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Discriminative Stimulus- and Open-Field Effects of the Enantiomers of 11-Hydroxy-Delta-8-Tetrahydrocannabinol in Pigeons and Gerbils

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JÄRBE, T. U. C., R. MECHOULAM AND J. ZAHALKA. *Discriminative stimulus- and open-field effects of the enantiomers of 11-hydroxy-delta-8-tetrahydrocannabinol in pigeons and gerbils.* PHARMACOL BIOCHEM BEHAV **47**(1) 113–119, 1994.—The cannabimimetic activity of the two enantiomers of 11-hydroxy-delta-8-tetrahydrocannabinol (11-OH-delta-8-THC) was evaluated in pigeons trained to discriminate between the presence and absence of (−)-delta-9-tetrahydrocannabinol [(−)-delta-9-THC]. (−)-11-OH-Delta-8-THC exhibited cannabimimetic activity with a potency (ED_{50}, 0.17 mg/kg) similar to that of delta-9-THC. The duration of action for (−)-11-OH-delta-8-THC was shorter than that observed for delta-9-THC. No cannabimimetic activity was seen after administrations of (+)-11-OH-delta-8-THC, indicating enantiomeric selectivity for the discriminable effects. A dose-related decrease in response rate occurred with (−)-11-OH-delta-8-THC, but not with (+)-11-OH-delta-8-THC; the latter compound produced an increase in responding at 3 mg/kg. Open-field behavior in Mongolian gerbils indicated marked suppression of rearing (vertical activity) after treatments with (−)-delta-9-THC and (−)-11-OH-delta-8-THC; this did not occur after (+)-11-OH-delta-8-THC. The results support the notion of cannabimimetic enantiospecificity.

THC cue Tetrahydrocannabinol Discrimination Stimulus Operant Pigeons Open-field Gerbils Structure-activity relationship (SAR) Enantiomers Stereoselectivity Cannabimimetic Marijuana

ENANTIOMERIC selectivity or preference is a characteristic trait for transmission via specific recognition sites in the nervous system. The structure-activity relationships (SARs) established over the last two decades of cannabinoid research indicate stereoselective preference for (−)-delta-9-tetrahydrocannabinol [(−)-delta-9-THC], over that of (+)-delta-9-THC. Thus, it was reported in the 1970s that (−)-delta-9-THC, the major active constituent of marijuana and hashish, was 13 to 20 times more active than the corresponding, dextrorotated enantiomer—that is, (+)-delta-9-THC—in various test assays (5). This difference in enantiomeric preference is, however, not very impressive in comparison to the marked selectivity disclosed for, for example, the opiate receptor system (27).

The clear-cut differentiation between the (−)- and (+)-isomers of the 11-position hydroxylated dimethylheptyl homolog of delta-8-THC (11-OH-delta-8-THC-DMH) suggested complete enantiomeric specificity in several pharmacological tests (cf. 25,29,30,31), including drug discrimination learning in rats and pigeons (19,31). The DMH side chain differentiates this compound from the natural 11-OH-delta-8-THC, a metabolite of the cannabimimetic cannabinoid delta-8-THC, which has a *n*-pentyl side chain. Thus, one might argue that the marked enantio-selectivity observed for the DMH com-

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pounds was due to the unnatural side chain. Therefore, the finding with the DMH homolog might not be applicable to the stereospecificity of natural THCs.

One reason for questioning the validity of the early investigations concerning comparatively low enantiomeric specificity for natural THCs relates to the route of synthesis (30). The starting material for preparing (+)-THC, commercial (+)-alpha-pinene, was only 90–95% pure. Hence, if further purification is not undertaken, the resulting product will contain also the active (−)-enantiomer. Given the absence of statements to the contrary, most likely the enantiomers used in the early studies may have contained 5–10% of the (−)-isomer. This (−)-THC impurity certainly contributes to, or may even fully explain, the comparatively low separation between the enantiomers for the various assays summarized by Dewey et al. (5).

