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Antipsychotics improve Δ^9-tetrahydrocannabinol-induced impairment of the prepulse inhibition of the startle reflex in mice

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Abstract

Recently, cannabinoid receptor agonists have been reported to impair prepulse inhibition (PPI) of the startle reflex. In the current study, we examined the effect of Δ^9-tetrahydrocannabinol (THC), the principal psychoactive component of cannabis, on the PPI, and found that THC (10 mg/kg, i.p.) impaired the PPI concomitant with a decrease in the startle response. Antipsychotics such as haloperidol (0.3 mg/kg, i.p.) and risperidone (0.1 mg/kg, i.p.), which are potent dopamine D_2 receptor antagonists, and SR141716 (10 mg/kg, i.p.), a CB_1 cannabinoid receptor antagonist, reversed these THC-induced PPI deficits. Moreover, THC (10 mg/kg) increased dopamine (DA) release in the nucleus accumbens but not medial prefrontal cortex over a 50–100-min period (time of PPI test) after treatment, and SR141716 (10 mg/kg) reversed this increase in DA release induced by THC. These results suggest that dopaminergic hyperfunction in the nucleus accumbens may be involved in THC-induced PPI deficits.

Keywords: Antipsychotic; Cannabinoids; Dopamine; Mouse; Nucleus accumbens; Schizophrenia; Prepulse inhibition

1. Introduction

We previously reported that Δ^9-tetrahydrocannabinol (THC), the principal psychoactive component of cannabis, caused spatial memory impairment, catalepsy and aggressive behavior in rats (Fujiwara and Egashira, 2004). In humans, cannabis abuse often precipitates a psychotic state known as "cannabinoid psychosis", which is associated with hallucinations, delusions and emotional liability, and resembles schizophrenia (McGuire et al., 1994; Johns, 2001). Importantly, cannabis-induced psychosis is responsive to treatment with antipsychotic drugs (Berk et al., 1999). Moreover, administration of THC to normal volunteers induced cognitive impairment in three dimensions closely resembling the impairment observed in schizophrenic patients (Emrich et al., 1997). Thus, cannabinoid psychosis resembles schizophrenia. However, a CB_1 cannabinoid receptor antagonist SR141716 had no effect on the positive and negative syndrome in schizophrenic patients (Meltzer et al., 2004). Therefore, the cannabinoid psychosis may be different from schizophrenia.

Schizophrenia has long been associated with abnormalities in information processing and attention mechanisms (Braff, 1993; Perry and Braff, 1994). In attempts to better understand the mechanisms underlying the physiopathology of schizophrenia, sensorimotor information gating processes have received much attention. One well-established method for evaluating sensory filtering is the prepulse inhibition (PPI) paradigm, which involves a reduction of the startle reflex by implementation of a weak intensity prepulse immediately before the startle stimulus. Disruption of the PPI in schizophrenic patients has been well described in several studies (Braff et al., 1992;

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Perry and Braff, 1994). On the other hand, cannabis use was found to induce attention deficits similar to those observed in acute schizophrenia (Skosnik et al., 2001). In rodents, disruption of the PPI occurs after acute administration of dopamine (DA) agonists (Swerdlow et al., 1986; Mansbach et al., 1988), and these DA agonist-induced PPI deficits can be reversed by both typical and atypical antipsychotics (Swerdlow and Geyer, 1993; Varty and Higgins, 1995a). Thus, dopaminergic neurons play an important role in regulating the PPI. In general, PPI is thought to be regulated by a prefrontocortico-limbic-striato-pallidal circuit that is connected to the primary acoustic startle response pathway through mesopontine and nigral projections (Swerdlow et al., 2001). The medial prefrontal cortex and nucleus accumbens are important sites in this circuit. Similarly, the cannabinoid receptor agonists such as WIN 55,212-2 and CP-55940 have been reported to impair the PPI in rats (Schneider and Koch, 2002; Martin et al., 2003). Conversely, the cannabinoid receptor agonist WIN 55,212-2 and THC have been reported to no impair PPI in grouped rats (Bortolato et al., 2005; Malone and Taylor, 2006). Thus, the action of cannabinoids on PPI is not corresponding. Here, we evaluated the effect of THC on the PPI in mice and found improvement effects of antipsychotics on THC-induced PPI deficits. Moreover, we measured extracellular DA in the medial prefrontal cortex and nucleus accumbens using in vivo microdialysis. In addition, we evaluated catalepsy and motor coordination to investigate the involvement of motor function in the THC-induced PPI deficits.

