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Cannabimimetic Activity (Δ^1-THC Cue) of Cannabidiol Monomethyl Ether and Two Stereoisomeric Hexahydrocannabinols in Rats and Pigeons[1]

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JÄRBE, T. U. C., A. J. HILTUNEN, N. LANDER AND R. MECHOULAM. *Cannabimimetic activity (Δ^1-THC cue) of cannabidiol monomethyl ether and two stereoisomeric hexahydrocannabinols in rats and pigeons.* PHARMACOL BIOCHEM BEHAV 25(2) 393–399, 1986.—Animals (rats and pigeons) trained to discriminate between the presence and absence of the effects of Δ^1-tetrahydrocannabinol (Δ^1-THC; 3 and 0.56 mg/kg, respectively) were tested for generalization with graded doses of Δ^1-THC as well as with two 7-hydroxyhexahydrocannabinol epimers which differ in the stereochemistry at the C-1 position only, and a cannabidiol (CBD)-like compound, cannabidiol monomethyl ether (CBDM). Δ^1-THC produced dose/time related effects in both rats and pigeons. Both 7-hydroxyhexahydrocannabinols generalized with Δ^1-THC in both species. Greater cannabimimetic activity was observed when the substituent at the C-1 position was equatorial (as in compound NL-105) than when the substituent was axial (compound NL-106) (for chemical structures see Fig. 1, below). Thus in the absence of other substituents the planarity at the C-1 position determines cannabimimetic activity. CBDM induced only vehicle appropriate responding at the doses of 3 and 10 mg/kg in both species; 30% Δ^1-THC appropriate responding occurred with 17.5 mg/kg (only tested in pigeons), a dose which also appeared to excert rate depressant effects. Thus, like CBD, CBDM has a low degree of cannabimimetic activity.

Drug discrimination Δ^1-THC Hexahydrocannabinol stereochemistry CBDM Rats Pigeons

REPEATED tests procedures for evaluating the onset and duration of effect at several intervals after a single injection of a drug dose is quite a new approach in drug discrimination learning (DDL). Comparing this approach with the conventional procedure in which all intervals are evaluated only once after separate injections of the drug doses yielded consistent results with respect to tetrahydrocannabinol (THC) in both rats [16] and pigeons [8], and repeated testing was concluded to be reliable and time saving. When the amounts of experimental compounds are limited tests can be carried out with considerably smaller quantities using such an approach.

In this DDL study repeated tests procedures examined more extensively both the potency and duration of effect of THC as well as the cannabimimetic activity [25] of some compounds chemically related to classical cannabinoids such as the cannabimimetic Δ^1-tetrahydrocannabinol (Δ^1-THC) and the noncannabimimetic cannabidiol (CBD). DDL has been suggested to be the procedure of choice when evaluating the cannabimimetic, THC-like potential of compounds (e.g. [25]).

Two stereoisomers of 7-hydroxyhexahydrocannabinol with C-1 substituents equatorial (NL-105) and axial (NL-106), respectively, were tested to evaluate if, in the absence of other variations, the planarity of the molecule at the C-1 position determines "hashish" activity as assessed in the DDL model (see below for chemical identification, section on Drugs).

The natural constituent CBD is not perceived as producing effects similar to Δ^1-THC, either in man or animals (for documentation see [8]). The chemically related compound cannabidiol monomethyl ether (CBDM) is a minor cannabinoid present in some hemp varieties [24]. CBDM was

[1]Parts of these data were presented at the International Union of Pharmacology, IUPHAR, 9th International Congress of Pharmacology Satellite Meeting: European Study Group for Internal Stimulus Control by Electrical Stimulation, Drugs and Other Means, ESISC, London, July 29–August 3, 1984 [11] and at the XVIII Nordic Congress for Physiology and Pharmacology, Uppsala, June 10–13, 1985 [15].

