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Δ9-Tetrahydrocannabinol Discrimination in Rats as a Model for Cannabis Intoxication[1]

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BALSTER, R. L. AND W R. PRESCOTT *Δ9-Tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication* NEUROSCI BIOBEHAV REV **16**(1) 55–62, 1992.—Studies of the discriminative stimulus effects of Δ9-THC are reviewed The results of generalization studies in rats trained to discriminate Δ9-THC from nondrug provide evidence for the pharmacological specificity of the Δ9-THC stimulus. Only cannabinoid analogs of Δ9-THC substitute fully for Δ9-THC The ability of cannabinoids to produce Δ9-THC-like discriminative stimulus effects appears to predict Δ9-THC- or marihuana-like effects in humans. Of the 11 cannabinoids tested in rats and humans, the results with 9 are in complete concordance, and results with the remaining two are inconclusive. This concordance provides evidence for the validity of Δ9-THC discrimination in rats as an animal model of cannabis intoxication A number of natural and synthetic cannabinoids have Δ9-THC-like discriminative stimulus effects They represent a 5,600-fold range of relative potencies Micromolar potency estimates and relative potencies to Δ9-THC for these compounds are provided. Correlations between these values and potencies for cellular actions of cannabinoids can be used to establish the neural substrates of cannabis intoxication

Cannabinoids Drug discrimination Psychoactivity Marihuana Drug abuse Cannabis Tetrahydrocannabinol

CANNABIS sativa L. plant materials are well known to produce a distinctive intoxication in human users which is widely believed to result from the central nervous system effects of its major active chemical constituent, Δ9-tetrahydrocannabinol (Δ9-THC) (20). Although Δ9-THC produces a wide spectrum of pharmacological actions (8), presumably it is this ability to produce subjective effects that accounts for self-administration of various forms of the cannabis plant, such as marihuana and hashish. Thus, in order to study various aspects of the chemistry and neurobiology of cannabis and cannabinoid chemicals, an animal model for Δ9-THC intoxication is needed.

Drug discrimination studies in animals have often been considered as a model for subjective drug effects in humans (1,40). In drug discrimination research, animals faced with two possible responses that would result in reinforcement delivery are trained to detect whether they received an active drug or a vehicle (placebo) injection in order to determine which response is correct. With appropriate control procedures, it can be shown that the discrimination between drug and vehicle is usually based upon the presence or absence of perceptible central nervous system effects of the drug and not on local or other peripheral effects that might accompany drug administration (1). Once trained, subjects can be tested with other chemicals to determine if they respond as if they had received the drug they had been trained to detect, i.e., whether the test compound substitutes for the training drug. Considerable research has demonstrated the pharmacological specificity of drug discrimination. Evidence from substitution tests in animal studies of this type often predicts that the test drug will produce subjective effects in humans similar to those of the training drug.

The purpose of this paper is to expand and update previous reviews (2,28) on the use of Δ9-THC discrimination in rats as an animal model of cannabis intoxication. The validity of the model will be demonstrated by the pharmacological specificity of substitution tests and by the concordance between Δ9-THC-like discriminative stimulus effects and THC- or marihuana-like effects in humans. An important goal of this review is to provide relative potency estimates for a large number of cannabinoids with Δ9-THC-like activity in this model which can be used in correlational studies with in vitro effects A strong positive correlation of potency for Δ9-THC-like discriminative stimulus effects in rats with potencies for cellular actions of cannabinoids will be extremely important in ascertaining the role of these actions in producing cannabis intoxication.

