shRNA of cofilin, and later they will undergo surgery for implantation of catheters in the jugular vein 1 week before SA sessions. In the same line of evidence, our results revealed that the inhibition of cofilin is sufficient to prevent the expression of cross-sensitization between stress and cocaine, suggesting that the cofilin regulation is crucial in the facilitatory influence of stress on the vulnerability to develop cocaine addiction.

Neurochemistry and Neuropharmacology

P258. Comorbidity Between Chronic Restraint Stress and Cocaine Self-Administration: Role of Glial Proteins in Nucleus Accumbens Plasticity

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Abstract not available

Neurochemistry and Neuropharmacology

P259. The Varieties of the Psychedelic Experience: Association Between Reported Subjective Effects, Binding Affinity Profiles and Molecular Structures of 18 Psychoactive Compounds

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Classic psychedelics are substances of paramount cultural and neuroscientific importance. The observation of cross-tolerance and a series of empirical studies support partial agonism at the serotonin 5-HT2A receptor as a common mechanism for the action of psychedelics. The diversity of subjective effects elicited by different compounds has been attributed to the variables of "set" and "setting," to the binding affinities for other serotonin receptor subtypes, and to the heterogeneity of transduction pathways initiated by conformational receptor states, as they interact with different ligands ("functional selectivity"). Here, we evaluated the hypothesis that such variety is related to the binding affinity profiles for a range of different neurotransmitter and transporters including (but not limited to) serotonin receptors. Building on previous experimental binding affinity data in combination with natural language processing tools

applied to a large repository of reports of psychedelic experiences (Erowid's Experience Vaults), we established that the similarity between the receptorome of 18 psychoactive compounds correlates with the closeness of their associated subjective effects. We also showed that the highest correlation could be achieved by considering a repertoire of receptors. Our methodological developments open the way to the systematic exploration of the relationship between the binding affinity profiles and subjective effects of other psychoactive compounds.

Neuroendocrinology and Neuroimmunology

P260. Retinal Effects of Optic Nerve Inflammation

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Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which may provoke blindness. A subset of RGCs expressing the photopigment melanopsin (mRGCs) regulates non-image-forming visual functions such as the pupillary light reflex (PLR) and circadian rhythms. We developed an experimental model of primary ON in rats through a microinjection of bacterial lipopolysaccharide (LPS) into the optic nerve. The aim of the present work was to analyze the consequences of ON at retinal level. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. At 4 days post-LPS, an increase in retinal Iba-1(+) area (a microglia/macrophage marker) that persisted until 21 days post-injection was observed, while GFAP-immunoreactivity increased at 21 days post-LPS. Moreover, at 21 days post-injection, LPS induced a significant loss of RGC number (by Brn3a immunoreactivity), whereas no changes in mRGCs number were observed. Experimental ON induced a decrease in the anterograde transport to the superior colliculus and suprachiasmatic nucleus (by CTB labeling) and a decrease in white and blue light-evoked PLR. These results suggest that experimental ON affects the retina at even early stages, and without changing mRGC number, it altered the non-image-forming visual system, supporting that alterations of circadian physiology could be a risk to the quality of life of patients with ON.

Neuroendocrinology and Neuroimmunology

P261. Leukocytes as Key Players in Optic Nerve Neuroinflammation

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Optic neuritis (ON) is a condition involving primary inflammation, demyelination, and axonal injury in the optic nerve which leads to retinal ganglion cell (RGC) loss, and a decrease in pupil light reflex (PLR) and visual evoked potentials (VEPs). Neuroinflammatory diseases are characterized by disruption of the blood–brain barrier (BBB) and increased leukocyte infiltration. The aim of the present work was to analyze the involvement of cell infiltration on visual damage induced by experimental ON. LPS or vehicle were injected into the optic nerve from adult male Wistar rats. BBB integrity was analyzed through Evans blue perfusion on WT-GFPþ/WT chimeric rats. At 6 hr post-LPS injection, an increase in albumin-Evan's blue leakage and increase in in optic nerve cellularity were observed. At 24 hr post-injection, e-GFP(+) cells (likely macrophages and neutrophils) were identify in LPS-injected optic nerves. Experimental ON induced an increase in the chemokine CCL2-immunoreactivity. The injection of Bindarit (a CCL2 inhibitor) and bone marrow depletion (by gamma irradiation) significantly prevented the effect of ON on PLR, VEP amplitude, and RGC number. In order to induce BBB breakdown, tissue plasminogen activator (tPA) was injected into the optic nerve. tPA microinjection mimicked the effect of ON on PLR and RGC number. These results indicate that BBB integrity loss and leukocyte recruitment play a key role in the visual damage induced by experimental ON.

