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Stereochemical Effects of 11-OH-Δ^8-THC-Dimethylheptyl in Mice and Dogs[1]

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LITTLE, P. J., D. R. COMPTON, R. MECHOULAM AND B. R. MARTIN. *Stereochemical effects of 11-OH-Δ^8-THC-dimethylheptyl in mice and dogs*. PHARMACOL BIOCHEM BEHAV **32**(3) 661–666, 1989.—The effects of the enantiomers of 11-hydroxy-Δ^8-tetrahydrocannabinol-dimethylheptyl (11-OH-Δ^8-THC-DMH) on spontaneous activity, rectal temperature, tail-flick latency, and catalepsy were studied in mice and in the dog static-ataxia model to determine the relative potency of each enantiomer. The (−)-enantiomer was active in all tests between 3–100 μg/kg, while the (+)-enantiomer was inactive at 30 mg/kg in the mouse and 1 mg/kg in the dog. The (−)-enantiomer was 100–800 times more potent than Δ^9-THC in the mouse. The high degree of enantioselectivity and potency are suggestive of an interaction at a specific site such as a receptor.

11-OH-Δ^8-THC-DMH Δ^9-THC Stereoselectivity Spontaneous activity Hypothermia Analgesia Catalepsy Static ataxia

Δ^9-TETRAHYDROCANNABINOL (Δ^9-THC), generally accepted as the major psychoactive constituent in marijuana, possesses a wide spectrum of pharmacological effects, some of which are unique to the cannabinoids. The mechanism(s) by which Δ^9-THC exerts its pharmacological effects have not been clearly elucidated (10). There are many hypotheses concerning the precise mechanism(s) of action of Δ^9-THC. These hypotheses generally are supportive of either a nonspecific membrane perturbation or favor a highly specific site of action (i.e., a receptor). There are several lines of evidence which suggest the possibility of a specific cannabinoid receptor. These include the development of structure-activity relationships (11,14), the demonstration of stereoselectivity (4) and the demonstration of specific binding sites for cannabinoids in the brain (12). The degree of stereoselectivity reported for the naturally occurring (−)-enantiomers and synthetic (+)-enantiomers of Δ^9- and Δ^8-THC varies according to the test system and species used (4). (−)-Δ^9-THC has been reported to be 5–100 times more potent than its (+)-enantiomer while (−)-Δ^8-THC was 4–33 times more potent than (+)-Δ^8-THC (4). It should be stressed that the stereochemical purity of most synthetic (+)-cannabinoids has not been reported and it is likely that there are impurities consisting of the respective (−)-enantiomers. While the degree of stereoselectivity demonstrated with the cannabinoids is not as great as that seen with the opiates (6), it is comparable to that demonstrated with stereoisomers of nicotine (9). Therefore, the degree of stereoselectivity demonstrated with Δ^9- and Δ^8-THC is consistent with the existence of a specific receptor. However, it is possible that a composite of biochemical and neurochemical effects are involved and that the different results between test systems reflect this fact.

Recently, the enantiomers of 11-hydroxy-Δ^8-THC, 1,1-dimethylheptyl homolog (11-OH-Δ^8-THC-DMH) were synthesized. They were obtained in crystalline form, apparently in essentially absolute stereochemical purity. These enantiomers were tested in the rat and pigeon for their discriminative stimulus properties and in the rat for antinociceptive and anticonvulsant properties (11). Since the stereoselectivity of cannabinoids apparently is species and model dependent, we examined the pharmacological effects of these enantiomers in mice for depression of spontaneous activity, hypothermia production, analgesia in the tail-flick procedure and for their ability to produce catalepsy. The enantiomers of 11-OH-Δ^8-THC-DMH were also tested in the dog static-ataxia model since this test is thought to be predictive of cannabinoids which are psychoactive in humans (14).

