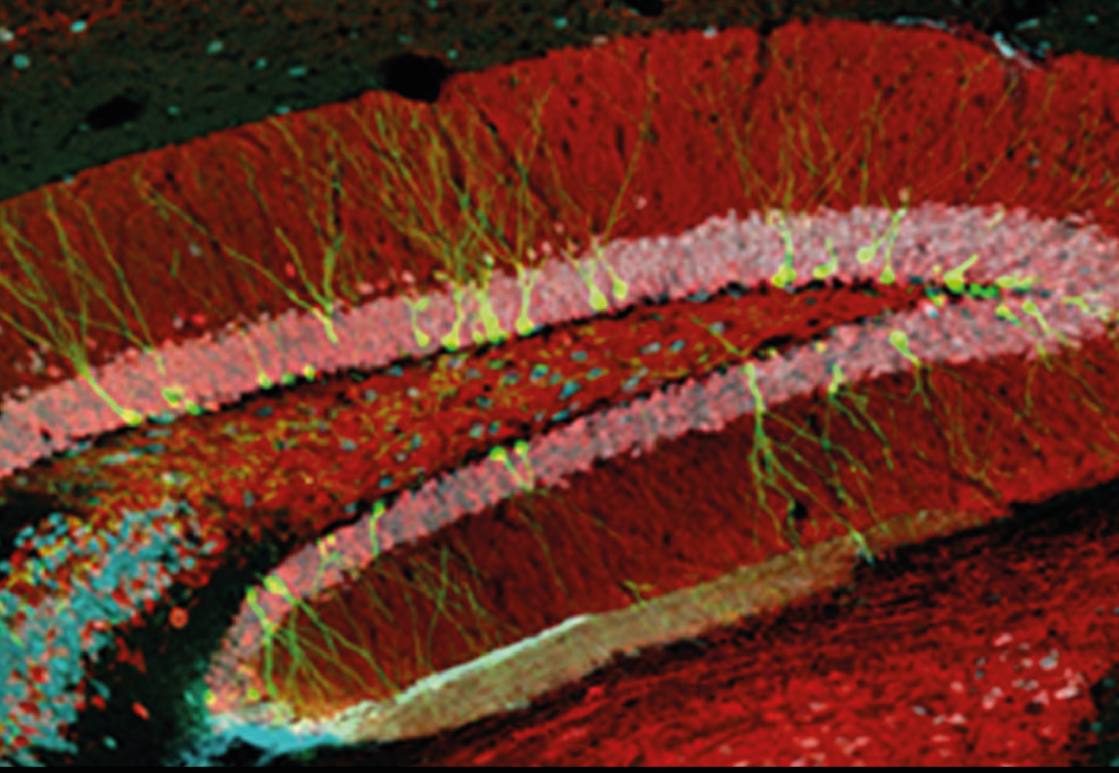

SAN
SOCIEDAD ARGENTINA DE INVESTIGACIÓN EN NEUROCIENCIAS

XXIX ANNUAL MEETING
AND SAN-ISN SMALL CONFERENCE AND COURSE

"New mechanisms of neuro-glial interaction: Their contribution to nervous system development and repair"

September 29 | October 3, 2014
Huerta Grande, Córdoba, Argentina

COMMITTEES

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A. Javier Ramos

Tomás Falzone

Fernanda Ledda

Gustavo Paratcha

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Meeting Organizing Committee:

Tomás Falzone

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Foto de tapa: Imagen obtenida por microscopía confocal, correspondiente a un corte de hipocampo obtenido de ratones adultos. En verde fluorescente pueden observarse neuronas granulares generadas en el cerebro adulto, marcadas por transduccion retroviral.

Créditos: Georgina Davies-Sala, Lab Schinder.

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Dear SAN members, friends and colleagues,

On behalf of the 2014 organizing committee and the SAN Board of Directors, it is my great pleasure to welcome you all to our XXIX Annual Meeting and to the SAN-ISN special small conference. As in previous years, Huerta Grande, Córdoba, is the place where we will gather. This retreat in the middle of the hills gives the unique opportunity to host us all in one place and provides the right atmosphere for scientific discussions.

With an increasing ageing population, neuroscience is a strategic area of research in the 21st century. Although far from the large-scale investments such as the USA BRAIN Initiative or the European Human Brain projects, the Argentinean neuroscience community continues to grow and SAN has now near 500 members. This mainly derives from the personal effort of each one of our members who, through a strong passion for their work, set free will to their imagination and explore new horizons, even with limited resources. The excellence of Argentinean neuroscience is reflected by the increasing number of publications in high-profile journals and the prestigious awards received by SAN members in 2014, such as the L´ORÉAL Unesco For Women in Science for Latin America and recognitions from the Humboldt Foundation.

We at SAN are committed to aid in deciphering the complexity of the brain and the nervous system, promoting high quality science and encouraging translational research that will ultimately benefit society through a better understanding of neurological diseases. This can only be achieved by bringing together scientists with diverse scientific background and expertise, different nationalities and at different stages of their career. We hope that the XXIX Annual Meeting will fulfill this objective. Thank you all invited speakers for coming from far away to share your newest discoveries. Thank you all neuroscience students for your energy and refreshing and renovating ideas. Thank you SAN members for your continuing support to the society. And last, but not least, thank all sponsors that make our Annual Meetings a reality.

Enjoy the meeting, establish new collaborations, come up with innovative ideas, meet old friends and make new ones.

Ana Belén Elgoyhen
SAN President

CONTENT

PROGRAM

SAN-ISN Small Conference and course

"New mechanisms of neuro-glial interaction: Their contribution to nervous system development and repair"

DAY 1: Monday September 29th

8:00-9:30	Registration
9:30-10:15	Welcome words by the SAN-ISN small conference and course organizers Description of the general organization of the course and initial orientation for the Project-writing workshop for students
10:15-10:45	Coffee break and post your poster
10:45-12:15	Lecture I: ***"Tripartite synapse: new glial roles"*** **Vladimir Parpura,** University of Alabama at Birmingham, USA
12:30-14:00	Lunch
14:30-16:00	Lecture II: "***Astrocytes: key function in the balance between excitatory and inhibitory synaptic inputs"*** **Flavia Gomes,** Universidade Federal do Rio de Janeiro, Brasil
16:00-17:30	Lecture III: ***"Characterization of astrocytes phenotypes modulating disease progression in inherited ALS"*** **Luis Barbeito,** Institut Pasteur, Montevideo, Uruguay
17:30-18:30	Poster viewing I & refreshments
18:30-21:00	Group activity meeting I: Project writing workshop for students
21:30	Dinner

DAY 2: Tuesday September 30th

7:30-8:30	Breakfast
8:30-10:00	Lecture IV: ***"Glia and the formation/plasticity of neural circuits"*** **Gabriel Corfas,** Director, Kresge Hearing Research Institute, University of Michigan, USA
10:30-11:00	Coffee Break and poster viewing II
11.00-12:30	Lecture V: ***"Functional role of microglial cells in Parkinson´s Disease"*** **Fernando Pitossi,** Instituto Leloir, Buenos Aires, Argentina
13:00-14:30	Lunch
14:30-16:30	Lecture VI: ***"The role of Schwann cells in degenerative and regenerative axonal programs"*** **Felipe Court,** Pontificia Universidad Católica de Chile, Santiago, Chile
16:30-17:00	Coffee Break and poster viewing III
17:00-18:30	Group activity meeting II: Project writing workshop for students
18:30-20:30	Group activity meeting II: Project writing workshop, student´s presentations
20:30-21:30	Round table and final conclusions of the SAN-ISN small conference and course
21:30	Dinner

XXIX CONGRESO ANUAL DE LA SOCIEDAD ARGENTINA DE INVESTIGACION EN NEUROCIENCIAS

DAY 1: Wednesday October 1st

09:00 Registration

10:00 Welcome by Organizers

10:10-12:30 **Symposium I: "The Good and the Bad of Neurotrophins"**
Chairs: **Laura Montroull y Andrea Cragnolini,** Instituto de Investigaciones Biológicas y Tecnológicas, Universidad Nacional de Córdoba, CONICET, Argentina

10:20-10:50 *"XIAP Regulates Sub-Lethal Caspase Activity in Axons and Synapses"*
Philip Barker, McGill University, Montreal, Canada

10:50-11:20 *"The multifaceted role of the p75 neurotrophin receptor in the brain"*
Wilma Friedman, Rutgers University, USA

11:20-11:50 ***"Role of the endocytic system in BDNF-mediated dendritic branching"***
Francisca Bronfman, Pontificia Universidad Católica de Chile, Santiago, Chile

11:50-12:20 ***"Endogenous BDNF/proBDNF level modification in neuronal death and survival"***
Daniel Mascó, Universidad Nacional de Córdoba-CONICET, Córdoba, Argentina

12:30-14:00 Lunch

14:30-16:00 **Short talks selected from poster abstracts** (parallel sessions):
Room A – Chair: **A. Javier** Ramos. Instituto de Biología Celular y Neurociencia (IBCN-CONICET), Universidad de Buenos Aires
Room B – Chair: **Fernanda Ledda.** Instituto de Biología Celular y Neurociencia (IBCN-CONICET), Universidad de Buenos Aires

16:15-19:15 **Poster Session I, Networking & Coffee break**
16:15-17:45 ***EVEN NUMBER poster presentation***
17:45-19:15 ***ODD NUMBER poster presentation***

19:15-20:15 **Eduardo de Robertis Plenary Lecture**
Chair: **Ana Belén Elgoyhen,** Instituto de Investigaciones en Ingeniería genética y Biología Molecular, Dr Héctor N. Torres, Argentina
"Unexpected interactions in the basal ganglia"
Bernardo Sabatini, Neurobiology Department, Harvard Medical School, Howard

Hughes Medical Institute, USA

20:15-20:45 **SAN Award to the Best Doctoral Thesis in Neuroscience 2014**
Chair: **Juan Goutman,** Instituto de Investigaciones en Ingeniería genética y Biología Molecular, Dr Héctor N. Torres, Argentina
"Stress-Induced Cocaine Sensitization: A Study of Glutamate Homeostasis and its Interaction with the Dopaminergic System in Nucleus Accumbens"
Constanza García Keller, Dpto de Farmacología, Fac. Ciencias Químicas, Universidad Nacional de Córdoba, Argentina - Department of Neurosciences, Medical University of South Carolina, USA

21:00-22:45 Dinner
Dinner activity: eat with the big shots I!
Students and postdocs can sign up to share the table with lecturers and symposia speakers

23:00 Asamblea Ordinaria SAN/ SFN Chapter

DAY 2: Thursday October 2nd

7:30-8:15 Breakfast

8:15-12:50 **SAN–ISN Symposium: "Deconstructing Adult Neurogenesis: From Neural Stem Cells to Neuronal Networks in Health and Disease"**
Chair: **Alejandro Schinder,** Fundación Instituto Leloir, Buenos Aires

8:15-9:00 ***"A novel view of neurogenesis and memory encoding in the dentate gyrus"***
Alejandro Schinder, Laboratory of Neuronal Plasticity, Fundación Instituto Leloir, Buenos Aires

9:00-9:50 ***"Analysis of neural stem cells in the adult mammalian brain, one cell at a time"***
Hongjun Song, Institute for Cell Engineering and Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore

9:50-10:40 ***"Brains in metamorphosis: physiological and forced neurogenesis in the adult brain"***
Benedikt Berninger, Adult Neurogenesis & Cellular Reprogramming, Institute of Physiological Chemistry University Medical Center, Johannes Gutenberg, University Mainz

10:40-11:10 Coffee Break

11:10-12:00 *"Adult Neurogenesis and Psychiatric Neurodevelopmental Disorders"*
Guoli Ming, Institute for Cell Engineering and Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore

12:00-12:50 ***"From pluripotent stem cells to cortical circuits"***
Pierre Vanderhaeghen, Institute for Interdisciplinary Research and Institute of Neuroscience, Free University of Brussels

13:00-14:45 Lunch

15:00-17:30 **Poster Session & Networking II & Coffee break**

15:00-16:15 ***ODD NUMBER poster presentation***

16:15-17:30 ***EVEN NUMBER poster presentation***

17:30-19:00 **IBRO Special Lectures**
Chair: **Marta Hallak**, Centro de Investigaciones en Química Biológica de Córdoba, CONICET

17:30-18:00 ***"The Global Mission of IBRO, and IBRO 2015 in Rio de Janeiro"***
Sten Grillner, IBRO Secretary-General, Karolinska Institute, Stockholm, Sweden

18:00-19:00 *"**The Blueprint of the Vertebrate Motor System – from Microcircuits to Selection of Behaviour"***
Sten Grillner, IBRO Secretary-General, Karolinska Institute, Stockholm, Sweden

19:00-19:30 Coffee Break

19:30-21:00 **Young Investigator Symposium**
Chair: **Tomás Falzone**, CONICET, Universidad de Buenos Aires

19:30-19:50 ***"Impact of axonal, autoreceptor mediated, synaptic events on cerebellar interneuron's activity"***
Javier Zorrilla de San Martin, Université Paris Descartes, France

19:50-20:10 *"Caspase-3 and Calpains become active during (and play a role in) injury-induced axonal degeneration but are not inhibited during NAD+-mediated protection"*
Nicolás Unsaín, McGill University, Canada/Instituto de Investigacion Médica Mercedes y Martín Ferreyra, CONICET, Argentina

20:10-20:30 *"Amyloid Precursor Protein Is an Autonomous Growth Cone Adhesion Molecule Engaged in Contact Guidance"*
Lucas Sosa, University of Colorado School of Medicine, USA/Centro de Investigaciones en Química Biológica de Córdoba, CONICET , Argentina

20:30-20:50 *"Neurogenin3 is a key regulator in serotonergic vs. glutamatergic neuronal cell fate"*

Abel Carcagno, Fundación Instituto Leloir, Argentina

21:00 Dinner

Dinner activity: eat with the big shots II!

23:00 PARTY!!!!

DAY 3: Friday October 3rd

8:00-9:00 Breakfast

9:00-11:00 **Symposium II: "Ion channels from development to behavior"**

Chair: **Nara Muraro**, Fundación Instituto Leloir, Argentina

9:00-9:30 ***"Inhibitory aminergic signaling in C.elegans: characterization and in vivo manipulation"*** **Diego Rayes**, Instituto de Investigaciones Bioquímicas de Bahía Blanca, Bahía Blanca, Argentina

9:30-10:00 ***"How do Drosophila clock neurons fire up?"***

Nara I. Muraro, Fundación Instituto Leloir, Argentina

10:00-10:30 *"Pumilio-2 regulates translation of Nav1.6 to mediate homeostasis of membrane excitability"*

Richard Baines, Faculty of Life Sciences, University of Manchester, UK

10:30-11:00 *"Activity-dependent regulation of coordinated ion channel expression: from mRNA to network output"*

David Schulz, Department of Biological Sciences, University of Missouri, USA

11:00-11:30 Coffee break

11:30-12:30 **Ranwel Caputto Plenary Lecture**

Chair: **Arturo Romano**, Instituto de Fisiología Biología Molecular y Neurociencias, Universidad de Buenos Aires

"Motor coordinates to study birdsong"

Gabriel Mindlin, Departamento de Física, Facultad de Ciencias Exactas y Naturales, UBA, Argentina

12:30 Closing remarks by organizers

13:00 Farewell Barbecue

16:00 Meeting adjourns

Recipients of Young ISN Neurochemistry Awards

Anabela Palandri, Córdoba, Argentina
María Paula Avalos, Córdoba, Argentina
Andrea Susana Guzmán, Córdoba, Argentina
María Vanessa Cadena, Buenos Aires, Argentina
Nonthue Alejandra Uccelli, Berazategui, Argentina
Jerónimo Lukin, Buenos Aires, Argentina
Laura Montroull, Córdoba, Argentina
Nicolás Unsain, Córdoba, Argentina
Luis Ernesto Acosta, Buenos Aires, Argentina
María Florencia Almeira Gubiani, Buenos Aires, Argentina
Diego Damián Alvarez, Buenos Aires, Argentina
Marcos Andrés Campolongo, Buenos Aires, Argentina
Micaela Daiana García, San Martín, Argentina
María Paula Ibáñez Rodríguez, Mendoza, Argentina
Nadia Kazlauskas, Buenos Aires, Argentina
Noelia Giselle Lino, Buenos Aires, Argentina
Magdalena Miranda, Buenos Aires, Argentina
Javier Andrés Muñiz, Buenos Aires, Argentina
Patricio Roberto Pavía, Buenos Aires, Argentina
Gonzalo Miguel Piñero, Buenos Aires, Argentina
María Celeste Solange Rivero Echeto, Buenos Aires, Argentina
Gerardo Ariel Rosciszewski, Buenos Aires, Argentina
María Micaela Sartoretti, Buenos Aires, Argentina
Silvio Temprana, Buenos Aires, Argentina
Lucila Brocardo, Bernal, Argentina
Octavio Gianatiempo, Buenos Aires, Argentina
Florencia Martina Soler García, San Luis, Argentina
Betina González, Buenos Aires, Argentina
Veronica Murta, Buenos Aires, Argentina
Constanza García Keller, Córdoba, Argentina
Alejandra Ivetth **Pérez** Alvarez, Caracas, Venezuela
Sonia Carolina Guerrero Prieto, São Bernardo do Campo, Brasil
Wagno Alcantara de Santana, Salvador, Brasil
Angelica Jhoan Alarcon Garcia, Bogotá, Colombia
Claudia Angelica Bonilla Escobar, Santo Andre, Brasil
Irene Riveros Barrera, Bogotá, Colombia
Cristian Ivan Giraldo León, Bogotá, Colombia
Nicolás Iván Bertone Cueto, Buenos Aires, Argentina
Victoria Rozes Salvador, Córdoba, Argentina

ABSTRACTS

Tripartite synapse: new glial roles

Vladimir Parpura

Part 1: Mechanisms of glutamate release from astrocytes

Astrocytes can release the excitatory transmitter glutamate which is capable of modulating activity in nearby neurons. This astrocytic glutamate release can occur through six known mechanisms: **(i) reversal of uptake by glutamate (ii) anion channel opening, (iii) Ca^{2+}-dependent exocytosis, (iv) glutamate exchange via the cystine-glutamate antiporter, (v) release through ionotropic purinergic receptors and (vi) functional unpaired connexons, 'hemichannels', on the cell surface. Although these various pathways have been defined, it is not clear how often and to what extent astrocytes employ different mechanisms. It will be necessary to determine whether the same glutamate release mechanisms that operate under physiological conditions operate during pathological conditions or whether there are specific release mechanisms that operate under particular conditions.**

Part 2: Vesicular release of glutamate mediates bidirectional signaling between astrocytes and neurons

The major excitatory neurotransmitter in the CNS, glutamate, can be released exocytotically by neurons and astrocytes. Glutamate released from neurons can affect adjacent astrocytes by changing their intracellular Ca^{2+} dynamics and, vice versa, glutamate released from astrocytes can cause variety of responses in neurons such as: an elevation of $[Ca^{2+}]_i$, a slow inward current, an increase of excitability, modulation of synaptic transmission, synchronization of synaptic events, and long-term potentiation, or some combination of these. This astrocyte-neuron signaling pathway might be a wide-spread phenomenon throughout the brain with astrocytes possessing the means to be active participants in many functions of the CNS. Thus, it appears that the vesicular release of glutamate can serve as a common denominator for two of the major cellular components of the CNS, astrocytes and neurons, in brain function.

Astrocytes: key function in the balance between excitatory and inhibitory synaptic inputs

Flavia Gomes

Assembly of synapses requires proper coordination between pre- and post-synaptic elements. Identification of cellular and molecular events in synapse formation and maintenance is a key step to understand human perception, learning, memory, and cognition. Astrocytes play important role in the development and maintenance of neuronal circuitry. Here we will discuss how astrocytes regulate the balance between excitatory and inhibitory synaptic inputs, critical for control brain function. We previously demonstrated that astrocytes induce excitatory synapses through transforming growth factor beta 1 (TGF-β1) pathway and control of the levels of the aminoacid, D-serine. Recently, we showed that inhibitory synapses are also induced by astrocyte secreted TGF-β1. TGF-β1 -induction of inhibitory synapse is dependent of glutamatergic activity and activation of CaM kinase II, which thus induces localization and cluster formation of the synaptic adhesion protein, Neuroligin 2, in inhibitory postsynaptic terminals. We will discuss that the balance between excitatory and inhibitory inputs might be provided by astrocytes signals, at least partly achieved via TGF-β1 downstream pathways.

Characterization of astrocytes phenotypes modulating disease progression in inherited ALS

Luis Barbeito

Motor neuron loss and reactive astrocytosis are pathological hallmarks of Amyotrophic Lateral Sclerosis, a paralytic neurodegenerative disease that can be triggered by mutations in Cu,Zn-superoxide dismutase-1 (SOD1). Dysfunctional astrocytes contribute to ALS pathogenesis, inducing motoneuron damage and accelerating disease progression. **However, it is unknown whether ALS progression is associated to the appearance of a specific astrocytic phenotype with neurotoxic potential.** We have recently reported the isolation of astrocytes with aberrant phenotype (referred as AbAs) from primary spinal cord cultures of symptomatic rats expressing the $SOD1^{G93A}$ mutation. Isolation was based on AbA's marked proliferative capacity and lack of replicative senescence, which allowed oligoclonal cell expansion during over 1 year. AbAs displayed astrocytic markers including GFAP, S100β, glutamine synthase and connexin 43, but lacked the GLT1 glutamate transporter and the glial progenitor marker NG2 glycoprotein. Notably, AbAs secreted soluble factors that induced motoneuron death with a 10-fold higher potency than neonatal $SOD1^{G93A}$astrocytes. AbA-like aberrant astrocytes expressing S100b and connexin43 but lacking NG2 were identified nearby motoneurons, its number increasing sharply after disease onset. In conclusion, AbA cells appear as a yet-unknown astrocyte population arising during ALS progression, with unprecedented proliferative and neurotoxic capacity, being potential cellular targets for slowing ALS progression.

Glia and the formation/plasticity of neural circuits

Gabriel Corfas

Since their initial discovery in the 1800s until recently, glial cells were considered to be the "connective tissue" of the nervous system, their formation was believed to be regulated by predetermined biochemical and cellular processes, and they were viewed as static components. Research during the last few years is providing a very different picture, one in which glia are actively involved in the development and plasticity of the nervous system. In my lecture I will discuss our recent findings on how experience changes glia, how glia regulate the formation of synapses, and the consequences that altered glia have on physiology, behavior and cognitive function. We will also discuss how trophic factor signaling pathways regulate neuron-glia interactions and the implications of these interactions for normal brain function and disease.

Functional role of microglial cells in Parkinson´s Disease

Fernando Pitossi

Parkinson ´s Disease (PD) is the second most common neurodegenerative disease in the population. Unfortunately, the aetiology of over 80% of PD cases is unknown. Lacking evidence on the aetiology, the study of the pathophysiology of the disease becomes more relevant to identify novel therapeutic targets. One patho-physiological feature consistently found in animal models and PD patients is robust microglial activation. However, microglia activation could mediate neurodegenerative or neuroprotective effects depending on the array of molecules associated with this activation and the molecular and cellular context in which they act. As a consequence, microglial activation remains an unreliable therapeutic target in PD treatment. We believe that identifying parameters that could determine a univocal role of microglial activation on neuronal cell death in the substantia nigra (SN), the main region affected in PD, is crucial to define new therapeutic targets against PD and select PD patients to be enrolled in anti-PD trials based on immunomodulation. We have found that microglial activation in the degenerating SN is "primed". Microglial cells can be shifted to a pro-inflammatory state by, not only central, but also sub toxic levels of systemic inflammation. This shift can dramatically exacerbate on-going neurodegeneration in the SN leading to increased and earlier motor symptoms, via Interleukin-1beta (IL-1) overproduction. In addition, we have observed that sustained but not acute expression of IL-1 or Tumor necrosis factor-alpha (TNF) in the SN leads to dopaminergic neuronal demise, motor symptoms and microglial activation. TNF effects are dose-dependent since, using a combination of knock-in mice, adenoviral vectors and the CRE/lox system we could demonstrate that low levels of TNF can be neuroprotective for nigral neurons, while higher levels could be detrimental.In conclusion, we have identified parameters that determine a given effect of pro-inflammatory cytokines on neuronal viability, paving the way to test new hypothesis, study the effects of immunomodulatory treatments, and identify downstream effector molecules on these newly generated models of PD.

The role of Schwann cells in degenerative and regenerative axonal programs

Felipe Court

Nervous system function relies in the coordinated action of neurons and glial cells. In recent years, the importance of glial cells for several aspects of nervous system function has been underscored. Phenomena like synaptic activity, conduction of action potentials, neuronal growth and regeneration, to name a few, are fine tuned by glial cells. We have proposed a model in which the axon has certain autonomy from the neuronal cell body, and its associated glial cell is a major regulator of local axonal programs, including a regenerative program of axonal extension (Court and Alvarez, 2005), a destruction program activated by various stimuli (Barrientos et al., 2011; Villegas et al., 2014) and unpublished data) and local protein synthesis in the axon (Court et al., 2008). Several intercellular mechanisms have been shown to operate on a local basis in the neuron-glia unit, including contact-mediated signaling and extracellular free ligands. Recently, another regulatory mechanism has emerged in which a cell releases vesicles containing RNAs and proteins, that are taken up by the recipient cell and the cargo is incorporated into the target cell (Simons and Raposo, 2009). Vesicular-mediated transfer of molecular cargoes between glial cells and neurons has been described in the nervous system (Lopez-Verrilli and Court, 2012; Lopez-Verrilli and Court, 2013). We have demonstrated vesicular-mediated transfer of ribosomes from Schwann cells (SCs), the peripheral glial cell type, to axons in vivo after axonal damage as well as during axonal regeneration (Court et al., 2008; Court et al., 2011). Recently, we have found that exosomes secreted by SCs and selectively internalized by axons increase neurite growth substantially and greatly enhance axonal regeneration in vitro and in vivo (Lopez-Verrilli et al., 2013). We have now used a combination of next-generation sequencing, proteomics and bioinformatic analysis to identify RNAs and proteins present in SC-exosomes, and to search for candidates mediating the functional effect of SC-exosomes over axonal regeneration. This mode of interaction provides a new dimension to the understanding of the intercellular regulation at large, and we foresee that a number of phenomena of the nervous system still poorly understood will be studied under this new light.

Eduardo de Robertis Plenary Lecture

Wednesday 1st, 19:15-20:15
Chair: **Ana Belén Elgoyhen**, Instituto de Investigaciones en Ingeniería genética y Biología Molecular, Dr Héctor N. Torres, Argentina

"Unexpected interactions in the basal ganglia"
Bernardo Sabatini
Neurobiology Department, Harvard Medical School, Howard Hughes Medical Institute, USA

The basal ganglia (BG) are a phylogenetically conserved set of subcortical nuclei necessary for coordinated motor action and reward learning. Accepted models postulate that the BG modulate cerebral cortex indirectly via an inhibitory output to thalamus, bidirectionally controlled from within the BG by direct (dSPNs) and indirect (iSPNs) pathway striatal projection neurons2-4. The BG thalamic output sculpts cortical activity by interacting with signals from sensory and motor systems5. Here we describe a direct projection from the globus pallidus externus (GP), a central nucleus of the BG, to frontal regions of the cerebral cortex (FC). Two cell types make up the GP-FC projection, distinguished by their electrophysiological properties, cortical projection patterns and expression of choline acetyltransferase (ChAT), a genetic marker for neurons that release the neurotransmitter acetylcholine (ACh). Despite these differences, ChAT+ cells, which have historically been identified as an extension of the nucleus basalis (NB), as well as ChAT- cells, release the inhibitory neurotransmitter GABA (γ-aminobutyric acid) and are inhibited by iSPNs and dSPNs of dorsal striatum. Thus GP-FC cells comprise a direct GABAergic/cholinergic projection that places frontal cortex under the inhibitory control of the striatum. Furthermore, iSPN inhibition of GP-FC cells is sensitive to dopamine 2 receptor signaling, revealing a pathway by which drugs that target dopamine receptors for the treatment of neuropsychiatric disorders can act in the BG to modulate frontal cortices.

IBRO Special Lectures

Thursday 2nd, 18:00-19:00
Chair: **Marta Hallak,** Centro de Investigaciones en Química Biológica de Córdoba, CONICET

"The Blueprint of the Vertebrate Motor System – from Microcircuits to Selection of Behaviour"
Sten Grillner
IBRO Secretary-General, Karolinska Institute, Stockholm, Sweden

The lamprey diverged from the vertebrate line of evolution leading up to mammals 560 million years ago. What is common in the organization of the nervous system of lamprey and mammals must have been present already very early in vertebrate evolution. We have previously shown that the basic organization of the brainstem spinal cord is conserved and also the midbrain control of eye and orienting movements. Recently we have shown in a series of studies that the detailed organization of the basal ganglia and related habenula complex is conserved with regard to transmitters, neuropeptides, expression of ion channel subtypes, neuronal activity pattern and connectivity (e.g. Stephenson Jones et al 2013). We now show that also the organization of pallium (corresponding to cortex) is similar in that we have specific projection neurons to the tectum/superior colliculus, the midbrain tegmentum and to reticulospinal neurons in the hindbrain. Moreover, stimulation of the pallial region can elicit eye, orienting, locomotor and oral movements and these effects are elicited by monosynaptic effects on the different motor centres. In conclusion, the basic features of the vertebrate motor system existed already at the dawn of vertebrate evolution.
Stephenson-Jones M, AA Kardamakis, B Robertson and S Grillner (2013) PNAS 110; 3670-09.

Ranwel Caputto Plenary Lecture

Friday 3rd, 11:30-12:30
Chair: **Arturo Romano**, Instituto de Fisiología Biología Molecular y Neurociencias, Universidad de Buenos Aires

"Motor coordinates to study birdsong"
Gabriel Mindlin
Departamento de Física, Facultad de Ciencias Exactas y Naturales, UBA, Argentina

Fundamental unresolved problems of motor coding and sensorimotor integration include what information about behavior is represented at different levels of the motor pathway. Insight into this issue is essential for understanding complex learned behaviors such as speech or birdsong. A major challenge in motor coding has been to identify an appropriate framework for characterizing behavior.
In this work we discuss a novel approach linking biomechanics and neurophysiology to explore motor control of songbirds. We developed a model of song based on gestures that can be related to physiological parameters the birds can control. This physical model for the vocal structures allowed a reduction in the dimensionality of the singing behavior
This is a powerful approach for studying sensorimotor integration and represents a significant methodological advantage. Our results also show how dynamical systems models can provide insight into neurophysiological analysis of vocal motor control. In particular, our work challenges the actual understanding of how the motor pathway of the songbird systems works and proposes a novel perspective to study neural coding for song production. It also illustrates the turbulent relationship between physics and biology...