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TABLE 1

DRUGS THAT FAILED TO SUBSTITUTE FOR Δ9-THC IN RAT DRUG DISCRIMINATION STUDIES

Drug	Maximum Generalization*	Dose(s) Tested (mg/kg)	Reference
BRL13776	33	3 2–17 8	(4)
Althesin	60	20	(4)
Amphetamine	0	0 32	(4)
Atropine	8	3 2	(4)
Baclofen	17	3 2	(4)
Cimetidine	18	10	(4)
Clonidine	25	0 056	(4)
Cyclazocine	17	1–10	(4)
Dexamethazone	18	0 56	(4)
Diazepam	52	0 32–17.8	(4)
Gamma hydroxy butyrate	20	32	(4)
Haloperidol	17	0 32	(4)
Imipramine	10	10	(4)
Iproniazid	17	32	(4)
Ketocyclazocine	17	1–10	(4)
Loperamide	36	10	(4)
LSD	8	0 1	(4)
Morphine	20	3 2	(4)
Muscimol	36	1 0	(4)
Oxotremorine	16	0 1	(4)
Pargyline	18	32	(4)
3-PPP	3	1–10	(13)
Pentazocine	17	10	(4)
Pentobarbital	16	10	(4)
Phencyclidine	33	3 2	(4)
Phenobarbital	36	32	(4)
Phenytoin	17	10–32	(4)
Pilocarpine	33	3 2	(4)
Piroxicam	27	10	(4)
Psilocybin	20	1 0	(11)
Thujone	0	10–100	(4)
Yohimbine	17	10	(4)

*Maximum level of Δ9-THC lever responding

METHOD

Study Selection

Although Δ9-THC discrimination studies have been performed in a number of species, we chose rat studies for this review. In all but one study (9), albino Sprague-Dawley rats were used. Rats have been used to study the widest diversity of compounds, and fairly standardized procedures have been employed for this species, facilitating potency comparison across laboratories. In addition, the rat is widely used for in vitro studies of cannabinoids. Additional criteria were also used to select studies to ensure maximum comparability. In all studies to be reviewed, a 2-lever operant drug discrimination procedure was used. Rats were trained to discriminate injections of Δ9-THC from vehicle injections Correct responding was reinforced under fixed-ratio schedules of food presentation. The training dose of Δ9-THC used in all studies reporting Δ9-THC-like compounds was either 3.0 or 3.2 mg/kg. The fact that a nearly identical training dose was used greatly facilitates potency comparisons. Injections were administered IP either 30 or 60 min prior to sessions in all but two studies In these cases (23,25), the testing of a cannabinoid

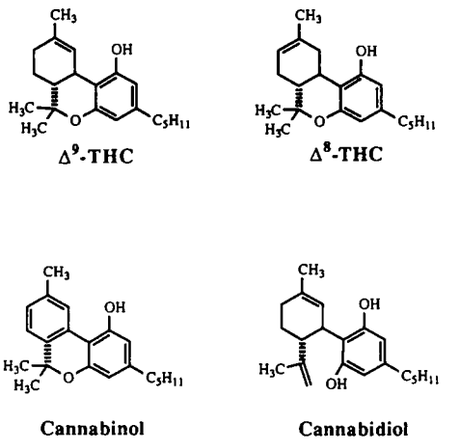

FIG 1 Structures of naturally occurring cannabinoids tested for Δ9-THC-like discriminative stimulus effects Abbreviations used in the text are indicated

congener with a very slow onset of action required up to 4 hours of pretreatment for its potent Δ9-THC-like effects to be seen.

The greatest procedural variations among the reviewed studies are the methods for conducting substitution test sessions and the measures of lever selection used for data analysis. In some studies (4, 46, 47), data were collected until the first fixed ratio was completed, and results are shown as the percentage of rats that completed the ratio on the Δ9-THC lever In other studies, test sessions were of a predetermined duration with responding either under extinction (9, 11, 32) or during reinforcement on both levers (13, 21–25). In these studies, the data reported are the average percentage of responses on Δ9-THC lever.

Data Analysis

Since a primary goal of this review was to obtain potency estimates for a series of cannabinoids, it was important to standardize the method of potency estimation as much as possible. The principal measure of potency presented is the ED_{50}, or the dose of each drug expected to result in 50% Δ9-THC lever selection, based upon the group data The ED_{50}'s were obtained from linear regression analyses of the dose-effect curves. For most studies (4, 21–24, 46–47), these analyses were performed by the authors and ED_{50} values were reported in the publication. For other studies, we calculated ED_{50}'s for some (32), or all (9,25), tested compounds based upon numerical or graphical data provided by the authors. In all cases, least squares linear regression was performed on the linear portions of the dose-effect curves after a $\log_{10}$ transformation of dose. Taking into account the variations in molecular weight, potency estimates are presented in both mg/kg and in μM/kg.

