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Delta-9-tetrahydrocannabinol differentially suppresses emesis versus enhanced locomotor activity produced by chemically diverse dopamine D_2/D_3 receptor agonists in the least shrew (*Cryptotis parva*)

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Abstract

The principal psychoactive component of marijuana, delta-9-tetrahydrocannabinol (Δ^9-THC), suppresses nausea and vomiting in cancer patients caused by chemotherapeutics such as cisplatin. Cisplatin induces vomiting via a number of emetic stimuli, including dopamine. Currently, there is controversy as to whether Δ^9-THC can prevent emesis produced by dopaminergic agonists such as apomorphine. The present investigation utilizes the least shrew to evaluate the antiemetic potential and the cannabinoid receptor by which Δ^9-THC may prevent emesis produced by four dopamine receptor agonists with differing selectivity for D_2 and D_3 receptors, i.e., a nonselective dopamine receptor agonist (apomorphine), a D_2-preferring receptor agonist (quinpirole), and two D_3-preferring receptor agonists (quinelorane and 7-OH DPAT). In addition, relative to its antiemetic doses, the motor suppressive doses of Δ^9-THC in dopamine D_2/D_3-receptor-agonist-treated shrews were also evaluated. Thus, different groups of shrews were injected with either vehicle (V) or varying doses of Δ^9-THC [0.5, 1, 2.5, 5, or 10 mg/kg, intraperitoneal (i.p.)] 10 min prior to administration of a 2 mg/kg dose of one of the four cited D_2/D_3 agonists. Immediately after the last injection, the frequency of vomiting for each shrew was recorded for the next 30 min. To investigate which cannabinoid receptor is involved in the antiemetic action of Δ^9-THC, various doses of the CB_1 receptor antagonist SR 141716A [0, 5, 10, and 20 mg/kg, subcutaneous (s.c.)] were administered to shrews 10 min prior to an injection of a fully effective antiemetic dose of Δ^9-THC (5 mg/kg, i.p.). Ten minutes later, each treated shrew was administered with a 2 mg/kg dose of apomorphine. The emesis frequency was recorded for the next 30 min. For locomotor studies, different groups of shrews received either vehicle or various doses of Δ^9-THC (0, 5, 10, 20, or 30 mg/kg) 10 min prior to an injection of vehicle or a 2 mg/kg dose of one of the four D_2/D_3 receptor agonists. The triad of motor behaviors (spontaneous locomotor activity, total duration of movement, and rearing frequency) were recorded for the next 30 min by a computerized video tracking system. Δ^9-THC dose-dependently attenuated the frequency of emesis as well as fully protecting shrews from vomiting produced by each one of the four cited dopamine D_2/D_3 receptor agonists with ID_{50s} ranging from 1 to 4 mg/kg. SR 141716A reversed the antiemetic activity of Δ^9-THC against apomorphine-induced emesis. Δ^9-THC also differentially suppressed the triad of motor activities in dopamine D_2/D_3-receptor-agonist-treated shrews with ID_{50s} ranging from 7 to 21 mg/kg. The results suggest that Δ^9-THC prevents emesis via cannabinoid CB_1 receptors in a potent and dose-dependent manner in D_2/D_3-receptor-agonist-treated shrews at doses well below those which cause significant motor depression.

Keywords: Δ^9-THC; Apomorphine; Quinpirole; Quinelorane; 7-OH DPAT; Emesis; Antiemetic; Dopamine D_2/D_3 receptors; Locomotor activity; Least shrew

1. Introduction

Significant clinical evidence indicate that the most active psychotropic component of marijuana plant, delta-9-tetrahydrocannabinol (Δ^9-THC), prevents emesis in

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cancer patients produced by chemotherapeutic agents such as cisplatin (Darmani, 2002; Tramér et al., 2001). Δ^9-THC and synthetic cannabinoids (e.g., CP 55, 940, and WIN 55, 212-2) produce cannabimimetic effects via cannabinoid CB_1 and CB_2 receptors, both of which belong to the G-protein-coupled receptor superfamily (Pertwee, 1999; Howlett et al., 2002). Cannabinoid CB_1 receptors are primarily located in the CNS and at lower density in peripheral tissues, whereas CB_2 receptors are mainly restricted to the periphery. Basic studies in different vomiting species have clearly shown that the cited cannabinoids prevent cisplatin-induced emesis via cannabinoid CB_1 receptors (Darmani, 2001a,b; Darmani et al., 2003; Kwiatkowska et al., 2004; Van Sickle et al., 2003). Cisplatin is one of the most potent emetogenic agents and seems to produce emesis in a nonspecific manner via the release of a number of emetic: (1) neurotransmitters, including serotonin, substance P, and dopamine (Saito et al., 2003; Veyrat-Follet et al., 1997; Kasabdji et al., 1996) and (2) mediators such as prostaglandins (Goto et al., 1998).