Neuroendocrinology and Neuroimmunology

P262. Neuroanatomical and Functional Characterization of the Ghrelin-Responsive Neurons of the Lateral Hypothalamic Area

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Ghrelin is a stomach-derived hormone that regulates a variety of biological functions via the growth hormone secretagogue receptor (GHSR), a receptor located in key brain areas that mediate the actions of the hormone. GHSR is highly expressed in the lateral hypothalamic area (LHA), which controls essential functions, including food intake, locomotor activity, and reward-related behavioral responses. Here, we used a mouse model in which the expression of enhanced green fluorescent protein (eGFP) is controlled by the promoter of GHSR (GHSR-eGFP mice) to gain neuroanatomical and functional insights of the GHSR-expressing neurons of the LHA. We found that GHSR neurons of the LHA are present from bregma −0.34 to bregma −2.70 in the antero-posterior axis, and particularly enriched in the anterior (aLHA) and tuberal region (tLHA). GHSR neurons of the LHA increase the level of the marker of neuronal activation c-Fos in response to centrally injected ghrelin and fail to increase c-Fos in response to systemically injected ghrelin. We also identified that a subset of GHSR neurons of the LHA are GABAergic and that no GHSR neurons of the LHA express orexin. Finally, we found that local intra-LHA rostral infusions of ghrelin increase food intake. Thus, current data provide evidence that ghrelin receptor signaling seems to target a subset of GABA neurons of the LHA that, in turn, affect food intake.

Neuroendocrinology and Neuroimmunology

P263. IGF1 Gene Therapy Delays Reproductive Senescence

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The hypothalamus, a region known to regulate many basic functions such as growth, development, reproduction, and metabolism, is thought to be a regulatory center of aging. Evidence demonstrates that the inhibition or activation of the transcription factor NF-κB in microglia or in neurons of the basal hypothalamus (HMB) affects the life expectancy and the "beginning" of aging as well as the release of GnRH. There is solid evidence that middle-aged (MA) rats have reduced activation of GnRH neurons, GnRH release, and an abnormal LH surge. These findings provide a link between inflammation, response to stress, and systemic and cerebral aging. In this project, we implemented long-term anti-inflammatory gene therapy for IGF1 in the HMB of MA female rats (8 months) up to 12 months, in order to modulate the inflammatory response mediated by NFkB and delay the appearance of reproductive cessation. Our results show that, at the end of the experiment, rats treated with IGF1 present a higher proportion of cycling rats compared to the control group. We also observed that IGF1 group has a higher number of axonal projections of the GnRH+ neurons. These results suggest that IGF1 prolongs the reproductive life of MA rats, maintaining GnRH+ neurons functionality.

Neuroendocrinology and Neuroimmunology

P264. The Blood–Cerebrospinal Fluid Barrier Transports Circulating Ghrelin Into the Brain

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Ghrelin is a 28-amino acid hormone secreted from the stomach which mainly acts in the brain to regulate food intake and neuroendocrine axes. However, the accessibility of circulating ghrelin to the brain is restricted, with no conclusive evidence of it crossing the blood–brain barrier. In this study, we hypothesized that ghrelin can reach its brain nuclei targets by crossing the blood–cerebrospinal fluid barrier (BCSFB), which is composed of the ependymal cells of the choroid plexus and the hypothalamic tanycytes. Using systemic injections of a fluorescent ghrelin tracer (F-ghrelin), we found that the cells of the BCSFB were able to internalize ghrelin. Also, in time-response studies, we found that systemically injected F-ghrelin reached the median eminence and the ventromedial arcuate nucleus at early time points, while, at later time points, F-ghrelin was found in the cerebrospinal fluid (CSF) as well as in brain parenchyma in close apposition to the dorsal wall of the third ventricle. Additionally, we found that central injections of either an anti-ghrelin antibody, which immuno-neutralizes CSF ghrelin, or a scrambled version of F-ghrelin, which was also found to be internalized by the cells of the BCSFB, partially impairs food intake and neuronal activation promoted by peripheral ghrelin. We thus conclude that the cells of the BCSFB can transport ghrelin from the circulation into the CSF and the brain parenchyma.