In addition to calculating potency estimates for each cannabinoid, we also calculated potency estimates relative to Δ9-THC. To do this, the potency of each tested cannabinoid was calculated relative to the potency of Δ9-THC in that study, using ratios of ED_{50}'s calculated as described above.

RESULTS

Twelve published studies met the selection criteria for inclusion in this review. They were performed in a number of differ-

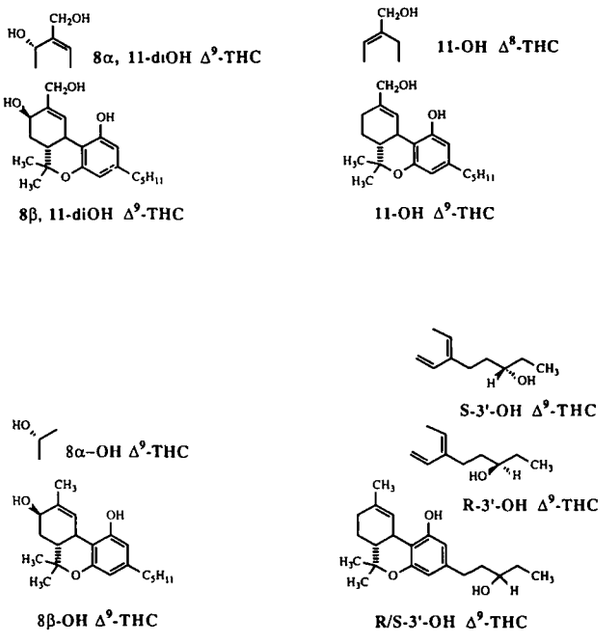

FIG 2 Structures of cannabinoid metabolites tested for Δ9-THC-like discriminative stimulus effects Only changed portions of isomers have been shown Abbreviations used in the text are indicated

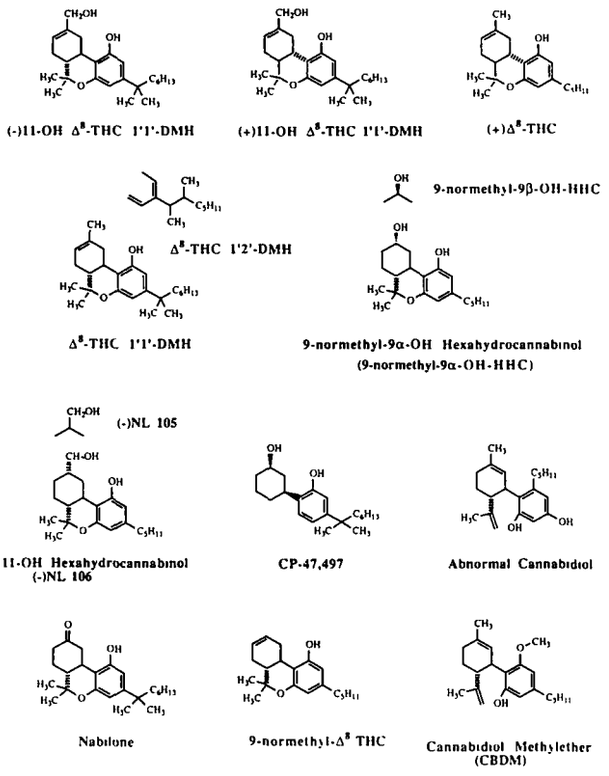

FIG 3 Structures of synthetic cannabinoids tested for Δ9-THC-like discriminative stimulus effects Only changed portions of isomers have been shown Abbreviations used in the text are indicated

ent laboratories in the United States and Sweden In all studies, Δ9-THC administration produced excellent stimulus control over lever selection which occurred at doses (2.0–3.2 mg/kg) that had little, if any, effects on overall rates of responding. In all studies, substitution tests were conducted with various doses of Δ9-THC, allowing the calculation of an ED_{50} potency estimate for purposes of comparison with the potency of the tested drugs.

