Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : Neurosciences Paris Seine/Sorbonne Université
Research Unit Director : Hervé Chneiweiss
Research Team Director : Jocelyne Caboche/Peter Vanhoutte
Team name : Signalisation Neuronale et Régulations Géniques

Address : Sorbonne Université/ 7quai Saint Bernard-Paris 75005

Supervisor of the Research Intern for this project : Jocelyne Caboche
Telephone : 01 44 27 53 52 ou 01 44 27 22 80

2. Internship project title:

REgulation and role of non-coding RNAs (microRNAs) in cocaine-induced neuronal and behavioral adaptation.

3. Internship Description :

Drug addiction is a clinically devastating neuropsychiatric disorder, resulting from neural adaptations at the molecular, cellular, and circuit levels following repeated drug exposure[1]. Drugs of abuse affect neuronal plasticity in key regions of the brain's reward circuitry, including the dorsal and ventral parts of the striatum, which receive dense dopaminergic (DA) inputs from the mesencephalon. By increasing the DA transmission in the striatum, drugs of abuse initially hijack the natural reward system and produce abnormal, chemically-driven "learning" of drug consumption[2]. Current research on psychostimulants, essentially focusing on cocaine, is trying to elucidate the mechanisms underlying neuro-adaptive changes in the striatum, which might underlie the transition from casual drug use to compulsive drug taking and addiction[3]. The addicted phenotype can persist for the length of an individual's life, with high levels of drug craving and relapses after withdrawal. This persistence indicates that ***drugs induce long-lasting changes in the brain, including gene regulation and epigenetic modifications are responsible for addiction***[4]***.*** Epigenetic mechanisms are complex, and include the regulation of miRNAs, a category of 21-25 nucleotides non-coding RNAs, that bind to complementary sequences on target mRNAs to repress translation. miRNAs are involved in multiple neuronal functions and possibly altered in several psychiatric conditions[5], including addiction[6]. Accumulating evidence identifies canonical miRNA biogenesis as a regulatory hub in response to a plethora of physiological and pathological stimuli and subsequent signaling cascades. In particular, the ERK pathway – which responds to addictive drugs and mediates drug-triggered

long-term striatal plasticity[7]– has been proposed to modulate miRNA biogenesis via the miRNA-generating protein TRBP in an *in vitro* model[8].

In this project the M2 student will investigate the modifications and signaling pathways involved in miRNAs production in the brain, following chronic exposure to cocaine, with a particular emphasis on TRBP[8]. Preliminary studies of the team indicate that TRBP phosphorylation, as assessed by immunohistochemistry, is increased in the striatum of mice after cocaine administration, and correlate with ERK phosphorylation, a marker of rapid neuronal activation by acute cocaine[7]. The role of TRBP in cocaine-induced alterations will be studied from TRBPflox/flox mice, which allows a conditional knock-out of TRBP in identified neuronal populations. The knock out of TRBP in striatal neurons, will be performed owing to viral infection with AAV encoding a recombinase (Cre) under a striatal neuron-specific promoter (PPTA-Cre). Two weeks after the viral infection (corresponding to the optimal delay for the expression of the transgene), conditional TRBP KO mice infected with PPTA-Cre and wild type mice will be chronically treated with cocaine. The locomotor sensitization induced by cocaine, will be studied in TRBP-D1R-SPN KO mice when compared to their controls. At the end of the treatment the brains will then be processed for miRNA extraction after dissection of the DS and NAc. miRNA levels, along with target mRNAs, will be studied by RT-QPCR, owing to protocols that are routinely used in the laboratory. A set of tissues will be prepared separately for immunocytochemical studies of striatal neuron markers, including phospho-ERK and phosphor-TRBP levels, as well as structural plasticity (spine density). Altogether this study will provide new insights into the molecular pathways involved in long-term neuronal and behavioral adaptations to cocaine.

References

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3- Koob, G.F., and Volkow, N.D. (2010). Neurocircuitry of Addiction. Neuropsychopharmacology *35*, 217–238.
4- Nestler, E.J. (2014). Epigenetic mechanisms of drug addiction. Neuropharmacology *76 Pt B*, 259–268.
5- Im, H.-I., and Kenny, P.J. (2012). MicroRNAs in neuronal function and dysfunction. Trends Neurosci. *35*, 325–334.
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7- Cahil E, Salery M, Vanhoutte P, Caboche J (2014) Convergence of dopamine and glutamate signaling onto striatal ERK activation in response to drugs of abuse. Front Pharmacol, 4:172.
8-Paroo, Z., Ye, X., Chen, S., and Liu, Q. (2009). Phosphorylation of the Human MicroRNA-Generating Complex Mediates MAPK/Erk Signaling. Cell *139*, 112–122.