Neuroendocrinology and Neuroimmunology

P265. Effects of Diazepam Treatment on Neuroinflammation at Hippocampus in a Chronic Model of Experimental Autoimmune Encephalomyelitis

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Experimental autoimmune encephalomyelitis (EAE) is an inflammatory demyelinating disease that mimics many of the clinical and pathological features of multiple sclerosis. Recently, we found that 2 mg/kg of chronic diazepam (Dz) treatment reversed motor signs of the disease and attenuates mRNA expression of inflammatory cytokines at hippocampus. In the present study, we aimed to analyze the mRNA expression of the highly conserved 18-kDa translocator protein (TSPO) at hippocampus as a biomarker of neuroinflammation and as the possible receptor that mediates the action of Dz in our experimental model. We also analyzed microgliosis and astrogliosis at hippocampus, as the upregulation of TSPO plays a role in the response of astrocytes and microglia during active brain disease. Female mice were immunized with MOG35-55 peptide or adjuvant alone and pertussis toxin. At first symptom, animals were injected with diazepam or saline alone every 48 hr. After recovery of clinical signs, brains were harvested for immunofluorescence against Iba1 and GFAP or mRNA expression of TSPO through RT-PCR. We found that Dz ameliorated microgliosis and astrogliosis at hippocampus of EAE animals. Interestingly, Dz downregulated TSPO expression in both EAE and control animals. Further experiments are needed in order to dilucidate a possible mechanism that could explain diazepam effects on motor signs of the disease and its anti-inflammatory effect at hippocampus.

Neuroendocrinology and Neuroimmunology

P266. Setting Up an In Vitro Model to Study Glial Response to Peripheric Immune Cells

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Healthy central nervous system provides limited interaction between parenchymal astrocytes and immune peripheral cells. After an ischemic event, the blood–brain barrier is compromised and leukocytes are drawn to the lesion, where a complex immune response arises involving both local and systemic cells. The detrimental or beneficial roles of this recruitment are still discussed. The aim of the present work is to shed some light on the systemic cues associated with the commitment of astrocytes to specific activating profiles in response to peripheral immune cells. To undertake this challenge, we set up an *in vitro* model where primary rat glial cells are co-cultured with eGFP+ leukocytes isolated from adult Wistar-TgN(CAG-GFP)184ys rats. Fixed leukocytes were used to analyze the effect of surface molecules. Using immunofluorescence, we evaluated astrocyte reactivity (GFAP), microglial activation (Iba1), and the formation of glial scar-like structures. Short-term (6 hr) and long-term (72 hr) effects were studied. Astrocytes in contact with both fresh and fixed leukocytes had a fibrillar morphology and increased GFAP expression. Cellular retraction and reorganization was evident, and scar-like structures were seen. Microglia in contact with leukocytes had an activated (round) morphology. These results indicate that both soluble factors and surface molecules in leukocytes are capable of inducing astrocytes' reactivity, but further research is necessary to determine more specific pathways involved.

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Neuroendocrinology and Neuroimmunology

P267. Regenerative Action and Immune Modulation of Bone Marrow Cell Transplant in Sciatic Nerve Injury

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Wallerian degeneration induced by nerve lesion is a simple and useful experimental approach to study peripheral nervous system degeneration and regeneration. We have shown systemically transplanted bone marrow cells to spontaneously migrate to and remain in the injured nerve for as long as 60 days. A small number of these cells upregulated markers unexpressed before transplant, leading to cell phenotypic changes and transdifferentiation to Schwann cells, while a significantly larger proportion left the tissue once the inflammatory phase had finished. They also enhanced axonal regeneration and remyelination, promoted functional recovery and prevented lesion-induced hyperalgesia. The aim of the present work is to evaluate whether transplanted bone marrow cells exert their well-established beneficial effect on sciatic nerve regeneration through immunomodulation. Adult C57BL/6 mice received intravenous bone marrow cell or vehicle transplant after 8-s nerve crush. Along recovery, functional aspects were evaluated through hot plate and walking track tests. Animals were then sacrificed for immunohistochemistry, ELISA, and flow cytometry studies. So far, the mouse model resembles results obtained in rats in terms of remyelination. Most interestingly, qPCR results showed that transplanted animals appear to undergo a downregulation of pro-inflammatory and an upregulation of anti-inflammatory cytokines. Further studies are required to fully corroborate immunomodulation effects.