The lack of a specific antagonist of Δ^9-THC has greatly hampered efforts to elucidate the mechanisms of action of the cannabinoids. The inactive (+)-enantiomer of 11-OH-Δ^8-THC-DMH was tested for its ability to block the effects of Δ^9-THC in

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the mouse behavioral paradigms. By examining the pharmacological profiles of the enantiomers of 11-OH-Δ^8-THC-dimethylheptyl and determining the degree of stereoselectivity which exists, insight into possible mechanisms of action of the cannabinoids may be gained.

METHOD

Subjects

Male ICR mice (Dominion Laboratories, Dublin, VA) weighing 24–30 g were used for all test procedures, and a minimum of 12 mice were utilized for each dose and time point. Mice were maintained on a 12-hr light/dark cycle and had free access to Purina Rodent Chow (Ralston Purina, St. Louis, MO) and water.

Drugs

Δ^9-THC was provided by the National Institute on Drug Abuse. The enantiomers of 11-OH-Δ^8-THC-DMH were synthesized as described elsewhere (11). All drugs were first dissolved in a 1:1 emulphor:ethanol solution, and diluted to the desired concentration with 0.9% saline to yield a final vehicle of 1:1:18 (emulphor:ethanol:saline). Mice were acclimated in the laboratory (ambient temperature 21–24°C) overnight. All drugs were administered intravenously (IV) in the tail vein with an injection volume of 0.1 ml/10 g of body weight, after injection each mouse was tested in all four procedures as described below.

Experimental Procedures for Mice

Mice were placed into individual photocell activity cages (28 × 16.5 cm) immediately after IV administration of the vehicle or cannabinoids. Mice were allowed to acclimate for 5 min and then interruptions of a single photocell beam were recorded for the next 10 min.

Rectal temperatures were determined prior to drug or vehicle administration with a telethermometer (Yellow Springs Instrument Co., Yellow Springs, OH) and a thermistor probe. Rectal temperatures were again measured 60 min after administration of the drug or vehicle. The dose required to produce a 3°C decrease in rectal temperature was determined by linear regression analysis of the dose-response data.

Tail-flick reaction time to a heat stimulus was determined following drug or vehicle administration using the method of D'Amour and Smith (1) as modified by Dewey *et al.* (2). Preinjection control values (2–4 sec) were determined for all animals. Mice were retested 20 min after IV administration of the drug or vehicle and the latency to the tail-flick response was recorded. A 10-sec maximum latency was set to prevent tissue damage. Data were recorded as change in latency between pre- and postinjection testing for each animal. Data were expressed as % maximum possible effect (% MPE) where % MPE was determined by the following method: [(test latency − control latency) ÷ (10 sec − test latency)] × 100.

Catalepsy was determined by using a slight modification of the ring test as developed by Pertwee (13). Mice were injected IV with either vehicle or cannabinoid and 1.5 hr after treatment were placed on a ring (5.5 cm dia.) which was attached to a ring stand at a height of 16 cm. Mice were rated for catalepsy by observers who were blind with regard to treatment. The amount of time (in seconds) in a 5 min test session in which the mouse was motionless (except for respiratory movements) was determined. Mice which either fell or actively jumped from the ring were allowed 5 such "escapes." If these "escapes" occurred before 2.5 min, the data were disregarded. An immobility index was determined by dividing the amount of time spent motionless by the length of the test session (maximum 300 sec) and multiplying by 100.

Time Course

Mice were injected with either vehicle, Δ^9-THC (10 mg/kg), or (−)-11-OH-Δ^8-THC-DMH (10 μg/kg) and tested in the above procedures. Groups of mice were tested at 5, 30, 60, 120, 240, 360, 480 min and 24 hr in the spontaneous activity procedure. The time course for the tail-flick procedure was determined at 20, 60, 120, 240, 360, and 480 min. Catalepsy was assessed at similar time points except the earliest time point which was 30 min, in addition a 24 hr assessment was also determined.

Antagonism Studies

The (+)-enantiomer was tested for its ability to attenuate the pharmacological effects of Δ^9-THC by pretreating mice with 10 mg/kg (+)-11-OH-Δ^8-THC-DMH IV. This dose was chosen because it had little or no pharmacological effects on its own. After a 10 min latency Δ^9-THC (6 mg/kg) was administered IV, and mice were tested in the above procedures.

