Effects of Δ^9 -tetrahydrocannabinol on stimulus control*

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METHOD

Subjects

Sixteen experimentally naive male albino rats, maintained at approximately 80% of their free-feeding weights, served as Ss.

Apparatus

The apparatus consisted of four standard rat operant chambers specially modified so that the floor could be tilted 25 deg. in 5-deg steps, either side of horizontal, and associated automatic programming and recording equipment (Lyons et al. 1973). Masking noise was supplied to each chamber throughout the experiment by a Grason-Stadler white-noise generator.

Procedure

Following preliminary magazine and leverpress conditioning, the rats were trained to discriminate between the flat floor S+ [variable interval (VI) 1-min reinforcement] and the floor rotated 15 deg counterclockwise from horizontal S- (extinction). Earlier work had shown this discrimination to be a particularly difficult one. Therefore, in order to facilitate the acquisition of this discrimination, the S- was "faded in." That is, the rats first learned to discriminate between the flat floor S+ and an S- rotated 25 deg counterclockwise from horizontal. Following mastery of this task, defined as seven responses in S+ for each response in S-, the S- was changed to 20 deg until criterion performance was achieved, at which time the S- was reduced to 15 deg. Throughout the experiment, reinforcement consisted of 50-mg Noyes rat pellets.

During each daily training session, 15 S+ periods were alternated with 15 S- periods in a quasirandom sequence. Each S+ and S- period was 50 sec in duration and each was separated from the next by a 10-sec blackout of the "houselight." During this blackout period, the floor position was changed to the next stimulus value.

Immediately following the last discrimination training session, all rats were tested, in extinction, for generalization to 11 different floor positions, ranging from -25 to +25 deg in 5-deg steps from horizontal. The test floor positions were randomized within a sequence and six different random sequences were presented to each animal. Each test stimulus was presented for 50 sec and each was separated from the next by the 10-sec blackout.

Two hours prior to the final discrimination training-generalization test session, the Ss were randomly assigned to one of four groups and were given intraperitoneal (IP) injections of 0.0, .25, .50, or 2.0 mg Δ^9 -THC per kilogram of body weight.¹ Injection volume was constant for all Ss.

RESULTS

The administration of .25 and .50 mg/kg Δ^9 -THC, but not of 0.0 or 2.0 mg/kg, produced significant increases in response rates over the mean rate for the five preceding nondrug discrimination sessions [for the .25-mg/kg group, $T(6) = 4.08$, $p < .05$; for the .50-mg/kg group, $T(6) = 3.1$, $p < .05$]. This increase in response rate under low doses of Δ^9 -THC is consistent with the biphasic dose-response function previously reported for rats responding for VI reinforcement under the drug (Grisham & Ferraro, 1972). More importantly, in the present context, no breakdown in discrimination performance was produced by any of the Δ^9 -THC doses used. For example, the mean percentage of the total responses which were made to the S+ did not differ

Sixteen rats received extended discrimination training between two floor-tilt positions and then were given an extinction generalization test along the floor-tilt dimension. The stimulus control effects of four doses of Δ^9 -tetrahydrocannabinol (Δ^9 -THC), 0.0, 0.25, 0.50, or 2.0 mg/kg of body weight, were assessed in groups of four rats each. Δ^9 -THC did not disrupt either discrimination performance or the occurrence of orderly generalization gradients. However, a significant dose-related enhancement of the postdiscrimination peak shift was obtained.

In the stimulus control context, a peak shift is a change in the model response category of a postdiscrimination generalization gradient away from the stimulus correlated with reinforcement (S+) so as to be further removed from the stimulus correlated with extinction (S-). Recently, Lyons and his coworkers have reported that the drug chlorpromazine does not disrupt discrimination performance but does produce a dose-dependent reduction of the peak shift in rat and pigeon Ss showing a strong peak shift during a saline control test condition (Lyons, Klipec, & Eirick, 1973; Lyons, Klipec, & Steinsultz, 1973). Lyons concluded from these data that although chlorpromazine had no effect on the discriminative control exerted by S-, the drug did attenuate the aversiveness of S- that is presumed to produce the peak shift, thereby reducing the peak shift.

The present experiment extends this prior work to Δ^9 -tetrahydrocannabinol (Δ^9 -THC), the major active constituent of marijuana. To date, the few animal studies which have investigated the effects of marijuana on simple discriminations have not always been in agreement (cf. Ferraro, 1972), and no investigation of the effects of marijuana on stimulus generalization has been reported in the literature. More explicitly, the purpose of the present experiment was to determine the effect of Δ^9 -THC on discrimination performance and on the aversiveness of S- as measured by the generalization gradient peak shift.

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Fig. 1. Mean percentage of responses to S+ that occurred to each of the test floor positions for the four drug groups.

reliably between the drug session (77%) and the immediately preceding nondrug discrimination session (81%).

Figure 1 presents the mean percentage of S+ responding that occurred to each of the generalization test stimuli. Under this percentage measure of generalization performance, responding to S+ is set equal to 100 and the responding to each of the test floor positions is taken as a percentage of this. Thus, a test stimulus score greater than 100 would indicate that more responding occurred to that test stimulus than it did to the S+ training stimulus. This relative measure of generalization is presented rather than the absolute number of responses to each test floor position in order to facilitate direct comparisons among the four experimental groups. It should be noted, however, that in the instance of this research, the same conclusions are derivable from both the absolute and the relative gradients.