Neuroendocrinology and Neuroimmunology

P268. Ghrelin Modulates Hippocampal Plasticity Changing Density and Morphology of Dendritic Spines

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Abstract not available

Neuroendocrinology and Neuroimmunology

P269. An Insulin-Like Peptide, INS-3, Bridges Neural Perception of Stressors With Intracellular Defensive Mechanisms in Non-Neuronal Cells of *C. elegans*

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Multicellular organisms coordinate the systemic response to stress. We have shown that in *Caenorhabditis elegans* the acute-stress response activates neurons that release tyramine (TA), the invertebrate analog of adrenaline/noradrenaline. TA stimulates the DAF-2/Insulin/IGF-1 pathway and precludes the nuclear translocation of the DAF-16/FOXO transcription factor through the activation of an adrenergic-like receptor tyra-3 in the intestine. In contrast, environmental long-term stressors reduce TA release allowing the induction of FOXO-dependent cytoprotective genes. However, how the insulin and tyraminergic pathway are linked is unknown. We here found that genetic silencing of an insulin-like peptide (ILP) (INS-3) increases the resistance to thermal and oxidative stress, reaching levels similar to tdc-1 (incapable of synthetizing TA) and tyra-3 null mutants. Moreover, unlike wild-type animals, exogenous TA does not impair oxidative or thermal stress resistance. In addition, double null mutants between TA-deficient and ILPs null mutants (tdc-1 or tyra-3 with ins-3 or 7) showed levels of stress resistance similar to those found in INS-3 single null mutants, suggesting genetic interaction. Intestinal expression of INS-3 rescues the resistance phenotype of INS-3 null mutants to wild-type levels. We proposed that TA released form the nervous system promotes intestinal release of ILPs, which activate DAF-2 in other cells, inhibiting the systemic stress response mediated by DAF-16/FOXO.

Neuroendocrinology and Neuroimmunology

P270. MeCP2 Regulates the Immune Response During an Autoimmune Challenge

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Rett syndrome (RTT) is a category of pervasive developmental disorders caused by mutation of MECP2, a gene that encodes methyl-CpG binding protein 2 (MeCP2), a ubiquitously expressed transcriptional regulator. The main goal of our project is to evaluate the role of altered immunity in the pathogenesis of this disorder. To this end, we evaluated the autoimmune response in the context of the experimental autoimmune encephalomyelitis (EAE). Male MeCP2 WT and MT mice were immunized with MOG 35-55 peptide, scored daily for EAE symptoms, and sacrificed at 12 dpi (acute stage) or at 30 dpi (chronic stage). We found that MT-EAE mice showed an accelerated onset of the disease and more severe clinical scores, accompanied by increased infiltration of lymphocytes in spinal cord. The level of microgliosis (Iba1+ cells) was analyzed by IHC and RT-PCR, and we found significant differences between EAE and control group. To determine the response of immune cells, we re-stimulated spleen mononuclear cells derived from WT and MT mice with MOG peptide *in vitro*. MT-EAE group showed increased IFN-γ levels in response to MOG in comparison with WT-EAE animals with no differences in the proliferation index. Also, the level of gene expression of TNF-α and IFN-γ was significantly increased in spinal cords from MT-EAE animals during chronic stage compared to WT. Our results indicate that MeCP2 has an active role in regulating the immune response and maintaining the neuroimmune homeostasis.