Symposium I: "The Good and the Bad of Neurotrophins"

Wednesday 1st, 10:10-12:30
Chairs: **Laura Montroull y Andrea Cragnolini**, Instituto de Investigaciones Biológicas y Tecnológicas, Universidad Nacional de Córdoba, CONICET, Argentina

Wednesday 1st, 10:20-10:50

"XIAP Regulates Sub-Lethal Caspase Activity in Axons and Synapses"

Philip Barker
Montreal Neurological Institute, McGill University, 3801 University St., Montreal, Canada, *H3A 2B4*

The ability of neurons to receive, process and transmit information relies on a highly complex and dynamic architecture. Most mammalian neurons initially produce an extensive set of processes that are subsequently pruned to retain only those that form part of the mature neuronal network. Significant, albeit less dramatic, re-sculpting also occurs throughout the neuron's life-span. The mechanisms that allow some neurites to be destroyed while others, derived from the same cell, are retained have not been extensively studied, perhaps because it was assumed that neurites withered away through a passive process. However, it is now certain that neurites are destroyed through phylogenetically conserved signaling mechanisms that induce local caspase activity. In addition, recent studies have indicated that activity-dependent changes in synaptic transmission also rely on sublethal caspase activity. The mechanisms that activate and regulate sublethal caspase activity in the nervous system remain poorly understood. Nerve growth factor (NGF) is a crucial survival signal for sensory and sympathetic neurons and we have examined the molecular signaling events that drive cell death and axonal degeneration after NGF withdrawal in peripheral neurons. Our studies show that X-linked inhibitor of apoptosis (XIAP) functions as a key regulator of caspase activity during developmental axonal degeneration. Based on these findings, we have explored the hypothesis that XIAP is required to regulate sublethal caspase activity in the central nervous system and our results demonstrate that XIAP is a potent regulator of activity-dependent changes in synapse function. Together, these studies show that XIAP plays a critical physiological role regulating caspase-dependent sub-lethal morphogenic events in the developing and adult nervous system.

Wednesday 1st, 10:50-11:20

"The multifaceted role of the p75 neurotrophin receptor in the brain"

Wilma Friedman

Department of Biological Sciences – RUTGERS University. Newark, NJ, USA

The p75NTR is induced in the brain following seizures and other types of brain injury and mediates neuronal death. The signaling mechanisms involve activation of the intrinsic caspase pathway, as well as suppression of Trk signaling by induction of the PTEN phosphatase which prevents Akt activation. However, p75NTR is also widely expressed in many brain regions during development, including the external granule layer of the cerebellum, where it does not appear to mediate neuronal death. Therefore, in addition to investigating the apoptotic role of p75NTR after brain injury, we have explored some of the non-apoptotic functions of this receptor during development.

Wednesday 1st, 11:20-11:50

"Role of the endocytic system in BDNF-mediated dendritic branching"

Francisca Bronfman

Departamento de Fisiología, Facultad de Ciencias Biológicas,
Pontificia Universidad Católica de Chile. Santiago, Chile.

Dendritic arborization of neurons is regulated by brain-derived neurotrophic factor (BDNF) together with its receptor TrkB. Endocytosis is required for dendritic branching and regulates TrkB signaling, but how post-endocytic trafficking determine the neuronal response to BDNF is not well understood. The monomeric GTPase Rab11 regulates the dynamics of recycling endosomes and local delivery of receptors to specific dendritic compartments. Our aim was to study whether Rab11-dependent trafficking of TrkB in dendrites regulates BDNF-induced dendritic branching in rat hippocampal neurons. We report that TrkB in dendrites is a cargo for Rab11 endosomes and both Rab11 and its effector MyoVb, an actin-based molecular motor, are required for BDNF/TrkB-induced dendritic branching. In turn, BDNF induces accumulation of Rab11-positive endosomes and GTP-bound Rab11 in dendrites. The expression of a constitutively active mutant of Rab11 is sufficient to increase dendritic branching by increasing TrkB localization in dendrites and enhancing sensitization to endogenous BDNF. On the other hand, increased Rab11-mediated TrkB signaling in dendrites is also required for BDNF-mediated nuclear activation of the transcription factor CREB. We propose a model where dendritic activation of Rab11 would increase recycling by promoting the interaction of Rab11 with Myosin Vb, increasing the amount of Rab11-positive endosomes in secondary dendrites, a process that would require actin filaments. Because Rab11 endosomes carry TrkB, sustained Rab11 activity results in increased endogenous TrkB receptor levels in dendrites, implying that this mechanism potentiates TrkB signaling in dendrites. Thus, this process provides a positive feedback mechanism to induce BDNF-dependent protrusion and the outgrowth of dendritic branches. On the other hand, TrkB signaling in Rab11 endosomes associated to cell bodies is required for nuclear signaling, process that allows the transcription of genes, including Rab11, required for increasing dendritic complexity.

Wednesday 1st, 11:50-12:20

"Endogenous BDNF/proBDNF level modification in neuronal death and survival"

Daniel Mascó

Universidad Nacional de Córdoba-CONICET, Córdoba, Argentina

Our research focusses on brain-derived neurotrophic factor (BDNF), a molecule known to be essential for a number of processes, including synaptic plasticity and positive events like neuronal survival. However, these functions has been challenged because the possibility that the same proteins may induce cell death. Animal models have revealed that its levels increase in pathological conditions such as Status Epilepticus. An important goal is then to explore whether the increase of BDNF levels or its interaction with neurotrophin receptors (TrkB and/or p75ntr) over prolonged periods of time are responsible for cell death.

SAN–ISN Symposium: "Deconstructing Adult Neurogenesis: From Neural Stem Cells to Neuronal Networks in Health and Disease"

Thursday 2nd, 8:15-12:50
Chair: **Alejandro Schinder**, Fundación Instituto Leloir, Buenos Aires, Argentina

Thursday 2nd, 8:15-9:00

"A novel view of neurogenesis and memory encoding in the dentate gyrus"

Alejandro Schinder
Laboratory of Neuronal Plasticity, Fundación Instituto Leloir, Buenos Aires, Argentina

The adult brain contains self-renewing neural stem cells that generate neurons through life. Extensive evidence has demonstrated that adult neurogenesis is highly regulated by brain function and that it is involved in information processing in specific circuits. For instance, ablation of adult hippocampal neurogenesis can impair spatial learning. We are interested in the specific modifications of hippocampal circuits produced by the incorporation of newly generated dentate granule cells (GCs). The impact of adult-born GCs on hippocampal function is greatly determined by their number, intrinsic properties, connectivity, and synaptic properties. In recent years, we have combined different approaches to investigate how adult-born GCs connect within the preexisting hippocampal network, building a spatio-temporal map of input/output connectivity. It takes almost two months to transit the road from neural stem cell to fully mature neuron. During this long transition, developing GCs go through different phases with distinctive functional properties. Work by our lab and several other groups is converging into the notion that adult neurogenesis may serve as a mechanism for the continuous generation of new cohorts of young and very plastic neurons that integrate in the network in a manner that is shaped by ongoing experience. In my talk I will focus our most recent experimental data on how local microcircuits change by adult neurogenesis, discuss its implications in hippocampal function, and propose a novel conceptual model on how newborn GCs may contribute to memory encoding.

Thursday 2nd, 9:00-9:50

"Analysis of neural stem cells in the adult mammalian brain, one cell at a time"

Hongjun Song

Institute for Cell Engineering and Department of Neuroscience,
Johns Hopkins University School of Medicine, Baltimore, USA

New neurons arise from neural stem cells throughout life in the dentate gyrus of the hippocampus. Traditionally, adult neural stem cells and neurogenesis have been investigated at the population level. Single-cell analyses provide high resolution information about heterogeneous stem cell properties and dynamic developmental process. I will present latest data from our ongoing studies to explore single-cell genetic lineage-tracing and single-cell RNA-seq of adult neural stem cell in the mouse hippocampus and their development.

Thursday 2nd, 9:50-10:40

"Brains in metamorphosis: physiological and forced neurogenesis in the adult brain"

Benedikt Berninger

Adult Neurogenesis & Cellular Reprogramming, Institute of Physiological Chemistry
University Medical Center, Johannes Gutenberg, University Mainz, Germany

In my talk I will discuss the topic of how new neurons integrate into the adult brain from two distinct angles. In the first part I will discuss the influence of experience on the incorporation of newly generated neurons in the adult dentate gyrus. I will describe how using a rabies virus-mediated synaptic tracing technique we found that the pattern of presynaptic connectivity impinging on newly generated neurons is strongly affected by exposure to an enriched environment during a critical period following its birth.
In the second part, I will discuss recent work showing that forced expression of the transcription factor Sox2 can lineage-convert reactive NG2 glia of the adult cerebral cortex into immature doublecortin-positive neurons in a model of traumatic cortical injury. I will discuss the implications of the NG2 glial origin of these de novo generated induced neurons for their connectivity.

Thursday 2nd, 11:10-12:00

"Adult Neurogenesis and Psychiatric Neurodevelopmental Disorders"

Guoli Ming

Institute for Cell Engineering and Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, USA

Adult neurogenesis occurs in discrete brain regions and recapitulates the complete process of neuronal development in a mature central nervous system, from proliferation and fate specification of adult neural progenitors, morphogenesis, migration, axon/dendritic development, and finally synapse formation, culminating in the full integration of new neurons into the existing circuitry. Mounting evidence over the past two decades suggest that new neurons born in the adult brain exhibit unique characteristics and participate in specific brain functions. Furthermore, cumulating studies suggest that aberrant adult neurogenesis may contribute to neurological and mental disorders. Psychiatric mental disorders, including schizophrenia and autism, are neurodevelopmental disorders with prominent genetic predisposition. I will discuss our recent work focusing on understanding the function of DISC1, a risk gene for schizophrenia and other major mental disorders, in neuronal development and the underlying signaling mechanisms using adult hippocampal neurogenesis as a model system.

Thursday 2nd, 12:00-12:50

"From pluripotent stem cells to cortical circuits"

Pierre Vanderhaeghen
Institute for Interdisciplinary Research and Institute of Neuroscience,
Free University of Brussels, Belgium

The cerebral cortex consists of several hundreds of different types of neurons, organized into specific cortical layers and areas, that display specific profiles of gene expression, morphology, excitability and connectivity.
Embryonic stem (ES) and induced (IPS) pluripotent stem cells constitute a promising tool for the modelling and treatment of human neural diseases. We previously discovered an intrinsic pathway by which pluripotent stem cells, whether of mouse or human origin, recapitulate in vitro the major milestones of cortical development, leading to the sequential generation of a diverse repertoire of pyramidal neurons that display most salient features of genuine cortical neurons.
Here we will describe how corticogenesis from pluripotent stem cells can be used to model neurodevelopmental diseases that display human-specific features, and how the transplantation of ES/iPS cell-derived cortical neurons can lead to functional integration into developing and damaged cortical circuits.

Symposium II: "Ion channels from development to behavior"

Friday 3rd, 9:00-11:00

Chair: **Nara Muraro**, Fundación Instituto Leloir, Argentina

Friday 3rd, 9:00-9:30

"Synaptic engineering: An ionic switch to C.elegans behavior"

Diego Rayes

Instituto de Investigaciones Bioquímicas de Bahía Blanca, Bahía Blanca, Argentina

Mapping the neural connections of nervous systems is often considered to be a fundamental step in understanding behavior. However, a neural connectivity map carries no information about the activity of neurons and the nature of the connections that each neuron makes. Neurons are embedded in neural networks, which require a delicate balance between excitation and inhibition to maintain network stability. Homeostatic processes, conserved from invertebrates to humans, can adjust synaptic and neuronal excitability to keep neural circuits functioning within their stable dynamic range. In these circuits, ligand-gated ion channels (LGICs) are the principal signaling components that mediate fast inhibitory and excitatory neurotransmission. Is it possible to reverse the behavioral output of a neural circuit by changing the ion selectivity of LGICs and the sign of a synapse? Do intrinsic developmental constraints or homeostatic and behavioral feedback mechanisms prevent switches in the sign of a synapse within a network? We are interested in addressing these questions using the neuronal circuit that mediates the escape response of the nematode Caenorhabditis elegans, the only animal with a completely defined neural wiring diagram . In this circuit tyraminergic neurons coordinate the suppression of head movements with backward locomotion through the activation of a group of Cys-loop biogenic amine-gated chloride channels recently described, the LGCCs. We analyzed the molecular and behavioral consequences of changing the ion selectivity of one of these LGCCs, LGC-55, from anionic to cationic. Our data show that the C. elegans connectome is established independently of the nature of synaptic activity or behavioral output and suggest that switches in LGIC ion selectivity could provide an evolutionary mechanism to change behavior.

Friday 3rd, 9:30-10:00

"How do Drosophila clock neurons fire up?"

Nara I. Muraro
Fundación Instituto Leloir, Argentina

Circadian rhythms have been extensively studied in the fruit fly where many clock genes that interlock through negative feedback loops and generate daily oscillations have been described. Clock genes are expressed in approximately 150 clock neurons in the Drosophila melanogaster brain, of which a particular subset, the pigment dispersing factor-expressing lateral neurons (LNvs) have been found to play a central role.

Still, little is known on the electrical properties of Drosophila clock neurons. The large subtype of LNvs (lLNvs) show spontaneous action potential firing organized in bursts and firing activity that follows a circadian pattern. This daily cycling of neuronal activity could be crucial to confer time of day information to other neurons by altering the release of neurotransmitters or neuropeptides, however, the mechanisms that allow this change in firing activity are not known. We have performed a behavioral genetic screen through the down regulation of candidate voltage-gated ion channels using RNA interference specifically in LNvs. Among the positive hits of the screen, the hyperpolarization-activated cation current Ih and the T-type calcium channel DmαG are being studied further. The role of these currents in Drosophila neurons has not been explored much; however, they have been shown to be key in generating complex neuronal behaviors such as bursting in mammalian neurons. We are using whole-cell patch clamp electrophysiology in ex-vivo

Drosophila brains to study the role of these ion channels in the establishment of lLNvs physiology. Moreover, not only intrinsic, but also synaptic factors, such as Acetylcholine and GABA are contributing to the establishment of the lLNvs firing mode.

Friday 3rd, 10:00-10:30

"Pumilio-2 regulates translation of Nav1.6 to mediate homeostasis of membrane excitability"

Richard Baines

Faculty of Life Sciences, University of Manchester, UK

The ability to regulate intrinsic membrane excitability, in order to maintain consistency of action potential firing, is critical for stable neural circuit activity. Without such mechanisms, Hebbian-based synaptic plasticity could push circuits toward activity-saturation or, alternatively, quiescence. Although now well documented, the underlying molecular components of these homeostatic mechanisms remain poorly understood. Our previous work in the fruit fly, Drosophila melanogaster, identified Pumilio, a translational repressor, as an essential component of one such mechanism. In response to changing synaptic excitation, Pum regulates the translation of the Drosophila voltage-gated sodium channel leading to a concomitant adjustment in action potential firing.

We have recently shown that Pum2 is central to a highly similar homeostatic mechanism regulating membrane excitability in rat visual cortical pyramidal neurons. Using RNA interference, we observed that loss of Pum2 leads to increased sodium current (INa) and action potential firing, mimicking the response by these neurons to being deprived of synaptic depolarisation. By contrast, increased synaptic depolarisation results in increased Pum2 expression and subsequent reduction in INa and membrane excitability. We further show that Pum2 is able to directly bind the predominant voltage-gated sodium channel transcript (NaV1.6) expressed in these neurons and, through doing so, regulates translation of this key determinant of membrane excitability. Taken together, our results show that Pum forms part of a ubiquitous homeostatic mechanism that matches neuron membrane excitability to synaptic depolarization.

Friday 3rd, 10:30-11:00

"Activity-dependent regulation of coordinated ion channel expression: from mRNA to network output"

David Schulz

Department of Biological Sciences, University of Missouri, USA

The nervous system faces an extremely difficult task. It must be flexible, both during development and in adult life, so that it can respond to a variety of environmental demands and produce adaptive behavior. At the same time, it must be stable, so neural circuits that produce behavior function throughout the lifetime of the animal, and stable changes produced by learning endure. Given the challenges of both normal channel protein turnover and short-term plasticity, how is the balance of membrane conductances maintained over long-term timescales to ensure stable electrophysiological phenotype? One possible mechanism is to dynamically regulate production of channel protein via feedback that constrains relationships at the channel mRNA level. Our recent hypothesis is that mRNA relationships emerge as a result of activity-dependent homeostatic tuning rules to ensure an appropriate ratio of mRNA for key ion channels is maintained. We have quantified multiple ion channel mRNAs from single identified motor neurons of the crustacean stomatogastric ganglion and identified distinct, cell-specific correlations among mRNAs for different suites of voltage-dependent channels. We have also determined that these correlations among channel mRNAs are dynamically maintained by an activity-dependent process. These results suggest that cell-specific regulation of steady-state mRNA levels may be a mechanism underlying functional cellular identity. Furthermore, the feedback from cellular activity to coordinated transcriptome-level interactions represents a novel aspect of regulation of neuronal output with implications for long-term stability of neuron function.

Thursday 2nd, 19:30-21:00
Chair: **Tomás Falzone**, CONICET, Universidad de Buenos Aires

Thursday 2nd, 19:30-19:50

"Impact of axonal, autoreceptor mediated, synaptic events on cerebellar interneuron's activity"

Javier Zorrilla de San Martin
Laboratoire de Physiologie Cérébrale, Université Paris 5, 45 Rue des Saints Pères, 75006 Paris, France

The existence of axonal ionotropic receptors in different neuronal types have been known since the early 60's but their role was mainly associated to the modulation of axonal activity and were not considered as an input to be integrated with inputs originating in other neurons. Juvenile cerebellar Molecular Layer Interneurons (MLIs) express presynaptic GABAARs which are activated every time the synapse releases GABA, therefore acting as autoreceptors. In this study, we used local caged-Ca2+ and caged-GABA photolysis in MLI's presynaptic varicosities to induce GABA release and activate GABAA autoreceptor mediated responses. The use of a minimized laser spot (λ=405 nm) for the photolysis allowed us to explore the heterogeneities among synapses and estimate key parameters for the axonal physiology. We measured the axonal space constant (τ=56±9 µm) evoking GABA-release in synapses located at different positions while performing somatic patch clamp recordings. Moreover, fitting these data with a computational model we estimated a mean autoreceptor synaptic conductance of 3 nS. Autoreceptor activation had variable consequences when using the estimated physiological [Cl-]i in current clamp mode. Depending on membrane potential it ranged from small depolarizations (amp: 1 to 7 mV) and action potential triggering to spiking inhibition. Furthermore, subthreshold depolarizations showed a strong sensitivity to TTX, unveiling an amplification mechanism that affects their amplitude and kinetics. Finally, single MLI filling with green Alexa followed by immunolabeling of vesicular GABA transporter and 3D analysis of confocal images showed a concentration of presynaptic specializationsat <100 µm of the somatodendritic compartment, a distance compatible with the space constant of the axon. These results support the view by which the MLI axons can act as input compartments providing signals that can be integrated locally in the axon and at cellular level with inputs coming from other neurons.

Thursday 2nd, 19:50-20:10

"Caspase-3 and Calpains become active during (and play a role in) injury-induced axonal degeneration but are not inhibited during NAD+-mediated protection"

Nicolás Unsain[1,2], Aaron D Johnstone[2] and Phil A Barker[2]

[1]Current affiliation: Instituto Investigación Médica Mercedes y Martín Ferreyra (INIMEC-CONICET), Córdoba, Argentina.

[2]Montreal Neurological Institute, McGill University, Montreal, Canadá.

After nerve injury, the distal portion of severed axons undergoes a degenerative process known as Wallerian degeneration (WD) that leads to axonal fragmentation. Treatment of axons with nicotinamide adenine dinucleotide (NAD+) protects against WD, indicating that the axonal degeneration induced in a regulated process. Our understanding of the molecular mechanism underlying this protection is still rudimentary.

Caspases are aspartate-directed proteases that play critical roles in the regulation and execution of apoptotic cell death during development and tissue maintenance. Initial studies suggested that axonal degeneration proceeded independently of caspases, but recent genetic loss-of-function studies have shown that caspases play a crucial role in developmental axonal pruning (Unsain et al., 2013. Cell Reports). On the other hand, calpains are calcium dependent proteases that play important roles in the execution of necrotic cell death. The precise role of these proteases in injury-induced axonal degeneration is a matter of current debate.

In this study, we use pure samples of axons undergoing degeneration (Unsain et al., 2014, in press. JoVE) to unveil a novel interplay among caspase-3, calpains and the NAD+-sensitive system. We observed that caspase-3 becomes activated in axons early during WD, together with calpains. Calpains, in turn, cleave the N-terminus of caspase-3 and facilitate its activation. Caspase-3 or calpain inhibition greatly delays the detachment of axonal debris from the substrate. We further show that in NAD+-protected axons caspase-3 or calpain activities are normal, suggesting that NAD+-mediated protection does not rely on the inhibition of these proteases. These results show an intriguing relationship between caspases, calpains and the mechanism underlying NAD+-mediated protection.

Thursday 2nd, 20:10-20:30

"Amyloid Precursor Protein Is an Autonomous Growth Cone Adhesion Molecule Engaged in Contact Guidance"

Lucas J. Sosa [1,2], J. Bergman[1], A. Estrada-Bernal[1], T. J. Glorioso[1], J. M. Kittelson[1], and K. H. Pfenninger[1]

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Amyloid precursor protein (APP) is a transmembrane glycoprotein, which is best known for its involvement in the pathogenesis of Alzheimer disease. Encoded on human chromosome 21 APP is overexpressed in Down syndrome (DS) brain and, thus, may contribute to DS-associated intellectual disability. However the physiological function of APP during brain development is poorly understood. APP is a prominent component of the adult as well as the developing brain. It is enriched in axonal growth cones (GCs) and has been implicated in cell adhesion and motility. We tested the hypothesis that APP is an extracellular matrix adhesion molecule. To this end we plated wild-type, APP-, or β1-integrin (Itgb1)- misexpressing mouse hippocampal neurons on matrices of either laminin, recombinant L1, or synthetic peptides binding specifically to Itgb1 or APP. We measured GC adhesion, initial axonal outgrowth, and substrate preference on alternating matrix stripes. Our results shows that substrates of APP-binding peptide alone sustain neurite outgrowth; APP dosage controls GC adhesion to laminin and APP-binding peptide as well as axonal outgrowth in Itgb1– independent manner; and APP directs GCs in contact guidance assays. It follows that APP is an independently operating cell adhesion molecule that affects the GC's phenotype on APP-binding matrices including laminin, and that it is likely to affect axon pathfinding in vivo.

Thursday 2nd, 20:30-20:50

"Neurogenin3 is a key regulator in serotonergic vs. glutamatergic neuronal cell fate"

Abel Carcagno, Daniela Di Bella and Guillermo Lanuza
Fundación Instituto Leloir, Buenos Aires, Argentina

The production of functionally diverse neuronal cell types at their correct locations requires the acquisition of specific progenitor identities in response to extrinsic positional cues. In the developing neural tube of amniotes, hindbrain serotonergic (5-HT) neurons and spinal V3 glutamatergic interneurons are produced from ventral progenitors, which possess a common transcriptional identity but are confined to distinct anterior-posterior territories. It is not completely understood how discrete progenitor pools expressing a seemingly identical molecular code give rise to divergent neuronal fates.

In this study, we identify that the expression of the transcription factor Neurogenin3 (Neurog3) in the spinal cord controls the correct specification of ventral neural tube cells. Gain-of-function experiments in the chick embryo show that Neurog3 represses the expression of the 5-HT determinant Ascl1 through a mechanism that is dependent on the activity of Hes proteins.

Conversely, the spinal cord of Neurog3 mutant mice displays abnormal elevated levels of Ascl1, which triggers the ectopic induction of the serotonergic differentiation program sequentially controlled by the transcription factors Gata2, Lmx1b and Pet1.

The ectopic spinal 5-HT neuron production in Neurog3 mutant mice resembles the serotonergic system of aquatic vertebrates, which interestingly lack Neurog3 expression.

In summary, our results show that Neurog3 serves as a mechanism for interpreting anterior-posterior signaling to impose the caudal border for the serotonergic rafe system in amniotes, and explain how equivalent progenitors within the hindbrain and the spinal cord can produce distinct functional neuron cell types.

MEETING |SAN AWARD TO THE BEST DOCTORAL THESIS IN NEUROSCIENCE 2014

Wednesday 1st, 20:15-20:45
Chair: **Juan Goutman**, Instituto de Investigaciones en Ingeniería genética y Biología Molecular, Dr Héctor N. Torres, Argentina

"Stress-Induced Cocaine Sensitization: A Study of Glutamate Homeostasis and its Interaction with the Dopaminergic System in Nucleus Accumbens"

Constanza García Keller
Dpto de Farmacología, Fac. Ciencias Químicas, Universidad Nacional de Córdoba, Argentina - Department of Neurosciences, Medical University of South Carolina, USA

In both, animals and humans, the repeated administration of psychostimulants increases the behavioral response to a new exposure. This phenomenon is called "sensitization" and extends to the stress-induced influence in stimulant behavioral effects of psychostimulants, called "cross-sensitization". Thus, drug addiction is a multifactorial disorder where individual previous experiences, i.e. influence of stress, interact and modulate the individual response to addictive drugs and increase the vulnerability to drug addiction (Chen and Anthony, 2004).

Acute or repeated psychostimulant treatment or acute or repeated stress induces long-term changes in behavioral and neurochemical expression of sensitization to the drug. Stress-induced mesocorticolimbic dopaminergic neuroadaptations that are thought to be initiated by the fact that both addictive drugs and stress increase the release of corticotrophin-releasing factor (CRF) into the ventral tegmental area (VTA), augment the response of dopamine neurons to glutamatergic inputs (Saal et al., 2003; Ungless et al., 2003). These adaptations in VTA glutamate transmission by stress are thought to mediate enduring changes in both dopamine and glutamate transmission in the nucleus accumbens (NAc, Pacchioni et al, 2007;Kalivas and Stewart, 1991).

The NAc is a heterogeneous structure that can be separated histologically into Core and Shell subdivisions (Pennartz et al., 1994). Dopamine release in Shell and Core is differentially sensitive to drugs of abuse (Di Chiara, 2002) and a role for glutamate in Core has been shown in the expression of cocaine-induced behavioral sensitization (Pierce et al., 1996). Here we endeavor to elucidate the plastic changes in NAc induced by a single restraint stress expressed tree weeks after the cocaine administration. Notably, certain stress-induced long-lasting neuroadaptations in the transmission or glutamatergic and dopaminergic pharmacology observed in the Core are similar to those observed after the cocaine withdrawal (Pierce et al, 1996). Specifically, we identified a role of AMPA receptor in the NAc), alteration in glutamate homeostasis, reflected in basal and synaptic glutamate released, decreased glutamate transporter (GLT-1) expression, and the differential impact in postsynaptic neurons of NAc Core and Shell (Conrad et al, 2008; Backer et al, 2003; Kalivas, 2009).Even more relevant is that pharmacological therapies proposed for the treatment of addiction to different drugs of abuse, including cocaine, in animal models (Knackstedt et al, 2010a;) and humans (LaRowe et al, 2007), could also be used in populations exposed to stressful events that are potentially vulnerable to developing comorbid substance abuse disorder. The similarity between acute stress-induced glutamatergic neuroadaptations in NAcore and those produced by the self-administration of addictive drugs, poses common points of pharmacological intervention that may be particularly useful in treating population suffering from stress disorders and substance use disorder.

Cellular and Molecular Neurobiology

P1.-GHSR1a constitutive activity decreases presynaptic voltage-gated calcium channels level in plasma membrane

Francina Agosti[1°], Eduardo Javier López Soto[1°], Valentina Martínez Damonte[1°], Alejandra Gandini[2°], Silvia Rodríguez[1°], Jacky Marie[3°], Michel Vignes[3°], Ricardo Félix[2°], Jesica Raingo[1°]

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Growth Hormone Secretagogue Receptor type 1a (GHSR1a) is the G protein-coupled receptor that has the highest constitutive activity known (around 50% of the maximum activity induced by its endogenous ligand, ghrelin). GHSR1a is highly expressed at appetite controlling brain nuclei where it mediates ghrelin orexigenic effects. The physiological effect of its constitutive activity remains largely unknown. We study how this constitutive activity impacts on presynaptic voltage-operated calcium channels (VOCC). We co-transfected HEK cells with the GHSR1a or a mutant without constitutive activity (GHSR1aA204E) and the presynaptic VOCC (CaV2.1 or CaV2.2), and we assayed VOCC expression levels by imaging and western blot. We found that constitutive activity decreases protein amount of the VOCC at the plasma membrane. Also when we incubated HEK cells expressing GHSR1a and CaV2.1 or CaV2.2 with Substance P Analog (GHSR1a inverse agonist) we detected the same VOCC level at the plasma membrane than when GHSR1aA204E is co-expressed with the VOCC. We are now interested in the intracellular mechanism implicated in GHSR1a constitutive activity. Regarding to this issue, we have found that the receptor signals via a Gi/o cascade since pre-incubation with Pertussis Toxin restores VOCC protein amount at the plasma membrane. We propose that GHSR1a constitutive activity can affect synapse activity by decreasing the availability of presynaptic
VOCC at the plasma membrane of the presynaptic terminal.

P2.-Association study of 6 polymorphisms –SNP- related to the developmental coordination disorder (DCD) in colombian children and adolescents from 7 to 16 years: pilot study

Angelica Jhoan Alarcón Garcia[1°], Rafael Antonio Vasquez Rojas[2°], Juan Jose Yunis Londoño[1°3°]

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Introduction: Developmental Coordination Disorder (DCD) is characterized by a deficit in the perceptual motor skills, which is not associated to a general medical condition and does not meet the criteria of a pervasive developmental disorder; a Genome Wide Association study for motor coordination problems in children with Attention Deficit Disorder and Hyperactivity established a possible association between the presence of 19 SNPs polymorphisms and the development of the DCD. Genes and polymorphisms with highest association were MAP2K5 (rs16951001, rs11638507, rs1724140, rs1878699) and CHD6 (rs4812506, rs761024) genes. Objective: To establish the association of MAPK5 and CDH6 SNPs polymorphisms as genetic risk factor for the development of Developmental Coordination Disorder in children and adolescents of Colombia between ages 7 to 16. Methodology: A case-control study. Two evaluations to determine the motor profile for each participant were applied. In addition, genetic material from buccal swab, was extracted and processed in the laboratory for genetic polymorphisms. Results: The most frequent motor difficulties were found in the dimension of manual dexterity and coordination, both in cases and controls; however there is not a statistically significant association between the presence of any MAP2K5 and CHD6 polymorphisms and the development of DCD in the sample analyzed so far.

