Universität Basel

Research Project

From the GABA-B receptor proteome to molecular mechanisms and brain functions

Third-party funded project

Project title From the GABA-B receptor proteome to molecular mechanisms and brain functions
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GABAB receptors (GABABRs) are the G protein coupled receptors (GPCRs) for the neurotransmitter GABA. They are promising drug targets for the treatment of mental and neurological disorders. Kinetic properties of native GABABRs are neither reproduced by cloned receptors nor regulated by GPCR kinases and arrestins. These findings suggested that native GABABRs rely on additional proteins that alter their signaling. In collaboration with Bernd Fakler (University of Freiburg i. Br.) we have used a comprehensive proteomic approach to identify 30 GABABR-associated proteins in the brain. These proteins now provide a means to study the functionality and architecture of native GABABRs in an unprecedented manner. Our data support that GABABRs are multiprotein complexes consisting of core components and interchangeable peripheral components. The core components include principal GABAB1 and GABAB2 receptor subunits, auxiliary K-channel tetramerization-domain (KCTD) subunits and the G protein. The KCTD subunits confer the fast activation kinetics and desensitization properties observed with native GABABRs to the cloned receptors. Peripheral components comprise known and novel effector channels, elements of the presynaptic release machinery, sushi domain (SD) interacting proteins and neuronal adhesion proteins. After the successful identification of native GABABR components we now plan to determine the functional relevance and mechanism of action of selected receptor components, bridging from molecular to in vivo studies. We propose to work on the KCTD proteins, G protein ß -subunits, hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, SD-interacting proteins and elements of the presynaptic release machinery. Defined GABABRs receptor complexes in heterologous cells will be studied using established biochemical, biophysical and electrophysiological assays that probe for allosteric receptor regulation, receptor signaling and trafficking. The relevance of GABABR components for native receptor signaling will be analyzed using knock-out/knock-down approaches. Eventually we aim at interfering with the interaction of selected proteins at the receptor to influence receptor-mediated responses. We plan to use drug-like interfering peptides that penetrate the blood-brain barrier. This approach may open up new opportunities for the treatment of mental and neurological disorders.

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