Procedure for Dog Static-Ataxia

Male mongrel dogs weighing 9–13 kg were used for these studies. Dogs were brought to an observation room and allowed to acclimate for 15 min. Observers noted their normal activity, posture, gait, etc. Dogs were then injected IV with a volume of 0.2 ml/kg of body weight with either vehicle, Δ^9-THC, or one of the enantiomers of 11-OH-Δ^8-THC-DMH. Their behavior was observed for 30 min and then rated (see Table 2) according to the Walton static ataxia scale as modified by Dewey *et al.* (3). Observers were blind with regard to treatment. Dogs were tested twice a week and dosing was counterbalanced such that no dog received the identical treatment on two consecutive test days in order to minimize the likelihood that tolerance would develop.

Data Analysis

ED_{50} values with 95% confidence limits (C.L.) were determined for reduction in locomotor activity, for the production of analgesia using the %MPE, and for the production of catalepsy using the immobility index by the method of Litchfield and Wilcoxon (7). Statistical differences between vehicle and drug treatment was determined by the Dunnett's *t*-test. ANOVA with a Scheffe post hoc test was utilized to determine statistical differences between the treatment groups in the time course and antagonism experiments.

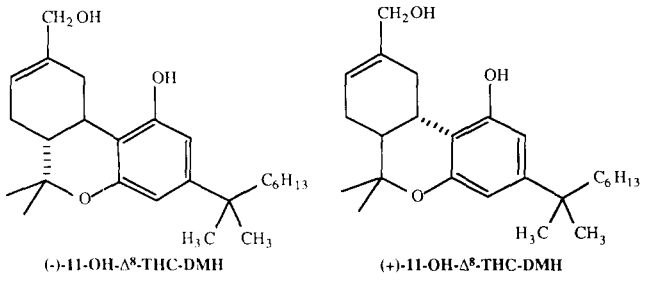
RESULTS

Effects of the Enantiomers of 11-OH-DMH-Δ^8-THC in Mice

The effects of the enantiomers of 11-OH-Δ^8-THC-DMH on mouse locomotor activity, rectal temperature, tail-flick and catalepsy are shown in Table 1. The (−)-enantiomer was active in a dose-responsive manner in all tests between 3–100 μg/kg. Spontaneous activity was reduced with an ED_{50} value of 4 μg/kg. The (−)-enantiomer also decreased rectal temperature, since it was not possible to obtain ED_{50} values for the decrease in rectal temperature, the dose which lowered rectal temperature by 3°C (after vehicle effects (−0.5°C) were subtracted) was chosen for the comparison of the relative activity of the enantiomers. The (−)-enantiomer decreased rectal temperature by 3°C at 21 μg/kg as determined by linear regression analysis. The (−)-enantiomer

TABLE 1

BEHAVIORAL EFFECTS OF THE ENANTIOMERS OF 11-OH-Δ^8-THC-DMH IN MICE



TRT	Spont. Act.*	Rect. Temp.†	T.F.‡	Cat.§
Vehicle	73 ± 9	−0.5 ± 0.3	−0.1 ± 0.3/4%	4 ± 3
		(−)-11-OH-Δ^8-THC-DMH		
1 μg/kg	86 ± 9	−0.3 ± 0.2	0.8 ± 0.6/12%	13 ± 5
3 μg/kg	26 ± 7	−3.8 ± 0.5	2.4 ± 1.2/32%	38 ± 5
10 μg/kg	15 ± 5	−2.8 ± 0.5	3.6 ± 1.2/52%	45 ± 7
30 μg/kg	10 ± 3	−4.0 ± 0.4	6.8 ± 0.3/100%	49 ± 6
100 μg/kg	2 ± 1	−6.3 ± 0.3	4.6 ± 1.0/69%	71 ± 6
ED_{50} μg/kg (95% C.L.)	4(1–14)	−3°C at 21	9(2–39)	19(3–111)
		(+)-11-OH-Δ^8-THC-DMH		
10 mg/kg	70 ± 19	−2.7 ± 0.4	0.2 ± 0.5/6%	18 ± 3
20 mg/kg	45 ± 14	−0.4 ± 0.5	−0.2 ± 0.1/0%	18 ± 7
30 mg/kg	45 ± 9	−1.8 ± 0.7	−0.2 ± 0.4/3%	23 ± 8
ED_{50}	N.D.¶	N.D.	N.D.	N.D.
Selectivity	>7500	>1400	>3333	>1575