P3.-Demyelination-remyelination in the CNS: ligand-dependent participation of the Notch signaling pathway

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In the CNS, myelination is a physiological process driven by oligodendroglial cells, while demyelination is a pathological process characterized by myelin loss around axons. Demyelination is followed by re-myelination, thus solving functional deficits.

This work focused on the study of Notch1 ligands, and their role in demyelination-remyelination process in a CPZ-induced demyelination model. Twenty-one-day-old Wistar rats were fed with a diet containing CPZ during 2 weeks. Demyelinated and control animals were sacrificed 7d before CPZ withdrawal (-7d), the day of CPZ withdrawal (0d), 7, 14 and 21d after CPZ withdrawal. Experiments were conducted for each survival time. We determined the levels of F3 by WB and characterized F3 expressing cells by IHC in the subventricular zone (SVZ) and corpus callosum (CC) of control and CPZ animals. We also characterized cell populations in primary neurosphere culture from SVZ of control and CPZ animals.

Results showed an increase in Olig2+ cells expressing F3 at -7d, 0d, +7d and +21d in the CC and SVZ of CPZ animals as compared to controls. Regarding the neurosphere culture, preliminary results showed an increase in Jagged-1+ cells in CPZ animals at -7d without changes in F3+ cells. Regardless at 0d the percentage of F3+ cells increased along with a decrease in Jagged-1 + cells. These results reinforce the notion of F3/contactin involvement in OPC differentiation during the remyelination process.

P4.-The Leucine-rich repeat transmembrane protein Lrig1 restricts hippocampal dendrite complexity modulating neurotrophin-induced TrkB signaling

Fernando Cruz Alsina, Francisco Javier Hita, Paula Fontanet, Dolores Irala, Fernanda Ledda, Gustavo Paratcha

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Characteristic patterns of dendritic arborization allow neurons to make activity processing appropriate for their function. Compared with the many identified factors that promote general dendritic growth and branching, little is known about the cell-type specific modulators that allow neurons to sculpt distinctive dendrite patterns. In the current study, we show that a transmembrane protein containing leucine-rich repeats and immunoglobulin-like domains in its extracellular region (Lrig1), is a physiological inhibitor of hippocampal dendrite morphogenesis and branching. In particular, knockdown of Lrig1 by shRNA enhances both primary dendrite formation and proximal dendritic branching, two phenotypes that resemble the effect of Brain-Derived Neurotrophic Factor (BDNF) on hippocampal neurons. Our results show that Lrig1 interacts with TrkB and that Lrig1 overexpression inhibits BDNF-dependent TrkB function associated to dendrite development. Finally, Lrig1-deficient hippocampal neurons display an enhanced proximal dendritic arborization as well as TrkB and Mitogen-Activated Protein Kinase (MAPK) activation in response to BDNF. Taken together, our findings reveal an unexpected role of Lrig1 in the control of hippocampal dendrite development through the inhibition of BDNF-induced TrkB signaling, and suggest that Lrig1 may function to increase the repertoire of TrkB signaling outputs to control patterns of dendritic morphology in
different neuronal populations.

P5.-Coronin-1a is involved in neuronal filopodia formation induced by M6a

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Gpm6a coding for neuronal membrane glycoprotein M6a has been identified as a stress-responsive gene in the hippocampus of chronically stressed animals. Its expression is down-regulated in response to stress and the effect is reversed by antidepressant treatment. A growing body of evidence indicates the importance of GPM6A in neurite extension, filopodium and spine formation and synaptogenesis. Up to this moment, signaling pathways that mediate neuroplastic effects of M6a and its involvement in chronic stress response remain unclear.

In order to identify protein-protein interactions that mediate GPM6A function, coimmunoprecipitation experiments of endogenous GPM6A from adult rat hippocampus were performed. Among potential interacting partners, the actin regulator coronin-1a (CORO1A) was identified. CORO1A controls diverse aspects of the F-actin polymerization and branching cycle.

Here we show that endogenous GPM6A as well as GST-fused 30 aa C-terminal peptide of GPM6Acoimmunoprecipitate with the antibody specific for CORO1A. Furthermore, our immunofluorescence studies show that CORO1A colocalizes with GPM6A in primary hippocampal neurons. Notably, overexpression of dominant-negative form of CORO1A interferes with filopodium formation induced by GPM6A in primary hippocampal neurons as well as in neuroblastoma cell line. Based on the data, we propose that CORO1A represents the link between actin cytoskeleton regulation and the function of GPM6A in filopodium outgrowth.

P6.-Activity-dependent neuronal maturation in the adult hippocampus

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The adult dentate gyrus contains neural stem cells that generate neurons that develop and mature during several weeks. Neuronal maturation is tightly regulated by physiological and pathological factors. We have recently demonstrated that the rate of maturation of adult-born dentate granule cells (GCs) is regulated by electrical activity in the local circuit; more active networks promote faster maturation rates. Interestingly, adult-born GCs display a high sensitivity to network activity during the initial stages of maturation corresponding to the first ten days of development. Increased network activity by running during this sensitive period promotes accelerated dendritic growth and increased afferent synaptogenesis (visualized as dendritic spine formation), as revealed by morphological analysis performed by three weeks of neuronal age. To investigate whether levels of intrinsic activity are sufficient to modulate maturation, we designed an approach to increase the activity of developing GCs during a restricted time window. We performed retroviral expression of receptors activated solely by synthetic ligands (RASSLs) capable of neuronal activation upon binding of the synthethic ligand clozapine-N-oxide (CNO). Oral administration of CNO to activate developing GCs was sufficient to accelerate dendritic growth and synapse formation. These experiments demonstrate that local signals that induce neuronal depolarization can control development and integration of adult-born neurons.

P7.-Morphological changes in subcortical white matter following cognitive training in *Macaca fascicularis*

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The predominant view of the subcortical white matter (scWhM) as an informatically passive impulse conduction structure has detached it from the formulation of dynamic models of complex mental processes. Yet, modern characterization of its neurono-gliopil composition suggests the possibility that it could allow for the intervention of active processes in information transfer. The present study was aimed at astroglial components. Monkeys were trained in a set of cognitive-demanding tasks, and untrained individuals served as controls. A quantitative immunohistochemical analysis involving the distribution of specific markers associated with astroglial characterization and molecular interactions was undertaken in scWhM of dorsolateral and ventral areas of the prefrontal cortex (PFC). Control specimens allowed to trace scWhM nonhomogeneities in such distribution, as suggestive of the dynamic condition within restricted regions of the PFC scWhM. Following cognitive training, -Spatial Delayed Response, Detour, and Delayed Match to Sample astrocyte density estimates showed a higher value in area 46V as compared to area 46D. This difference was not observed in untrained monkeys. These results indicate that cognitive training results in PFC scWhM astroglial changes, thus suggesting its involvement in cognitive processes

P8.-Neurodegeneration associated to copper and cholesterol administration in Wistar rats

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Copper (Cu) and cholesterol (Cho) are associated to neurodegeneration. We have demonstrated that supplementation of Wistar rats for 2 months with Cu (3 ppm-drinking water) associated to Cho (2 %-diet) produced oxidative and inflammatory damages in cortex (CT) and hippocampus (HYP). It also increased Aβ (1-42)/(1-40) ratio in brain. The aim of this work was to study the effect of CuCho in Wistar rats over time (2 to 6 months) in order to investigate a possible synergistic action during the progression of the neurodegeneration. We measured total and non-ceruloplasmin bound-Cu (NCBC), Cho (free and sterified), markers of oxidative stress (OS), inflammation, programmed cell death (caspase-3 and calpains) in CT and HYP, and the ratio Aβ (1-42)/(1-40) in plasma and brain. Our results shows a time-dependent increase of NCBC, free and sterified Cho, OS and inflammatory biomarkers in CT and HYP that agree with an increased GSSG/GSH ratio, and decreased VitE levels. Only calpains activity increase after 2 months, whereas caspase-3 activity does it after 4 months. Then, calpains relieve caspase-3. Increases in Aβ (1-42)/(1-40) ratio was found in CT and HYP after 4 and 6 months. After 2 months, only HYP shows such increase. This ratio increased in plasma in a time-dependent fashion. We conclude that this model could be used to study the mechanisms underlying the neurodegenerative action of CuCho, contributing to find new markers of neurodegenerative risk in susceptible populations.

P9.-Effect of Constant Low Light Exposure on Rat Retina: A Model of Retinal Degeneration

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The retina is part of the central nervous system adapted to capture light photons and transmit the information to brain. It has been shown that light in excess may cause retinal degeneration (RD) or accelerate genetic retinal disorders; however, the mechanism of retinal cell death is not well characterized yet.

In order to study the process of RD produced by low light, Wistar rats were exposed to constant white light of 200 lux intensity from 1 to 7 days. Control animals were kept in light (200 lux) / dark (0 lux) cycles 12hs /12hs or constant darkness .

We found that the exposure to constant light reduces photoreceptors cells only after seven days of exposure (ONL reduction). We also demonstrated that photoreceptor death was by an apoptotic mechanism caspase-3-independent.

The analysis of rhodopsin demonstrated that both, the expression and the location in the outer segment was not altered prior to photoreceptor death, but it was more phosphorylated in ser334 in relation to control animals.

Because oxidative stress is considered a major cause in certain RD, reactive oxygen species were measured using 2'7'-dihydroethidium (DHE) and CAT activity was analyzed too. Both results showed no significant differences between experimental groups.

Based on these results we conclude that retinal damage by constant low light exposure could be an useful model for studying the mechanisms involved in phototransduction defects.

P10.-Measuring synaptic protein acetylation

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During long term memory (LTM) consolidation, changes occur that affect the nervous system at different scales, and many of these changes take place at the inter-neuronal contact, the synapse. Different cellular and molecular mechanisms underlie the temporal phases of Memory: induction requires an increase in intracellular calcium, early persistence depends on post -translational modifications (PTM) and late stages need gene transcription and protein synthesis. Our aim is to study the lysine acetylation of synaptic proteins and their signaling pathway during long term memory consolidation in the hippocampus of the mouse.

Reversible lysine acetylation affects mRNA stability, and the localisation, interaction, degradation and function of proteins, suggesting that this PTM may be responsible for some of the local changes that occur distal from the neuronal soma.

Many non-histone proteins systems were found to be regulated by acetylatation, among them two are our focus: the acetylation of Tubulins (α and β) and its effects in protein transport, and the interaction between NF-kappa B and lysine acetyl transferases (KATs).

Here we report the conditions to evaluate protein acetylation at the synapse, and its mayor subcellular localization.

P11.-Network of photoreceptors: An analysis of a model of high complexity

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The retina is composed of a mosaic of different cells that generate a signal that will ultimately build an image in the cortex. The first stage involves photoreceptors, which convert light stimuli into an electrochemical response (through photo-transduction). Understanding the interaction between photoreceptors and the downstream layers of neurons in the retina is important because the process has a key role in the formation of the signal sent to the brain.
Here, we used a mathematical model of the dynamics of a photoreceptor that involves both a modification of the H-H model and characterization of the compartmentalized intracellular Ca2+ concentration. Our objective was to model the ionic conductance of each cellular type in the retina in order to characterize the total contribution to image processing in the first phase of the visual pathway. All the simulations were performed using the software Neuron.
We observed that the network performed as expected. In future experiments, our plan is to continue using the software Neuron to perform simulations in cell layers of the retina which will allow us to make simple connections between them. Since these simulations require a major compute capacity, we will use the HPC Gemini Cluster, presented previously by our group.

P12.-Cell reprogramming to model epilepsy

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Epilepsy is the third most common neurological disorder, affecting patients of all ages. It is estimated that 1% of the global population will develop epilepsy at some point in their lives. The available therapies act on the symptoms and not the causes Lack of models to study this disease is a major obstacle to understand this illness. The Benign Focal Childhood Epilepsies (BFCEs) represent the most prevalent syndromes in the pediatric population. Unpublished results relate mutations in the FGD6 gene with BFCEs. We sought to model BFCEs by cellular reprogramming of skin fibroblasts of patients carrying an FGD6 mutation that could be the cause of the epileptic phenotype.
We include in the study 2 patients carrying a mutation on the FGD6 gene in homocigosis, 2 related, asymptomatic controls carrying a mutation on the FGD6 gene in heterocigosis and 1 non-related control. At least 3 clones of induced pluripotent stem cells (iPS) from each participant were characterized by 9 quality control assays including pluripotent identity by ICQ and PCR, differentiation capability by ICQ and RT-PCR, karyotyping. iPS were derived into neuroepithelial (NE) tissue.
Preliminary results show a reduced axon development and a significantly lower number of neurons in NE samples carrying the FGD6 mutation in homocigosis compared with the controls.
These results suggest that samples from BFCEs patients carrying an homocygous mutation in FGD6have deficits in neuronal maturation and/or differentiation

P13.-Maternal protein malnutrition affects morphological and neurological development in mouse littermates

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Maternal undernutrition alters brain maturation of the embryo resulting in cognitive and socio-emotional deficits and producing disturbances in learning and memory. These changes extend the postnatal period and continue throughout adulthood, mainly regulated through epigenetic modifications, although they are poorly understood.

Our aim is to study molecular basis of deficits in mice caused by a low-protein diet (LP) during development and lactation. We focus our study on the consequences of poor protein nutrition on morphological and neurological development and methylation machinery.

The experimental design includes 2 groups of CF-1 mice: a normal nourished mums (20% protein) and low-protein malnourished mums (8% of protein) from 5 days before mating to end of lactation. We monitor weight and the morphological and neurological development in both sexes littermates. We evaluate the changes on mRNA expression of glucocorticoid receptor (GR) and methylation machinery members at P21.

LP reduced the weight of the littermates without affecting the litter size. We also observed a delay on development parameters such as outer ear detachment, opening of auditory pavilion and sound tactil and visual reflex. Preliminar data showed increased expression of GR and MeCP2 on female LP hippocampus. We also evaluate if DNA methylation is affected by LP.

In summary, maternal undernutrition affects brain development, the stress response and methylation machinery.

P14.-Improved design of Angiotensin II AT2 riboprobes

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Angiotensin II (Ang II), the active component of the renin–angiotensin system, binds and activates two major subtypes of receptors, namely AT1 and AT2. Ang II receptor expression is highly modulated during brain development. The aim of this work was the generation of AT2 receptor riboprobes to study its expression in rat cerebellum. The PCR fragments of AT2 receptors were subcloned in the p-GEM T easy vector. The identity of the subcloned inserts was verified by RFLP. The restriction endonucleases Eco RI, Ssp I and Pvu II were used. The insert was extracted from the vector with restriction enzymes. The AT2 riboprobes were obtained by transcription in vitro using SP6 or T7 RNA polymerases in both sense and antisense orientations to provide non-specific control and specific probes. The AT2 riboprobes were labeled with non radioactive digoxigenin and analized by Northern blot. In situ hybridization was performed using the synthetized AT2 riboprobes on fresh frozen coronal sections of PND15 rat cerebellum. We observed specific signal in Purkinje cell layer in coincidence with our previous data by autoradiography and immunohistochemistry. In conclusion, the AT2 riboprobes generated here allows sensitive and efficient detection of AT2 receptor gene expression in rat cerebellum.

P15.-Role of Wnt5a in the neuronal development and its participation on the glyphosate induced neurotoxicity

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Neuronal cells must develop and acquired its characteristic polarized morphology in order to establish complex neuronal networks. Among different molecules involved in neuronal development, the Wnt factors have been identified as key morphogens that regulate different neuronal events. Proper control of neuronal morphogenesis is critical and sensitive; therefore, it can be affected by environmental substances, resulting in an abnormal functionality of the nervous system. In this work, we study the Wnt5a effects during early stages of neuronal development. Our results showed that cultured hippocampal neurons stimulated by Wnt5a exhibited longer and more branched axons compared to controls. To go further we identified the Wnt pathway mediating this process. Our observations showed that Wnt5a positively regulated axon growth through the activation of CaMKII, an effector of the non-canonical Wnt/Ca pathway.

On the other hand, we have previously found that cultured neurons are highly vulnerable to the exposition to glyphosate (the active component of Roundup).Neurons exposed to glyphosate exhibited a markedly delay in their development characterized by a decrease in axonal and dendrite growth and complexity. To identify the intracellular mechanism, we analyzed the Wnt5a/CaMKII pathway and observed a significantly reduction in the Wnt5a expression, and CaMKII activity. Taken together, we postulate that Wnt5a/CaMKII pathway as a main target pathway of glyphosate neurotoxicity.

P16.-From axonal transport to physiology. Neuronal specific dependence for Kif5b, an ubiquitous molecular motor

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The molecular motor family kif5 transport cargos such as app, mitochondria and ion channels, along the axon to the synapses. Many studies have focus on its molecular properties, although its role in neuron function and physiology remains unclear. Because Kif5b knockout mice are lethal, we deleted kif5b from neurons using a conditional cre strategy to achieve a better comprehension of the relevance of kif5b in neuronal physiology. Mice with kif5b alleles flanked by loxp sequences and expressing cre recombinase under the nestin promoter were generated. Surprisingly, kif5b conditional knockout mice were viable, showed similar brain volume and have no apparent phenotype. Interestingly, their locomotor response was impaired showing less covered distance and more pauses in an open field assay. To test for locomotors impairments associated with fine coordination we perform a rotarod test. During the first trials knockout mice showed higher number of fallings although they reach a normal performance at the last trial. To test whether locomotor coordination defects were induced by compromised nigrostriatal neurons we conditionally deleted kif5b from dopaminergic neurons. Contrary to what we expected locomotor ability was not impaired neither in the open field or the rotarod assay. Taken together, these results suggest the presence of specific neuron dependence for kif5b and support the interesting possibility that dopaminergic neuronal pathways are not affected by kif5b deletion.

P17.-Behavioural phenotypes rescued in Tau Knock-out mice by human Tau re-expression

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Tau is a microtubule-associated protein predominantly expressed in neurons and involved in many neuronal processes. However, the essential role of Tau in the adult brain is still controversial. Early evidence demonstrated that no gross behavioural nor neurochemical dysfunctions were observed in TauKO mice. However, recent reports suggest that the lack of Tau might be detrimental in aged mice. The aims of this work are: 1) to further evaluate the behavioral phenotypes of middle-aged TauKO mice; 2) to assess whether expression of human Tau leads to any phenotypic rescue in TauKO mice and 3) to analyze if Tau isoforms content is related to the phenotypic rescue. The 'rescued ' group are TauKO mice on which Tau expression was restored by the human Tau transgene (Htau). Wild-Type, TauKO and Htau mice were analyzed in the open field and the rotarod to assess spontaneous locomotion and motor coordination. Cognitive performance was tested in the novel object recognition (NOR) task. Tau isoforms content (depending on exon 10 alternative splicing) was determined by qPCR. Together, our results show that the lack of Tau has a significant effect over motor and cognitive behaviours, and that Tau re-expression in Htau mice fully rescues motor phenotypes but not the deficit in the NOR test. The molecular analyses so far indicate that the human tau transgene has specific splicing patterns in the mouse brain, which might underlie such differences in the behavioural rescue. *Equal contribution.

P18.-GHSR1a constitutive and ligand evoked activity inhibits GABAergic transmission in primary neuronal cultures

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GHSR1a constitutive and ligand evoked activity inhibits GABAergic transmission in primary neuronal cultures Ghrelin receptor (GHSR1a) activity modulates neuronal circuits that control appetite. GHSR1a is a G protein coupled receptor that shows constitutive and ligand-evoked activation. Previously we found that presynaptic voltage gated calcium channels are inhibited by both GHSR1a activities. Since GHSR1a is scattered expressed in many brain areas, in order to evaluate its presynaptic impact we need to develop an experimental setting with a large number of neuron expressing the receptor. We have built a lentiviral system suitable for evaluating the effect of GHSR1a on synaptic activity in hypothalamic neurons. We designed lentiviral transference plasmids containing the sequence of GHSR1a or a mutant lacking constitutive activity (GHSR1aA204E) both tagged with YFP. We first corroborated their functionality by imaging, inmunocytochemistry and electrophysiology. Next we infected neuronal cultures and evaluated synaptic activity. We found that inhibitory postsynaptic currents (IPSCs) are smaller when GHSR1a was expressed in comparison with GHSR1aA204E. This effect is dependent on voltage-operated calcium channels since control and infected cultures response to 0,5M sucrose stimulation was identical. Also ghrelin application decreases IPSCs on these infected cultures. We can suggest then that both GHSR1a constitutive and ligand evoked activity inhibit GABAergic transmission.

P19.-Different roles of the TrkB and p75NTR neurotrophin receptors in the Preconditioning effect in a coculture model of Status epilepticus in vitro.

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Previous studies from our laboratory have shown that after 3 h of neuronal hyperactivation of a co-culture of hippocampal neurons and astrocytes, more than 50 % of neurons died 24 hours later. However, a short preconditioning stimulus (PS), applied 24h and not 5h, before the excitotoxic stimulus (ES), induce an almost complete neuroprotection. It is possible that modifications in the BDNF receptors TrkB and/or p75ntr could participate in the neuroprotetion effect. To asses this question different pharmacological inhibition of the receptors was performed. Also we evaluated the possibility whether a PS modifies the proliferation rate in the astrocyte, and its modification by the pharmacological treatment. TrkB receptor blockade induced by the inhibitor Ana-12 totally blocked the neuroprotective effect of the PE 24 h. Similar effect was obtained when BDNF was sequestered in the culture media by TrkB fusion protein (TrkB-fc). On the other hand, the neuroprotection effect of the PC 24h was not modified after the addition of p75ntr blocking function antibody at 24h. The PS 5h before the ES induces a significant increase in astrocyte proliferation only when they were cultured alone, but when co-culture in the present of neurons, only the PS 24h induces a significant increase in astrocyte proliferation. Taking together all these results indicate that modifications in the endogenous relationships among BDNF receptors activation have a key role in cell death and survival determination.

P20.-Gene regulatory network controlling late neurogenesis in the developing spinal cord

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The regulatory networks that control lineage specification in the developing nervous system are not completely understood. We identified the critical role of two transcriptional regulators controling late neurogenesis in the embryonic neural tube. At developmental stages in which spinal cord precursor cells are massively committed towards gliogenesis, we found that the ventral neuroepithelium gives also rise to a defined class of neurons: Cerebrospinal Fluid-contacting Neurons (CSF-cN). Genetic labeling and expression analysis in the mouse spinal cord show that the transcription factors Ascl1, Gata3 and Gata2, are sequentially expressed in CSF-cN lineage. Using knock-out mice, we show that Ascl1 is necessary for CSF-cN development. By performing time-restricted deletions of Ascl1, we found that Ascl1 initiates CSF-cN differentiation and it is also necessary at postmitotic stages of newborn neurons. Gata3 lays genetically downstream of Ascl1, as Gata3 is not expressed in ventral progenitors in Ascl1 mutant. The analysis of Gata3 knockout mice and conditional deletion indicate that Gata3 instructs postmitotic CSF-cN differentiation. Fate-mapping experiments show that in the absence of Ascl1, late neuronal progenitors that fail to acquire CSF-cN identity become into ependymal cells that cover the surface of the central canal. In summary, we demonstrate that both Ascl1 and Gata3 are sequentially induced and both control late neuronal differentiation in the developing spinal cord.

P21.-Differential Regulation of Myelin Basic Protein Isoforms and Deiminated Isomers by Calmodulin

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Myelin basic protein (MBP) is essential for compact myelination of the CNS. MBP interactions with different cellular components are regulated by calmodulin (CaM) and by its post-translational modifications (PTM). We defined 4 different CaM-binding sites (A-D) on MBP isoforms. The binding to CaM of sites A, C and D is Ca2+-dependent, presenting also differential strength of interaction. Site C, which shows the strongest interaction with CaM, has two preserved primary-sequence motifs (KXXK and RXXR) that are present in MBP isoforms 1, 2, 3 and 5. Whereas the alternative splicing that generates the MBP isoforms 4 and 6 presents a site that only preserves the RXXR motif with a weaker interaction with CaM (site D). The relevance of these CaM-binding sites of MBP isoforms 1, 3, 4, 6 and their respective C-terminus truncated mutants (ΔC) was evaluated by co-transfection of cells with CaM cDNA. Considering that the deiminated peptides of the MBP CaM-binding sites have impaired MBP-CaM interaction, our essays also included a mutant of MBP3 (rmC8) to evaluate the effects of deimination, a PTM correlated with multiple sclerosis (MS) pathogenesis. A clear variation of MBP distribution and reduced co-localization with CaM was observed for the ΔC variants of each isoform, showing rmC8 the more significant change. These results suggest that the CaM-binding sites C and D are the major responsible of MBP-CaM interaction, and that the deimination of their arginine residues may account for MS.

P22.-Selective Oxidation of Alpha-Synuclein Promotes its Cytotoxicity

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Parkinson's disease is a progressive neurodegenerative disorder, histologically defined by intracellular aggregates of proteins, α-Synuclein (aSyn) mainly, and lipids. Aggregation of aSyn has been associated with selective loss of dopaminergic neurons, in combination with external factors related to lipid and protein oxidation and mitochondrial malfunction. Early intermediates of aSyn aggregates are thought to be the main "culprits", rather than mature amyloid fibrils. But a comprehensive description of the relationship between protein aggregation and neuronal death is still missing. We decided to evaluate the effects of aSyn oxidation and formation of crosslinked oligomers.

Tunable oxidative modifications of aSyn were achieved using a photo-sensitizer to generate stable covalent oligomers by specific crosslinking of Tyr residues. Different species were isolated and characterized by a complementary set of techniques that demonstrated the presence of diTyrosine crosslinks. This led to reduced aggregation in vitro and increased toxicity towards differentiated SH SY5Y cells. These results suggest that oxidative modifications seem to alter the conformation of aSyn and its tendency to aggregate, possibly stabilizing more toxic species or avoiding its neutralization into amyloid fibers. We anticipate these investigations will assist in the identification of initial molecular triggers leading to neurodegeneration associated with the exposure to ROS promoting compounds.

P23.-Hypothalamic tanycytes mediate ghrelin uptake into brain tissue

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Ghrelin is a stomach-derived hormone that acts in the brain to regulate food intake, stress, and glucose homeostasis. Small doses of peripherally administrated ghrelin mainly activate neurons in the hypothalamic arcuate nucleus; however, higher doses also activate neurons in dorsal periventricular hypothalamic sites suggesting the passage of ghrelin from the periphery to the cerebrospinal fluid (CSF). Tanycytes are highly specialized ependymal cells that form a blood–cerebrospinal fluid barrier at the level of the median eminence/arcuate nucleus. Recently, it has been proposed that tanycytes could transport hormones from the blood to the CSF.

Here, we hypothesize that tanycytes are able to perform ghrelin uptake from either the periphery and/or the CSF. In order to test this possibility, we centrally injected mice and rats with fluorescent ghrelin and mapped its localization in the ependymal and periventricular hypothalamic areas. In addition, we developed an in vitro model of primary cultures enriched in tanycytes.

We found that hypothalamic tanycytes are able to incorporate ghrelin injected centrally from the third ventricle to the hypothalamic parenchyma. In the in vitro system, we detected tanycytes-like cells, which were immuno-reactive for vimentin and incorporated fluorescein ghrelin tracer added to the culture media.

We conclude that hypothalamic tanycytes could be an important physiological checkpoint regulating the hypothalamic actions of ghrelin.

P24.-Inhibition of CDK5 alters Dopamine Transporter endocytosis in N2A neuroblastoma cells

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Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common childhood brain disorders. Previous studies from our lab have demonstrated that transgenic mice lacking p35 protein (p35KO), the specific activator of Cyclin dependent kinase 5 (Cdk5) exhibit behaviors resemble those described in animal models of ADHD. P35KO mice show spontaneous locomotor hyperactivity, elevated striatal Dopamine (DA) synthesis, but with a low DA turnover. These behavioral and biochemical phenotypes are reverted by Methylphenidate and d-Amphetamine (Amph), drugs used in ADHD treatment. Although we have shown that p35KO mice have an altered dopaminergic system, the dynamic and activity of Dopamine Transporter (DAT) still remain unknown.
DAT mediates uptake of DA from the synaptic cleft and it is involved in some forms of ADHD in human. In this work we studied the role of Cdk5 activity in DAT constitutive and substrate-mediated trafficking using N2A neuroblastoma cells. We found that Amph exposure increased DAT localization in endosomes compartments. Besides, inhibition of CDK5 activity decreased DAT superficial levels, affecting both constitutive and substrate induced DAT endocytosis.
These results suggest that Cdk5 activity modulates DAT trafficking to the plasma membrane, and may help us to elucidate DAT contribution in p35KO animal model of ADHD and its treatment.

P25.-WNT7B and FRIZZLED7 are involved in the regulation of dendrite architecture by the non-canonical WNT pathways

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Wnt proteins are well known morphogens that interact with membrane receptors such as Frizzled (Fz), Ryk, Ror and IGF-1R, activating at least three signalling pathways: Wnt/β-catenin, planar cell polarity (PCP) and Calcium pathways. In the nervous system, Wnt proteins regulate neuronal polarization and migration, axon pathfinding, dendrite morphogenesis and synapse formation.
Previously, we identified the transmembrane Frizzled7 (Fz7) protein as a potential Wnt7b receptor to regulate dendrite formation. Currently, we examined the contribution of the non-canonical Calcium pathway on dendritic development. Our observations indicated that Wnt7b-Fz7 regulate dendrite development through the activation of CaMKII. Furthermore, we evaluated the participation of the PCP pathway and its effector JNK on the dendrite growth induced by Wnt7b-Fz7. We found that hippocampal neurons exposed to Wnt7b, as well as those overexpressing Fz7, exhibited an increase in the activity of CaMKII and JNK. In addition, the inhibition of CaMKII using a specific shRNA, blocked the Wnt7b and Fz7 effects on dendrite morphogenesis. These evidences show that Wnt7b and Fz7 would play a key role in dendrite development and complexity, through the PCP and Calcium pathways, suggesting a potential overlapping of the two non-canonical Wnt signaling in this process.

P26.-Novel modulators of the neurotrophic actions of NGF and its receptor TrkA

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NGF is a member of the neurotrophins, a family of growth factors critically involved in the development and function of the nervous system. It was originally described as a survival and differentiation factor of sensory and sympathetic neurons. The physiological relevance of the in vitro effects of NGF on the survival of peripheral neurons has been substantiated by the reduction in the number of sensory and sympathethic neurons observed in NGF-mutant mice. Two receptors have been identified for NGF: TrkA, a high affinity receptor; and p75, a low affinity receptor. Different signaling pathways are activated upon NGF binding to TrkA receptor, including those mediated by Ras/Mitogen activated kinase (MAPK), PI3-kinase (PI3K)/Akt and PLCγ.