2. Materials and methods

2.1. Animals

Male ddY mice (Kyudo, Saga, Japan), 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 to 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.

2.2. Drugs

THC (the purity is about 95% or more) was isolated from cannabis by Professor Y. Shoyama (Department of Medicinal Resources Regulation, Graduate School of Pharmaceutical Sciences, Kyushu University). SR141716 and risperidone were a generous gift from Sanofi Synthelabo (Montpellier, France) and Janssen Research Foundation (Beerse, Belgium), respectively. THC and SR141716 were emulsified in 1% Tween 80 solution and administered intraperitoneally (i.p.) 60 min before the tests. Haloperidol (5 mg/ml; Serenace Injection; Dainippon Pharmaceutical Co. Ltd., Osaka, Japan) was diluted with saline. Risperidone was dissolved in saline. Haloperidol and risperidone were each administered i.p. 30 min before the test.

2.3. PPI of the startle reflex

PPI of the startle reflex was measured as described previously (Egashira et al., 2005). The startle responses were measured in an illuminated startle chamber (39 cm × 38 cm × 58 cm; SR-LAB System; San Diego Instruments, San Diego, CA, USA), consisting of a Plexiglas cylinder (diameter: 8 cm, length: 16 cm) mounted on a removable frame with a base unit. Movement of a mouse within the cylinder was detected by a piezoelectric accelerometer attached below the frame. A loudspeaker mounted 25 cm above the cylinder provided background white noise and acoustic stimuli. The acoustic stimuli and piezoelectric responses from the accelerometer were controlled and digitized by the SR-LAB software and an interface system. The startle amplitude was defined as the average of 100 m s^{-1} readings collected from the beginning of the startle stimulus onset. During the session, the background noise was kept constant at 65 dB. The mice were placed in the cylinders 10 min prior to the initial startle stimuli and only background noise was offered during this acclimation period. To measure the acoustic startle response and PPI, four trials were carried out: no stimulus, startle stimulus only (120 dB, 20 ms broadband burst) and two types of startle stimulus preceded by a prepulse (a 20 ms broadband burst). The onset of the prepulse was separated from the startle onset by a 100 ms prepulse-startle interval (PSI), and the prepulse intensities used were 70 and 80 dB. Each trial was repeated nine times in a random order and separated by an average interval of 30 s (15–35 s). The PPI was calculated as a percentage of the pulse-alone startle amplitude using the following formula: [1 − (startle amplitude following prepulse–pulse pair / startle amplitude following pulse only)] × 100.

2.4. Catalepsy test

Mice were tested for catalepsy using the bar test once for all before the rota-rod test. The forelimbs were placed on a horizontal metal bar (height: 5.5 cm, diameter: 0.2 cm) and the time during which both forelimbs remained on the bar was determined up to a maximum of 30 s. If the catalepsy time was 30 s, it was regarded as the drug-induced catalepsy and scored as "+"; otherwise, it was scored as "−". The incidence of catalepsy was expressed as the percentage of mice scored as "+".

2.5. Rota-rod test

Motor coordination was measured using the rota-rod test as described previously (Egashira et al., 2004b). Mice were placed on a rotating rod (diameter: 3 cm; Neuroscience Inc., Tokyo, Japan) with a non-skid surface and the latency to fall was measured for up to 2 min. The rotating speed was 5 or 15 rpm.

2.6. Brain microdialysis for DA release

Animals were anaesthetized with sodium pentobarbital (50 mg/kg, i.p.; Tokyo Kasei, Tokyo, Japan) and stereotaxically implanted with a guide cannula (AG-4; EICOM, Kyoto, Japan)

