Regulation of affective states by bimodal GABAergic transmission in the mouse Medial Habenula

Sujet proposé par

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UMR8003
Synapses of Affective Behaviors

M2 Research project title

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Keywords

ex vivo electrophysiology, in vivo fiber photometry and optogenetics

Description of the project

Hedonic affective states are essential for guiding appropriate responses to both positive (i.g. food, social interactions) and negative (i.g. threats, dangers) environment signals. Disequilibrium of hedonic balance leads to disproportionate sensitivity to anxiogenic, aversive, and/or rewarding stimuli resulting in pathological behavioral disfunctions indicative of depression or addiction. The epithalamic habenular complex (Hb) activity, a molecularly diverse structure that relays forebrain structures with midbrain monoaminergic nuclei, is known to bidirectionally regulate affective states. Neurons within the medial division of the habenula (MHb) exhibit numerous unique synaptic properties which allow them to titrate emotional behavioral states. For example, the two principle inhibitory neurotransmitters in the CNS, GABA and Glycine, paradoxically have been found to induce excitatory currents within the MHb. Indeed, our team has found that MHb neurons express a novel form of cation permeable glycinergic receptors and that these excitatory receptors are necessary for the expression of aversive states (Otsu et al. 2019). Activation of ionotropic GABA receptors also induces excitatory currents due to an exceptionally high intracellular chloride concentration found in MHb neurons. This excitation is counterbalanced by the activity of inhibitory metabotropic GABAb receptors also present on MHB neurons (Choi et Shin 2016). Given these bimodal effects of GABAergic signalling on MHb neurons, how GABAergic afferent activity modulates neuronal activity and subsequently affective states remains to be determined. The goal of this M2 master project will be to first characterize how different physiological regimes of GABAergic afferent activity may shift the balance of excitatory ionotropic GABA and inhibitory metabotropic signalling within the MHb. This will be combined with viral tract tracing and immunohistochemical techniques to understand the origin and specific targets of GABAergic afferents. Based on these results, the M2 candidate will use in vivo optogenetic techniques to determine how physiological patterns GABAergic afferent activity in the MHb influences affective behaviors.

Methods and techniques

The M2 student will perform patch clamp, current- and voltage-clamp experiments in acute slices from the mouse brain containing the Medial Habenula (MHb). He/she will have the possibiltiy to use an ex vivo electrophysiological set-up fully equipped for optogenetic experiments. The optogenetics experiments will permit investigations on how GABAergic synaptic afferents onto MHb neurons affect cellular activity. Part of the stage duration will also be devoted to in vivo investigations. The GABAergic afferents to MHb neurons will be stimulated in freely-moving animals via a blue-light-emitting laser coupled to an implanted fiber optics. We will examine how this stimulation affects the mouse behavior during simple anxiety-related tests. In summary the student will perform a comprehensive analysis of the unsual excitatory nature of MHb GABAergic afferents, learning and applying both ex vivo and in vivo investigative approaches on a daily basis. Prefrence will be given to candidates envisaging a possible three-year PHd course following the M2 stage.

References (at least 3)

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