THE DISCRIMINATIVE STIMULUS PROPERTIES OF DELTA-9-TETRAHYDROCANNABINOL: GENERALIZATION TO SOME METABOLITES AND CONGENERS[1]

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I. INTRODUCTION

Animals can be readily trained to choose which of two response levers to press for reinforcement dependent upon whether they received a drug or vehicle injection. Such drug discriminations have become important in behavioral pharmacology because they can be used to classify drugs. Animals tested with drugs similar to the training drug respond as if they had received the training drug and respond primarily on the lever which was correct after drug injections, i.e., they generalize the stimulus properties of the training drug to the test drug. Animals tested with drugs dissimilar from the training drug respond either on the lever which was correct after vehicle injections during training or distribute their responses on both levers. Generally speaking, drug clas-

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sifications using this procedure result in grouping together drugs with similar pharmacological properties which produce similar subjective effects in intoxicated humans (1).

Delta-9-tetrahydrocannabinol (THC) has been used as a training drug in about 15 drug discrimination studies in a variety of species. It functions effectively and generalization tests with other drugs provide evidence for the specificity of the procedure. A number of investigators have proposed the use of a THC-vehicle discriminations in animals as a test for drugs with marijuana-like intoxicating effects in humans (2-5). In this paper we report more extensively on the results of our testing of various synthetic cannabinoids and THC metabolites in rats trained to discriminate THC from vehicle in a two-bar operant task. Prelimnary conclusions were included in earlier reports (5,6).

II. METHODS

A. Subjects

Fifteen male Holtzman rats with no previous experimental history which weighed between 311 and 391 g when given free access to food and water were used. They were deprived of food until they reached 80 percent of their free-feeding weights, and subsequently maintained at this weight by adjusted feedings after each experimental session. Except for an hour each day consumed by injections and the experimental session, rats were housed individually with free access to water.

B. Apparatus

Training and testing of rats was carried out in standard operant chambers equipped with two response bars. A bar press with a force of approximately 15 g constituted a response. Centered in the wall between the two bars was an opening through which a 0.1 ml mixture of sweetened condensed milk and tap water (1:2) could be made accessible by means of an electrically operated dipper. Each chamber was illuminated by a six-watt bulb and placed in a ventilated enclosure for light and sound attenuation. Solid state programming equipment and electromechanical counters were used to control the experimental contingencies and record data.

C. Procedure

Thirty minutes prior to their first introduction to the experimental chamber, eight rats were injected with 3.0 mg/kg of THC, while the additional seven rats were injected with vehicle. Subsequently, daily injections were administered on a double alternation regimen, so that two consecutive injections of THC alternated wth two consecutive injections of vehicle. Training to bar-press was completed in the first four consecutive sessions, during which each response on one bar resulted in milk presentation, while responding on the other bar had no programmed consequence. The correct bar was determined by whether the prior injection was THC or vehicle. For eight rats the left bar was correct after THC and the right bar correct after the vehicle. The converse was true for the remaining rats. These bar-injection pairings remained fixed for each rat throughout the study. After the initial training, session length was set at 30 minutes and rats were placed on a fixed ratio-10 (FR-10) schedule of reinforcement, where 10 responses on the correct bar resulted in milk presentation. Responses on both bars were recorded.

D. Types of Sessions

Starting with Session 5, there were three types of sessions used in the study and they are designated training, check (C), and test (T) sessions. All sessions had in common that they began 30 minutes after an i.p. injection and responses on both bars were recorded. Training sessions were of two kinds since they followed the injection of either THC or vehicle and lasted 30 minutes, throughout which the reinforcer was presented on a FR-10 schedule for responding on the appropriate bar. Check sessions (C) also followed injections of either 3.0 mg/kg THC or vehicle, but for the first 2.5 minutes of the session the reinforcer was not presented. The initial 2.5 minutes of a check session provided a measure of stimulus control of responding by THC or vehicle, and the session was completed with 27.5 minutes of FR-10 reinforcemet on the appropriate bar. A test session (T) folllowed the injection of THC doses other than 3.0 mg/kg or doses of novel cannabinoids. A test session lasted only 2.5 minutes during which no reinforcement was given, and this provided a measure of stimulus generalization to 3.0 mg/kg THC and vehicle injection.