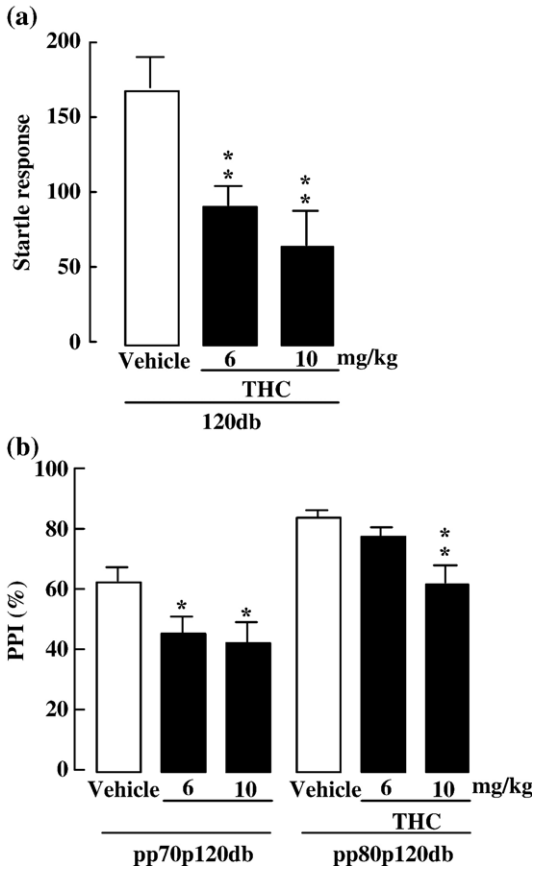

Fig. 1. Effects of THC on the prepulse inhibition. THC was injected i.p. 60 min before the tests. Values are expressed as means±S.E.M. (n=8). *P<0.05, **P<0.01 vs. vehicle (one- or two-way ANOVA followed by Student–Newman–Keuls post-hoc test).

at the medial prefrontal cortex (A: +2.2 mm, L: −0.3 mm, V: −2.9 mm from the bregma) or nucleus accumbens (A: +1.7 mm, L: +0.9 mm, V: −3.9 mm from the bregma) according to the atlas of Franklin and Paxinos (1997). On 3 days after the surgery, a dialysis probe (A-I-4-02, 2.0 mm probe membrane, EICOM) was inserted into the guide cannula and perfused with Ringer's solution (147.0 mM NaCl, 4.0 mM KCl and 2.2 mM $CaCl_2$; Wako Pure Chemical Industries Ltd., Osaka, Japan) at a constant flow rate of 2 μl/min using a microsyringe pump (ESP-64, EICOM). A stabilization period of 2 h was allowed before the experiment. Microdialysis samples (50 μl) were collected at 25-min intervals over a 75-min period (baseline) before THC (10 mg/kg, i.p.) and SR141716 (10 mg/kg, i.p.) administration and over a 50–100-min period (time of PPI test) after drug treatment. The high-performance liquid chromatography-electrochemical detector (HPLC-ECD) system (EICOM) utilized an Eicompak SC-5ODS column (3.0 mm i.d. ×150 mm, EICOM) and was set at a potential of +750 mV against an Ag/AgCl reference electrode. The mobile phase contained 0.1 M acetate–citrate buffer (pH 3.5), 190 mg/l sodium 1-octanesulfonate, 5 mg/l EDTA and 16% methanol. The flow rate was maintained at 0.25 ml/min. DA release in the brain was calculated using PowerChrom (version 2.2.4, EICOM). After completion of the microdialysis experiment, the animals were anaesthetized with ether and their heads were removed. The brain was removed, frozen and cut into 40 μm thick slices. The position of the guide cannula in the medial prefrontal cortex or nucleus accumbens was confirmed by microscopic examination. Only data from animals in which the implantation was made at the desired site were analyzed.

2.7. Statistics

Values were expressed as means±S.E.M. The data for the PPI were analyzed by two-way analysis of variance (ANOVA) followed by Student–Newman–Keuls post-hoc test. The data for the acoustic startle response were analyzed by one-way ANOVA followed by Student–Newman–Keuls post-hoc test. The data for the catalepsy test were analyzed by Fisher's exact probability test. The data for the motor coordination test were analyzed by the unpaired t-test. DA release was analyzed using the unpaired t-test or one-way ANOVA followed by the Bonferroni test. The level of statistical significance was set at P<0.05.

