Full Paper

2,5-Dimethoxy-4-iodoamphetamine (DOI) Inhibits Δ^9 -Tetrahydrocannabinol-Induced Catalepsy-Like Immobilization in Mice

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Abstract. The effect of the serotonin 5-HT_{2A/2C}-receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) on Δ^9 -tetrahydrocannabinol (THC)-induced catalepsy-like immobilization was studied in mice. DOI (0.3 and 1 mg/kg, i.p.) significantly inhibited the catalepsy-like immobilization induced by THC (10 mg/kg, i.p.). In contrast, the selective 5-HT_{2C}-receptor agonist 8,9-dichloro-2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)-one (WAY 161503) had no effect on this catalepsy-like immobilization. Moreover, the 5-HT_{2A}-receptor antagonist ketanserin (0.3 mg/kg, i.p.) reversed the inhibition of THC-induced catalepsy-like immobilization caused by DOI (1 mg/kg), whereas the selective 5-HT_{2C}-receptor antagonist 6-chloro-2,3-dihydro-5-methyl-*N*-[6-(2-methyl-3-pyridinyl)oxyl]-3-pyridinyl]-1*H*-indole-1-carboxamide (SB 242084) did not affect this inhibitory effect of DOI. On the other hand, ketanserin (0.3 and 1 mg/kg, i.p.) enhanced the catalepsy-like immobilization induced by THC (6 mg/kg, i.p.). Thus, on the basis of these results, it appears that 5-HT_{2A}-receptor mechanisms might be responsible for the inhibitory effect of DOI on THC-induced catalepsy-like immobilization.

Keywords: Δ^9 -tetrahydrocannabinol, cannabinoid, catalepsy, 2,5-dimethoxy-4-iodoamphetamine (DOI), 5-HT_{2A} receptor

Introduction

Δ^9 -Tetrahydrocannabinol (THC), the principal psychoactive component of marijuana, is known to cause catalepsy in mice and rats (1, 2). This effect is attenuated by the cannabinoid CB₁-receptor antagonist rimonabant (2, 3), indicating that it is mediated by CB₁ receptors. In contrast, rimonabant is unable to affect catalepsy induced by the D₂-receptor antagonists haloperidol and raclopride (4, 5), indicating that catalepsy induced by D₂ blockade does not involve stimulation of CB₁ receptors. The mechanism mediating THC-induced catalepsy is different from that mediating D₂-receptor antagonist-induced catalepsy. Moreover, we observed that THC-induced catalepsy was inhibited by air blowing, sound,

and tactile stimuli and that the same dose (10 mg/kg) of THC had no effect on motor coordination in a rotarod test (3). Thus, THC-induced catalepsy is clearly distinct from that induced by large doses of major tranquilizers, which cause extrapyramidal side effects (EPS) such as akinesia. Instead, the cataleptic immobilized state induced by THC may be thought to represent a decreased motivation towards movement. Therefore, we have called this cataleptic immobilized state catalepsy-like immobilization (1).

Serotonin (5-HT) is implicated in the control of motor behavior, including catalepsy. For example, selective 5-HT-reuptake inhibitors (SSRIs) attenuate haloperidol-induced catalepsy in mice (6). In addition, the 5-HT_{1A}-receptor agonists 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) and buspirone and the 5-HT_{2A/2C}-receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) attenuate D₂-receptor-mediated catalepsy (7 – 11). Moreover, the anti-cataleptic effects of 8-OH-DPAT

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and DOI are antagonized by a selective 5-HT_{1A}-receptor antagonist and a 5-HT_{2A/2C}-receptor antagonist, respectively (11, 12), indicating that the serotonergic system is involved in the onset of catalepsy.

Recently, we reported that 8-OH-DPAT and buspirone inhibited THC-induced catalepsy-like immobilization and that these inhibitory effects were reversed by *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexane carboxamide (WAY100635), a selective 5-HT_{1A}-receptor antagonist (3). Moreover, WAY100635 enhanced the catalepsy-like immobilization induced by THC (6 mg/kg, i.p.). These findings suggest that the 5-HT_{1A} receptors are involved in THC-induced catalepsy-like immobilization.

