Jaroslav Blahoš

jaroslav.blahos@img.cas.cz

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www.img.cas.cz/research/jaroslav-blahos

LABORATORY OF

MOLECULAR PHARMACOLOGY

G-protein-coupled receptors, neurotransmitters, metabotropic glutamate receptors, cannabinoid receptors

In the picture:
1. Denisa Vozárová | **2.** Lenka Chlupisová | **3.** Alena Hájková **4.** Irina Sheveleva | **5.** Matej Gazdarica | **6. Jaroslav Blahoš**

Not in the picture:
Michaela Dvořáková

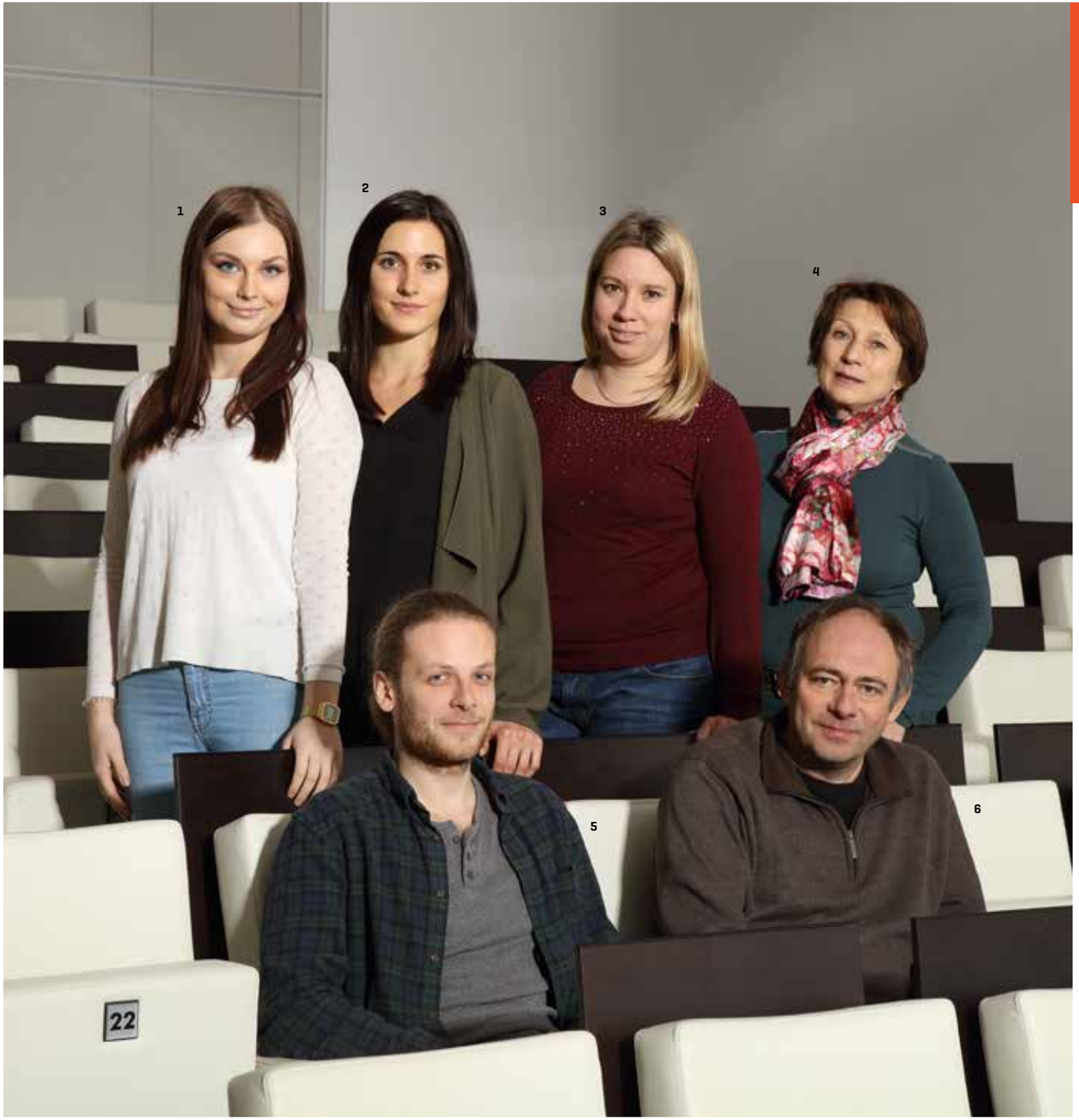
We detected a novel interacting partner of Cannabinoid Receptor 1 (CB1R). Recently, we published our data revealing that SGIP1 interferes with internalization of the activated CB1R. Moreover, this interaction affects signalling of the receptor in a biased manner. The G-protein activation was unaffected, while other pathways were modulated. Both CB1R and SGIP1 are located predominantly pre-synaptically, where the receptors show modest internalization upon agonist stimulation, while the CB1R expressed in heterologous systems are readily internalized. Genetically altered mice are now under use to reveal the SGIP1 role in this phenomenon. Overexpression of SGIP1 in animals is associated with obesity. The functional significance of the SGIP1 protein in CB1R interaction in energy homeostasis is studied in animal models.

Metabotropic glutamate receptors (mGluRs) belong to Class C-G-protein-Coupled Receptors (GPCRs) forming homodimers. Using the mutagenesis approach combined with a functional expression system we showed that within their dimeric complexes, only one subunit reaches the active state. The activation process of mGluRs is initiated by agonist binding that causes conformational changes of the extracellular ligand-binding domains. This is followed by relative movement of the transmembrane regions of the two subunits, and finally a conformational change within one of the heptahelical transmembrane domain can be transmitted to the intracellular signalling machinery. The recently resolved crystal structure of mGluR1 is in accord with our model of activation mechanism being asymmetrical, as suggested by our functional data. Recently we also disclosed that splice variants mGluR1a and mGluR1b form heterodimers in vivo. The functional relevance of the splice variant combinations in the dimeric mGluR1 complexes in vivo are now under investigation using genetically modified mice.

Selected recent papers:

Lahaie N, Kralikova M, Prézeau L, Blahos J, Bouvier M: Post-endocytotic deubiquitination and degradation of the GABAB receptor by USP14, **Journal of Biological Chemistry 2016**, Jan 27; jbc. M115.686907, Shared senior co-authorship.

Hájková A, Techlovská Š, Dvořáková M, Chambers J N, Kumpošt J, Hubálková P, Prezeau L, Blahos J: SGIP1 Alters Internalization and Modulates Signaling of Activated Cannabinoid Receptor 1 in Biased Manner, **Neuropharmacology 2016**, 107 August 2016: 201–214.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