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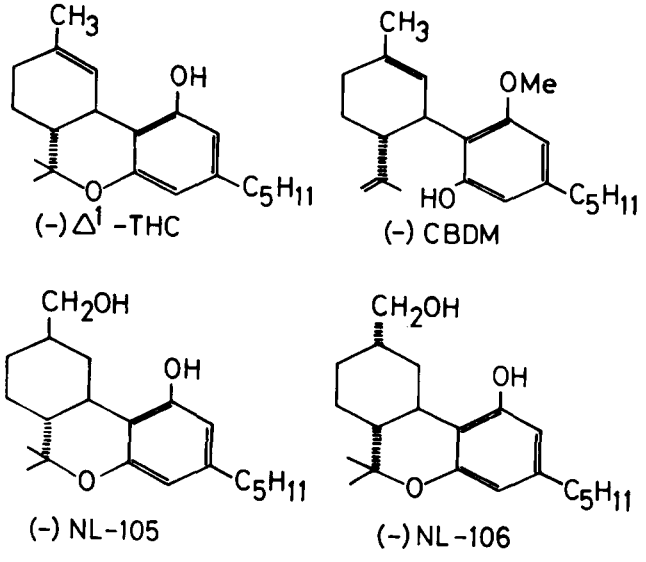

FIG. 1. Chemical structure of the compounds used in this study. Δ^1-Tetrahydrocannabinol ((−)Δ^1-THC); CBDM is the abbreviation for cannabidiol monomethyl ether; NL-105 and NL-106 are two 7-hydroxyhexahydrocannabinols differing only in the stereochemistry at the C-1 position. For further information see text.

TABLE 1

Hrs	Δ^1-THC	NL-105	NL-106
	Rats		
0.5	0.85 (0.94)	0.24 (0.95)	1.58 (0.98)
1.5	1.07 (0.94)	0.44 (0.997)	2.16 (0.96)
4.5	4.78 (0.79)	—	—
	Pigeons		
0.5	0.53 (0.92)	0.03 (0.99)	2.60 (0.58)
1.5	0.16 (0.91)	0.02 (0.87)	1.72 (0.97)
4.5	0.25 (0.94)	—	—
9.0	1.21 (0.70)	—	—

Median dose (mg/kg) effect estimates, ED_{50}, according to logarithmic regression analysis and within brackets the corresponding fits (r) for the regressions are given. The upper portion reflects data for rats (based on the results from Figs. 2 and 3) and the lower section shows the data for pigeons (based on the results from Figs. 4 and 5). Absence of an estimate (—) means that no value in the dose-generalization curve determination was above 50% drug appropriate responding (% RDP). Hours reflect the passage of time since injection until testing.

included in the present study to examine further the importance of an intact "pyran" ring for cannabinoids in eliciting cannabimimetic activity [20,22].

Two species, rats and pigeons, were trained to discriminate between the presence and absence of Δ^1-THC and since repeated testing was utilized we therefore could monitor the time-course of the stimulus effects after a single injection of a given dose of the test substance.