Using a cDNA microarray screening for new signaling modulators of NGF, we identified tetraspan membrane glycoproteins whose multimolecular complexes have four transmembrane domains. The aim of our study was to explore, by real-time RT-PCR and gain of function assays, the role of tetraspan glycoproteins in NGF-mediated TrkA signaling and biology. The data presented in this study suggest that tetraspans constitute a class of proteins with capacity to regulate NGF-induced neuronal differentiation.

P27.-Pea3 transcription factors are key mediators of hippocampal dendrite growth during development

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The development of a complex, type specific dendrite morphology plays a major role in governing the functional properties of neurons and neural circuits. Many neurodevelopmental disorders are due to structural abnormalities of dendrites and their connections. The size and shape of dendritic arbors result from the interplay of intrinsic genetic programs and extrinsic signals. Identifying transcriptional programs and signaling pathways triggered by extracellular cues that control neuronal circuit formation is of great importance in order to be able to decipher and understand the functioning of mature nervous system. In this work we identified two members of the Pea3 family of transcriptional factors, Etv4 and Etv5, as key regulators of growth and elaboration of pyramidal cell dendrites in the developing hippocampus. Gain and loss of function assays indicate that these transcription factors play a crucial role in the establishment of hippocampal connectivity. We also provide evidence indicating that Etv4 and Etv5 are induced by the neurotrophin, BDNF. All together, our data indicates that BDNF induce a transcriptional program which play a crucial role in the establishment of hippocampal connections.

P28.-Filopodia formation driven by M6a´s oligomerization

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M6a is a tetraspan neuronal membrane glycoprotein that belongs to the proteolipid protein family (PLP). In our laboratory we showed that M6a induces filopodia formation and neurite extension, but the mechanisms underlying this functions remain unknown. Our hypothesis is that M6a interacts with an external stimuli that could produce homo- or hetero-associations of M6a, driven by its transmembrane domains (TMD). Then, the M6a auto/phosphorylation would lead to filopodia formation. Here we studied if M6a oligomerization and interaction through its TMDs are involved in M6a´s function. We determined by crosslinking assays that M6a forms oligomers in the neuronal membrane and we performed an assay designed to determine homotypic interactions between TMDs (TOXCAT) and found that the interactions between M6a´s TMDs might be aiding this oligomerization. We found that certain glycine residues present in TMD2 and TMD4 are necessary to drive this interaction. Consistently, in neurons these residues are needed for filopodia formation. Moreover, we studied three non-synonymous SNPs from the NCBI database present in the sequence of GPM6A of the coding sequence of the TMDs and found that the presence of one of this SNPs impairs TMD2 interaction. We also found that all SNPs impair M6a induced filopodia formation. In this work we found evidence that the interactions between M6a´s TMDs might be involved in the signal transmission of the M6a signalling pathway, reinforcing our hypothesis.

P29.-Phosphorylation of M6a at Serine-267 induces filopodia formation in rat hippocampal neurons

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The neuronal membrane glycoprotein M6a is a member of the proteolipid protein family. M6a has 278 amino acids that form four transmembrane domains, two external loops, and the N- and C-terminal regions in the cell cytoplasm. M6a induces neurite outgrowth, increases filopodium/spine density and participates in synaptogenesis, but the mechanism of action remains unknown. We previously demonstrated that the lack of both PKC and CK phosphorylation sites of M6a at the C-terminal domain impaired filopodium mobility in neurons. Recently, a phosphorylated form of M6a at S-267 has been found in postnatal and in 21-days old mouses brains. In silico analysis of residue 267 showed that it could be a target of PKC. To analyze the importance of the phosphorylation of M6a we overexpressed mutants S267A-M6a (non-phosphorylatable) or S267D-M6a (constitutively phosphorylated) in hippocampal neurons and quantified filopodium formation. The results showed that both M6a wild type and S267D mutant significantly increased the number of processes in 20 um of neurite length compared with control group. However, in S267A expressing neurons the number remained at control levels. By treating M6a expressing neurons with different doses of Gö6976, a PKC inhibitor, we determined that the calcium dependent PKCs are involved in M6a-induced filopodia. In summary, we concluded that phosphorylation of S267 is implicated in M6a filopodia formation pathway and might involve PKC calcium dependent isoforms.

P30.-The pineal gland: thinking outside the box

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The pineal gland (PG) has been considered a homogeneous organ composed mainly of melatonin-synthesizing pinealocytes. We studied the PG beyond pinealocytes via a detailed characterization of the different cell lineages from E15 to adulthood. We analyzed markers for immature and mature pinealocytes, astrocytes, microglia, nerve fibers, blood vessels, and mitosis. Also, we challenged the local microglia by superior sympathetic ganglionectomy (SCGx) and decentralization (SCGd). Pax6 and vimentin were expressed in the entire PG ontogeny with the highest levels at earlier stages; their radial, rosette-like and randomly distributed arrangements correlated well with PG organogenesis. Serotonin, a marker for more mature Pax6-negative pinealocytes, was evident after birth. Mitotic pH3-positive cells were seen in the embryonic and neonatal PG, and their distribution was consistent with each stage. A heterogeneous astrocytic population was regionally dispersed in the adult PG. Surprisingly, microglia invaded the PG from E15 onward and showed an active morphology and proliferative potential in all the stages analyzed, being in close contact with and, in some cases, engulfing Pax6-positive precursors and nerve fibers. SCGx activated the local microglia with consequent enhancement of precursor and nerve fiber engulfment. In brief, the PG is not a homogenous organ. Microglia present in an organ without BBB within the CNS support immunological functions recently attributed to the PG.

P31.-Progesterone effects on transcription factors that drive oligodendrogenesis after spinal cord injury

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After spinal cord injury, primary mechanical insult is followed by the activation of a secondary cascade of events that ultimately causes progressive degeneration of the neural tissue and demyelination. In previous publications we have shown that progesterone acts as a remyelinating agent favoring oligodendrocytes precursor cells differentiation. In this work, we analyzed the effects of progesterone on the expression of the transcription factors that drives remyelination after spinal cord injury. Our results shown that 3 days after injury, progesterone administration enhanced RNAm expression of the pro differentiating factors, Mash 1, Sox 10, Nkx2.2 and Olig 2. Progesterone also increased the number of oligodendrocytes precursor cells which expressed Olig 2. Twenty one days after lesion, progesterone increased the expression of the pro myelinating factor, Olig 1, and reduced the expression of the inhibitors Id-2 and Hes-5. These results suggest that short time of progesterone treatment might enhance olygodendrocytes precursor cells differentiation by increasing stimulating transcription factors. Long time of progesterone treatment might stimulate myelination by increasing the expression of myelinating factors and by reducing the expression of inhibitors of myelination. Progesterone could be a promising therapeutic agent for patients with spinal cord injury and it also could be use as a treatment for demyelinated diseases.

P32.-Array Tomography as a Tool for Tracking the Distribution of ASIC1a at the Neuromuscular Junction

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The maintenance of the extracellular pH proves to be critical for ensuring normal cellular function. At the presynaptic terminal of neuromuscular junctions (NMJs) H+ are co-released with acetylcholine and pumped in and out of the synaptic cleft after prolonged stimulation. Interesting candidates for sensing H+ are acid-sensing ion channels (ASICs). ASICs are voltage-independent cation-permeable ion channels, activated by extracellular acidosis. In this regard, we have shown that ASIC1a inhibits synaptic transmission during high frequency stimulation in female mice, which prompted us to hypothesize that ASIC1a may be involved in preventing muscle weakness after repetitive tetanic contraction and helping recovering neuromuscular transmission after muscle acidosis. Besides, by basic immunohistochemistry we have observed that ASIC1a seems to be located at the presynaptic terminal. However, another technique, by which we would be able to describe more accurately the distribution of ASIC1a at the NMJ and identify possible interactions with other presynaptic proteins, needed to be found. For that purpose, we took advantage of array tomography, a new imaging method which combines and extends superlative features of modern optical fluorescence and electron microscopy methods. Our results showed that, contrary to what had been suggested, ASIC1a may be located in Schwann cells, which lead us to rethink the mechanism by which ASIC1a exerts its modulatory role on synaptic transmission.

P33-Two signaling pathways mediate presynaptic voltage gated calcium channels inhibition by ghrelin receptor activation

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Growth hormone secretagogue receptor type 1a (GHSR1a) has the highest constitutive activity of any G protein coupled receptor (GPCR). GHSR1a mediates the orexigenic effects of the gut-derived hormone ghrelin, which plays an important role in the control of food intake and other homeostatic functions. GHSR1a is present at presynaptic terminals in the hypothalamus and it regulates neuronal activity, but the mechanism of its actions remains poorly understood. Presynaptic voltage gated calcium channels, CaV2.1 and CaV2.2, control neurotransmitter release and their activities are modulated by GPCRs. Here we show that constitutive as well as agonist-dependent GHSR1a activation triggers a strong impairment of both CaV2.1 and CaV2.2 currents. Constitutive GHSR1a activity reduces CaV2 currents by a Gi/o-dependent mechanism that involves persistent reduction in channel numbers in the plasma membrane, whereas, ghrelin-dependent GHSR1a inhibition is reversible and involves altered CaV2 current gating via a Gq-dependent pathway. Additionally, this inhibitory pathway requires Gβγ dimers and elicits different profiles depending on the β-subunit subtype. Interestingly, we found that inhibition of both CaV2.1 and CaV2.2 activity by GHSR1a activation impacts consequently inhibiting GABAergic transmission in hypothalamic neurons. Thus our data show that GHSR1a activity is key factor mediating overall CaV2 channel function and modulate GABAergic neurotransmission in hypothalamic neurons.

P34.-TDP-43 transgenic mouse models display altered brain polysomal profiles

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TAR DNA-binding protein 43 (TDP-43), encoded by the TARDBP gene, has been identified as the major pathological protein in a group of neurodegenerative diseases including Frontotemporal Dementia (FTD) and amyotrophic lateral sclerosis (ALS). In addition, TDP-43 is a nucleic acid-binding protein that regulates multiple aspects on mRNA metabolism. We are studying in vivo the intrinsic properties and physiological role of TDP-43 to define its involvement in neurodegenerative disease. To do this, we are using two different models: (1) Transgenic mice overexpressing human wild-type TDP-43 protein (hTDP-43-WT) or a cytoplasmically localized form (hTDP-43-ΔNLS) and (2) TDP-43 knock-down using a lentiviral-based shRNA approach. To investigate if TDP-43 has any participation in regulating active translation and therefore in maintaining protein levels we performed subcellular fractionation of brain areas by sucrose gradient centrifugation. The polysome profile of hTDP-43-WT brains was significantly altered by a shift towards light fractions as compared to wild-type littermates, indicating a decrease in global mRNA translation. That change correlates with a shift of TDP-43 protein. Preliminary analysis of hTDP-43-ΔNLS cortical polysome profiles suggests changes in mRNA levels from all gradient fractions. These results provide initial evidence for a potential role of TDP-43 regulation of global mRNA translation.

P35.-Study of the adaptive evolution of the α9α10 cholinergic nicotinic receptor

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A great variety of nicotinic acetylcholine receptor (nAChR) subunits are expressed in different regions of the central nervous system. Thus, functional diversity across species can be achieved by the differential expression of alternative subunits. In contrast, cochlear hair cells only express α9 and α10 subunits, which form the heteromeric receptor that mediates efferent inhibition of vertebrate inner ear hair cells. Phylogenetic analysis has shown that mammalian α10 subunits have been under positive selection and acquired non-synonymous substitutions in their coding regions. We propose that these evolution-driven changes on a very conserved protein, are the only basis for functional diversity across species in the α9α10 nAChR. To test this hypothesis, we have compared the properties of rat, chicken and Xenopus tropicalis nAChRs formed by α9 and/or α10 subunits expressed in Xenopus laevis oocytes. Whereas chicken and X. tropicalis α10 subunits form functional homomeric receptors, rat α10 subunits are only functional when co-expressed with α9. Current-voltage curves show that rat α9α10 nAChR presents a lower degree of outward rectification compared to its avian counterpart, while amphibian α9α10 nAChR shows inward rectification, indicating differential channel properties. We propose that non-synonymous substitutions in the coding region of the mammalian α10 subunits are responsible for the differential functional properties between mammalian and non-mammalian α9α10 nAChRs.

P36.-Arc is required for pattern separation across the spatial and the object domains in the dentate gyrus and perirhinal cortex

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Successful memory involves not only remembering information over time but also keeping memories distinct and less confusable. The ability to separate the components of memories into distinct memory representations relies on pattern separation, a computational process by which differences are amplified to disambiguate similar events. Despite the importance of this mnemonic function, the molecular mechanisms and signals necessary for the behavioral manifestations of this process remain unknown. Although pattern separation has been localized to the dentate gyrus of the hippocampus and shown to occur in a spatial domain, this cognitive function is thought to take place also during processing of other types of information. The perirhinal cortex (PRH) is involved in the acquisition and storage of object memories. Thus, we hypothesized that this structure is involved in pattern separation of object memories.. In this work, we used both a hippocampal-dependent and a PRH-dependent task and manipulated the load of pattern separation during information encoding. We showed that acquisition/ consolidation of pattern-separated memories depend on the expression of Arc on both tasks, and that interaction between Arc and BDNF is necessary for successful pattern separation. These findings suggest that Arc, an immediate early gene known to regulate synaptic plasticity and mediate memory formation, is involved in the molecular mechanisms underlying pattern separation.

P37.-Regional differences of astrocyte response to neurotrophins

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Astrocytes represent a heterogeneous population of cells whose responses may differ among brain regions. Reactive astrocytes proliferate and migrate toward the lesion and also release chemical mediators that includes neurotrophins (NTs). We have previously demonstrated that a brain injury induces the expression of the neurotrophic receptor (NTR) p75ntr on astrocytes which also mediates the anti-proliferative effect of NGF. The aim of this study was to assess the responses of astrocytes from different brain areas to NTs and evaluate how a brain lesion affect the expression of NTRs. In vivo, we observed that the stab wound lesion, induced p75ntr expression in brain tissues obtained from the areas surrounding the injury while the other BDNF receptor, truncated TrkB (TrkB-t), decreased. This change in the pattern of expression of NTRs could make the injured tissue sensitive to differents NTs. In cultured astrocytes from hippocampus (hip), cortex (cx) and striatum (st) we found that the mechanical injury (scratch) induced the expression of both, p75ntr and TrkB-t. When astrocytes were injured and treated with NGF we found that astrocytes from hip, cx and st responded by migrating to the injured area. However, the treatment with BDNF induced migration but only in astrocytes from st. Taken together, these results showed that astrocytes have regional differences in terms of responses to neurotrophins which may serve to modulate different aspects of gliosis after mechanical injury.

P38.-To die or to not die... The fight between TrkB and p75ntr signaling

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Neurotrophins are secretory proteins that bind to target receptors influencing survival activity. Brain Derived Neurotrophic Factor (BDNF) is initially synthesized as proBDNF that is cleaved to release BDNF. BDNF binds to TrkB leading to neuron survival and proBDNF interact with p75ntr leading to apoptosis. We showed that 3h of neuronal hyperactivation in a co-culture of hippocampal neurons and astrocytes induces neuronal death. Also we demonstrated that Status Epilepticus (SE) in vivo induced death through a decrease in TrkB expression and a switch among BDNF/TrkB to BDNF/p75ntr and proBDNF/p75ntr binding. We hypothesize that this phenomenon has a key role in the development of neuronal death. To test this we added to the co-culture TrkB-Fc immediately after the excitotoxic insult and we found an increase in neuronal death. To test whether the neuronal death was due to proBDNF/p75ntr signaling in absence of TrkB signaling, we administrated unilaterally TrkB-Fc and anti proBDNF in the hippocampal CA1 immediately after SE. Neuronal damage was assessed by FJB. We found an important decrease in the number of FJB positive cells in the infused hippocampus as compared with non-infused hippocampus. Since it has been suggested that proNT signaling is able to suppress Trk-mediated survival signaling, our next goal is to determinate whether proBDNF is able to suppress TrkB signaling. To test this we are going to overexpress TrkB in the hippocampal CA1 using lentivirus system before SE.

P39.-Sensing Light by Horizontal Cells in the Chicken Retina: A New Player in the Photoreceptive System

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Retinal ganglion cells expressing the photopigment melanopsin (Opn4) display intrinsic photosensitivity. In the chicken retina, two Opn4 genes, Opn4x and Opn4m have been described of which Opn4x was phound to be confined to the forming GC layer and optic nerve at early embryonic days (E), but by E15 its expression was mostly in Prox1 (+) horizontal cells (HCs). The aim of this work was to obtain HC primary cultures and to characterize them by biochemical and morphological assays. Disaggregated chicken retinas at E15 were subject to a discontinuous 1 to 4% bovine serum albumin gradient. Phases were examined with specific antibodies against Opn4x and HC markers. Then, immunopanning against Opn4x with the 2,5 % phase was performed to obtain cultures of HCs that express this photopigment. Primary cultures were also examined by flow cytometry and RT-PCR. Finally HC cultures were exposed to light or kept in the dark to assess intrinsic photosensitivity by Calcium Imaging.The results show that only the fraction corresponding to the 2.5% BSA contained most cells displaying PROX-1 immunoreactivity. Also Opn4x-immunoreactivity was observed in this phase. Cultures obtained by immunopanning were highly enriched in Opn4x (+) HCs and exhibited positive light responsiveness as compared with dark controls. In conclusion, by means of this methodological procedure we obtained primary cultures of HCs expressing Opn4x and we also provide the first insight about their intrinsic light sensitivity.
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P40.-Nanoparticles for targeted drug delivery to glial cells after brain ischemia

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During the last years, mounting evidence has shown that glial conversion into the proinflammatory phenotype occurring after brain injury is associated with increased neurodegeneration. Necrotic cells release specific DAMP (ie. S100B, HMGB-1) that induce neuroinflammation by the activation of NFkB-dependent pathways in glia. Unfortunately, global NFkB blockage is not neuroprotective since it seriously affects neuronal survival. Some polyamidoamine (PAMAM) dendrimers were shown to be incorporated specifically by glial cells. Our project aims to design nanoparticles suitable for targeted drug delivery to reactive glial cell in order to prevent glial conversion into the proinflammatory-neurodegenerative phenotype. In the present work we tested different types of dendrimers and liposomes and we found that a new type of core-shell tectodendrimer (G5G2.5 PAMAM) is time- and dose-dependently incorporated by primary astrocytes and microglia, but not by hippocampal neurons co-cultured with glia. The exposure to oxygen and glucose deprivation (OGD), an in vitro model of ischemia, specifically increased astroglial uptake of the G5G2.5-FITC dendrimer. In vivo, increased uptake of the dendrimer was observed in the ipsilateral hemisphere after ischemia by cortical devascularization. In conclusion, the G5G2.5 showed a marked preference for astroglia and microglia in vitro and in vivo, making it suitable as a specific drug carrier for glial cells.

P41.-Study of the impact of ghrelin receptor dimerization with other G-protein coupled receptors on calcium channel modulation

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Growth hormone secretagogue receptor type 1a (GHSR1a) activity modulates neuronal circuits that control appetite and energy expenditure. GHSR1a is a G protein-coupled receptor prone to constitutive and ligand-evoked activation. It has been described that GHSR1a can form dimers with other G protein coupled receptors, the melanocortin receptor type 3 (MCR3) and the dopamine receptor type 2 (D2R) and that this interaction affects the signaling of both receptors. Presynaptic voltage gated calcium channels (VGCC) are very sensitive to G protein mediated pathways and this regulation impacts on synaptic transmission. Here we aimed to understand how dimerization between GHSR1a and MC3R or D2R modifies VGCC inhibition by these receptors activity. We found that co-expression of MC3R negatively impacts on GHSR1a constitutive activity mediated inhibition of VGCC (Type CaV2.2) while D2R co-expression has no effect. On the other hand we found that dopamine mediated inhibition of VGCC remains unchanged when GHSR1a is co-expressed. Our data suggest that dimerization of GHSR1a with other physiological relevant receptors could impact on VGCC modulation.

P42.-First evidence of the proteasome fast axonal transport mediated by molecular motors and membrane interaction

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Local protein degradation by the ubiquitin-proteasome system in neurons depends on the correct positioning of this complex "machinery". Abnormal protein degradation is suggested as an early event in Alzheimer disease (AD), linking protein degradation impairments with proteasome transport defects. However, the properties of proteasomes axonal transport remain unknown.

In order to demonstrate that proteasomes are being transported in vivo, we performed a sciatic nerve ligation showing proteasome accumulation at both sides of the nerve. To reveal proteasome axonal transport dynamics we used live-cell imaging experiments in primary hippocampal neurons. To understand whether proteasome movement depends on molecular motors we used a shRNA to knock down molecular motor expression. To assess whether proteasomes associate with intracellular membranes we performed a botton loaded sucrose density gradient. Finally, by live imaging in dual color channel we showed that fast and actively transported proteasome associates to different vesicles and membranes organelles to reach distant locations. Taken together our results demonstrate for the first time that the proteasome complex is transported throughout axons using different processive molecular motors and "Hitch-hiking" on multiple vesicles, this mechanism assure the correct transport and localization of this degradative "machinery" that when impaired could lead to local aberrant protein accumulation such as those observed in AD.

P43.-Myelin-Associated Glycoprotein modulates programmed cell death of motoneurons during early postnatal development via NgR/p75NTR receptor-mediated activation of RhoA signaling pathway

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Myelin-Associated Glycoprotein (MAG) is a minor constituent of the nervous system expressed at the periaxonal layer of myelinated axons. By Nogo-receptors (NgRs), MAG exerts a nurture effect on axons it ensheaths. Pharmacological activation of NgRs has a modulatory role on p75NTR-dependent postnatal apoptosis of motoneurons (MNs). NgRs are part of a receptor complex which includes p75NTR, Lingo-1 and gangliosides. Upon ligand binding, this multimeric complex activates RhoA/ROCK signalling in a p75NTR-dependent manner. The aim of this study was to analyze a modulatory role of MAG on MNs apoptosis during postnatal development. A time course study showed that Mag-null mice suffer a loss of MNs during the first postnatal week. Also these mice exhibited increased susceptibility in an animal model of MNs apoptosis induced by nerve-crush injury, which was prevented by MAG-Fc treatment. The protective role of MAG was confirmed in in vitro models of p75NTR-dependent MN apoptosis. Lentiviral expression of shRNA sequences targeting NgRs abolished protection by MAG-Fc. Analysis of RhoA activity using a FRET-based RhoA biosensor showed that MAG-Fc activates RhoA. Pharmacological inhibition of p75NTR/RhoA/ROCK pathway or overexpression of a p75NTR mutant lacking binding to RhoA blocked MAG-Fc protection. Overall these findings identify a new protective role of MAG as a modulator of apoptosis of MNs during postnatal development by a mechanism involving p75NTR/RhoA/ROCK signaling pathway.

P44.-Microglial Alterations Before And After Plaque Deposition in PDAPP-J20 MICE, Model of Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease without effective therapy and the principal cause of dementia. Brain amyloid deposits are classical histopathological hallmarks that generate an inflammatory reaction affecting neuronal and glial function. The identification of early cell changes and of brain areas involved could help to design new successful treatments. Hence, we studied early alterations of hippocampal microglia and their progression during the pathology in PDAPP-J20 transgenic mice, carrying human APP gene with Swe and Ind mutations, at 3, 9 and 15 months (m) of age. Age-matched non transgenic mice were used as controls. At 3 m, before plaque formation, Iba1+ cells from transgenic mice already exhibited signs of activation and larger soma size in the hilus (42.16 ± 5.95 µm2 vs 34.54 ± 2.01 µm2, p<0.05), whereas these alterations appeared later on stratum radiatum. Iba1 immunohistochemistry revealed increased cell density and immunoreactive area in PDAPP mice from 9 m onwards selectively in the hilus, in coincidence with prominent amyloid deposition, evidenced by Congo Red staining. At advanced stages, microglial cells seem to be intimately involved in amyloid degradation. Colocalization of Iba1 with ubiquitin or p62 was exclusively found in cells contacting deposits in AD mice from 9 m onwards. Our work emphasizes the role of glia in AD onset and focuses on a brain subfield revealed as especially susceptible in this disease.

P45.-Remyelination by Bone Marrow Mononuclear Cells: efficiency in cell tracking vs efficiency in cell functionality.

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In order to assess bone marrow mononuclear cell (BMMC) remyelination ability we used a model of sciatic nerve crush. We demonstrated spontaneous migration of endogenous and transplanted wild type BMMCs to the demyelinated nerve. Also, BMMCs were shown to exert a beneficial effect by accelerating the demyelination process and, subsequently, remyelination. In this work, and in order to attain long-lasting cell labeling, we used BMMCs isolated from adult rats of the transgenic strain [Wistar-TgN(CAG-GFP)184ys] (BMMCs-EGFP+) to evaluate their remyelination ability. BMMCs-EGFP+ were transplanted on adult wild type Wistar rats. At different survival times, epifluorescence and confocal microscopy were used to evaluate BMMC-EGFP+ migration and their effect on sciatic nerve remyelination. Results showed BMMC-EGFP+ arrival at the nerve as from 3 days post transplant. In terms of their remyelination effect, results showed a marked decrease in MBP levels (a major myelin protein) as from 5 days after transplant and after 14 days signs of nerve fiber regeneration and remyelination began to be evident. In turn, when comparing BMMC and BMMC-EGFP+ performance, results showed a lower yield in the isolation of BMMCs-EGFP+ and a different migration kinetics for different transplant time points. On the basis of these results, BMMCs-EGFP+ appear to be less efficient than BMMCs in helping the remyelination process , although further studies are required to elucidate the nature of their deficiency.

P46.-Effects of propranolol applied before and after the processing of novelty as a modulator of frustration

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The consummatory successive negative contrast (cSNC) paradigm is an animal model for study of frustration in which acceptance of 4% sucrose is assessed in animals that had been exposed to 32% sucrose. These downshifted animals usually exhibit significantly less sucrose acceptance than animals that always received the 4% sucrose solution. On the other hand, exposing Wistar rats to a novel situation, as the exploration of an open field (OF), prior to the first downshift trial (S1) generates memory impairment on the frustration. The opposite pattern was observed when the OF was applied prior to the second trial (S2) as it generates an accentuation of frustration. With the aim of investigate the implications of nora-adrenergic system in the phenomenon, propranolol (β-adrenergic blocker) was administered 15 minutes before or immediately after the OF. The drug blocked the effect of OF in S1 when it had been injected previously, and it had no effect when it had been applied immediately after. Both treatments showed a blocking effect in S2. These results provide new information on functional and pharmacological dissociations during the first and second trials of cSNC and the different memory processes involved in it.

P47.-Electroretinographic signals in a model of retinal degeneration in rats

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The retina is a light-sensitive multi-layered tissue that lines the back of the eye. When it receives a light stimuli, biopotentials in all its layers are activated, from the outer layer (photoreceptors: rods and cones) to ganglion cells and finally to a specific area of the brain. This biopotentials can be measured to determine the functional state of photoreceptors, in a model of retinal degeneration (RD) in rats.

In order to study the progress of RD produced by low light, Wistar rats were exposed to constant white light of 200 lux intensity from 1 to 7 days. Control animals were kept in light (200 lux) / dark (0 lux) cycles 12hs /12hs (LD) or constant darkness (DD). ERG signals were registered in every group according to ISCEV standards.

We found that the exposure to constant light reduces photoreceptors cells only after seven days of exposure (ONL reduction). We also show that the dysfunction of these cells could occur before the ONL reduces.

ERGs of control and experimental groups were compared. The analysis of the principal parameters of the ERG (Amplitude (μV) and latency time (ms)) shows that there could be an increasing dysfunction in the photoreceptor's biopotentials as the RD progress.

Based on these results we conclude that retinal damage by constant low light exposure could be a useful model to study the progressive dysfunction in photoreceptor cells and to detect if the damage is still reversible.

P48.-Genetic characterization of the promoter polymorphism in SLC6A4 gene (5HTTLPR) in a sample of Colombian population with Major Depression: Pilot Study

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Introduction: Studies have reported that one of the genetic risk factors for the development of Major Depression is the presence of the short allele (s) of the 5HTTLPR polymorphism located in the promoter of gene SLC6A4, that produces less transcriptional activity, and as a consequence, less of serotonin transport from neuron to neuron. Objective: To determine the genotype of the promoter polymorphism in the gene SLC6A4 (5HTTLPR) in a sample of Colombian population with Major Depression (MD) and control group. Metodology: Case-control study; Cases represent patients with Major Depression according to DSM5 without any co-morbidity and a control population. Each participant was interviewed by a psychiatrist, inquiring of basic information and stressful life events. The Hamilton scale was used to evaluate the severity of the depression. A blood sample was taken for 5HTTLPR genotyping. Results: The most frequent stressful life events in the last year were relative´s illness, financial problems and complicated situations at the work or study places. The population studied was found to be in Hardy Weinberg equilibrium. Thus far, we have not found any significant statistical associations between MD, stressful life events and 5HTTLPR genotype.

P49.-Guillain Barre Syndrome-Associated Anti-Glycan Antibodies Alter Growth Cone Tubulin Cytoskeleton Via RhoA/ROCK Pathway from Growing DRGs Neurons

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Axon regeneration is a response of injured nerve cells critical for the nerve repair in human acute immune neuropathies such as Guillain Barré Syndrome (GBS).Clinical studies associate the presence of anti-ganglioside antibodies (anti-Gg abs) with poor recovery in GBS.Passive transfer of mAb (GD1a/GT1b,clone 1B7) or patient-derived anti-Gg Abs in an animal model halts axon regeneration.The aim of this work is to study the molecular bases of axonal regeneration inhibition produced by anti-Gg Abs. Two in vitro models were developed including co-cultures of dorsal root ganglion (DRG) explants with peripheral nerve and culture of primary dissociated DRG neuron (DRGn) where the inhibitory effect of mAb 1B7 was confirmed.Fluorescent-tagged cytoskeleton components were used to study their dynamics at growth cones (GC) by time-lapse video microscopy together with immunofluorescence analysis of microtubules.Studies of 1B7-triggered signaling events included measurement of RhoA GTPasa activity using a FRET-based biosensor and activity of its downstream target Collapsin-Response-Mediator Protein-2 (CRMP-2) by phospho-specific mutants and western blot.1B7-treated explants showed a ganglioside-dependent inhibition of axon regeneration associated with the presence of dysthrophic GC. Also, 1B7 treatment induced a RhoA/ROCK-dependent collapse of tubulin cytoskeleton via inactivation of CRMP-2 at T-555.Overall, our data provide knowledge about the mechanisms determining impaired nerve repair.

