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BRIEF REPORT

Δ^9-Tetrahydrocannabinol and Synthetic Cannabinoids Prevent Emesis Produced by the Cannabinoid CB_1 Receptor Antagonist/ Inverse Agonist SR 141716A

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There is substantial clinical evidence that Δ^9-tetrahydrocannabinol (Δ^9-THC) and its synthetic analogs (nabilone and levonantradol) can prevent emesis in cancer patients receiving chemotherapy. Limited available animal studies also support the antiemetic potential of these cannabinoids. The present study investigates the mechanism of antiemetic action of cannabinoids in an established animal model of emesis, the least shew (Cryptotis parva). Since cannabinoid agonists prevent emesis, it was hypothesized that blockade of either the cannabinoid CB_1 receptor or the cannabinoid CB_2 receptor would induce vomiting. Thus, the emetic potential of SR 141716A (CB_1 receptor antagonist) or SR 144528 (CB_2 receptor antagonist) was investigated. Both intraperitoneal (0, 1, 2.5, 5, 10 and 20 mg/kg, n = 7–15 per group) and subcutaneous (0, 10, 20 and 40 mg/kg, n = 6–9 per group) administration of SR 141716A caused emesis (ED_{50} = 5.52 ± 1.23 and 20.2 ± 1.02 mg/kg, respectively) in the least shrew in a dose-dependent manner. Indeed, both the frequency of emesis and the percentage of animals vomiting increased with increasing doses of SR 141716A. Significant effects were seen at the 10- and 20-mg/kg doses for the IP route, while only the 40-mg/kg dose produced significant emesis via the SC route. The CB_2 antagonist failed to produce emesis via either route of administration. SR 141716A at an IP dose of 20 mg/kg was used to induce emesis for drug interaction studies. Thus, varying doses of three different classes of cannabinoid agonists [CP 55, 940 (0, 0.1, 0.5 and 1 mg/kg), WIN 55, 212-2 (0, 1, 5 and 10 mg/kg), and Δ^9-THC (0, 5, 10 and 20 mg/kg)], were administered IP to different groups of shrews 10 min prior to SR 141716A injection. The frequency of emesis was recorded for 30 min following the administration of SR 141716A. The order of potency for redcing both the frequency of emesis and the percentage of shrews vomiting was CP 55, 940 > WIN 55, 212-2 > Δ^9-THC which is consistent with an action on the CB_1 receptor. These results suggest that the antiemetic activity of Δ^9-THC and its synthetic analogs reside in their ability to stimulate the cannabinoid CB_1 receptor. Furthermore, the antiemetic potency of CP 55, 940 is 45 times greater than Δ^9-THC. On the other hand, blockade of CB_1 receptors can induce vomiting, which implicates an important role for endogenous cannabinoids in emetic circuits.

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In the early 1970s, accumulating anecdotal reports by young cancer patients suggested that smoking marijuana would alleviate the nausea and vomiting caused by chemotherapeutic agents. Since then, both government- and industry-sponsored clinical trials were initiated to test the antiemetic potential of Δ^9-tetrahydrocannabinol (Δ^9-THC) and some of its synthetic analogs such as nabilone and levonantradol (Gralla 1999; Voth and Schwartz 1997). This literature suggests that both Δ^9-THC and its tested analogs are useful antiemetics in some patients for the prevention of nausea and vomiting associated with cancer chemotherapy. Though cannabinoids appear to be a more efficacious class of antiemetics than dopamine D_2 receptor antagonists for the prevention of chemotherapy-induced vomiting, the efficacy of tested cannabinoids to date seems not to be as high as the more potent antiemetics such as the selective 5-HT_3 receptor antagonists (Gralla 1999). However, one interesting advantage of cannabinoids is that many of the patients who are protected from the acute phase of emesis, also respond well during the delayed phase of chemotherapy-induced emesis which 5-HT_3 receptor antagonists poorly control (Abrahamov et al. 1995; Chan et al. 1987; Dalzell et al. 1986).

