Forum Mini review

New Perspectives in the Studies on Endocannabinoid and Cannabis: Abnormal Behaviors Associate With CB$_1$ Cannabinoid Receptor and Development of Therapeutic Application

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Received September 27, 2004; Accepted October 27, 2004

Abstract. $\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC), the major psychoactive component of marijuana, induces catalepsy-like immobilization and impairment of spatial memory in rats. $\Delta^9$-THC also induces aggressive behavior in isolated housing stress. These abnormal behaviors could be counteracted by SR141716A, a CB$_1$ cannabinoid receptor antagonist. Also $\Delta^9$-THC inhibited release of glutamate in the dorsal hippocampus, but this inhibition could be antagonized by SR141716A in an in vivo microdialysis study. Moreover, NMDA and AMPA-type glutamate receptor enhancers improved the $\Delta^9$-THC-induced impairment of spatial memory. On the other hand, $\Delta^9$-THC markedly inhibited the neurodegeneration in experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis and reduced the elevated glutamate level of cerebrospinal fluid induced by EAE. These therapeutic effects on EAE were reversed by SR141716A. Taken together, our results demonstrate that the inhibition of glutamate release via activation of the CB$_1$-cannabinoid receptor is one mechanism involved in $\Delta^9$-THC-induced impairment of spatial memory, and the therapeutic effect of $\Delta^9$-THC on EAE, and a $\Delta^9$-THC analog might provide an effective treatment for psychosis and neurodegenerative diseases.

Keywords: $\Delta^9$-tetrahydrocannabinol, CB$_1$ cannabinoid receptor, glutamate, spatial memory, experimental allergic encephalomyelitis

Introduction

$\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC), the principal psychoactive component of marijuana, has been known to impair immediate memory, short-term memory, and spatial cognition in humans (1–3). $\Delta^9$-THC has also been reported to impair performance in the radial maze in rats (4–7). Moreover, $\Delta^9$-THC induces catalepsy-like immobilization and aggressive behavior (8, 9). Thus, $\Delta^9$-THC induces abnormal behaviors in rats. On the other hand, cannabinoids have been used to treat a variety of diseases, and recently interest has increased again. Cannabinoids have potential for the development of useful agents for the treatment of pain, emesis, asthma, multiple sclerosis (MS), and other disorders (10).

The present article introduces our recent study related to the abnormal behaviors induced by $\Delta^9$-THC and the therapeutic effects of $\Delta^9$-THC on experimental allergic encephalomyelitis (EAE), an animal model of MS.

Involvement of the CB$_1$ cannabinoid receptor in $\Delta^9$-THC-induced abnormal behaviors in rats

Two cannabinoid receptors have been cloned: the CB$_1$ cannabinoid receptor in the central nervous system (11) and the CB$_2$ cannabinoid receptor in immune cells and peripheral tissues (12). $\Delta^9$-THC binds both CB$_1$ and CB$_2$ cannabinoid receptors. We previously reported that $\Delta^9$-THC impaired spatial memory in the eight-arm radial maze and that this impairment was reversed by the CB$_1$ cannabinoid receptor antagonist SR141716A (5), suggesting that the action of $\Delta^9$-THC is CB$_1$ cannabinoid receptor-mediated. We also reported that $\Delta^9$-THC selectively impaired working memory in a reference and working memory task using an eight-arm radial maze in which food was laid as bait in four of the eight...
arms (5). Moreover, synthetic cannabinoid receptor agonists CP55,940 and WIN55,212-2 impaired the rats’ performance in the radial maze task (13). In contrast, SR141716A alone enhanced spatial memory in the delayed task in the radial maze (14). Thus, CB1 cannabinoid receptors appear to play an important role in learning and memory, especially working memory. We also reported that the microinjection of Δ9-THC impaired spatial memory when injected into the dorsal and ventral hippocampus (7). These regions have a high density of CB1 cannabinoid receptors (15 – 18). Moreover, the intra-hippocampal microinjection of CP55,940 impaired maze performance (13). These findings would suggest that Δ9-THC impairs spatial memory through direct action at CB1 cannabinoid receptors in the dorsal and ventral hippocampus.

On the other hand, Δ9-THC also induces catalepsy-like immobilization and aggressive behavior in rats (8, 9). These abnormal behaviors were antagonized by SR141716A (our unpublished data). We have also found that the microinjection of Δ9-THC induces catalepsy-like immobilization when it is injected into the nucleus accumbens, amygdala, or hypothalamus, where the CB1 cannabinoid receptors are expressed (unpublished data). These findings suggest that Δ9-THC induces abnormal behaviors through CB1 cannabinoid receptors in the brain sites such as the nucleus accumbens, amygdala, and hypothalamus.