Pharmacological Specificity

The results of substitution tests with noncannabinoid compounds are summarized in Table 1. Most of these data were obtained by Browne and Weissman (4). Drugs representing a wide variety of pharmacological classes failed to substitute for the Δ9-THC stimulus. In no case did any dose of these drugs result in greater than an average of 60% Δ9-THC lever selection. This degree of drug-lever responding can result from indiscriminate responding on the two levers. The dose of althesin which produced 60% Δ9-THC lever selection markedly reduced rates of responding, suggesting that this intermediate level of Δ9-THC lever selection may have been due to disruption of behavior (4). Other drugs shown in Table 1 which produced intermediate levels of drug-lever selection accompanied by response rate suppression included diazepam, loperamide and phencyclidine. Although the data in Table 1 provide good evidence for the pharmacological specificity of the Δ9-THC stimulus, it should be noted that a number of drug classes have not been evaluated in this model These include methylxanthines, adenosine agonists, site-selective serotonergic antagonists, and substituted amphetamine hallucinogens. In addition, only a limited number of drugs from each class have been tested, and in many cases only at one dose Thus further research to provide additional evidence concerning the pharmacological specificity of the Δ9-THC stimulus in rats is clearly needed.

Substitution Tests With Cannabinoid Analogs of Δ9-THC

A large number of cannabinoids have been evaluated for their ability to produce Δ9-THC-like discriminative stimulus effects. Figures 1–4 show the structures of these compounds as well as the abbreviations used in this review. The benzopyran nomenclature will be used for all compounds. When not otherwise indicated, the optical rotation of all compounds is levorotatory.

Table 2 lists the cannabinoids that fully substituted for Δ9-THC. Shown are the ED_{50}'s for each compound, in mg/kg and μM/kg, as well as their potency relative to Δ9-THC on both a mg/kg and micromolar basis. For the seven compounds for which data are available from more than one reference (including Δ9-THC), the simple averages of the potencies and relative potencies from all tests are provided. Table 3 shows the individual test results for these seven compounds, which generated the averages presented in Table 2 These data demonstrate the general consistency of the results across laboratories. The greatest variation seen is the data for 11-OH-Δ8-THC, where a 14-fold potency difference was found by two laboratories This potency difference between laboratories is reduced to a 5-fold difference when potency relative to Δ9-THC in each study is calculated; however, some caution should be exercised in using the potency estimate in Table 2 for this compound.

Table 2 shows that 22 different cannabinoids have been shown

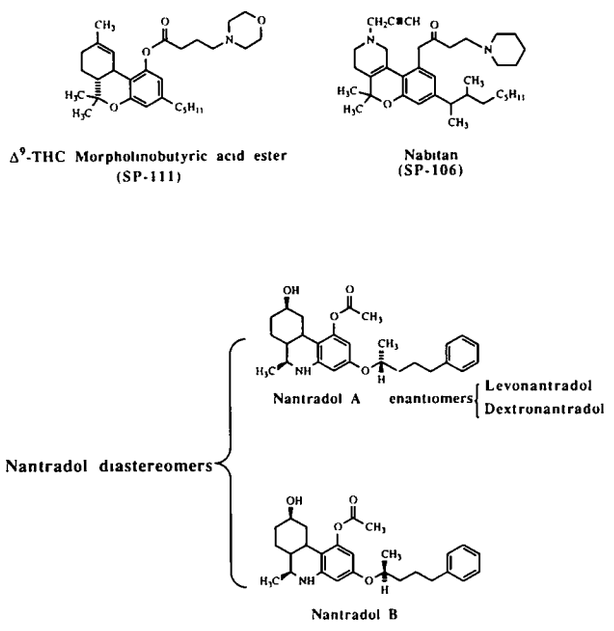

FIG 4 Structures of synthetic cannabinoids containing four ring moieties which have been tested for Δ9-THC-like discriminative stimulus effects Abbreviations used in the text are indicated

to substitute for the Δ9-THC stimulus. They are listed in rank order molar potency relative to Δ9-THC. The most potent compound is (−)11-OH-Δ8-DMH, which is 100-fold more potent than Δ9-THC The least potent compound is 9-nor-Δ8-THC, which is 56-fold less potent than the Δ9-THC on a micromolar basis. Thus the tested cannabinoids evidence about a 5,600-fold range of relative potencies

