CSC-RUB PhD Project Proposal

Title: Composition and gating properties of heteromeric kainate receptors

Sector of research: Neuroscience, Pharmacology, Biophysics

Degree awarded: PhD in Neuroscience

Keywords:

synaptic signaling; ionotropic glutamate receptors; heteromer formation; ion channel gating; imaging; electrophysiology; high resolution imaging;

Supervisor of PhD project:

Prof. Andreas Reiner, Cellular Neurobiology, Department of Biology and Biotechnology

Research focus of supervisor:

My research focuses on molecular and cellular aspects of signaling at glutamatergic synapses, which play a key role for central nervous system function and disease. To dissect glutamate receptor signaling and the functional diversity of this receptor family, my lab combines state-of-the-art chemical, biochemical, electrophysiological and imaging approaches. A key part of our research is the development and application of novel chemo-optogenetic approaches, as these tools allow us to control and probe neuronal communication and the contribution of specific receptor complexes with light and high precision. Our findings have important mechanistic implications for receptor gating, pharmacological manipulation, and synaptic function/dysfunction, i.e. during ischemic conditions.

Publications:

1. Splicing and editing of ionotropic glutamate receptors: A comprehensive analysis based on human RNA-Seq data. Herbrechter R., Hube N., Buchholz R. & Reiner A. # (2021) *Cell. Mol. Life Sci.* 78: 5605-5630.

2. Subunit-selective iGluR antagonists can potentiate heteromeric receptor responses by blocking desensitization. Pollok S. & Reiner A. # (2020). *Proc. Natl. Acad. Sci. USA* 117: 25851-25858.

3. Glutamatergic signaling in the central nervous system: Ionotropic and metabotropic receptors in concert. Reiner A. # & Levitz J. # (2018). *Neuron* 98: 1080-1098.

4. Tethered ligands reveal glutamate receptor desensitization depends on subunit occupancy. Reiner A. & Isacoff E.Y. (2014). *Nat. Chem. Biol.* 10: 273-280

5. Assembly stoichiometry of the GluK2/GluK5 kainate receptor complex. Reiner A., Arant R.J. & Isacoff E.Y. (2012). *Cell Rep.* 1: 234-240.

For a full publication list see PubMed:
https://www.ncbi.nlm.nih.gov/pubmed/?term=andreas+reiner+not+winker

Summary of research plan

Background: Kainate receptors form a subclass of ionotropic glutamate receptors (iGluRs) with mostly modulatory functions at different synapses in the central nervous system. Most of these receptors appear to be heteromers composed of different subunits (GluK1-5 and their splicing isoforms), which equips these complexes with peculiar trafficking, gating and signaling properties. The functional consequences of heteromer formation, however, remain largely unknown, since most work has so far focused on few, mostly homomeric kainate receptor representatives.

Study objective: This project will address the composition neuronal kainate receptors and the functional consequences of receptor heteromerization. We seek to clarify which complexes are predominantly present in different neuronal subtypes, investigate their composition (assembly stoichiometries) and study the functional consequences for gating *in vitro* and *in situ*.

Expected Results: The project will provide insight into cell-type specific dominance of certain kainate receptor combinations and their preferred assembly configurations. Besides consequences on trafficking and receptor recycling, we expect to see a wide variation in key gating properties, such as activation threshold, susceptibility to ligand-induced desensitization, and speed of recovery. Determining these parameters should also give more detailed insight into their respective synaptic functions and allow to test specific hypothesis, e.g. on the role of recovery from desensitization. The findings will also have direct implications for subtype-specific pharmacological interventions.

Methods: Receptor gating will be studied using patch-clamp electrophysiology and ultra-fast ligand application, i*n vitro* and in organotypic brain slice cultures. Receptor expression, composition and trafficking will by studied using NGS data analysis, pull-down experiments and advanced tagging/high resolution imaging techniques, incl. single -molecule imaging. Expression of genetically-modified receptor subunits is performed with AAVs and will be extended to CRISPR/Cas-mediated manipulations. State-of-the-art infrastructure is available at the department and international collaborations will support the project.

Candidate Requirements: Required is an excellent university degree in Biology, Biochemistry, Biophysics, Molecular Medicine, or a related discipline. A very high motivation to engage in independent experimental research, the ability to work in an interdisciplinary team, and very good English skills are mandatory. For this project we specifically seek candidates with experience in the area of neurobiology, as well as electrophysiology or fluorescence microscopy.

Motivation for CSC application: We offer excellent training and research possibilities in a collaborative and interdisciplinary research environment. The candidate will perform hands-on, cutting-edge research in the field of glutamate receptor biology and receive training in patch-clamp electrophysiology, fast ligand-application techniques, and high-resolution fluorescence microscopy. The project gives opportunity for collaboration and publication on an international level. The participation in international meetings is strongly encouraged. Further training will be provided by integration into the *International School of Neuroscience (IGSN)* and the *Rub Research School* (part of the *Research Academy Ruhr*), which provides guidance and supports interdisciplinary skill development.