Dopamine receptor antagonists are clinically used for the control of nausea and vomiting (Mitchelson, 1992). Dopamine receptors are classified into two main branches, the D_1 family (comprising the D_1 and D_5 subtypes) and the D_2 family (consisting of the D_2, D_3, and D_4 subtypes) (Levant, 1997). Although the exact role of the different subtypes of dopamine receptors in the mediation of emesis is not fully understood, it is generally well accepted that dopaminergic agonists induce emesis via the stimulation of dopamine D_2 receptors in the chemoreceptor trigger zone located in the area postrema outside the CNS (Andrews et al., 1990; King, 1990). More recent studies also indicate a role for dopamine D_3 receptors in the area postrema for the production of vomiting (Darmani et al., 1999; Yoshida et al., 1995; Yoshikawa et al., 1996). On the other hand, central dopamine D_2 and D_3 receptors, respectively, located on neurons of the mesoaccumbens projection and vestibulocerebellum are implicated in the control of enhanced locomotor activity (Essman et al., 1993; Levant, 1997). Cannabinoid CB_1 receptor agonists elicit a number of behavioral responses that include reduced movement, catalepsy, hypothermia, and analgesia (Martin et al., 1995). Evidence is mounting in support of functional interactions between the cannabinoid CB_1 receptor and dopaminergic system in the mediation of some of these behaviors. For example: (1) Δ^9-THC and endocannabinoids, as well as potent synthetic cannabinoid CB_1 receptor agonists, attenuate motor hyperactivity and stereotypical behaviors induced by indirect- or direct-acting selective and nonselective dopamine D_2 receptor agonists (Beltramo et al., 2000; Gorriti et al., 1999; Maneuf et al., 1997; Pryor et al., 1978); (2) injection of D_2 agonists into the basal ganglia nuclei opposes motor effects produced by CB_1 receptor agonists (Sañudo-Peña et al., 1996; Sañudo-Peña and Walker, 1998); (3) dopamine D_2 receptor agonists reverse, while D_2 antagonists potentiate, the cataleptic effects of cannabinoids (Anderson et al., 1996; Moss et al., 1981; Meschler et al., 2000); and (4) dopamine D_2-preferring agonists (quinpirole and bromocriptine) potentiate the hypothermic and antinociceptive effects of Δ^9-THC, while selective D_2 antagonists (sulpride and raclopride) prevent the induced CB_1-receptor-mediated effects (Nava et al., 2000).

These interactions between cannabinoid CB_1 and dopamine D_2 receptor systems suggest that cannabinoids may modulate the emetic activity of dopamine D_2/D_3 receptor agonists. However, the scant available data appear to be equivocal since Δ^9-THC and its synthetic analog nabilone seem to lack antiemetic activity against apomorphine-induced emesis in the dog (Shannon et al., 1978; Stark, 1982), while both cannabinoids prevent the induced emesis in the cat (London et al., 1979; McCarthy et al., 1984). The initial aim of the present study was to investigate the antiemetic dose–response potential of Δ^9-THC against a number of structurally diverse dopamine D_2/D_3 receptor agonists in the least shrew (*Cryptotis parva*) since no truly selective D_2 or D_3 agonist is commercially available. Thus, the following dopaminergic emetic agents that enhance locomotor activity (Darmani et al., 1999; Levant, 1997) were utilized: (i) apomorphine (a nonselective dopamine agonist), (ii) quinpirole (a D_2-preferring agonist), and (iii) quinelorane and 7-OH DPAT (two D_3-preferring agonists). The second goal was to determine whether the antiemetic effect of Δ^9-THC is CB_1-receptor-mediated. While some clinical findings suggest that Δ^9-THC prevents chemotherapy-induced emesis at sedative doses (Review: Darmani, 2002), we have previously shown that Δ^9-THC's motor suppressive activity in naive shrews occur at relatively larger doses than its antiemetic activity (Darmani, 2001a). Thus, our final aim was to ascertain whether the observed differential antiemetic and motor suppressive activities of Δ^9-THC in drug-naive shrews persist in dopamine D_2/D_3-receptor-stimulated shrews.

2. Materials and methods

2.1. Animals and apparatus

The subjects were least shrews (*C. parva*) which were bred and maintained in the animal facilities of the Kirksville College of Osteopathic Medicine. Both male and female shrews (4–5 g, 35–50-days old) were used throughout the study. The animals were kept (3–5 per cage) on a 14:10 h light–dark cycle at a room temperature of 21 ± 1 °C in open-top clear polycarbonate cages ($20 \times 18 \times 21$ cm) lined with heated dry loam soil and wood chippings. A wooden nest box ($5.5 \times 5.5 \times 9$ cm) containing dry grass, a food bowl, and a lick tube water bottle were placed in each cage. Shrews were fed twice daily. In the morning, 5–6 mealworms

(Tenebrio sp) were given per animal, and, in the evening, each shrew was offered a 6-g mixture consisting of two-thirds dry cat food (PMI Nutrition Cat Formula) and one-third canned cat food (Kozy Kitten) in sufficient water to give the mixture a paste-like consistency. All animals received care according to the "Guide for the Care and Use of Laboratory Animals," DHSS Publication (revised, 1985). The American Association of Accreditation of Laboratory Care has certified the KCOM Animal Facilities, and the Institutional Animal Care and Use Committee of KCOM has approved these studies.

The frequency of vomiting for each shrew was recorded by a trained observer using a multiple tally counter. For the study of motor behaviors, three parameters of locomotion [spontaneous locomotor activity (total distance moved in meters in the plane of observation), total duration of movement in seconds (the total time recorded for any type of movement), and frequency of rearing] were measured using a computerized video tracking, motion analysis, and behavior recognition system, Ethovision (Version 2.3, Noldus Information Technology, Costerweg, Netherlands). A rearing event was recorded as a 20% decrease in surface area when a shrew stands upright, as seen by the overhead video camera (Darmani et al., 2003).

2.2. Drugs

The following drugs were purchased from Sigma/RB1, St. Louis, MO: R (−) apomorphine HCl, (+)-2-dipropylamino-7-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide *R*(+)-7-hydroxy-DPAT HBr, quinelorane 2HCl, (−) quinpirole 2HCl, and delta-9-tetrahydrocannabinol (Δ^9-THC). Δ^9-THC was initially dissolved to twice the stated concentration in a 1:1:18 solution of ethanol/emulphor/0.9% saline and then further diluted by the addition of an equal volume of saline. All other drugs were dissolved in distilled water. Drugs were administered at a volume of 0.1 ml/10 g body weight.

