Abstract

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Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease.

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Abstract

Microglial activation is an invariant feature of Alzheimer's disease (AD). It is noteworthy that cannabinoids are neuroprotective by preventing β-amyloid (Aβ)-induced microglial activation both in vitro and in vivo. On the other hand, the phytocannabinoid cannabidiol (CBD) has shown anti-inflammatory properties in different paradigms. In the present study, we compared the effects of CBD with those of other cannabinoids on microglial cell functions in vitro and on learning behavior and cytokine expression after Aβ intraventricular administration to mice. CBD, (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo-[1,2,3-d,e]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone [WIN 55,212-2 (WIN)], a mixed CB(1)/CB(2) agonist, and 1,1-dimethylbutyl-1-deoxy-Δ(9)-tetrahydrocannabinol [JWH-133 (JWH)], a CB(2)-selective agonist, concentration-dependently decreased ATP-induced (400 μM) increase in intracellular calcium ([Ca(2+)](i)) in cultured N13 microglial cells and in rat primary microglia. In contrast, 4-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-6,6-dimethyl-bicyclo[3.1.1]hept-2-ene-2-methanol [HU-308 (HU)], another CB(2) agonist, was without effect. Cannabinoid and adenosine A(2A) receptors may be involved in the CBD action. CBD- and WIN-promoted primary microglia migration was blocked by CB(1) and/or CB(2) antagonists. JWH and HU-induced migration was blocked by a CB(2) antagonist only. All of the cannabinoids decreased lipopolysaccharide-induced nitrite generation, which was insensitive to cannabinoid antagonism. Finally, both CBD and WIN, after subchronic administration for 3 weeks, were able to prevent learning of a spatial navigation task and cytokine gene expression in β-amyloid-injected mice. In summary, CBD is able to modulate microglial cell function in vitro and induce beneficial effects in an in vivo model of AD. Given that CBD lacks psychoactivity, it may represent a novel therapeutic approach for this neurological disease.

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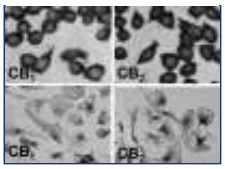
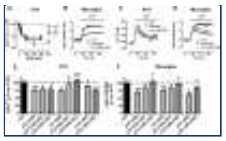
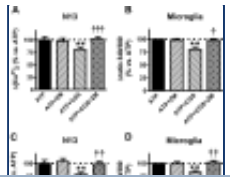
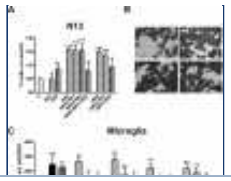
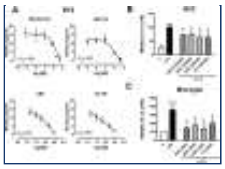
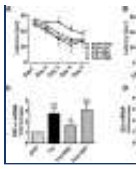

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