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# Factors Influencing Tolerance to the Effects of $\Delta^9$-THC on a Conditioned Avoidance Response[1]

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LARSEN, FEROL F. AND GORDON T. PRYOR. *Factors influencing tolerance to the effects of $\Delta^9$-THC on a conditioned avoidance response.* PHARMAC. BIOCHEM. BEHAV. 7(4) 323–329, 1977. – Male, Fischer strain rats were resistant to the impairing effects of $\Delta^9$-THC (15–60 mg/kg, IG) on performance of a conditioned pole-climb avoidance response (CAR) after daily subacute pretreatment for 4 or 6 days. A single administration of 20 mg/kg $\Delta^9$-THC independent of the performance test did not attenuate the subsequent impairment caused by $\Delta^9$-THC when tested 1–6 days later; however, administration 2 hr before each test attenuated the effect on subsequent tests given at intervals of 1–5 weeks. Similarly, subacute treatment with 20 mg/kg $\Delta^9$-THC for 4 days independent of the performance test attenuated the impairment caused by $\Delta^9$-THC during tests given to separate groups of rats 1 or 6, but not 14 days later. However, when the tests for tolerance were conducted repeatedly in the same rats, the attenuation appeared to persist for intervals up to 5 weeks. The results are discussed in terms of metabolic, functional and compensatory (behavioral) tolerance.

$\Delta^9$-THC  Pole-climb conditioned avoidance response  Tolerance to $\Delta^9$-THC
Compensatory (behavioral) tolerance  Pharmacological tolerance

A NUMBER of investigators have demonstrated that the magnitude of many of the effects of the cannabinoids [including the major psychoactive ingredient of marihuana, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)] is reduced or abolished after repeated exposure in most species (see [24,25] for recent reviews). However, an issue has been raised [4, 20, 21] as to whether this reduction in effect on behavioral measures represents so-called pharmacological tolerance in the classical sense [9] or a compensatory adaptation or relearning by the animal while under the influence of the substance. The issue seems to have its origins in the experimental protocol originally employed to demonstrate tolerance by which animals were repeatedly exposed to the cannabinoid(s) during performance of a learned response (e.g., [22]). Under these conditions the opportunity to develop adaptive mechanisms that would compensate for any adverse effects of the substance was maximal. To test the hypothesis that simultaneous exposure and performance were necessary to demonstrate the diminution of effect, Carder and Olson [4] administered marihuana extract (IP) to some rats before, and to other rats after, daily test sessions in which the operant task was reinforced with food or water. They concluded that exposure to the extract after the test session was not sufficient to induce tolerance.

More recently Manning [21] reported the use of an experimental design that first involved establishing stable spaced operant responding for food. The rats were then treated with vehicle or $\Delta^9$-THC for 12 consecutive days without behavioral testing. When treated and tested on the thirteenth day the effects of $\Delta^9$-THC were as great in the rats pretreated with the drug as they were in those that were drug naive. However, continued testing under the influence of the drug resulted in a rapid recovery to baseline performance. This led Manning also to conclude that, although pharmacological tolerance could not be ruled out, "performance in the drug state is a far more rapid means of developing tolerance to the effect of THC on spaced responding than is mere exposure to THC [p. 272]."

On the other hand, Johansson *et al.* [10] trained rats in a two-way shuttlebox with IP injections of vehicle or 15 mg/kg $\Delta^8$-THC given 2 hr after each of eight sessions. When both groups were treated with $\Delta^8$-THC 30 min before the ninth session, performance by the group that had been exposed to $\Delta^8$-THC was not significantly different from that on the previous day, indicating tolerance, whereas performance by the group that received $\Delta^8$-THC for the first time was markedly impaired. Similar results were reported for $\Delta^9$-THC by Webster *et al.* [35] using a continuous avoidance task.

Since 1972 we have been engaged in an extensive preclinical evaluation of the acute and subacute interactions between $\Delta^9$-THC and a number of drugs in rats [31].

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[2] Requests for reprints should be addressed to GTP.

From the outset, our experimental design has been similar to Manning's [21] in that daily subacute treatment (6–13 days) was always given independently of any behavioral testing [27, 28, 30, 31]. Under these conditions we have demonstrated a clear reduction in the effects of $\Delta^9$–THC on a pole-climb conditioned avoidance response (CAR), rotarod performance, photocell activity, heart rate, body temperature, and open-field behavior as compared with acute administration. Thus, our experience in this regard is unlike that of Carder and Olson [4] and Manning [21], but similar to that of Johansson *et al.* [10] and Webster *et al.* [35].