*Spontaneous activity values are the number of interruptions of a photocell beam. †Rectal Temperature values are the change in pre- and post-drug rectal temperature. ‡Tail-flick values are the latency (in sec) for the tail-flick response and % MPE (10 sec max). §Catalepsy values are the % of time spent immobile on the ring. ¶N.D. ED_{50} values were not able to be determined.

produced analgesia in mice as measured by the tail-flick test with an ED_{50} value of 9 μg/kg. The (−)-enantiomer produced catalepsy in mice with an ED_{50} value of 19 μg/kg. The (+)-enantiomer failed to produce dose-responsive effects in any of the test systems in the mouse.

Time Course for the Effects of (−)-11-OH-Δ^8-THC-DMH in Mice

The time courses for the reduction in locomotor activity and production of analgesia and catalepsy for (−)11-OH-Δ^8-THC-DMH (10 μg/kg), Δ^9-THC (10 mg/kg), and vehicle are shown in Figs. 1–3. These doses were chosen because at the time of their peak effects the responses of either drug were comparable. The time course for spontaneous activity can be seen in Fig. 1. Δ^9-THC and (−)-11-OH-Δ^8-THC-DMH produced maximal decreases in spontaneous activity (93 and 73% respectively) 5 min after injection. By 30 min there was no significant difference between the spontaneous activity of Δ^9-THC and vehicle-treated mice. This remained true until the 4 and 6 hr time points at which times the activity of vehicle-treated mice were significantly

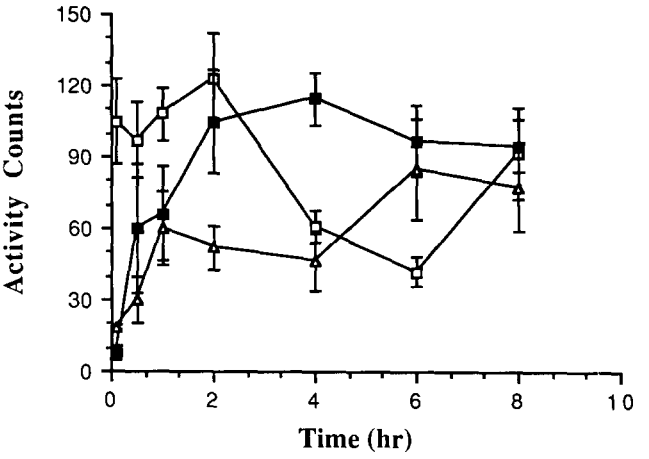


FIG. 1. Time course for the effects of vehcile (□), 10 mg/kg Δ^9-THC (■) and 10 μg/kg (−)-11-OH-Δ^8-THC-DMH (△) on spontaneous activity. The means ± SE (N = 12) are presented.

($p<0.005$) less than the activity of the mice treated with Δ^9-THC. By 8 hr there were no significant differences between the vehicle- and Δ^9-THC-treated mice. In contrast, the activity of mice treated with (−)-11-OH-Δ^8-THC-DMH remained significantly ($p<0.05$) depressed when compared to vehicle-treated mice up to 2 hr. By 4 hr there were no significant differences between the spontaneous activity in these two groups.