3. Results

3.1. Effect of THC on the PPI of the startle reflex

THC significantly reduced the startle amplitude (6 and 10 mg/kg: P<0.01, Fig. 1). Moreover, THC dose-dependently

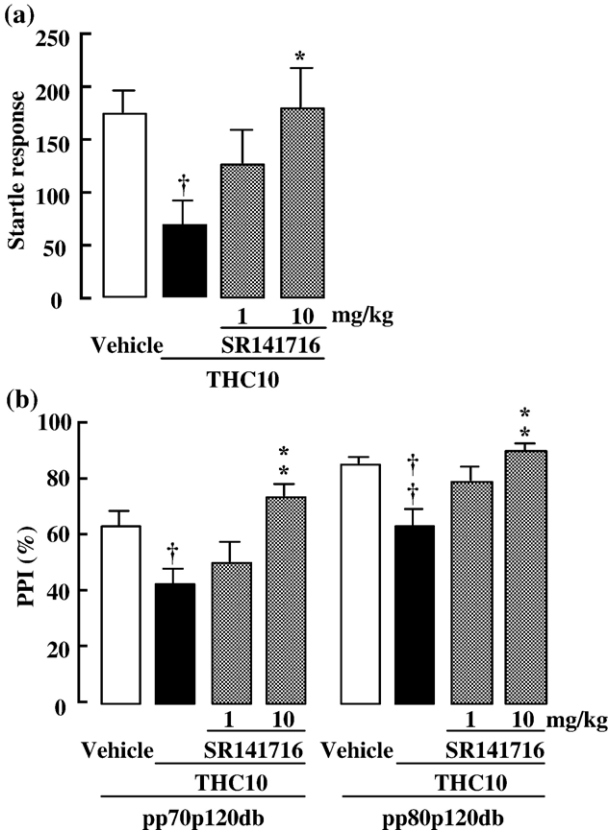

Fig. 2. Effects of SR141716 on THC-induced impairment of the prepulse inhibition. THC and SR141716 were injected i.p. 60 min before the tests. THC 10: THC 10 mg/kg (i.p.). Values are expressed as means±S.E.M. (n=5–8). †P<0.05, ††P<0.01 vs. vehicle, *P<0.05, **P<0.01 vs. THC (one- or two-way ANOVA followed by Student–Newman–Keuls post-hoc test).

decreased the %PPI [drug: $F(2,42)=10.189$, $P<0.001$; prepulse: $F(1,42)=41.868$, $P<0.001$; interaction: $F(2,42)=1.021$, $P>0.05$]. THC at doses of 6 and 10 mg/kg decreased the % PPI following prepulse stimulation at 70 and 80 dB (6 mg/kg: 70 dB: $P<0.05$; 10 mg/kg: 70 dB: $P<0.05$, 80 dB: $P<0.01$).

3.2. Effects of SR141716, haloperidol and risperidone on the THC-induced PPI deficits

SR141716 at a dose of 10 mg/kg reversed the THC-induced decrease in the startle amplitude ($P<0.05$, Fig. 2). Concomitantly, SR141716 at the same dose reversed the THC-induced decrease in the %PPI [drug: $F(3,45)=14.071$, $P<0.001$; prepulse: $F(1,45)=43.220$, $P<0.001$; interaction: $F(3,45)=0.461$, $P>0.05$] following prepulse stimulation at 70 and 80 dB (70 and 80 dB: $P<0.01$). In contrast, the same dose of SR141716 alone had no effects on the startle amplitude and % PPI (startle amplitude: vehicle: 172.39±20.81, SR141716: 163.63±53.33; %PPI-70 dB: vehicle: 61.85±4.38, SR141716: 50.33±9.31; %PPI-80 dB: vehicle: 83.06±2.22, SR141716: 71.93±4.15). Similarly, haloperidol (0.1 and 0.3 mg/kg) reversed the THC-induced decrease in the startle amplitude ($P<0.05$, Fig. 3). Haloperidol (0.1 and 0.3 mg/kg) also reversed the THC-induced decrease in the %PPI [drug: $F(3,64)=9.119$, $P<0.001$; prepulse: $F(1,64)=53.765$, $P<0.001$; interaction: $F(3,64)=0.558$, $P>0.05$] following prepulse stimulation at 80 dB (0.1 mg/kg: $P<0.05$, 0.3 mg/kg: $P<0.01$). In addition, haloperidol (0.3 mg/kg, i.p.) alone increased on the startle amplitude, but had no effect on %PPI (startle amplitude: vehicle: 188.76±46.59, haloperidol: 304.61±9.83, $P<0.05$; %PPI-70 dB: vehicle: 55.03±7.90, haloperidol: 46.89±5.65; %PPI-80 dB: vehicle: 76.76±1.38, haloperidol: 77.70±5.05). On the other hand, risperidone had no significant effect on the THC-induced decrease in the startle amplitude (Fig. 4), but showed a dose-dependent ability to increase the startle response. Risperidone (0.03 and 0.1 mg/kg) reversed the THC-induced decrease in the %PPI [drug: $F(3,84)=17.819$, $P<0.001$; prepulse: $F(1,84)=68.959$, $P<0.001$; interaction: $F(3,84)=0.085$, $P>0.05$] following prepulse stimulation at 70 and 80 dB (0.03 mg/kg: 80 dB: $P<0.05$; 0.1 mg/kg: 70 and 80 dB: $P<0.01$). In addition, risperidone (0.1 mg/kg, i.p.) alone had no effects on the startle amplitude and %PPI (startle amplitude: vehicle: 188.76±46.59, risperidone: 417.13±102.69; %PPI-70 dB: vehicle: 55.03±7.90, risperidone: 44.42±5.22; %PPI-80 dB: vehicle: 76.76±1.38, risperidone: 68.16±5.22). Also, PPI tests could not be carried out at a higher dose (0.3 mg/kg) of risperidone because it caused sedation.