Some of the differences in results obtained by various investigators may be due to differences in dose, route of administration, or, especially, the behavioral task and the consequences of poor performance on such tasks to the subject (see [8] for a discussion of such a behavioral model of marihuana tolerance). However, an attempt to fit all of the diverse results from different experimental paradigms into a single either-or-concept may have created an unnecessary polarization of the issue. If a diminished drug effect is observed following repeated exposure, one or more of the following mechanisms could be responsible: (1) changes in the disposition of the drug making less drug available at the target receptors (metabolic tolerance); (2) changes in the characteristics of the target receptors such that more drug is required to cause an equivalent response (functional or cellular tolerance); and/or (3) adaptive changes in other systems that compensate for the drug effects even though the same amount of drug has the same effect on the target receptors that were responsible for the initially observed response (compensatory, homeostatic (see [9]), or behavioral tolerance).

There is no compelling evidence that metabolic tolerance plays an important role in the diminished effects of exposure to the cannabinoids (e.g., [2, 7, 12, 23, 33], but see [15,19]). However, if the criterion of tolerance after mere exposure is accepted as evidence for functional tolerance, the studies cited above clearly indicate that both functional and compensatory tolerance may operate to varying degrees depending on the circumstances and the influence of as yet only poorly understood variables. The issue then becomes the extent to which each mechanism plays in the diminished effects of cannabis observed for a particular response.

The experiments reported here were designed to examine some of the factors that may influence the reduction in effect of $\Delta^9$–THC on CAR performance following subacute treatment. We will show that tolerance can be demonstrated easily by repeated exposure to the drug in the absence of behavioral testing but that its rate of development and its persistence are clearly enhanced by simultaneous exposure to the drug and the testing situation. The issue of whether or not this or similar paradigms clearly distinguish between functional tolerance and compensatory tolerance is then discussed.

## GENERAL METHOD

### *Animals*

Male albino rats of the inbred Fischer strain were used throughout. The animals were 55–60 days old and weighed between 140 and 160 g when they were received from Simonsen Laboratories, Inc. of Gilroy, CA. The rats were housed individually in wire mesh hanging cages and were allowed free access to food and water throughout the experiment. They were maintained on a 12 hr light/dark cycle with the room temperature at 22°C ± 1°C.

### *Apparatus*

Each of 12 escape-avoidance chambers consisted of a 30 × 36 × 40 cm wooden box housed inside a sound-attenuated, ventilated enclosure. Scrambled, constant-current shock (1 mA) applied to the grid floor served as the unconditioned stimulus (UCS). The learned response was a downward displacement of a 1.27 cm diameter aluminum pole suspended from the center of the ceiling. A 7.5 W light and a loudspeaker in the ceiling of the chamber provided ambient light and an ambient 4 kH tone. The 12 chambers were interfaced with a Digital Equipment Corporation PDP 8/F computer (located in an adjoining room) that provided automatic control of stimuli and data collection. The data were recorded on both a teletype and on punched paper tape for subsequent processing.

### *Procedure*

The rats were trained and tested for CAR performance in groups of 12. Each rat was pretrained in a single 30-trial session to escape a 1.0 mA footshock (UCS) by pulling or climbing a 20 cm pole. This response closed a microswitch and terminated the stimulus. The rats were then given three, daily sessions (one 30-trial followed by two 60-trial sessions) to learn to avoid the footshock by pulling or climbing a 13 cm pole in the presence of each conditioned stimulus (CS). The CS was an increase in the intensity of either the ambient light or the ambient tone or a low intensity, nonaversive current (120 $\mu$A) applied to the grid floor. Each CS was presented as a pulsating stimulus at the rate of 2.5 times per sec. The CS preceded the UCS by 10 sec; both then remained on for 30 sec unless terminated earlier by the animal's response.

The three stimuli were presented randomly for 20 trials each, with the total 60-trial session requiring approximately 2 hr. The interval between trials was random and averaged 1.5 min (15 sec to 3 min). At the end of this training procedure the average performance was greater than 80% CAR.