2.3. Experimental protocols

2.3.1. Emesis studies

The present protocols were based on our previous dopamine-related emesis studies (Darmani et al., 1999) as well as our preliminary results. To determine the antiemetic potential of Δ^9-THC against D_2/D_3 receptor agonists, a nonselective (apomorphine), a D_2-preferring (quinpirole), and two D_3-preferring (quinelorane and 7-OH DPAT) agonists were utilized to induce emesis. A 2-mg/kg intraperitoneal (i.p.) dose of each compound produce their maximal emetic response in the least shrew (Darmani et al., 1999) and was chosen to induce emesis in the present study. On the test day, the animals were transferred to the experimental room and were allowed to acclimate for at least 1 h prior to experimentation. The laboratory fume hood was turned on to produce a constant white noise during the experimental procedures. To habituate the shrews to the test environment, each animal was randomly selected and transferred to a 20×18×21-cm empty clean clear plastic holding cage and was offered four meal worms 30 min prior to experimentation. Then, large groups of shrews were injected with either vehicle (V) (i.p.) or varying doses of Δ^9-THC (0.5, 1, 2.5, 5, or 10 mg/kg, i.p., n=7–10 per treatment for each dopamine agonist). Ten minutes later, different groups of both vehicle- and Δ^9-THC-treated shrews received a 2-mg/kg i.p. dose of either apomorphine, quinpirole, quinelorane, or 7-OH DPAT. Immediately after the dopamine D_2/D_3 agonist injection, each shrew was placed in the observation cage, and the frequency of vomiting (mean±S.E.M.) was recorded for individual shrews for the next 30 min.

To demonstrate whether the antiemetic effect of Δ^9-THC is a cannabinoid CB_1-receptor-mediated event, nonemetic subcutaneous (s.c.) doses of the selective CB_1 receptor antagonist SR 141716A (0, 5, 10, and 20 mg/kg, n=8–10 per group) were used to reverse the antiemetic capacity of a fully effective dose of Δ^9-THC (5 mg/kg, i.p.) against apomorphine (2 mg/kg, i.p.)-induced emesis. Thus, at 0 time, different groups of shrews were injected subcutaneously with the cited doses of SR 141716A and were then offered four meal worms. Ten minutes later, each shrew received Δ^9-THC (5 mg/kg, i.p.). After another 10 min, each animal was injected with a 2 mg/kg dose of apomorphine, and the frequency of induced emesis was recorded for the next 30 min, as described previously.

2.3.2. Locomotor studies

On the test day, shrews were brought in their home cages from animal quarters and were allowed for at least 1 h to a semidark environment. The reduced light condition was necessary for the computerized Ethovision System to work efficiently. The parameters of Ethovision were set to record three motor activities: (1) total distance moved,(2) total duration of movement, and (3) rearing behavior. To determine motor suppressive effects of Δ^9-THC against increased motion parameters produced by dopamine D_2/D_3 agonists, each shrew was further acclimated in an empty white plastic dummy observation cage (28×28×24 cm) for 1 h prior to testing. Then, different groups of shrews were injected with either vehicle (i.p.) or varying doses of Δ^9-THC (5, 10, 20, or 30 mg/kg, i.p., n=7–12 per group for each dopamine agonist). Ten minutes later, each treated shrew received a 2 mg/kg dose of either apomorphine or one of the other cited dopamine D_2/D_3 agonists. Each shrew was then individually placed in an observation cage of the same dimension, and the discussed triad of motor parameters were recorded for 30 min immediately following the dopamine agonist injection. A further control group (n=8) comprising varying doses of Δ^9-THC (0, 5, 10, 20, and 30 mg/kg) and the vehicle of dopamine agonists were also tested. The motor suppressive dose–response effects of Δ^9-THC in drug-naive shrews has already been published (Darmani, 2001a).

2.4. Data analysis

The frequency of emesis data were analyzed by the Kruskal–Wallis (KW) nonparametric one-way analysis of variance (ANOVA) and post hoc analysis by Dunn's multiple comparisons test. A P value of 0.05 was necessary to achieve statistical significance. The incidence of emesis (number of animals vomiting) was analyzed by the Fisher's Exact Test to determine whether there were differences between groups. When appropriate, pairwise comparisons were also made by this method. Two-factor analyses of variance of total distance moved and total duration of movement for different Δ^9-THC doses (0, 5, 10, and 20 mg/kg) and four different D_2/D_3 receptor agonists (0 and 2 mg/kg) were performed separately, which were followed by post hoc analysis via Chi-square tests of the regression parameters. For the rearing behavior, a two-factor analysis of the frequency of rearing for Δ^9-THC doses (0, 5, 10, and 20 mg/kg) and different D_2/D_3 receptor agonists (0 and 2 mg/kg) was performed using Poisson regression followed by post hoc analysis by Chi-square tests of the regression parameters. Since, in both the apomorphine- and the D_2/D_3-vehicle-treated shrew groups, a 30 mg/kg Δ^9-THC was also included (e.g., 0, 5, 10, 20, and 30 mg/kg), the discussed statistical procedures were repeated for these two treatment groups for the analysis of the discussed three parameters of locomotor activities. The ID_{50} values for the reduction of both emesis (the inhibitory dose that reduced emesis frequency by 50% or the inhibitory dose that prevented emesis in 50% of shrews) and locomotor parameters were calculated by the use of a computerized program (GraphPad InPlot, San Diego, CA). Two-tailed unpaired t test was used to compare individual ID_{50s} for (i) different drugs for a given emetic or motor behavior and (ii) a given drug for different emetic and motor behaviors.