In the present study, drug discrimination and open-field behavior assays were used to examine the cannabimimetic activity of highly purified enantiomers of 11-OH-delta-8-THC. (−)-11-OH-Delta-8-THC is an active metabolite of (−)-delta-8-THC (2); (+)-11-OH-delta-8-THC is a metabolite of (+)-delta-8-THC (13). In laboratory animals, the cannabimimetic (35) effects of THC have been found to be highly robust and valid in tests for response generalization from a THC discriminative stimulus to the stimulus effects of other compounds (1,20,34). In previous communications, it has been observed that not only the potency, but also the onset and duration of effect, may be affected by changes in the molecular arrangement of cannabimimetic agents (e.g., 18,19). Therefore, the time course of the discriminative stimulus effects and response rate by pigeons were examined using a repeated test procedure (14).

Examining open-field performance provides an assessment of the effects of drugs on a variety of unconditioned behaviors. Indeed, anandamide, an endogenous constituent acting as a "cannabinoid" ligand in the mammalian brain (4), produces significant depression of behavior in open-field tests for rodents (9). Studying gerbils increases the generality of findings across species. Recent investigations of the THC receptor indicate that it is phylogenetically old (15) and has a distribution in the brain which is similar across species (11,26).

MATERIALS AND METHODS

Animals

Seven male White-Carneaux pigeons (Palmetto Pigeons Plant, Sumter, SC) were used for training and testing. The animals were housed individually under standard laboratory conditions (temperature 20–22°C, relative humidity about 50–60%, and 12-h light-dark cycle). Pigeons were deprived of food to maintain their weight at 75–80% of their expected free-feeding weights. Shellgrit and water for pigeons were freely available in the home cages. The average (± SE) free-feeding weights were 585 (± 10.3) g for pigeons.

Sixty-six male Mongolian gerbils (*Meriones unguiculatus*) from our breeding stock (Department of Psychology, University of Uppsala) were used. The animals were experimentally naive at the start of the experiments. The weights ranged from 58 to 95 g, with a mean (± SE) weight of 71.6 (1.1), and the gerbils were between 6 and 18 months old when the experiments began. Except during the experimental sessions (see open-field procedure), the animals were housed in groups of four in macrolone cages (16 cm × 33 cm × 45 cm) under standard laboratory conditions as described above. Animals had free access to pelleted food (Astra Ewos, type R3) and tap water at all times except during the experimental sessions. The numbers of gerbils used for each test condition are indicated in the Results.

Apparatus

The experimental chambers used for discrimination training and testing with pigeons have been described elsewhere in more detail (14,17). Chambers contained two white response-keys mounted on the front panel, and a food magazine located between and 19 cm below the response keys. White noise was provided to all chambers to mask extraneous sounds. Electromechanical relay programming and recording equipment were used to control delivery of food and to register the performance of the animals.

Discrimination Training Procedure

The training proceeded as described elsewhere (e.g., 18,19). The animals had to peck the appropriate response key under a fixed ratio (FR) 15 schedule of reinforcement; reinforcement was 4-s access to grain (chicken pellets, type No. 22, AB Joh. Hansson, Uppsala, Sweden). Which key was correct depended upon whether (−)-delta-9-THC or its vehicle had been administered prior to the session. Responses on the inappropriate key had no programmed consequences. The training dose of (−)-delta-9-THC was 0.56 mg/kg administered intramuscularly (IM, 1 ml/kg) 90 min prior to session onset. Pigeons were trained until 40 reinforcements were delivered or 20 min had elapsed, three days a week (Mondays, Wednesdays, and Fridays). The schedule of drug- or vehicle-training sessions was random, with no more than two similar sessions occurring consecutively. To avoid potential interanimal cues, the daily order of drug or vehicle sessions for animals trained in the same chamber was varied (6).

The criterion for the acquisition of the discrimination was the completion of the first fixed ratio on the correct, injection-appropriate key on at least 8 out of 10 consecutive training sessions. Correct selection was defined as the number of responses for the first reinforcement (FRF) being equal to or less than 29. Customarily, median FRF is 15 (e.g., 14,18,19).

Discrimination Testing Procedure

Repeated testing was utilized (14) in which two and, in one instance, three (see below) successive test probes of six trials each were conducted after a single injection of a drug test dose. Tests were generally conducted 90 and 270 min postinjection. For each test, reinforcement was provided for responses on either key under the training schedule of reinforcement, and ended after either the delivery of six reinforcers or 20 min. Between test probes, animals remained in their home cages.

Drugs and doses were tested in an unsystematic, mixed order. Tests were conducted once a week as described elsewhere (e.g., 19); training was conducted on intervening days. Approximately half the number of tests was preceded by a drug-training session; the other half was preceded by a non-drug-training session. Tests were conducted if a subject's performance during two preceding training sessions had been correct. If not correct, additional training was implemented before new tests occurred.