### *Drugs*

$\Delta^9$–THC was prepared under contract with the NIDA by the Research Triangle Institute as a 1% (w/v) solution in sesame oil. When necessary this stock solution was diluted with laboratory grade sesame oil (Fisher Scientific) that also served as the placebo control. All treatments were administered by the intragastric route (IG) using a 5-cm, 18-gauge curved feeding needle (Popper and Sons, Inc.).

### *Data Analysis*

Each performance measure was first analyzed by a one-way or two-way analysis of variance depending on the particular experimental design [16]. Significant effects were evaluated by *t*-tests between selected pairs of means using the pooled degrees of freedom and error variance from the analysis of variance. Since the results were essentially the same for all three CS in the experiments reported here, the data were combined as total CAR.

EXPERIMENT 1

We have previously shown that the impairing effect of 10 mg/kg Δ⁹-THC on CAR performance diminished after exposure to the drug alone for six days [27, 28, 30, 31]. This experiment was designed to investigate the relationship between the dose of Δ⁹-THC administered subacutely and the development of this type of tolerance as well as its persistence after termination of subacute treatment.

*Method*

After CAR training, separate groups were given 6 ml/kg sesame oil (N = 35), or 15, 30, or 60 mg/kg Δ⁹-THC (N = 5–7 per group) in 6 ml/kg sesame oil daily for six days. On the seventh day subgroups (N = 6–8 per subgroup) of those treated subacutely with sesame oil were given either sesame oil or 7.5, 15, or 30 mg/kg Δ⁹-THC in sesame oil. The animals treated subacutely with Δ⁹-THC were given the same dose of Δ⁹-THC on the test day as they had received subacutely. All animals were given a 60-trial test 2 hr after their respective treatments. A higher range of doses of Δ⁹-THC was given subacutely than acutely in anticipation of a shift to the right of the dose response function after subacute treatment [26]. All animals were retested using the same dose and time schedule on Days 14, 28 and 62. The animals remained in their home cages and were not treated or handled between tests except for routine maintenance.

*Results and Discussion*

After treatment with sesame oil for six days, Δ⁹-THC caused a dose-related impairment of CAR performance when administered on Day 7 (Fig. 1, Panel a). The differences from controls treated subacutely with sesame oil and given sesame oil on Day 7 were significant for doses of 15 and 30 mg/kg Δ⁹-THC ($ts(46) \geq 2.9$, $ps \leq 0.01$). The CAR performance of groups treated subacutely with Δ⁹-THC and given Δ⁹-THC on Day 7 did not differ significantly from sesame oil treated controls (all $ts(46) \leq 0.8$). Therefore, tolerance was essentially complete to this effect of Δ⁹-THC for all doses tested.

Panels *b*, *c* and *d* in Fig. 1 show the results of retesting the animals on Days 14, 28 and 62 in an attempt to monitor the loss of tolerance expected to occur after termination of the subacute treatment. As shown in Panel *b* there was no apparent or significant loss of tolerance after 1 week in the rats that had been treated subacutely on Days 1–6 with Δ⁹-THC as determined by comparison with sesame oil treated controls (all $ts(46) \leq 1.0$). Of considerably more interest, however, was the fact that the groups initially treated subacutely with sesame oil and then treated with Δ⁹-THC and tested once on Day 7 were apparently resistant to the effects of the second dose given on Day 14. None of the differences from controls treated with sesame oil throughout was significant in these groups during the second test (all $ts(46) \leq 1.2$).

