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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