E. Order of Sessions

The basic order of session types was a double alternation

of daily THC and vehicle (V) training sessions (THC, THC, V, V, THC, THC, etc.). This order was altered starting with session 30 when a check session (C) occurred every 3rd session (THC, THC, C, V, THC, C, etc.). Whether a check session was preceded by a 3.0 mg/kg THC or vehicle injection was determined by the double alternation sequence. In determining a THC dose-response curve, a test session occurred every 3rd session in the place of a check session. During the period when doses of novel cannabinoids were tested, a check session occurred every 3rd session and a test session every 6th session.

F. Drug Procedure

The 15 rats were divided into two groups that were distinguished by the novel cannabinoids tested in each. The number of animals tested was largely determined by the amount of drug available. The order of drugs tested and number of animals used for Group I were: delta-9-THC (N = 7); 11-OH-delta-9-THC (N = 7); 8alpha-OH-delta-9-THC (N = 2); 8beta-OH-delta-9-THC (N = 3); 8alpha,11-diOH-delta-9-THC (N = 3); 8beta,11-diOH-delta-9-THC (N = 2); 11-nor-9beta-OH-HHC (N = 7); delta-9-THC (N = 6); 11-OH-delta-8-THC (N = 6). The order of drugs tested and number of animals used for Group II were: 11-nor-9alpha-OH-HHC (N = 8); 11-nor-delta-8-THC (N = 7); cannabidiol (N = 4); abnormal cannabidiol (N = 4); delta-9-THC (N = 8); 11-OH-delta-8-THC (N = 8).

The structure of the metabolites tested are presented in Figure 1, while the structures of the synthetic and other natural products are shown in Figure 2. In pure and suspension form, the cannabinoids were stored in the dark at about 4°C until used. The suspending agent used for the cannabinoids were emulphor (EL 620), which was prepared as described (7,8). On each day of administration, stock suspensions were diluted with saline so that the volume injected was 1 ml/kg, except in cases where a dose larger than 30.0 mg/kg was given. To administer the 60.0 mg/kg dose of 11-nor-delta-8-THC and the 100.0 mg/kg doses of cannabidiol and abnormal cannabidiol volumes of 2.0 ml/kg and 3.3 ml/kg, respectively, were used. Vehicle control injections during training were 1 ml/kg of saline solution containing emulphor and ethanol, to correspond with the amount of emulphor and ethanol in the 3.0 mg/kg THC training dose. In testing for generalization to THC, the vehicle injection for a particular test drug consisted of a saline solution which corresponded in volume and in emulphor and ethanol concentration to that in the dose of drug tested.

