Selective regulation of presynaptic receptors by SGIP1

Abstract

Cannabinoid receptor 1 (CB1R) is involved in a plethora of physiological processes, such as memory formation, motor coordination, anxiety, pain perception, and immune response. The properties of many minor cannabinoid receptor ligands remain unknown. The activity of CB1R is regulated by Src homology 3-domain growth factor receptor-bound 2-like endophilin interacting protein 1 (SGIP1). Several splice variants of SGIP1 have been described in the literature, but their specific functional roles are unknown. SGIP1 inhibits CB1R internalization and enhances β-arrestin and G protein-coupled receptor kinase 3 (GRK3) interactions with the receptor. In mice, deletion of *Sgip1* results in altered mood-related behavior, decreased anxiety-like behavior, and decreased acute nociception. In this work, we tested the effect of *Sgip1* deletion on chronic nociception. We further explored the pattern of alternative splicing of *Sgip1* in the brain. In addition, we tested the effect of the minor cannabinoid hexahydrocannabinol (HHC) on CB1R signaling. We found that *Sgip1* deletion results in an increase in chronic nociception in male but not in female mice. We detected 15 *Sgip1* splice variants in the mouse brain. The *Sgip1* exons that undergo alternative splicing encode portions of the MP domain and proline-rich region of the Sgip1 protein. We found that the pharmacological activity of (9R)-HHC epimer is higher than that of (9S)-HHC epimer, and the activity of (9R)-HHC epimer is similar to that of Δ^9-tetrahydrocannabinol (THC). These results demonstrate that SGIP1 is an important player in pain sensitivity and other functions controlled by CB1R, that multiple *Sgip1* splice variants are expressed in the brain, and that cannabinoid HHC has similar properties to the common cannabinoid THC.

Keywords

alternative splicing, cannabinoid receptor 1, endocytosis, hexahydrocannabinol, nociception