LABORATORY OF

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Endocannabinoids, cannabinoid receptor, receptors coupled to G-proteins

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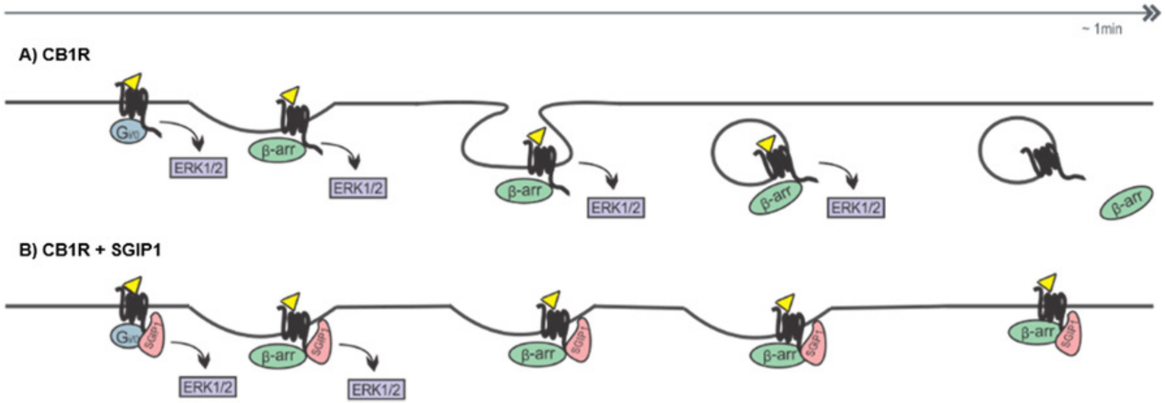
We detected the Src homology 3-domain growth factor receptor-bound 2-like (endophilin) interacting protein 1 (SGIP1) as a novel cannabinoid receptor 1 (CB1R) interacting partner. SGIP1 is functionally linked to clathrin-mediated endocytosis, and its overexpression in the hypothalamus leads to an energy regulation imbalance resulting in obesity in rodents. We reported that SGIP1 prevents endocytosis of activated CB1R and that it alters signalling via CB1R in a biased manner. CB1R – beta 2 arrestin-associated signalling is profoundly changed, most likely as a consequence of prevention of the receptor's internalization, an inhibition mediated by SGIP1. To study the role of SGIP1 in vivo, we developed SGIP1 knockout mice to explore their phenotype. In a recent manuscript, we report alterations in the emotionality of SGIP1 knockout mice based on open field, elevated plus maze, and light/dark box tests. We discovered that mouse coping with despair in an inescapable situation is enhanced by SGIP1 deletion. In the tail immersion test, the antinociceptive effects of CB1R agonists were significantly enhanced in the SGIP1 knockout mice. In evaluating responses to D9-tetrahydrocannabinol in cannabinoid tetrad tests, interesting differences were found compared to wild-type mice, including modification of responses in models of acute, and chronic pain.



Proposed model of SGIP1 effect on CB1R internalization and signalling. A) Transfected cells without SGIP1. Upon CB1R agonist-induced signalling through Gi/o, the receptor associates with b-arrestin and is readily internalized, which allows massive ERK1/2 activation. B) In cells expressing SGIP1, internalization is prevented at early stages. Therefore, G-protein signalling is unaltered. However, the extent of CB1R signalling via the ERK1/2 pathway is decreased, as SGIP1 competes with FCHo1/2 proteins required for the initial stages of clathrin-coated pit formation. Thus, the internalization of CB1R is abrupt at the early stage, when the pits are in the initial phases of growth, or even before this event. SGIP1 prevents ERK1/2 signalling of the receptor-b-arrestin complex that would occur during further steps of internalization. Conversely, b-arrestin association with CB1R is enhanced, as their dissociation, which normally occurs in internalized endocytic compartments, does not occur.

Selected publications:

1. SGIP1 alters internalization and modulates signaling of activated cannabinoid receptor 1 in a biased manner. Hájková A, Techlovská Š, Dvořáková M, Chambers JN, Kumpošt J, Hubálková P, Prezeau L, Blahos J.*. Neuropharmacology. 2016 Aug;107:201-214. doi: 10.1016/j.neuropharm.2016.03.008. Epub 2016 Mar 9.
2. SGIP1 is involved in regulation of emotionality, mood, and nociception and modulates in vivo signalling of cannabinoid CB1 receptors. Dvorakova M, Kubik-Zahorodna A, Straiker A, Sedlacek R, Hajkova A, Mackie K, Blahos J.*. Br J Pharmacol. 2021 Apr;178(7):1588-1604.
3. SGIP1 modulates kinetics and interactions of the cannabinoid receptor 1 and G protein-coupled receptor kinase 3 signalosome. Gazdarica M, Noda J, Durydivka O, Novosadova V, Mackie K, Pin JP, Prezeau L, Blahos J.*. J Neurochem. 2022 Mar;160(6):625-642.