Sensory Systems

P271. Exploring Learning Paradigms to Study Contextual Modulation of Olfactory-Based Behavior in Head-Fixed Mice

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Abstract not available

Sensory Systems

P272. Spiral Ganglion Neuron Degeneration in Mice With Impaired Potassium Homeostasis of the Cochlea

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Spiral ganglion neurons (SGNs) relay auditory information from the cochlea to central nuclei in the central nervous system. Their fibers receive inputs from inner hair cells

(IHCs), which are the source of sound transduction. The voltage-activated potassium channel KCNQ4 is not only mainly expressed in outer hair cells (OHCs) but also has been observed in IHCs and auditory pathway nuclei. Impaired activity of this channel causes OHCs degeneration, producing a sensorineural hearing loss, named DFNA2. The phenotype is initially explained by OHC death; however, it progresses over time to profound deafness exceeding OHC function. Thus, it is postulated that a neuronal component could also be involved. We set out to study the role of SGNs in the progression of the hearing loss developed by KCNQ4 knock-out mice. We analyzed cochlear cell survival through time and localization using immunofluorescence on cochlear preparations. We found a significant decrease of SGN densities in basal portions of the cochlea as early as 40 weeks of age (W). By 52W, the loss was also present in apical turns, and overall density of both regions decreased more than 50% by 60W. We also found loss of IHCs starting at 40W in basal turns, progressing toward the middle turn by 58W. Exploring mechanisms of cell death, we found Cleaved Caspase 3 to be active on both OHCs and cells of SGNs. Our findings suggest a neuronal component involved in DFNA2-like deafness, and that apoptosis could be a mechanism active during cell degeneration.

Sensory Systems

P273. Responses to Visual Motion Stimuli of Neurons From a Crab Assessed by Multielectrode Recording

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One of the main challenges in neuroscience nowadays is to understand the concerted functioning of individual neurons dedicated to particular behaviors in the behaving animal. This goal first requires to attain an adequate characterization of the behavior as well as an identification of the key neuronal elements associated to that action. Such conditions have been considerably attained for the escape response to visual stimuli in the crab *Neohelice*. In fact, a combination of *in vivo* intracellular recording and staining, with behavioral experiments and modeling, led us to postulate that a microcircuit formed by four classes of identified lobula giant (LG) neurons operates as a decision-making node for a number of important visually guided components of the crab's escape behavior (Tomsic D. (2016) Visual motion processing subserving behavior in crabs. Curr Opin Neurobiol. 41:113–121). These studies, however, were done by recording LG neurons individually. In order to investigate the concerted functioning of the LG group, we began to use multielectrode extracellular recordings. Here, we describe the methodology and show results of simultaneously recorded responses from different LG neurons to a variety of visual stimuli. The different LG classes can be distinguished by their electrical activity and differential responses to visual stimuli. Simulataneous recordings confirmed the rightfulness of previous interpretations about LG interactions assumed from independent intracellular recordings. The current results establish the bases for and show the feasibility of our next goal of recording the activity of LG neurons in the behaving animal.

Sensory Systems

P274. Why Is the Macula Particularly Susceptible to Dry Age-Related Macular Degeneration? Lessons From Mice

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Dry age-related macular degeneration (dAMD), the elderly main cause of blindness, is characterized by retinal pigment epithelium (RPE) and photoreceptors atrophy circumscribed to the macula. The fact that only the macula is damaged by dAMD, raises the question as to why is this area particularly susceptible. It has been suggested that RPE oxidative damage plays an important role in dAMD pathogenesis. However, the exact mechanisms of the disease are still elusive and hard to study, as mice do not have a macula. We have developed a dAMD model induced by superior cervical ganglionectomy (SCGx) in C57BL/6J mice, which reproduces the disease hallmarks exclusively circumscribed to the temporal region of the RPE/outer retina. In this context, the aim of this work was analyzing RPE regional differences that could explain dAMD localized susceptibility. Lower melanin content, thicker basal in foldings, higher mitochondrial mass, and higher levels of antioxidant enzymes were found in the temporal RPE compared with the nasal region. Moreover, SCGx

induced a decrease in the antioxidant system, and in mitochondria mass, as well as an increase in mitochondria superoxide, lipid peroxidation products, nuclear Nrf2 and heme oxygenase-1 levels, and in the occurrence of damaged mitochondria exclusively at the temporal RPE. These findings suggest it might not be dAMD pathophysiology but the macular RPE histologic and metabolic specific attributes, which conditions the localization of the disease.

