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BRIEF COMMUNICATION

Comparison of the Discriminative Stimulus Properties of Δ^9-THC and Psilocybin in Rats[1]

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GREENBERG, I., D. KUHN AND J. B. APPEL. *Comparison of the discriminative stimulus properties of Δ^9-THC and psilocybin in rats.* PHARMAC. BIOCHEM. BEHAV. 3(5) 931–934, 1975. – Male albino rats were trained to respond differentially on the left or right lever in a 2-lever chamber on the basis of which drug had been given intra-peritoneally (IP) 30 min before experimentation. In 1 group 1.0 mg/kg of Δ^9-THC and control injections (vehicle) served as the discriminative stimuli associated with each lever and in another group the drug stimuli were 1.0 mg/kg of Δ^9-THC and 1.0 mg/kg of psilocybin. The results confirmed those of other experiments using different procedures; that Δ^9-THC can acquire discriminative control over responding. The fact that Δ^9-THC and psilocybin were also found to differentially control lever choice demonstrates that these 2 drugs probably produce discriminably different states in rats.

Δ^9-THC Psilocybin Discrimination State dependent Learning

HALLUCINOGENS such as LSD and mescaline can be easily discriminated from saline by rats, i.e., each drug can control choice responding [5,10]; however, appropriate doses of these compounds are probably more similar to each other (as well as to psilocybin) than to other kinds of drugs [5,17]. Δ^9-THC can also control choice responding [2, 4, 9, 11] and has been reported to be discriminably different from LSD, at least in rats [2].

Studies of drug tolerance and cross-tolerance support the results of drug discrimination studies. For example, rats tolerant to 1 hallucinogen (LSD) show cross-tolerance to other related hallucinogens such as psilocybin and possibly mescaline [1] but do not show cross-tolerance to Δ^9-THC [18]. More recently, Järbe and Henriksson [11] have reported a lack of generalization to THC for a variety of drugs including stimulants, depressants, morphine, etc. Thus, at least on the animal level, the differences between the cannabinoids and some hallucinogens appear to be qualitative.

The purpose of the present study was to further test this hypothesis. Specifically, in one experiment we attempt to replicate the results of previous studies which show that a relatively small dose of THC (1.0 mg/kg) can control choice responding. In the second experiment an attempt is made to maintain stimulus control with 1.0 mg/kg of THC and 1 relatively weak indole-amine hallucinogen, psilocybin (1.0 mg/kg). These doses apparently have similar behavioral effects in rats [1,5].

METHOD

Animals and Apparatus

Twelve experimentally naive Sprague-Dawley rats weighing approximately 300 g at the start of experimentation were used. They were housed individually with ad lib food and were maintained at 80 percent of ad lib body weight by restricting water intake. The apparatus consisted of 2 Lehigh Valley (Model No. 1316) experimental chambers contained in sound and light attenuating enclosures. Each box contained 2 levers on the front panel separated by a liquid feeder. Each reinforcement consisted of 0.1 ml of tap water; sessions were 30 min long. Electromechanical programming and recording equipment were located in an adjoining room.

Procedure

The training procedure has been described in detail

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elsewhere [12]. Briefly, 6 rats were trained to perform at stable rates on a tandem variable interval 1 min fixed ratio 10 (Tand VI 1 FR 10) schedule with a reset (punishment) contingency added to the FR component. Rats were first shaped to respond on a CRF schedule on 1 lever and then on the other with the first lever removed from the chamber to prevent presenting the rats with a choice before differential cues (drugs) were given. Simultaneoulsy, the reinforcement requirement was gradually raised from CRF to FR 10. Animals remained on the FR 10 schedule for 2 days on each lever. The VI schedule was then introduced such that the animal eventually had to emit 10 responses after an average interval of 1 min to obtain reinforcement. The rats worked on this schedule for 2 days on each lever.

Finally, a punishment (reset) contingency was added to the FR 10 component in order to prevent superstitious chaining from the incorrect to the correct lever. Thus, following each VI 1, 10 responses on the correct lever were required for reinforcement. Both levers were available to the rat only when drug training began. The correct lever was defined by the drug or vehicle (control) injection given before testing. Responses on the incorrect lever were recorded but had no programmed consequences other than resetting the stepper during the FR sequence.

Δ^9-*THC as a Discriminative Stimulus*

Ampules of Δ^9-THC dissolved in 25 mg/25 ml alcohol (obtained from NIMH Center for the Study of Narcotic and Drug Abuse) were first subjected to vaccum to remove the alcohol. The resinous THC was then suspended in 0.5 ml of Triton-X-100 and this suspension was diluted with 0.9 percent sodium chloride to a concentration of 1.0 mg/ml of THC. Either THC or vehicle (1.0 mg/kg) was given 30 min prior to experimentation 5 days a week. The drugs were given randomly with the restriction that the same drug state not exist for more than 3 consecutive days. Only data obtained prior to the first reinforcement were analyzed daily to eliminate the confounding effects of dipper cues on choice behavior [5]. Test days of 5 min extinction periods were run on 4 separate occasions (2 vehicle, 2 THC) to assess the degree of control the drugs had over choice responding. To eliminate possible position perference, 3 of the 6 rats were required to respond on the left lever for reinforcement after THC and 3 on the right lever after THC. The opposite lever for each group, respectively, was correct after vehicle injections.

Δ^9-*THC and Psilocybin as Discriminative Stimuli*

Psilocybin, in powder form from NIMH, was dissolved in 0.9 percent sodium chloride to a concentration of 1.0 mg/ml for use in training with 1.0 mg/ml THC. As before, 4 extinction test days were run (2 psilocybin, 2 THC). The pharmacological and behavioral procedures and controls described previously were used here with a naive group of 6 animals. Since 2 of these rats died during the course of training, the data reported are from only 4 animals.

