論 文 要 旨

FFAR1/GPR40 Contributes to the Regulation of Striatal Monoamine Releases and Facilitation of Cocaine-Induced Locomotor Activity in Mice

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Abstract

The free fatty acid receptor 1 (FFAR1) is suggested to function as a G protein-coupled receptor (GPR40) for medium-to-long-chain free fatty acids. Previous studies on the expression of FFAR1 revealed that the nigrostriatal region is one of the areas which express abundant FFAR1 mRNA/protein in the central nervous system (CNS). However, the role of FFAR1 in the CNS has been still largely unclarified. Here, we examined a possible functional role of FFAR1 in the control of extracellular concentrations of striatal monoamines and cocaine-induced locomotor activity. Microdialysis analysis revealed that the basal level of extracellular dopamine (DA) was significantly elevated, while the basal serotonin (5-HT) level tended to be reduced in the striatum of FFAR1 knockout (-/-) mice. Interestingly, local application of a FFAR1 agonist, GW9508, markedly augmented the striatal 5-HT release in FFAR1 wild-type (+/+) mice, whereas topical application of a FFAR1 antagonist, GW1100, significantly reduced the 5-HT release. However, the enhanced 5-HT release was completely lost in -/- mice. Although acute administration of cocaine enhanced the locomotor activity in both +/+ and -/- mice, the magnitude of the enhancement was significantly reduced in -/- mice. In addition, intraperitoneal injection of GW1100 significantly decreased the cocaine-induced locomotor enhancement. These results suggest that FFAR1 has a facilitatory role in striatal 5-HT release, and the evoked 5-HT release might contribute to enhance cocaine-induced locomotor activity.