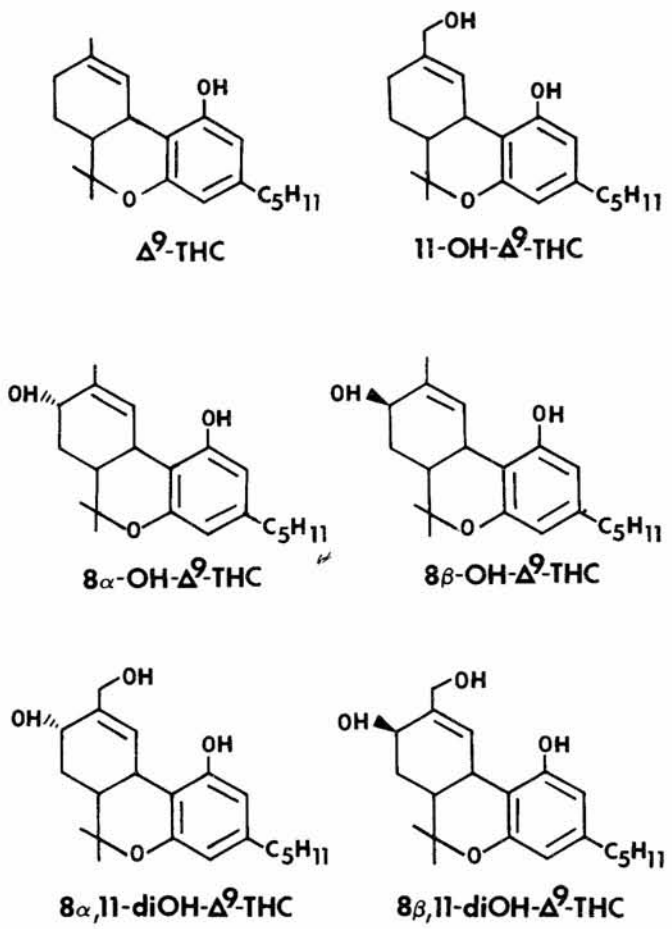


FIGURE 1. Structures of THC and its metabolites.

G. Measurement of Drug Effects

The results to be reported are based upon the number of responses on each of the two bars during the 2.5 min. extinction periods which constituted test sessions or initiated check sessions. Responding during extinction periods gives a measure of stimulus generalization to vehicle and the 3.0 mg/kg THC training dose. Drug effects are characterized throughout this paper as the mean response rate during extinction periods and the percent THC bar-responses. The results of test sessions were compared for statistical significance to the most proximate vehicle check session using a two-tailed, paired t-test.

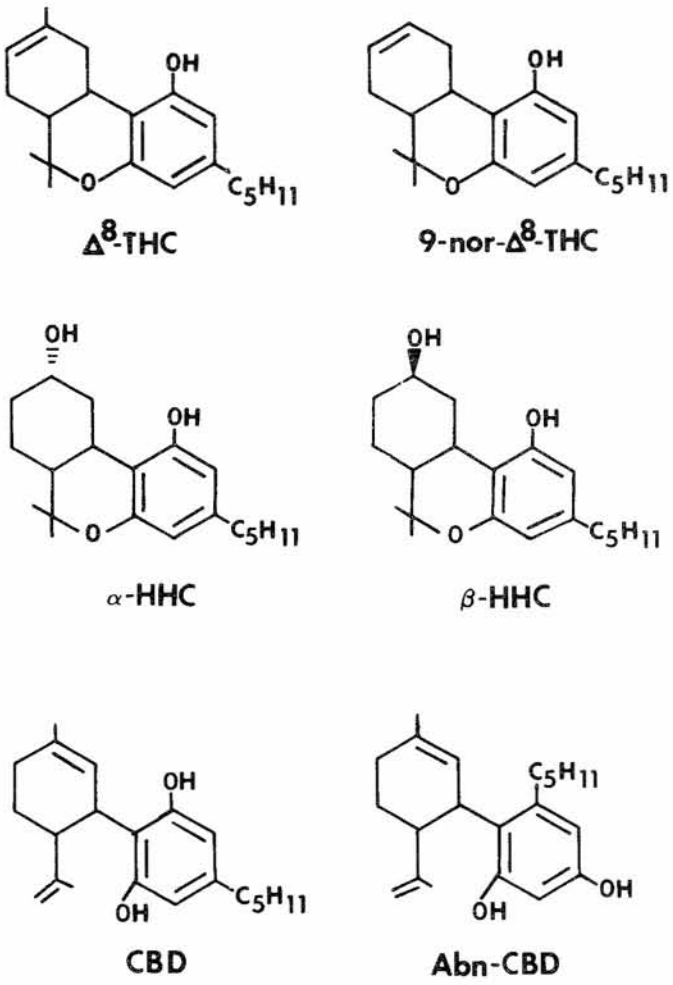


FIGURE 2. Stuctures of delta-8-THC and the congeners tested.