3. Results

The 2 mg/kg dose of the four dopamine D_2/D_3 receptor agonists produced robust frequencies of vomiting (Fig. 1A) in a manner similar to our previously published dose–response studies (Darmani et al., 1999). The Kruskal–Wallis nonparametric ANOVA test showed that Δ^9-THC significantly reduced the frequency of emesis produced by (1) apomorphine (KW 4, 37=21.94, P<0.0002), (2) quinpirole (KW 4, 35=19, P<0.0008), (3) quinelorane (KW 3, 32=25.16, P<0.0001), and (4) 7-OH DPAT (KW 3, 28=13.8, P<0.003) (Fig. 1A). Dunn's multiple comparison post hoc test revealed that Δ^9-THC reduces the frequency of emesis produced by the cited dopamine D_2/D_3 receptor agonists in a dose-dependent manner, with ID_{50} ranging between 1±1.5 to 1.7±1.3 mg/kg (Fig. 1A and Table 1). In addition, the Fisher's Exact Test showed that Δ^9-THC also protected shrews from vomiting (Fig. 1B) in response to (1) apomorphine (χ^2=20.89, P<0.0001; ID_{50}=1.81±1.1 mg/kg), (2) quinpirole (χ^2=14.8, P<0.003; ID_{50}=3.1±1 mg/kg),

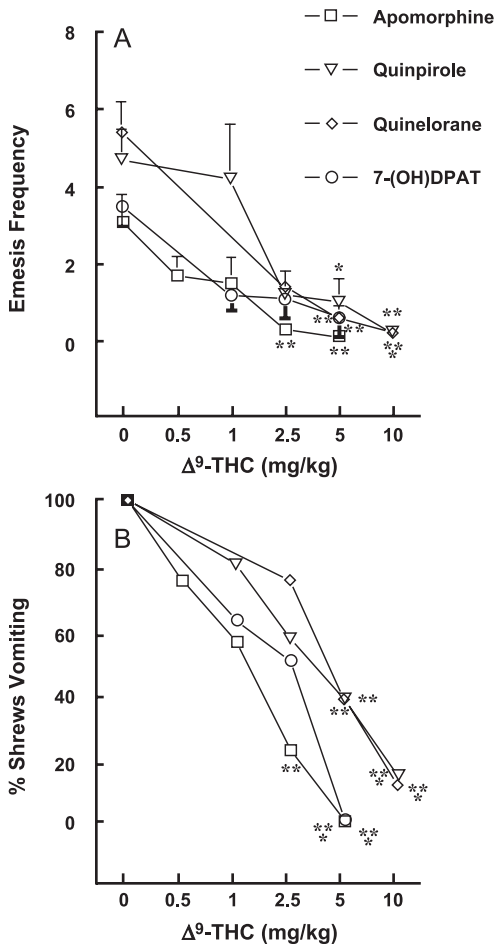


Fig. 1. The antiemetic effects of the cited doses of Δ^9-THC against emesis produced by a 2 mg/kg dose of either a nonselective (apomorphine)-, a D_2 (quinpirole)-, or two D_3 (quinelorane and 7 (OH) DPAT)-dopamine-receptor-preferring agonists. Graph A depicts attenuation in the frequency (mean±S.E.M.) of induced vomiting, whereas graph B shows reductions in the percentage of shrews vomiting in response to different D_2/D_3 agonists. At 0 time, different groups of shrews were treated with either vehicle (n=8–10 mg/kg for each D_2/D_3 agonists) or Δ^9-THC [0.5 (n=8), 1 (n=7–9), 2.5 (n=8–9), 5 (n=8–9), and 10 (n=9) mg/kg for each D_2/D_3 agonists]. Ten minutes later, different groups of both vehicle- and Δ^9-THC-treated shrews received a 2 mg/kg dose of one of the D_2/D_3 agonists. The frequency of emesis was recorded for each shrew for the next 30 min. Significantly different from corresponding Δ^9-THC-vehicle-treated controls at P<0.05 (*), P<0.01 (**), and P<0.001 (***).

(3) quinelorane (χ^2=17.6, P<0.002; ID_{50} 4±1 mg/kg), and (4) 7-OH DPAT (χ^2=12.7, P<0.005; ID_{50}=1.8±1.3 mg/kg). Furthermore, post hoc analysis showed that Δ^9-THC caused significant reductions in the number of shrews vomiting in response to dopamine D_2/D_3 receptor agonists in a dose-dependent manner.

Fig. 2 shows the ability of subcutaneously administered SR 141716A (a cannabinoid CB_1 antagonist) to reverse the antiemetic action of a fully effective dose of Δ^9-THC (5 mg/kg) against apomorphine (2 mg/kg)-induced emesis. The Kruskal–Wallis ANOVA test indicated that SR 141716A (5, 10, and 20 mg/kg) caused a significant reversal in the ability of Δ^9-THC to reduce the frequency

Table 1
Comparative calculated ID_{50} (mg/kg) values for Δ^9-THC in the least shrew for suppressing the frequency of emesis as well as motor behaviors in shrews treated with a 2 mg/kg dose of the cited dopamine D_2/D_3 receptor agonists

Dopamine D_2/D_3 agonists	Vomit	Locomotor Parameters		
	Frequency	TDM	TDOM	Rearing
Apomorphine	1.0±1.5	20.3±1.4[a]	21.3±2.4[a]	BP
Quinpirole	1.7±1.3	15.6±1.3[a,b]	15.9±2[a]	BP
Quinelrane	1.3±1.4	6.7±1[a,b,c]	11.7±1.7[a,b]	BP
7-OH DPAT	1.5±1.1	11.0±1.5[a,b,c,d]	6.7±1[a,b,c,d]	BP

TDM—total distance moved, TDOM—total duration of movement, BP—robust biphasic effect. For ID_{50} calculation and statistical details, see text.
[a] $P<0.05$ relative to corresponding ID_{50} for vomit frequency.
[b] $P<0.05$ relative to ID_{50} for apomorphine.
[c] $P<0.05$ relative to ID_{50} for quinpirole.
[d] $P<0.05$ relative to ID_{50} for quinelorane.

of apomorphine-induced emesis (KW 3, 31=7.94, $P<0.05$). However, Dunn's multiple comparison post hoc test failed to show a significant dose effect probably due to large intergroup variations (Fig. 2A). On the other hand, the Fisher's Exact Test showed both an overall significance ($\chi^2=8.79$, $P<0.03$) and a significant dose effect (at the 20 mg/kg SR 141716A dose) to reverse the protective effect of Δ^9-THC (Fig. 2B).

