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): IBENS (Institut de Biologie de l'Ecole Normale Supérieure)
Research Unit Director: Pierre PAOLETTI
Research Team Director: Pierre PAOLETTI
Team name: Glutamate Receptors and Excitatory Synapses
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2. Internship project title:

Exploring the role and dynamics of glycine and D-serine as NMDAR co-agonists in neural tissue

3. Internship Description :

NMDA receptors (NMDARs) are ionotropic glutamate receptors involved in multiple aspects of brain physiology and pathology (1). Unlike other neurotransmitter receptors, the activation of NMDARs requires simultaneous binding of two distinct agonists, L-glutamate plus the co-agonist glycine or the atypical neuromessenger D-serine. The unique co-agonist dependence of NMDARs is thought to render these receptors highly sensitive to the activity of their surrounding microenvironment. Decades after the discovery that D-serine and glycine act as NMDAR co-agonists, their availability, and dynamics at excitatory synapses remain controversial.

Canonical NMDARs are tetrameric assemblies composed of two GluN1 subunits, binding glycine or D-serine, and two GluN2 subunits binding glutamate. Although wild-type GluN1 subunits do not discriminate between glycine and D-serine, we recently identified a single point mutation in the GluN1 agonist-binding domain that strongly decreases glycine affinity (>50 fold increase in EC_{50}) without affecting D-serine affinity. Taking advantage of this mutation, we recently generated genetically-modified inducible knock-in animals (GluN1-KI) harboring glycine-insensitive GluN1 subunits. We are currently characterizing the functional properties of the glutamatergic synapses onto principal cells in acute hippocampal slices from this original mouse model. Our preliminary results indicate that the co-agonist site occupancy depends on the cell type and the activity regime, i.e, it is dynamically regulated and synapse-dependent.

This project aims at identifying the dynamics of NMDAR co-agonists at glutamatergic synapses onto inhibitory neurons. Inhibitory GABAergic neurons play critical roles in normal brain function and their malfunction has been implicated in many brain disorders, especially schizophrenia and autism (2). Synapses on principal cells and on interneurons differ in their morphology, functional properties and glial coverage. This has already been shown to impact the dynamics of synaptic glutamate (3). We will take advantage of the GluN1-KI mouse to explore the identity of NMDAR co-agonists at excitatory synapses onto interneurons. The key experimental approach will be patch-clamp recordings onto acute brain slices. Further effort will be devoted to elucidate the impact of the co-agonist site occupancy onto short-term and long-term synaptic plasticity. This project should provide important insights into the diversity of excitatory synapses with potential implications for new therapeutic opportunities.

(1) Paoletti et al., 2013. Nat Rev Neurosci, 14, 383.
(2) Tremblay et al., 2016, Neuron 91, 260.
(3) Yao et al., 2018. Nat Comm, 9, 4000.