On the other hand, we previously reported that DOI attenuated the THC-induced impairment of spatial memory observed in rats in the eight-arm radial maze (13). Moreover, THC, CB₁-receptor agonists and an endogenous cannabinoid inhibited the DOI-induced 5-HT_{2A}-receptor-mediated behaviors in mice (14, 15). These findings suggest that 5-HT_{2A} receptors are involved in CB₁-receptor-mediated behaviors. However, the effect of DOI on THC-induced catalepsy-like immobilization has not been studied. In the present study, we investigated the effect of DOI on THC-induced catalepsy-like immobilization in mice.

Materials and Methods

Animals

Male ddY mice (Kyudo, Saga), aged 6 weeks and weighing 25–30 g, were housed in groups of five in a temperature-controlled room (23 ± 2°C) on a 12-h light–dark cycle (lights on 07:00–19:00), with food and water available ad libitum. All procedures regarding animal care and use were carried out based on the regulations established by the Experimental Animal Care and Use Committee at Fukuoka University, Japan.

Drugs

THC (≥95% purity) was isolated from *Cannabis* by Professor Y. Shoyama (Department of Pharmacognosy, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka). (±)-2,5-Dimethoxy-4-iodoamphetamine hydrochloride (DOI), ketanserin tartrate, and 6-chloro-2,3-dihydro-5-methyl-*N*-[6-(2-methyl-3-pyridinyl)oxyl]-3-pyridinyl]-1*H*-indole-1-carboxamide dihydrochloride (SB 242084) were purchased from Sigma-Aldrich (St. Louis, MO, USA). 8,9-Dichloro-2,3,4,4a-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoxalin-5(6*H*)-one hydrochloride (WAY 161503) was purchased from Tocris Cookson (Ellisville, MO, USA). THC was emulsified in 1% Tween 80 solution and administered intra-

peritoneally (i.p.) 30 min before tests. DOI, ketanserin, SB 242084, and WAY 161503 were dissolved in saline and administered i.p. immediately after the first test (30 min after THC injection). The observer did not know which agent was being tested.

Catalepsy test

The catalepsy test was modified from that described previously (3). Mice were tested for catalepsy using the bar test at 30, 60, and 90 min after THC administration. The forelimbs were placed on a horizontal metal bar (height, 5.5 cm; diameter, 0.2 cm) and the length of time during which both forelimbs remained on the bar was determined up to a maximum of 30 s.

Open-field test

The procedure follows that previously described by Egashira et al. (16). Mice were singly placed in the centre of a circular open field (grey iron, diameter = 60 cm) enclosed by a parapet (height, 50 cm) with an upper opening (diameter, 90 cm). The floor was divided into 19 equal blocks by thin black lines. The apparatus was placed in a sound-proof dark room, illuminated by a 100 W bulb, placed 80 cm above the center of the open field floor. The numbers of line crossings and rearings were recorded during a 3-min test session. The activity of mice used in this study was measured once before the test. DOI was administered i.p. 30 min before the test.

Statistical analyses

Results from the open-field test were evaluated for statistical significance using the Student's *t*-test. The data from the catalepsy test were analyzed by one-way and two-way (repeated-measures) analysis of variance (ANOVA), followed by the Student's *t*-test or Tukey-Kramer's post-hoc test. The criterion for statistical significance was considered to be $P < 0.05$. Values are expressed as means ± S.E.M.

Results

Effect of THC on catalepsy

Repeated-measures ANOVA revealed a drug effect [$F(1,17) = 135.583$, $P < 0.0001$], a time effect [$F(2,34) = 5.322$, $P < 0.01$], and a drug × time interaction [$F(2,34) = 3.882$, $P < 0.05$]. THC at a dose of 10 mg/kg significantly caused catalepsy-like immobilization at 30, 60, and 90 min after THC administration (30 min: $P < 0.01$; 60 and 90 min: $P < 0.001$ by Student's *t*-test, Fig. 1).

Effect of DOI on the duration of THC-induced catalepsy

Repeated-measures ANOVA revealed a drug effect [$F(2,25) = 4.067$, $P < 0.05$], a time effect [$F(2,50) =$

Fig. 1. Effect of THC on catalepsy. THC was administered i.p. 30 min prior to the test. Values are expressed as means $\pm$ S.E.M. ** $P < 0.01$, *** $P < 0.001$, compared with Tween.

Fig. 2. Effect of DOI on the duration of THC-induced catalepsy. THC was administered i.p. 30 min prior to the test. DOI was administered i.p. immediately after the first test (30 min after THC injection). Values are expressed as means $\pm$ S.E.M. * $P < 0.05$, ** $P < 0.01$, compared with THC + saline.