Panel *c* shows the results after an additional two weeks

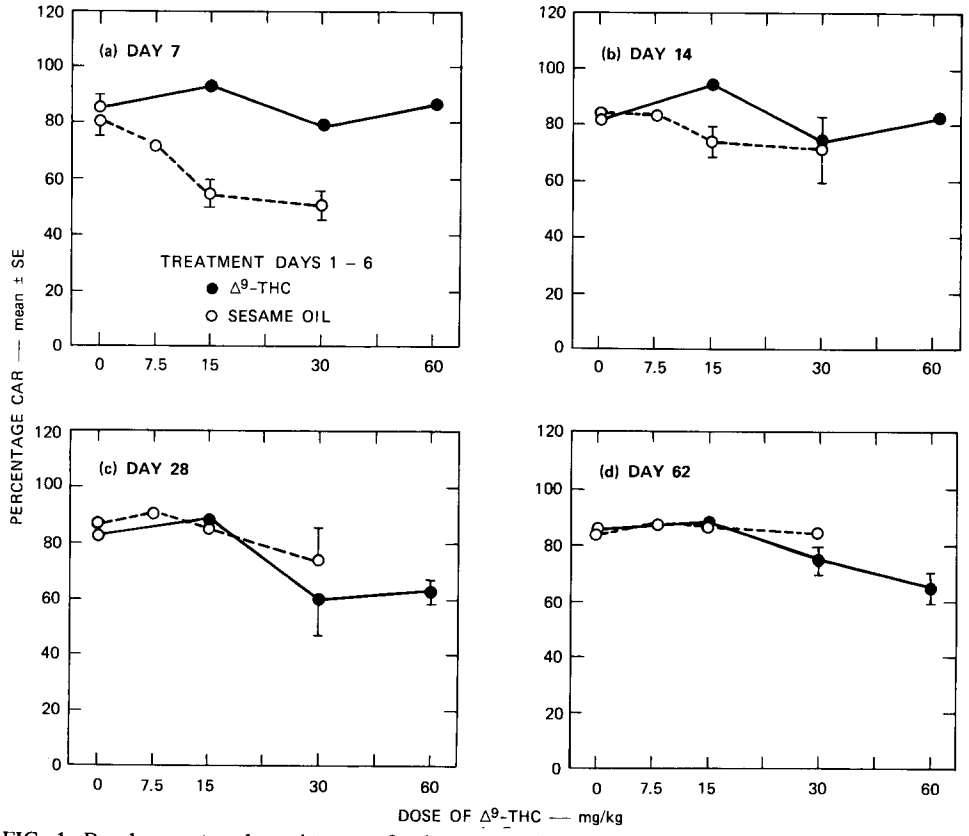


FIG. 1. Development and persistence of tolerance to the effects of Δ⁹-THC on performance of a conditioned avoidance response as a function of dose. After subacute treatment with sesame oil (acute) or Δ⁹-THC (subacute), for six days, the rats were tested for tolerance on Days 7 (Panel *a*), 14 (Panel *b*), 28 (Panel *c*), and 62 (Panel *d*). For those points on the graph where no limits are shown the SE was less than the radius of the point.

of no drug treatment. The groups originally treated subacutely with 30 or 60 mg/kg $\Delta^9$-THC on Days 1–6 appeared to show some loss of tolerance on Day 28 as indicated by comparisons with sesame oil-treated controls ($ts(46)$ = 2.2, 1.8; $ps \leq 0.05$, 0.1, respectively). However, there was still no significant effect of any of the doses of $\Delta^9$-THC on the groups treated originally with sesame oil on Days 1–6 compared with sesame oil-treated controls.

The final test was given five weeks later (Panel *d*). Only the group originally treated subacutely with 60 mg/kg $\Delta^9$-THC differed significantly from controls treated with sesame oil throughout ($t(46) = 2.8$, $p \leq 0.01$).

These results showed that a significant reduction in the impairing effect of $\Delta^9$-THC on a previously learned CAR occurred after independent repeated administration of the drug. Moreover, the apparent tolerance was complete on this measure after six days of treatment and it appeared to be independent of dosage over the range of doses tested. The tolerance after subacute treatment with $\Delta^9$-THC appeared to dissipate very slowly when the animals were repeatedly treated and tested to monitor its loss. Of more interest was the finding that a single administration of $\Delta^9$-THC before each test given at increasingly long intervals of up to five weeks appeared sufficient to attenuate completely the impairment initially caused by $\Delta^9$-THC on all succeeding tests.

## EXPERIMENT 2

The results of Experiment 1 clearly demonstrated a marked loss of effect of $\Delta^9$-THC on CAR performance after repeated independent administration of the drug. However, in this and other experiments in our laboratory [27–30] the animals were always tested within 2 hr after drug administration. Therefore, it was possible that subacute treatment caused a temporal shift in the effects of $\Delta^9$-THC that might represent metabolic tolerance. Indeed, we have found that fasting retards both the absorption and effects of $\Delta^9$-THC on CAR performance when given IG in sesame oil [29]. Since $\Delta^9$-THC influences food and water intake and weight gain (see [1]), and gastric motility [3], any or all of these effects could conceivably contribute to, or account for, the apparent tolerance seen in Experiment 1. Therefore, the present experiment was done to compare the time course of the effects of $\Delta^9$-THC in rats pretreated subacutely with sesame oil or $\Delta^9$-THC.