III. RESULTS

A. THC as a Discriminative Stimulus

Figure 3 shows the effects produced by various doses of THC as percent THC bar responses and response rates. When tested in 7 rats at the beginning of the study (open circles), the largest dose of 4.0 mg/kg produced the highest proportion of THC bar responses, while the smallest dose of 0.3 mg/kg

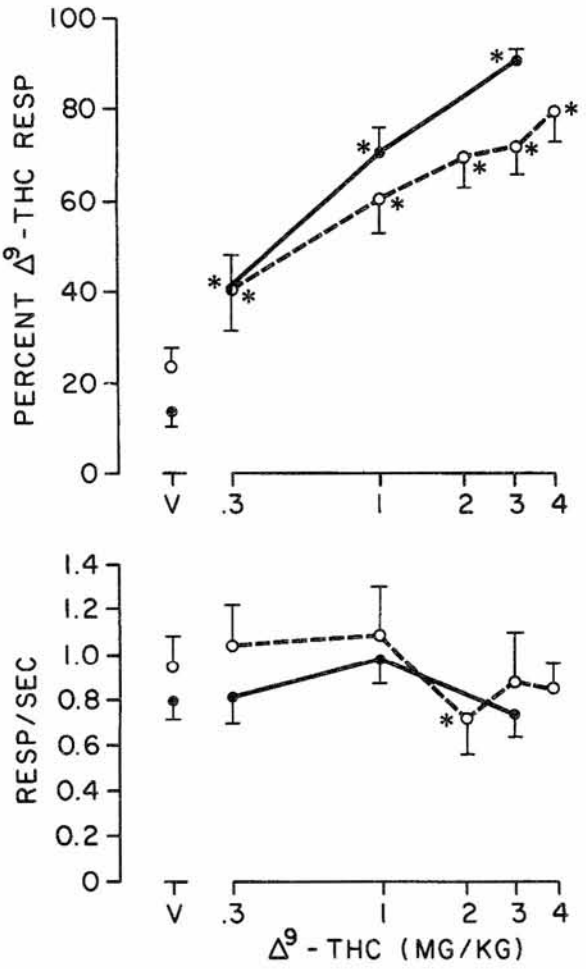


FIGURE 3. Effects of THC on percent THC-bar responses and response rate. Abscissas: dose, log scale. Ordinates: percent THC responses and response rate during 2.5 minute extinction periods. Open circles, first determination (N = 7); closed circles, second determination (N = 14). The points at V are the mean of vehicle injections. Each point represents the mean of one observation in each rat. The vertical lines show one standard error above and below the mean. (*$p < 0.05$ compared to vehicle)

resulted in the highest proportion of responses on the vehicle bar. Similar results were obtained when a THC dose-response

curve was determined in 14 rats near the end of the study and following the testing of other cannabinoids (closed circles). These two dose-response curves, together with the results from check sessions throughout the study, indicate that THC functioned in a dose-related manner as a discriminative stimulus, and that stimulus control of responding by 3.0 mg/kg THC and vehicle injections remained relatively stable during the testing of a number of THC metabolites and congeners.

The effects on mean response rates produced by THC doses is shown in the bottom plot of Figure 3. Thoughout the study there was a higher variability associated with response rates than that obtained for percent THC bar responses. As shown, there was a small but significant ($p < 0.05$) decrease in mean response rate produced by 2.0 mg/kg THC when tested at the beginning of the study in these seven rats. This small decrease in mean response rate may be due to the level of training of this group, where behavioral tolerance had not yet completely developed to the disruptive effects of THC. This explanation is further suggested since significant changes from vehicle values were not produced by other THC doses in this determination nor when the THC dose response curve was redetermined in all 14 remaining rats near the end of the study.

B. Generalization of 11-OH-delta-9-THC to THC

Results of test doses of 11-OH-delta-9-THC on percent THC bar responses and mean response rates are shown in Figure 4. The two points on the left of each plot show the result of check sessions where the 3.0 mg/kg training dose of THC produced 88 percent and vehicle 22 percent of total responses on the THC bar, while response rates did not differ. Test doses of 11-OH-delta-9-THC were generalized to THC as a function of dose. 11-OH-delta-9-THC at a dose of 0.1 mg/kg resulted in 34 percent of the total responses being on the THC bar, while 0.3 and 1.0 mg/kg produced 73 and 97 percent, respectively. Mean response rate, on the other hand, decreased as a function of dose. While the 3.0 mg/kg dose of THC did not alter the mean response rate, it was markedly decreased by 1.0 mg/kg of the 11-hydroxy metabolite. Thus, at 1/3 the THC training dose, the 11-hydroxy metabolite produced THC-like discriminative stimulus effects and markedly decreasd the mean response rate.