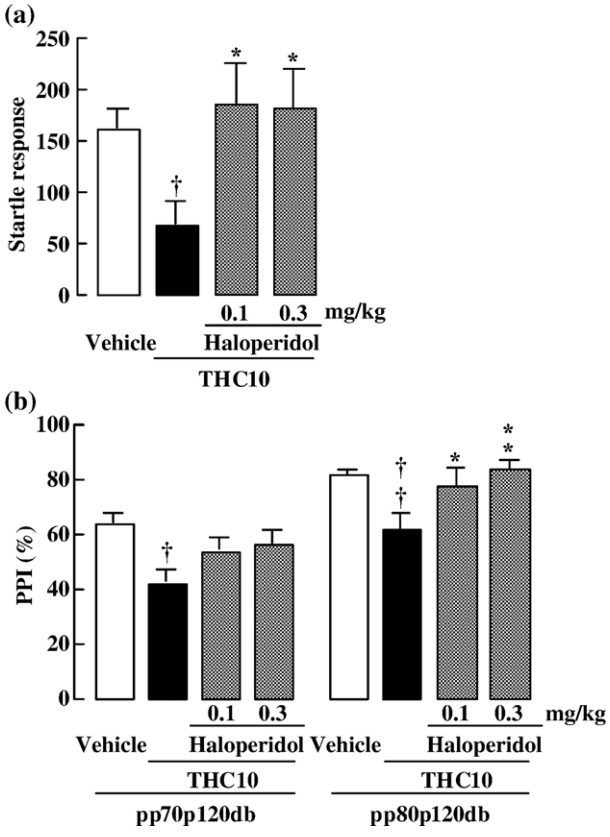

Fig. 3. Effects of haloperidol on THC-induced impairment of the prepulse inhibition. THC and haloperidol were injected i.p. 60 and 30 min before the tests, respectively. THC 10: THC 10 mg/kg (i.p.). Values are expressed as means± S.E.M. ($n=8$–12). †$P<0.05$, ††$P<0.01$ vs. vehicle, *$P<0.05$, **$P<0.01$ vs. THC (one- or two-way ANOVA followed by Student–Newman–Keuls post-hoc test).

