Cannabidiol and (−)Δ^9-tetrahydrocannabinol are neuroprotective antioxidants

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Abstract

The neuroprotective actions of cannabidiol and other cannabinoids were examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate. Glutamate toxicity was reduced by both cannabidiol, a nonpsychoactive constituent of marijuana, and the psychotropic cannabinoid (−)Δ^9-tetrahydrocannabinol (THC). Cannabinoids protected equally well against neurotoxicity mediated by N-methyl-D-aspartate receptors, 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid receptors, or kainate receptors. N-methyl-D-aspartate receptor-induced toxicity has been shown to be calcium dependent; this study demonstrates that 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid/kainate receptor-type neurotoxicity is also calcium-dependent, partly mediated by voltage sensitive calcium channels. The neuroprotection observed with cannabidiol and THC was unaffected by cannabinoid receptor antagonist, indicating it to be cannabinoid receptor independent. Previous studies have shown that glutamate toxicity may be prevented by antioxidants. Cannabidiol, THC and several synthetic cannabinoids all were demonstrated to be antioxidants by cyclic voltametry. Cannabidiol and THC also were shown to prevent hydroperoxide-induced oxidative damage as well as or better than other antioxidants in a chemical (Fenton reaction) system and neuronal cultures. Cannabidiol was more protective against glutamate neurotoxicity than either ascorbate or α-tocopherol, indicating it to be a potent antioxidant. These data also suggest that the naturally occurring, nonpsychotropic cannabinoid, cannabidiol, may be a potentially useful therapeutic agent for the treatment of oxidative neurological disorders such as cerebral ischemia.

Cannabinoid components of marijuana are known to exert behavioral and psychotropic effects but also to possess therapeutic properties including analgesia (**1**), ocular hypotension (**2**), and antiemesis (**3**). This report examines another potential therapeutic role for cannabinoids as neuroprotectants and describes their mechanism of action in rat cortical neuronal cultures.

During an ischemic episode, large quantities of the excitatory neurotransmitter glutamate are released. This event causes neuronal death by over-stimulating N-methyl-D-aspartate receptors (NMDAr) and 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid (AMPA) and kainate-type receptors and results in metabolic stress and accumulation of toxic levels of intracellular calcium (**4**). *In vitro* and *in vivo* studies (**4**, **5**, **6**) have demonstrated that such neurotoxicity can be reduced by antioxidants or antagonists to NMDAr and AMPA/kainate receptors. Antioxidants such as α-tocopherol (**5**, **6**) are effective neuroprotectants because

of their ability to reduce the toxic reactive oxygen species (ROS) formed during ischemic metabolism. Cannabinoids like (−)Δ^9-tetrahydrocannabinol (THC) and its psychoactive analogues also have been reported to be neuroprotective against glutamate toxicity *in vitro*(**7**). Cannabinoids have been suggested to prevent glutamate neurotoxicity by activating cannabinoid receptors (**7**, **8**), which can reduce calcium influx through voltage sensitive calcium channels (**8**, **9**). A synthetic cannabinoid (HU-211) also has been demonstrated to be neuroprotective even though it does not activate cannabinoid receptors. This compound is an atypical cannabinoid, however, in that it, unlike other cannabinoids, directly antagonizes NMDAr (**10**) and possesses some antioxidant properties (**11**). The present study examines classical cannabinoids as neuroprotectants *in vitro* but focuses on the nonpsychoactive cannabinoid cannabidiol. Like THC, cannabidiol is a natural component of the marijuana plant, *Cannabis sativa*, although unlike THC, cannabidiol does not activate cannabinoid receptors and so is devoid of psychoactive effects (**12**). This study reports that cannabidiol and other cannabinoids such as THC are potent antioxidants that protect neurons from glutamate-induced death without cannabinoid receptor activation.