Molecular mechanism of Cannabinoid receptor 1 regulation by SGIP1

Abstract

Src homology 3-domain growth factor receptor-bound 2-like endophilin interacting protein 1 (SGIP1) has been identified as an interacting partner of cannabinoid receptor 1 (CB1R). Their protein-protein interaction was confirmed by co-immunoprecipitation. SGIP1 hinders the internalization of activated CB1R and modulates its signaling in HEK293 cells. Employing whole-cell patch-clamp electrophysiology, we have shown that SGIP1 affects CB1R signaling in autaptic hippocampal neurons.

Using a battery of behavioral tests in SGIP1 constitutive knock-out ($SGIP1^{-/-}$) and WT mice, we investigated the consequences of SGIP1 deletion on behavior regulated by the endocannabinoid system. In $SGIP1^{-/-}$ mice, exploratory levels, working memory and sensorimotor gating were unaltered. $SGIP1^{-/-}$ mice showed decreased anxiety-like and depressive-like behaviors. Fear extinction to tone was enhanced in $SGIP1^{-/-}$ females. Several cannabinoid tetrad behaviors were altered in the absence of SGIP1. $SGIP1^{-/-}$ males exhibited abnormal THC withdrawal behaviors. SGIP1 deletion also reduced acute nociception, and $SGIP1^{-/-}$ mice were more sensitive to antinociceptive effects of CB1R agonists and morphine.

CB1R-SGIP1 interaction results in profound modification of CB1R signaling. Furthermore, *in vivo* findings suggest SGIP1 is a novel modulator of CB1R-related behavior.

Keywords

Anxiety, autaptic hippocampal neurons, cannabinoid receptor 1, endocannabinoid system, G protein coupled receptor, pain, SGIP1, tolerance, whole-cell patch-clamp electrophysiology