P50.-New properties of motor protein dependent transport in the axonal guidance of the telencephalic axonal tracts

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Wiring of the brain relies, at first, on the correct outgrowth of axons to reach the appropriate target area and establish synaptic contact with correct cells. Several guidance receptors present in the surface of axonal growth cones read and execute directional cues present in the extracellular environment of the navigating growth cone. The exact timing, levels, and localization of expression of the guidance receptors in the growth cone therefore determine the outcome of guidance decisions. Membrane trafficking and cargo delivery are essential in developing neurons for delivering molecules that are required for elongation and guidance of the growing axonal. To test the hypothesis that axonal transport impairment can cause axonal guidance defects in the major axonal tracts, we use mice lacking the kinesin light chain 1(KLC1) subunit of the anterograde motor kinesin-1. KLC1-/- postnatal mouse brain exhibited dysgenesis of the corpus callosum, anterior commisure and internal capsule. Using carbocyanine tracer labeling and immunofluorescence staining for L1-CAM, we found that a population of callosal axon fail to cross the midline in KLC1-/- mice, forming a rudimentary corpus callosum. In addition, a subset of corticothalamic axons was misrouted or fails to cross the cortico-striatal boundary in KLC1-/- neonatal brain. These results suggest that KLC1 is required for the pathfinding and axonal guidance of the developing telencephalic axonal tracts in the developing brain.

P51.-Guess who's learning too!

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NFkB activation has been shown to be necessary for long-term memory consolidation in the mouse inhibitory avoidance learning paradigm. NFkB is activated in the nucleus of hippocampal cells in a specific temporal window during consolidation. Previous results showed that the transcription factor is also present in the synapse and is activated at a different temporal window than in the nucleus during consolidation. In this paradigm mice are placed on an illuminated platform with an entrance to a dark compartment, the experimental group receives an electric shock when entering the dark compartment. Delay on entering the compartment is evaluated 48hrs later. The behavioural control group, are mice who experience the same context as the experimental group but do not receive an electric shock, 48hrs later this group of mice do not show a delay to enter the compartment. Nonetheless when analysing the activation of NFkB we found that this group of mice have elevated activation when comparing to naïve. This raised the questions of what was this change due to? What is hippocampus encoding for? is it the whole memory or just the context? We argue that this might be an appetitive learning situation for the mice, where they associate the context to a safe place and that this information may not be discriminated by the hippocampus. This work aims to discuss these results and the role of the hippocampus in learning of this task.

P52.-The small G-protein RAS modulates olfactory memory and synaptic plasticity of neuromuscular junction in Drosophila

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RASopathies are a group of genetic disorders caused by mutations in genes encoding for components of the Ras/MAPK signaling pathway. These mutations produce a higher activity of the pathway, which is a hallmark of these disorders. Learning disability is a common cognitive alteration in this group of disorders. The small G-Protein Ras appears to be a central component in RASopathies. However, its role in memory and plasticity is poorly understood.

Here we present studies showing the role of Ras on olfactory memory and synaptic plasticity in an ex vivo preparation of the Drosophila neuromuscular junction (NMJ).

Suppressing Ras activity by genetic manipulations in mushroom bodies, a brain region essential for learning and memory in insects, reduced memory after 24hr spaced training, but not after massed training or immediate memory. Enhancing Ras activity increased memory after massed training.

On the other hand, NMJ stimulated with high K+ concentration in a spaced protocol produced new synaptic boutons, whereas a pseudo-massed did not. Enhancing Ras activity in motor neurons blocked boutons formation after a spaced stimulation, while Ras suppression promotes the formation of new boutons after both types of stimulation.

These observations provide new insight on the role of Ras in spaced training for memory formation and in spaced stimulations for structural plasticity.

P53.-Astrocyte Heterogeneity Derived from a Single Spinal Cord Progenitor Domain

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Astrocytes are highly heterogeneous in their morphology and specification. An interesting question is to unravel the origin of such diversity. By performing genetic fate mappings of a defined subset of progenitors, termed p0, in the neural tube, we identified that it generates astrocytes that follow a stereotyped migration pathway. We named them as "vA0" (ventral astrocytes from p0 progenitor domain). Their differentiation starts at stage E14.5 in the mouse embryo and follow radial migration from the ventricular zone to the white matter. In the postnatal spinal cord, the location of vA0 is exclusively restricted to a macrodomain at the sulcus limitans. To assess vA0 cell morphologies, we generated fluorescent mosaic embryos. We found that during development, vA0 cells exhibit two types of morphologies which are closely associated with their positioning in the spinal cord: 1) without processes and 2) displaying a radial shape with cellular processes toward the ventricle and the pia mater. At neonatal stage, vA0 precursors generate both fibrous (radial morphology, mostly on the white matter, contacting the pia) and protoplasmic astrocytes (star-shaped, located on the grey matter). Furthermore, a small proportion of vA0 still retain a radial morphology with processes contacting the pia. In summary, we found that a restricted set of progenitors gives rise to astrocytes that occupy a defined region of the CNS but display morphological heterogeneity in the postnatal spinal cord.

P54.-PEDF expression in normal and illuminated rat retina

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Continuous illumination (CI) of rat retina produces photoreceptor degeneration resembling human retinal degenerative diseases. Pigment epithelium-derived factor (PEDF) is a secreted protein which promotes the differentiation of primitive retinal cells; is antiangiogenic, regulates cell cycle and induces apoptosis. In order to shed some light on the processes underlying retinal degenerations, we studied PEDF distribution in control (CTL) and illuminated (IL) rat retinas. Sprague Dawley rats were submitted to CI (12000 lux) during 1, 2, 5 and 7 days. The tissue was processed either by immunocytochemistry (ICC) or by Western Blot (WB) using a PEDF mouse monoclonal antibody (Chemicon Int). Results were quantified by image analysis. Data were statistically analysed by ANOVA (ICC) or Student´s t test (WB). CTL animals showed PDEF immunoreactivity (PDEF-IR) in inter photoreceptor matrix (IPM). After 2 days of CI, there was a significant decrease in the OD of PDEF-IR in the IPM and a significant increase in the outer nuclear layer and in Müller cell processes in the inner retina. WB showed a significant decrease of PEDF at days 1, 5 and 7 of CI.Our results show that, as retinal injury progresses, PEDF decreases in the IPM and probably diffuses to other retinal layers due to the destruction of retinal outer limiting membrane. Determination of PEDF by WB shows that there is a general decrease of PEDF in the retinal tissue along CI. (Supported by CONICET PIP1098-UBACYT 20020100100329).

P55.-Analysis of expression and function of voltage-activated potassium KCNQ channels on mouse eye

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Neuronal potassium channels KCNQ (Kv7) are important for neuron physiology because they regulate their excitability. Four of the five KCNQ channel genes are mutated in human genetic diseases. There are transgenic mice for KCNQ3, -4 and -5 channels, which we used in previous works, allowing the study of protein function and mutation-associated pathologies. Recent publications showed the expression of KCNQ2 to -5 in primate eye and also a possible link between Kcnq5 gen and refractive errors. For these reasons, we investigate the expression and function of these channels in wild-type, Kcnq4-/- and Kcnq5dn/dn mice. We found a weak labeling of KCNQ4 in retinal pigmented epithelium cells, which is enhanced in pigmented cells of ciliary body. KCNQ3 was found only in cells of the non-pigmented epitehlium of the ciliary body. Opposite to what was reported in other species, no KCNQ channel subunits were found in mouse retina. Besides, immature mouse retinal neurons in culture did not show M-like potassium currents, which are generated by KCNQ channels in neurons. Our results suggest that KCNQ channels may participate in the formation of aquous humor of the eye, providing part of the companion positive current during chloride transport trough the epithelium.

P56.-Abolition of the Sex Difference in Ngn3 By Estradiol is Depending on Sex Chromosome Complement

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Although the role of gonadal steroids in sexual dimorphism is undeniable, a growing body of evidences indicates that some sexually dimorphic traits cannot be solely explained as a result of gonadal steroid action. Recent works from our laboratory have shown that the sex difference in the neuritogenic transcription factor neurogenin3 (Ngn3) in hypothalamic neurons is depending on sex chromosome complement; moreover 17β-estradiol (E2) abolishes this sex difference. In order to study if cell-autonomous actions of sex chromosomes are involved in the effect of E2 on Ngn3, we evaluated Ngn3 mRNA in neuronal cultures of transgenic mice which combine a deletion of the Sry gene from the Y chromosome with its reinsertion into an autosome. This model comprises XX and XY gonadal males (XXM and XYM) and XX and XY gonadal females (XXF and XYF). Neuronal hypothalamic cultures of E15 embryos were performed segregated by sex and genotype. After 72h in vitro the cultures were incubated for 2 h with E2 (10-10M) or vehicle. The mRNA transcript levels of Ngn3 were measured by qRT-PCR. The E2-treatment resulted in a significant increase in the expression of Ngn3 only in cultures of neurons carrying XY chromosomes ($p<0.001$), irrespectively of the gonadal type (XYM and XYF). E2 did not significantly affect Ngn3 mRNA levels in XX cultures. These findings indicate that sex chromosome complement mediates both cell-autonomous and hormonal actions on Ngn3 in the hypothalamus.

P57.-Photic Sinchronization of Circadian Rhythms in Mammals: The Role of Second Messengers Downstream Protein-Kinase G

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Light entrainment of mammalian circadian rhythms requires the activation of specific signal transduction pathways in the suprachiasmatic nuclei (SCN). This pathway depends on the circadian time (CT) at which the light is applied. Later in the night (at CT18), light exposure causes phase advances by activation of the NO-GC-PKG pathway leading to enhanced circadian clock gene transcription (i.e, the Period family). Little is known about the steps between PKG and Per1 and the mechanism involved for phase advances. Two specific PKG substrates, G-substrate (GS) and the dopamine- and cAMP-regulated phosphoprotein (DARPP-32), have been characterized and identified in a few restricted areas in the central nervous system. The SCN and the cerebellum are very rich in GS, whereas the SCN and the retina are rich in DARPP-32. There is no evidence on the possible role of these substrates in photic entrainment. In this work we performed western blot analysis of SCN tissue for detecting GS, DARPP-32, and there phosphorylated forms after light pulses (15 min, 300 lux). Increased levels of the phosphorylated GS and DARPP-32 forms were found. Immunohistochemistry at CT6, CT14 and CT18 demonstrated a restricted distribution of the substrates in the SCN. These results provide the first evidence that GS and DARPP-32 are involved in the pathway transmitting photic signals to the SCN.

P58.-SRm160, a splicing factor behind the clock

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Many physiological processes vary in a daily fashion anticipating the light and dark oscillations that arise from the rotation of the Earth. The molecular and physiological processes that sustain the endogenous mechanism that anticipates these changes are known as the circadian clock. To further understand the molecular mechanisms behind this clock we carried out a genetic screen with emphasis on the role played by alternative splicing. Using the fly Drosophila melanogaster as a model organism we genetically disrupted the expression of the majority of splicing regulators and assessed the locomotor activity rhythms of these individuals. Through this strategy we identified the gene SRm160 as a strong candidate to regulate the cellular machinery necessary to sustain overt rhythms.
A null mutation of this gene is lethal, characterized by a developmental arrest at the 2nd larval stage, preventing the assessment of adult locomotor rhythms. On the other hand, Silencing the expression of this gene specifically in pacemaker neurons overcame such lethality and caused a significant loss of behavioral rhythmicity. Noteworthy, this behavioral effect is not associated with alterations in cell morphology or viability of the neurons. Conversely, a decreased SRm160 level dampens molecular oscillations in the central pacemaker and interrupts the daily oscillations in the neuropeptide Pigment Dispersing Factor, the main synchronizer of the fly circadian system.

P59.-Circadian Rhythmomas: Chronobiology of a Glioma Cell Line

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The mammalian circadian system is controlled by a central oscillator located in the suprachiasmatic nuclei (SCN) of the hypothalamus, in which glia appears to play a prominent role. Gliomas are the primary brain tumors with the highest incidence and mortality, frequently located in the hypothalamic region. In addition, tumor development and their sensitivity to antitumor drugs are modulated by several clock genes, and chronopharmacologic treatments result in a higher efficiency and lower toxicity of the chemotherapeutic drugs. We studied the effects of hypothalamic gliomas in the photic synchronization of the circadian clock in mice, resulting in minor alterations on circadian variables, such as an advanced phase angle under light-dark (LD) conditions, and slower resynchronization rate after a sudden change in the LD cycle. Analysis of the expression of the clock gene Bmal1 in the glioma cell line LN-229 showed that these cells possess a functional molecular clock. Moreover, treatment of LN-229 cells at different phases of the circadian clock with Temozolomide (TMZ, the chemotherapeutic agent against gliomas) indicated a phase-dependent effect of the drug in an acute treatment scheme, but not in a long-exposure treatment protocol. Our results suggest minor alterations in the circadian system of mice carrying hypothalamic gliomas and a time-dependent sensitivity of glioma cells to TMZ, supporting further studies of in vivo chronopharmacological approaches with TMZ.

P60.-Dopamine signaling: the missing link between circadian and interval timing

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Two of the main biological timing mechanisms operate in the second-to-minute (interval timing) and on a daily basis (circadian rhythms). Interval timing involves the interaction of cortico-striatal circuits via dopaminergic pathways, while circadian rhythms modulate physiological and behavioural functions. We have previously reported that circadian disruption impairs interval timing in mice. In this work we studied the involvement of dopamine signaling in the interaction between both timing systems. We found that levodopa injections improved timing performance in mice with circadian disruptions, suggesting that a daily increase of dopamine is necessary for a correct performance. Moreover, striatal dopamine levels exhibited a daily rhythm under light/dark (LD) conditions, with higher levels during the night. This rhythm was abolished by constant light (LL). We also demonstrated a daily oscillation in tyrosine hydroxylase levels, dopamine turnover and the circadian clock gene Per2 in the striatum and substantia nigra. In all cases, these oscillations were lost under LL. We also found a daily oscillation of striatal dopamine receptor D2 mRNA, and we are currently studying D2R protein levels.

Our results suggest that the lack of rhythmicity in dopamine signaling could be responsible for impaired performance in the timing task, and add further support to the notion that circadian and interval timing share some common processes, interacting at the level of the dopaminergic system.

P61.-Influence of maternal experience on behavioral response to the maternal separation stress in mother rats: Preliminary results

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Pregnancy and postpartum are periods of maximum neuronal and behavioral plasticity in a female life. In the present study we investigated whether reproductive experience (number of pregnancies and parturition) affects the behavioral response to an environmental stress as the early mother-pup separation by studying parameters known to be affected by long-term stress. Primiparous (1 reproductive experience) and multiparous (MP) (2 reproductive experiences) age-matched female Wistar rats were subjected to either animal facility conditions or daily 4,5h of separation from pups (MS) from postpartum day (PPD) 1-21. Maternal care (pup retrieval) and maternal behavior was evaluated during early postpartum. After weaning, anxiety (elevated plus maze) and spatial memory (object location) were assessed. The preliminary results suggest that MP females show a greater efficiency in maternal care. During early postpartum, multiparity and separation from pups induces an increase of active maternal behaviors. MP rats show a trend towards better performance in spatial memory. Contrary to expected, MP females showed increased anxiety-like behaviors. Although preliminary, the present results support the conclusion that reproductive experience influences the maternal mind. The behavioral changes in the transition to motherhood and the consequences of disrupting the natural dam–pup interaction as well as the neurobiological mechanisms for
these effects, however, remain to be identified.

P62.-The Metacognitive Abilities of Children and Adults

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Metacognitive ability, or the capacity to reflect upon one's own knowledge, is a key trait in our cognitive repertoire which is developed during childhood. Whether kids in school age can perform as well as adults in metacognitive tasks is a question that has not been addressed directly before. Here, we make a direct comparison of metacognitive ability in children and adults, showing conclusively for the first time that 6-8 year old children have a level of metacognitive access similar to that of adults. Further, we apply a signal detection theory model that allows us to separate metacognitive ability with the propensity of risk taking, two factors that have so far been confounded in studies assessing metacognition in children. Using the model, we show that children have a suboptimal tendency towards risky decisions. We then show how the natural predisposition to overconfidence can be partially mitigated by imposing a conservative normative strategy. The extent to which this actually has an effect seems to be progressive with age, which we show by comparing adults, 6-8 year olds, and a group of preschoolers in the 3-5 age range.

P63.-The Occurrence of a Temporal Prediction Error During Reinforced Reactivation is Critical to Induce Memory Destabilization

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The experiments consisted to examine whether the violation of two contextual fear conditioning memories (CFC) can be induced when the animals are exposed to a reinforced reactivation (CS-USs). To confirm that the occurrence of a prediction error based on time estimations about USs arrival is a crucial process involved in memory destabilization (and not merely the absence of the US), two CFC which have different expectation about the USs arrival were submitted to a reinforced reactivation (i.e., retraining session), either under identical conditions compared to the original training or by slightly altering the temporal relationship between USs. Immediately after retraining, rats received a systemic injection of Midazolam (MDZ), a fasting acting GABA-A receptor agonist able to disrupt CFC memory reconsolidation. The results indicate that the detection of a discrepancy between expectation and experience is not just observed with non-reinforced training: a difference between training and re-training is also critical for memory destabilization.

P64.-Conditional overexpression of the neurodegenerative disease-related protein TDP-43 leads to cognitive and social abnormalities in transgenic mice

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TDP-43 mislocalization and aggregation are hallmark features of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), diseases known as "TDP-43 proteinopathies". We have previously shown in mice that inducible overexpression of human wild-type TDP-43 protein (hTDP-43-WT) or a cytoplasmically localized form (hTDP-43-ΔNLS) in forebrain neurons evokes neuropathological changes that recapitulate several features of TDP-43 proteinopathies. Moreover, detailed behavioral phenotyping demonstrated that TDP-43-ΔNLS mice present motor, cognitive and social abnormalities displaying several core behavioral features of FTD. In the present study, we performed a variety of tests to evaluate the effect of hTDP-43-WT expression on behavioral phenotype. Our results indicate that young hTDP-43-WT transgenic mice, in opposition to TDP-43-ΔNLS mice, present a normal motor phenotype compared to control littermates, as assessed by rotarod performance, spontaneous locomotor activity in the open field test and a milder degree of spasticity shown by a clasping phenotype. We are currently performing a broader behavioral characterization and these studies suggests an impairment in cognitive and social domains in the absence of overt motor abnormalities, providing further validation for its usage as a model for FTD. The results from these studies will contribute to address in vivo the pathogenic mechanisms underlying TDP-43 proteinopathies.

P65.-Is major depression a matter of size?

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Major Depressive Disorder (MDD) is a severe mental disorder that is often chronic and recurrent. Previous studies have shown reduced hippocampal and amygdalar volume in MDD patients compared to controls. However, there is opposing evidence. Then, the aim of this work was to study the volume of subcortical structures (thalamus, caudate, putamen, pallidum, brain stem, hippocampus, amygdala and nucleus accumbens (Nac) bilaterally) in MDD patients before and after treatment and healthy controls. We found a reduction in the left Nac volume in MDD compared to healthy controls ($p<0.05$) with no changes after treatment. Also we found a correlation between BDNF expression mRNA in lymphocytes of peripheral blood and left ($p<0.01$) and right ($p<0.0001$) caudate, and left ($p<0.05$) putamen in controls; and with bilateral thalamus ($p<0.01$), bilateral putamen ($p<0.01$), and right accumbens ($p<0.05$) in patients. A previous meta-analysis showed a hippocampal volume reduction only in patient with recurrent and persistent MDD. On the other hand, a preliminary study showed reduced left Nac volume in the postmortem brain of mood disorder patients. Peripheral correlation of gene expression and brain structures volume could be indicative of an interaction between the two systems. Also reduced Nac volume could be a diagnostic tool for MDD. To confirm these hypotheses, replication in a larger sample size is warranted.

P66.-The Effect of Palatable Solutions in the Memory Impairment Induced by Sleep Deprivation in Rats

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Deprivation of REM sleep or sleep deprivation (PS) in rats induce cognitive prejudice. Previous studies have shown that exposure to stress is also capable of producing similar consequences, which may indicate that stress and its hormonal mediators could be responsible for the cognitive deficits. Previously, it was shown that the supply of palatable substances to animals deprived of sleep, during PS, is able to reduce the release of ACTH and corticosterone, hormones involved in the stress response and allegedly Responsible for the cognitive prejudice. In the present study, 60 rats divide into two grous Controle (CTL) and PS were offered water, Sacarose (30%) or Sucralose (6%) to drink during the PS period (96h) induce by the flower pot technique, at the end of this period rats were train and test in the fear conditioning task. During the PS period they were weighed daily and food and fluid intake was assessed twice a day. Compared to their control counterparts, all PS rats lose weight during the PS, chow more than the CTL during the night 3 and 4 of the PS, and drink more Sacarose, but there was no significative diference in freezing behavior of the training or test in the fear conditioning task. This may suggest that the reduce of ACTH and corticosterone induce by the palatable solutions is not enough to revert the prejudice on memory by the glucocorticoids or that the HPA axis play a secondary role in this phenomenon and that other mechanism may account for this prejudice.

P67.-Functional corticostriatal disconnection and behavioral exploitation-exploration imbalance emerge as intermediate phenotypes for a neonatal dopamine dysfunction

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Alterations in dopamine (DA) neurotransmission in adulthood produce severe behavioral and physiological disturbances, as exemplified by Parkinson's disease. However, the consequences of early postnatal deficiencies in DA transmission are less well understood. Locomotor hyperactivity and learning deficits in juvenile rodents following neonatal DA depletion have been taken as evidence of face validity for attention deficit hyperactivity disorder (ADHD). But the underlying cognitive and physiological intermediate phenotypes remain unknown. Here, we show that neonatal DA depletion results in exacerbated local exploration, deficits in foraging for information and failure to exploit shelter, nutritional and social resources. In vivo electrophysiological recordings and morphological reconstructions of striatal medium spiny neurons (MSNs) revealed a functional corticostriatal disconnection affecting medial prefrontal inputs more markedly than cingulate and motor ones, accompanied by a contraction of the MSNs dendritic tree without changes in spine density. Thus, deficits in foraging decisions and neurodevelopmental frontostriatal disconnection emerge as candidate intermediate phenotypes for deficient DA neurotransmission in early life. From a bottom up viewpoint our findings suggest that ADHD and other neuropsychiatric conditions presumably linked to developmental alterations of the DA system should be evaluated for deficits in foraging decisions and corticostriatal connectivity.

P68.-Early social stimulation and the stress response in an animal model of autism

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Autism is a severe neurodevelopmental disorder characterized by poor social interaction and communication, and by stereotyped or restricted behaviors. Symptoms appear in early childhood and persist in adulthood. Several clinical studies suggest that early social stimulation as the most effective treatment for autistic children, who show significant improvements in social behavior through these approaches. In addition, evidences suggest that patients with autism have alterations in stress and inflammatory responses.

It was previously shown that the prenatal exposure to valproic acid (VPA) at gestational day 12.5 results in reduced social interaction in the adult offspring. In those experiments VPA-treated mice were weaned with other VPA mice.

Here, we compared VPA mice weaned with VPA mice (VPA-VPA mice) and VPA-Saline groups (VPA-Sal), containing 2-3 VPA-exposed mice per cage along with 2-3 Saline mice. This design allowed VPA and Sal mice to interact in the home cage from postnatal day (P)21 to P60. At P60, VPA-Sal mice showed higher levels of sociability than VPA-VPA mice, showing that this treatment can rescue at least some of the behavioral alterations observed in our model.

We have previously identified alterations in inflammatory and stress responses after an inflammatory stimulus. Here, we further that analysis, studying the stress response to social novelty and whether this response in modulated by postnatal social stimulation.

P69.-Two-trial spaced training in Drosophila reveals that repetition and spacing in learning improves memory by similar mechanisms

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Long-term memory (LTM) deficit has been detected in animal models of Neurofibromatosis type-1 (NF1) and Noonan syndrome (NS), two disorders caused by mutations that enhance the activity of ERK1/2. NF1 mutant mice and patients showed a memory improvement by additional training, whereas in animal models of NS the memory deficit can be restored by a longer spacing between trials of training. Therefore, it seems that two strategies can provide memory recovery in these models; however, the mechanisms involved remain obscure.

Based on the time course of ERK activity during training we developed a protocol of training. Unexpectedly, our studies provide evidence indicating that both, over-training and longer spacing during training share the same molecular properties.

We found that LTM can be produced by multiple trials of training with a regular spacing (7 trials spaced by 15 min) or by a fewer number of trials with a longer spacing (2 trials spaced by 30 min). Other memory (ARM) was unaffected by repetition or spacing. This suggested that repetition and spacing are equivalent since the ability of the long protocol to induce LTM can be substituted by a longer spacing in a short protocol. Memory produced by those protocols requires the same molecular component (i.e. the small G-protein RAS). Our studies support the idea that ERK activity during training can be used to design learning protocols which improves memory.

P70.-Cocaine induced sensitization is associated with decrease activity of the Wnt/βcatenin pathway in Dorsal Striatum

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In the case of the Wnt canonical or Wnt/β catenin pathway, the interaction between Wnt and Frizzled results in the activation of Dishevelled; which in turn, inhibits GSK-3β and stabilize β catenin. We recently found that Wnt canonical pathway is differentially involved in cocaine induced sensitization. For instance, its inhibition in Prefrontal Cortex is essential for development of cocaine sensitization; while an increased activity in Nucleus Accumbens is necessary for the expression. Since our main goal is to elucidate the role of Wnt/β catenin pathway in cocaine sensitization, we also investigated whether or not changes in the Dorsal Striatum (DS) have a significant role in it. In order to do that, adult Wistar rats received daily cocaine injections for 7 days. All animals were tested for cocaine induced locomotor activity on days 1 and 7, while one group was also tested on day 28. They were sacrificed 24hs after day 7 or 28. Our results showed that cocaine induced a decrease in Wnt/β catenin pathway signaling in DS in order to exhibit behavioral sensitization either after day 7 or 28. Even though a pharmacological inhibition of this pathway in DS did not induce behavioral sensitization. On the other hand, after 21 days of abstinence the pathway activity is increased in DS. So far our data suggests that changes in the Wnt/ β catenin pathway in DS are necessary but not sufficient to induce behavioral sensitization.

P71.-The influence of stress on the structural plasticity associated with fear extinction memory

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Fear extinction results in the suppression of the fear response once the conditional stimulus does not predict the threatening event anymore. Different anxiety disorders have typical deficits in both extinction memory formation and expression.
Given the particular role of the infralimbic medial prefrontal cortex (mPFC-IL) in extinction memory, we planned to define whether acute stress may impact on the synaptic structural remodeling in mPFC-IL in fear trained rats, and thus account for the changes in the dynamic of extinction memory induced by a single stress exposure.
Stressed animals were fear conditioned to context and later on trained in an extinction paradigm (context re-exposures without footshock). Animals were sacrificed for dendritic spines analysis (structural plasticity) either 1 day after fear conditioning (pre-extinction) or 1 day after the end of extinction training (post- extinction).
We observed that before extinction, stressed animals regardless of conditioning, presented a higher dendritic spine density, particularly mature spines, in comparison to non-stressed animals. On the other hand, after extinction training, conditioned animals independently of the stress exposure, presented a reduced density of dendritic spines in comparison to non-conditioned animals.
Thus, changes in the dynamic of the extinction fear memory might not be supported by synaptic structural remodeling in IL-mPFC.

P72.-Effect of Intra-Core, but Not Intra-Shell, mGlu I Antagonist Administration in Restraint Stress-Induced Reinstatement on Extinguished Cocaine-Conditioned Animals

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Previous results from our lab showed that intra-core administration of an mGlu II receptor agonist, LY479234, modified restraint stress-induced reinstatement in extinguished cocaine-induced conditioned place preference (CPP) in rats. Since several studies suggest that group I metabotropic glutamatergic receptors (mGlu I), are involved in cocaine reward the goal of the current study was determine if these receptors also exert an influence in restraint-stress induced reinstatement. In the present experiments, we determine if the intra-core vs. intra-shell administration of MPEP (mGlu I antagonist) could differentially influence the stress-induced reinstatement. Male Wistar rats were conditioned with cocaine (10 mg/kg i.p.) during four alternated drug/vehicle sessions, and extinguished with successive vehicle associations. The following day, animals were microinfused, intra-core or intra-shell, with MPEP (1 or 10 ug/side) or vehicle and 5 min later exposed to a 30 min restraint-stress session (Stress animals) or left undisturbed in their home-cages (Non-Stress animals). Results demonstrate that, the intra-core administration of LY 479234 blocked the restraint stress-induced reinstatement, while the intra-shell administration did not exert any influence. The current results support the hypothesis of the specific participation of mGlu I receptors of Nucleus Accumbens Core how a possible mechanism to understand stress-triggered reinstatement in extinguished cocaine-conditioned.

P73.-Involvement of δCamkII protein in persistent forms of memory

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CaMKII is an abundant synaptic signaling molecule essential for memory formation and synaptic potentiation. In mammals, CaMKII exists in multiple isoforms derived from four closely related genes: α, β, γ, and δ. Little information is known about the role of the δCaMKII in memory processes. In a previous study, we showed that δCamk2 gene is specifically expressed in persistent forms of memory. We found that histone acetylation occurred at δCamk2 promoter region only during consolidation of persistent memory and that Camk2d mRNA levels were specifically induced 3h after strong training in a Novel Object Recognition (NOR) task. In the present work, we carried out experiments aimed at determining the role of δCaMKII expression and its epigenetic regulation on recognition memory persistence. We used two different NOR protocols: one group of mice received a standard training which led to 24hs long-term memory (LTM) and the other group received a strong training which induced 7 days LTM. In the first experiment, we measured Camk2d expression 24 hs after training and found an increment of its mRNA on both trained groups. Secondly, we knocked down Camk2d expression 3hs after strong training with an antisense oligodeoxynucleotide and found memory impairment seven days after. Finally, we analyzed the level of nucleosome remodeling at the Camk2d promoter during persistent memory consolidation. Our results support that Camk2d expression is specifically required for long-lasting memories.

P74.-Sex differences in human reconsolidation of episodic memories

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Consolidated memories might undergo destabilization and reconsolidation process, allowing for the incorporation of new information into a reactivated memory. Destabilization of human episodic memories seem to depend on reactivation taking place in the original learning context. We explored such phenomena using two independent list of objects. In day 1, subjects (male and female college students) learned List 1 in context A or B. In day 2, subjects learn List 2 (same or alternative context, counterbalanced). A control group did not learn any new objects on day 2. Finally, on day 3, all groups were asked to recall freely the objects from List 1. Replicating previous reports, intrusions from List 2 objects on List 1 where observed during the test only for the group that learn List 2 in the same context of List 1. Also, the number of correctly recalled objects was smaller for the group showing intrusions. Total number of remembered objects (intrusions plus correctly recalled objects) did not differed between groups. Surprisingly, sex differences emerged at test: male subjects showed twice more intrusions than females, while female subjects remembered more correct objects than males. This data suggests the total amount of retrievable information will be distributed between correct or incorrect information depending on the experimental treatment, and that memory destabilization (and hence intrusions from List 2 into List 1) is more easily achieved in males than in females.