3.1. Locomotor studies

Two-factor analyses of variance resulted in highly significant differences between Δ^9-THC doses (0, 5, 10, and 20 mg/kg) {[$\chi^2(3)=28.4$, $P<0.0001$] and [$\chi^2(3)=21.4$, $P<0.001$]} and among the D_2/D_3 receptor agonists and their corresponding vehicle {[$\chi^2(4)=10.7$, $P<0.0001$] and [$\chi^2(4)=3$, $P<0.02$]} for the locomotor factors total distance moved and total duration of movement, respectively. There were also significant interactions between Δ^9-THC doses and D_2/D_3 receptor agonists for the respective cited motor factors {[$\chi^2(12)=5.4$, $P<0.0001$] and [$\chi^2(12)=2.2$, $P<0.01$]}. Since the vehicle- and apomorphine-treated groups also contained a 30-mg/kg Δ^9-THC subgroup, a two-factor analysis of variance of these subgroups was also performed, and the results exhibited similar significant overall differences.

Post hoc Chi-square tests revealed that, relative to corresponding vehicle (Δ^9-THC vehicle+D_2/D_3 receptor agonist vehicle)-treated controls, the 2 mg/kg dose of apomorphine, quinpirole, and quinelorane significantly increased spontaneous locomotor activity (i.e., total distance moved) by 37% ($P<0.05$), 67% ($P<0.001$), and 80% ($P<0.001$), respectively (Fig. 3A). However, the more D_3-receptor-preferring agonist, 7-OH DPAT, caused no significant effect. Δ^9-THC (5, 10, 20, and 30 mg/kg) altered spontaneous locomotor activity in vehicle-treated control group in a biphasic-like manner, and a significant change (51% reduction, $P<0.01$) was only observed at its 30 mg/kg dose (ID_{50}=30±5 mg/kg) (Fig. 3A). Δ^9-THC also reduced the apomorphine-induced increase in locomotor activity (39% at 10 mg/kg, $P<0.01$ and 99% at 30 mg/kg, $P<0.001$), with an ID_{50} of 20.3±2.4 mg/kg (Fig. 3A; Table 1). In addition, Δ^9-THC (5, 10 and 20 mg/kg) attenuated spontaneous locomotor activity in quinpirole (ID_{50}=15.6±1.3 mg/kg)-, quinelorane (ID_{50}=6.7±1 mg/kg)-, and 7-OH DPAT (ID_{50}=11±1.5 mg/kg)-treated shrews (Fig. 3A). Although the 10 mg/kg dose of Δ^9-THC only significantly attenuated (62%, $P<0.001$) spontaneous locomotor activity in quinelorane-treated shrews, its 20 mg/kg dose significantly reduced this motor parameter in quinpirole (90% decrease, $P<0.001$)-, quinelorane (78% decrease, $P<0.001$)-, and 7-OH DPAT (61% decrease, $P<0.05$)-treated shrews.

Relative to vehicle-treated controls, none of the D_2/D_3 receptor agonists significantly affected the total duration of movement (Fig. 3B). Δ^9-THC pretreatment significantly and dose-dependently reduced the total duration of movement in shrews treated with (1) dopamine D_2/D_3 receptor agonist

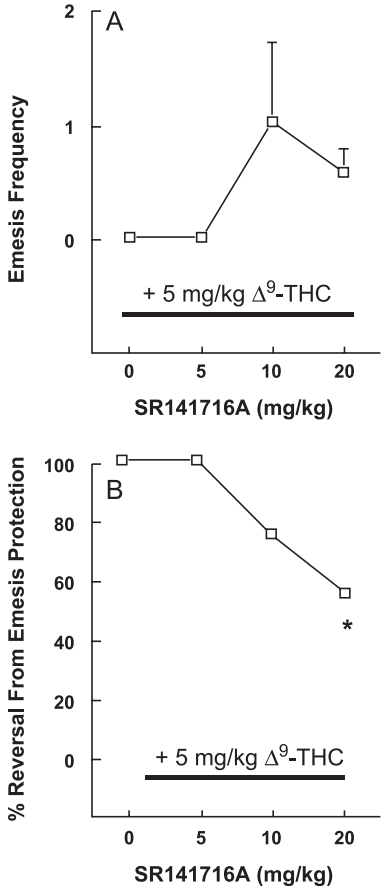
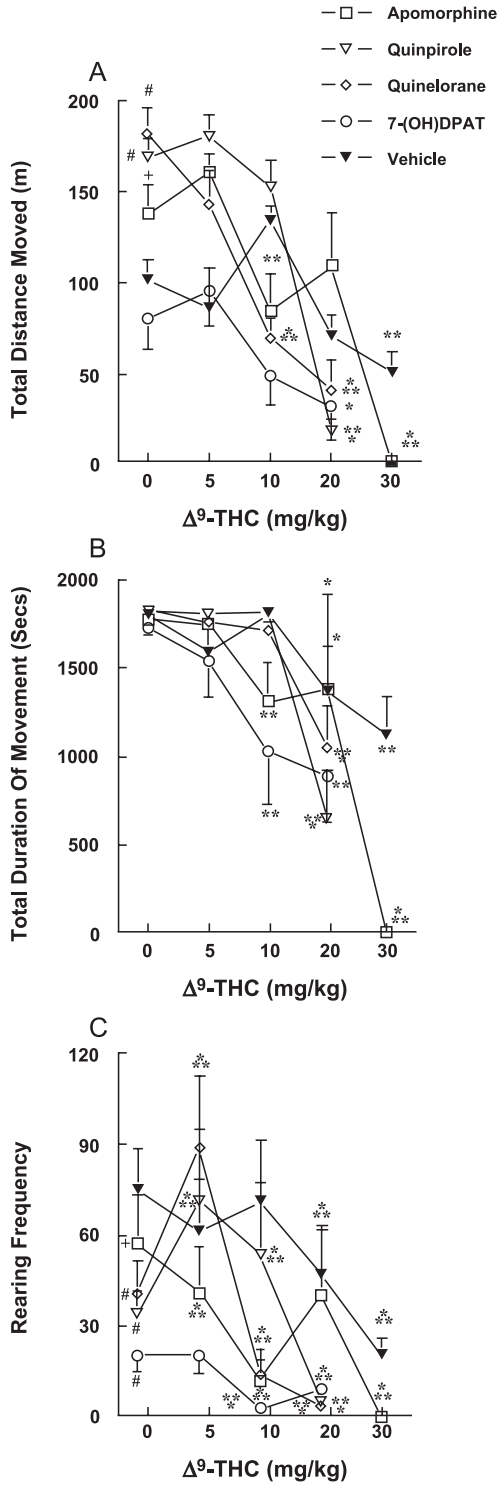