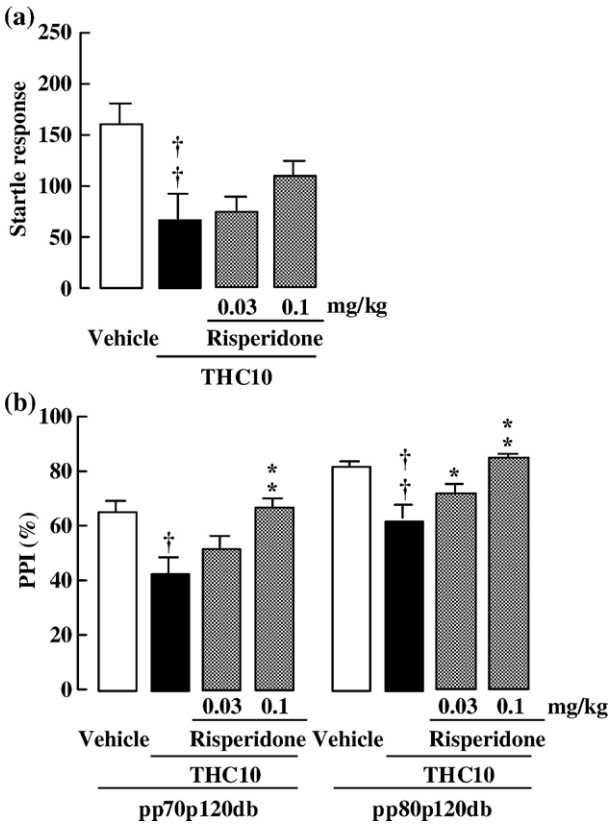

Fig. 4. Effects of risperidone on THC-induced impairment of the prepulse inhibition. THC and risperidone were injected i.p. 60 and 30 min before the tests, respectively. THC 10: THC 10 mg/kg (i.p.). Values are expressed as means ±S.E.M. ($n=8$–14). ††$P<0.01$ vs. vehicle, *$P<0.05$, **$P<0.01$ vs. THC (one- or two-way ANOVA followed by Student–Newman–Keuls post-hoc test).

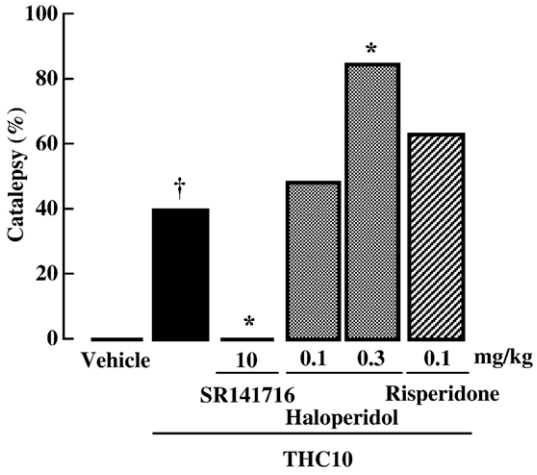

Fig. 5. Effects of SR141716, haloperidol and risperidone on THC-induced catalepsy. THC and SR141716 were injected i.p. 60 min before the test, while haloperidol and risperidone were injected i.p. 30 min before the test. THC 10: THC 10 mg/kg (i.p.). Values are expressed as means±S.E.M. (n=8–15). †P<0.05 vs. vehicle, *P<0.05 vs. THC (Fisher's exact probability test).

3.3. Effects of SR141716, haloperidol and risperidone on the THC-induced catalepsy

In the bar test for catalepsy, THC (10 mg/kg, i.p.) induced significant catalepsy (Fig. 5). SR141716 (10 mg/kg, i.p.) completely reversed the THC-induced catalepsy. In contrast, haloperidol (0.3 mg/kg, i.p.) significantly enhanced the THC-induced catalepsy, while risperidone (0.1 mg/kg, i.p.) had no significant effect.

3.4. Effects of SR141716, haloperidol and risperidone on motor coordination in THC-treated mice

In the rota-rod test for motor coordination, THC (10 mg/kg, i.p.) had no effect on the motor coordination at 5 rpm (Fig. 6).

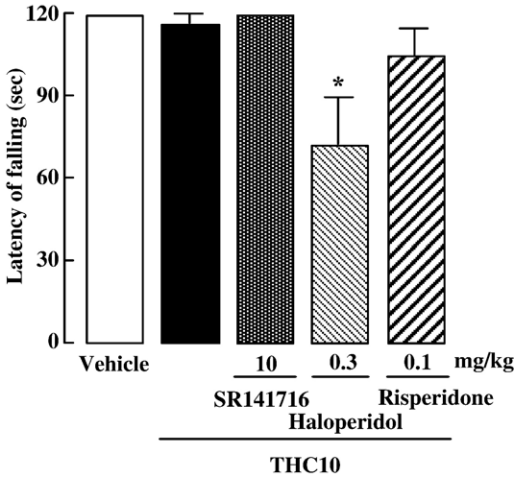

Fig. 6. Effects of SR141716, haloperidol and risperidone on motor coordination in THC-treated mice. THC and SR141716 were injected i.p. 60 min before the test, while haloperidol and risperidone were injected i.p. 30 min before the test. THC 10: THC 10 mg/kg (i.p.). The rotating speed was 5 rpm. Values are expressed as means±S.E.M. (n=8–15). *P<0.05 vs. THC (unpaired t-test).