Table 4 lists cannabinoids that did not fully substitute for Δ9-THC The maximum dose tested is also provided. It is possible that these compounds are incapable of producing Δ9-THC-like effects and thus represent either totally inactive cannabinoids or cannabinoids with CNS actions dissimilar from those of Δ9-THC On the other hand, scarce supplies of most of these compounds precluded their being tested at very high doses. Thus it is possible that higher doses could yield evidence for Δ9-THC-like effects. For this reason, a potency relative to Δ9-THC is also provided for these compounds indicating the minimum ratio for discriminative stimulus effects. It can be seen that only cannabidiol and abnormal cannabidiol were tested at high enough doses to establish a clear lack of THC-like activity.

Concordance With Human Testing

Table 5 shows the relationship between Δ9-THC-like discriminative stimulus effects in rats and marihuana or Δ9-THC-like subjective and/or behavioral effects in humans. Of the eleven compounds tested in both species there is clear agreement in nine As first pointed out by Weissman (46), this relationship is not only qualitative, but also is generally true for potency correlations The only divergence among the human and rat data is seen with the 8-hydroxylated metabolites of Δ9-THC. Both the α and β isomers were tested by Ford et al. (9) and were not found to substitute fully for Δ9-THC, although scarce quantities

TABLE 2

CANNABINOIDS WITH Δ9-THC-LIKE DISCRIMINATIVE STIMULUS EFFECTS

Drug	Molecular Weight	Hour Preinjection	ED_{50} mg/kg	ED_{50} μM/kg	Potency Relative to Δ9-THC mg/kg	Potency Relative to Δ9-THC μM/kg	References
(−)11-OH-Δ8-THC-1'1'DMH	386 6	1 5	0 02	0 04	0 01	0 01	(23)
Levonantradol	438 6	1	0 02	0 05	0 02	0 02	(4)
Nantradol A	438 6	1	0 08	0 18	0 09	0 07	(4)
Nantradol	438 6	1	0 09	0 21	0 10	0 07	(4)
CP-47,497	318 5	1	0 10	0 31	0 15	0 15	(47)
S'-3'-OH-Δ9-THC	330 5	0 5	0 25	0 76	0 17	0 16	(32)
Δ8-THC-1'1'-DMH	370 6	1 5	0 35	0 94	0 20	0 17	(23)
Δ8-THC-1'2'-DMH	370 6	4	0 21	0 57	0 23	0 19	(25)
R/S'-3-OH-Δ9-THC	330 5	0 5	0 31	0 94	0 21	0 20	(32)
NL105	332 5	0 5	0 24	0 72	0 28	0 27	(22)
11-OH-Δ9-THC	330 5	0 5–1	0 28	0 84	0 31	0 30	(4, 9, 24, 32, 46)
Nabilone	372 6	1	0 29	0 78	0 35	0 30	(4,46)
11-OH-Δ8-THC	330 5	0 5	0 60	1 82	0 57	0 54	(4, 9, 24)
SP-111	469 7	0 5	1 17	2 49	1 00	0 67	(24)
9-Normethyl,9β-OH-HHC	318 5	0 5–1	0 53	1 67	0 74	0 73	(4, 9, 46, 47)
Nantradol B	438 6	1	1 19	2 71	1 35	0 97	(4)
Δ9-THC	314 5	0 5–1	0 81	2 58	1 00	1 00	(4, 9, 21– 25, 32, 45, 46)
R'3-OH-Δ9-THC	330 5	0 5	1 67	5 05	1 11	1 06	(67)
SP-106 (nabitan)	546 8	1	1 85	3 38	2 10	1 21	(4)
NL106	332 5	0 5	1 58	4 75	1 86	1 76	(22)
Δ8-THC	314 5	1	1 81	5 76	2 23	2 23	(4,46)
Cannabinol	310 4	0 5–1	7 59	24 44	10 36	10 49	(4, 21, 46)
9-Normethyl-Δ8-THC	300 4	0 5	23 10	76 89	53 60	56 10	(9)