28.251, $P < 0.0001$] and a drug $\times$ time interaction [$F(4,50) = 2.512$, not significant, NS]. The 5-HT_{2A/2C}-receptor agonist DOI (0.3 and 1 mg/kg, i.p.) significantly reduced the duration of THC-induced catalepsy at 30 min after DOI administration [$F(2,25) = 13.796$, $P < 0.0001$ by one-way ANOVA; 0.3 mg/kg DOI: $P < 0.05$; 1 mg/kg DOI: $P < 0.01$, by Tukey-Kramer's post-hoc test; Fig. 2]. In addition, 1 mg/kg DOI had no effect on the amount of ambulation and rearing in the

Fig. 3. Effect of WAY 161503 on the duration of THC-induced catalepsy. THC was administered i.p. 30 min prior to the test. WAY 161503 was administered i.p. immediately after the first test (30 min after THC injection). Values are expressed as means $\pm$ S.E.M.

open-field test. Ambulation was 43.4 ± 10.3 with saline ($n = 7$) and 42.1 ± 9.1 with DOI ($n = 7$) (NS by Student's *t*-test). Rearing was 6.0 ± 2.7 with saline and 7.9 ± 3.0 with DOI (NS by Student's *t*-test).

Effect of WAY 161503 on duration of THC-induced catalepsy

Repeated-measures ANOVA revealed a drug effect [$F(2,39) = 0.201$, NS], a time effect [$F(2,78) = 15.206$, $P < 0.0001$], and a drug $\times$ time interaction [$F(4,78) = 0.473$, NS]. The selective 5-HT_{2C}-receptor agonist WAY 161503 (1 and 3 mg/kg, i.p.) had no effect on the duration of THC-induced catalepsy (Fig. 3).

Effects of ketanserin and SB 242084 on the reduction effect of DOI on the duration of THC-induced catalepsy

Repeated-measures ANOVA revealed a drug effect [$F(4,47) = 4.841$, $P < 0.01$], a time effect [$F(2,94) = 11.685$, $P < 0.0001$], and a drug $\times$ time interaction [$F(8,94) = 4.627$, $P < 0.0001$]. The 5-HT_{2A}-receptor antagonist ketanserin (0.3 mg/kg) reversed the DOI (1 mg/kg)-induced reduction in the duration of THC-induced catalepsy, 30 min after ketanserin administration [$F(4,47) = 6.929$, $P < 0.001$ by one-way ANOVA; ketanserin, 0.3 mg/kg: $P < 0.01$ by the Tukey-Kramer's post-hoc test, Fig. 4]. In contrast, the selective 5-HT_{2C}-receptor antagonist SB 242084 (10 mg/kg) did not affect the DOI-induced reduction in the duration of THC-induced catalepsy. At a dose of 0.3 mg/kg, ketanserin had no effect on the duration of THC-induced catalepsy.

Fig. 4. Effects of ketanserin and SB 242084 on the DOI-induced reduction in the duration of THC-induced catalepsy. THC was administered i.p. 30 min prior to the test. DOI, ketanserin, and SB 242084 were administered i.p. immediately after the first test (30 min after THC injection). Values are expressed as means $\pm$ S.E.M. ** $P < 0.01$, compared with THC + saline; ## $P < 0.01$, compared with THC + DOI + saline.

Effect of ketanserin combined with THC on catalepsy

THC (6 mg/kg)-induced catalepsy-like immobilization is more appropriate for investigating the enhancement effect of a drug on catalepsy-like immobilization. In this study, we investigated the enhancement effect of ketanserin on THC (6 mg/kg)-induced catalepsy-like immobilization. Repeated-measures ANOVA revealed a drug effect [$F(5,45) = 12.587$, $P < 0.0001$], a time effect [$F(2,90) = 22.574$, $P < 0.0001$], and a drug $\times$ time interaction [$F(10,90) = 3.896$, $P < 0.001$]. Ketanserin (0.3 and 1 mg/kg) combined with THC (6 mg/kg) significantly induced catalepsy-like immobilization compared with THC alone, at 30 or 60 min after ketanserin administration [$F(5,45) = 9.551$, $P < 0.0001$ by one-way ANOVA; ketanserin, 0.3 mg/kg: $P < 0.05$, ketanserin, 1 mg/kg: $P < 0.01$ by the Tukey-Kramer's post-hoc test, Fig. 5]. The same dose of THC or ketanserin alone did not induce catalepsy.