Open-Field Procedure

On the day of testing, the animals were handled intermittently for 30 min and then placed individually in separate

cages. These precautions, which are routinely applied in this laboratory (e.g., 21, 23), were taken to minimize the potential incidence of "spontaneous seizures" (33) during testing. After being treated IP with the appropriate solutions (4 ml/kg except otherwise indicated), the gerbils were returned to their respective individual cages until testing in the open-field arena began 30 min later.

The open-field arena was a grey-painted wooden box (60 × 60 × 50 cm) with an open top, a white floor divided into 16 squares (15 × 15 cm), and a circle marked in the center of the field. The squared floor was covered with an acrylic plate (60 × 60 cm), which was cleaned between trials. The gerbils were placed, one at a time, in the center of the field for 5 min observation.

The following behavioral categories were recorded: ambulation (the number of squares crossed), rearing (the number of times the gerbil stood erect on its hind-legs), latency (the time in seconds to leave the starting area, the circle in the center of the field), grooming (the number of cleaning bouts), and urination and defecation (the number of urination spots and fecal boli deposited during the 5-min observation period).

Drugs

(−)-11-Hydroxy-delta-8-THC was prepared by oxidation of (−)-delta-8-THC following a published procedure (3). As (−)-delta-8-THC, used as starting material, was prepared from natural, crystalline (−)-cannabidiol of presumably absolute optical purity (10), it can be assumed that (−)-delta-8-THC, and hence also (−)-11-hydroxy-delta-8-THC, were obtained at the same level of chiral purity. (+)-11-Hydroxy-delta-8-THC was prepared following the route described for (+)-11-hydroxy-delta-8-THC-DMH (HU-211) (32), except that olivetol rather than 3-(1,1-dimethylheptyl)-resorcinol was used to reach a high (or essentially absolute) level of chiral purity. The important intermediate in this synthesis, (+)-4-oxo-myrtenyl pivalate, was recrystallized four times with pentane and analysed on a Daicel Chemical Industries 10-μm Chiral-Pak column (column dimensions 250 mm × 4.6 mm; mobile

