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) : INSERM UMR839
Research Unit Director : Jean-Antoine Girault
Research Team Director : JC Poncer/S Lévi
Team name : Plasticity of cortical networks and epilepsy

Address : Institut du Fer à Moulin, 17 rue du Fer à Moulin, 75005 Paris

Supervisor of the Research Intern for this project : Sabine Lévi
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2. Internship project title:

Tuning of GABAergic synaptic plasticity by Cl- second messenger signaling pathway

3. Internship Description :

We recently demonstrated the contribution of a novel signaling pathway, the chloride (Cl-) sensitive WNK1 kinase and of its downstream effector the SPAK kinase, in the rapid homeostatic control of GABAergic inhibitory synapses of the hippocampus (Heubl et al., Nature Communications 2017 Nov 24;8(1):1776). In this regulation Cl- acts as a second messenger to tune the activity of the main neuronal KCC2 and NKCC1 K+/Cl- cotransporters, and to regulate thereby neuronal chloride homeostasis.

We wish now to investigate the contribution of the WNK/SPAK signaling pathway and of the second messenger Cl- in the direct regulation of GABAA receptors in the context of synaptic plasticity in the hippocampus. For this purpose, we will determine by western blot whether the WNK/SPAK signaling pathway is activated (by phosphorylation) upon pharmacological induction of long term depression (iLTD) or potentiation (iLTP) of inhibitory GABAergic synapses. We will then use a combination of pharmacological (WNK and SPAK inhibitors) and genetic tools (shRNA against WNK and SPAK) to inactivate WNK and SPAK kinases and to test their impact on iLTP and iLTD using imaging techniques (by studying rapid changes in GABAA receptor number at synapses by single particle tracking and super-resolution) and electrophysiological approaches (whole cell patch-clamp recordings). We will then characterize the molecular pathway leading to the activation of the kinases and linking WNK and SPAK to the regulation of receptor trafficking. In particular, we will test the possibility that chloride acts as a second messenger in the regulation of iLTP and iLTD to activate the Cl-sensitive WNK kinase and we will try to identify GABAA receptors key threonine residues targeted by WNK/SPAK.

Altogether, this work may help to identify a novel signaling pathway controlling the synaptic plasticity of inhibitory GABAergic synapses.

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