Unlike the relatively large body of clinical reports, only a few published animal studies on the antiemetic effects of cannabinoids are available. Several cannabinoids can block cisplatin- or apomorphine-induced emesis in a variety of animal species including the cat, the pigeon and the least shrew (Cryptotis parva) (McCarthy and Borison 1981; McCarthy et al. 1984; London et al. 1979; Stark 1982; Darmani 2000). Until recently, an animal model of emesis had not been employed for investigating the cannabinoid receptor involved in the antiemetic effect of Δ^9-THC and other cannabinoids. In the present study, the least shrew (Cryptotis parva) has been used as an animal model of emesis. This species was recently introduced as a new serotonergic (Darmani 1998) and dopaminergic (Darmani et al. 1999) experimental model of vomiting. The least shrew is a small insectivore (adult weight 4–6 g) that lives in various ecological niches in Central and North America. The family Soricidae, to which shrews belong, constitute over 266 species (Churchfield 1990). Over the last decade, Japanese investigators have established the house musk shrew (Suncus murinus) as an experimental model for the various emetic stimuli (Matsuki et al. 1988; Torii et al. 1991). Suncus murinus is relatively a larger animal (adult being 50–100 g in weight) and is endogenous to Asia and Africa.

While the antiemetic effects of Δ^9-THC appear to be receptor-mediated, it is unclear whether the cannabinoid CB_1 and/or CB_2 receptors are involved in emesis. Involvement of CB_1 receptor appears most likely since Δ^9-THC produces most of its effects via this site (Pertwee 1997). If activation of cannabinoid receptors prevent emesis, then blockade of these receptors may produce vomiting. Thus, the present study investigated: (1) whether administration of the selective cannabinoid CB_1-receptor antagonist SR 141716A (Rinaldi-Carmona et al. 1994), or the CB_2-receptor antagonist SR 144528 (Rinaldi-Carmona et al. 1998), can induce emesis in the least shrew (Darmani 1998; Darmani et al. 1999); and (2) whether the induced emesis can be blocked by the cannabinoid agonists Δ^9-THC and its newly introduced synthetic analogs CP 55, 940 and WIN 55, 212-2 (Pertwee 1997).

MATERIALS AND METHODS

Animals and Drugs

Shrews (Cryptotis parva) were bred and maintained in the animal facilities of the Kirksville College of Osteopathic Medicine, Kirksville, Missouri. Both male and female shrews (4–6 g, 45–70 days old) were used throughout the study. The animals were kept on a 14:10-h light-dark cycle at a humidity controlled room temperature of 21 $\pm$ 1°C with ad lib supply of food and water. The feeding and maintenance of shrews are fully described elsewhere (Darmani 1998; Darmani et al. 1999). The following drugs were purchased from Research Biochemicals Inc., Natick, MA: Δ^9-tetrahydrocannabinol (Δ^9-THC) and R(+)-WIN 55, 212-2 mesylate. CP 55, 940 was obtained from Pfizer (Groton, CT). SR 141716A and SR 144528 were generously donated by Professor B.R. Martin. All drugs were dissolved in a 1:1:18 solution of ethanol: emulphor: 0.9% saline to twice the stated drug concentrations. These drugs concentrations were further diluted by the addition of an equal volume of saline. This procedure was necessary, because the 1:1:18 vehicle mixture can cause emesis in up to 20% of animals by itself. The final vehicle mixture induced emesis only very rarely. All drugs were administered at a volume of 0.1 ml/10g of body weight. All animals received care according to the "Guide for the Care and Use of Laboratory Animals," DHSS Publication, revised, 1985.

Experimental Protocols

The present protocols were based upon our previous emesis studies in the least shrew (Darmani 1998; Darmani et al. 1999). On the test day, the shrews were transferred to the experimental room and were allowed to acclimate for at least 1 h prior to experimentation. To habituate the shrews to the test environment, each animal was randomly selected and transferred to a 20 $\times$ 18 $\times$ 21 cm clean clear plastic cage and offered 4 meal worms (Tenebrio sp) 30 min prior to experimentation. Different groups of shrews were then injected either in-

traperitoneally or subcutaneously with vehicle (n = 11–12) or varying doses of the CB_1 antagonist SR 141716A (1, 2.5, 5, 10 and 20 mg/kg, n = 7–15), or the CB_2 antagonist SR 144528 (10, 20 and 40 mg/kg, n = 8–11 per group). Immediately following injection, each shrew was placed in the observation cage and the onset latency to first vomit as well as the frequency of vomiting (mean ± SEM) were recorded for each individual shrew for the next 60 min. These data showed that intraperitoneal administration of 20 mg/kg of SR 141716A produced a robust frequency of emesis. This dose and route of administration of SR 141716A was chosen for subsequent studies in which the antiemetic effects of Δ^9-THC as well as its synthetic analogs CP 55, 940 and WIN 55, 212-2 were investigated.