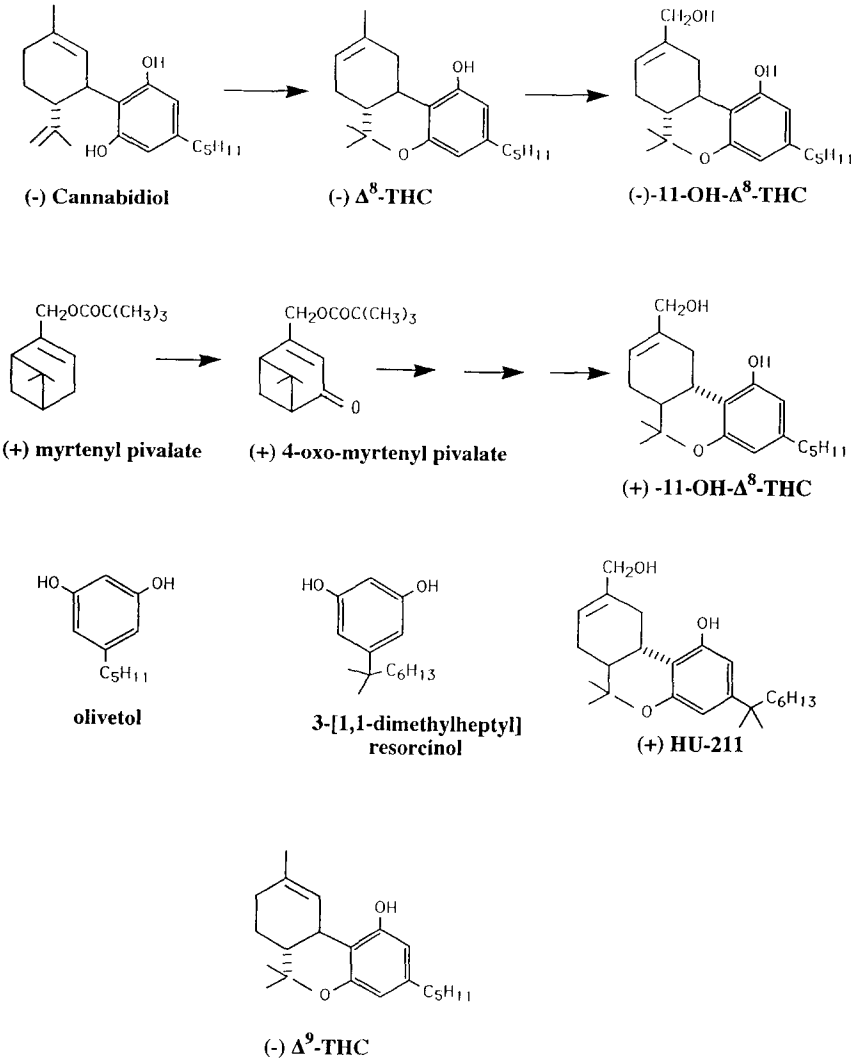

FIG. 1. Chemical reaction sequences and individual compounds described in this article.

phase n-hexane mixed with 1-20% isopropanol; flow rate 1 ml/min; monitored at 220 and 270 nm). The analysis indicated that (+)-4-oxo-myrtenyl pivalate had essentially absolute chiral purity (>99.9% enantiomeric excess) (S. Levin, manuscript in preparation). As the reaction proceeding from (+)-4-oxo-myrtenyl pivalate to (+)-11-hydroxy-delta-8-THC does not lead to racemization (cf. 32), the latter compound is therefore also of essentially absolute chiral purity (>99.9% enantiomeric excess). A flow diagram of the various steps in the synthesis of the 11-position hydroxylated compounds is provided in Fig. 1. (−)-Delta-9-THC was supplied by the U.N. Cannabis Research Programme (Vienna).

All compounds were dissolved in ethanol (99.5%) and refrigerated at −4°C. From these stock solutions, appropriate amounts were withdrawn the day before testing took place. The ethanol was evaporated under a stream of nitrogen and the residue dissolved in a propylene glycol/polysorbate-80 mixture using a sonicator. Suspensions were prepared shortly before administration, and contained propylene glycol, Tween-80, and physiological (0.9%) saline (5, 2, and 93%, v/v), unless otherwise indicated.

Data Analysis

The data obtained for each pigeon were the percentage of responses on the drug-associated key out of the total number of responses emitted, as well as the rate of responding. Median dose effect estimates (ED_{50}) for the discrimination test data were determined by logarithmic regression analysis. The *A* test (28) was used to analyze response rate; this test statistic is equivalent to the Student's paired *t* test. For the open-field study with gerbils, the values represent average counts over the 5-min observation period, with the exception of latency, which is expressed as the time in seconds to leave the center area of the open-field arena. Analysis of variance (ANOVA, completely randomized design) was used to assess overall effects. Tukey's HSD and Scheffee's *F* were used for a posteriori comparisons between means (24). Comparisons are considered statistically significant when $p < 0.05$.