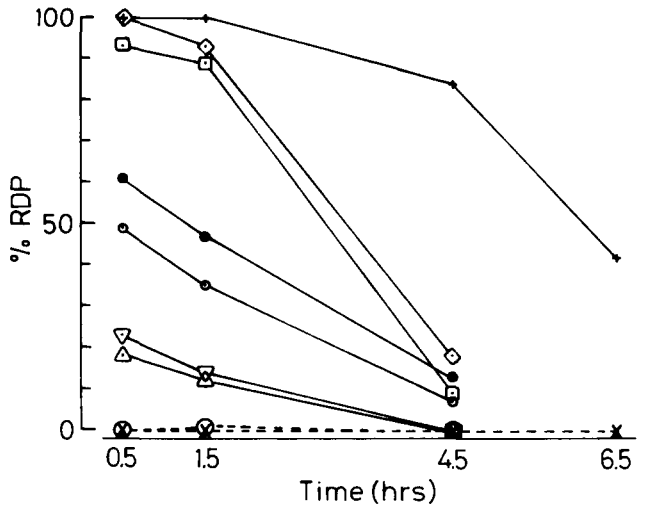

FIG. 2. Dose generalization results with different doses of Δ^1-tetrahydrocannabinol (Δ^1-THC) in rats trained to discriminate between 3 mg/kg of Δ^1-THC and vehicle. The doses tested in each of the 14 participating rats were: 5.6 mg/kg (+—+), 3 mg/kg (◇—◇), 1.75 mg/kg (□—□), 1 mg/kg (○—○), 1st determination; ●—●, 2nd determination, 0.56 mg/kg (▽—▽), 0.3 mg/kg (△—△), and vehicle (○— —○) as well as the vehicle used for 5.6 mg/kg of Δ^1-THC (X— —X). The latter vehicle consisted of 5% (v/v) of propylene glycol, 4% tween-80 (v/v), and 91% saline. The vehicles for the other doses were similar in contents except that less amounts of tween-80 (2%) was used. All administrations were IP (2 ml/kg) · % RDP=percentage of responding to drug position, and Time (hr) refers to the time elapsed until testing after a single injection of the drug dose.

METHOD

Animals

A pool of 14 male Sprague-Dawley rats (ALAB AB, Sollentuna, Sweden) and 7 male White-Carneaux pigeons (Palmetto Pigeons Plant, Sumter, SC) were available for training and testing. The animals were housed individually under standard laboratory conditions (temperature 20–22°C; relative humidity of about 50–60%; and 12 hr light-dark cycle). The animals were deprived of water (rats) or food (pigeons) to maintain their weight at 75–80% of their free-feeding weights. This was accomplished through individual rationing of water and food, respectively; other nutrients such as food pellets for rats (type R3, Ewos AB, Södertälje, Sweden) and shellgrit and water for pigeons were freely available in the home cages. The average (±SEM) free-feeding weights were 322 (±7.6) g and 585 (±10.3) g for rats and pigeons, respectively.

Apparatus

The experimental chambers, adapted after Ferster and Skinner [5], has been described elsewhere in more detail [8]. The rat chambers contained two response levers separated by a recess in which a water reward could be presented by a retractable drinking cup. The reward was a 4 sec access to sweetened water (saccharin 0.1%). Essentially the same set-up was used for the pigeons. Thus, in the pigeon chamber there were two response keys on the front panel, and the food magazine was located between the response keys. The reinforcement was a 4 sec access to grain (chicken pellets, type No. 22, AB Joh. Hansson, Uppsala, Sweden).

