Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors

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Abstract

The mechanism of action of cannabidiol, one of the major constituents of cannabis, is not well understood but a noncompetitive interaction with mu opioid receptors has been suggested on the basis of saturation binding experiments. The aim of the present study was to examine whether cannabidiol is an allosteric modulator at this receptor, using kinetic binding studies, which are particularly sensitive for the measurement of allosteric interactions at G protein-coupled receptors. In addition, we studied whether such a mechanism also extends to the delta opioid receptor. For comparison, (-)-Δ^9-tetrahydrocannabinol (THC; another major constituent of cannabis) and rimonabant (a cannabinoid CB_1 receptor antagonist) were studied. In mu opioid receptor binding studies on rat cerebral cortex membrane homogenates, the agonist ^{3}H-DAMGO bound to a homogeneous class of binding sites with a K_D of 0.68±0.02 nM and a B_{max} of 203±7 fmol/mg protein. The dissociation of ^{3}H-DAMGO induced by naloxone 10 μM (half life time of 7±1 min) was accelerated by cannabidiol and THC (at 100 μM, each) by a factor of 12 and 2, respectively. The respective pEC_{50} values for a half-maximum elevation of the dissociation rate constant k_{off} were 4.38 and 4.67; ^{3}H-DAMGO dissociation was not affected by rimonabant 10 μM. In delta opioid receptor binding studies on rat cerebral cortex membrane homogenates, the antagonist ^{3}H-naltrindole bound to a homogeneous class of binding sites with a K_D of 0.24±0.02 nM and a B_{max} of 352±22 fmol/mg protein. The dissociation of ^{3}H-naltrindole induced by naltrindole 10 μM (half life time of 119±3 min) was accelerated by cannabidiol and THC (at 100 μM, each) by a factor of 2, each. The respective pEC_{50} values were 4.10 and 5.00; ^{3}H-naltrindole dissociation was not affected by rimonabant 10 μM. The present study shows that cannabidiol is an allosteric modulator at mu and delta opioid receptors. This property is shared by THC but not by rimonabant.

Keywords

^{3}H-DAMGO binding ^{3}H-Naltrindole binding (-)-Δ^9-Tetrahydrocannabinol Cannabinoid CB_1 receptor Rat cerebral cortex Rimonabant

Abbreviations

AEBSF

4-(2-aminoethyl)benzenesulfonyl fluoride

^{3}H-DAMGO

^{3}H-Tyr-D-Ala-Gly-N-methyl-Phe-Gly-ol

^{3}H-NTI

^{3}H-naltrindole

CBD

(-)-cannabidiol

THC

(-)-Δ^9-tetrahydrocannabinol

Notes

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