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Acquisition and Extinction of Variable Interval Schedule Behavior by Rats under Δ⁹-Tetrahydrocannabinol[1]

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FERRARO, D. P., J. P. GLUCK AND G. B. HERNDON. *Acquisition and extinction of variable interval schedule behavior by rats under Δ⁹-tetrahydrocannabinol.* PHARMAC. BIOCHEM. BEHAV. 2(4) 487–491, 1974. – Twenty eight rats were given 10 acquisition sessions under a variable interval 30 sec schedule of water reinforcement for lever-press responding. This training was followed by one extinction session in which no responses were reinforced. The rats were divided into 4 groups and were administered either 0, 0.5, 2.0 or 8.0 mg Δ⁹-THC per kg of body weight throughout both variable interval schedule acquisition and extinction. The presence of Δ⁹-THC during acquisition suppressed variable interval response rates and decreased the number of reinforcements obtained in a dose-related manner. Likewise, a dose dependent decrease in extinction responding was obtained as compared to nondrug control extinction responding.

Marihuana (cannabis) Δ⁹-Tetrahydrocannabinol Acquisition Extinction Operant behavior Variable interval schedule

THE ACUTE and chronic effects of Δ⁹-tetrahydrocannabinol (Δ⁹-THC) on previously established behavior have now been studied extensively [7]. The usual procedure has involved first training experimental animals to perform one of a variety of learned behavioral tasks and then administering acute or repeated doses of Δ⁹-THC in order to determine how the drug affects the performance of ongoing behavior. By comparison, only a small amount of research has been devoted to the issue of whether Δ⁹-THC affects the processes of acquisition and extinction.

With respect to the acquisition of new behavior under Δ⁹-THC, the available data seem discrepant. In the conditioned shock avoidance situation, Δ⁹-THC has retarded the process of acquisition in some instances [9, 12, 16] and enhanced learning in others [3, 9, 18]. A similar range of Δ⁹-THC effects has been obtained in the food-reinforced maze learning context. The administration of Δ⁹-THC early in maze learning either has had no effect [10] or it has produced a retardation [16] or enhancement [5] of learning. Admittedly, too many differences in procedure exist among these acquisition experiments to permit direct comparisons between them. However, it seems likely, as in the case of other drug-behavior interactions, that the discrepancies reported might be partially resolved by careful study of one particular drug (e.g., dose) or task-related (e.g., positive vs negative reinforcement) parameter.

The effects of Δ⁹-THC on the extinction of behavior are even less well determined. Indeed, only two relatively recent experiments have instituted extinction of previously learned behavior under Δ⁹-THC. In one of these [13], increased resistance to extinction of a conditioned shock avoidance response was observed while in the other [10], either no extinction effect or a more rapid extinction of maze learning performance was obtained.

The extinction effects of Δ⁹-THC in the latter two experiments need to be cautiously interpreted. This is because in both instances the original learning was carried out in a nondrug state. Since Δ⁹-THC has been shown to produce state-dependent learning [4, 9, 12], it is not possible in these experiments to differentiate completely the effects of Δ⁹-THC on extinction from those produced by the drug state change *per se*. We now report an experiment in which the effects of Δ⁹-THC were investigated in a situation where several dose levels of Δ⁹-THC were maintained throughout the course of both acquisition and extinction of learned behavior.

METHOD

Animals

Twenty-eight naive male albino rats from the University of New Mexico breeding colony were used. The rats, which

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were approximately 120 days old at the beginning of experimentation, were allowed free access to food in their individual home cages and were weighed daily at the same time. Two weeks prior to experimentation each rat was exposed to a 24 hr water deprivation regimen under which only the amount of water necessary to maintain body weight at 80% of free-feeding weight was provided.

Apparatus and Drug

The experimental chambers were 4 identical rat operant boxes equipped with a single response lever (1.9 cm in length and 0.6 cm in diameter) which required approximately 15 g downward force through 0.4 cm for a closure of the lever microswitch. Reinforcement was provided by a liquid dipper which made 0.02 cc of water available for 2 sec.