TABLE 3

COMPARISONS OF POTENCY ESTIMATES FROM SUBSTITUTION TESTS FOR Δ9-THC-LIKE DISCRIMINATIVE STIMULUS EFFECTS FROM DIFFERENT STUDIES

Cannabinoid	Hour Preinjection	ED_{50} (mg/kg)	Potency Relative To Δ9-THC (mg/kg)	Reference
11-OH-Δ8-THC	0.5	0 08	0 19	(9)
	0 05	1 12	0 96	(24)
11-OH-Δ9-THC	1	0 22	0 25	(4)
	0 05	0 17	0 39	(9)
	0 05	0.53	0.45	(24)
	0 05	0 26	0 17	(32)
	1	0 21	0 28	(46)
9-nor,9β-OH-HHC	1	0.65	0.74	(4)
	0 5	0 14	0 32	(9)
	1	0 70	0 95	(46)
	1	0 64	0 94	(47)
Cannabinol	1	6 77	7 69	(4)
	0 5	8 39	13 11	(21)
	1	7 60	10 27	(46)
Nabilone	1	0 36	0 41	(4)
	1	0.22	0 30	(46)
Δ8-THC	1	2 02	2 30	(4)
	1	1 60	2 16	(45)
Δ9-THC	1	0 88	1 00	(4)
	0 5	0 43	1 00	(9)
	0 5	0 64	1 00	(21)
	0 5	0 85	1 00	(22)
	0 5	0 66	1.00	(23)
	0 5	1 17	1 00	(24)
	0 5	0 92	1 00	(25)
	0 5	1.15	1.00	(32)
	1	0 74	1 00	(46)
	1	0 68	1 00	(47)

of test compound allowed only limited testing. At the highest-dose tested, however, the 8β-OH-Δ9-THC isomer resulted in 50% drug lever selection. There was a dose-related increase in drug-lever selection at the two lower doses and an apparent absence of behavioral toxicity. Thus it is possible that the negative rat data reflect low potency rather than a lack of Δ9-THC-like efficacy. Such data emphasize the importance of testing over a full dosage range before concluding a complete absence of Δ9-THC-like effects. The clinical literature concerning the two epimers of the 8-OH metabolite of Δ9-THC is also somewhat equivocal. Perez-Reyes et al (37) conclude that only the 8β-OH-Δ9-THC compound is weakly THC-like, while Hollister (15) reports both the α and β to be active. Indeed, the later study concludes the β epimer to be two-thirds as potent as 8α-OH-Δ9-THC. Both studies involved intravenous administration using comparable doses. In conclusion, it is quite possible that the two exceptions to the concordance between animal and human test results shown in Table 5 are the result of incomplete tests rather than true exceptions.

Additional work using cannabinoids in human subjects will provide further evidence of the validity of drug discrimination as a model of cannabis intoxication In addition, tests in rats of the several compounds that have been tested in humans and for which we have not found rat drug discrimination results will also provide evidence on the validity of the model. Synhexyl (17) and tetrahydrocannabinovivarin (15) both appear to produce cannabis-like effects in humans, while cannabidiol-dimethylether (20), cannabichromene (20) and the major urinary metabolite 11-nor-9-carboxy-Δ9-THC (43) do not The psychoactivity of two additional compounds is unclear based on the clinical literature. The cannabinoid Δ6a,10a-THC produced conflicting evidence of cannabis-like effects in humans (14, 15, 20), and its synthetic analog Δ6a10a-dimethyl-heptyl pyran is reported to be both active (39,41) and not active (30). The animal drug discrimination paradigm, which allows for the study of a wider dose range, would help clarify the psychoactivity of these drugs.