P75.-Retrieval or reconsolidation of a fear memory can be independently affected by an appetitive experience

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Consolidated memories can be transiently destabilized if appropriate reactivation conditions are met. After destabilization memories need to reconsolidate in order to persist and this process can be modulated by various means. Unrelated emotional experiences, such as stress, can modulate retrieval, destabilization, reconsolidation and extinction process. However, there is no experimental evidence on the effects of an unrelated emotionally appetitive experience on this processes. We used contextual fear conditioning and voluntary sucrose consumption in Wistar rats to explore this possibility. Our data suggest that: a) The appetitive experience can diminish the retrieval of the aversive memory, when given immediately before its reactivation. However, such effects is circumscribed to the retrieval process, since the memory remains intact 24 hs later; b) the appetitive experience can interfere with the reconsolidation process of the aversive memory, when given after its reactivation, as seen 24 hs later in a fear memory test; c) if the appetitive experience takes place after extinction of the aversive memory no effect is seen 24 hs later. Our data suggest that appetitive experiences can independently alter the retrieval or the reconsolidation process of aversive memories. Importantly, it seems that appetitive experiences can only affect fear memories in a permanent way if memory destabilization takes place first.

P76.-Development of a retrieval-induced forgetting paradigm in rodents to model adaptive forgetting in the mammalian brain

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Over a century of research has presumed that forgetting reflects passive mechanisms such as decay and interference. In the last two decades, however, a growing human literature on retrieval-induced forgetting (RIF) has pointed to inhibitory control processes that resolve retrieval competition as a cause of adaptive forgetting. However, the lack of animal-based models for RIF has precluded the understanding of the neurobiological mechanisms. Using spontaneous recognition memory in rats, we have successfully developed a rodent paradigm for RIF. We were able to show that forgetting of an item associated with a particular context happens under conditions that cause competition between memory traces for two items that share a particular retrieval cue. Forgetting is long lasting and independent of the selected retrieval cue and it is controlled by the medial Prefrontal Cortex (mPFC) in rats, homologue to the Dorsolateral Prefrontal region in humans. Our results provide evidence that adaptive forgetting occurs in non-human animals and that homologue regions are required for it. These results suggest that this type of forgetting is achieved by top down inhibition exerted by mPFC over the brain structures that store the memory traces.

P77.-Neurosteroids and Gabaergic Activity on Lateral Septum

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Lateral septal nucleus, which can be divided into dorsal, intermediate and ventral parts, receives its major input –a glutamatergic one– from the hippocampal formation and projects a GABAergic output to the medial septal. GABAergic neurons are one of the most frequent neuronal types present in the lateral septum of the rat's brain. Their activity could potentially affect learning and memory performance, among others. The aim of this work was to study whether pregnenolone and pregnenolone sulphate can modify GABA release. Lateral septum, according to the experimental group, was microinjected with 1µl of either: 1) saline; 2) pregnenolone 12µM; and 3) pregnenolone sulphate 12µM. GABA concentration, our output, was measured by dynamic superfusion (briefly, slices of brain tissue are incubated with [H3]GABA, and then its release is chemically elicited by a solution of K+ 28mM. Finally, [H3]GABA is measured by a beta counter). Our results showed that pregnenolone sulphate increased GABA release while in contrast pregnenolone had no effect regarding control group values. Since previous evidence from our lab showed different memory performance according to the neurosteroid and the behavioral paradigm utilized (i.e. appetitive vs aversive), it is possible to think that –at least in part– the difference reported here could be attributed to the sulphonation state of the neurosteroid, as a sort of putative molecular switch.

P78.-Ghrelin increases memory consolidation through hippocampal mechanisms dependent of glutamate release and NR2B subunits of the NMDA receptor

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*G*hrelin (Ghr) is a 28 amino acid peptide that participates in the modulation of several biological processes. Ghr administration into the hippocampus (hp) improves learning and memory in different behavioral paradigms such as the step down test. However, the possible mechanisms underlying this effect on memory facilitation have not yet been clarified. In this work, we combined electrophysiology, evoked glutamate release from synaptosomes, behavioral paradigms, immunohistochemical detection, pharmacological NMDAR blockade and hippocampal neurons cultures in order to examine if the increase in synaptic efficacy induced by Ghr in hp could be related to A) changes in glutamate release from synaptosomes, B) modification in [Ca2+]i levels in hippocampal neurons C) changes in the expression of the NR2B-subunits containing NMDAR. We also studied if Ghr reverts the cognitive deficit and LTP impairment induced by an NR2B-specific antagonist, Ro-26181. The results show that Ghr increases glutamate release in a dose dependent manner and it also augment of [Ca2+]i levels. The immunohistochemical experiments demonstrated that Ghr enhances NR2B-subunits expression and it also reverted the deleterious effects of the NR2B-specific antagonist, upon behavioral and electrophysiological parameters. These effects are consequence of the specific stimulation of GHS-R1a, since administration of selective antagonist D-Lys3-GHRP-6, prior to the peptide, prevented the Ghr-induced effects.

P79.-The promoting influence of stress on hippocampal structural plasticity and on fear memory is modulated by GABAergic signaling within the Basolateral Amygdala Complex

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GABAergic signaling in the Basolateral Amygdala Complex (BLA) plays a crucial role in the modulation of stress-induced promoting influence on fear memory. Moreover, accumulating evidence suggest that the dorsal hippocampus (DH) is a downstream target of BLA neurons in contextual fear. Given that hippocampal structural plasticity is proposed to provide a substrate for the storage of long-term memories, the main aim of this study was to evaluate the modulation of GABA neurotransmission in the BLA on spine density in the DH following stress on contextual fear learning. Prior stressful experience promoted contextual fear memory and enhanced spine density in the DH. Intra-BLA infusion of Midazolam, a positive modulator of GABAa sites, prevented the facilitating influence of stress on both fear retention and hippocampal structural plasticity. Similarly to the effects induced by stress, the blockade of GABAa sites within the BLA ameliorated fear memory emergence and increased structural remodeling in the DH. These findings suggest that structural changes in DH associated to the promoting influence of stress on fear memory are under the control of GABAergic transmission in BLA.

P80.-Intergenerational effects of perinatal protein malnutrition on maternal and offspring behavior

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Pregnancy and lactation are critical periods in which environment has a strong impact on offspring's brain development. Maternal malnutrition is a known cause of impaired development and dietary protein content is especially influential. In rodents, behavioral transmission through maternal care of environmentally induced changes has been demonstrated to persist across generations. In the present study we assessed the impact of perinatal protein restriction on maternal and offspring behavior in mice of both sexes. Further, we determined if the observed effects were transmitted to the following generation. We observed that mothers fed with reduced protein diet spent significantly less time licking and grooming their pups. The offspring showed half the number of climbs in the cage escape test, less than a half of the distance travelled on the open arms in the elevated plus maze and twice the immobility time in females in the tail suspension test. Maternal behaviour of the female offspring was negatively affected and the second generation showed between a third and a fourth less climbs in the cage escape test, nearly a fourth less distance travelled by males in the elevated plus maze and about forty percent more immobility time in males in the tail suspension test. These findings show that perinatal protein restriction has a detrimental effect on maternal and offspring behavior that can be transmitted at least partially to a second generation.

P81.-Stress induced by maternal manipulation during late gestation increases ethanol intake in offspring

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Infant rats exhibit a particular sensitivity to ethanol's motivational effects. Stress is an important factor mediating sensitivity to ethanol's effects. Although the association between alcohol use and stressful events has been extensively investigated in adult humans and rats, the effects of stressors on development of preference for ethanol during ontogeny has not been studied. We evaluated infantile ethanol consumption responses as a function of prenatal stress induced by maternal manipulation during late gestation. At gestational days 17-20, rat females received a daily intragastric administration (i.g), or were not disturbed. At postnatal days (PDs) 14 and 15, pups were evaluated in terms of 0, 3 or 5% ethanol consumption. At the end of ethanol intake at PD 15 (30 min), body blood samples were collected and ethanol levels were measured. Percentage of body weight gained at PD 14 and 15 (%BWG) and blood ethanol levels (BEL's) served as dependent variables. %BWG significantly varied as a function of ethanol concentration and day of evaluation; prenatal manipulation failed to show a strong modulation of this variable. However, BEL's from pups whose mothers were prenatally manipulated were higher than those levels achieved by control subjects. These results are the first in suggesting that maternal manipulations, induced by i.g. during the last four days of pregnancy, are enough to facilitate ethanol intake even when consummatory responses (%BWG) were not conclusive.

P82.-Hippocampal alpha7 nicotinic receptors modulate memory reconsolidation of an inhibitory avoidance task in mice: possible participation of the MAPK pathway

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CF-1 male mice were trained in an inhibitory avoidance task using a high footshock (1.2 mA, 1s). A retention test was given 48 hours later. Immediately after it, mice were given intra-dorsal hippocampus infusions of either choline (Ch, an α7 nicotinic acetylcholine receptor agonist, 0.08 µg/hippocampus), PD098059 (PD, an inhibitor of ERK1/2 phosphorylation, 0.10 - 1.00 µg/hippocampus) or a cocktail of Ch (0.08 µg/hippocampus) and PD (0.1- 1.00 µg/hippocampus). Memory retention was tested again 24 h later. Ch and PD impaired retention performance. Ch effects were reversed by PD in a dose dependent manner. These results suggest that hippocampal α7nAChRs play a critical role in reconsolidation of an inhibitory avoidance response in mice and that these effects might be mediated, at least in part, by an activation of the MAPK signaling pathway.

P83.-Studing the function of the reconsolidation process: Analysis of the reactivation of the Contextual Pavlovian Conditioning memory triggered by the prediction error in the crab Neohelice granulata

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According to the traditional view on memory, once a memory has been consolidated, the memory remains as a permanent trace. When retrieved, memories may undergo a labile state that is sensitive to modification. This process, called reconsolidation, can lead to memory updating through the integration of new information into a previously consolidated memory background. According to some learning theories associative learning depends on prediction error (PE) – a discrepancy between expectation based on previous learning and actual events. If reconsolidation were to function as an update mechanism its induction should depend on PE-driven learning during memory reactivation. Reconsolidation may only take place when memory reactivation involves an experience that engages new learning (prediction error). Thus far, it has not been possible to determine the optimal degree of novelty required for destabilizing the memory. Using the Contextual Pavlovian Conditioning paradigm (CPC) of the crab Neohelice granulata we explore the optimal degree of novelty require to trigger reconsolidation. Varying the presence/absence or the time point presentation of the US during memory reactivation we demonstrated that PE was a necessary condition for reconsolidation to occur. We found that time is a core part of the CS-US association, and that ambiguous information must be presented during reactivation in order to trigger reconsolidation.

P84.-A novel spherical treadmill apparatus for the head-fixed behaving rat

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We introduce a novel training apparatus for rodents that allows animals to perform motor responses while being head fixed.

This apparatus was developed for the purpose of recording extracellular neuronal activity in the motor cortex of an animal while it performs a motor task. It consists of a freely rotating spherical treadmill and an iron structure where animals are head fixed. Once secured to the structure, animals are placed over the treadmill with their limbs on the sphere so they can walk in any direction. Head fixation is achieved by an x-shaped aluminum piece that is surgically implanted on the skull.

Movements of the animal are measured as rotations of the spherical treadmill. Sphere speed and rotation direction are detected with a 60fps video camera, using custom designed software. The software also allows a wide control of training parameters and performs data storage for posterior analysis.

Here we report training a Long Evans rat in an operant conditioning task where walking on the treadmill after presentation of an auditory stimulus was rewarded with a drop of water.

P85.-Rearing in an Enriched Environment Can Prevent Most Behavioral Alterations Induced by Acute Noise Exposure, Independently of the Exposure Age

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In previous studies we showed that exposure of 15-days-old rats to noise during 2 h can induce hippocampus-related alterations, including changes in anxiety-like behaviors. Nevertheless, no data on the behavioral effects induced in rats of different ages have been obtained yet. Moreover, as the use of strategies of neuroprotection has not been explored in our model, rearing noise-exposed animals in an enriched environment (EE) was used.
Therefore, the aim of the present work was to test if EE can prevent behavioral changes induced by exposure to noise at different ages.
Rats of 7 and 15 days were exposed during 2 h to white noise (95-97 dB) for one day. After weaning, groups of 3-4 rats were transferred to an enriched cage, consisting of toys, a wheel, tunnels and ramps, while other groups were placed in standard cages. One week later, different behavioral tests were performed.
Results show that rats exposed at 7 days had a better performance in associative memory task, whereas no significant changes were found in rats exposed at 15 days. On the other hand, a decrease in anxiety-like behaviors was observed in both groups. EE rearing almost fully prevented these noise-induced behavioral changes.
These findings suggest that although behavioral differences between noise-exposed animals at different ages were observed, significant changes might be generated after visual, social and/or physical stimulation during the peri-adolescence period, independently of the exposure age.

P86.-Role of Medial Prefrontal Cortex and Perirrhinal Cortex during Reconsolidation in Object Recognition Memory Task in Rats

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Episodic memory contains information regarding "what", "where" and "when". In rodents, is evaluated using the spontaneous object recognition task (SOR). The perirhinal cortex (PRH) plays a critical role in object recognition, however other structures are also involved. We have shown that serotoninergic modulation of medial Prefrontal Cortex (mPFC) is involved during retrieval in versions of the SOR in which the memory of the object is associated with temporal or spatial information, like the object in context task (OIC). We suggest that mPFC exerts top-down inhibition of the less relevant information. During reconsolidation, consolidated memories become labile again after reactivation. We propose that reconsolidation in the OIC will occur only for the reactivated (retrieved) object memory trace. However, it is still unknown if reconsolidation occurs in this task; and which structures are involved. The goal of this work was to determine if there is reconsolidation in the OIC and the role of mPFC and PRH cortices in it. Infusion of emetine in the PRH after the retrieval blocked the reconsolidation of only one of the object memories. However, infusion of 5-HT2a antagonist in mPFC allowed labilization of both memory traces during the retrieval making them susceptible to emetine. These results suggest that there is reconsolidation in the OIC and that 5-HT2a receptors in mPFC control memory reactivation allowing the expression and reconsolidation of the most relevant memory trace.

P87.-Assessment of memory extinction of an inhibitory avoidance task

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Memory processes occurring after a memory reactivation modify the behavioral output measured in the following tests. Such processes may increase or decrease the values taken as memory indicators. A decrease is interpreted as memory impairment, and is usually explained in terms of memory reconsolidation impairment or of memory extinction development (and also as extinction enhancement, depending on certain conditions). On the contrary, an increase is interpreted as memory improvement, usually explained by reconsolidation improvement, however it is not clear what should be expected about how extinction contributes to this change. Memory extinction was mostly assessed by using fear conditioning tests, but much less in the inhibitory avoidance task. In this latter task, the extinction development should be accompanied by a progressive decrease in retention latencies to step-through. The contextual conditions under which the extinction develops in an inhibitory avoidance task in mice are analyzed and presented in this work.

P88.-Disruption of fear memory reconsolidation by an appetitive stimulus in ethanol withdrawn rats pre-treated with D-cycloserine

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We have recently reported that a contextual fear memory formed during ethanol (ETOH) withdrawal is resistant to pharmacological disruption after recall. D-cycloserine (DCS, a NMDA receptor partial agonist) administration before memory reactivation promoted vulnerability to the disruptive effect of propranolol on fear memory reconsolidation in ETOH withdrawn rats. Here, we examined whether the memory reconsolidation process can be impaired by the presentation of an appetitive stimulus after retrieval in ETOH withdrawn rats. Male Wistar rats made dependent via an ETOH containing liquid diet (6% v/v) for 14 days. Contextual fear conditioning was performed 3 days after withdrawal. The following two days, animals received alcohol-free beer (BEER) for 2 hours/day. The next day, rats received DCS (5 mg/kg i.p) or saline (SAL) 30 min before a 5 min retrieval session. Fifteen minutes after, animals were given 2 hours access to BEER. Memory retention was evaluated one and seven days later. An affective attenuation of freezing was observed in DCS/BEER treated ETOH group, SAL/BEER and DCS/BEER treated control animals. However, SAL/BEER treatment was ineffective in ETOH group. These effects lasted up to one week. These findings strengthen our assumption that ethanol withdrawal facilitates the formation of fear memory resistant to labilization after recall. On the other hand, they indicate that DCS/BEER is an effective disruptor of fear memory reconsolidation in ETOH dependent rats.

P89.-Positive emotional induction interferes with the reconsolidation of autobiographical memories

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Memory traces can become labile upon retrieval and must be re-stabilized. The disruption of this reconsolidation process can abolish a consolidated memory. In a previous study, we showed that a positive induction post- retrieval of an aversive autobiographical memory impaired the original trace, suggesting potential reconsolidation interference. The aim of the present study was to characterize the reconsolidation interference in our paradigm. To address this goal, healthy participants (18 to 35 years old; 20 women) were divided into two control groups. The first group (ANGRY/6h/POSITIVE) was tested on 3 consecutive days: Day 1, autobiographical memories were reactivated by means of the autobiographical memory test. Participants were presented a negative adjective (angry). After 6h., (outside the reconsolidation window), the interference images (IAPS- positive) was presented. On day 2, (7 days after day 1), memories were again retrieved. Day 3: (30 days after day 2), an additional test was performed as on day 2. The second group (ANGRY/NO-INTERF) was identical to the first group except that participants did not receive any interference. Results: Compared with the group that received the positive interference within the reconsolidation window, the content of the amount of details in the control groups did not change during successive retrievals. Here we provide evidence that an aversive memory can be updated with positive information provided during the reconsolidation window.

P90.-Cortical interneuron impaired function and psychiatric diseases.

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The human cerebral cortex it´s probably the most evolved cell structure all over nature. Studies shows that human brain is not just a scaled up version of less evolved primates, but differs in number of specialized areas and microstructure. The cerebral cortex is composed by two types of neurons: projection neurons and interneurons. They use glutamate and GABA as the main neurotransmitters and are excitatory and inhibitory, respectively. It has been documented that each type of neuron follows a different developmental program. While projection neurons are born at the pallium, GABAergic interneurons are born in the subpallium. Abnormal development of cortical interneurons is thought to be the cause of some psychiatric diseases, such as schizophrenia and bipolar disorders. Schizophrenia is a complex syndrome characterized by heterogeneous collection of symptoms that include altered perception, decreased motivation and cognitive deficits. Despite intensive research, little progress has been made in designing effective treatments for patients suffering from this devastating disease. The pharmacological approach that it is still used today is the administration of antipsychotics (dopamine D2 receptors antagonists) that are only effective on the positive symptoms, and not on the cognitive or negative aspects of the disease. The aim of our work is to explore different animal models to identify interneuron abnormalities in the context of psychiatric diseases.

P91.-Role of the hilar cells of the dentate gyrus in pattern separation and storage in the hippocampus: a computational model

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The hippocampus (HIP) plays a fundamental role in episodic memory. We implemented a biologically plausible HIP model using Python programming language, based on a previous work by our group (Weisz & Argibay, 2009).

We decided to add hilar cells (HC) in the Dentate Gyrus (DG) in order to upgrade the performance of the model. This would improve the ability of the network to distinguish between two similar inputs and lower the interference when patterns are stored in CA3.

The original model included the Entorhinal Cortex (EC), DG, CA3 and CA1. We also modelled HC in the DG. The performance of the network (w/o HC) was evaluated by means of the input correlation (between original patterns in EC and the cues presented at retrieval) and the output correlation (between original EC patterns and the output of the network). Pattern separation was assessed with correlation matrixes among each pattern in EC and in DG. For this purpose, we designed a set of highly correlated input patterns and evaluated the output generated in DG.

We observed no clear difference of performance when the input was randomly generated. On the contrary, using highly correlated input patterns, the model with HC showed better pattern separation (DG patterns were less correlated) and better overall performance.

Our results agree with those of Myers et al about the role of HC in pattern separation, and extend them by showing an improvement in overall performance of the complete HIP network.

P92.-Pressure patterns in birdsong as the activity of the telencephalon is thermally manipulated

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We studied the pressure patterns used by domestic canaries (Serinus canaria) during song production, and their changes as the telencephalic nucleus HVC is cooled. We tested the hypothesis that the patterns emerge from the interaction of two times scales, one of which is affected by the temperature modulations. In particular, our model assumes that the pressure patterns are the solutions of a basic neural oscillator being driven by a temporal signal, which is affected by the thermal manipulations. Under this hypothesis, we investigate the changes in the forcing as a function of the temperature.

P93.-Specificity quantification of texture discrimination processes in vibrissal system

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Rodents can discriminate finely textured objects through active rhythmic movement of their whiskers. The tactile discrimination process originates in the vibrissa primary afferents, in that, if two stimulus evoke distinct responses, probably less sweeps are necessary to recognize their origin. In this work, such process is called "specificity" and we have quantified it as the number of sweeps required to discriminate friction situations. For this, we analyzed the multifiber discharge from a deep vibrissal nerve when the vibrissa sweeps materials (wood, metal, acrylic, sandpaper) having different textures. We polished these surfaces with sandpaper (P1000) to obtain close degrees of roughness and we induced vibrissal movement with two-branch facial nerve stimulation. The afferent discharges were characterized according to their spectral content, amplitude and autoregressive modeling. These features were used to train two-level perceptrons with the back-propagation algorithm. The neural networks were subjected to processes of training, which consisted in presenting the features belonging to 25, 20, 15, 10 and 5 sweeps respectively. Subsequently the features of new sweeps were subjected to classification processes. Preliminary results have shown that neural networks were able to discriminate friction situations by simply observing the features of 5 sweeps. In this way, we quantified the specificity of peripheral vibrisal system through misclassification.

P94.-Permutation entropy applied to the characterization of the clinical evolution of epileptic patients under pharmacological treatment

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Different techniques aroused in information theory and tools from non linear systems theory have been applied to the analysis of electrophysiological time series. Several clinically relevant results have emerged from the use of concepts such as entropy, chaos and complexity in analyzing electrocardiograms (ECG) and electroencephalographic records (EEG). In this work we develop a method based on the permutation entropy (PE) to characterize EEG records from different stages in the treatment of a chronic epileptic patient.

Our results are useful for quantifying clearly the evolution of the patient along certain lapse of time and allow to visualize in a very convenient way the effects of the pharmacotherapy.

P95.-Discriminability measures and time–frequency features: An application to vibrissal tactile discrimination

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In the present study we have proposed four discriminability measures to evaluate the feasibility of differentiating experimental conditions: information measures based on information theory, percentage overlap based on Linacre method, Bhattacharyya distance and univariate standard distance. All discriminability measures were evaluated on experimental protocols related to vibrissal tactile discrimination.

Time–frequency features were extracted from afferent discharges and then, pairwise comparisons were realized by using the proposed discriminability measures. Our results reveal the existence of time–frequency patterns which allows differentiating of sweep conditions from multifiber recordings.

Currently, statistical methods used to justify significant differences in experimental conditions have rigorous criteria that must be met for correct validation of results. Discriminability measures proposed here are robust and can be adjusted to different experimental conditions

Discriminability measures allowed determining the time intervals where two sweep situations have the highest probability to be differentiated from each other. High discriminability percentages were observed into protraction phase, although to a lesser degree, it was also observed in retraction phase. It was demonstrated that sensibility of discriminability measures are different. This revealing a greater ability to highlight percentage changes of pairwise comparisons.

P96.- From bipolar to unipolar recordings

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The recording techniques employed in electrophysiology laboratory influence the nature of the biosignals that are recorded during electrophysiological exploration processes. Unipolar recordings are useful for source localization during mapping procedures, but have a great susceptibility to far-field interferences that can obscure low-amplitude signals of interest. Bipolar recordings are standard in most laboratories because rejection of far-field signal facilitates identification of local potentials, but the signal of interest can be beneath either recording electrode. Here we have proposed calculation methods that allow to estimate the electrophysiological information of unipolar recordings from bipolar recordings. For this have been used two bipolar EEG recordings, e.g. C3-Pz and C4-Pz (with common active electrodes) to estimate the unipolar recordings of three channels (C3, C4 and Pz). Three techniques for solving linear equation systems were used: pseudo-inverse matrix, Tikhonov regularization and least squares. Unipolar recordings estimated with the proposed methods were statistically compared with real unipolar recordings both time- and frequency- domain. Preliminary results show the feasibility of obtaining unipolar recordings from bipolar recordings. The methodology proposed is versatile and can be used for a wide variety of electrophysiological applications.

P97.-Selective neurons in the nucleus HVC of the domestic canary

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Vocal learning is a particularly rare feature shared between humans and few other examples in the animal kingdom, oscine birds among them. For this reason, birdsong has become a favourite animal model to study this behaviour.
During learning, sensori-motor experience shapes the neuronal connections within the motor system, which finally converges into a network capable of generating stereotyped motor commands. These drive the vocal device, giving rise to the specie's characteristic song.
The motor commands emerge from the interaction between different parts of the song system.
In this work we have explored part of it, by measuring in vivo extracellular single unit signals from a telencephalic nucleus (HVC). This nucleus is part of the motor system and integrates motor patterns with auditory ones. It has the particularity
of having neurons that selectively respond to the bird's own song (BOS). Moreover, the activity elicited when exposed to BOS is similar to the activity generated during song production. In this work we report preliminary measurements of neural responses in anaesthetized Canaries (Serinus Canaria) being exposed to the playback of their own song.
The results show that these projecting neurons have sparse response to the BOS, with precise temporal coding to particular syllables. Furthermore, we analysed these recordings in terms of a biomechanical model of the syrinx and found that the spikes occur simultaneously with specific motor gestures.

P98.-Experimental validation of a minimal model for birdsong production

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Songbirds are known as an animal model for studying sensorimotor vocal learning and control of a complex behavior such as singing. The song is generated from neural instructions that command the respiratory system and the syrinx (vocal organ of birds), with striking similarities to what is observed in humans. Interestingly, there are neurons in a songbird's brain telencephalic nucleus HVC that respond selectively to the auditory presentation of the bird's own song (BOS).

In this work we used a synthetic song that has been achieved by modeling the functioning principles of the biomechanical periphery. Recent experimental evidence (Amador et. al, 2013) showed that this low-dimensional model of the syrinx presented biological relevance, by comparing firing properties in the evoked response of HVC neurons to BOS and SYN renditions.

We have since then developed a computational program that automatically generates a synthetic song using as input only a recorded bird's song.

In this work we present the stereotactic device built in our laboratory to perform extracellular recordings in anesthetized zebra finches (Taeniopygia Guttata), with which we measured the evoked neuronal response to several auditory stimuli: Bird's own Song (BOS), Synthetic Song (SYN), Reverse song (REV) and Conspecific song (CON). The experimental evidence gathered by this protocol could serve as a basis to assess the state of validation of the low-dimensional model of the songbird's vocal organ.

P99.-Similar extrapyramidal side effects with typical and atypical antipsychotics chronic treatment

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Haloperidol, typical antipsychotic, or atypical antipsychotic as Clozapine and Olanzapine may induce hypokinetic (catalepsy) or hyperkinetic (tardive dyskinesia - TD) extrapyramidal symptoms. Different mechanisms have been suggested to explain the neural plasticity for both side effects. The aim of this study was to assess motor side-effects with typical or atypical chronic treatment. Methods: C57BL male mice (n = 6-8/group) divided in: Group 1: Haloperidol 2 - 6mg/kg/ip x 90 days (Hal); Group 2: Olanzapine 10mg/kg/ip x 90 days (Olz); Group 3: Clozapine 20mg/kg/ip x 90 days (Clz); Group 4 and 5(vehicle): Salina; or DMSO30% (UFABC Animal ethics committees protocol 014/2013). Behavioral analysis: Catalepsy, TD, Open Field and Rota Rod activity were evaluated. Results: At week 1, Hal and Olz showed evident cataleptic effect, and from 2nd week in all treatments was observed cataleptic effect [ANOVA, $F(4,25)= 23.77$; $P < 0.001$, Duncan test, $P < 0.05$]; decreased Rota Rod time [$F(4,26)= 6.30$; $P = 0.019$], and altered exploratory behavior in Open Field [$F (4,26) = 4.89$; $P = 0.004$]. TD was not observed. Conclusion: although atypical antipsychotics have a lower impairment in motor activity compared to haloperidol (typical), it was significant decreased when compared with control groups.

P100.-Cortical Responses to Speech Production

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Recent studies indicate that neural population dynamics driving different motor actions follow a surprisingly simple structure in different animal systems . Moreover, cortical neurons encode gestures of low-dimensional models of song production in birds . These investigations open new venues to understand the motor code and to design bio-prosthetic devices commanded by cortical activity.
To investigate the implications of these ideas in human vocal production, we analyzed the cortical activity of patients with pharmacologically intractable epilepsy implanted with subdural electrodes. They performed an overt single-phoneme repetition task designed to elicit sensory-motor activations. For a patient implanted with a multi-electrode superficial array, specific electrodes showed increased neural activity across the high-gamma frequency range, revealing the spiking of populations of neurons during task . In line with recent results on speech production , individual electrodes showed one of two types of cortical responses: production or sensory-motor.

P101.-Electrophysiological characterization of muscle activation in 6-OHDA rat model of Parkinson's disease

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Parkinson´s disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of the substantia nigra which are, in part, responsible for the motor control. PD patients develop motor symptoms (tremor, bradykinesia and rigidity) and, although this symptoms appear early, evidence of the disease progression before the onset of symptoms have not been studied in detail. Electromyographic (EMG) patterns could offer important quantitative information about the motor function declination at different stages of the disease. EMG activity of hindlimb muscles in healthy and PD rats was recorded during dynamic and static contractions (normal gait and specific postures respectively). The PD model was induced by unilateral infusion of the neurotoxin 6-hydroxydopamine (6-OHDA) and the effectiveness of the lesion was verified by the apomorphine test. EMG was characterized in frequency domain by using parametric and non-parametric spectral estimation. Frequency content of dynamic EMG remained into bandwidth of 30-400 Hz (fundamental frequency component at 200 Hz) in healthy rats, while in PD rats the bandwidth was 1-150 Hz (fundamental frequency component at 30 Hz). In static contractions no significant differences were found. Our preliminary results show significant differences between EMG of healthy and parkinsonian rats. Future researches will be aimed to detect patterns of the disease progression from EMG recordings before the appearance of motor symptoms.