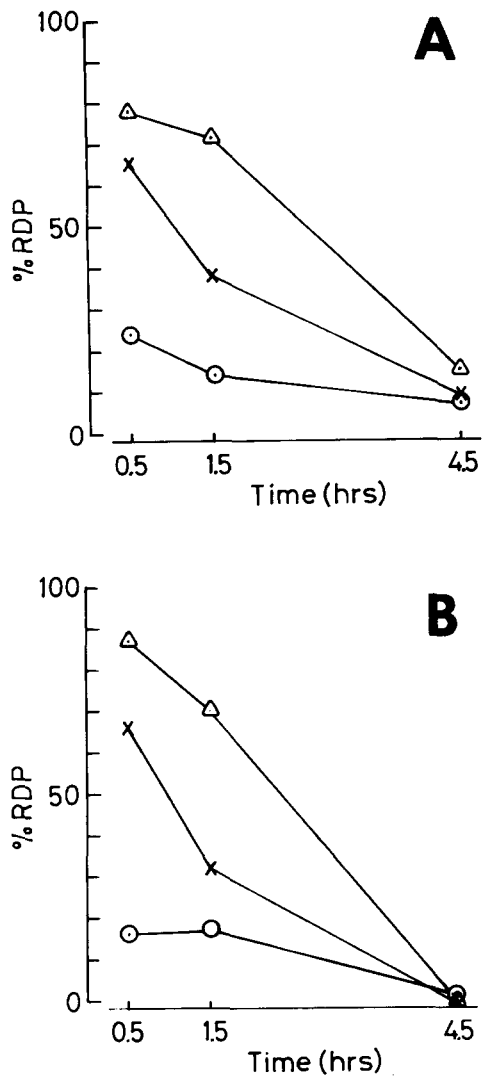

FIG. 3. Dose generalization results with different doses of NL-105 (Fig. 3A) and NL-106 (Fig. 3B), respectively, are shown: 1 mg/kg (△—△), 0.3 mg/kg (X—X), and 0.1 mg/kg (○—○) for NL-105 (n=14); 3 mg/kg (△—△), 1.75 mg/kg (X—X), and 1 mg/kg (○—○) for NL-106 (n=9). The data points are based on one observation in each of the participating animals. The vehicle was the same as for Δ^1-THC and all administrations were IP, 2 ml/kg. % RDP=percentage of responding to drug position, and Time (hr) refers to the time elapsed until testing after a single injection of the drug dose.

Procedure: Discrimination Training

The training program is described in more detail elsewhere [8]. In brief, the animals were first trained to respond on either of the two levers/keys to obtain sweetened water (rats) or grain (pigeons) according to a fixed ratio (FR1) schedule of reinforcement. The requirement for obtaining the reward was then gradually increased until a fixed ratio of 10 (FR10; rats) or 15 (FR15; pigeons) was in operation. During this initial period only one of the two levers/keys was available in the chambers. Likewise, when injections were given before the sessions, only the correct lever/key (left or right) for a given training session was available. Such "forced" discrimination training with only the appropriate lever/key available in the chamber occurred during 12 or 14 sessions with Δ^1-THC and 8 or 10 sessions with vehicle in rats and pigeons, respectively. Thereafter, the free-choice discrimination training began with both levers/keys available, and the animals had to choose the correct lever/key to obtain access to the reinforcement. Which lever/key was correct depended on whether Δ^1-THC or its vehicle had been administered prior to the session. The rats were trained in 15 min sessions, 5 days a week, whereas a training session for the pigeons ended after 52 reinforcements or after 20 min had elapsed. The pigeons were trained 3 days a week. The training doses of Δ^1-THC were 3 mg/kg (rats) and 0.56 mg/kg (pigeons). Injections were intraperitoneally (IP, 2 ml/kg, rats) or intramuscularly (IM, 1 ml/kg, pigeons) 0.5 and 1.5 hr before the onset of the training sessions, respectively.

Procedure: Discrimination Testing

After the animals had selected the correct lever/key (left or right) at the onset of each training session for at least 8 out of 10 consecutive training days, the animals entered the test phases. A repeated tests procedure was utilized [8,16], in which several test probes of six trials each were run in succession after a single injection of a specified dose of the drug. Common intervals examined were 0.5, 1.5, and 4.5 hr for the rats, and 0.5, 1.5, 4.5 and 9 hr for the pigeons. Both levers/keys were operable throughout testing and the animals could gain reinforcement by working on either or both of the two levers/keys. The reward was delivered according to the requirements of the training sessions (FR10 and FR15 for rats and pigeons, respectively); this was in effect on each separate trial. Each test probe ended after the animals had received six rewards or a pre-set time (15 or 20 min for rats and pigeons, respectively) had elapsed since the initiation of the test probe. Between the test probes the animals waited in their home-boxes. Tests were conducted once or twice a week, usually averaging 3 (rats) or 2 (pigeons) test days in each 2-week period. Test drugs and doses were studied in an unsystematic, mixed order.

Data Analysis

The results are presented as the average percentage responding on the drug associated lever/key out of the total number of responses during the test probe (% RDP). Other statistics and measures used are indicated in the appropriate Results section.

Drugs

The suspensions for the drugs contained propylene glycol, tween-80 and physiological (0.9%) saline (usually 5, 2, 93%, v/v, respectively), and mixing was done according to Järbe *et al.* [16]. The exact composition of vehicles are given in the figure- and table-legends. The (−)-*trans*-Δ^1-THC was obtained through the courtesy of Dr. Braenden and Dr. Lumsden (U.N. Narcotics Lab., Geneva, Switzerland), and the other drugs were prepared according to procedures described by Mechoulam *et al.* [19] and Shoyama *et al.* [24]. Chemical structures are given in Fig. 1. The training doses of Δ^1-THC and injection-to-session intervals used are identical to those in previous DDL studies from this laboratory (e.g. [8,16]) and are thought to induce marked and stable effects [17].