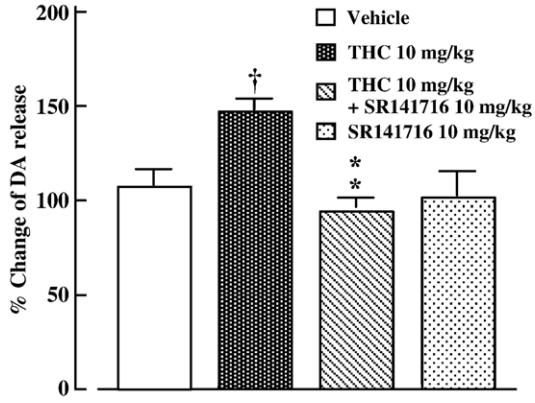

Fig. 7. Effects of THC on DA release in the nucleus accumbens assessed by in vivo microdialysis. THC (10 mg/kg, i.p.) and SR141716 (10 mg/kg, i.p.) were administered immediately after sampling. Values are expressed as percentages (means±S.E.M. of 15–18 animals) of the baseline concentration. †P<0.05 vs. vehicle, **P<0.01 vs. THC (one-way ANOVA followed by the Bonferroni test).

THC (10 mg/kg, i.p.) also had no effect on the motor coordination at 15 rpm (THC: 120.0±0.0 s). SR141716 (10 mg/kg, i.p.) also had no significant effect in THC-treated mice. Haloperidol (0.3 mg/kg, i.p.) significantly decreased the latency of falling compared to THC alone (THC 10 mg/kg+ haloperidol 0.3 mg/kg: P<0.05), whereas risperidone (0.1 mg/kg, i.p.) had no significant effect in THC-treated mice. In addition, SR141716 (10 mg/kg, i.p.), haloperidol (0.3 mg/kg, i.p.) or risperidone (0.1 mg/kg, i.p.) had no significant effect on the motor coordination in non-THC treated mice (SR141716: 110.6± 9.4 s, haloperidol: 90.7±11.9 s, risperidone: 100.2±8.1 s).

3.5. Effects of THC on DA release in the medial prefrontal cortex and nucleus accumbens

THC at a dose of 10 mg/kg, which impaired the PPI, increased DA release in the nucleus accumbens after 60–120 min compared with vehicle [F(3,65)=5.6, P<0.01 by one-way ANOVA, P<0.05 by the Bonferroni test, Fig. 7], but had no significant effect on DA release in the medial prefrontal cortex (vehicle: 97.0±9.2%, THC 10 mg/kg: 111.6±9.9%). Moreover, SR141716 at a dose of 10 mg/kg, which reversed the PPI deficits, reversed the increase in DA release induced by THC in the nucleus accumbens compared with THC alone (P<0.01 by the Bonferroni test), whereas the same dose of SR141716 alone did not cause a significant decrease in DA release.

4. Discussion

In the present study, THC significantly reduced the PPI of the startle reflex. In addition to PPI deficits, THC also decreased the startle reactivity. Therefore, this decrease in the startle reactivity appears to contribute to the PPI deficits. Conversely, THC has been reported to no impair PPI in grouped rats (Malone and Taylor, 2006). Our results are also suggestive that genetic differences might be critical for the incidence of THC-

induced PPI deficits. The present data reveal that THC (10 mg/kg) induced catalepsy, but had no effect on motor coordination in the rota-rod test. We also found that haloperidol (0.3 mg/kg) and risperidone (0.1 mg/kg), which improved the THC-induced PPI deficits, did not reverse this THC-induced catalepsy. Moreover, we previously confirmed that THC (10 mg/kg) had no effect on locomotor activity in the open-field test (Egashira et al., 2004a). Therefore, it is unlikely that the THC-induced PPI deficits are due to catalepsy, disruption of motor coordination and sedation.