For these interaction studies, different doses of either CP 55, 940 (0, 0.1, 0.5 and 1 mg/kg, n = 6–8 per group), WIN 55, 212-2 (0, 1, 5 and 10 mg/kg, n= 6–9 per group), or Δ^9-THC (0, 5, 10 and 20 mg/kg, n = 7–9 per group) were administrated intraperitoneally to different groups of shrews 10 min prior to SR 141716A (20 mg/kg, IP) injection. Emesis was recorded for 30 min immediately following SR 141716A administration as described above.

Statistical Analysis

The data were analyzed by the Kruskal-Wallis nonparametric one-way analysis of variance (ANOVA) and posthoc analysis by Dunn's multiple comparisons test. A p-value of $<.05$ was necessary to achieve statistical significance. The ED_{50} (the effective dose that produced emesis in 50% of animals) and ID_{50} (the inhibitory dose that prevented emesis in 50% of shrews) were calculated by the use of a computerized program (Graph Pad InPlot, San Diego, CA).

RESULTS

The Kruskal-Wallis nonparameteric ANOVA test indicated that intraperitoneal administration of SR 141716A dose-dependently increased the percentage of shrews vomiting (ED_{50} = 5.52 ± 1.23) ($Kw_{58,5}$ = 28.1, $p < .0001$) (Table 1). Dunn's multiple comparisons test showed that relative to the vehicle-injected control group, significant enhancements in the number of animals exhibiting emesis occurred in the groups injected with the

Table 1. Dose-dependent Emetogenic Effects of Different Routes of Administration of the Cannabinoid CB_1 (SR 141716A) and CB_2 (SR144528) Antagonists

Drugs	Number of animals vomiting/tested	Vomiting frequency	Latency to first vomit (minutes)
SR 141716A			
Intraperitoneal			
0	1/12	0.08 ± 0.08	19.20
1	2/10	0.5 ± 0.3	21.24
2.5	0/8	0 ± 0	—
5	8/15	0.93 ± 0.3	13.0
10	9/12*	1.7 ± 0.5*	8.78
20	7/7***	05.7 ± 0.52***	5.28
Subcutaneous			
0	0/9	0	—
10	0/6	0	—
20	2/7	2 ± 1.3	10.32
40	4/7*	2.9 ± 1.5*	9.40
SR 144528			
Intraperitoneal			
0	1/11	0.09 ± 0.09	10.21
10	0/8	0 ± 0	—
20	2/10	0.2 ± 0.13	12.28
40	2/10	0.3 ± 0.2	8.39
Subcutaneous			
0	0/9	0 ± 0	—
10	1/7	0.14 ± 0.14	3.49
20	0/7	0 ± 0	—
40	0/7	0 ± 0	—

Values for vomiting frequency and latency for first vomit are mean of those animals which exhibited vomiting. Animals which failed to vomit were not included in these mean values.

The above parameters were recorded for 60 min following either the intraperitoneal or subcutaneous administration of the cited selective cannabinoid antagonists.

*$p < .05$.

**$p < .01$.

***$p < .001$ indicate significant differences relative to vehicle control by Dunn's multiple comparisons test.

10 ($p < .05$) and 20 mg/kg ($p < .001$) doses of SR 141716A. Moreover, the larger doses of SR 141716A induced emesis more rapidly. Indeed, depending upon the dose of SR 141716A administered, the mean latency to onset of first vomit in responsive animals varied from 5.28 to 19.20 minutes. In addition, the frequency of SR 141716A induced emesis also increased in a dose-dependent manner ($Kw_{58,5} = 34.9$, $p < .0001$) (Table 1). Again, significant enhancements in the number of vomiting episodes occurred at the 10 ($p < .05$) and 20 mg/kg ($p < .001$) doses. When administered subcutaneously, SR 141716A appeared to be a less efficacious emetogen (Table 1). Indeed, the Kruskal-Wallis ANOVA test indicated that although SR 141716A can increase both the frequency ($Kw_{25,3} = 9.5$, $p < .003$), and the percentage of animals vomiting ($ED_{50} = 20.2 \pm 1.02$ mg/kg) ($Kw_{25,3} = 9.5$, $p < .02$), a significant effect ($p < .05$) was only observed at the 40-mg/kg dose by the Dunn's multiple comparisons posthoc test (Table 1). The CB_2 antagonist, SR 144528, over the dose range of 10–40 mg/kg, IP and SC, failed to produce a significant degree of emesis in the least shrew (Table 1).