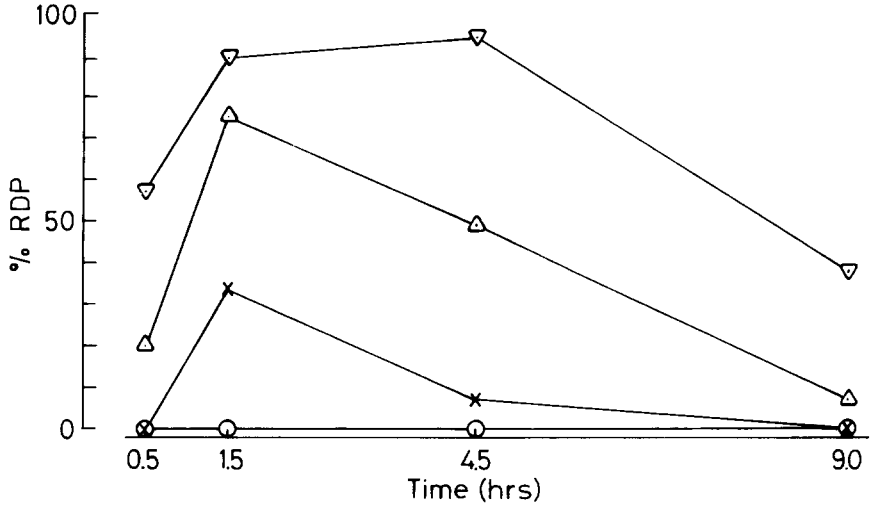

FIG. 4. Dose generalization results with different doses of Δ^1-tetrahydrocannabinol (Δ^1-THC) in pigeons trained to discriminate between 0.56 mg/kg of Δ^1-THC and vehicle. The doses shown are: 0.56 mg/kg (▽—▽), 0.3 mg/kg (△—△), 0.1 mg/kg (X—X), and the vehicle (○—○); 5% of propylene glycol, 2% of tween-80, and 93% of saline, v/v. All administrations were IM, 1 ml/kg. The data points represent the average of two determinations per dose and animal (n=7). % RDP=percentage of responding to drug position, and Time (hr) refers to the time elapsed until testing after a single injection of the drug dose.

RESULTS

Rats

In Fig. 2 the dose response curve for rats trained to discriminate between 3 mg/kg of Δ^1-THC and vehicle is shown. The average percentage of responses (% RDP) is presented for five doses (0.3, 0.56, 1, 1.75, and 3 mg/kg) lower or equal to the training dose (3 mg/kg) as well as for one dose (5.6 mg/kg) higher than the training dose of Δ^1-THC. This figure clearly shows that the stimulus effects of THC are both dose- and time-dependent. Included is also a repeated test with the vehicle used for 5.6 mg/kg of Δ^1-THC. Although not shown in this figure tests with other vehicles employing larger injection volumes than those used here and both less or greater amounts of the suspending agents consistently produce only vehicle appropriate responding.

The estimates of the dose expected to induce 50% RDP (ED_{50}) are shown in Table 1. At the 6.5 hr interval no meaningful estimates can be derived since only one dose of Δ^1-THC (5.6 mg/kg) was then evaluated. The dose of 1 mg/kg of Δ^1-THC was examined on two occasions, the second examination occurring approximately half a year after the first one. The two determinations resulted in reasonably concordant results, the difference being only about 10% RDP (the higher value noticed in the 2nd test).

