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

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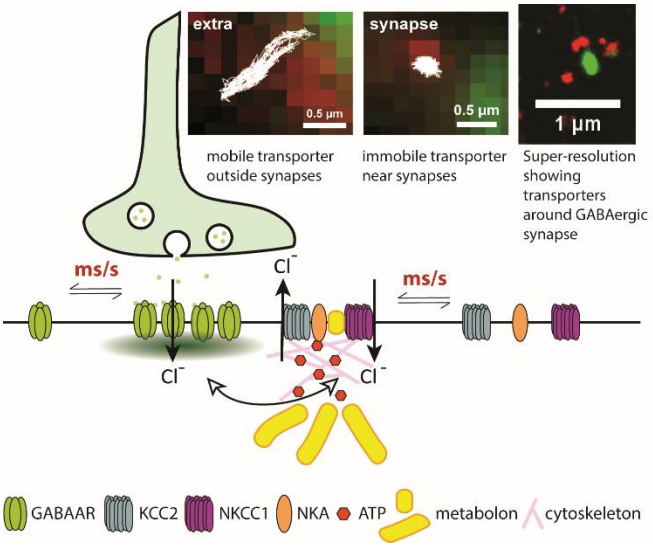
The main inhibitory neurotransmitter receptors in the brain are type A γ-aminobutyric acid receptors ($GABA_A$Rs). Upon activation, $GABA_A$Rs selectively conduct Cl- through their pore. The direction of Cl^- flux through the channels depends on the transmembrane electrochemical Cl- gradient. Therefore, 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].



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[2]. 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.

KCC2 is a secondary active transporter that uses the electrochemical K^+ gradient generated by the Na^+/K^+

The project aims to disclose the existence and function of a metabolon at the GABAergic post-synapse. This will involve a multidisciplinary approach, spanning different levels of analysis (from molecules to functional studies in mice brain tissue), using biochemistry, electrophysiology, and state-of-the-art imaging techniques such as STORM/PALM microscopy, single particle tracking (SPT) and FRET imaging in live tissue. This project will also lead to a technological breakthrough by developing 3D 2-color SPT in live acute and organotypic tissue.

Key words: GABA, synaptic plasticity, hippocampus, chloride homeostasis, nanoscale microscopy, electrophysiology.

Recent publications from the lab in relation with the proposed project:

1. Côme E, .. Levi S. **2019** KCC2 membrane diffusion tunes neuronal chloride homeostasis. **Neuropharmacology**. pii: S0028-3908(19)30091-7. doi: 10.1016/j.neuropharm.2019.03.014. [Epub ahead of print]
2. Côme E, .. Levi S. **2019** Reciprocal Regulation of KCC2 Trafficking and Synaptic Activity. **Front Cell Neurosci.** 13:48.
3. Heubl M, .. Levi S. **2017** GABAA receptor dependent synaptic inhibition rapidly tunes KCC2 activity via the Cl--sensitive WNK1 kinase. **Nat Commun**. 8, 1776.
4. Battaglia S, .. Lévi S. **2018** Gephyrin phosphorylation conditions $GABA_A$R membrane dynamics and homeostatic plasticity. **eNeuro** 2018 Jan 18;5 (1).