Fig. 2. The ability of different subcutaneous doses of the CB_1 receptor selective antagonist SR 141716A (0, 5, 10, and 20 mg/kg) to reverse the antiemetic effects of a fully effective dose of Δ^9-THC (5 mg/kg, i.p.) to protect shrews from apomorphine (2 mg/kg, i.p.)-induced emesis. SR 141716A reversed Δ^9-THC-reduction in the emesis frequency (graph A) as well as blocking the ability of Δ^9-THC to protect shrews from vomiting caused by apomorphine. At 0 time, shrews received either vehicle (s.c.) or the cited doses of SR 141716A (s.c.), at 10 min, an injection of Δ^9-THC (5 mg/kg, i.p.), and, at 20 min, a 2 mg/kg dose of apomorphine. Emesis parameters were recorded for 30 min following the last injection. *Significantly different from vehicle control at $P<0.05$.

vehicle [24% (P<0.05) and 38% (P<0.01) reductions at 20 and 30 mg/kg, respectively, ID_{50}=37.5±1 mg/kg], (2) apomorphine [26% (P<0.01), 22% (P<0.05), and 99% (P<0.001) reductions at 10, 20, and 30 mg/kg, respectively, ID_{50}=21.3±2.4 mg/kg), (3) quinpirole [64% (P<0.001) reduction at 20 mg/kg, ID_{50}=15.9±2 mg/kg], and (4) 7-OH DPAT [40% (P<0.01) and 49% (P<0.01) reduction at 10 and 20 mg/kg doses, respectively, ID_{50}=6.7±1 mg/kg].



Poisson regression of rearing frequency for two-factor analysis of Δ^9-THC doses (0, 5, 10, and 20 mg/kg) and D_2/D_3 receptor agonists and their vehicle resulted in highly significant differences between Δ^9-THC [$\chi^2(3)$=714, P<0.0001] and D_2/D_3 receptor agonists [$\chi^2(4)$=1074, P<0.0001] (Fig. 3C). There was also significant interaction between Δ^9-THC and D_2/D_3 receptor agonist treatments [$\chi^2(12)$=903.9, P<0.0001]. Because the vehicle- and apomorphine-treated groups also contained a 30-mg/kg Δ^9-THC subgroup, a two-factor analysis of these subgroups was also performed, and the results exhibited similar overall differences. Post hoc Chi-square tests showed that a 2 mg/kg dose of apomorphine, quinpirole, quinelorane, and 7-OH DPAT significantly reduced [23.3% (P<0.05), 46.2% (P<0.001), 54.3% (P<0.001), and 78.5% (P<0.001) reduction, respectively] the rearing frequency relative to that observed for the vehicle-treated control group (Fig. 3C). In general, the cited doses of Δ^9-THC caused moderate to severe biphasic effects (i.e., significant increases and decreases) in rearing frequency in both vehicle- and D_2/D_3-receptor-agonist-treated shrews, as shown in Fig. 3C.

4. Discussion

The most important finding of the present study is that, depending upon the dopamine D_2/D_3 receptor agonist used to induce emesis, 2.5 to 10 mg/kg doses of Δ^9-THC potently and dose-dependently attenuate the frequency of emesis and fully protect shrews from vomiting caused by structurally diverse nonselective (apomorphine) and dopamine D_2 (quinpirole)- and D_3 (quinelorane and 7-OH DPAT)-receptor-preferring agonists. These findings appear to resolve the current controversy as to whether (London et al., 1979; McCarthy et al., 1984) or not (Shannon et al., 1978; Stark, 1982) cannabinoids can prevent emesis produced by direct acting dopaminergic agonists such as apomorphine. The inability of both Δ^9-THC and its analog nabilone to protect dogs from apomorphine-induced emesis (Shannon et al., 1978; Stark, 1982) while protecting both cats (London et al., 1979; McCarthy et al., 1984) and shrews (present study) suggests species differences in the antiemetic efficacy of cannabinoids. Indeed, nabilone has also been shown to lack

Fig. 3. The dose–response effects of Δ^9-THC on the triad of motor behaviors in least shrews treated either with vehicle or a 2 mg/kg dose of the cited dopamine D_2/D_3 receptor agonists. At 0 time, shrews received i.p. either vehicle (n=10) or varying doses of Δ^9-THC [5 (n=8), 10 (n=8), and 20 (n=9) mg/kg per group]. Ten minutes later, different groups of treated shrews received either an i.p. injection of one of the D_2/D_3 receptor agonists or their vehicle. The cited motor behaviors were recorded for 30 min following the last injection by a computerized video tracking, motion analysis, and behavior recognition system (Ethovision). Significantly different from corresponding 0 mg/kg Δ^9-THC group in corresponding D_2/D_3-agonist-treated shrews at P<0.05 (*), P<0.01 (**), and P<0.001(***). Significant differences between vehicle+vehicle control group and vehicle-treated control shrews that had received a 2 mg/kg dose of one of the cited D_2/D_3 agonists at P<0.05 (+) and P<0.01 (#).

significant antiemetic activity against cisplatin-induced emesis in the dog (Gylys et al., 1979). In addition, at doses greater than 0.5 mg/kg, Δ^9-THC by itself produces profound emesis in the dog (Shannon et al., 1978; Lowe, 1946).