P102.-Neural activity alterations and functional connectivity deficits in a developmental mouse model of schizophrenia

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Restricted genetic ablation of NMDA receptors in cortical parvalbumin interneurons, during early postnatal development, resulted in impaired maturation of GABAergic cell function, which was sufficient to trigger the development of schizophrenia-like phenotypes in adulthood. The medial prefrontal cortex (mPFC) has been involved in the development of schizophrenic symptoms. Normal refinement of mPFC connectivity continues up to young adulthood and includes synaptic pruning of local and distant inputs, including hippocampal ones. To elucidate the pathophysiological changes leading to schizophrenia-like phenotype in our model we focused in the status of neuronal activity and functional connectivity of mPFC. Single unitary neuronal activity was recorded using tetrodes placed in the mPFC of urethane anesthetized control and mutant mice. Local field potentials were acquired from mPFC and ventral hippocampus (vHP) to characterize global brain states and to analyze neuronal entrainment with cortical rhythms. Global analysis of all recorded units shows a significant increase in the mean firing rate in mutant mice during desynchronized state, but not during slow wave state, compared with controls. Neuronal entrainment to delta, theta, and gamma oscillations will be presented independently for each state. Our results are consistent with the notion that an hyperactive, uncoordinated cortical network, with decreased signal to noise ratio, will be subjacent to the behavioral phenotypes.

P103.-Optical photorelease of dopamine in freely moving animals

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Ruthenium-based caged compounds are complexes capable of releasing biologically relevant molecules when irradiated with visible light. This raises the possibility of stimulating neurons and tissues with high spatial and temporal resolution. In past studies, they have been used in different systems to activate neuronal receptors in vitro as well as in vivo experiments. The last member incorporated to the ruthenium-based caged compounds family is Rubi-Dopa, a complex that releases the neuromodulator Dopamine when irradiated with blue/green light. This complex has recently been used to activate dopamine receptors at the level of single dendritic spines. In the present work, we report for the first time the use of a ruthenium-based caged compound in live, freely-moving rats. The animals were chronically implanted in prefrontal cortex with a multi-electrode matrix containing a cannula through which the complex is injected and a fiber optic is placed that allows the light to activate it. As the animal is allowed to freely explore the arena, neuronal activity is recorded before, during and after the dopamine release. We found significant changes in neuronal activity induced by dopamine uncaging, as changes in the strength and frequency range of the phase-amplitude modulation in prefrontal cortex. Thus, we present here a novel method for the administration and activation of ruthenium-based caged compounds in live, freely-moving animals, opening the possibility to stimulate many kinds of neuronal receptors without any previous treatment.

P104.-Circulating or cerebrospinal fluid ghrelin regulates different neuronal circuits within the dorsal vagal complex

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The dorsal vagal complex (DVC) of the brainstem includes the nucleus of the solitary tract (NTS), the area postrema (AP) and the dorsal motor nucleus of the vagus. The DVC is an integrative center that regulates food intake and relays autonomic neural circuits. The ghrelin receptor, also known as growth hormone secretagogue receptor (GHSR), is expressed in the DVC. Here, we performed an anatomical characterization of the distribution of GHSR in the DVC using a transgenic mouse in which the green fluorescent protein is controlled by the GHSR promoter. Also, we used double staining with markers of neuronal populations to characterize the GHSR-expressing neurons, and we used the marker of cellular activation c-Fos to study the responsiveness of GHSR-expressing neurons to ghrelin. We confirmed that GHSR-expressing neurons exist in all three components of the DVC. These GHSR-expressing neurons failed to express corticotrophin releasing factor, thyrotropin releasing hormone, neuropeptide Y, choline acetyl-transferase, tyrosine hydroxylase or Met-enkephalin. Interestingly, peripherally administered ghrelin mainly activates GHSR-expressing neurons of the AP, while centrally administered ghrelin activates GHSR-expressing neurons of both the AP and the NTS. Thus, GHSR-expressing neurons of the AP seem to sense plasma ghrelin, while GHSR-expressing neurons of the NTS mainly respond to cerebrospinal fluid ghrelin. The phenotype of these GHSR-expressing neurons remains to be determined.

P105.-Ghrelin signaling is required for escalation in high-fat intake during repeated binge eating episodes

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Many people suffering eating disorders display binge eating episodes, in which an excessive amount of palatable foods is rapidly consumed. Ghrelin is a stomach derived hormone that strongly increases food intake. Little is known about the neuronal circuitries activated during binge eating episodes or the role of ghrelin on this behavior. Here, we used a combination of behavioral and neuroanatomical studies in genetically or pharmacologically manipulated mice to determine the neuronal brain centers activated in a binge eating model induced by intermittent access to high fat diet (HFD). We also examined the potential role of ghrelin in the modulation of this behavior. First, we confirmed that Intermittent and limited access to HFD induces binge eating events with an escalating profile. By using c-Fos immunostaining, we found that HFD binging activated neuronal populations of the mesolimbic pathway, including dopamine-neurons of the ventral tegmental area (VTA) and orexin neurons of the lateral hypothalamus. Orexin signaling blockage failed to affect escalation of HFD binging events and c-Fos induction in the VTA. Interestingly, ghrelin signaling was required for escalation of HFD binging events and full c-Fos induction in the VTA. Thus, we conclude that ghrelin signaling is required for escalation in HFD intake during repeated binge eating episodes presumably by regulating the sensitivity of the mesolimbic pathway to the rewarding stimulus.

P106.-Unveiling the CRF Neurons of the Amygdala: Neuroanatomical and Functional Characterization using a Novel Transgenic Mouse Model

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The amygdalar corticotrophin releasing factor (CRF)-producing neurons have been implicated in mediating behavioral and physiological responses related to fear, anxiety, stress and reward. Yet, the study of this set of neurons has been hindered by their challenging identification. By means of a novel transgenic mouse line in which humanized green fluorescent protein (GFP) is under the control of the CRF promoter (CRF-GFP mice), we were able to overcome this issue, allowing for a detailed neuroanatomical insight as well as serving as functional exploratory tool. CRF neurons were observed mainly along the IPAC, with a distribution ranging from the medial part of the CeA to the posterior part of the anterior commissure. Using c-Fos as a marker of neuron activation we explored the response of these neurons by exposing CRF-GFP mice to different experimental paradigms known to activate this region: ghrelin treatment, melanocortin 4 receptor agonist treatment, a conditioned taste aversion paradigm, a high fat diet binging paradigm, a high fat diet withdrawal paradigm, i.p. LPS treatment, a social defeat protocol, and a fasting-refeeding protocol. Of all the cited conditions, only the former three protocols showed a significant increase of c-fos expression in CRF neurons, suggesting they are mainly involved in specific responses related to these paradigms. Overall, this novel CRF-GFP line provides a powerful tool to investigate this intriguing neuronal subset.

P107.-Unbiased prediction of the degree of midbrain dopaminergic neuron loss in parkinsonian mice using behavioral parameters

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Parkinson's disease is a neurodegenerative disorder in which nigrostriatal dopaminergic neurons are vastly degenerated by the time diagnosis is reached. Here we explore how accurately behavioral parameters predict the degree of dopaminergic denervetion in 6-hydroydopamine (6-OHDA) treated mice. Although some treated mice clearly show hemiparkinsonism, symptom severity is highly variable and some animals seem to perform like controls. We conducted an unbiased multivariate cluster analysis over the following parameters: i.spontaneous turning asymmetry, maximum velocity and total distance travelled, from video-tracks obtained in an Open Field; ii.motor coordination in an accelerating rotarod; iii.forelimb voluntary use in the cylinder test. As result we found two clusters, one constituted by symptomatic 6-OHDA mice with 84±5% substantia nigra neurons loss. The other group contains a mixed population of sham and asymptomatic 6-OHDA mice with a mild -yet significant- loss of nigral neurons. We consider that the latter 6-OHDA group models a pre-clinical stage of the disease. Further analysis revealed a linear relationship between nigrostriatal degeneration and symptom severity, arguing against a biological threshold for symptom onset. Overall, the data show that subjects with small lesions may elude diagnosis despite extensive behavioral testing, due to individual variability and the limited sensitivity of diagnostic procedures, resembling clinical settings.

P108.-Analysing limited electrophysiological data by artificial sample generation

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During electrophysiological studies of animal behavior, subjects are required to achieve a certain (high) performance, in order to consider that they have learned a task. Given the finite number of trials an animal executes during a session before it gets satiated or exhausted, incorrect trials are a minority and statistically hard to analyze. When the purpose of a research is to understand the neural mechanisms that lead to an incorrect response, robust procedures to extract information from limited trials are required.

In this work we propose a new method for the generation of samples which retain the statistics exhibited by real extracellular multielectrode recordings. The method compensates the bias produced by a reduced number of samples, and is tested for several statistical measures.

P109.-Dorsal raphe nucleus lesion modulates sodium appetite

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Previous studies from our laboratory have shown that acute Na depletion (SD) by peritoneal dialysis produces a rapid and significant drop in serum and CSF Na concentration within 1-4 hours later; however sodium appetite (SA) became evident just 20 hours later when the extracellular sodium levels has been recovered. To explain the long delay between the SD and SA after the onset of hypovolemia/ hyponatremia, our hypothesis proposes that the stimulatory effects of angiotensin II on sodium appetite normally involve interactions with tonic inhibitory brain serotonin (5-HT) circuits, particularly 5HT neurons of the dorsal raphe nucleus (DRN), which should be inhibited in order to release SA. The aim of this work was to analyze the DRN participation in the temporal dissociation between SD and the appearance of SA behavior, particularly, 2h after SD when the rats are hypovolemic/hyponatremic but SA is not evident. In adult male Wistar rats we investigated the effects of DRN transitory lesion induced by 2% lidocaine injection on hypertonic-NaCl intake 2h after SD stimulated by Furosemide combined with low-sodium diet. DRN lesion (0.5 µl site) increased NaCl intake, 2 h after SD in comparison with sham-lesioned rats (p=0.005; DRN-lesion=0.6ml/100 bw vs DRN-sham lesion= 0ml). In summary, these results show that DRN modulates sodium intake during the delay of SA appearance, being in part responsible for the temporal dissociation between SD and the behavioral arousal.

P110.-Development of a feedback circuit for input specification in adult-born dentate granule cells

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Adult neurogenesis provides a continuous pool of new granule cells (GCs) to the dentate gyrus (DG) of the hippocampus. The specific contribution of adult-born GCs to the hippocampal network remains unknown. New GCs develop and mature over several weeks; during this process they become integrated in the preexisting network. Immature GCs become highly active due to their low spiking threshold that renders low input specificity, shifting upon maturation towards sparse activity as a consequence of their high spiking threshold. The impact of this dual function in the circuit remains unclear, and it will be determined by the output networks activated by new neurons at different stages of maturation. We have used optogenetics to map the networks activated by adult-born GCs. Mossy fibers, the axons of GCs, would typically activate interneurons in the hilus and CA3 region, as well as CA3 pyramidal cells. We found that as adult-born GCs transition towards fully mature stages they acquire the capacity to exert a powerful feedback inhibition onto the granule cell layer through the activation of local GABAergic interneurons in the polymorphic region. In addition, they activate distal CA3 targets that elicit feed-forward GABAergic inhibition and excitation of CA3 pyramidal cells. We are currently aiming to refine the identification of individual populations of GABA interneurons that participate in this process at the proximal and distal regions.

P111.-Theta-oscillations in visual cortex emerge with experience to convey expected reward time and reward rate

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The primary visual cortex (V1) is widely regarded as faithfully conveying the physical properties of visual stimuli. Thus, experience induced changes in V1 are commonly rationalized as learning to better perceive the visual world. However, experience-dependent plasticity can also be interpreted in a reinforcement learning (RL) framework. Previous studies have demonstrated that single units within V1 can learn to predict the time of rewards associated with visual cues. In order to study what changes emerge in V1's local field potential during a reinforcement learning task, we performed chronic recordings using linear arrays that span the entire cortical depth while rats learned visual cue-reward contingencies. Repeated exposure to the visual cue induced the emergence of stimulus evoked oscillations observable in a large V1 area and across every cortical layer. Early in training, the duration of this visually evoked oscillation showed a direct relationship with the intensity of the visual cue ($p<0.05$). However, with training, oscillations evolved to report the time interval to expected reward while diminishing their relationship to stimulus intensity ($p< 0.05$). We also found a strong correlation between the oscillation prevalence and the rate at which the animals received reward. These results demonstrate that evoked-responses in V1 evolve from relating the physical properties of retinal stimuli to conveying when reward (given those stimuli) should be expected.

P112.- JM-20, a new hybrid benzodiazepine - dihydropyridine molecule prevents neuronal cell death in different in vitro model of Parkinson's diseases

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INTRODUCTION: Parkinson's disease (PD) is currently the second most common neurodegenerative disorder in the countries which creates an urgent search for new therapeutic strategies that help reduce after-effects the disease and improve quality of life for patients. The present work evaluated the effect of JM20, a synthetic "alkaloid-like", on neural cells to determine their protection against the cellular damages characterized in PD. MATERIAL AND METHODS: As in vitro models of PD neural PC12 cells were exposed to 0.5 mM Dopamine (DA) or 100 µM 6-OHDA and treated immediately with JM20 (0,0001 to 1 µM) or after 30 min and 1 h damage. Effects on cell viability and dose-response were analyzed by MTT and tripan blue exclusion assay 24 h after experiment. Protection against mitochondrial damage was investigated in purified cerebral mitochondria from rats. RESULTS: JM20 protected cells against toxicity induced by DA or 6-OHDA, and the majority of cells preserved the phenotype comparable with untraded controls. Moreover, JM20 (0,0001 to 1 µM) protected the cerebral mitochondrias against DA and 6OHDA damage, with reduction in swelling (13%), ROS production (20%) and membrane potential (40%). CONCLUSION: These findings indicate that JM20 presents a promising neuroprotective effects involving the preservation of mitochondrial functionality and viability and may be considered as a potential new agents for the treatment of Parkinson's disease.

P113.-Stress and vulnerability to develop cocaine addiction: role of glutamatergic transmission

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Clinical evidence supports the idea that individuals suffering posttraumatic stress disorder (PTSD) are vulnerable to developing substance use disorders (SUDs). We previously investigated the role of excitatory synapses and glutamate (Glu) transmission in nucleus accumbens (NA) in mediating the cross-sensitization between acute and chronic stress and cocaine and found evidence supporting stress-induced plasticity in glutamatergic synapses.

Here, we attempted to mimic how exposure to a single acute stressful life event can create an enduring vulnerability to developing SUDs. Thus, rats were exposed to acute restraint stress (2 hours) and 3 weeks later the NA core was examined for changes in glutamate transport and Glu receptor-mediated synaptic currents. We also determined if acute stress potentiated the acquisition of cocaine self-administration (SA).

Our results showed that acute stress produced a reduction in Glu transport, as the level of GLT-1 transporter was reduced and the electrically released synaptic Glu induces an NMDA current that has a longer decay time. Acute restraint stress also augmented the acquisition of cocaine SA. Thereby, acute stress produced enduring changes in glutamatergic transmission in the NA similarly to those observed after cocaine which supports the idea that a shared neuropathology may contribute to comorbidity between PTSD and SUDs.

P114.-Modulation of GABAA-rho1 receptors by L-cysteine

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The role of redox mechanisms in the regulation of cell function in the central nervous system has been extensively studied. Many neurotransmitter receptors, including glutamate and GABAA receptors, as well as diverse voltage-gated ion channels and transporters are sensitive to redox modulation. GABAA-rho1 receptors mediate tonic currents elicited by ambient concentrations of GABA in the retina. We have previously demonstrated that GABAA-rho1 receptors responses are potentiated by nitric oxide, glutathione, ascorbic acid and reactive oxygen species through thiol modification of the cysteine residues within the rho1 subunit.

Previous reports suggested that the endogenous redox agent L-cysteine modulates calcium channels and induces selective neurotoxicity in the mouse retina, but the effect on GABAA receptors has not been determined yet. In the present study we analyzed the effect of L-cysteine on responses mediated by GABAA-rho1.

Homomeric GABAA-rho1 receptors were expressed in Xenopus laevis oocytes and GABA-evoked chloride currents were recorded by two-electrode voltage-clamp in the presence or absence of L-cysteine. L-cysteine inhibited GABAA-rho1 receptors responses. This inhibition was dose-dependent, reversible, voltage independent and depended on GABA concentration. GABAA-rho1 receptor responses were insensitive to L-cystine, the oxidized form of L-cysteine. The mechanism of action of L-cysteine is currently under study.

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P115.-Serotoninergic alterations in CB1R knockout mice

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The endocannabinoid system, consisting of endocannabinoids (eCBs) and its target receptors (CB1R and CB2R), is essential in the development of the nervous system. It plays an important role in the neuromodulation of synaptic activity, neurogenesis and synaptogenesis. CB1R is involved in physiological processes such as appetite, memory, pain regulation, mood and learning.
The CB1R is found mainly in presynaptic neurons, is expressed primarily in the central nervous system and is primarily responsible for the effects of cannabinoids on the brain.
It was found that both the absence of CB1R in experimental mice, and the use of CB1R antagonist, in humans, generate depressive behavior.
In the present work, using CB1R knockout mice, we demonstrated that the absence of this receptor leads to changes in both the consolidation of the neuronal cytoskeleton, as in the serotonergic system and the ultrastructure of synaptic processes.

P116.-Previous stress diminishes the interfering effect of midazolam on fear memory reconsolidation. Effect of intra basolateral amygdala D-cycloserine administration

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A fully consolidated memory can enter into a new labile state when is retrieved, requiring an additional restabilization process defined as reconsolidation. However, there are conditions in which this phenomenon is constrained. For instance, the recall of memories induced by robust training, among others, are known as boundary conditions. Previous studies in our laboratory have shown that a stressful event prior to a contextual fear conditioning generates a memory that is resistant to the disruptive effect of Midazolam (MDZ) on reconsolidation, and this resistance can be reverted by D-cycloserine (DCS). The goal of this study was to evaluate the anatomical locus of the effect of DCS in the reversal of such resistance. As expected, stressed rats were resistant to the disruptive effect of MDZ, additionally, DCS infusion intra-basolateral amygdala (BLA) before reactivation restored MDZ interference, with no effect per se in DCS/SAL group. By the other hand, in the non stressed groups, all animals administered with MDZ despite of the pretreatment with DCS or SAL exhibit memory interference at Test. This result suggests that BLA is, at least, one of the brain structures involved in memory resistance due to the stressful experience and that activation of NMDA receptors is crucial for memory labilization. Finally, we propose that the occurrence of a negative emotional state at the moment of learning limits the subsequent emergence of the labilization/reconsolidation process.

P117.-Methamphetamine and modafinil differentially alter mRNA expression of epigenetic regulators in the mouse prefrontal cortex

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Chronic methamphetamine (METH) leads to long-lasting cognitive dysfunction in humans and animal models. Modafinil (MOD) is a wake-promoting compound that is being prescribed off label for the treatment of METH dependence. We previously demonstrated that modafinil can rescue METH-induced deficits on memory retention through a mechanism that involves restoration of ERK signaling in the mPFC. In this study, we used cPCR to measure mPFC epigenetic regulators mRNA, include HATs, HDACs, DNMTs, and TETs. We also quantified c-Fos expression as a marker of neuronal activation. METH (1 mg/kg sc) was administered as a single dose or repeatedly for 7 days and we evaluated the effects of a single dose of MOD (90 mg/kg ip) given alone or after METH (METH-MOD). Tissues were collected 1 hr after administration. We found that single dose and repeated METH treatments caused increased expression of Tet1 mRNA and decreased Hdac1, Hdac2, Hat1, and Dnmt3A. METH withdrawal also showed decreased expression of Hdac1 and Hdac2. MOD showed decreased Hdac2 and increased c-Fos expression. The METH-MOD group showed a differential expression pattern when compared with METH and MOD alone: decreased Tet2, Hdac1 and Hdac2 mRNA levels to lower values than METH. Our results show that METH and MOD exert differential effects on epigenetic marker expression in the mPFC, with METH altering a larger set than MOD. These differences could be related to the METH-induced cognitive impairments and mPFC abnormalities.

P118.-Activation of Cannabinoid CB1 Receptor within Nucleus Accumbens Core Underlies Restraint Stress-Induced Reinstatement in Extinguished Cocaine–Conditioned Animal

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Endocannabinoid system, primarily through their actions at CB1 receptor, is implicated in drug relapse. Moreover, the Nucleus Accumbens (NAc), a high density cannabinoid CB1 receptors brain region, is involved in cocaine and stress-induced reinstatement. Previous results from our lab demonstrated that in extinguished cocaine-conditioned animals evaluated in a conditioned place preference test (CPP), the restraint-stress reinstated the cocaine CPP and that phenomenon depends on the glutamatergic transmission within NAc. Additionally, in our lab it has been revealed that intra-Core administration of AM251, a CB1 antagonist, abrogated that restraint stress-induced reinstatement. According to the previous protocol, extinguished cocaine-conditioned Wistar rats were microinjected intra-Core with a CB1 agonist, ACEA, (0, 0.001 or 0.01 fmol/side) or vehicle, and subsequently assigned to the following treatments: 1) Stressed Animals (SA): 15 min-restraint exposure, a non-reinstatement session, and 2) Control Animals (CA). Intra-core ACEA administration facilitated the restraint stress-induced reinstatement in SA. Our results support the hypothesis of the influence of CB1 receptors in restraint stress-induced reinstatement. Future studies will focus on a possible glutamate dependent mechanism within NAc Core to explain the effect of CB1 receptor activation on restraint stress-induced reinstatement.

P119.-Genotoxicity and alteration of spontaneous and evoked activity of the nervous system induced by repeated exposure to low levels of chlorpyriphos

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Chlorpyriphos (CPF) is an organophosphorous acetylcholinesterase inhibitor widely used as an insecticide in agriculture that can induce severe neurotoxicity and lethality in humans and wild life. The goal of this work was to evaluate in rats the effects of daily subcutaneous injections CPF during one week at doses of 0.1, 1 and 10 mg/kg or the CPF vehicle. In one set of animals we assessed the auditory startle reflex and its inhibition by a sub-threshold sound pulse (PPI) at the end of treatment. After euthanasia we measured in the same animals the activities in blood of acetylcholinesterase (AChE) carboxilesterase (CbE) and buticholinesterase (BChE) and evaluated genotoxicity by the alkaline comet assay (ACA). In a second set of animals under the same treatment regime and one day after its completion, we recorded the electroencephalogram and its power spectrum (EEGp) and somatosensory evoked potentials (SEP) under urethane anesthesia. The results indicated a dose-dependent inhibition of AChE, CbE and BChE, and increased PPI. A dose related shift towards high frequencies in EEGp and increased amplitudes of the first negative wave of the SEP were found in CPF treated rats. ACA indicated significant genetic damage only at a dosage of 10 mg/kg. The existence of EEGp, SEP, PPI and ACA changes in animals that received low doses of CPF indicate that even in the absence of clinical signs of intoxicacion, CPF induces significant neurophysiological alteration and genotoxicity.

P120.-Chronic intermittent intake of caffeine and cocaine in mice induced differential effects on locomotor sensitization and glutamatergic gene expression in mPFC

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Caffeine (Caf) is a psychoactive drug commonly used as a regular component of many drinks, foods and medications. Concomitant consumption of caffeine with recreational psychostimulant drugs of abuse, such as cocaine (Coc), can provoke severe reactions and long-term consequences. In this study we explored the effects of Coc, Caf, and their combination (Coc+Caf). Male C57/BL-6 mice were treated with a Coc (10mg/kg), Caf (5mg/kg), their combination (CC5) (10mg/kg Coc+5mg/kg Caf) or vehicle (Veh) in a intermittent binge protocol. We investigated the effects of both psychostimulants in locomotion at day 1 and day 13th post treatments. On day 1 Caf and Coc administration induced hyperlocomotion and the CC5 exhibited higher locomotor activity compared to the Caf group but not Coc group. At day 13 Coc, Caf and CC5 groups showed increased locomotor activity compared to day 1 and CC5 group showed a higher value than others. 24h after treatments, animals were sacrificed and mPFC were used for RT-PCR. We found that the drugs decreased expression of Gria1 and Psd95. For Grin1 Coc showed increased mRNA, Caf decreased it and was able to block Coc effects. Mecp2 and HDAC2 mRNA decreased following all drug treatments. Our results show that the combination of Coc and Caf exerts differential effects on locomotor activity, sensitization and glutamatergic gene expression in mPFC. Caf by itself induced a marked sensitization and potentiated some effects of Coc.

P121.-Perinatal protein deprivation facilitates morphine cross-sensitization to cocaine in adult rats

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In order to study the influence of early nutritional insult on the development of cross-sensitization to the rewarding properties of cocaine in adult rats, different groups of control (C) and protein deprived (D) rats were pretreated twice a day for three days with escalating doses of morphine (5, 10 and 20 mg/kg, s.c.). After the development of sensitization, the rewarding effect of cocaine was evaluated in D- and C-rats in a Conditioned Place Preference (CPP) paradigm.
Dose-response curves to cocaine (3, 5, 7.5, 10 and 15 mg/kg i.p.) evidenced a conditioning effect in D-rats with doses of 5, 7.5 and 10 mg/kg, whereas no effect was observed with the lowest dose used (3 mg/kg). In C-rats, cocaine elicited place preference only with the higher dose of cocaine (15 mg/kg).
Moreover, when the animals where pretreated twice a day for three days with increasing doses of morphine, only D-rats showed sensitization to rewarding properties with low doses of cocaine (5 and 7.5 mg/kg i.p.), which correlates with an over-expression of FosB in selective brain areas related to the rewarding circuit.
Similar brain and plasma morphine / cocaine levels were previously observed in D- and C-rats, so pharmacokinetic alterations induced by early undernutrition might be ruled out.
These results suggest that a deficient nutritional status during the gestational period may induce in adult subjects a lower threshold for developing a behavioral cross-sensitization to cocaine.

P122.-Repeated intermittent treatment with cocaine, caffeine or their combination alters intrinsic and synaptic properties of ventrobasal thalamic neurons

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Cocaine is a highly dangerous illegal stimulant that can cause dependence, and long-term consequences when abused. Caffeine is a stimulant drug found in a range of commercially available products. In addition, "PACO" drug samples have reported quantities of caffeine mixed with other stimulants, including cocaine. The objective of this study was to assess the effects of chronic caffeine/cocaine binge administration on total calcium current and glutamatergic/GABAergic evoked and spontaneous activity, in Ventrobasal (VB) thalamic neurons. We used male mice C57/BL6J (P30-90) to administer chronic binge of caffeine (Caf) (5mg/kg), cocaine (Coc) (10mg/kg) and their combination (CC5) (Caffeine 5mg/kg + Coc 10mg/kg), compared them to control receiving saline solution; and performed whole-cell patch clamp using a N-methyl-D-glucamine (NMDG) solution for perfusion, cutting and incubation of slices. We observed that peak calcium current density (pA/pF) during whole-cell patch clamp recording of VB neurons decreased significantly at -20mV after the two psychostimulants were administered together (Cocaine n=7, CC5 n=7, Control n=3 VB neurons; Kruskal Wallis one way analysis H:13, $p<0.001$, Dunn´s Post-Hoc test $p<0.05$). No changes were observed comparing Coc and control conditions.
Our data suggest that co-administration of Coc and Caf is more drastically affecting Ca2+ transients in the VB thalamic nucleus compared to the other treatments used.

P123.-Blockage of ANG II AT2 receptors modifies cerebelar foliation process

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Angiotensin II exerts its physiological effects through binding to two receptor subtypes: AT1 and AT2 receptors. Ang II AT2 receptor expression is highly modulated during development. In the fetus, AT2 receptors predominate in all tissues and decline shortly after birth, being restricted to a few organs including cerebellum. The aim of the present study was to analyze the effect of antagonist of Ang II type 2 receptor on developing cerebellum. Treatment was performed during the last week of pregnancy with vehicle and PD 123319 (AT2 antagonist,1.0 mg/kg/day). The offspring was analyzed at different ages: P3, P5 and P8. Morphological studies by histological analysis and indirect Immunofluorescence using AT2 antibody were perform. The blockage caused several differences in cerebellum foliation. The detailed analysis revealed alterations in cerebellar layering: increased thickness of the EGL arises from increased proliferation of granule cell precursors, and impaired formation of the characteristic Purkinje cell monolayer. Consequently, the present study demonstrates changes cerebellum foliation in animals born from mothers treated with PD123319. Although treatment lasted for one week before birth important effects on cerebellum development in P8 animals were observed, indicating that the damage continued even when there was no longer exposure to the drugs. These observations confirm previous assumptions that Ang II AT2 receptor plays an important role in cerebellum development.

P124.-Expression of key steroidogenic enzymes in developing brain: hormonal compensation of sex chromosomes-induced sex differences

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The aim of this study was to investigate the brain expression of key steroidogenic enzymes and the mitochondrial cholesterol transporter Star in transgenic mice in which the effect of gonadal sex (testes vs. ovaries) and sex chromosome complement (XX vs. XY) are dissociated. We have evaluated by qPCR the expression of star (steroidogenic acute regulatory protein), cyp11a1 (cytochrome P450-side chain cleavage), cyp19a1 (cytochrome P450-aromatase), srd5a1 and srd5a2 (5 alpha reductase I and II) in the stria terminalis (ST), anterior amygdaloid area (AAA) and amygdala of E16 mouse brain. ANOVA indicated that cyp11a1, star, srd5a1 and srd5a2 did not differ between genotypes in these brain areas. However, XY mice showed higher expression levels of cyp19a1 than XX ($P<0.05$) independently of gonadal sex in ST and AAA. Next, we have evaluated the effect of E2 (10-10M) and dehydrotestosterone (DHT, 10-10M) on cyp19a1 expression in neuronal amygdala cultures. ANOVA revealed a significant interaction between genotype and treatment ($P<0.05$). E2 and DHT increased aromatase levels in XX cultures (males and females) to similar levels of XY. These results suggest that gonadal steroids could compensate differences induced by sex chromosomes in aromatase expression early in mouse brain development.

P125.-Neuronal regulation of the stress response in *C. elegans*: Role of the neurotransmitter tyramine

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Faced with physiological or environmental challenges, isolated cells and unicellular organisms can trigger the stress response autonomously. However, this response should be coordinated in multicellular organisms, as uncoordinated responses in individual cells may be harmful for survival. Recent studies in C.elegans showed that the systemic regulation of starvation and heat shock cellular responses depend on neurons which sense amino acids and ambient temperature, respectively. In both cases, the identity of the neurohormonal signalling that modulates these cellular responses are unknown. By analyzing the C.elegans neuronal wiring diagram we found that the circuits implied in both stress responses converge in one tyraminergic neuron called RIM. We evaluated the heat shock and starvation resistance of C.elegans strains deficient on tyramine synthesis as well as in null mutants of the currently known tyramine receptors. We determined a higher stress resistance in these mutants compared with wild-type animals. We also quantified the lipid profile of these strains in the absence and presence of exogenous tyramine. Our results suggest that under prosperous conditions a basal level of tyramine is released but this signal must be repressed in order to mount a coordinated stress response when the environmental conditions become adverse. This study contributes to a better understanding of the neurohormonal signalling that controls the stress response in multicellular organisms.