Table 2 shows the ability of three cannabinoids (CP 55, 940; WIN 55, 212-2 and Δ^9-THC) in preventing emesis induced by the cannabinoid CB_1 receptor antagonist/inverse agonist SR 141716A. The cited doses of CP 55, 940 (0.1–1 mg/kg) attenuated both the percentage of animals vomiting ($ID_{50} = 0.35 \pm 2.2$ mg/kg) ($Kw_{25,3} = 19.8$, $p < .0002$) and the frequency of vomitings in a dose-dependent manner (Table 2). However, a significant decrease in both the percentage of shrews vomiting ($p < .01$) and the frequency of vomitings ($p < .01$) was seen at the 1 mg/kg dose of CP 55, 940. In a similar manner, intraperitoneal administration of WIN 55, 212-2 (1–10 mg/kg), dose-dependently antagonized the ability of SR 141716A to induce emesis in different shrews ($ID_{50} = 3.95 \pm 1.2$) ($Kw_{28,3} = 10.8$, $p < .01$) as well as reducing the frequency of the induced emesis ($Kw_{28,3} = 10.6$, $p < .01$) (Table 2). However, significant reductions ($p < .05$) were only observed for both emetic parameters at the 10 mg/kg dose. The Kruskal-Wallis nonparametric ANOVA test also showed that intraperitoneal injection of Δ^9-THC can reduce the percentage of shrews vomiting in response to SR 141716A administration ($ID_{50} = 15.2 \pm 3.2$ mg/kg) ($Kw_{29,3} = 22.6$, $p < .0001$), as well as attenuating the frequency of the induced emesis ($Kw_{29,3} = 20.04$, $p < .0002$). However significant reductions in emetic parameters ($p < .001$) were only seen at the 20-mg/kg dose of Δ^9-THC (Table 2).

DISCUSSION

The least shrew appears to be an excellent new animal model of emesis (Darmani 1998; Darmani et al. 1999). Both dopamine D_2- and serotonin 5-HT_3-receptor agonists induce vomiting in a potent manner in this species. Furthermore, 5-HT_3 receptor antagonists block cisplatin-induced emesis in these animals (Darmani 1998). There is overwhelming clinical evidence that Δ^9-THC and some of its synthetic analogs (nabilone and levonantradol) can prevent emesis in some cancer patients receiving chemotherapy (Gralla 1999; Voth and Schwartz 1997). Likewise, as described in the introduction, some cannabinoids prevent cisplatin- or apomorphine-induced emesis in a number of different species including the least shrew.

Until the present study the mechanism of antiemetic action of cannabinoids was not known. Therapeutically effective antiemetics antagonize the emetic action of

Table 2. Dose-dependent Antiemetic Effects of Intraperitoneally Administered Cannabinoids Against the CB_1 Receptor Antagonist (SR 41716A)-induced Vomiting

Drug	Dose (mg/kg)	Number of animals vomited/tested	Vomiting frequency
Control	0	8/8	2.9 ± 0.2
CP 55, 940	0.1	6/6	3 ± 0.4
	0.5	3/7	1.1 ± 0.5
	1	0/7***	0 ± 0**
WIN 55, 212-2	1	5/6	2.5 ± 1
	5	3/8	1 ± 0.5
	10	3/9*	0.9 ± 0.5*
Δ^9-THC	5	6/7	3.1 ± 0.7
	10	8/8	2 ± 0.3
	20	1/9***	0.1 ± 0.1***

Different shrews received intraperitoneally either vehicle or the cited doses of CP 55, 940; WIN 55, 212-2 or Δ^9-THC 10 min prior to administration of SR 141716A (20 mg/kg, IP). The emetic parameters were recorded for the next 30 min immediately following the SR 141716A injection.

*$p < .05$.