The time course for the production of catalepsy by Δ^9-THC and (−)-11-OH-Δ^8-THC-DMH was similar up to 4 hr (Fig. 2). The peak effects occurred at 30 min, and the degree of catalepsy production did not differ significantly between Δ^9-THC and (−)-11-OH-Δ^8-THC-DMH. At 4 hr the cataleptic response in mice treated with Δ^9-THC decreased such that there was now a significant difference ($p<0.005$) between mice treated with (−)-11-OH-Δ^8-THC-DMH and Δ^9-THC; however, the degree of catalepsy produced by Δ^9-THC was still significantly ($p<0.005$) greater than that of vehicle-treated mice. The immobility index was not significantly different between vehicle- and Δ^9-THC-treated mice at 6 hr, whereas it remained significantly elevated in

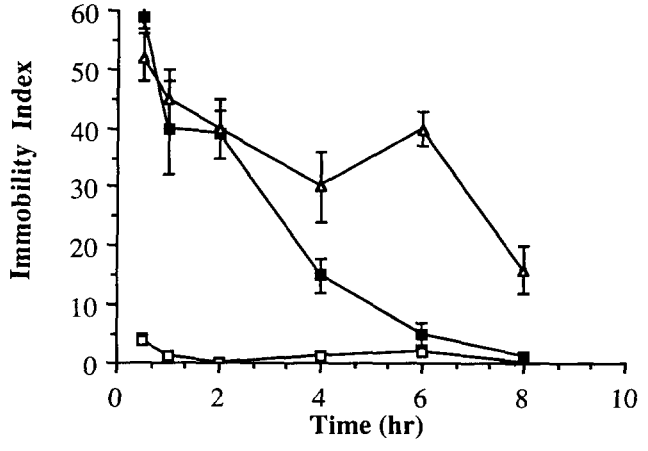


FIG. 2. Time course for the effects of vehicle (□), 10 mg/kg Δ^9-THC (■) and 10 μg/kg (−)-11-OH-Δ^8-THC-DMH (△) on production of catalepsy. The means ± SE (N = 12) are presented.

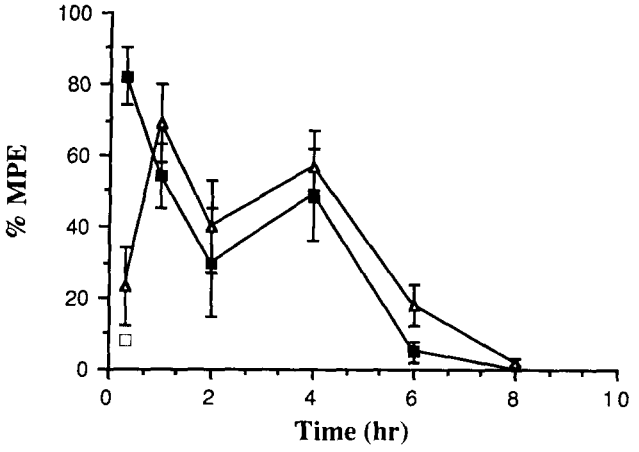


FIG. 3. Time course for the effects of vehicle (□), 10 mg/kg Δ^9-THC (■) and 10 μg/kg (−)-11-OH-Δ^8-THC-DMH (△) on tail-flick activity. The means ± SE (N = 12) are presented.

the (−)-11-OH-Δ^8-THC-DMH-treated mice at 6 and 8 hr. At 24 hr both treatments failed to produce catalepsy (data not shown).

The time course for the effects of (−)-11-OH-Δ^8-THC-DMH, Δ^9-THC and vehicle for the tail-flick are shown in Fig. 3. The effects of the vehicle were only determined at 20 min, since previous time course studies have shown the vehicle to be ineffective. The time course for the production of antinociception was similar for Δ^9-THC and (−)-11-OH-Δ^8-THC-DMH with the exception that the peak effects occurred at different times. The peak analgesic effect of Δ^9-THC was 20 min after injection, whereas the peak effect of (−)-11-OH-Δ^8-THC-DMH was at 1 hr. The analgesic effects of Δ^9-THC and (−)-11-OH-Δ^8-THC-DMH remained significantly greater than that produced by vehicle up to 4 hr, but by 6 hr there were no significant differences between the three treatment groups.