### *Method*

The rats were pretrained using the same protocol as in Experiment 1. After pretraining, they were given four daily treatments with either sesame oil (N = 38) or 20 mg/kg $\Delta^9$-THC (N = 22). On the fifth day, separate subgroups (N = 7–8 per subgroup) were given a 30-trial test 2, 4 or 8 hr after treatment with sesame oil or 20 mg/kg $\Delta^9$-THC. Separate sesame oil-treated control rats were tested at each time to be sure that performance did not change over the course of the day. Because there were no appreciable differences attributable to when the controls were tested their data were combined.

### *Results and and Discussion*

Figure 2 shows that the CAR performance of those groups treated for the first time with 20 mg/kg $\Delta^9$-THC was maximally impaired when they were tested begining 2

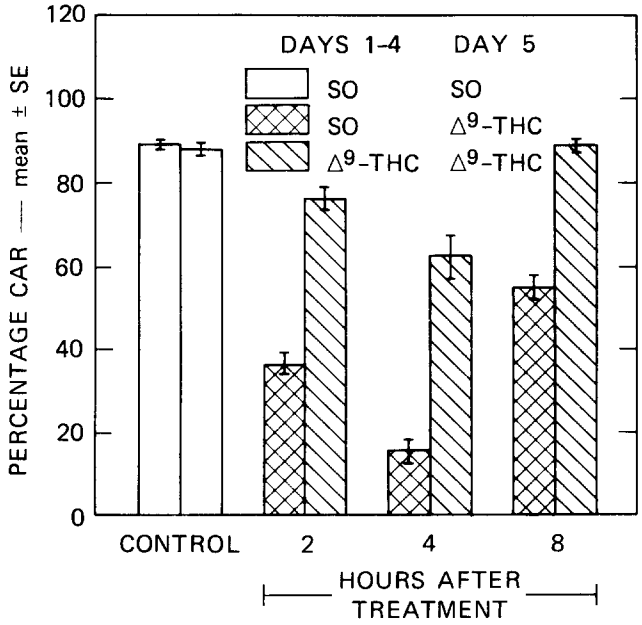


FIG. 2. Effect of 20 mg/kg $\Delta^9$-THC (IG) on performance of a conditioned avoidance response as a function of time after treatment in rats pretreated with sesame oil or 20 mg/kg $\Delta^9$-THC for four days. Subgroups of control rats were tested at each time, but because there were no appreciable differences among the groups the data were combined.

or 4 hr later ($ts(52)$ = 6.7 and 8.6 compared with sesame oil-treated controls, respectively; $ps \leq 0.01$). By 8 hr significant recovery from the acute effects of $\Delta^9$-THC was apparent ($ts(52)$ = 2.9 and 4.9 compared with 2 and 4 hr, respectively; $ps \leq 0.01$). Performance by the groups treated subacutely with $\Delta^9$-THC showed a similar time course of impairment. However, the impairment of each of these groups was significantly less than in each of the corresponding groups treated with $\Delta^9$-THC for the first time (all $ts(52) \geq 4.0$, all $ps \leq 0.01$).

The impairment caused by 20 mg/kg $\Delta^9$-THC in this experiment appeared to be greater than that in Experiment 1. However, this difference can be explained by the fact that the test session consisted of 30 trials in this experiment compared with 60 trials in Experiment 1. Further analysis of the data from Experiment 1 showed that significant improvement in performance occurred between the first and last 30-trial blocks and, thus, the average impairing effect over the entire session was less than during the first 30 trials. The improvement in performance within the 60-trial test session could be attributed to partial recovery from the effects of $\Delta^9$-THC over time or to the development of acute compensatory tolerance that occurred within the test session. The results of the present experiment provide evidence for the latter interpretation because the impairment after 4 hr was as great or greater than after 2 hr. Manning [20] reported evidence for a similar acute compensatory tolerance to $\Delta^9$-THC.