Synthetic (−) Δ^9-THC-*trans*-tetrahydrocannabinol (96% Δ^9-THC, 3% Δ^8-THC, and 1% cannabinol; Batch No. SSC-66907) was obtained in a 0.2 g/cc solution with dehydrated alcohol from the National Institute of Mental Health and stored under refrigeration. All drug and vehicle control injections were given by the intraperitoneal route, 1 cc/kg at 2.0 hr prior to the experimental session. The vehicle consisted of 0.975 cc isotonic saline, 0.020 cc dehydrated ethyl alcohol, and 0.055 cc Tween 80. For drug administrations, amounts of the drug solution were substituted for like amounts of the dehydrated alcohol used in the vehicle so that the alcohol content of drug and vehicle alone injections was the same.

Procedure

During preliminary training the rats were trained to make the lever-press response by the method of successive approximations and then were allowed to obtain 100 reinforcements under a procedure which reinforced every response. The 28 rats were next randomly assigned to one of 4 drug conditions which were in effect for the remainder of the experiment. The drug conditions differed in the dose of Δ^9-THC administered. These drug doses were either 0, 0.5, 2.0 or 8.0 mg Δ^9-THC per kg of body weight (mg/kg Δ^9-THC). Drug vehicle alone was administered to the 0 mg/kg dose group.

The reinforcement schedule acquisition phase of the experiment consisted of giving the 4 groups of rats a 29-min exposure to a variable interval (VI) reinforcement schedule on each of 10 consecutive days. Under a VI schedule, reinforcement is made available after different time periods which vary in length around some mean value. In the present experiment the mean interreinforcement interval or time separating reinforcement availabilities was 30 sec (VI 30 sec), and the range of interreinforcement intervals was from 8 to 90 sec.

On the day following the tenth VI 30 sec acquisition session, the rats were given a single 30-min session of extinction in which no responses were reinforced. Response rates were collected in 5-min periods during the last 15 min of the tenth VI 30 sec acquisition session and throughout the following extinction session.

RESULTS

In this experiment reinforcement was delivered only for the first lever-press response which occurred after a variable interreinforcement interval had elapsed. Therefore, the animal needed only to maintain a constant minimum response rate in order to obtain all the available reinforcements, the minimum rate being determined by the shortest interreinforcement interval. Under the present VI 30 sec schedule this interval was 8 sec and, thus, the minimum response rate was 0.125 responses per sec. Although VI schedules do not explicitly reinforce rates of response, the contingencies of these schedules are such that animals typically respond at response rates which are considerably higher than the specified minimum rate [2]. The question of experimental interest here was whether the presence of Δ^9-THC would modify the acquisition of VI schedule behavior as compared to the VI behavior of the nondrug (0 mg/kg) group.

The course of VI schedule acquisition is shown for the 4 dose groups in Fig. 1. Overall response rates were corrected for the time the reinforcement dipper was presented by subtracting total reinforcement time from the session length prior to computing response rates. As can be seen in Fig. 1, mean corrected response rates increased for all 4 groups across the 10 VI acquisition sessions, $F(9,234) = 9.11$, $p<0.01$. The absolute response rates were inversely related to drug dose with higher drug doses producing lower response rates. An analysis of variance indicated that this main effect of drug dose was significant, $F(3,24) = 8.60$, $p<0.01$, but that there was no significant drug dose by session interaction. A series of multiple comparisons [6] revealed that only the 8.0 mg/kg dose significantly ($p<0.01$) reduced response rate as compared to the other drug doses, among which no significant differences were obtained.