Sensory Systems

P275. Enriched Environment Exposure Protects the Visual Pathway Alterations Induced by Experimental Glaucoma in Adult Rats

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Glaucoma is a leading cause of blindness, characterized by retinal ganglion cell (RGC) loss and optic nerve (ON) damage. Increased intraocular pressure (IOP) is the most accepted risk factor for glaucomatous neuropathy; however, many patients with successful IOP control continue to lose vision. Enriched environment (EE) is a paradigm that involves sensory, cognitive, motor, and social stimulation. The aim of this work was to analyze whether the exposure to EE prevents glaucomatous alterations. Adult male Wistar rats received 30% of chondroitin sulfate in the anterior chamber of one eye and vehicle in the contralateral eye, once a week, and were housed in standard environment or EE for 10 weeks. Animals were subjected to functional (electroretinogram and flash visual evoked potentials [VEPs]), and histological analysis. EE housing which did not affect IOP prevented the decrease in VEPs and oscillatory potential amplitude as well as the reduction in the RGC number detected by immunostaining against Brn3a. The number of axons identified by toluidine blue stain was also preserved by the exposure to EE. Moreover, EE housing prevented the reduction in the positive area for myelin basic protein and luxol fast blue stain area in the ON. The increase in Iba1 (a microglia/macrophage marker) positive area in the retina and ON was also preserved. These results suggest that the EE housing protects the visual pathway against damage induced by experimental glaucoma in adult rats.

Sensory Systems

P276. The Novel Opsins Opn3 and 5 Non-Visual Opsins Are Expressed in Cells of the Inner Vertebrate Retina. Potential Roles and Physiological Implications

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The avian retina is composed of different types of photoreceptors responsible for image and non-image forming tasks: visual photoreceptor cells (cones and rods), the intrinsically photoresponsive retinal ganglion (ipRGCs), and horizontal cells. Nonvisual opsins Opn3 and Opn5 were shown to be expressed in the inner retina of vertebrates, responding to blue and UV light, respectively. The retina contains an endogenous circadian clock that temporally regulates its physiology and which is synchronized by light. To investigate expression and light regulation of Opn3 and Opn5 in the developing retina, we evaluated their expression at different embryonic (E) days and in primary cultures of neuronal and glial cells and their light responses by PCR and immunochemistry. Opn3 and Opn5 traces were detected very early in development likely in newborn RGCs, amacrine, and glial cells, and a significant increase was seen by E10 and later on. Opn3 and Opn5 were found in RGCs and Muller cell cultures by E10 and E15, respectively. In postnatal retinas, a clear light/dark difference was found in Opn3 and Opn5 proteins with higher values in the inner retina during the light phase. In addition, blue light increased expression of Opn3 in Muller cells, and it also promoted a change in its subcellular localization in neuronal cells. Results show the early appearance of these opsins during development and particularly in inner retinal cells at the light phase suggesting an important role during the day.

Sensory Systems

P277. When Senses Work Together: How Multimodal Integration Helps You Stay Alive

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An essential task of the nervous system is to make behaviorally adaptive decisions based on various sources of information coming from the environment. In this context, multisensory integration is the process that combines the different sensory signals associated to a single event. Multisensory integration increases the likelihood of detecting a relevant event, especially when the unimodal information is limited or ambiguous. This is especially critical when the task is related to threat avoidance: slight enhancement on detection of a predator cues can determine an animal's survival. In fish, the escape response (C-start) is a robust overt behavior easy to quantify with a well-understood neuronal basis. Here, we analyze behavioral responses of goldfish (*Carassius auratus*) to visual and auditory stimuli, shown individually or combined, and quantify the escape probability. We show how sensory cues that individually trigger responses with a low rate combine to enhance risk detection. Complete information about an event is infrequent in real-life scenarios. Here, we discuss how animals use available sources of information for optimal decision-making.

Sensory Systems

P278. Oxaliplatin-Induced Peripheral Neuropathy and Neuropathic Pain: Mechanisms Involved and Possible Therapeutic Strategies