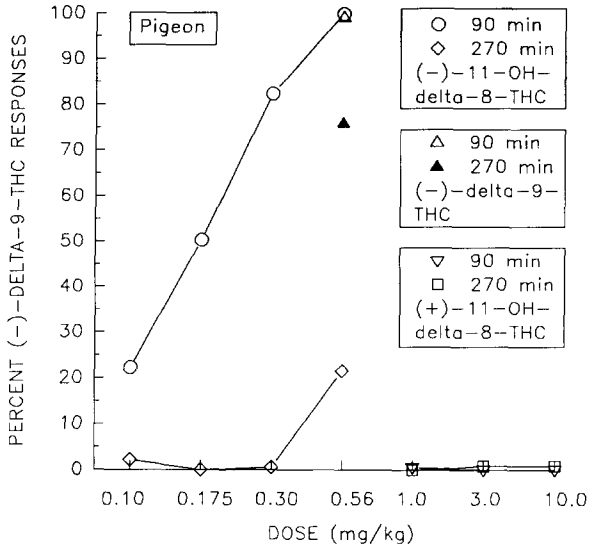

FIG. 2. Substitution test results with enantiomers of 11-OH-delta-8-THC for pigeons trained to discriminate between 0.56 mg/kg of (−)-delta-9-THC and vehicle. Y axis, percentage of responses to the drug-associated key; X axis, drug dose in mg/kg. The data points are based on one observation per animal ($n = 7$) and test interval except for 0.56 mg/kg (−)-11-OH-delta-8-THC at the 90-min postinjection tests, where three birds did not respond, and for 3 and 10 mg/kg of (+)-11-OH-delta-8-THC, where $n = 4$. All administrations were IM 1 ml/kg except for 3 and 10 mg/kg of (+)-11-OH-delta-8-THC, where the volume was 2 and 3 ml/kg, respectively. The amounts of Tween-80 used were 2%, 3%, and 4% for the three doses (1, 3, and 10 mg/kg) of (+)-11-OH-delta-8-THC. In all cases the percentage of propylene glycol was 5%, and consequently the amount of saline ranged between 93% to 91%.

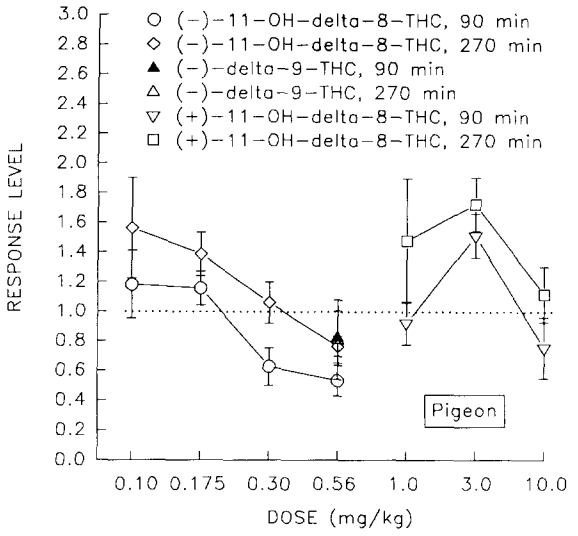

FIG. 3. Response output for pigeons in tests with delta-9-THC and the enantiomers of 11-OH-delta-8-THC. Response level refers to the quotient between the time to complete the initial six reinforcements during the most recent vehicle-training session and time in the particular test session in question. A quotient of unity (i.e., 1.0, as represented by the dotted line) means that the time to obtain six reinforcements during testing was the same as that recorded during the most recently preceding non-drug-training session. Consequently, scores above 1.0 reflect an increased response output, whereas values below 1.0 reflect a decreased response output, respectively. All response-level data points are based only on responding animals (a responder received at least one reinforcement during a test probe of six trials). Due to a lack of responding, the mean value for 0.56 mg/kg of (−)-11-OH-delta-8-THC at 90 min postinjection is based on the performance of four responding birds. For 3 and 10 mg/kg of (+)-11-OH-delta-8-THC, $n = 4$. Other details are as in the legend of Fig. 2.

RESULTS

Drug Discrimination—Pigeons

Baseline performance. During periods of testing, the pigeons averaged (± SEM) 95.7 (4.3)% correct selections during training sessions with (−)-delta-9-THC, and 95.5 (1.7)% correct selections during vehicle-training sessions.

Discrimination tests. A dose-related increase in the percentage of (−)-delta-9-THC-appropriate responding occurred after injections of (−)-11-OH-delta-8-THC at the 90-min test interval (cf. Fig. 2); the ED_{50} value is 0.17 mg/kg, and the correlation coefficient (*r*) for the regression is 0.99. A comparatively short duration of cannabimimetic activity for (−)-11-OH-delta-8-THC is indicated by the much reduced degree of (−)-delta-9-THC-appropriate responding (maximum 22%) seen at the subsequent test interval occurring 270 min postin-

jection. Thus, ED_{50} is >0.56 mg/kg at this latter interval. At the same interval, tests with 0.56 mg/kg of (−)-delta-9-THC produced 76% THC-appropriate responding; thus, ED_{50} for (−)-delta-9-THC is <0.56 mg/kg at 270 min postadministration.

Tests with the (+)-isomer engendered very little THC-appropriate responding (<1%) during both the probes occurring at 90 as well as 270 min after administration (cf. Fig. 2). An additional test conducted 9 h after administration of 10 mg/kg of (+)-11-OH-delta-8-THC yielded only vehicle-appropriate responding (not shown). Doses higher than 10 mg/kg of the (+)-isomer were not examined due to a limited supply of materials.