RESULTS

Table 1 (top) shows percent correct responding after either THC or vehicle injections over the course of 43 days of training. Choice responding for the first 25 days was about 60 percent correct. On extinction test days 3 of the 4 discrimination tests were significantly different from random responding ($p<0.05$) with only the first THC test day falling below significance. Thus, the injections exerted moderate but significant control over differential lever choice producing about 70 percent correct responding after either THC or vehicle.

Representative response rates after either injection are also shown in Table 1 (top). Rates after both vehicle and THC injections gradually increased throughout approximately the first 30 days and were approximately equal (25 resp/min) from Day 30 to the end.

While the initial depression in rate following THC may reflect some behaviorally toxic effect of the drug, this effect was transient since, after Day 30, the animals could not be distinguished on the basis of response rate alone. During this time (the last 13 days), choice responding nonetheless indicated that the animals could discriminate injections of THC from injections of the vehicle control.

Table 1 (bottom) indicates percent correct responding during the THC vs. psilocybin discrimination. As before, responding fluctuated around the random level for approximately 30 days. Performance during the last 3 of the 4 extinction test days were significantly different from random ($p<0.05$) indicating that THC and psilocybin acquired differential control over lever choice.

Table 1 (bottom) also demonstrates that response rates after THC remained higher than those after psilocybin, expecially from Day 30 to the end of experimentation when the rats responded at a rate of more than 40 resp/min after THC compared to 21 resp/min after psilocybin. These data indicate that with respect to rate effects, cross-tolerance was not seen between THC and psilocybin. Furthermore, when the rate differential between the two drugs was greatest, accuracy of responding continued to increase.

DISCUSSION

The results of the present two experiments indicate that lever choice behavior in the rat was state-dependent [16], i.e., the drug stimuli came to exert control over responding. THC was found to exert moderate control in the 2-lever task which confirms other investigations showing that THC and vehicle injections can control differential responding on various tasks including approach-avoidance conflict responding [2,11], choice responding in a water T-maze [9] and lever choice in a procedure which is similar to our own [4]. The advantage of the present technique is that it is apparently more sensitive than those hitherto reported: i.e., a much lower dose of THC can control differential responding.

When THC and psilocybin were used as discriminative stimuli, it was found that the rats learned to respond appropriately after either injection. Harris and Balster [7] reported that psilocybin at doses of 0.2 and 0.4 mg/kg produced weak or no control over lever choice when compared with control injections. However, when a larger dose of psilocybin (1.0 mg/kg) is used, psilocybin cues are sufficiently great to enable rats to make a better discrimination than was the case when THC and control injections were given.

THC has been regarded as a CNS depressant [3,13] and has been shown to impair acquisition of various tasks in rats [8,15], both of which might have contributed to depressed rates following THC (below that of control) in the first experiment. Nevertheless, depression disappeared around

TABLE 1

Extinction Test Day	Drug Administered	Percent Total Responding on Correct Level	Bar-Press Rate (resp/min)
		Δ^9 THC vs Saline	
27	Vehicle	70 ($p<0.05$)	24
32	THC	64 (N.S.)	26
37	Vehicle	80 ($p<0.05$)	24
43	THC	90 ($p<0.01$)	27
		Δ^9 THC vs Psilocybin	
26	Psilocybin	63 (N.S.)	20
31	THC	80 ($p<0.05$)	43
36	Psilocybin	86 ($p<0.05$)	21
44	THC	83 ($p<0.05$)	41

Day 30 and from then to the end of the experiment the rates after THC and vehicle were essentially equal. Although the procedure did not allow for direct assessment of tolerance, the results did indicate that rates after THC gradually recovered and equalled non-drug rates with repeated injections while at the same time the rats' choice responding indicated that they could still discriminate THC from control injections. While Bueno and Carlini [4] have also demonstrated that rats can respond differentially to THC as measured in a lever-choice task after they become tolerant to the drug's disruptive effects measured in a rope-climbing task, this study confounds tolerance and discriminability by using different responses since it is well-known that tolerance may develop to some drug effects and not to others [6,14]. By using only one response type in the present report (bar-pressing) and extracting two different measures (choice and rate) from it, it can be seen that when drug effects on one facet of the response measure are no longer evident (rate decrease) tolerance to another facet (choice) does not develop. Thus, the rate data may not simply reflect discrimination learning but indicate instead that accuracy (discriminability) continued to increase even when the disruptive effects of the drugs were no longer evident.

Similar results were seen in the THC-psilocybin group. Although there was no control group with which to compare the rates after THC and psilocybin, differences in rate were noticeable by Day 25 and these differences remained consistent through Day 40 when THC rates were elevated above rates after psilocybin by 20 resp/min (Table 1). Although there remains the distinct possibility that the animals discriminated two levels of intensity of the same stimulus (i.e., the drugs were differentiated by quantitative, rather than qualitative differences), this is doubtful since there was tolerance to the rate depressing effect of each drug but no cross tolerance was evident. Had the animals based their discrimination on quantitative differences of similar stimuli, greater cross-tolerance would have been observed. While cross-tolerance among various hallucinogens has been reported [1], it has not been shown between THC and either indole- or phenethylamine hallucinogens [18]. THC has presently been shown to be different from psilocybin, at doses of each drug which have similar behavioral effects, by virtue of these two drugs' ability to serve as discriminative stimuli. Considering these data as well as other investigations comparing THC and various hallucinogens with respect to tolerance and discriminability, one might hypothesize that the differences between these two drug classes in animals appears to be qualitative, i.e., they are distinct and cannot be differentiated as separate points on a dosage continuum (quantitative). Full dose-discrimination curves will be required before the above hypothesis can be clearly confirmed or denied.

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