Evaluation of the Antagonistic Properties of (+)-11-OH-Δ^8-THC-DMH in Mice

The effects of pretreatment with (+)-11-OH-Δ^8-THC-DMH on the activity of Δ^9-THC in mice are shown in Fig. 4. Δ^9-THC (6 mg/kg) produced a robust effect in all tests; however the pretreatment with (+)-11-OH-Δ^8-THC-DMH did not significantly attenuate any of the effects produced by Δ^9-THC. In all cases (whether pretreated with a vehicle or (+)-11-OH-Δ^8-THC-DMH) Δ^9-THC produced effects which were significantly different ($p<0.05$) than that of vehicle-treated groups.

Behavioral Effects of the Enantiomers of 11-OH-Δ^8-THC-DMH in the Dog

The effects of the enantiomers of 11-OH-Δ^8-THC-DMH, Δ^9-THC, and vehicle on the overt behavior of dogs are shown in

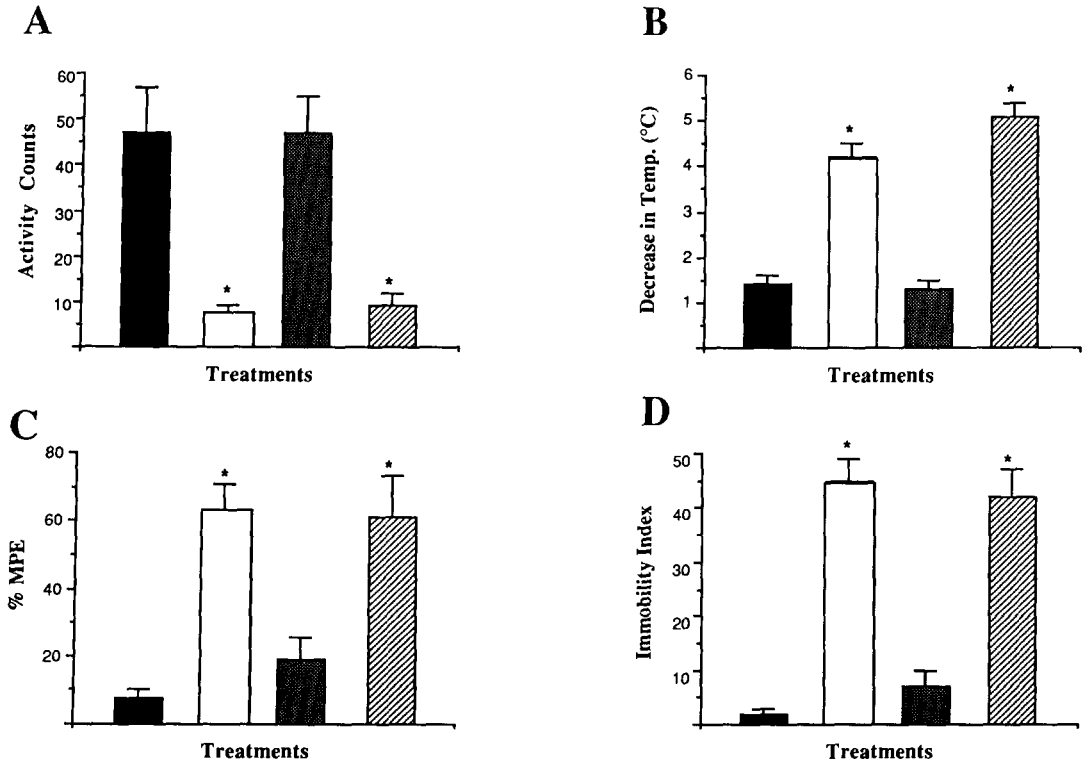


FIG. 4. Evaluation of the antagonistic potential of (+)-11-OH-Δ^8-THC-DMH. Mice received an IV injection of either vehicle or (+)-11-OH-Δ^8-THC-DMH (10 mg/kg) 10 min prior to a second IV injection of either vehicle or Δ^9-THC (6 mg/kg) which resulted in the following four groups: vehicle + vehicle: solid black bar, vehicle + Δ^9-THC: open bar, (+)-11-OH-+Δ^8-THC-DMH + vehicle: solid gray bar and (+)-11-OH-Δ^8-THC-DMH + Δ^9-THC; striped bar. The means ± SE (N = 18) are presented. Panel A represents the spontaneous activity procedure, panel B represents the hypothermic response, panel C is activity in the tail-flick procedure and panel D represents activity in the catalepsy procedure. Asterisks represent statistically ($p<0.05$) different than vehicle + vehicle controls.

TABLE 2

THE EFFECTS OF THE ENANTIOMERS OF 11-OH-Δ^8-THC-DMH IN THE DOG

Rating Scale*	
Score	Behavioral Effects
0	No effect
1	Slight depression of activity, slight static ataxia after standing in one position for 3–5 min.
2	Walks with prance-like placement of feet, exaggerated reflex to a swinging hand, static ataxia after dog standing in one position for 2–3 min.
3	Tail is often tucked, some loss of tone in hind legs, static ataxia more pronounced and seen after standing in one position for 1–2 min.