Involvement of the glutamatergic neuronal system in Δ9-THC-induced impairment of spatial memory in rats

Δ9-THC and WIN55,212-2 have been reported to inhibit acetylcholine (ACh) release in the dorsal hippocampus using brain microdialysis, but the inhibition effects can be antagonized by SR141716A (19, 20). Moreover, cannabinoids inhibit the release of glutamate in rat hippocampal cultures (21). Nakazi et al. (22) reported that synthetic cannabinoid receptor agonists inhibited both the electrically and Ca2+-induced release of serotonin (5-HT) in mouse brain cortex slices via presynaptic CB1 cannabinoid receptors. We previously reported that Δ9-THC (6 mg/kg, i.p.), which impairs spatial memory, markedly reduced release of ACh and 5-HT in the dorsal or ventral hippocampus (6, 23). We also reported that cholinesterase inhibitors and 5-HT agonists improved Δ9-THC-induced impairment of spatial memory (6, 23). These findings suggest that the ACh and 5-HT neuronal systems may be involved in Δ9-THC-induced impairment of spatial memory. On the other hand, we have found that Δ9-THC (6 mg/kg, i.p.) inhibits the release of glutamate in the dorsal hippocampus, and this inhibition is antagonized by SR141716A in an in vivo microdialysis study, indicating that the release of glutamate is mediated by the CB1 cannabinoid receptor (unpublished data). Moreover, we have found that d-cycloserine, a partial agonist at the glycine modulatory site on the NMDA receptor, and aniracetam, a positive modulator of the AMPA receptor, improve the Δ9-THC-induced impairment of spatial memory (unpublished data). These findings suggest that Δ9-THC may impair spatial memory, at least in part, by inhibiting the release of glutamate through CB1 cannabinoid receptors in the dorsal hippocampus.

It has been demonstrated that activation of the CB1 cannabinoid receptor inhibits N- and P/Q-type Ca2+ channels in cultured hippocampal neurons (24, 25). These channels are known to be required for the release of transmissions from the hippocampal synapses (26, 27). Moreover, cannabinoids have been shown to inhibit adenylate cyclase activity (28, 29) and enhance voltage-sensitive K+ channels (30). These cellular effects would be expected to inhibit neurotransmitter release. Therefore it is possible that presynaptic CB1 cannabinoid receptor activation inhibits the release of glutamate.

In addition, Δ9-THC and the cannabinoid receptor agonists have been shown to impair long-term potentiation (LTP) in rat hippocampal slices, a candidate mechanism for learning and memory (31 – 33). It has been thought that the inhibitory effect of the cannabinoids on LTP is related to the inhibition of glutamate release via presynaptic CB1 cannabinoid receptors (34). Thus, the glutamatergic neuronal system may be involved in the Δ9-THC-induced impairment of spatial memory.

Involvement of the glutamatergic neuronal system in the therapeutic effect of Δ9-THC on EAE

EAE is an autoimmune disease of the central nervous system (CNS) that has been characterized and proposed as a valid animal model for the study of human MS (35, 36). It is widely accepted that the most common pathological abnormality in MS is an inflammatory demyelination in the CNS, but recent studies have highlighted the additional presence of axonal damage (37, 38). The cause of demyelination and axonal damage remains unclear, but several lines of evidence support the possibility that glutamate-induced excitotoxicity plays a role in these pathological changes in MS. Glutamate concentration in the cerebrospinal fluid (CSF) is reported to be elevated in patients suffering from acute MS (39, 40). In EAE, glutamate-metabolizing enzymes, glutamine synthetase, and glutamate dehydrogenase are downwardly regulated in astrocytes (41). We have found that the glutamate level of CSF is
elevated immediately after the onset of EAE (unpublished data). Recently, amelioration of EAE by NMDA- and AMPA-type glutamate receptor antagonists was reported (42 – 44). Moreover, riluzole, an inhibitor of glutamate transmission, has been reported to reduce inflammation, demyelination, and axonal damage in the spinal cord and attenuate the clinical severity of EAE (45). We have also found that riluzole inhibits EAE and reduces an elevated glutamate level of CSF induced by EAE (unpublished data). These findings suggest that the glutamate neuronal system is essential to the mechanism of EAE.

Cannabinoids have been reported to inhibit both clinical and histologic EAE (46 – 48). We have found that Δ⁹-THC ameliorates both clinical severity of EAE and histological signs in the lumbar spinal cord and reduces the glutamate level of CSF (unpublished data). Moreover, we have found that these therapeutic effects on EAE are reversed by SR141716A, suggesting that the action of Δ⁹-THC was CB₁ cannabinoid receptor-mediated (unpublished data). Therefore, we conclude that one mechanism of the ameliorative effect of Δ⁹-THC on EAE is an inhibition of glutamate release through the CB₁ cannabinoid receptors in the CNS, in particular the spinal cord. Thus, the glutamatergic neuronal system may be involved in the therapeutic effect of Δ⁹-THC on EAE, and Δ⁹-THC has potential use as a drug for the treatment of acute exacerbations of MS.

Conclusions

In conclusion, the present findings show that Δ⁹-THC may impair spatial memory, at least in part, by inhibiting glutamate release through the CB₁ cannabinoid receptor (Fig. 1). Also we suggested that Δ⁹-THC induces abnormal behaviors such as catalepsy-like immobilization and aggressive behavior through the CB₁ cannabinoid receptor. Moreover, we concluded that one mechanism of the improving effect of Δ⁹-THC on EAE is an inhibition of glutamate release through the CB₁ cannabinoid receptor (Fig. 1). Cannabinoid receptor agonists, and in addition antagonists/inverse agonists of this receptor, might be developed as therapeutic agents.

Acknowledgments

Part of this study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (No. 16591174). The authors are grateful to Professor Y. Shoyama, Department of Medicinal Resources Regulation, Graduate School of Pharmaceutical Sciences, Kyushu University, for his kind supply of natural Δ⁹-tetrahydrocannabinol. The authors are grateful to Sanofi Synthelabo (Montpellier, France) for the gift of SR141716A.

References


