Abstract

The cannabinoid receptor 1 (CB1R), a member of the G-protein coupled receptors superfamily, is a key player in endocannabinoid signalling. The CB1R is found presynaptically in neurones where it modulates synaptic plasticity. Precise description of the molecular mechanisms of synaptic neurotransmission is crucial for understanding of brain diseases and development of new therapeutic aproaches. Possible pharmacological targets of CB1R signalling include the treatment of various ailments such as energy imbalance disorders (anorexia, obesity), drug addiction, pain, insomnia, and some psychiatric conditions.

This study reveals the "Src homology 3-domain growth factor receptor-bound 2-like (endophilin) interacting protein 1" (SGIP1) as a novel interacting partner of the CB1R. The SGIP1 is an intracellular neuronal protein localized predominantly in axon terminals and is involved in clathrin mediated endocytosis. The overexpression of SGIP1 imbalance energy homeostasis and leads to obesity.

We show that SGIP1 affects CB1R signalling via ERK1/2 whereas G-protein signallization remains unaltered. The SGIP1 also hinders CB1R internalization from the cell surface and supports its interaction with β-arrestin2.

Also, we demonstrated heterodimerization of the main splice variants of metabotropic glutamate receptor 1 (mGluR1a and mGluR1b) *in vivo*. MGluR1 represents the interconnection between endocanabinoid and glutamatergic system via mGluR1 stimulation of endocannabinoid production. Our results show the crucial influence of mGluR1 heterodimerization on mGluR1b distribution in neurones. While mGluR1b homodimers are retained in cell bodies, the mGluR1a/1b heterodimers are transported into the synaptic terminals.

The pharmacological importance of endocannabinoid system is undeniable. So far many aspects and principles of its function and signalling remains elusive. Our results represents a piece of knowledge in the very complex mosaic that the endocannabinoid system represents.