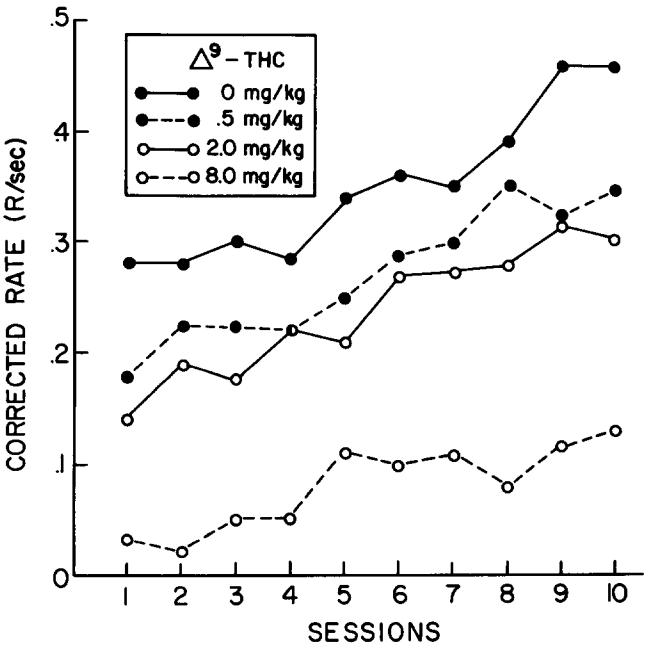

FIG. 1. Mean corrected response rates obtained during the 10 VI schedule acquisition sessions for the 4 Δ^9-THC dose groups.

Of particular interest in Fig. 1 is the fact that the response rates for the 8.0 mg/kg group remained below the minimum VI 30 sec rate of 0.125 responses/sec throughout most of acquisition while the response rates for the other 3 groups were consistently above the minimum value. This suggests that only the 8.0 mg/kg group should have obtained considerably less than the maximum number of VI reinforcements, which in this experiment was 58 reinforcements per 29-min session.

Figure 2 presents the mean number of VI reinforcements obtained each session by the 4 dose groups. The 0 mg/kg control group obtained close to or the maximum number of reinforcements each session while the number of reinforcements obtained by the 3 Δ^9-THC drug groups fell off in a dose-related manner. An analysis of variance on the number of reinforcement data yielded a significant main effect of drug dose, $F(3,24) = 11.75$, $p<0.01$, and a significant drug dose by session interaction, $F(27,234) = 2.21$, $p<0.01$. As can be inferred from Fig. 2, both of these significant effects may be largely attributed to the 8.0 mg/kg group which showed a large increase in the number of reinforcements across sessions and yet did not obtain more than two thirds of the reinforcements available in any one session. As was the case for response rate, multiple comparisons yielded significant ($p<0.01$) group differences in the number of reinforcements only between the 8.0 mg/kg group and the other 3 groups, among which no significant differences were obtained.

When terminal acquisition response rates differ between groups, it is difficult to make direct between-group comparisons of extinction performance which are independent of the different terminal acquisition response levels. Accordingly, in those situations where direct between-group comparisons of resistance to extinction are desired, it is often appropriate to use some method of transforming the extinction data so as to control for differences in acquisition response level. In the present experiment, the obtained extinction data were analyzed according to Anderson's [1] shape function method for comparing different populations in extinction.

The shape function method assumes that extinction is a unidimensional process and requires estimates of the asymptotic extinction and terminal acquisition response levels. For the present analysis, the asymptotic extinction response rate was assumed to be zero. Individual animal's response rates, obtained during the last three 5-min periods of the tenth VI schedule acquisition session, were used to estimate the level of terminal acquisition. It will be noted that when these latter acquisition data were subjected to an analysis of variance, neither a significant main effect of 5-min time period nor a time period by drug dose interaction was obtained.

