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

Internship Proposal
Academic Year 2019-2020

1. Host team:

Research Unit (e.g. Department or Institute): **Neuroscience Paris-Seine; CNRS/UMR8246; INSERM/UMRS1130; Sorbonne Université**.

Research Unit Director: **Dr Hervé CHNEIWEISS**

Research Team Director: **Dr VANHOUTTE Peter & Dr Jocelyne CABOCHE**

Team name: **Neuronal Signaling & Gene Regulations**

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Supervisor of the Research Intern for this project: **Dr Peter VANHOUTTE**

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2. Internship project title:

Role of dopamine-glutamate heteromers in stress responses induced by withdrawal from cocaine

3. Internship Description:

Drug addiction is a chronic and relapsing psychiatric disorder that results from prolonged drug consumption by vulnerable individuals, leading to compulsive drug intake despite deleterious consequences. Drug-evoked long-term neuronal activity changes within the so-called brain reward circuit are fundamental for the instatement of the enduring behavioral alterations that are characteristic of addiction. Despite their distinct brain targets, all drugs of abuse hijack the natural reward system by artificially increasing dopamine (DA) concentration in the mesolimbic system, resulting in persistent alterations in excitatory glutamate (Glu) transmission-dependent plasticity.

The striatum is considered a key target structure of drugs of abuse within the reward circuit because it is at the crossroad of converging glutamate signals arising from limbic, thalamic and cortical regions, which encode components of drug-associated stimuli and environment, along with DA transmission that mediates reward prediction error and incentive values. We previously unraveled the key role of the integration of Glu and DA signals striatal neurons in cocaine-induced long-term adaptations [1,2]. We showed that the interaction (i.e heteromerization) between the DA D1 (D1R) and Glu NMDAR and DA D2 (D2R) with NMDAR, which is favored by cocaine exposure, controls the development and maintenance of cocaine-induced behavioral responses, respectively [3] (Andrianarivelo et al. in prep).

One important feature of addictions is the high rate of relapse after withdrawal from the drug, the stress being a major predisposing factor for the reinstatement of drug intake. This project aims at studying the role of these heteromers in cocaine withdrawal-mediated stress responses.

This project falls into two main goals:

- **Aim1:** Study the impact of a withdrawal from cocaine on the modulation of D1R/NMDAR and D2R/NMDAR heteromers in the reward circuit (NAc, Amygdala, Prefrontal Cortex). Endogenous heteromers will be detected by Proximity Ligation Assay, routinely used in the lab, from brain slices prepared from mice that have been subjected to a withdrawal before and after anxiety tests (O-maze; dark-light).
- **Aim2:** Study the role of these heteromers in stress responses induced by withdrawal from cocaine. This will be achieved owing to a virally-mediated expression of peptides disrupting either heteromers [3,4,5] in a time-controlled manner. In mice that have been chronically exposed to cocaine, we will evaluate whether blockade of D1R/NMDAR or D2R/NMDAR during the withdrawal is able to alleviate withdrawal-induced stress responses.

[1] Pascoli et al. (2011) Biological Psychiatry 69: 218-227.
[2] Pascoli et al. (2014) Biological Psychiatry 76: 917-926 2014
[3] Cahill et al. (2014) Molecular Psychiatry 19:1295-1304
[4] Andrianarivelo et al. (2018) Neuropharmacol. pii: S0028-3908(18)30903-1.
[5] Liu et al. (2006) Neuron 52, 897–909