DISCUSSION

It is clear from this review that Δ9-THC discrimination in rats is an excellent animal model of cannabis-like intoxication in

TABLE 4

CANNABINOIDS THAT FAIL TO SUBSTITUTE FULLY FOR Δ9-THC IN DRUG DISCRIMINATION STUDIES

Drug	Molecular Weight	Maximum Dose Tested (mg/kg)	Minimum Potency Relative to Δ9-THC (mg/kg)	(μM/kg)	References
Dextronantradol	438 6	3 2	>7	>3	(4)
(+) 11-OH Δ8 1'1-DMH	386 6	10	>26	>5	(23)
(+) Δ8-THC	314 5	10	>32	>11	(25)
CBDM	328 5	10	>30	>11	(22)
9-Normethyl,9α-OH-HHC	318 5	10	>31	>23	(9)
8α,11-diOH-Δ9-THC	346 5	12	>35	>25	(9)
8β,11-diOH-Δ9-THC	346 5	12	>35	>25	(9)
Cannabidiol	314 5	32	>102	>47	(4, 46, 47)
8α-OH-Δ9-THC	330 5	30	>91	>66	(9)
8β-OH-Δ9-THC	330 5	30	>91	>66	(9)
Abnormal cannabidiol	314 5	100	>318	>232	(9)
Cannabidiol	314 5	100	>318	>232	(9)

*Minimum potency relative to Δ9-THC based upon the potency estimate for Δ9-THC obtained in the cited study and the highest dose of the cannabinoid tested.

TABLE 5

CORRESPONDENCE BETWEEN Δ9-THC-LIKE DISCRIMINATIVE STIMULUS EFFECTS IN RATS AND CANNABIS-LIKE INTOXICATION IN HUMANS*

		Cannabis-Like Intoxication in Humans?	
		Yes	No
THC-Like in Rats			
Yes	Δ9-THC	(15, 20, 38, 44)	
	Δ8-THC	(16,27)	
	11-OH-Δ9-THC	(15, 29, 38)	
	11-OH-Δ8-THC	(15)	
	CBN	(36)	
	Levonantradol	(28)	
	Nabilone	(26, 31, 34)	
	Nabitan	(19,45)	
No	8α-OH-Δ9-THC	(15)	8α-OH-Δ9-THC (37)
	8β-OH-Δ8-THC	(15,37)	CBD (3, 5, 15, 36)

*Shown in parentheses are the references for the published reports

humans. This conclusion is based primarily on data showing an good correspondence between Δ9-THC-like discriminative stimulus effects and marihuana-like subjective effects in human subjects for a series of Δ9-THC analogs. Further support for the validity of this model is the evidence for the pharmacological specificity of the Δ9-THC stimulus in rats. A large number of drugs that are psychoactive but do not produce a cannabis-like intoxication in humans fail to substitute for Δ9-THC when tested in generalization studies Even drugs such as LSD and phencyclidine, which produce hallucinogenic effects in humans, are not recognized as Δ9-THC-like by rats, consistent with the qualitatively different types of intoxication produced by these drugs and cannabis. The data showing the pharmacological specificity of Δ9-THC discrimination is consistent with the classification of cannabinoids as having a unique spectrum of pharmacological effects and suggests that a unique neural substrate may exist for their behavioral effects

Since Δ9-THC-like discriminative stimulus effects of test drugs in rats can predict cannabis-like intoxication in humans, this animal model should prove helpful in drug development There are a number of potential therapeutic applications of cannabinoids, including useful analgesic, antiemetic, antiglaucoma and anticonvulsive effects (33) For these uses, the production of a cannabis-like intoxication would be an unwanted side effect Indeed, the marketed synthetic cannabinoid, nabilone, produces these effects in the animal model and in humans (34). Drug discrimination procedures in animals should prove useful for evaluating compounds for this side effect, with the goal of retaining the therapeutically useful activity at doses below those that produce Δ9-THC-like discriminative stimulus effects, or the development of active compounds that are unable to substitute for Δ9-THC at any dose It is also clear that the results of drug discrimination studies should be useful in evaluating the Δ9-THC-like abuse potential of compounds undergoing regulatory consideration.

Perhaps of more fundamental importance to the area of drug abuse will be the use of cannabinoid drug discrimination procedures to evaluate drugs that might block or attenuate cannabis intoxication and thus be useful in the pharmacotherapy of cannabis abuse. Animal models of cannabinoid self-administration have been difficult to establish (5,48) Thus a search for drugs that could alter cannabinoid discrimination in animals would be a useful strategy for developing potential treatments.

