Universität Basel

Research Project

MHV - Investigating the function of GABAb receptor-interacting proteins by FRET assays

Third-party funded project

Project title MHV - Investigating the function of GABAb receptor-interacting proteins by FRET assays
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GABA$_B$ receptors are the principal inhibitory G-protein coupled receptors in the brain and hold considerable promise as therapeutic targets for the treatment of neurological and psychiatric disorders, including anxiety, depression, addiction, epilepsy, and chronic pain. They are composed of two different subunits, GABA$_{B1}$ and GABA$_{B2}$.

For a long time, it was believed that the different responses observed in the brain in response to GABA$_B$ receptor activation reflected the presence of different GABA$_B$ receptor subtypes. However, we now know that the only molecular diversity in the GABA$_B$ system arises from the two isoforms of the GABA$_{B1}$ subunit: GABA$_{B1a}$ and GABA$_{B1b}$. Surprisingly, these two isoforms have very similar pharmacological and biophysical properties *in vitro*, which makes it difficult to explain the pharmacological and kinetic differences of native GABA$_B$ responses.

A family of four sequence-related proteins were recently found to interact with the receptor and to modify the GABA$_B$-mediated response when coexpressed with the receptor *in vitro*. The present project aims at elucidating the molecular events underlying the kinetics changes that these auxiliary proteins impose on the GABA$_B$ receptor response. Assays based on Fluorescence Resonance Energy Transfer (FRET) will be used to investigate whether these proteins interact with different components of the GABA$_B$-mediated signalling cascade, and how these interactions are modulated upon receptor activation.

These experiments will allow us to provide a mechanistic explanation of how these proteins modify kinetic and pharmacological properties of GABA$_B$ responses and contribute to the functional heterogeneity observed with native GABA$_B$ responses. Identification of the function of these proteins will spark drug discovery efforts, as this provides an opportunity for a more selective interference with the GABA$_B$ receptor system.

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