SCIENCES SORBONNE UNIVERSITÉ

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) : INSERM UMR1270
Research Unit Director : Jean-Antoine Girault
Research Team Director : JC Poncer/S Lévi
Team name : Plasticity of cortical networks and epilepsy

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2. Internship project title:

A metabolon at the GABAergic post-synapse to fuel synaptic transmission

3. Internship Description :

The main inhibitory neurotransmitter receptors in the brain are type A γ-aminobutyric acid receptors ($GABA_ARs$). Upon activation, $GABA_ARs$ selectively conduct Cl- through their pore. The direction of Cl^- flux through the channels depends on the transmembrane electrochemical Cl- gradient. Therefore, Cl^- homeostasis, which in neurons depends mainly on the K^+-Cl^- transporter KCC2, critically determines the polarity and efficacy of GABAergic transmission in the brain[1]. Several neurological and neuropsychiatric disorders are associated with a down-regulation of KCC2 expression and altered GABA signaling. The lab works at discovering novel regulatory mechanisms of KCC2 that may represent targets for therapeutic intervention in these disorders. We recently reported that synaptic GABAergic activity tunes within seconds KCC2 membrane diffusion and thereby Cl^- homeostasis and GABA signaling[1-2].

KCC2 is a secondary active transporter that uses the electrochemical K^+ gradient generated by the Na^+/K^+ ATPase (NKA), the function of which relies on ATP hydrolysis and is the major source of ATP consumption in the brain[1]. Thus, the proximity of NKA and a rapid local increase in ATP levels would be required to boost KCC2 function in response to increased synaptic activity[3]. Interestingly, KCC2 directly interacts with NKA and key membrane components of the mitochondrion, which produces ATP via the glycolytic metabolon. Furthermore, KCC2 and NKA membrane-associated metabolon proteins are not evenly distributed at the neuronal surface but they aggregate near the GABAergic postsynaptic density. The close proximity of these proteins suggests they form a macromolecular complex and are linked functionally. Therefore, **we postulate that the function of the metabolon is to fuel the synapse with energy required**

for KCC2 function, and the tuning of Cl- homeostasis and GABAergic transmission in response to local activity changes.

Although a metabolon has been recently identified at the pre-synapse and shown to regulate synaptic vesicles turnover[4], the existence and function of a metabolon at the post-synapse is unknown. We will address this question in 3 specific aims in order to:

1) confirm at the nanoscale the existence of a metabolon at/near the GABAergic postsynaptic density in hippocampal neurons,
2) examine the dynamic regulation of the metabolon upon modulation of neuronal and glycolytic activities,
3) disclose the contribution of the metabolon in the efficacy and plasticity of GABAergic transmission.

The project will involve a multidisciplinary approach, spanning different levels of analysis (from molecules to functional studies in mice brain tissue), using electrophysiology, and state-of-the-art imaging techniques such as STORM/PALM microscopy, single particle tracking (SPT).

Altogether, these experiments may report for the first time the existence of a metabolon near the postsynaptic GABAergic density that could rapidly influence synaptic transmission. Manipulations of the activity of the metabolon may be of therapeutic interest in epilepsy as well as many other disorders involving impaired GABA signaling.

References:

1. Côme E, .. Levi S. **2019** KCC2 membrane diffusion tunes neuronal chloride homeostasis. **Neuropharmacology**. doi: 10.1016/j.neuropharm.2019.03.014

2. Heubl M, .. Levi S. **2017** GABAA receptor dependent synaptic inhibition rapidly tunes KCC2 activity via the Cl--sensitive WNK1 kinase. **Nat Commun**. 8, 1776

3. Düsterwald KM, .., Raimondo JV. **2018** Biophysical models reveal the relative importance of transporter proteins and impermeant anions in chloride homeostasis. **Elife**. 7. pii: e39575. doi: 10.7554/eLife.39575.

4. Jang S, .., Colón-Ramos DA. **2016** Glycolytic Enzymes Localize to Synapses under Energy Stress to Support Synaptic Function. **Neuron**. 90, 278-91