C. Generalization of 11-OH-delta-8-THC to THC

The effects of 11-OH-delta-8-THC, also indicated in Fig.

4, are much like those of 11-OH-delta-9-THC in both potency of stimulus effects and concomitant response rate decreasing effects. Both metabolites are about three times as potent as THC in producing similar stimulus effects. In addition, at equi-

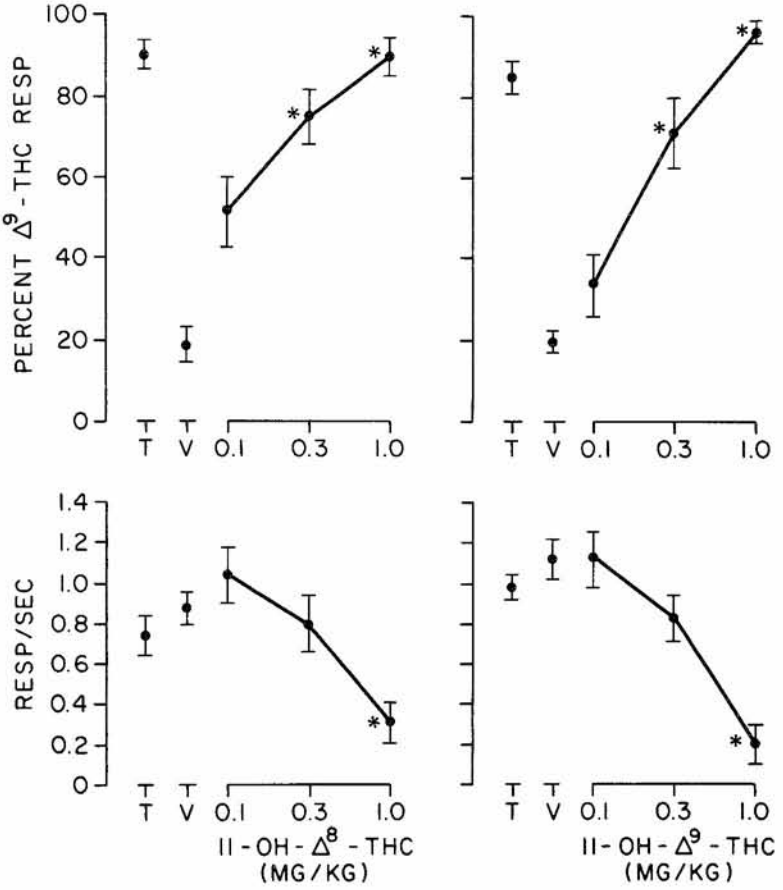
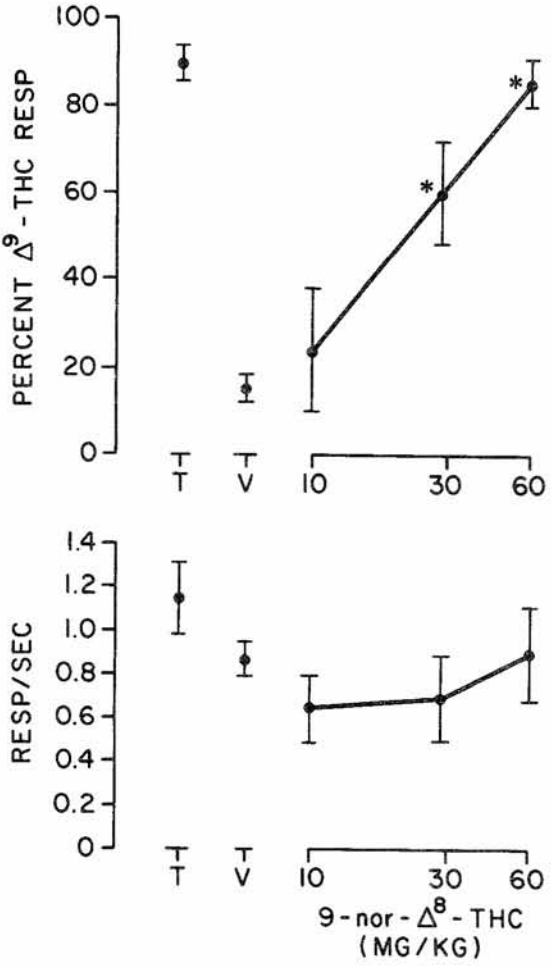