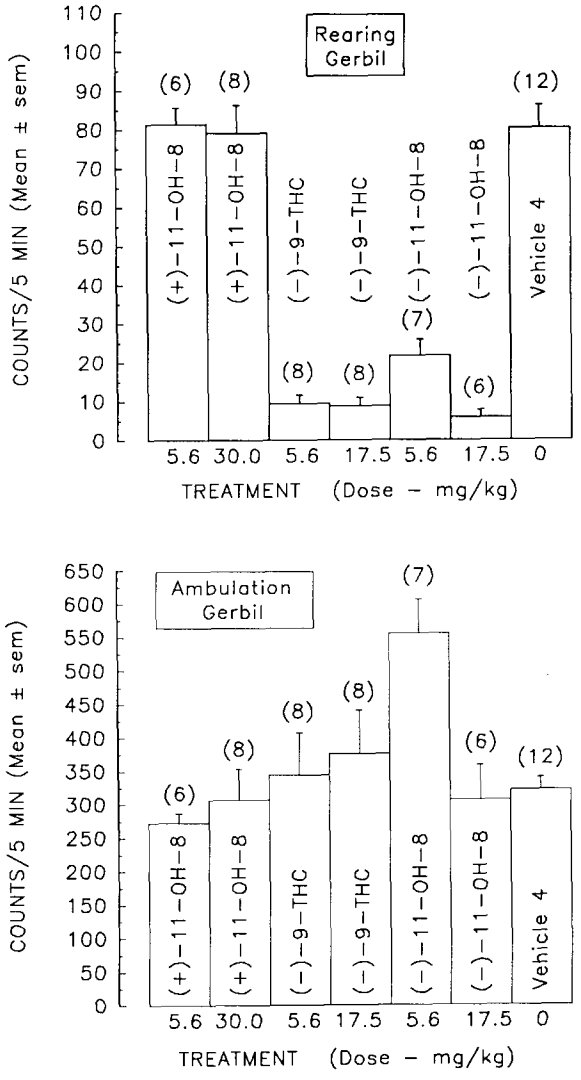

FIG. 4. Effects of cannabinoids on two open-field behaviors—rearing (top) and ambulation (bottom)—in male gerbils. Y axis, average counts during a 5-min observation period; X axis, treatment levels. The number of gerbils on which the means are based are indicated by numbers within brackets at the top of the bars. (+)-11-OH-8 = (+)-11-hydroxy-delta-8-tetrahydrocannabinol; (−)-9-THC = (−)-delta-9-tetrahydrocannabinol; (−)-11-OH-8 = (−)-11-hydroxy-delta-8-tetrahydrocannabinol; vehicle refers to 4 ml/kg of the suspension.