P126.-Evidence of postnatal astro and microgliosis in the valproic acid model of autism

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Autism is a neurodevelopmental disorder characterized by the presence of stereotyped or restrictive behaviors, and impairments in communication and sociability. The exact underlying causes of this disorder are still unclear.
As previous studies have shown a link between autism and neuroinflammation, our working hypothesis is that central inflammatory processes are responsible for the behavioral phenotype. Moreover, we hypothesized that there is a developmental critical window in which maturation and consolidation of the neural systems responsible for these symptoms typically occur.
Using the valproic acid (VPA) model of autism, we previously detected an activated glial state in the cerebellum and the hippocampus of adult mice. The aim of this work is to identify the specific time window when inflammation appears and to study its correlation with the behavioral phenotype that we observe.
We used immunofluorescence to characterize the central inflammatory state from P7 to P42. We found higher GFAP+ density and activated microglia in the hippocampus (CA1 and DG), and glial alterations in the cerebellum of VPA mice at early ages (P21 and P28). Also, we evaluated the peripheral inflammatory response and found that VPA mice have a normal corticosterone response postnatally.
Our next step is to test whether modulation of the neuroinflammatory state during this critical period with an anti-inflammatory drug can revert the autism related behaviors.

P127.-Does L-DOPA have neuroendocrine effects?

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L-3,4-dihydroxyphenilalanine (L-DOPA) is a precursor in dopamine (DA) biosynthesis, and it is released by hypothalamic neurons. In the anterior pituitary (AP), DA is the main regulator of lactotrope function, and its actions are modulated by estrogens (E2). Although L-DOPA is the main drug for Parkinson's desease treatment, there are not systematic studies about its neuroendrocrine effects. Our hypothesis is that L-DOPA has direct effects on AP function, including the modulation of its tissue homeostasis.

Administration of L-DOPA (50mg/kg, ip, 6h) to ovarectomized female (OVX) rats increased the percentage of hypodiploid cells in the AP, while it did not affect cell cycle progression. In vitro, L-DOPA decreased the percentage of apoptotic anterior pituitary cells, only in the absence of E2. In GH3 cells, L-DOPA had an antiapoptotic effect in the absence of E2.

Dopa- decarboxylase (AADC) converts L-DOPA to DA. We investigated its pituitary expression by immunofluorescence. The three lobes of pituitary gland express AADC. In AP, we observed expression of this enzyme in lactotropes and other cell types.

In conclusion, L-DOPA modifies the apoptotic rate of AP cells. These actions are modulated by E2. The fact that AADC is expressed in pituitary gland suggests that there may be local synthesis of DA from L-DOPA, as it occurs in other tissues. In parkinsonian patients, L-DOPA treatment may produce neuroendocrine effects that need to be understood in more detail.

P128.-Long-term effects of lifelong aerobic exercise on the stress response in middle-aged and old rats

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In order to understand the adaptive changes in adrenal glands, brain and behavior in response to lifelong endurance exercise, within the context of aging, we performed biochemicals, histopathological and behavioural studies in rats at middle (8 months) and old age (18 months). We designed an aerobic training programme with the treadmill running, considering that the adaptive response of the hypothalamo-pituitary-adrenal (HPA) axis differs between volitional and forced exercise. The levels of corticotrophin-releasing factor (CRF) in brain, hypothalamus and pituitary were affected by age and exercise, resulting significantly higher in old runners. Levels of brain corticosterone were found higher in younger runners and remarkably lower in old ones. Exercise did not change plasma or adrenal corticosterone levels in the absence of adrenocorticotropic hormone (ACTH). Aging produces a moderate increase of the noradrenaline without affecting the adrenergic response or the medular histoarchitecture. Old rats showed a significant decrease of the adrenal cortical activity accompanied by the reduction of fascicular and reticular cortical layers. Histological analysis revealed a significant increase in the adrenal cortex only in the young runners, caused by hypertrophy and/or hyperplasia of the fascicular and reticular layers. We conclude that chronic moderate exercise in the long-term can prevent or reduce some of the physiological and behavioral consequences of stressor exposure.

P129.-Toll-like receptors TLR2 and TLR4 are involved in reactive gliosis and microglial activation after ischemic brain injury

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Reactive gliosis is a generic glial response to brain injury. The beneficial or detrimental role of reactive gliosis is controversial. It is clear, however, that reactive astrocytes may suffer a conversion to the proinflammatory neurodegenerative phenotype. TLR are innate immunity receptors activated by DAMP proteins released by necrotic cells after brain injury.

In this work we studied the role of TLR2 and TLR4 in the astroglial conversion into the reactive proinflammatory phenotype. For that purpose we used primary astrocytic culture exposed to in vitro ischemia (OGD) or transfected with plasmids expressing TLR2 or TLR4. Astrocytes were then exposed to LPS (PAMP) or HMGB-1 (DAMP) to imitate the in vivo situation where reactive astrocytes are exposed to a DAMP gradient from necrotic cells. For the in vivo studies, animals were exposed to the cortical devascularization model of ischemia.

We found that TLR2, TLR4, MyD88 adaptor and proinflammatory IL1beta expressions were increased in glial cells exposed to OGD. TLR overexpressing astrocytes showed increased response to LPS and HMGB1 and presented a sustained NFkB activation. Conditioned medium obtained from HMGB-1-exposed astrocytes was able to activate microglia. In vivo, TLR4 and TLR2 expression were observed in glial cells of the ischemic penumbra, but interestingly, TLR4 expression was also associated with neurons.

Our results show that TLRs have a main role in the neuro-glial crosstalk after brain injury.

P130.-Connexin 43 contributes to gap junction coupling in olfactory ensheathing glia

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Gap junction coupling mediated by connexins is essential for glial cell functions, including potassium buffering and support for synaptic transmission. Olfactory ensheathing cells (OECs) are specialized glial cells that wrap olfactory sensory neuron axons from the olfactory epithelium to the olfactory bulb (OB) and express Cx43. We hipothesize that Cx43 mediates the formation of OEC networks important for plasticity of the olfactory nerve. Here we show that OECs located in external layers of the OB display lower immunoreactivity for Cx43 than internal OECs. This correlates with indicators of a lower degree of gap junction coupling, i.e. significantly lower membrane conductance and smaller amplitude of membrane currents sensitive for meclofenamic acid (MFA 100 µM), a gap junction blocker. We used inducible Cre-Lox technology to delete Cx43 coding sequences in OECs in juvenile or adult mice. We show that mice with the induced Cx43 deletion have OECs with significantly reduced Cx43 immunoreactivity, smaller membrane conductance and lower sensitivity to MFA, suggesting that Cx43 contributes to gap junction coupling in OECs. In addition, Cx43 deletion was not compensated by an upregulation of Cx30, a compensation that was reported in astrocytes. Our data validates the Cre-Lox system to manipulate candidate genes in OECs and establishes the context to ask questions regarding the function of Cx43 in the plasticity of the olfactory nerve.

P131.-Behavioural characterization of the response to polarization motion stimuli in an arthropod

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Visual detection of a prey, a predator or a conspecific is essential for an animal's survival. We study a particular type of visual detection, the perception of polarized light. Many animals rely on it as a compass cue in navigation, to detect bodies of water and to cut through haze. Preliminary results showed that the crab Neohelice granulata reacts with body orientation responses to changes in the orientation of polarized light. Our goal is to characterize the behavioural response of Neohelice when faced to polarization motion stimuli that possess the same intensity and spectral light composition that the background, but a different polarization angle. For achieving this, we presented such stimuli in a modified LCD screen which displayed images with an even intensity, but different angles of polarization. We assessed the response of the crabs to different looming stimuli. The crabs where mounted on a polyethylene sphere where they could walk freely, and the LCD was placed to one side of it. Two sensors registered the movement of the animals. We then related their locomotive response to the dynamics of the different looming stimuli. We found that when faced to polarization stimuli, they displayed clear evasive responses. Our next step is to study the coding of the polarization information in the photoreceptors cells.

P132.-Differential calcium responses of visual columnar neurons to different parameters of visual motion stimuli

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Visual motion perception is critical to many animal behaviours. The visual system must process efficiently different visual cues (colour, velocity, direction of movement, size, contrast, etc) so that animals can respond to relevant stimuli. It achieves this by segmenting visual information into separate visual pathways, but to what extent are these parallel streams separated in the brain?

We begin to answer this question by studying the population activity of small field columnar neurons in the third optic ganglion of a crab. There, giant tangential neurons collect motion information from columnar neurons and relay it to the midbrain where behavioural responses are shaped. We mass stained columnar neurons with calcium sensitive dyes in order to study their responses to different visual motion stimuli. We found that visual columnar neurons activity varies as a function of visual parameters in accordance with behaviour. Black figures moving at higher speeds elicit faster and stronger responses than the slow ones. Figures differing from white to black against a grey background showed higher response for dark than for clear figures. Bars with different angular sizes presented two peaks of response for larger bars (each peak corresponding to each contrast edge), and only one peak for the small bars.

As columnar neurons provide visual input to the giant tangential neurons we discuss which parameters of their calcium responses best explain the escape response of the animals.

P133.-Effects of loud noise on the efferent system of the inner ear

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Noise induced hearing loss (NIHL) is a major hazard in society. Despite several identified details about its etiology, the underlying mechanisms that induce NIHL have been only partially identified. Here, we intend to address the role of the efferent olivocochlear system in NIHL. We made use of a murine model of enhanced noise protection, the Chrna9L9'T knock-in (KI), a mouse in which the α9 nicotinic receptor subunit bears a mutation and leads to enhanced medial efferent activity and a mouse model lacking the α9 subunit of the nicotinic receptor (Chrna9 knockout (KO)).

We exposed mice to noise and measured auditory brainstem responses (ABR), which reflect synchronized discharges from neurons along the auditory pathway. We also tested outer hair cell function by recording the distortion product otoacoustic emissions. Acoustic trauma produced large auditory threshold shifts in WT and Chrna9 KO mice one day after exposure. However, one week later, thresholds returned to normal in WT, whereas in the Chrna9 KO they did not recover. In contrast, Chrna9L9'T KI mice were resistant to the same noise exposure. Suprathreshold ABR amplitudes were reduced in both WT and Chrna9 KO mice. Notably, they did not recover 1 week after exposure, suggesting an irreversible loss of cochlear nerve synapses. In contrast, Chrna9L9'T KI mice showed no changes following noise trauma. We used immunohistochemistry to visualize efferent neurons and found disorganized terminals after trauma.

P134.-A new preparation for extracellular electrophysiological recordings at the level of the optic nerve in the crab *Neohelice granulata*

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This work presents a new preparation for extracellular electrophysiological recordings at the level of the optic nerve in the crab Neohelice granulata. This method allows to measure Movement Detector Neurons (MDNs) in response to different kind of visual stimuli. Our main findings were that: a) the response of the MDNs correlates to the visual stimuli applied,), b) the MDNs do not have strongly directional responses c) MDNs are tightly tuned to detect objects approaching on a direct collision course (looming stimuli) and, d) a quantitative characterization of the MDNs firing rate in response to looming stimuli with different dynamics of approach. Finally, we analyzed the applications of this technique and compared the results to the ones obtained previously with intracellular recordings.

P135.-Wide-field stimulation system for measuring of visuomotor behaviors in arthropods

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In this work we describe the development of a wide-field stimulation system for measuring of visuomotor behaviors. The system is based on the projection of an image generated by a flat projector on a conical translucent screen surrounding the animal. Visual stimuli are designed in spherical coordinates, we calculate its projection onto the cone and finally the image needed to be generated by the projector. The proposed device, simplifies the generation of visual stimuli and allows open or closed loop behavioural experiments. Finally, we show examples of its application to measurement of visuomotor behavior in the crab Neohelice granulata.

P136.-Transcranial ultrasound modulates ketamine-xylazine effects in mice

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Pulsed application of low intensity ultrasound waves induces microscopic vibrations which change brain tissue excitability, providing new means for non-invasive and localized functional brain stimulation and consciousness alterations.
We used a 445 KHz immersion ultrasound transducer coupled to the CF-1 mice head (n=4) with ultrasound gel. Sonication protocol consisted of a tone burst of 0.5 ms and pulse repetition frequency of 1 kHz applied for 500 ms.
Sonication began 15 minutes after the ketamine (80 mg/kg i.p.)-xylazine (10 mg/kg i.p.) injection and was delivered at 0.5 Hz until the onset of voluntary animal movements. A unique set of mice was put under this procedure and tested for different ultrasound intensities (150 mW/cm2, 300 mW/cm2, 450 mW/cm2 and 600 mW/cm2) with an inter-session time of one week.
Although lower intensities (300 mW/cm2) were able to produce motor responses they failed to alter anesthesia duration.
However, intensities higher than 600 mW/cm2 (Ispta, corresponding Isppa=1.2 W/cm2) altered anesthetic effects reducing recovery times from anesthesia in 20 min +/- 6min (mean +/- s.e.m) as measured by the time to the onset of voluntary movement.
Together with the fact that brain stimulation can be assessed in a non-invasive form, our results contribute to a wider range of anesthesia recovery procedures and minimally consciousness state research.
Keywords: Anesthesia; ultrasound; neurostimulation; brain; consciousness

P137.-ATP and adenosine modulate acetylcholine release through P2Y and P1 receptors at the efferent-inner hair cell synapse in the developing inner ear

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Before the onset of hearing (postnatal day 12 in mice) inner hair cells (IHCs) are transiently innervated by medial olivocochlear (MOC) efferent fibers. Acetylcholine (ACh) released by these fibers activates $\alpha9\alpha10$ nicotinic receptors coupled to SK2 calcium-activated potassium channels, leading to inhibitory post synaptic currents (IPSCs). During this period, IHCs fire spontaneous sensory-independent action potentials that are required for normal development of the auditory pathway. This activity is driven and/or modulated by ATP released from cochlear supporting cells. ACh release from efferent fibers also contributes to this modulation. By electrically stimulating MOC fibers and recording IPSCs, we showed that ATP decreases ACh release in a reversible and concentration-dependent manner. In this work, we demonstrate that this effect is through P2Y receptor activation, as the specific P2Y agonist 2-MeSADP mimicked the effect of ATP. Moreover, the non-hydrolyzable ATP analog ATPγS decreased ACh release as well, indicating that this modulation is driven by ATP itself. We further tested if adenosine can also modulate ACh release. Adenosine reversibly decreased the quantal content. CGS15943, a specific P1 receptor antagonist, abolished the effect of adenosine. On the other hand NECA, a specific P1 agonist, decreased ACh release. Our results suggest that both ATP and adenosine inhibit ACh release at the MOC-IHC synapse through the activation of
P2Y and P1 receptors, respectively.

P138.-Carbonic anhydrase pH regulation modulates short term plasticity at the mouse neuromuscular junction

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Previous studies (Groisman and Uchitel, 2013) have shown that synaptic vesicle recycling is affected by changes in pH buffer capacity using Acetazolamide (AZ), the specific inhibitor of carbonic anhydrase (CA), an enzyme responsible for regulating the extra- and intracellular pH. AZ is used to treat certain types of epilepsy and ataxia but its mechanism of action is still unknown.
To analyze the effect of changing buffer capacity on transmitter release, synaptic potentials were recorded at the ex vivo levator auris longus neuromuscular junctions (NMJs) treated with AZ (100 µM) in bicarbonate buffer (BB). In normal Ca/Mg solution, a reduced amplitude and increased frequency of spontaneous miniature end plate potentials were observed, without effect on evoked quantal content measured at low and high frequency stimulation. However, evoked release of AZ treated NMJs, studied with a pair pulse protocol in low release probability conditions (low Ca, high Mg in BB extracellular solution) showed a reduction in pair pulse facilitation, (measured at 5, 10 and 20 ms. pulse interval). To get further insight into the role of pH changes in transmitter release, the above experiments were repeated in a high capacity buffer (Hepes 10mM, pH 7.4). In those conditions facilitation ratio was reduced and the addition of AZ had no further effect. These results suggest short term plasticity of transmitter release may be affected by pH sensitive vesicle recycling mode.

P139.-Characterization of responses mediated by low threshold calcium conductances in a nonspiking neuron

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Voltage activated conductances boost distal synaptic signals counteracting electrotonic decay, increasing their chances to summate with other events in the neuritic tree. We study how a low threshold voltage-activated Ca2+ conductance (LT-VACC) shapes the synaptic response in the neuritic tree of the leech premotor nonspiking (NS) neurons, which express low threshold spikes (LTS). We show that NNC 55-0396 dihydrochloride, a specific blocker of LT-VACC in vertebrates, blocked the conductance that underlies the LTS of NS neurons. This allowed us to evaluate the role of LT-VACC in the amplification and propagation of synaptic signals in NS neuron. Inhibition of LT-VACC reduced the magnitude of NS synaptic responses and hindered its fast components. Blocking LT-VACC had a larger effect the larger were the responses, leaving unaffected responses that were slower and smaller. When NS neurons were stimulated with sinusoidal current waves, the successive cycles exhibited temporal summation that could be recorded in the contralateral soma. NNC strongly diminished this temporal summation, diminishing the maximal amplitude of the response, and reduced its ability to propagate. Literature shows that LT-VACC either supports local graded amplification of synaptic signals or global all-or-none effects. This work presents the first description of a neuron in which LT-VACC produces a graded boosting of synaptic signals while supporting an effective active propagation.

P140.-Carbonic anhydrase modulates short term plasticity at central synapses

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Acetazolamide (AZ) is known to inhibit the action of carbonic anhydrase (CA), an enzyme responsible for regulating the extra- and intracellular pH. AZ is used to treat certain types of epilepsy and ataxia but its mechanism of action is still unknown. At the mouse neuromuscular junction our lab have reported that changes in buffer capacity, by inhibiting CA, produces changes in the mode of vesicle recycling and also affects short term synaptic plasticity. Our aim is to extend those studies to synaptic transmission at central synapses
Whole-cell voltage-clamp recordings were performed in brain stem slices at visually identified MNTB neurons and at the CA1 hippocampus pyramidal cells. Synaptic currents were evoked by stimulating their inputs. Transmitter release and pair pulse ratio (PPR) were not affected by AZ at normal Ca/Mg bicarbonate buffered external solution. However, studied in low release probability conditions showed that AZ reduces PPR at the Calyx of Held. In similar conditions AZ has no effect on excitatory input to CA1 pyramidal cells but in contrast increases the PPR at the inhibitory synapses. These results suggest that changes in pH during synaptic transmission may affect differentially excitatory and inhibitory synapses via a presynaptic vesicle recycling mechanism.

P141-Voltage-gated Ca2+ channels (VGCC) that support ACh release at the mouse efferent-inner hair cell synapse during early stages of development

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Inner hair cells (IHC) are innervated by medial olivocochlear (MOC) fibers since birth to the onset of hearing (postnatal day (P) 12). At P9-11 ACh release is supported by P/Q- and N-type VGCC and negatively regulated by L-type VGCC coupled to BK channels. We have reported that at P5-7, P/Q- and R-type but not N-type VGCC support release and that BK channels exert a negative control. Surprisingly, L-type VGCC agonists and antagonists Bay-K and nifedipine, respectively, enhanced ACh release.

To further elucidate the role of L-type and N-type VGCC at P5-7, we analyzed the frequency of spontaneous inhibitory synaptic currents (sIPSCs) in whole-cell voltage-clamped IHCs bathed in high K+ solution. Nifedipine 3 µM decreased (25,85±8,44%, n=2) and Bay-K 10 µM increased (358,70±5,04%; n=2) sIPSC frequency, as expected if these VGCC mediate K+-evoked release. ω-CgTx 500 nM, had no effect on sIPSC frequency (control 2,86±0,65 Hz; n=5; ω-CgTx 3,06±0,06 Hz, n=3; p>0,05), confirming that N-type VGCC are not functionally expressed at P5-7. In addition, ω-AgaIVA did not affect the quantum content (m) (120,80±9,21%; n=3; p>0,05) of electrically-evoked IPSCs in IHCs from P3 cochleas, suggesting that P/Q-type VGCC do not support release at P3. Bay-K, however, enhanced m by 382±120% (n=2), suggesting that L-type VGCCs support release at this stage. These results show there are significant changes in the VGCC that support and/or modulate ACh release at the MOC-IHC synapse during development.

P142.-Localized calcium signals in inner hair cells of the developing inner ear following efferent fiber stimulation

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Efferent cholinergic neurons project from the brainstem to inhibit outer hair cells (OHC) of the mammalian inner ear. This inhibitory synapse combines the entry of calcium through $\alpha 9\alpha 10$ nicotinic receptors with the activation of nearby SK2 calcium-dependent potassium channels to hyperpolarize the hair cell. The presence of a thin near-membrane cistern that is co-extensive with the efferent terminal contacts, presenting both ryanodine receptors and calcium pumps, let us hypothesize that it may play a role in calcium homeostasis.
Before the onset of hearing (postnatal day 12 in mice) inner hair cells (IHCs) are transiently innervated by efferent fibers and exhibit the same cisterns juxtaposed to synaptic contacts. By electrically stimulating this fibers and recording IPSCs combined with calcium imaging techniques, we measure calcium influx to hair cells during efferent activation of the nicotinic receptors. We found a localized increase in calcium signals temporally coincident with the activation of the nicotinic receptor. Between two and three calcium hotspots were found in each cell, presenting a calcium signal intensity that correlates with the amplitude and kinetics of the IPSCs. Consequently, minimal and maximal stimulation experiments exhibit three different levels of activity. Thus, we suggest that multiple and independent efferent synaptic contacts are present in a single IHC.

P143.-Can neurosecretion be independent of calcium entry? Some new answers for an old question

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Recently we noted that a brief depolatization resembling an action potential applied on mouse chromaffin cells in conditions of complete inhibition of Ca2+ currents (Ica) induced a moderate exocytotic process. To study more systematically this phenomenon we applied square depolarizations (-80 to +10 mV) of variable duration in presence of (i) 0 mM external Ca2+ or (ii) 5 mM Ca2+ and 100 µM Cd2+, what provoked an increase in capacitance that saturated at 17±2 y 14±1 fF respectively (~12 vescles). To buffer any possible contaminant Ca2+ that might enter to the cell or any release from internal stores we made experiments in 0 extracellular Ca2+ and 4 mM intracelular BAPTA, obtaining again a significant exocytosis (14±2 fF) in response to 100 ms depolarizations. The calcium release inhibitor 2-APB was also unable to block this exocytosis process (15±2 fF). Moreover, this Ica independent exocytosis process followed a sigmoid dependence with membrane potential, reaching the 50% of the saturating value at approximately -30 mV. When this vesicle pool was completely depleted by application of a 100 ms depolarization, it recovered with a time constant of 1.04±0.18 s. These preliminary results suggest the existence of a pool of vesicles sensitive to changes in membrane potential, which is released in absence of a measurable Ca2+ entry.

P144.-Activation of presynaptic GABAB receptors enables sustained transmission at high rate of stimulation in cholinergic olivocochlear-hair cell synapses

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During development, medial olivocochlear (MOC) neurons transiently innervate cochlear inner hair cells (IHCs). Although ACh is the main neurotransmitter at this synapse, an abundant GABA innervation is also present. Electrical stimulation of efferent fibers triggers the release of ACh but also activates presynaptic GABAB receptors that reduce ACh release. The mechanism of action of GABA is through the inhibition of P/Q type Ca2+ channels. We are now studying the consequences of GABAB-mediated inhibition in the short-term plasticity properties of this synapse. Inhibitory synaptic currents (IPSC) were recorded in IHCs of acutely isolated organs of Corti while MOC fibers were electrically stimulated. In controls, 15 pulses applied at high frequency (50-100 Hz) progressively decreased IPSC amplitudes. At 50 Hz, the amplitude of the last IPSC of the train was reduced to 32% with respect to the first one. This reduction increased to 53% at a 100 Hz train. At low-frequency (10 Hz), the GABAB agonist, baclofen, reduced IPSC amplitudes throughout the train. However, at higher stimulus rates, the initial IPSC was reduced but the following responses were always larger than controls. A maximal enhancement of 43% was observed for the last IPSC of the train at 100 Hz. These results show that activation of GABAB receptors reduce synaptic depression, suggesting that gabaergic inhibition enables sustained transmission during high-frequency stimulation at the MOC-inner
hair cell synapse.

P145.-Properties of the olivocochlear efferent synapse relevant for the regulation of the auditory periphery

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In mammals, the auditory sensory epithelium contains two types of mechanotransducer cells, inner and outer hair cells (IHCs and OHCs, respectively). IHCs are involved in conveying acoustic stimuli to the central nervous system while OHCs are implicated in sound amplification. OHC and IHC activity (IHC only transiently during development) is modulated by the medial olivocochlear system (MOC).

The synapse between the MOC fibers and cochlear hair cells is cholinergic, fast and inhibitory. Inhibition is brought about by Ca2+ entry through the α9α10 nicotinic cholinergic receptor (nAChR) and the subsequent activation of Ca2+-sensitive K+ channels of the SK2 type. At the MOC-IHC synapse, ACh release is supported by P/Q- and N-type voltage-gated Ca2+ channels (VGCC) whereas those mediating release at the MOC-OHC synapse remain unknown.

In previous work, performed in apical cochlear explants, we showed that the strength of the MOC-OHC synapse increases upon high frequency stimulation due to summation and facilitation. Recent studies suggest that in the basal region, where high frequency sounds are decoded, the cholinergic response is mediated by the α9α10 nAChR coupled to BK channels. As the kinetics of BK and SK2 channels are different, the short term plasticity (STP) properties of this synapse may also vary. We aim at elucidating, by electrophysiological methods, the VGCC mediating release at the MOC-OHC synapse and its STP properties along the tonotopic axis of the cochlea.

P146.-BAW 2014, La Plata: "Electric Brain"

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Here we shortly describe the activities performed at the first BAW that took place at La Plata City, at the Natural Science Museum, organized by members of the Neurophysiology and Electrophysiology Labs of the IMBICE. We structured the activities as a circuit with four stations plus a central area where younger children could draw, paint neurons and make brain hats. The first station consisted in a dynamic introductive talk about the brain and neuroscience plus the possibility of looking and touching real brains from different species. The second station offered the possibility to look at small brains (from a frog and a cockroach) and brain pieces under a magnifier, and watch neurons in brain slices with a microscope. The third station was aimed at showing neurons in action: we recorded the electrical activity from a cockroach leg's sensitive neurons and stimulated motor neurons with electrical signals from different sources. The last station was aimed at demonstrating how fast neurons work by giving interactive talks about how the electrical signals in the brain and spinal cord give account for the reaction time our body has, and then by performing different measurements of reaction times and reflexes. At times, in the central area, we also carried out a representation of neurotransmission using a giant neuron made of recycled material. We estimate that more than 600 people with a very wide range of ages and previous knowledge about biology and neuroscience visited the BAW.

P147.-Brain Awarenes Week Córdoba - Getting to know our brain

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The activity consisted on talks, performances, film projections and a theater play. 1-What's up Brain? Interactive talks for the general public: 1) Are we programmed for stress? We tried to answer questions such as what is the stress response? How does it have evolved? How is it studied in the lab? How does it impact our health? 2) The gender of neurons. Talk to discuss about sexual differentiation of the brain. People aged between 20-60 years old participated each day. 2-The dancing brain: Street performance in which dancers start to dance amongst people while several scientist in their lab coats study their behavior and then they explain to the audience how the audiovisual information is processed and how we coordinate the body. They also handed a brochure with more information about the brain and its functions related to music and dance. The performance was repeated 3 days in the City center and in the university cafeteria. 3-Movie festival. We selected two Argentinean movies related to neuroscience topics and after the projection we discussed the concepts with the people and the researchers and physicians that we invited. El hijo de la novia: Alzheimer's disease. El día que me amen: Depression and anxiety. People between 25-60 years old participated each day.4-Theater play "Power to the Ants!" Two ants helped by a cockroach investigate how humans learn and how memory works with the intention of taking over the world. The audiences were families with school-aged children.

P148.-What do you have in your head? An approach to neuroscience in middle schools of Rio Ceballos and Villa Carlos Paz

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As part of Brain Awareness Week 2014 promoted by the Sociedad Argentina de Neurociencias (SAN), the team made visits to two public middle schools located in small cities of the province of Córdoba, in order to promote knowledge of the brain and neuroscience to young students (IPEM School No. 316, Villa Carlos Paz and the IPEM n ° 144 "Mariano Moreno", Rio Ceballos). The choice for the location was motivated by the lack of this kind of activities performed in the interior of the province. Students and teachers manifested on several occasions that this was the first outreach activity at school that they witnessed. The workshop started explaining general concepts about the study of neuroscience, its importance and applications. Immediately after, students were divided into three groups and different topics related to the functioning of the human brain were exposed: reasoning, hemispheric laterality and optical illusions, among others. For each cluster of students, after basic concepts were shown, different activities were proposed: games, experiments and riddles. These activities allowed discovering, understanding and enhancing the knowledge about brain functioning.

P 149.-The Brain Awareness Week in Bariloche

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The Brain Awareness Week is a world-wide campaign aiming at increasing public awareness of the progress and benefits of brain research. During March 2014 in Bariloche we organized a number of events, focusing on the impact of brain research in public health, education, neurological impairments, addictions and artificial intelligence. We organized a sequence of 5 talks given by renown scientists, and attended by approximately 1300 people. The talks were uploaded to the web site of the event (fisica.cab.cnea.gov.ar/semanadelcerebro) and have been used by high-school teachers in their classes. We also offered an interactive exhibition, where visitors could monitor their own EEG, observed the brains of several animal models, got involved in perceptual illusions, saw movies of decoding procedures that reproduce mental images from fMRI data, and were informed of current neuroscience research lines in Bariloche. Approximately 1200 people attended the exhibition, 900 of which where high-school students. The week was was declared of interest by the local authorities, and received financial support from 10 governmental and non-governmental institutions.

LISTS

Room A

ST1.-Retrieval or reconsolidation of a fear memory can be independently affected by an appetitive experience

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ST2.-Evidence of postnatal astro and microgliosis in the valproic acid model of autism

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ST3.-Early social stimulation and the stress response in an animal model of autism

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ST4.Guess who's learning too!

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ST5.-Dopamine signaling: the missing link between circadian and interval timing

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ST6.-Nanoparticles for targeted drug delivery to glial cells after brain ischemia

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Room B

ST7.-Two signaling pathways mediate presynaptic voltage gated calcium channels inhibition by ghrelin receptor activation

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ST8.-Cell reprogramming to model epilepsy

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ST9.-The Leucine-rich repeat transmembrane protein Lrig1 restricts hippocampal dendrite complexity modulating neurotrophin-induced TrkB signaling

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ST10.-First evidence of the proteasome fast axonal transport mediated by molecular motors and membrane interaction

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ST11.-From axonal transport to physiology. Neuronal specific dependence for Kif5b, an ubiquitous molecular motor

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ST12.- SRm160, a splicing factor behind the clock

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