FIGURE 4. Effects of 11-OH-delta-9- and delta-8-THC on the percent of THC responses and response rate. Abscissas: dose, log scale. Ordinates: percent THC responses and response rate during 2.5 minute extinction periods. The points at the left of the four plots are the result of THC and vehicle check sessions and represent the mean of two observations in 7 rats for 11-OH-delta-9-THC and the mean of two observations in 14 rats for 11-OH-delta-8-THC. Each point at doses of 11-OH-delta-9-THC and 11-OH-delta-8-THC represents the mean of one observation in 7 and 14 rats, respectively. The vertical lines show one stan-dard error above and below the mean. (*$p < 0.05$ compared to vehicle)

potent doses for producing discriminative stimulus effects, the 11-hydroxy metabolites have a response rate decreasing component which the parent THC largely lacks.

D. Generalization of 11-nor-delta-8-THC to THC

Figure 5 shows the effects produced by graded doses of 11-nor-delta-8-THC. As indicated in the top plot of percent THC bar responses, a 10.0 mg/kg dose produced vehicle-like effects. At a dose of 60.0 mg/kg, 11-nor-delta-8-THC generalized to THC. Thus, 11-nor-delta-8-THC was about 1/20 as



potent as THC. As shown in the bottom plot of Figure 5, mean response rates after 11-nor-delta-8-THC were not significantly different from vehicle values.

E. Generalization of 11-nor-9beta-OH-HHC (9beta-HHC) to THC

As shown in Figure 6, 9beta-HHC generalized to THC as a function of dose and in a manner very similar to the 11-hydroxy metabolites. 9beta-HHC produced THC-like stimulus effects at 1/3 the dose of THC. Also like 11-OH-delta-9-THC, 1.0 mg/kg 9beta-HHC markedly decreased mean response rate.

F. Effects of 11-nor-9alpha-OH-HHC (9alpha-HHC)

Fig. 6 shows that 9alpha-HHC had no effect on mean response rate over a 10-fold range of doses and at a dose 10 times that of 9beta-HHC, which markedly decreased responding. However, 9alpha-HHC produced a distribution of responding different from vehicle and 3.0 mg/kg THC. Over this 10-fold dose range, 9alpha-HHC resulted in responses being more evenly distributed on the two response bars.

G. Effects of 8alpha-OH-delta-9-THC; 8beta-OH-delta-9-THC; 8alpha,11-diOH-delta-9-THC; and 8beta,11-diOH-deta-9-THC

We used all the drug available to us and tested high doses of these metabolites in a selected small number of animals which had the most stable performances. The results are shown in Table I. None of the metabolites were significantly different from vehicle. There was no indication that 8alpha-OH-delta-9-THC and the dihydroxy metabolites producted THC-like effects at doses 4 to 10 times the THC training dose. The results with 8beta-OH-delta-9-THC were only mildly suggestive

FIGURE 5. Effects of 11-nor-delta-8-THC on the percent of THC responses and response rate. Abscissas: dose, log scale. Ordinates: percent THC responses and response rate during 2.5 minute extinction periods. The points at the left of the two plots are the result of THC and vehicle check sessions and represent the mean of two observations in 7 rats. Each point at doses of 11-nor-delta-8-THC represents the mean of one observation in 7 rats (14 sessions). The vertical lines show one standard error above and below the mean. (*$p < 0.05$ compared to vehicle)

of THC activity, and this was not significantly different from vehicle effects.

H. Lack of Generalization of THC to Cannabidiol and Abnormal Cannabidiol

As indicated in Table I, neither the plant constituent cannabidiol nor its synthetic analog abnormal cannabidiol were generalized to THC at doses of 30.0 and 100.0 mg/kg.