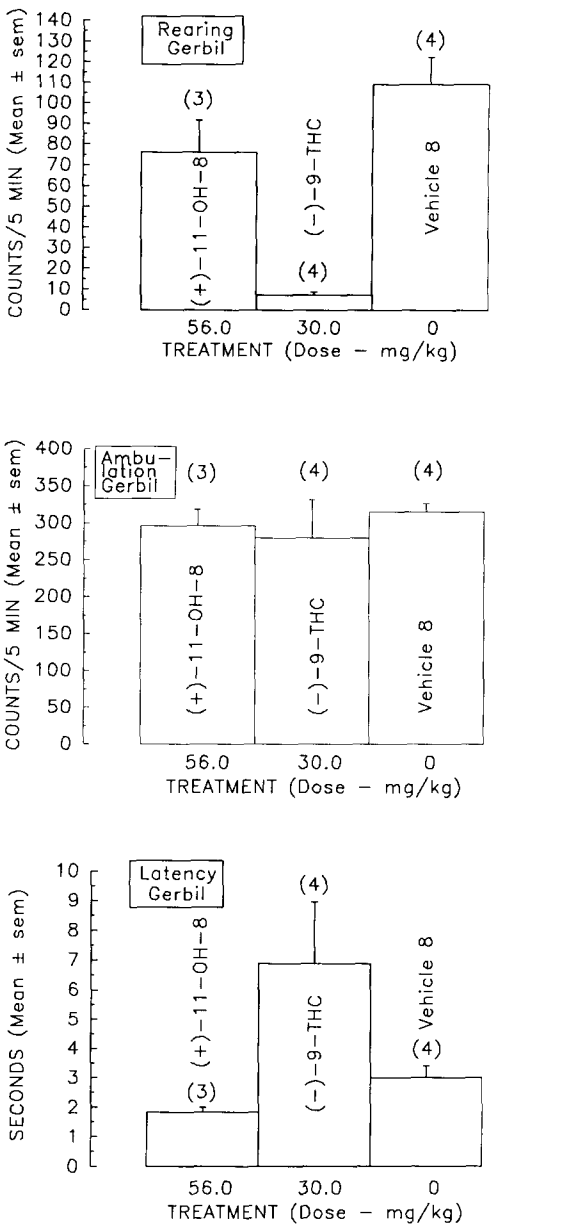

FIG. 5. Effects of cannabinoids on three open-field behaviors—rearing (top), ambulation (middle), and latency (bottom). Y axis, average counts during a 5-min observation period, except for latency, which refers to mean seconds to leave the start area of the open-field arena; X axis, treatment levels. The number of gerbils on which the means are based are indicated by numbers within brackets at the top of the bars. For abbreviations, see legend of Fig. 4. The volume of 8 ml/kg rather than 4 ml/kg was used for these suspensions.

Response level. Figure 3 shows the response data pertaining to the discrimination tests. During tests with (−)-11-OH-delta-8-THC, there was a downward trend in response rate as a function of dose. The effect appeared more marked at 90 min as compared to 270 min postinjection. In fact, three out of the seven birds tested did not receive any reinforcement during the probe conducted 90 min after administration of 0.56 mg/kg (−)-11-OH-delta-8-THC (data not included when

computing the response data shown in graph 3). With (+)-11-OH-delta-8-THC response output was either not changed, or slightly increased as compared to the response output during vehicle-training sessions. The increase seen with 3 mg/kg of the (+)-isomer was statistically significant, the *A* values being 0.271 and 0.269 for the 90 and 270 min postinjection intervals, respectively ($p < 0.01$).

Open-Field—Gerbils

Rearing. ANOVA indicated significance, $F(6, 48) = 51.65$, $p < 0.0001$, and subsequent HSD indicated that the four groups treated with (−)-delta-9-THC and (−)-11-OH-delta-8-THC, while not differing among themselves, differed from the vehicle- and (+)-11-OH-delta-8-THC–treated gerbils (cf. Fig. 4, top graph).

Ambulation. ANOVA indicated significance, $F(6, 48) = 3.57$, $p < 0.005$, and subsequent HSD indicated that animals treated with 5.6 mg/kg of (−)-11-OH-delta-8-THC exhibited more crossings during the 5-min test period than any other group, except for the animals treated with 17.5 mg/kg of (−)-delta-9-THC; the latter group, however, did not differ significantly from the other groups (cf. Fig. 4, bottom graph).

Grooming and latency. ANOVA applied to these parameters did not indicate overall significance, $F(6, 48) = 2.03$ (grooming) and 1.45 (latency), $p > 0.05$.

Defecation and urination. ANOVA indicated significance, $F(6, 48) = 2.56$, $p < 0.03$, for urination but not for defecation, $F(6, 48) = 1.75$, $p > 0.05$. Scheffe's test applied to the means of the four groups of gerbils treated with the levo-rotated compounds versus the means of the remaining three groups [(+)-11-OH-delta-8-THC as well as the vehicle group] indicated marginal significance ($0.05 < p < 0.10$) for the urination parameter. The combined means for (−)-delta-9-THC and (−)-11-OH-delta-8-THC treatment groups were 0 (urination) and 0.03 (defecation) counts. The corresponding values for the (+)-11-OH-delta-8-THC- and vehicle-treated groups were 0.29 (urination) and 0.57 (defecation) counts.

An additional set of gerbils ($N = 11$) were examined after treatments with vehicle (8 ml/kg, $n = 4$), 30 mg/kg (−)-delta-9-THC ($n = 4$), and 56 mg/kg (+)-11-OH-delta-8-THC ($n = 3$), the latter *n* because one animal died shortly after injection. These results are shown in Fig. 5. As before, treatment with 30 mg/kg (−)-delta-9-THC suppressed rearing, $F(2, 8) = 24.15$, $p = 0.0004$, and HSD indicated that the rearing scores for the animals treated with (−)-delta-9-THC were significantly lower as compared to those of the two other groups; the latter two groups did not differ significantly. Ambulation did not differentiate among the groups, $F(2, 8) = 0.28$, $p > 0.05$; cf. middle section of Fig. 5. The latency score of 6.9 (± 2.1) s for the 30 mg/kg (−)-delta-9-THC group, however, approached significance, $F(2, 8) = 3.76$; $p = 0.07$; cf. lower section of Fig. 5. The other comparisons were not significant.