As shown in Fig. 1, orderly generalization gradients were obtained for all four groups along the floor-tilt dimension. However, the peak of the gradient for the nondrug control group did not occur at the S+ training stimulus. Instead, the peak was shifted away from the S+ to the +5-deg stimulus, i.e., a peak shift occurred. Of greater interest here is the fact that Δ^9 -THC produced a dose-related increase in the peak shift. As the dose of the drug increased, there was an increase in the peak of the

generalization gradient at the +5-deg stimulus and a general elevation of responding to all test stimuli on the side of the gradient to which the peak shift occurred. An analysis of variance performed on the generalization test data yielded a significant effect of stimuli [$F(9,108) = 28.88, p < .01$] and a significant Δ^9 -THC Dose by Stimuli interaction [$F(27,108) = 3.12, p < .01$].

DISCUSSION

The enhancement of the peak shift produced by Δ^9 -THC is exactly opposite to the effect of chlorpromazine on the peak shift reported by Lyons et al (1973). By and large, theoretical interpretations of the peak shift have hypothesized that this phenomenon is due to aversive properties which accrue to the S- during discrimination training when responses in the presence of S- go unreinforced (e.g., Terrace, 1972). If it is assumed that chlorpromazine acts to reduce the aversive properties of S-, then the failure to find a peak shift under chlorpromazine would be consistent with the more general aversive stimulus interpretation of the peak shift. According to this theoretical position, the present finding of an enhanced peak shift would imply that Δ^9 -THC acted to increase the aversiveness of S-.

Presumably any aversive effects of Δ^9 -THC would be dose related; such was the case in the present study. Unfortunately for the present interpretation, there are only a few reports in the literature regarding the aversive properties of Δ^9 -THC, and none of these have been done in a stimulus control context. Perhaps the most striking evidence of the aversive properties of Δ^9 -THC that has been obtained to date is the finding that Δ^9 -THC produces a dose-related "bait shyness" in rats (Elsmore & Fletcher, 1971; Glick & Milloy, 1972). Nevertheless, our interpretation of the enhancement of the peak shift in terms of the aversiveness of Δ^9 -THC is consistent with a large body of literature regarding the control exerted by S- on the shape of the generalization gradient.

One possible mechanism which might account for the aversive action of Δ^9 -THC on the peak shift is that of "drug novelty" (e.g., Baum, 1969; Amit, Ziskind, & Baum, 1973) which, briefly described, is the hypothesis that a novel drug experience in and of itself produces a general aversive (fear) state in the pharmacologically naive S. As applied to this experiment, it would have to be assumed that the injection of Δ^9 -THC created a general state of fear and that it was this general state which produced the enhanced peak shift observed during generalization testing under Δ^9 -THC. Since the drug novelty hypothesis assumes a general fear-arousing effect, it would have to be further assumed that if drug novelty were operative in the present experiment, discrimination behavior under the drug would also be affected, most probably in the direction of suppressing ongoing responding to both S+ and S-. No such effects were observed in the drug groups. Indeed, differential responding was maintained between S+ and S- in all drug groups, while in the two lowest dose groups, an increase in responding occurred to both S+ and S-. Thus, it appears that Δ^9 -THC did not produce a general fear-arousing effect, but rather served specifically to increase the aversiveness of S- in the generalization test situation.

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NOTE

1. Synthetic Δ^9 -THC was made available in a dehydrated alcohol solution by Dr. Monique Braude of the NIMH. All doses were taken from NIMH Batch SSC-69060 (93% Δ^9 -THC, 3.2% Δ^8 -THC, and 3.1% cannabinol). The drug vehicle consisted of 0.975 cc isotonic saline, 0.020 cc dehydrated ethyl alcohol, and 0.005 cc Tween 80.

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Food intake as a function of age and food deprivation*

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The purpose of this experiment was to determine whether or not there were age differences in the effects of increasing durations of food deprivation on food intake in rats. The experiment was carried out according to a 3 by 3 by 3 by 7 mixed design consisting of three age groups of 12 female Sprague-Dawley rats each (4, 11, and 24 months), subdivided into three sequence-effects control groups (ABC, BCA, CAB), with each rat exposed to each food-deprivation duration (24, 48, and 96 h), and refeeding measured for 7 days. The dependent variables were: latency to eat, amount of

food per day consumed during refeeding, and body weight. Prior to food deprivation, the 4-month-old rats ate less than the 11-month-old rats or the 24-month-old rats, but these differences were proportional to age differences in body weight. The effects of duration of deprivation, order, and days of refeeding were proportional across age, suggesting equal responsivity to the effects of these factors on food intake across a large segment of the life span of the female rat.

The purpose of this experiment was to determine whether or not there were age differences in the effects of increasing durations of food deprivation on the food intake of rats. On the basis of *indirect* evidence, such as crossings in the Columbia obstruction apparatus, Jerome (1959) concluded that the degree of hunger consequent upon a given duration of food deprivation was inversely related to age. In view of the lack of direct evidence, it

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