4	Marked static ataxia, sways forward and backward and/or side to side, almost falls after standing in one position for a minute.
5	Cannot stand for longer than 30 sec w/o falling, dog frequently plunges about.
6	Dog lies prostrate on the floor.

Behavioral Effects of the Enantiomers of 11-OH-Δ^8-THC-DMH in the Dog

Treatment	N	Rating
Vehicle	4	0
Δ^9-THC (0.2 mg/kg)	4	2
(−)-11-OH-Δ^8-THC-DMH		
3 μg/kg	3	1 (postural effects)
5 μg/kg	3	1 (slight ataxia)
10 μg/kg	3	3
(+)-11-OH-Δ^8-THC-DMH		
1 mg/kg	3	1 (sedation only)

*Rating scale based on a modified version of the Walton Static Ataxia Scale [Dewey *et al.*, (3)].

Table 2. (−)-11-OH-Δ^8-THC-DMH produced static ataxia in the dog in a dose-related manner between 3–10 μg/kg. At 3 μg/kg no static ataxia was seen, however postural changes such as splaying of the hind and forelimbs were noted. At a dose of 5 μg/kg, dogs were slightly ataxic; however, it was only after the dogs remained in one place for an extended period of time. At 10 μg/kg static ataxia was pronounced in all dogs. In contrast, a dose of 1 mg/kg of the (+)-enantiomer failed to produce static ataxia. Many of the dogs were sedated following treatment with the (+)-enantiomer, however there were no signs of ataxia in any of the dogs.

DISCUSSION

The degree of stereoselectivity and potency demonstrated with the enantiomers of 11-OH-Δ^8-THC-DMH greatly exceeded that which has been previously demonstrated for the enantiomers of Δ^9-THC, Δ^8-THC, and other cannabinoids in mice. (−)-11-OH-Δ^8-THC-DMH was active between 3–100 μg/kg while the (+)-enantiomer was inactive up to 30 mg/kg in the mouse. The findings are consistent with the results found in the rotarod test and a number of antinociceptive tests in rats (11). (−)-11-OH-Δ^8-THC-DMH was also very potent in the dog static-ataxia model, which is a syndrome unique for cannabinoids and is highly predictive of the psychoactive component of the cannabinoids' pharmacological spectrum (14). The degree of stereoselectivity and potency of the (−)-enantiomer of 11-OH-DMH-Δ^8-THC is certainly consistent with existence of a specific receptor or some other highly selective mechanism of action.

