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 (NPS), INSERM**
Research Unit Director : **Hervé Chneiweiss**
Research Team Director : **Nathalie Lereche et Régis Lambert**
Team name : **Neuronal networks and physiopathological rhythms**
Address : **9 quai Saint Bernard, Bât. B - 75252 PARIS CEDEX 05**

Supervisor of the Research Intern for this project : **Marco Diana and Eric Schwartz**

Telephone : **(33) 01 44 27 38 89**
E-mail : Marco.diana@upmc.fr, eric.schwartz@upmc.fr

2. Internship project title:

Optogenetic dissection of an habenular circuit regulating aversive behavior

3. Internship Description :

The recent development of novel optogenetic and chemogenetic tools in neuroscience has led to innovative strategies to dissect the physiological mechanisms underlying the activity of neural circuits and to link their anomalies with pathological behaviors. This Master 2 project proposes to use state-of-the-art experimental techniques to characterize the Dorsal Diencephalic Conduction system (DDC), a neuronal network mediating negatively-valued, aversive associations between challenges from the external environment and internal emotional states.

The Medial Habenula (MHb) and the Interpeduncular Nucleus (IPN) are key relay nuclei belonging to the DDC. The synaptic connections linking the MHb with its unique postsynaptic target, the IPN, have been shown to regulate several aspects of complex behaviors such as depression, anxiety, fear, sensitivity to pain, drug addiction and withdrawal.

These important functions notwithstanding, most of the synaptic and circuital mechanisms of the MHb-IPN axis remain unknown.

The MHb receives glutamatergic and GABAergic inputs from anterior septal areas, whereas its efferences to the IPN are mixed glutamatergic and cholinergic. Importantly, the MHb is completely devoid of intrinsic, local synaptic circuits. A mainly GABAergic nucleus, the IPN, in turn, inhibits caudal dopaminergic and serotoninergic nuclei. The dysfunction of these nuclei is tightly associated with altered

emotional conditions, thus probably explaining the importance of the MB-IPN axis in regulating emotional associations.

Current dogma suggests that increases in MHb activity leads to a depression of serotoninergic and dopaminergic systems. Nevertheless, the influence of the MHb in controlling behavior appears to be more subtle, as recent data demonstrate a bi-directional regulation of aversion by the DCC.

We believe that this ambiguity may derive, at least in part, from the specific properties of the synaptic afferences to the MHb.

An exceptional aspect of the synaptic inputs to the MHb is that their valence (excitatory or inhibitory) is not dictated by the chemical phenotype of the afferent neuron. Indeed, activation of the GABAergic inputs to the MHb increases, rather than decreases, MHb neuronal excitability.

We thus propose that the final excitatory or inhibitory effect of MHb activation on serotonin and dopamine levels in the brain is instead dictated by the specific pattern of afferent activity and by the distinct dynamic synaptic properties of the glutamatergic and GABAergic inputs to the MHb. Consistent with this hypothesis, by combining ex-vivo and in-vivo optogenetics our laboratory has recently showed that the rapid depression in synaptic efficacy of the glutamatergic inputs to the MHb resulting from repeated stimulations imposes precise constraints to the activity patterns of this input that can successfully lead to the modulation of anxious states in-vivo (Otsu et al. 2017).

In the course of this Master 2 project, we will investigate the precise anatomical connectivity and the physiological properties of the excitatory GABAergic afferents to the MHb using a combination of viral anatomical techniques, optogenetics, and electrophysiology in transgenic mouse models (for ex: VIAAT-Cre, VGluT2-Cre and ChAT-ChR2 mice).

In conclusion, we seek to recruit a motivated candidate, interested in extending his/her Master 2 internship into a doctoral thesis in our team, with the ultimate goal of identifying with in-vivo behavioral experiments how specific patterns of afferent activity influence emotional behaviors via modulation of the serotoninergic and/or dopaminergic tone in the brain.