The results of the present experiment clearly showed that the reduction in effect of $\Delta^9$-THC on CAR performance after subacute treatment in Experiment 1 was not caused by a shift in the time of peak effect. Therefore, an explanation of the apparent tolerance in terms of differences in the rates of absorption of $\Delta^9$-THC caused by subacute treatment was not supported.

## EXPERIMENT 3

The results of Experiment 1 suggested that the impairment of CAR performance caused by Δ⁹-THC could be completely eliminated by a single administration of the drug before the behavioral test given one week earlier. Davis and Borgen [5] reported that the loss of effect of Δ⁹-THC on an operant task was inversely related to the frequency of exposure to the drug and the test when given at 1-, 3-, 7- or 14-day intervals. However, even with daily administrations they found only partial tolerance on this task.

Therefore, one of the questions raised by the results of Experiment 1 was whether the loss of effect of Δ⁹-THC could be accounted for by rapid and persisting pharmacological tolerance, or whether this effect could represent compensatory tolerance that required performance of the response under the influence of the drug. To answer this question, the present experiment was done in which a single treatment with Δ⁹-THC was given prior to and independent of the test for tolerance. Moreover, in the event that tolerance after a single independent treatment did occur, the spacing between the drug treatment and the test was varied to see what the temporal limits were.

### *Method*

Following CAR training, separate groups of animals (N = 10 per group) were given a single administration of 20 mg/kg Δ⁹-THC in 2 ml/kg sesame oil. The first group was treated immediately after the last training session and the other groups were treated 1, 4 or 6 days later. On the seventh day all rats were given a 30-trial test 2 hr after receiving 20 mg/kg Δ⁹-THC. Separate groups (N = 9–10 per group) were treated with sesame oil on the same schedule prior to testing and on the seventh day they were treated with either sesame oil (N = 19) or 20 mg/kg Δ⁹-THC (N = 9). Because there were no differences attributable to when they received sesame oil earlier, the data were combined within each of these two groups.

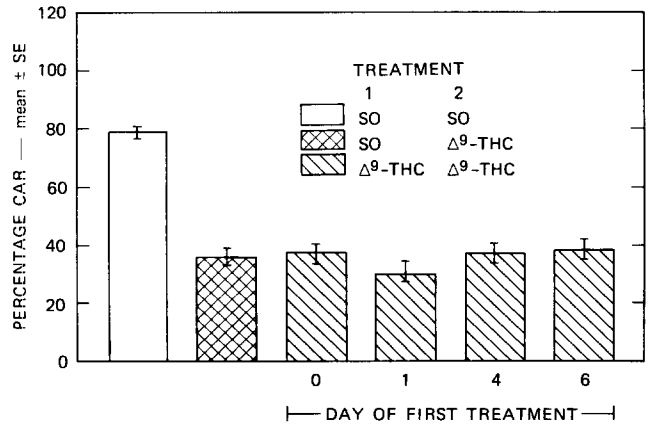


FIG. 3. Effect of a single exposure to 20 mg/kg Δ⁹-THC (IG) independent of performance of a conditioned avoidance response on the subsequent effect of 20 mg/kg Δ⁹-THC on that response. Rats were treated with sesame oil or 20 mg/kg Δ⁹-THC 0, 1, 4 or 6 days after pretraining and tested on the next day. Data from the groups treated first with sesame oil were combined because there were no significant effects of this treatment.

### *Results and Discussion*

Figure 3 shows that the CAR performance of all groups that were treated with 20 mg/kg Δ⁹-THC 2 hr before the test on Day 7 was significantly impaired relative to sesame oil-treated controls regardless of whether they were pretreated once earlier with sesame oil or Δ⁹-THC (all $ts(53) \geq 4.6$, all $ps \leq 0.01$). Moreover, there were no significant differences among any of the groups treated with Δ⁹-THC.

These results clearly show that a single treatment with Δ⁹-THC independent of the test was insufficient to attenuate the subsequent impairment of CAR performance caused by Δ⁹-THC. Therefore, the results seen in Experiment 1 may represent compensatory tolerance such that the animals relearned to perform the CAR during the course of a single session under the influence of the drug. The number of independent exposures to Δ⁹-THC necessary to induce measurable pharmacological tolerance to the effects of Δ⁹-THC on CAR performance was not determined in this experiment but it must lie between one (this experiment) and four (Experiment 2). Therefore, it appears that tolerance can develop much more rapidly when there is the opportunity to perform the response being measured under the influence of Δ⁹-THC.