Figure 3 A presents the results of tests with NL-105 in rats trained to discriminate between 3 mg/kg of Δ^1-THC and vehicle. From this figure it can be seen that the doses of NL-105 needed to produce drug appropriate responding are lower in comparison to Δ^1-THC. This is reflected by the logarithmic regression analyses as shown in Table 1. Although not shown in Fig. 3 A, or in Table 1, a test with 1.75 mg/kg of NL-105 (n=5) induced 100, 100, and 80% RDP at the intervals indicated in Fig. 3 A. This was accompanied by severe rate decreasing effects as none of the 5 animals tested received all the six rewards available during the 1st test probe; during the 2nd test probe the rate decreases were still noticeable, whereas during the 3rd test probe a return to a more normalized level of responding was evident since all the 5 rats took their six rewards.

In Fig. 3 B the drug appropriate responding induced by NL-106 is shown and the ED_{50} values are given in Table 1. Due to a lack of materials doses higher than those presented could not be tested.

Pigeons

In Fig. 4 the dose response curve of Δ^1-THC for pigeons trained to discriminate between 0.56 mg/kg of Δ^1-THC and vehicle is shown. The data in this figure are the average of two different determinations, one test occurring at the beginning of the experiment and the other test occurring at the end of the experimental period. ED_{50} values for Δ^1-THC are given in Table 1.

As for rats also other vehicles than that used here have been examined in pigeons and in congruence with the rat data only nondrug appropriate responding occurred in the present repeated tests procedure.

Figure 5A presents the results of tests with NL-105 in pigeons trained to discriminate between the presence and absence of 0.56 mg/kg of Δ^1-THC. It appears that the duration of Δ^1-THC like responding was shorter with NL-105 than for the training compound. Thus there was no drug appropriate responding 4.5 hr after administration of 0.1 mg/kg of NL-105 whereas this dose of NL-105 produced close to 100% RDP when tested 1.5 hr after injection. The results with Δ^1-THC were that at both of these intervals >90% RDP occurred with Δ^1-THC. ED_{50} values for NL-105 are shown in Table 1.

In Fig. 5 B the percentage of drug appropriate responding in tests with NL-106 is presented. NL-106 seems weaker in its THC-like effects in comparison to both Δ^1-THC and NL-105.