(−)-11-OH-Δ^8-THC-DMH was also a very potent cannabinoid being 775, 1143, 178, and 79 times more potent than Δ^9-THC in decreasing spontaneous activity, and producing hypothermia, analgesia and catalepsy. The increased potency of (−)-11-OH-Δ^8-THC-DMH when compared to Δ^9-THC can be related to the structural modifications of the former compound. 11-OH-Δ^9-THC, an active metabolite of Δ^9-THC, is approximately 3–5 times more potent than the parent compound (15). Substitution of the pentyl side chain with a dimethylheptyl side chain dramatically increases the potency of a number of cannabinoids, including those which possess very little activity. Substitution of the pentyl side chain with a 1,1-dimethylheptyl side chain in Δ^{6a-10a}-THC increased the potency 1000 times (8), making a relatively inactive compound 500 times more potent than Δ^9-THC. It is likely that the high degree of stereoselectivity demonstrated with the enantiomers of 11-OH-Δ^8-THC-DMH as compared to that with the enantiomers of Δ^9-THC is a reflection of the increased potency of the (−)-enantiomer due to the structural changes. Therefore the modest degree of stereoselectivity demonstrated with Δ^9-THC may be the result of the relative potency of the naturally occurring (−)-enantiomer, and the enhanced stereoselectivity with the dimethylheptyl homologs is in part a reflection of the potency of the (−)-enantiomer.

The time course of the effects of (−)-11-OH-Δ^8-THC-DMH was examined in mice and compared to a dose of Δ^9-THC that produced a similar magnitude of effects. It has been reported in monkeys and dogs that dimethylheptyl derivatives of Δ^9-THC have very long durations of action, with overt behavioral effects lasting up to 72 hr (5). In mice, a dose of 10 μg/kg of (−)-11-OH-Δ^8-THC-DMH had a slightly longer duration of action than 10 mg/kg of Δ^9-THC in spontaneous activity and catalepsy, however by 8 hr mice were essentially unaffected. In the dog static-ataxia model, with a dose of 10 μg/kg, static ataxia was observed for approximately the first 4 hr after which sedation pronounced. Approximately 12 hr later the dogs appeared normal. The duration of action of the dimethylheptyl analogs is most likely related to dose. A dose of 100 μg/kg produced long-lasting (72 hr) effects in the dog, however when the dose was reduced to 40 μg/kg observable effects were noted for only 5 hr (5). There are many possible reasons that high doses of dimethylheptyl derivatives of cannabinoids exert long-lasting effects. It may be due to pharmacokinetic factors such as increased storage in fat depots due to an increase in lipophilicity, differences in plasma protein binding characteristics, or in metabolism, etc. On the other hand, it may be that the alkyl side chain serves as an anchor to orient the cannabinoid at its site of action, and a branched aliphatic chain such as a dimethylheptyl has a higher affinity for this site than an unbranched aliphatic side chain.

The lack of a specific antagonist of Δ^9-THC has greatly hampered the elucidation of the mechanisms of action of the cannabinoids. (+)-11-OH-Δ^8-THC-DMH was tested for its ability to block the effects of Δ^9-THC in mice. There was no attenuation of the effects of Δ^9-THC by pretreatment with (+)-11-OH-Δ^8-THC-DMH, in fact there was a slight increase (approximately 18%) in the degree of hypothermia and analgesia produced when both compounds were administered suggesting that the (+)-enantiomer may have some weak agonist properties. The (+)-enantiomer was shown to possess analgetic properties in mice and rats when administered in the presence of cupric chloride (11), however we failed to demonstrate antinociceptive activity both in the absence and presence of cupric chloride.

In conclusion, the degree of stereoselectivity demonstrated with the enantiomers of 11-OH-Δ^8-THC-DMH greatly exceeded

that which had been demonstrated previously for the cannabinoids. The degree of stereoselectivity is on the order of that demonstrated with the opiates, a well defined receptor system (6). It is likely that the extreme potency of (−)-11-OH-Δ^8-THC-DMH unmasks the true stereoselectivity of the cannabinoids. The stereoselectivity and the potency of the (−)-enantiomer is certainly consistent with the existence of a specific receptor for the cannabinoids which is involved in the mediation of some of the pharmacological effects of the cannabinoids.

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