## EXPERIMENT 4

The results of Experiment 1 also suggested that apparent tolerance to the effect of Δ⁹-THC on CAR performance could persist for many weeks when each repeated test for tolerance included exposure to the drug. In view of the results of Experiment 3 it was possible that this long persistence of tolerance was also a reflection of compensatory tolerance learned under the influence of the drug at successive test sessions. In order to determine how long the attenuation of the effects of independent subacute treatment with Δ⁹-THC lasted we tested separate groups of rats only once at selected intervals after the last of four daily treatments.

### *Method*

Following training, rats were treated with sesame oil (N = 38) or 20 mg/kg Δ⁹-THC (N = 21) for four days. Then, separate subgroups (N = 7 per subgroup) were tested only once on either Day 5, 10 or 18. For each test, rats that had been treated subacutely with sesame oil were treated with sesame oil (N = 18) or 20 mg/kg Δ⁹-THC (N = 20) to provide controls for the time of testing after training and for the acute effects of Δ⁹-THC at these times. Because there were no significant differences in performance in this regard, the data were combined within each of these two groups. The animals that were treated subacutely with Δ⁹-THC were given 20 mg/kg Δ⁹-THC before the test. All animals were given a 30-trial test 2 hr after administration of sesame oil or Δ⁹-THC.

### *Results and Discussion*

As expected and shown in Fig. 4, acute administration of 20 mg/kg Δ⁹-THC significantly impaired CAR performance compared with sesame oil-treated controls ($t(54) = 7.1$, $p \leq 0.01$). Also, as expected, this impairment was significantly attenuated by independent subacute exposure to Δ⁹-THC when the rats were treated and tested one day after the last treatment ($t(54) = 4.3$, $p \leq 0.01$ compared with

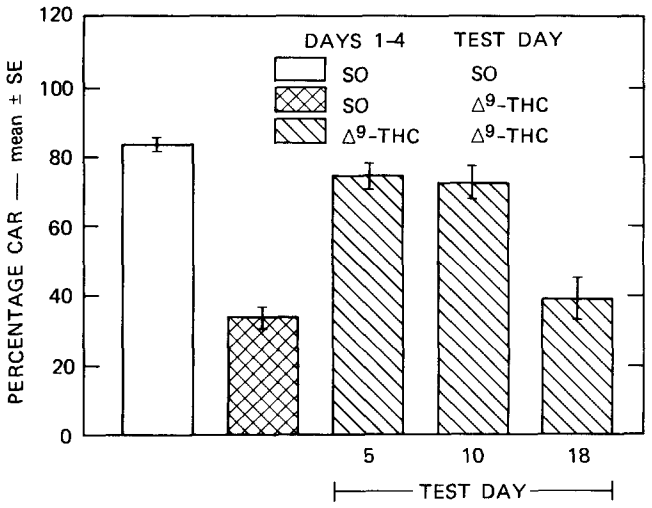


FIG. 4. Effects of subacute treatment with 20 mg/kg $\Delta^9$-THC (IG) for four days on the subsequent effect of 20 mg/kg $\Delta^9$-THC on performance of a conditioned avoidance response as a function of time after the last subacute treatment. Data for the subgroups treated subacutely with sesame oil at each time were combined because there were no differences among these subgroups.

acute administration on Day 5). The attenuation of effect caused by subacute treatment with $\Delta^9$-THC was also significant for the groups treated and tested on Day 10 compared with acute administration ($t(54) = 4.0$, $p \leq 0.01$). However, by Day 18 the effect of $\Delta^9$-THC was similar in magnitude to that caused by the acute administration of $\Delta^9$-THC to drug-naive rats ($t(54) = 4.6$, $p \leq 0.01$ compared with sesame oil-treated controls).

