ISN International Society for Neurochemistry

ISN-Small Conference (ISN-CC)

Neurobiology of Drug Addiction
October 22-23

Principal Speakers

Silvia L. Cruz (México)

Neurobiology of volatile solvent misuse

Inhalant misuse is a worldwide problem that affects mainly adolescents and young adults. Inhalants are the only group of drugs defined by their route of administration rather than by structure or mechanisms of action. Solvents containing toluene are the most commonly products intentionally inhaled to experience psychoactive effects. Toluene can be found in pure form and in many commercial products including paints, glues, paint thinner, inks and varnishes, to mention a few. This presentation will summarize: a) the physicochemical and pharmacological properties of toluene; b) the clinical and preclinical evidence showing that toluene and related solvents produce significant behavioral actions (lack of locomotor coordination, learning and memory impairment, antidepressant and antianxiety-like effects, etc.); c) the voltage and ligand-gated ion channels affected by main solvents; and d) the behavioral, developmental and electrophysiological changes associated with repeated toluene exposure. The main objective is to review the more relevant research concerning the neurobiological basis for solvent misuse and to present some implications for research and treatment.

María Estela Andrés (Chile)

Compulsive behaviors, the role of dopamine D2 and kappa opioid receptors of the mesolimbic system.

Compulsive behaviors are common to several psychiatric diseases as addiction and obsessive-compulsive disorders. The dopamine mesolimbic system is the major circuitry involved in the generation of goal-directed behaviors. Dopamine D2 receptors (D2R) and kappa opioid receptors (KOR) are protein Gi-coupled receptors highly expressed in the mesolimbic system. D2R and KOR share several functions in dopamine mesencephalic neurons as regulation of dopamine release and uptake, dopamine neurons firing, among other functions. In this class, we will analyze animal models of compulsive disorders, the role of D2R and KOR regulating dopamine neurotransmission and their functional crosstalk in

physiological and pathological conditions. In addition, we will analyze the anatomical localization of KOR and D2R in the mesolimbic system and their colocalization in development and adult animals. Finally, we will review the potential role of KOR as therapeutically targets to control compulsive behaviors.

Peter W Kalivas (USA)

Neurobiology of Addiction

Drug addiction involves two primary circuits in the brain. The first is reward circuitry that largely consists of the mesocorticolimbic dopamine system. Addictive drugs activate this circuit, which gives them reinforcing value and keeps a person interested and coming back to re-experience the drug effects. Most addictive drugs activate this circuit much more strongly than a biological reward. This super-activation produces pathologies in the circuit, in particular in the prefrontal cortex and nucleus accumbens. Interestingly, while dopamine circuits mediate the reward and induce long term addictive behaviors, such as vulnerability to relapse, the long term changes are not so much in dopamine as they are in glutamate and GABA transmission. In particular, enduring pathological changes are found in the glutamatergic projections from the prefrontal cortex to the nucleus accumbens, and in the GABAergic projection from the nucleus accumbens to the ventral pallidum. In this talk, we will explore these basic circuits and how they regulate normal reward, and learning and memory processing. We will then discuss how different classes of addictive drug interact with the circuitry to make a given drug more or less addictive. Finally, we will explore some of the latest thinking on how drugs produce long lasting changes in the circuitry, and what we might do to reverse these changes as part of an addiction therapy.

Bruno Averbeck (USA)

Neural systems underlying reinforcement learning

To survive, animals must find food, avoid harm and reproduce. Learning is critical to solving these problems as environments often change, and animals have to adapt to these changes. Reinforcement learning (RL) is the behavioral process of learning from the outcomes of decisions to make better choices in the future. The neural systems underlying these processes are, therefore, critical for adapting to changes in the environment. However, when these systems are driven too far they also underlie disorders including addiction and acquired forms of anxiety like PTSD. The standard model of RL focuses on dopamine and its role in the striatum. Specifically, this model suggests that the activity of dopamine neurons, which codes errors in the prediction of rewards, drives plasticity on frontal-cortical synaptic inputs to the striatum. Through this process striatal medium spiny neurons represent and track the values of choices. However, recent work by our lab has shown that the amygdala also

plays an important role in RL. Specifically, when animals have to learn the values of visual images, the amygdala and ventral striatum play important roles. However, when animals have to learn the values of actions, the dorsal striatum is important. In addition, the amygdala can rapidly update value estimates, whereas the striatum adapts more slowly. The slower striatal learning is, however, less sensitive to noise.

Verónica Alvarez (USA)

Circuit and synaptic mechanisms mediating the behavioral response to drugs of abuse and their contribution to promoting drug abuse

Drugs and substance with abuse potential have very diverse chemical structures and properties. Stimulant drugs such a cocaine and met-amphetamine differ dramatically on their pharmacological targets within the brain from non-stimulant drugs such as opioids and alcohol. Yet all drugs of abuse share the ability to produce strong rewarding effect and serve as powerful reinforcers. They all share the ability to increase dopamine concentration in the nucleus accumbens. In this lecture, we will discuss the varied molecular targets of the most commonly abused drugs and different ways by which they affect the cortical mesolimbic circuit. The lecture will then focus on the actions of cocaine and ethanol. It will show data on the synaptic mechanisms by which cocaine and ethanol affect the basal ganglia circuit to produce behavior and the potential impact of these mechanisms in driving compulsive drug use and abuse.

Marcelo Rubinstein (Argentina)

Central mechanisms controlling satiety, food intake and adiposity

Body weight and energy balance are controlled by brain circuits that promote foraging, food intake or satiety by integrating multiple metabolic and environmental signals. Peripheral organs, such as the adipose tissue, pancreas, liver and gastrointestinal tract, release hormones in response to nutrient flux that are sensed by specialized neurons located in the arcuate nucleus of the hypothalamus. In particular, a group of arcuate neurons expresses proopiomelanocortin (*Pomc*), a gene that encodes anorexigenic neuropeptides collectively known as melanocortins. I will present genetic and functional studies that are contributing to understand how the hypothalamus defends a particular body weight and limits food intake by activating satiety mechanisms that depend on *Pomc*. By studying a large variety of transgenic and mutant mouse strains in combination with molecular evolution and behavioral approaches we were able to define with unanticipated resolution the neuronal transcriptional code of *Pomc*, identify the cis-acting regulatory elements and transcription factors controlling hypothalamic Pomc expression, and characterize their functional importance in the regulation of food intake and body weight. These studies highlight the power

and limitations of central satiety pathways and may contribute to improve individual and collective strategies to curb pandemic obesity.

Martine Cador (France)

Too much sucrose at adolescence: vulnerability to depressive disorders at adulthood?

Adolescence is a critical period for the still maturing brain. Adolescence is characterized by consumption of drugs such as cannabis and alcohol but also by high content sugar foods and drinks which can represent till 20% of the calorie daily intake. The effects such high sugar consumption on later brain functioning and behavior is still not clearly understood. We have developed since several years a preclinical project on the study of the long term neural and behavioral effects of adolescent sugar overconsumption. We found that an unlimited consumption of sucrose during the sole period of adolescence in rats (PND30-PND46) generates a behavioral and neurobiological profile at adulthood characterized by a deficit in hedonic perception, in motivation and in dopaminergic markers which can sign a depressive-like phenotype actually reversed by a chronic antidepressant treatment. These data suggest that an excessive consumption of very reinforcing sugary foods or drinks during adolescence might modify the brain developmental trajectory and favor the appearance of a depressive state at adulthood.