Discussion

In the present study, THC (10 mg/kg) caused catalepsy-like immobilization at 30, 60, and 90 min after THC administration in mice, results that are essentially consistent with previous findings (3). We found that the

Fig. 5. Effect of ketanserin combined with THC on catalepsy. THC was administered i.p. 30 min prior to the test. Ketanserin was administered i.p. immediately after the first test (30 min after THC injection). Values are expressed as means $\pm$ S.E.M. * $P < 0.05$, ** $P < 0.01$, compared with THC + saline.

5-HT_{2A/2C}-receptor agonist DOI significantly inhibited THC-induced catalepsy-like immobilization. In contrast, the selective 5-HT_{2C}-receptor agonist WAY 161503 had no effect on THC-induced catalepsy-like immobilization. We also found that the 5-HT_{2A}-receptor antagonist ketanserin completely reversed the inhibitory effect of DOI on THC-induced catalepsy-like immobilization, whereas the selective 5-HT_{2C}-receptor antagonist SB 242084 did not affect this inhibitory effect of DOI. Thus, our findings indicate that DOI inhibits THC-induced catalepsy-like immobilization through a direct action on 5-HT_{2A} receptors. In addition, DOI at the effective dose (1 mg/kg) had no effect on locomotor activity or rearing, suggesting that DOI inhibits THC-induced catalepsy-like immobilization without affecting motor activity. Furthermore, we found that ketanserin enhanced the catalepsy-like immobilization induced by THC. Hence, these findings suggest that 5-HT_{2A} receptors are involved in THC-induced catalepsy-like immobilization.

DOI inhibits D₂-receptor-mediated catalepsy (7, 11). This inhibitory effect is antagonized by a 5-HT_{2A/2C}-receptor antagonist (11), in support of an anti-cataleptic effect of DOI mediated via this 5-HT₂ receptor. There is a relatively high density of 5-HT₂ receptors in the dopamine-rich neostriatum, providing a possible site for interactions between DOI and D₂-receptor antagonists.

On the other hand, microinjection of THC into the nucleus accumbens has been reported to induce catalepsy-like immobilization in mice (17). We have found that microinjection of THC into the nucleus accumbens, amygdala, or hypothalamus, which contain a moderately high-density of CB₁ receptors (18, 19), induces catalepsy-like immobilization in rats (1). We also found that THC decreases extracellular 5-HT levels in the rat nucleus accumbens and that this effect is antagonized by rimonabant (unpublished data). Considering the existence of a high density of 5-HT_{2A} receptors in the nucleus accumbens (20, 21), these findings suggest that inhibition of 5-HT neurotransmission in the nucleus accumbens may be involved in THC-induced catalepsy-like immobilization.

Presynaptic CB₁-receptor-mediated inhibition of glutamate and γ -aminobutyric acid (GABA) release from neurons in the nucleus accumbens has previously been demonstrated (22–24). Immunocytochemical and electrophysiological studies have demonstrated the presence of CB₁ receptors at both GABAergic and glutamatergic synapses in the nucleus accumbens (23, 24). Moreover, the non-competitive *N*-methyl-D-aspartate-receptor antagonist MK-801 increases extracellular levels of 5-HT in the rat nucleus accumbens (25). Moreover, MK-801 and the selective GABA-reuptake inhibitor tiagabine have been reported to modify THC-induced catalepsy-like immobilization in mice (26, 27). Hence, the possibility exists that THC inhibits 5-HT release through GABAergic or glutamatergic mechanisms.

In this study, it appears that there is a difference between the THC + DOI + saline-treated group and THC + DOI + SB 242084-treated group at 90 min after THC treatment. The 5-HT_{2C} receptors have been thought to modulate mesolimbic dopamine (DA) function and the expression of DA-dependent behaviors. SB 242084 has also been reported to antagonize haloperidol-induced catalepsy (28). Moreover, SB 242084 has been reported to enhance hyperactivity induced by MDMA, amphetamine, fenfluramine, cocaine, and methylphenidate (29). Therefore, SB 242084-treated mice may exhibit a tendency toward a reduced duration of THC-induced catalepsy.

In conclusion, DOI inhibited THC-induced catalepsy-like immobilization, possibly via 5-HT_{2A} receptors, while ketanserin enhanced this immobilization. Thus, on the basis of these results, it can be proposed that 5-HT_{2A} receptor-dependent mechanisms predominate in the DOI-mediated effects on THC-induced catalepsy-like immobilization.

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