## GENERAL DISCUSSION

These results are relevant to some of the questions that have been raised about the development of tolerance to the effects of $\Delta^9$-THC on learned behavior [4,21]. We repeatedly observed attenuation of the impairing effects of $\Delta^9$-THC on the avoidance task used in these experiments when the drug was given independently of the opportunity to perform the response. Therefore, our results clearly showed that independent exposure to $\Delta^9$-THC was sufficient to induce tolerance to its effects on this task. Our results differ from those of Manning [21] who found that independent exposure was insufficient to induce tolerance to the effects of $\Delta^9$-THC on an operant schedule that required a low rate of spaced responding (DRL, 30-sec). The effect of $\Delta^9$-THC on his behavioral task was to increase response rates, whereas the effect on our task was to decrease responses. Also, the consequences of a response error to the subject imposed by our task (painful footshock) were different than those in the DRL task (reduction of food reinforcement) and could, as discussed by Ferraro [8] and others [32,34], be an important determinant of whether or not tolerance is observed. Indeed, the fact that Carder and Olsen [4] and Manning [21] used appetitive tasks and were unable to demonstrate tolerance with mere exposure, whereas we, along with Johansson *et al.* [10] and Webster *et al.* [35], used aversively motivated tasks and demonstrated such tolerance, is clear evidence in support of this notion.

Of equal importance in the experiments reported here was the result that when allowed to respond under the influence of $\Delta^9$-THC the tolerance that developed was much more rapid in onset and lasted longer than that caused by independent exposure to the drug. This result is clearly similar to that which Kalant and his coworkers [11, 13, 14] described as behaviorally augmented tolerance for alcohol and other drugs. In the introduction we suggested that theoretically there can be three qualitatively different types of tolerance that involve different mechanisms: (1) metabolic; (2) functional or cellular; and (3) compensatory (homeostatic) or behavioral. Kalant and coworkers concluded that behaviorally augmented tolerance could not be distinguished from functional or cellular tolerance by their experiments with alcohol. Our results with $\Delta^9$-THC are such that we are left in the same position. Nevertheless, as also recognized by Le Blanc *et al.* [14] for alcohol, the operation of two different mechanisms cannot be totally discounted. Indeed, our results do not unequivocally exclude the possibility that compensatory mechanisms (as distinguished from a reduction in response to the drug at the target receptors) were not also operating, even when the $\Delta^9$-THC was administered independent of the test.

The argument that because there was no opportunity to perform the specific learned response (i.e., the CAR) while under the influence of the drug, the attenuation of effect must have been due entirely to functional tolerance, can be questioned. If one of the effects of $\Delta^9$-THC is to impair sensory-motor performance in general and this effect was responsible for the impairment of CAR performance, then it is possible that the animals could have acquired compensatory adaptive responses outside of the actual test environment, viz., in their home cages. Admittedly, the need for acquiring such compensatory adaptive mechanisms was probably less in their home cages than in the CAR test environment, but it would be present to some degree in order to eat and drink. This could explain the relatively slow development of tolerance after simply exposing the animals to the drug. Indeed, several investigators (see [1]) have reported that $\Delta^9$-THC initially causes a decrease in food and water intake and a consequent loss of body weight that recovers after repeated drug administration. Although the recovery has usually been attributed to the development of tolerance to the effect of $\Delta^9$-THC on motivation, it could also be interpreted as a partial adaptation to any depressant sensory-motor effects that interfered with the animal's normal feeding behavior. Viewed in this way, the magnitude and/or rate of tolerance development to the effects of $\Delta^9$-THC on a behavioral task would be a function of the motivation involved, the consequences of an error to the subject, and the similarity of the measured response to the responses permitted while under the repeated influence of the drug (transfer of training).

If our behavioral experiments have not conclusively distinguished between tolerance that occurs as a change in response to the drug at the cellular level as opposed to an adaptive mechanism that occurs in other systems to compensate for the drug effect, then one might argue that experiments demonstrating attenuation of the effects of $\Delta^9$-THC on physiological measures such as heart rate and body temperature would be more compelling (e.g., [17,18]). However, since such physiological functions operate in a homeostatic manner and respond to demands within the limits possible, compensatory adaptation could be involved for them as well.

We suggest that the only way to empirically distinguish functional tolerance from compensatory tolerance is to identify and prevent the specific response that is affected from occurring during exposure to the drug. This requires knowing precisely which systems are affected and how they are related to the response being measured, a difficult task indeed, and one that has not been successfully accomplished thus far. Because of this, we suggest that subsequent research may be more fruitfully directed toward establishing and characterizing the various factors that influence the development of tolerance to the effects of marihuana rather than attempting to provide the crucial experiment to distinguish between functional and compensatory tolerance.

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