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Chemotherapy-induced peripheral neuropathy and neuropathic pain are common and debilitating side effects of cancer therapy. No available strategies can limit the neuropathy. We evaluated the use of 17a-hydroxyprogesterone caproate (HPGC) as a neuroprotective agent and studied glial activation as a possible contributor to neuropathy. Male rats were injected with oxaliplatin (OXA) and HPGC following prophylactic (HPGCp) or therapeutic (HPGCt) schemes (starting either before or after chemotherapy) and pain development was evaluated. Animals receiving OXA showed a decrease in paw mechanical and thermal thresholds ($p < .001$ vs. CTL from Day 3 in both cases). Animals treated with HPGCp showed patterns of response similar to those detected in CTL animals ($p > .05$), while those treated with HPGCt showed a reversion of both hypersensitivities after HPGC administration ($p > .05$ vs. CTL). In addition, a significant increase in the mRNA levels of GFAP, Iba1, TNFa, and IL1b was detected in the dorsal root ganglia and dorsal horn of OXA animals ($p < .05$ vs. CTL) and significantly lower levels of all markers in OXA+HPGC animals ($p < .05$ vs. OXA). These results show that HPGC administration reduces glial activation parameters and prevents/reverts mechanical and thermal hypersensitivities induced by OXA, suggesting a promising therapeutic strategy.

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Sensory Systems

P279. Neural Circuits Supporting Context and Experience-Dependent Representation of Olfactory Information

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Abstract not available

Sensory Systems

P280. On and Off Visual Channels Adapt Differentially to Object Motion Allowing Arthropods to Recognize Novel Stimuli Occurrence

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Object motion detection provides essential cues for a wide variety of behaviors such as mate, prey, or predator detection. In insects and decapod crustaceans, encoding of object motion is associated to visual processing in the third retinotopic optic neuropil, the lobula. Due to the thin caliber of

the small-field lobula columnar neurons, almost all we know about object motion detection arises from studies on their postsynaptic and larger lobula output neurons. Here, we used calcium imaging to study the activity of the columnar neurons that feed onto the crab's lobula when stimulated by object motion stimuli that varied in contrast polarity. Dark edges translating over clear backgrounds evoked more powerful responses than stimuli with the opposite contrast relation. Besides, columnar neurons that were habituated to edge motion with certain contrast polarity recovered when stimulated with the opposite one. As lobula output neurons have been implicated in driving alert and defensive responses, we also studied the modulation of the crab cardiac activity (a variable indicative of animal internal state) to variations in the same visual parameters. We found a high correlation between the activity of the columnar neurons and changes in cardiac activity. These results are consistent with the involvement of the lobula in object motion coding. Moreover, the differential adaptation observed for the on and off visual channels allows arthropods to recognize novel visual stimuli.

Sensory Systems

P281. Effect of CB1 Receptor Modulation on Gene Expression in Light Induced Retinal Degeneration

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Light-induced retinal degeneration (LIRD) is a model that resembles human retinal degenerative diseases as AMD. Endocannabinoids are neuromodulators whose effects are mediated by G protein-coupled receptors named CB1 and CB2. Our previous results showed that the administration of ACEA (CB1 agonist) before continuous illumination stress is neuroprotective, decreasing apoptosis and glial reactivity, while AM251 (CB1 antagonist) worsened these parameters in LIRD. Our aim was to evaluate the effect of CB1 modulation on gene expression in LIRD. The right eyes of rats were intravitreally injected either with ACEA or AM251, while the left eyes received vehicle as controls. Later, rats were subjected to continuous illumination (12.000 lux) for 24 hr. Retinas were dissected and were processed by qRT-PCR. Data were statistically analyzed using Student's *t* test, and differences were considered significant when $p < .05$. The eyes treated with ACEA showed significant lower mRNA levels of BAD, BCL2, CYP1A1, adrenomedullin, and DAGL-B. Conversely, the eyes treated with AM251 showed significant higher mRNA levels of apoptotic genes BAD, BAX, BCL2, TNF; receptors CB1, TRPV1, and aryl hydrocarbon receptor; angiogenic factors, adrenomeduline and VEGF; and enzymes FAAH, DAGL-A and B, and NAPE. Although further work is needed, CB1 receptor agonism may be considered a potential neuroprotective strategy in AMD.

