Sorbonne Université/China Scholarship Council program 2021

Thesis proposal

Title of the research project: Role of the schizophrenia associated receptor GluD1 in excitatory synaptic neurotransmission

Joint supervision: no

Joint PhD (cotutelle): no

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Institution: Sorbonne université

Doctoral school (N°+name): ED 158, “Cerveau, Cognition, Comportement”

Research laboratory: Neuroscience Paris Seine, CNRS UMR8246, INSERM U1130

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SORBONNE UNIVERSITÉ

Subject description (2 pages max):

1) Study context

Neurons compute fast excitatory and inhibitory synaptic events, but also slower neuromodulations that produce long lasting changes. These modulations govern neuronal development and plasticity, while their impairment leads to many neuropsychiatric disorders such as Parkinson's disease, addiction, autism and schizophrenia (SZ). Classical hypotheses postulate that alterations of dopamine (DA) and glutamate transmission are critical in SZ. Among the ionotropic glutamate receptors, genetic association studies have established the GRID1 gene, which codes for GluD1, as a strong candidate gene for SZ, bipolar disorder, and major depressive disorder [1]. Likewise, transgenic mice devoid of GluD1 exhibit several behavioral correlates of SZ, such as hyperactivity, depression-like behavior, hyperaggressiveness and deficits in social interaction. However, the molecular and cellular link between GluD1 and these pathologies is still unknown. Our lab showed that GluD1 is widely expressed in the rodent and human brain with high expression levels in regions such as the cerebral cortex, hippocampus, striatum and midbrain [2]. GluD1, which forms with GluD2 the delta family of ionotropic glutamate receptors (iGlu, [1]). Unlike other iGlu, glutamate does not bind GluDs and does not trigger directly the opening of GluD ion channel. Over the past years we have shown that GluD opening occurs in midbrain DA neurons via the activation of metabotropic glutamate receptors mGlu1/5[3, 4]. This ion channel opening is responsible for the mGlu mediated slow excitation of DA neurons. More importantly we have demonstrated that GluD ion function was essential for the bursting activity of DA neurons [4]. This latter aspect is of high relevance because alteration of DA neurons activity and thus DA neurotransmission has large impact is target structures. Bursting activity signals novelty and reward expectation and is associated with enhanced release of DA [5]. Alteration of DA neurotransmission cause defect of reward based learning. In addition, we have identified two human mutations in GluD1 from patient suffering of intellectual disabilities (ID) and spastic paraplegia. For one of them we have generated a transgenic mice carrying this mutation to study its impact at the synaptic, cellular and behavioral levels.

Little is known to date about the cellular and synaptic functions of GluD1 as well as its role in synaptic circuitry. This is in part due to the lack of selective pharmacology for GluDs. Thus, **the major goals of this proposal is to elucidate the functional role of GluD1 in excitatory synaptic transmission at single cell and network levels, in vitro and in vivo, using mouse model of human pathology and, to develop new molecular and opto-pharmacological tools allowing to assess the specific role of GluD1 in the activity of DA neurons.**

2) Details of the proposal

The PhD student will be trained by the members of the team and will use already existing reagents and animal models necessary for its project. This project relies on a large amount of published and unpublished data obtained from our lab.

Study of ID associated GluD1 mutant. Our preliminary results indicate that this mutation cause an alteration of spine maturation and of mGlu1/5-dependent intracellular signaling. The PhD student will participate to the characterization of this mutation. The morphological analysis will be performed in collaboration with Nicolas Heck and Peter Vanhoutte (Neuroscience Paris Seine). The behavioral evaluation will be achieved in parternship with the institut Clinique de la souris (Strasbourg, France). The PhD student will focus on identifying the functional synaptic alteration using patch-clamp electrophysiology. He/she will benefit of our great expertise and will investigate

particularly the mGlu-dependent gating of GluD1 ion channel and the mGlu-long term plasticity. Using routine protocol, we will determine the basic properties of glutamatergic transmission on

Mechanism of GluD1 ion channel in activity of DA neurons. Recently [6], have developed a tool that enables control of the ion channel in GluD receptors using light. We produced a genetically modified version of GluD2 with a light-sensitive molecule attached. Under green light, the light-sensitive molecule blocks the channel and prevents ions from passing through. Under violet light, the molecule twists, and ions can flow through the channel. In this project, the PhD student will validate this tools in neurons using lentiviral vectors used in the lab. He wil decipher the mechanism of bursting activity in DA neurons and the quantitative contribution of GluD1. He/She transpose this tool to GluD1 and establish the contribution of GluD1 in vitro and in vivo in the bursting activity. This will be performed in collaboration with Alexandre Mourot (ESPCI Paris) based on the technology he developed [7]. It consists in placing a thin optic fiber (100-200 µm diameter) directly into the glass capillary used for in vivo juxtacellular recordings, so to ensure light to be projected onto the recorded neuron. Such approach will eventually be used in behavioral paradigm of reward-based learning in which bursting activity of DA neurons is essential.

3) References

1. Yuzaki, M. and A.R. Aricescu, *A GluD Coming-Of-Age Story.* Trends Neurosci, 2017. **40**(3): p. 138-150.
2. Hepp, R., et al., *Glutamate receptors of the delta family are widely expressed in the adult brain.* Brain Struct Funct, 2015. **220**(5): p. 2797-815.
3. Ady, V., et al., *Type 1 metabotropic glutamate receptors (mGlu1) trigger the gating of GluD2 delta glutamate receptors.* EMBO Rep, 2014. **15**(1): p. 103-9.
4. Benamer, N., et al., *GluD1, linked to schizophrenia, controls the burst firing of dopamine neurons.* Mol Psychiatry, 2018. **23**(3): p. 691-700.
5. Faure, P., et al., *Role of nicotinic acetylcholine receptors in regulating dopamine neuron activity.* Neuroscience, 2014. **282**: p. 86-100.
6. Lemoine, D., et al., *Probing the ionotropic activity of glutamate GluD2 receptor in HEK cells with genetically-engineered photopharmacology.* Elife, 2020. **9**.
7. Durand-de Cuttoli, R., et al., *Manipulating midbrain dopamine neurons and reward-related behaviors with light-controllable nicotinic acetylcholine receptors.* Elife, 2018. **7**.

4°) Profile of the Applicant (skills/diploma…)

We seek highly motivated applicants with a passion for neuroscience who hold a Master's degree in neurosciences or related fields. Some prior experience in one or more methods of molecular and cell biology, biochemistry, electrophysiology, optogenetics are desirable. Training in animal handling and surgery will be an asset. It is important that the applicant have a good knowledge of computer based analysis tools in electrophysiology and/or microscopy. Excellent oral and written English communication skills and the ability to efficiently integrate in an interdisciplinary and multinational research team are expected.

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