DISCUSSION

The enantiomeric pair of 11-OH-delta-8-THC was examined for cannabimimetic potential in pigeon and gerbils. The levo-rotated compound—that is, (−)-11-OH-delta-8-THC—occasioned THC-appropriate responding, whereas the dextro-rotated (+)-isomer failed to do so in the dose range tested. Open-field data from gerbils gave additional support for a differentiation between the (−)- and (+)-isomers.

The observation that (+)-11-OH-delta-8-THC did not disclose response generalization with (−)-delta-9-THC is congruent with a stereospecific separation between the enantiomers. Thus, although the highest dose of (+)-11-OH-delta-8-THC examined here is 58 times larger than the ED_{50} for (−)-11-OH-delta-8-THC, essentially only responding appropriate for the vehicle condition occurred, <1% (−)-delta-9-THC–appropriate responding. The demonstrated separation in cannabimimetic activity is considerably higher than that reported previously for naturally occurring cannabinoids (5,27). This reinforces the assumption that low purity of (+)-THC may have been responsible for the limited enantiomeric preference with regard to cannabimimetic activity for delta-9- and delta-8-THC demonstrated in the past.

Whereas most measures in the open-field test did not clearly differentiate between the various treatment groups, rearing (vertical activity) consistently was suppressed by the levo-rotated THCs; this did not occur with (+)-11-OH-delta-8-THC. The differential effects on rearing as well as the discrimination data are consistent with the recent demonstration that the parent compound of (+)-11-OH-delta-8-THC, (+)-delta-8-THC, was inactive in the mouse ring test at the dose of 50 mg/kg, whereas the (−)-isomer was active at a dose of 1 mg/kg (30).

Surprisingly, ambulation for gerbils was not decreased by the cannabimimetics. In other laboratory animals, the doses of THC examined here would have suppressed most behaviors (5), including ambulation (16,17). Grunfeld and Edery (12) reported that sand digging in gerbils was reduced after IP administration of levo-rotated THCs and that gerbils (as well as mice and rats) exhibited a decrease in spontaneous motility. However, the reduced motility could be overcome or "reverted by simple sensorial stimuli such as finger clicking or touching" (12). It is possible that the change from group to single housing, as well as the open-field testing, served as arousal stimuli, thereby counteracting inferred depressant effects of THC on motility for the gerbils in this study.

Although the dextro-rotated THCs may not be cannabimimetic, they need not necessarily be devoid of any pharmacological effects. For example, (+)-11-OH-delta-8-THC-DMH has antiemetic properties (7) and acts as a functional *N*-methyl-D-aspartate receptor blocker (8,36). The increased response output observed in the present discrimination tests with 3 mg/kg of (+)-11-OH-delta-8-THC may indicate intrinsic activity. Although the change of response rate was limited to the middle dose of (+)-11-OH-delta-8-THC tested here, a similar narrow dose-effect window has been emphasized previously for the antiemetic effects of the corresponding dimethylheptyl homolog (7).

The present potency estimate for (−)-11-OH-delta-8-THC being ≥ (−)-delta-9-THC is in good agreement with an earlier determination in pigeons (22). The duration of cannabimimetic activity for (−)-11-OH-delta-8-THC was relatively short (ED_{50} at 270 min postinjection > 0.56 mg/kg). In comparison, the ED_{50} value for (−)-delta-9-THC is 0.25 mg/kg (19). A comparatively short duration of action for THC-like stimulus effects has previously been observed with two hexahydrocannabinols (18). Thus, it appears that hydroxylation at the 11-position of THC reduces the duration of cannabimimetic action [see also (19)].

In conclusion, the examination of the present pair of enantiomers extends previous demonstrations emphasizing the strict stereospecific requirement for the expression of cannabimimetic activity. The major importance derives from the fact that the compounds investigated and reported on here represent a primary active metabolite of a naturally occurring active cannabinoid, and its enantiomer, and that essentially complete

separation as regards cannabimimetic activity was recorded between these two enantiomers.

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