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Synaptic Transmission and Excitability

P282. Effect of Rab11a in the Regulated Exocytosis of Mouse Chromaffin Cells

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Chromaffin cell exocytosis is coupled to voltage-dependent Ca^{2+} channels (VDCCs) activation. These cells present various pools of vesicles with different maturation level. The Immediately releasable pool (IRP) is composed of ready releasable vesicles very close to VDCCs and is released by short depolarizations. More prolonged stimulations are able to release the totality of the ready releasable pool and, if maintained, exocytosis depends on the transport of vesicles from reserve pools. Some RabGTPases are involved in the secretion pathway, but Rab11a has not yet been studied in chromaffin cells. We evaluated the effect of Rab11a on chromaffin cell exocytosis by expressing GFP-Rab11aQ70L, a constitutively active form, and mCherry-Rab11aS25N, a dominant negative form. We used patch clamp/whole cell to measure membrane capacitance. We observed a strong decline in the release of the IRP when either Rab11a mutants were expressed. In addition, both mutants showed a significant reduction in the total change of the membrane capacitance in response to ten 50 ms depolarizations (2 Hz), evidencing a decrease in the whole number of ready releasable vesicles. Images taken by confocal microscopy showed that mCherry-Rab11aS25N affected the distribution of GFP-neuropeptide Y (NPY)-labeled secretory

vesicles: NPY was concentrated in one big spot. These results suggest that Rab11a modulates the generation of secretory vesicles needed for the regulated exocytosis in chromaffin cells.

Synaptic Transmission and Excitability

P283. Cognitive Interference and NOS-1 inhibition Are Therapeutic Strategies to Prevent Benzodiazepine Withdrawal Expression

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Abstract not available

Synaptic Transmission and Excitability

P284. Mesenchymal Stem Cells Therapy Reversed Hippocampal Atrophy, Neurodegeneration, Loss of Presynaptic Proteins, Reactive Microglia and Behavior Impaired in a Rat Model of Sporadic Alzheimer's Disease

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Abstract not available

Synaptic Transmission and Excitability

P285. D1/D5 Dopamine Receptor Stimulation Increases Striatal Cholinergic Interneuron Excitability in a Mouse Model of L-DOPA-Induced Dyskinesia

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Abstract not available

Synaptic Transmission and Excitability

P286. Altered Pacemarker Currents in Thalamic Ventrobasal Neurons of Leptin-Deficient Mice

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The hyperpolarization-activated cyclic nucleotide-gated (HCN) and KV7 (M) channels are voltage-gated ion channels that carry h and M currents, respectively (Ih, IM). The expression of HCN1-4, Kv7.2, and Kv7.3 isoforms is abundant in the thalamus. Both channels are activated at subthreshold potentials and have biophysical properties that mirror each other. Because of their opposite voltage dependences and directions, they both function similarly as intrinsic, slow "voltage clamps," tending to stabilize the resting membrane potential (RMP) by opposing depolarizing or hyperpolarizing inputs. Subtle modifications of RMP impact on T-type calcium channels, and this has profound consequences for action potential (AP) generation. Here, we studied the electrophysiological expression of h, M, and T-type currents in ventrobasal (VB) neurons in brain slices from wildtype (WT) or the leptin-deficient mouse (ob/ob). Ih density and its kinetic properties were altered in the ob/ob mice. Ih density decreased by 30% (WT, $n = 19$; ob/ob, $n = 21$) and both, time constants of activation and deactivation were increased (WT, $n = 14$; ob/ob, $n = 20$). The IM blocker XE991 sped up Ih activation and deactivation kinetics but only in the ob/ob ($n = 7$) and not in the WT ($n = 9$), suggesting an IM overexpression. Depolarization conveyed by a decreased Ih activation in the ob/ob diminished the deinactivation of T-type channels, thereby altering the generation of an LTS, which in turn triggers a burst of APs.

Synaptic Transmission and Excitability

P287. Effect of Inhomogeneous Sub-Cellular Distribution of Ion Conductances on the Oscillatory Activity of Thalamocortical Neurons

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Thalomocortical neurons (TC) have two firing modes: tonic and bursting. These firing modes, in combination with the synaptic connectivity, create thalamocortical physiological oscillations that are correlated with global brain states, like sleep and arousal, and pathological oscillations, like spike and wave discharges, which are characteristic of idiopathic epilepsies. To study the role of TC neurons on the generation and maintenance of theses oscillations, we developed a multicompartment model that includes seven ionic conductances, which have been previously measured in our laboratory. In this study, we began with a model tuned to generate intrinsically repetitive bursting. Then, we explored the parameter space and found the combinations of parameters that are consistent with this firing mode. We also incorporated the main synaptic inputs into the model (sensory, cortical, and from the reticular thalamus) to determine how TC neurons bursting behavior is affected by the combination of these inputs when the compartmentalized distribution ion channels is considered.