Neurobiology of Drug Addiction
ISN-Symposium

October 24
8:30-10:30 h

Chairs: Dr. Liliana M. Cancela and Marcelo Rubinstein

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

8:30-9:00 Verónica Álvarez (USA)
Dissecting the roles of dopamine D2 receptors in the basal ganglia and motivated behaviors
Dopamine actions in the nucleus accumbens are responsible for generating most of the behaviors triggered by stimulant drugs such as cocaine. This is in large part known because antagonists for the two main types of dopamine receptors expressed in the accumbens, D1 and D2 receptors, can block the behavioral response to cocaine. Dopamine D1 receptors are mainly expressed in the direct-pathway projection neurons of the striatum. D2 receptors, however, are expressed on the indirect-pathway projection neurons, as well as on cholinergic interneurons and the synaptic terminals of glutamate inputs and dopamine inputs to the striatum. Veronica Alvarez will present data from multiple studies in which her laboratory and that of Dr. Rubinstein used genetic tools to dissect out the specific contributions of the dopamine D2 receptors expressed in different cell-types in driving motivated behaviors; from the response to stimulant drugs, to alcohol induced sedation and stimulation.

9:00-9:30 Bruno Averbeck (USA)
Neural systems underlying reinforcement learning
To survive, animals must find food, avoid harm and reproduce. Learning is critical to solving these problems as environments often change, and animals have to adapt to these changes. Reinforcement learning (RL) is the behavioral process of learning from the outcomes of decisions to make better choices in the future. The neural systems

underlying these processes are, therefore, critical for adapting to changes in the environment. However, when these systems are driven too far they also underlie disorders including addiction and acquired forms of anxiety like 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.

9:30-10:00 Martine Cador (France)

Opiate withdrawal memories: Behavior and neural network

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

10:00-10:30 Peter W Kalivas (USA)

Using the Neurobiology of Willpower to Treat Drug Addiction

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