IV. DISCUSSION

THC functioned well as a discriminative stimulus for lever-choice behavior in rats. This has been observed in many other studies with rats (2-5,9-10) and pigeons (12,13). A training dose of about 3.0 mg/kg THC has been consistently successful for drug discrimination in rats. At this dose we obtained excellent stimulus control, greater than 80% correct bar responding, during check sessions. This dose of THC had specificity for discriminative stimulus effects since no differences were seen between overall response rates on THC and vehicle sessions. Rats trained under these conditions can be

TABLE I. Results of Generalization Tests with Secondary Delta-9-THC Metabolites, Cannabidiol and Abnormal Cannabidiol

Drug	Dose (mg/kg)	N	Percent of THC Responses	
			Mean	S.E.M.
8alpha-OH-delta-9-THC	15	2	28.0	14.4
	30	2	26.9	5.9
8beta-OH-delta-9-THC	3	3	20.4	6.8
	15	3	29.8	9.9
	30	3	50.8	11.9
8alpha-11-diOH-delta-9-THC	12	3	21.0	7.8
8beta-11-diOH-delta-9-THC	12	2	6.1	3.3
Cannabidiol (CBD)	30	4	6.8	4.4
	100	4	19.1	9.4
Abnormal CBD	30	4	15.9	14.7
	100	4	13.0	9.0

repeated tested with other drugs to determine if the stimulus control exerted by THC will be genralized to them.

Of the drugs we tested for generalization to the THC cue, only the 11-hydroxy (11-OH) metabolites of both delta-9- and delta-8-THC and the synthetic cannabinoids 11-nor-delta-8-THC and 11-nor-9beta-OH-HHC resulted in levels of THC bar responding comparable to that obtained with THC itself. The 11-OH

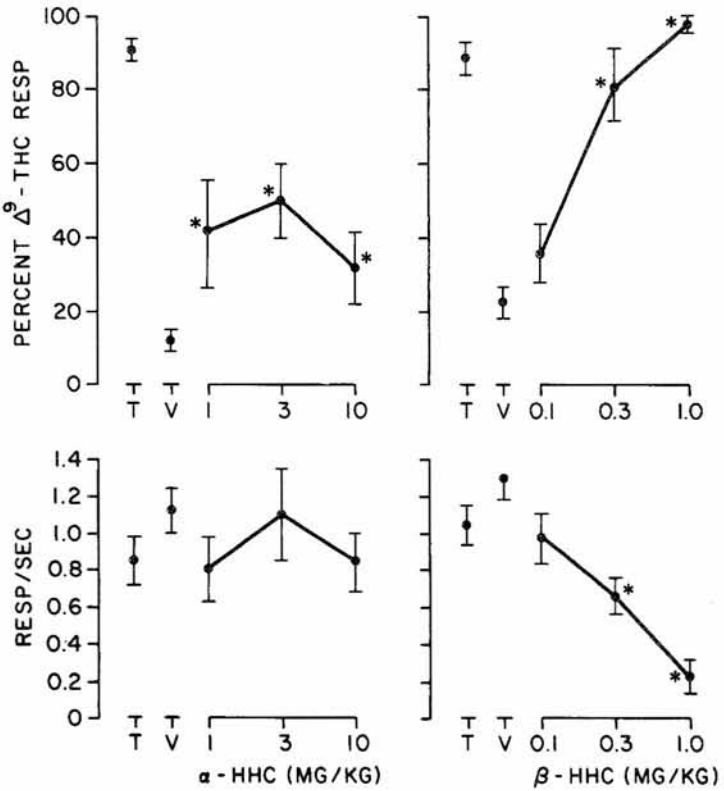


FIGURE 6. Effects of 11-nor-9beta-OH-hexahydrocannabinol (9beta-HHC) and 9alpha-HHC on the percent of THC responses and response rate. Abscissas: dose, log scale. Ordi-nates: percent THC responses and response rate during 2.5 minute extinction periods. The points at the left of the two plots are the result of THC vehicle check sessions and represent the mean of two observations in 7 rats for 9b-HHC (14 sessions) and in 8 rats for 9alpha-HHC (16 sessions). Each point at doses of 9beta-HHC and 9alpha-HHC represents the mean of one observation in 7 and 8 rats, respectively. The vertical lines show one standard error above and below the mean (*$p < 0.05$ compared to vehicle)

metabolites of delta-9- and delta-8-THC have been reported by others as well to be generalized to THC in rats (3,4,13) and pigeons (13). The greater potency of the metabolites over THC was also seen in these other studies. These compounds produce marijuana-like subjective effects in humans (14,15) and are more potent than THC in humans as well. Other drugs that produce marijuana-like effects in humans and that are generalized to THC in animal studies include hashish extract, delta-8-THC and nabilone (2,4).