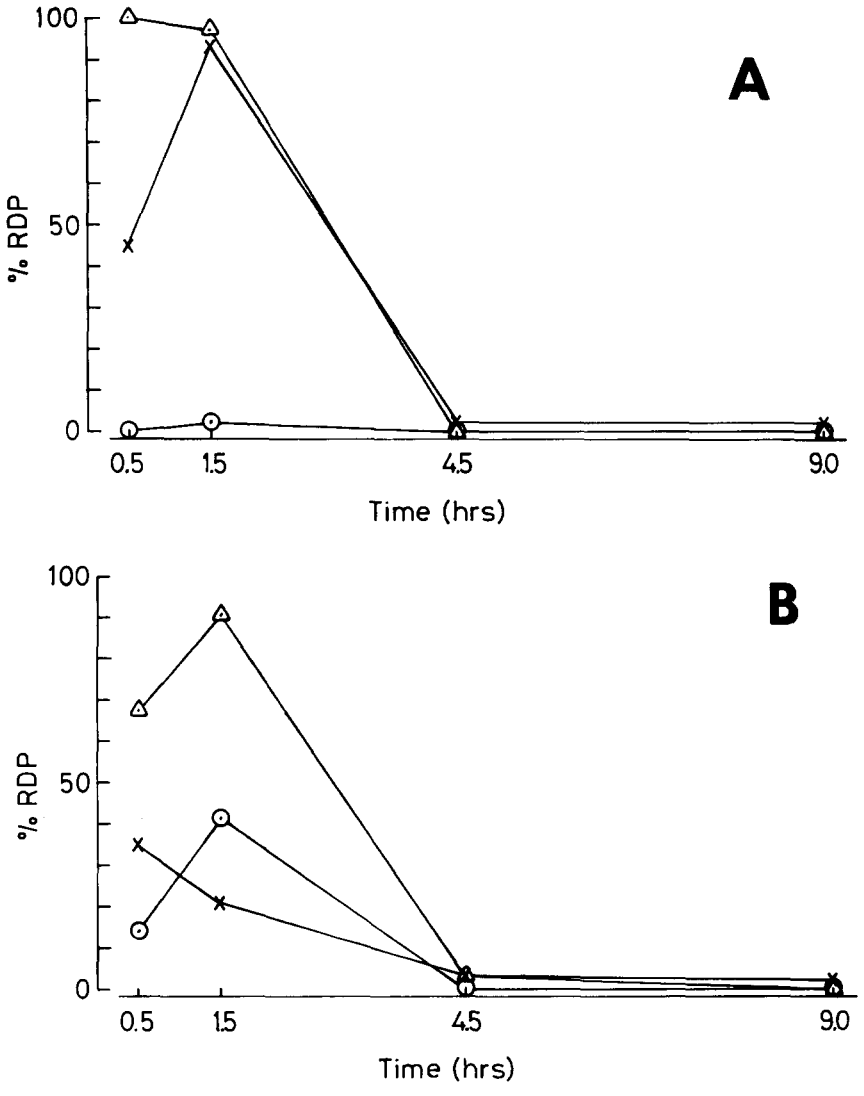

FIG. 5. Dose generalization results with different doses of NL-105 (Fig. 5A) and NL-106 (Fig. 5B) in pigeons trained to discriminate between 0.56 mg/kg of Δ^1-THC and vehicle. The doses of NL-105 and NL-106 were, respectively: 0.1 mg/kg (△—△), 0.03 mg/kg (X—X), and 0.01 mg/kg (○—○) for NL-105 (n=7); 3 mg/kg (△—△), 1.75 mg/kg (○—○), and 1 mg/kg (X—X) for NL-106 (n=7). The data points are based on one observation in each of the participating animals. The vehicle was the same as for Δ^1-THC except with 3 mg/kg of NL-106 where 3% rather than 2% tween-80 was used. All administrations were IM, 1 ml/kg. % RDP=percentage of responding to drug position, and Time (hr) refers to the time elapsed until testing after a single injection of the drug dose.

The duration of effect of NL-106 was similar to that of NL-105 in that both compounds produced, e.g., no drug responding 4.5 hr after injection whereas for 0.56 mg/kg of Δ^1-THC >90% RDP occurred. ED_{50} values for NL-106 are shown in Table 1.

At no intervals (0.5–4.5 hr) examined did the doses of CBDM (3 and 10 mg/kg; n=9 and 5, respectively) tested induce Δ^1-THC like responding in rats (0% RDP). No apparent rate changes were evident in these tests. At the same dose levels (3 and 10 mg/kg), CBDM likewise did not induce a substantial % RDP in pigeons (see Table 2). At the dose of 17.5 mg/kg about 30% RDP was evident at the earlier intervals. The latter dose also reduced the response output; in fact at the 0.5 hr interval only 3 out of 4 birds tested received reinforcement. Higher doses could not be tested due to a lack of materials.

DISCUSSION

One purpose of this study was to examine more closely the dose/time effects of graded doses of the training drug (Δ^1-THC) using repeated testings procedures both in rats and pigeons. That the largest degree of effect occurred 30 min after injection in rats is in keeping with earlier DDL data from this laboratory when the time course was assessed with the more conventional technique of determining one time

TABLE 2
PIGEONS

Dose (mg/kg)	n	Time (hr)	% RDP
3.0	4	0.5	0.8
3.0	4	1.5	4.2
3.0	4	4.5	0.0
3.0	4	9.0	0.3
10.0	4	0.5	0.0
10.0	4	1.5	3.8
10.0	4	4.5	0.0
10.0	4	9.0	0.0
17.5	4	0.5	33.3*
17.5	4	1.5	29.2
17.5	4	4.5	0.5
17.5	4	9.0	0.0

Repeated testings of CBDM in pigeons trained to discriminate between Δ^1THC (0.56 mg/kg) and vehicle (see the Drug section). The vehicle for CBDM contained 5% propylene glycol, 2 or 3% tween-80, and 93 or 92% saline with the doses 3 and 10 mg/kg, respectively, and the volumes being 1 and 2 ml/kg (IM). The highest dose (17.5 mg/kg) contained 4% tween-80 at the expense of saline, and given in 3 ml/kg. Dose expressed as milligram per body weight; n = the number of animals used per test; * = results based on the performance of three birds as one bird did not respond during the test probe; time = time in hours elasped since injection until testing; and %RDP = percentage of responding to drug (Δ^1-THC) appropriate position.