Another important use of the results of cannabinoid discrimination research will be to establish the cellular mechanisms for cannabis intoxication A powerful approach to this question is to use structure-activity correlations between cellular actions of a series of cannabinoids and their potency and efficacy in drug discrimination studies. This approach has been very useful for establishing receptor mediation of opioid intoxication (18) and for establishing the role of serotonergic and catecholaminergic substrates for the subjective effects of hallucinogens and cocaine-like stimulants, respectively (10,35). The cannabinoids that have been studied for Δ9-THC-like discriminative stimulus effects comprise about a 5,600-fold potency range Δ9-THC itself lies roughly midway in this potency series, with a number of synthetic cannabinoids having been synthesized that are substantially more potent than Δ9-THC, and the naturally occurring cannabinol as well as some other synthetic cannabinoids being 2–50 times less potent than Δ9-THC. As new cannabinoids are synthesized that prove to be useful tools for exploring the cellular pharmacology of this class, it will be important to establish their potency for discriminative stimulus effects

In carrying out potency correlation studies using drug discrimination data, it is important to bear two issues in mind. The first concerns the use of data for cannabinoids that fail to substitute fully for Δ9-THC. As shown in Table 4, a number of these drugs have been tested over only a limited dose range, often because of inadequate supplies for in vivo evaluation If the highest dose tested failed to substitute for Δ9-THC, but also failed to produce any changes in rates of responding or other evidence of toxicity, it cannot be said with certainty that the compound is completely devoid of Δ9-THC-like effects, only that its potency must exceed the highest tested dose We have provided the minimal potency relationship that these compounds would have relative to Δ9-THC; however, if these numbers are used in a correlational analysis, the correlation coefficient may be underpredicted when including data for compounds that would have been totally inactive even at higher doses. A less conservative approach would be to consider these compounds as inactive and assign them an infinite potency relative to Δ9-THC.

Another issue to bear in mind for potency correlations using these results concerns the treatment of data for noncannabinoids that fail to substitute for the Δ9-THC stimulus, shown in Table 1 Since most of these drugs appear to be qualitatively unlike Δ9-THC, they could also be assigned an infinite potency relative to Δ9-THC In nearly every case, that would probably be a reasonable assumption, however, one feature of drug discrimination research suggests caution in this regard. In generalization tests, doses above those that totally suppress lever pressing behavior cannot be evaluated. If drugs have multiple cellular actions, only their most potent action is likely to be revealed in drug discrimination research. This is unlike the situation in many biochemical studies, such as ligand binding, where more potent actions at one site may not interfere with less potent actions at another site. It is possible that some of the drugs shown in Table 1 will have biochemical effects at high concentrations that are similar to those of Δ9-THC. Since these cellular effects may occur at higher concentrations than other notable actions of these drugs, when they are studied in drug discrimination procedures, these more potent actions can mask possible Δ9-THC-like effects which may be present at higher doses When tested in combination with antagonists for the more potent actions, these drugs may reveal Δ9-THC-like effects. An example of this phenomenon is mixed-acting benzomorphans, which normally show opiate-like discriminative stimulus effects, but when higher doses are tested in combination with naltrexone, their phencyclidine-

like effects are unmasked (18,42) The cautious investigator will be aware of this difficulty of carrying out in vitro vs. in vivo potency comparisons using drug discrimination data.

Certain aspects of these results of drug discrimination studies of cannabinoids bear upon likely cellular mechanisms for these effects. Since Δ9-THC-like discriminative stimulus effects are not produced by drugs with prominent actions at dopamine, GABA, opioid, serotonin or phencyclidine receptors, among others, these actions can probably be excluded as likely mechanisms for Δ9-THC discrimination On the other hand, the wide potency range of cannabinoids is consistent with a receptor-mediated drug action. The precise structural requirement for activity, including the stereoselectivity of drugs such as Δ9-THC and levonandrodol, provides additional support for receptor mediation. Recently, a cannabinoid binding site in the brain has been characterized (7,12). It will be important to compare affinities of cannabinoids for this site with their potencies for discriminative stimulus effects to ascertain the functional role of this site in mediating cannabis intoxication.

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