A number of studies have suggested that the antiemetic activity of Δ^9-THC and synthetic cannabinoids is mediated via cannabinoid CB_1 receptors since selective CB_1 receptor antagonists (e.g., SR 141716A or AM 251) reverse their antiemetic activity against cisplatin- or morphine-induced emesis in several animal models of emesis (Darmani, 2001a,b; Darmani et al., 2003; Van Sickle et al., 2001, 2003). Moreover, SR 141716A by itself produces emesis at large doses (>10 mg/kg, i.p. or >40 mg/kg, s.c.) in the least shrew, which Δ^9-THC and synthetic cannabinoids completely prevent (Darmani, 2001a). In the present study, SR 141716A also appeared to reverse the protective capacity of Δ^9-THC against apomorphine-induced emesis. However, in our previous studies against cisplatin-induced emesis, a 10 mg/kg s.c. dose of SR 141716A was required to significantly but partially reverse the antiemetic effects of a 5 mg/kg dose of Δ^9-THC against both emesis protection and reduction in the frequency of emesis, whereas, in the present study, a larger dose of SR 141716A (20 mg/kg, s.c.) was needed to produce a significant partial reversal in the protective capacity of Δ^9-THC against apomorphine-induced emesis. The main reason for large doses of SR 141716A needed to reverse the antiemetic effect of Δ^9-THC is that the antagonist was administered subcutaneously (s.c.) in both studies. Being a highly lipid soluble agent, it is expected to be absorbed into general circulation slowly from the s.c. route. Another mechanism that may explain the inability of SR 141716A to fully reverse the antiemetic activity of Δ^9-THC against both indirect (cisplatin) and direct (apomorphine) dopaminergic emetic stimuli is probably that activation of dopamine D_2 receptors leads to the production and release of the antiemetic endocannabinoid, anandamide (Giuffrida et al., 1999). The concomitant presence of both Δ^9-THC and enhanced levels of endogenous anandamide may provide insurmountable antiemetic capacity. In addition, anandamide is also an endovanilloid, and vanilloid VR1 agonists rapidly desensitize these receptors, which leads to broad spectrum antiemetic action (Andrews et al., 2000).

Since some clinical studies have suggested that the antiemetic action of Δ^9-THC can be due to sedation (Review: Darmani, 2002) and the major effects of cannabinoids are hypoactivity and catalepsy in animals (Review: Martin et al., 1995), we also investigated the relative motor suppressive effects of Δ^9-THC pretreatment in both vehicle (control)- and dopamine D_2/D_3-receptor-agonist-injected shrews. A 2 mg/kg dose of the four tested D_2/D_3 receptor agonists were chosen to determine their direct motor effects in drug-naive shrews because, at this dose, their maximal emetic effects occur (Darmani et al., 1999). Administration of D_2/D_3 receptor agonists in rodents produce biphasic U-shaped locomotor activity effects (Levant, 1997). More recent evidence in dopamine D_2 and D_3 receptors knockout mice suggest that, at low doses (<0.1 mg/kg), D_2/D_3 receptor agonists suppress spontaneous locomotor activity via presynaptic D_2 autoreceptors, whereas larger doses of such agents increase motor activity via postsynaptic D_2 receptors (Boulay et al., 1999; Pritchard et al., 2003; Xu et al., 1997). Although a 2 mg/kg dose of the more D_3-receptor-preferring agonist, 7-OH DPAT, failed to alter spontaneous locomotor activity in vehicle-pretreated shrews, other tested D_2/D_3 receptor agonists (apomorphine, quinpirole, and quinelorane) significantly potentiated the behavior in these animals. However, all of these dopamine D_2/D_3 receptor agonists significantly but differentially attenuated the basal rearing frequency. On the other hand, none of the D_2/D_3 agonists altered the total duration of movement which consisted of total time spent for tremor, side to side, up and down, as well as spontaneous locomotor activity movements. Unlike the observed differential effects of dopamine D_2/D_3 receptor agonists on the discussed triad of motor behaviors, all of these ligands produced robust frequencies of emesis in this insectivorous vomiting species. The present findings along with the previously published agonist/antagonist studies (see Introduction) provide further evidence that stimulation of both dopamine D_2 and D_3 receptors probably contribute to the production of emesis.