We further found that SR141716 reversed the THC-induced PPI deficits and decrease in the startle reactivity. These findings suggest that THC induces these PPI deficits and decrease in the startle response through direct action via CB_1 cannabinoid receptors. This hypothesis is supported by previous findings that the cannabinoid receptor agonist CP 55940 induced a decrease in the startle response and PPI deficits, and that these effects were reversed by SR141716 (Martin et al., 2003). On the other hand, SR141716 had no effect on the positive and negative syndrome in schizophrenic patients (Meltzer et al., 2004). Therefore, the cannabinoid psychosis may be different from schizophrenia.

The results of the present study also revealed that haloperidol and risperidone improved the PPI deficits concomitant with a decrease in the startle response. Thus, antipsychotics are able to improve THC-induced PPI deficits. Similarly, WIN 55,212-2 also impaired the PPI and the effect was reversed by haloperidol (Schneider and Koch, 2002). In humans, cannabis-induced psychosis is responsive to treatment with antipsychotic drugs (Berk et al., 1999). To reverse the PPI deficits, antipsychotics such as haloperidol and risperidone probably interact with the mechanism involved in cannabinoid-associated psychosis. Haloperidol and risperidone are potent dopamine D_2 receptor antagonists, and dopamine D_2 receptors are correlated to the risk of developing schizophrenia and other psychoses (Hirvonen et al., 2005; Seeman et al., 2005). More importantly, cannabinoids enhanced DA release in the nucleus accumbens in rats (Cheer et al., 2004). Swerdlow et al. (1994) reported that PPI was disrupted in rats when DA was infused into the nucleus accumbens and that this effect was blocked by haloperidol. We also found that THC at a dose of 10 mg/kg, which impaired the PPI, increased DA release in the nucleus accumbens. Moreover, these effects were reversed by SR141716 at a dose of 10 mg/kg, which improved the PPI impairment induced by THC. These findings suggest that this THC-induced increase in DA release in the nucleus accumbens is involved in the THC-induced PPI deficits. Therefore, it is possible that these antipsychotics inhibit THC-induced PPI deficits through blockade of dopamine D_2 receptors.

The observation that SR141716 reversed the THC-induced catalepsy is consistent with previous findings (Tseng and Craft, 2004). These findings indicate that THC caused the catalepsy via CB_1 cannabinoid receptors. In contrast, haloperidol (0.3 mg/kg) enhanced the THC-induced catalepsy. Marchese et al. (2003) also reported that haloperidol produced dramatic catalepsy in THC-treated rats. Moreover, haloperidol at the same dose decreased the latency of falling in the rota-rod test compared to THC alone in the present study. Thus, haloperidol (0.3 mg/kg), which improved the THC-induced PPI deficits, impaired the motor function. In addition, haloperidol improved the THC-induced decrease in the startle response and PPI deficits. In contrast, risperidone (0.1 mg/kg) improved the THC-induced PPI deficits without the impairment of motor function and significant alterations of startle response. Risperidone is potent not only as dopamine D_2 receptor antagonists but also have 5-HT_{2A} and 5-HT_7 receptor antagonist properties. Ketanserin, a 5-HT_2 receptor antagonist, and SB-258741, a 5-HT_7 receptor antagonist, have been reported to reverse the PPI deficits induced by an NMDA antagonist (Varty and Higgins, 1995b; Pouzet et al., 2002). Therefore, these differences in the sensitivity on the THC effects may be due to different profile of affinity to 5-HT_{2A}, 5-HT_7 and D_2 receptors, and it is possible that risperidone reverses the THC-induced PPI deficits through a concurrent blockade of D_2, 5-HT_{2A} and 5-HT_7 receptors.

In conclusion, the present study has revealed that THC reduces the level of PPI concomitant with a decrease in the startle response in mice. Antipsychotics such as haloperidol and risperidone, which are potent dopamine D_2 receptor antagonists, and SR141716 can improve these THC-induced PPI deficits. Moreover, THC increased DA release in the nucleus accumbens, and SR141716 reversed this increase in DA release induced by THC. These results suggest that dopaminergic hyperfunction in the nucleus accumbens may be involved in THC-induced PPI deficits.

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