There was an interesting difference between the results with THC and with both 11-OH metabolites in our study suggesting that their effects, although similar, may not be equivalent. Unlike THC, where greater than 80% drug bar responding could readily be produced by doses that had no effects on overall response rates, both 11-OH-delta-9- and -delta-8-THC only produced complete generalization at doses that markedly suppressed responding. These compounds way be less specific for marijuana-like subjective effects with a greater propensity for behavioral disruption at intoxicating doses.

The two synthetic cannabinoids, 9beta-HHC and 11-nor-delta-8-THC, which were generalized to THC by rats, have not been evaluated for marijuana-like effects in humans, however, we would predict effects similar to THC. Generalization to THC by 9beta-HHC in rats has also been reported by Weissman (4), and this compound as well as 11-nor-delta-8-THC shares many pharmacological properties with THC in animal tests (16,17). The fact that both these compounds cannot be 11-hydroxylated but yet retain THC-like effects suggests that 11-OH metabolites of THC are not solely responsible for the effects of THC. This is consistent with our finding that THC produces behavioral effects when injected directly into the brains of monkeys at a time when no metabolic conversion has occurred (18). The 9alpha-isomer of HHC was not generalized to THC demonstrating the importance of the orientation of the 9-substituent relative to the plane of the cyclohexane ring for hexahydrocannabinols.

We tested both alpha and beta isomers of the 8-OH and 8,11-diOH metabolites of THC for THC-like discriminative stimulus effects. We were limited by the availability of only small supplies of these compounds. None of them were completely generalized to THC. The monohydroxy metabolites were tested up to 30 mg/kg, 30 times the lowest dose of THC that resulted in appreciable THC bar responding. Jarbe and McMillan also tested both of these compounds at comparable doses in pigeons for generalization to THC and also found no activity (13). Both the alpha and beta 8,11-diOH metabolites were also without THC-like effects at 12 mg/kg in our study and at 10 mg/kg in the study using pigeons (13). However, Jarbe and McMillan were able to test higher doses of the 8beta,11-diOH

compound (40 mg/kg) and found evidence for generalization to THC. Thus, the lack of THC-like effects of the 8-OH and 8,11-diOH metabolites of THC may be more quantitative than qualitative. Nonetheless, their relative lack of potency compared to THC (at least 30 fold), combined with their relatively low levels in brain after THC or marijuana administration, suggests that they contribute little if anything to the acute CNS effects of marijuana.

Cannabidiol and abnormal cannabidiol were not generalized to THC at doses up to 100 mg/kg. Similar results for cannabidiol have been reported by others (4,12,19). Cannabidiol also lacks marijuana-like effects in humans (20).

We believe that these results point again to the utility of a drug discrimination based on THC in animals as a sensitive and specific method for demonstrating THC-like behavioral effects of drugs. It also appears to predict well drugs that will produce marijuana intoxication in humans. Cannabinoids such as delta-8-THC, 11-OH-delta-9-THC, 11-OH-delta-8-THC, and nabilone, which produce these effects, are generalized to THC in animal studies. Cannabinoids such as cannabidiol and the 8-OH and 8,11-diOH metabolites of THC, which are essentially inactive in humans, are not generalized to THC in animal studies. Tests in humans of potent cannabinoids such as 9beta-HHC and SP-111 (13), which are generalized to THC by rats, would help confirm the predictive value of this procedure. It is also important to point out that drugs from other classes, including other hallucinogens, such as LSD, mescaline, and phencyclidine, are not generalized to THC nor is THC generalized to them (see reviews 3-5). Thus, this method has greater specificity.

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