The mean transformed extinction response rates are presented across successive 5-min periods of extinction for each Δ^9-THC dose group in Fig. 3. First of all, the expected significant decrease in response rate across the 30 min of

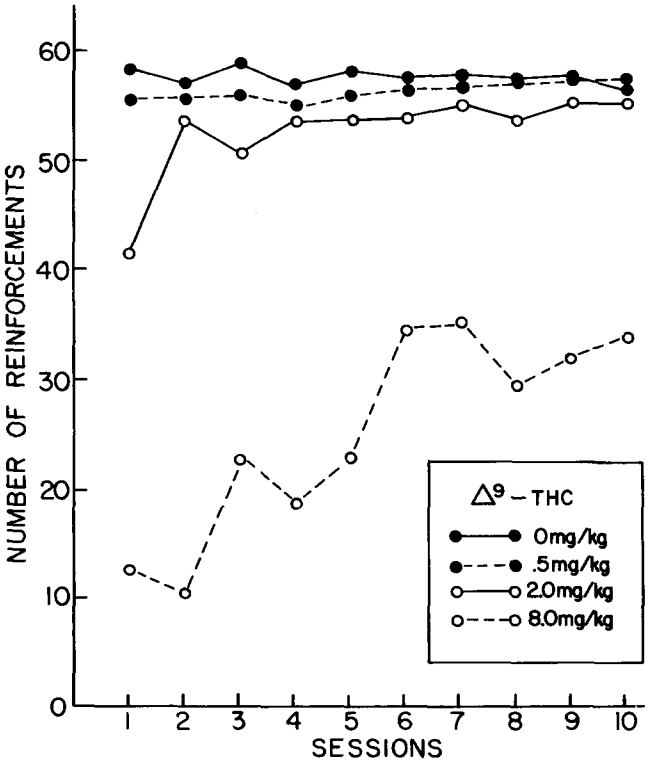

FIG. 2. Mean number of reinforcements obtained during the 10 VI schedule acquisition sessions for the 4 Δ^9-THC dose groups.

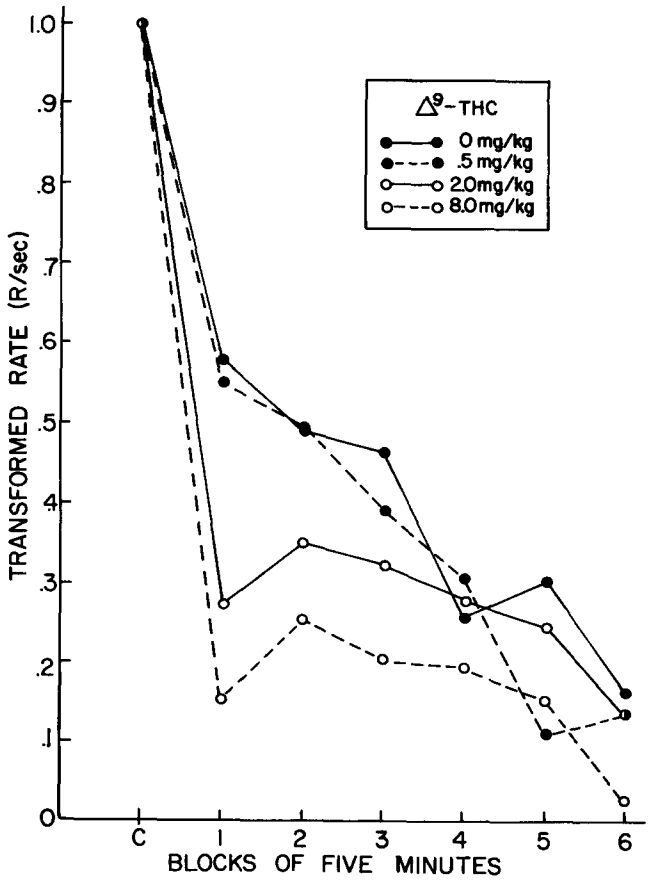

FIG. 3. Mean transformed response rates obtained during successive 5-min periods of the extinction session for the 4 Δ^9=THC dose groups. The data points plotted at *C* on the abscissa represent terminal acquisition response levels which become equalized between groups under the Anderson [1] shape function method used here.

extinction was obtained for the 4 groups, $F(5,120) = 22.50$, $p<0.01$. Furthermore, as was observed during acquisition, response rates during extinction were inversely related to drug dose in that the higher drug doses produced lower rates of response.