Similar to our published study in drug-naive shrews (Darmani, 2001a), Δ^9-THC (5–30 mg/kg) pretreatment in the present study altered spontaneous locomotor activity in shrews that subsequently had received a vehicle (V) injection (see the Δ^9-THC-V dose–response control line in Fig. 3A) in a biphasic-like manner, and a significant reduction (ID_{50}=30±5 mg/kg) was observed only at its highest tested dose. Relative to the attained Δ^9-THC-V dose–response control line, Δ^9-THC pretreatment more potently suppressed spontaneous locomotor activity in shrews that subsequently received a 2 mg/kg dose of either apomorphine, quinpirole, quinelorane, or 7-OH DPAT (ID_{50}=6.7 to 20.3 mg/kg). Indeed, significant reductions were apparent from 10 mg/kg Δ^9-THC dose in apomorphine- and quinelorane-treated shrews, while quinpirole- and 7-OH-DPAT-injected animals exhibited significance from 20 mg/kg Δ^9-THC. Moreover, although none of the tested dopamine D_2/D_3 receptor agonists by themselves altered the duration of movement in shrews, Δ^9-THC also more significantly attenuated this motor parameter in D_2/D_3-agonist-treated shrews (ID_{50s}=6.7 to 21.3 mg/kg) relative to the attained Δ^9-THC-V dose–response control line (ID_{50}= 37.5±1 mg/kg). Likewise, although all of the tested dopamine D_2/D_3 receptor agonists significantly but differentially attenuated the basal rearing frequency in shrews, Δ^9-THC treatment also more potently reduced the rearing frequency in these D_2/D_3-receptor-stimulated animals compared to the Δ^9-THC-V dose–response control line. Thus, irrespective of the direct effect of dopamine D_2/D_3 receptor agonists on the triad of motor activities, it appears that Δ^9-THC more effectively reduces the discussed motor behaviors in dopamine D_2/D_3-receptor-stimulated animals relative

to both naive (Darmani, 2001a) and vehicle-exposed (current control) shrews because (1) the relative inhibitory dose–response motor effect of Δ^9-THC shifted to the left in dopamine D_2/D_3-agonist-exposed shrews and (2) the Δ^9-THC ID_{50} values are lower in the D_2/D_3-agonist-exposed shrews relative to both the current control group or in drug-naive shrews (Darmani, 2001a). Simultaneous activation of dopamine D_2 receptors by direct acting agonists such as quinpirole and CQP 201–403 has also been shown to enhance the hypothermic and motor suppressive effects of Δ^9-THC in rodents (Ferrari et al., 1999; Nava et al., 2000).

The motor suppressive effects of Δ^9-THC appear to be mediated via cannabinoid CB_1 receptors since SR 141716A has been shown to dose-dependently reverse Δ^9-THC's motor depressive effects in both shrews (Darmani, 2001a) and rodents (Compton et al., 1993; Rinaldi-Carmona et al., 1994). Unlike the discussed possible clinical association between antiemetic and sedative activity of Δ^9-THC, the present results show that, although Δ^9-THC appears to be more potent in suppressing motor behaviors in dopamine D_2/D_3-receptor-stimulated shrews, there is still a clear dose divergence between motor depressive and antiemetic effects of Δ^9-THC. Indeed, the antiemetic ID_{50s} of Δ^9-THC in reducing the frequency of emesis produced by each of the D_2/D_3 agonists are 5–20 times lower than its ID_{50} values in reducing motor parameters in D_2/D_3-agonist-treated shrews (see Table 1). Moreover, different loci are responsible for the antiemetic (Van Sickle et al., 2003; Darmani and Johnson, 2004) and motor suppressive effects (Sañudo-Peña and Fride, 2002) of cannabinoids. For example, Δ^9-THC appears to attenuate emesis via several loci in the dorsal vagal complex of the brainstem and gastrointestinal tract, whereas its locomotor inhibition is mediated via the extrapyramidal structures such as the striatum. The striatum is key component of the forebrain dopaminergic motor system that stimulates motor activity in basal ganglia which controls planning and execution of motor behaviors (Nakano et al., 2000; Parent and Hazrati, 1995). Cannabinoid CB_1 agonists affect the function of these systems (Sañudo-Peña and Fride, 2002; Howlett, 1995). Interactive mechanisms that may influence motor function through cannabinoid and dopaminergic systems include (1) the high expression rates of CB_1 and D_2 receptors within the same neurons in motor areas such as the striatum (Hermann et al., 2002), (2) interactions at the level of G-protein/adenylate cyclase signal transduction as activation of either CB_1 or D_2 receptors in striatal tissue results in an inhibition of cAMP accumulation, whereas simultaneous activation of both receptors lead to an augmentation of cAMP accumulation (Glass and Felder, 1997), and (3) activation of presynaptic cannabinoid CB_1 receptors inhibits release of numerous neurotransmitters from central and peripheral neurons, including dopamine (Howlett et al., 2002). Whether dopaminergic D_2/D_3 and cannabinoid CB_1 receptors are expressed on the same neurons in emetic nuclei of the brainstem remains to be investigated, both receptor systems are found in these nuclei (Darmani et al., 2003; Glass et al., 1997; Van Sickle et al., 2001, 2003; Veyrat-Follet et al., 1997). Some of the discussed interactive mechanisms may also mediate the antiemetic effect of Δ^9-THC against dopaminergically induced emesis in the brainstem.

In summary, the current results extend our published findings in that Δ^9-THC not only blocks emesis produced by nonselective indirect dopamine agonists such as cisplatin (Darmani, 2001a) but also prevents vomiting induced by selective direct acting dopamine D_2/D_3 receptor agonists. Thus, as with the case of serotonergically induced emesis (Darmani and Johnson, 2004), the present findings imply that Δ^9-THC may also prevent dopaminergically induced emesis via both pre- and postsynaptic mechanisms.The findings of this study further help to confirm that (1) the antiemetic activity of Δ^9-THC against apomorphine as well as the more dopamine D_2 (quinpirole)- and D_3 (quinelorane and 7-OH DPAT)-preferring agonists are probably species-dependent, (2) Δ^9-THC's antiemetic action against dopamine D_2/D_3 agonists is mediated via the stimulation of cannabinoid CB_1 receptors, and, (3) as with the case of cisplatin-induced emesis (Darmani, 2001a), there is a clear divergence in the antiemetic and motor suppressive effects of Δ^9-THC in D_2/D_3-receptor-agonist-treated shrews since its antiemetic action occurs at much lower doses.

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