**$p < .01$.

***$p < .001$ indicate significant differences relative to vehicle control by Dunn's multiple comparisons test.

endogenous neurotransmitters such as acetylcholine, dopamine, histamine, serotonin or substance P (Naylor and Rudd 1996). Unlike these receptor antagonists, cannabinoids decrease emesis as a result of agonist action at cannabinoid CB_1 and/or CB_2 receptors (Pertwee 1997). Thus, it seemed reasonable that antagonism of one or both cannabinoid receptors should induce emesis. This proposal appears to be true since the intraperitoneal or subcutaneous administration of the selective CB_1 antagonist/inverse agonist, SR 141716A, caused emesis in a dose-dependent manner in the least shrew (ED_{50} = 5.52 ± 1.25 mg/kg). Indeed, both the percentage of animals vomiting and the frequency of induced emesis were significantly increased in response to administration of increasing doses of SR 141617A. Intraperitoneal injection of SR 141716A caused profound emesis at 10 mg/kg or greater doses. However, SR 141716A is a less efficacious emetic (ED_{50} = 20.2 ± 1.02 mg/kg) when administered via the subcutaneous route since only the largest dose employed (40 mg/kg) caused significant emesis. At 10 mg/kg or larger doses, SR 141716A has also been found to increase the spontaneous locomotor activity in mice following intravenous administration (Compton et al. 1996). Peripheral administration of such doses of SR 141716A also produces other motor behaviors such as the head-twitch response, lateral scratchings or wet-dog shakes in drug-naive mice and rats (Aceto et al. 1998; Cook et al. 1998; Darmani and Pandya 2000; Rubino et al. 1998). The present and the cited studies suggest that SR 141716A produces these effects either by antagonizing the action of an endogenous cannabinoid(s), or by exerting an inverse agonist action. The selective cannabinoid CB_2 antgonist SR 144528 failed to produce significant emesis in the least shrew either via the intraperitoneal or the subcutaneous routes. Thus, the present results suggest that cannabinoid agonists may produce their antiemetic action via the activation of CB_1 receptors.

To show that SR 141716A-induced emesis is a cannabinoid receptor-mediated event, the antiemetic effect of three structurally different classes of cannabinoid receptor agonists (CP 55, 940; WIN 55, 212-2 and Δ^9-THC) were investigated. The cited cannabinoids blocked the ability of SR 141716A to induce emesis in a dose-dependent manner with the following antiemetic ID_{50} rank order: CP 55, 940 < WIN 55, 212-2 < Δ^9-THC. This antiemetic potency rank order in the least shrew, mirrors both the affinity of these cannabinoids for CB_1 and CB_2 receptors (Matsuda 1997; Pertwee 1997) and their ED_{50} potency values for the CB_1 receptor-mediated tetrad of behaviors in mice (Abood and Martin 1992). These results further support the suggestion that cannabinoids exert their antiemetic action via CB_1 receptors. However, the nonpsychoactive (HU-211) enantiomer of the potent cannabinoid HU-210, which lacks affinity for CB_1 receptors, has also been reported to prevent cisplatin-induced emesis (Feigenbaum et al. 1989). Since HU-211 stereoselectively blocks the glutamate NMDA receptor, its antiemetic property is probably related to antagonism of this excitatory receptor. Indeed, NMDA antagonists can prevent emesis produced by a variety of emetic stimuli (Lehmann and Karrberg 1996; Lucot 1998).

Apart from the present study, very little is known regarding the antiemetic structure activity relationship of different cannabinoids in any species. Furthermore, as yet no clinical study has demonstrated a better margin of safety for one cannabinoid antiemetic versus another. Even though there is no information regarding the therapeutic index of CP 55, 940 in man, the present antiemetic potency order in the least shrew indicates that this cannabinoid possesses a superior antiemetic property than Δ^9-THC. Indeed, relative to Δ^9-THC, the index of psychoactivity of CP 55, 940 (i.e., its ED_{50} in producing the tetrad of behaviors) only varies from 4–25 times in mice (Abood and Martin 1992); whereas the antiemetic potency of this cannabinoid is 45 times greater than Δ^9-THC in the least shrew. In the case of SR 141716A-induced emesis, the most potent tested cannabinoid in the present study, CP 55, 940, also caused the greatest degree of antiemetic activity. Indirect evidence from nonemetic species also support the involvement of CB_1 receptors in emesis. Thus, different classes of cannabinoid agonists (anandamide, methanandamide, nabilone, Δ^9-THC and WIN 55, 212-2) reduce gastrointestinal motility and intestinal transit in rodents via SR 141716A-sensitive CB_1 receptors (Calignano et al. 1997; Colombo et al. 1998; Izzo et al. 1999; Krowicki et al. 1999; Shook and Burks 1989). Furthermore, these studies have shown that the emetic doses of SR 141716A employed in the present study, also promotes defecation and GI motility in rodents.

In summary, the present and published studies suggest that the antiemetic activity of cannabinoid agonists is mediated by the CB_1 receptor and endogenous cannabinoid neurotransmitter system may play an important regulatory role in emesis.

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