The analysis of variance on transformed response rates across 5-min extinction periods did not yield a significant main effect of drug dose. Nevertheless, a significant drug dose by extinction time-period interaction was obtained, $F(15,120) = 2.97$, $p<0.01$. Observation of Fig. 3 suggests that this interaction occurred because the higher Δ^9-THC dose groups responded more slowly than did the lower dose groups early in extinction while at the end of the 30-min extinction period, all groups responded at more comparable rates. This suggestion was confirmed by a series of multiple comparisons ($p<0.05$) which showed that: the 0.05 mg/kg group did not differ from the control group at any point in extinction; the 2.0 mg/kg group was significantly different from the control group during the first two 5-min extinction periods; the 8.0 mg/kg group was significantly different from the control group during the first three 5-min extinction periods; and no between-group differences existed during the last three 5-min extinction periods. More generally, the existence of a significant drug dose by extinction time interaction rejects the null hypothesis that resistance to extinction is unaffected by Δ^9-THC dose.

DISCUSSION

It is not clear from the existing literature whether appetitively reinforced learning in rats is enhanced, retarded, or unaffected by Δ^9-THC [5, 10, 16]. The data obtained in the present experiment suggest that the effects of Δ^9-THC on acquisition behavior are dose related. As the drug dose was increased from 0 to 8.0 mg/kg Δ^9-THC, the level of responding achieved during VI schedule acquisition was decreased and there was a concomitant decrease in the number of reinforcements obtained. Although response rate is only an indicant of acquisition performance under a VI schedule of reinforcement, the fact that fewer than the maximum number of reinforcements were obtained at the higher drug doses supports the contention that Δ^9-THC can retard the acquisition of behavior.

The present experimental situation differs from other operant reinforcement schedule investigations of Δ^9-THC effects in that the drug was administered throughout acquisition rather than only after the schedule-controlled behavior had been established. It may be that Δ^9-THC has differential effects between these two situations. For example, while the lower doses of Δ^9-THC used here decreased VI response rates during the acquisition process, in another comparable experiment these same drug doses acted to increase VI response rates when administered after the VI behavior had been thoroughly acquired [11].

There may also be a difference between administering the drug during or after acquisition with respect to the development of tolerance to Δ^9-THC. When Δ^9-THC is repeatedly administered following the acquistion of reinforcement schedule-controlled behavior, tolerance to the suppressive effects of Δ^9-THC on response rate typically develops rapidly [8,15]. In the present situation Δ^9-THC suppressed VI response rate, relative to the control group, from the first VI session. This drug-induced effect did not dissipate across the 10 sessions of schedule acquisition. While tolerance might well have been observed in our situation if acquisition had been prolonged, it is also conceivable that behavior acquired under a drug could become specific to that drug state and, thus, not exhibit tolerance even after long-term exposure [7].

Previous investigations of the effects of Δ^9-THC on the extinction of learned behavior may have been confounded by drug state-change effects in that the drug was not administered to the animals during the acquisition phase which preceded extinction [10,13]. This source of possible confounding was controlled for in the present experiment since the variable interval schedule behavior was acquired and extinguished in the same drug state. In this context, it was found that extinction responding decreased as the dose of Δ^9-THC was increased.

The obtained data are consistent with a previous report of Δ^9-THC effects on extinction of behavior learned under appetitive reinforcement [10] but conflict with the report that Δ^9-THC increased the resistance to extinction of a response learned under aversive contingencies [13]. It has elsewhere been hypothesized that Δ^9-THC may increase the aversiveness of situations associated with complete nonreinforcement as a function of drug dose [14]. The dose-dependent decrease in extinction responding obtained in this experiment would be expected if, as suggested by this hypothesis, the aversiveness of the behavioral transition from reinforcement to extinction was increased by the increasing doses of Δ^9-THC used. It has been shown that, in general, manipulations which increase the aversiveness of the extinction situation tend to prolong the course of extinction of behavior originally learned under aversive contingencies [17]. Consequently, it would also be expected from this hypothesis that Δ^9-THC should enhance resistance to extinction of aversively controlled behavior in a dose-related manner. Research related to this hypothesis is now being planned.

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