interval per test occasion [7, 13, 14]. The marked reduction in effect at the interval of 4.5 hours after injection of Δ^1-THC doses of 3 mg/kg and less was anticipated [1, 12–14]. Because the training dose was 3 mg/kg, a higher dose of Δ^1-THC (i.e., 5.6 mg/kg) would be expected to induce more long lasting effects as indeed was shown to be the case (see also [9,10]). As for the rats, orderly dose/time characteristics were yielded by the repeated tests procedure also in pigeons. However, the onset of action and duration of effect of Δ^1-THC differ between the two species, the activity being more protracted in pigeons. This is perhaps related to the different modes of administration employed, IP and IM, respectively. In pigeons the maximum degree of effect was seen 1.5 hours after injection (see also [7, 8, 14]), and in subsequent test probes % RDP levelled off to approach zero at the completion of the testing day 9 hours after administration. Hence this and other data suggest that repeated tests produce reliable time course estimates.

Another purpose of this study was to examine the cannabimimetic activity of two hexahydrocannabinols (NL-105 and NL-106) differing only in the stereochemistry of the substituent at the C-1 position. Both compounds were found to substitute for the Δ^1-THC stimulus in both species, indicating similarities in effect between the three compounds. However in line with the prediction that when the C-7 substituent is equatorial rather than axial, enhanced activity should be apparent. NL-105 was considerably more potent than the enantiomer NL-106. This confirms and extends earlier findings using related enantiomers [4, 6, 19, 26]. With the pairs of 7-acetoxyhexahydrocannabinols studied by Mechoulam *et al.* [19] the compound having the acetoxymethyl group in equatorial position was about 5–10 times less active than Δ^1-THC in eliciting a THC syndrome [18] in rhesus monkeys; the enantiomer where the acetoxymethyl group was axial did not elicit the syndrome even at the dose of 5 mg/kg. Apparently the corresponding alcohols used in this study were much more potent which might suggest that the acetylation *per se* reduced activity. However as the alcohols and the esters were tested in different animals and in different tests the comparison is tenous at best. Since comparatively higher doses of the compound having the substituent in the axial position were evaluated in the present study this also probably explains why cannabimimetic activity was detected with NL-106. Yet also in this study the difference in potency is marked as evinced by the ratio between the ED_{50} values of the two NL compounds (about 7 and 18 in rats and pigeons at the 30 and 90 min injection-test intervals, respectively). There is no readily apparent explanation for the greater differentiation between the NL compounds in pigeons as compared to rats. Furthermore the duration of action was considerably shorter with the NL compounds as compared to Δ^1-THC in pigeons but only slightly so in rats. This may be due to pharmacokinetic factors rather than reflecting biologically significant differences in the CNS substrates subserving Δ^1-THC induced DDL of these species. This will have to await further research.

CBDM did not substitute for Δ^1-THC in either species at the doses tested which is in concert with the lack of cannabimimetic activity also noted for the chemically related agent CBD [8]. It would appear the CBDM has a pharmacological profile similar to that of CBD as indicated by the present DDL results and previous findings [3]. This is consistent with the generalization that opening of the pyran ring in classical cannabinoids abolish, or at the least drastically reduces cannabimimetic activity [20,22].

In summary the present data provide additional support for the utility of repeated test procedures to assess the time course after a single administration of a drug dose. Given a specific biochemical recognition site for THC [2, 4, 21, 23] the results with the NL compounds suggested greater affinity for the "planar" enantiomer (NL-105) than for the enantiomer (NL-106) in which the hydroxymethyl group protrudes out of the plane of the molecule and thereby possibly hinders the approach of the molecule to its target [19]. Like CBD, CBDM has a low degree of THC-like, cannabimimetic activity.

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