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Behavioral Tolerance to Marihuana as a Function of Amount of Prior Training[1]

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OLSON, J. AND B. CARDER. *Behavioral tolerance to marihuana as a function of amount of prior training.* PHARMAC. BIOCHEM. BEHAV. 2(2) 243–247, 1974. – Rats were trained to run an alley for food reinforcement. Rats dosed with marihuana distillate before each session from the beginning of training showed a very slow improvement of performance during training. Rats that first received marijuana after reaching asymptotic performance showed a disruption of performance under the drug. These rats, however, rapidly developed a tolerance to the drug. It was concluded that increased prior training increases the rate of behavioral tolerance development.

Behavioral tolerance Marihuana Learned tolerance

OVER the past few years there have been numerous demonstrations of a profound behavioral tolerance to marihuana and its active principles [2, 5, 10, 11]. Most recently, reports have indicated that learning plays an important role in the development of this behavioral tolerance [3]. Rats which were repeatedly tested under the influence of marihuana in a lever press situation rapidly developed a tolerance to the effects of the drug on lever performance. Rats that were tested each day in the lever press situation and then given the drug outside the lever press situation failed to show tolerance on a subsequent test, even though they had received an equal amount of training on the lever press task and an equal number of experiences with the drug. Apparently the opportunity to respond under the influence of the drug was crucial to the development of tolerance to the drug.

It should be pointed out that the role of learning in the development of behavioral tolerance is by no means restricted to marihuana. Kalant [8] has described a number of studies indicating the role of learning in the development of tolerance to alcohol and barbiturates. Other studies suggest the importance of learning in the development of tolerance to amphetamines [4] and opiates [1,6].

The view that behavioral tolerance involves a learned compensation for the behavioral effect of a drug suggests several new ways of looking at tolerance. Tolerance becomes a process of behavioral adaptation which is similar to any process in which an organism is required to adapt a previously learned response to an altered set of conditions. Thus, the principles of behavioral psychology that have been developed for situations like adaptation to stimulus change should apply to the process of tolerance.

The present experiment is an attempt to support the view that behavioral tolerance is a form of learned compensation by examining the effects of the amount of prior training on the rate of tolerance development. It is well established that if a distracting stimulus is presented to an organism that is performing a learned response, that the magnitude and the persistence of the resulting disruption of behavior will decrease as the proficiency of the animal on the task increases [13]. A very well trained animal is quite difficult to disrupt, and rapidly achieves good performance, while the poorly trained animal is easily disrupted and achieves good performance much more slowly. In the present study, we observed the development of behavioral tolerance in animals with varying degrees of prior training. The prediction was that behavioral tolerance should develop most rapidly in those animals with the greatest amount of prior training.

METHOD

Animals

Thirty male Sprague-Dawley rats, 90–120 days old at the beginning of the experiment were used. They were maintained in individual cages with continuous access to water. For several days prior to, and throughout, the experiment they were deprived of food on a 24 hr schedule. They were fed sufficient food, after each experimental session, to maintain them at about 80% of their free-feeding weight.

Drugs

Marihuana was obtained from NIMH in the form of

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marihuana distillate, with a Δ-9-THC content of 171 mg/g. This was diluted in propylene glycol to yield a solution of 6 mg THC/ml. Doses are specified in terms of mg of THC/kg of bodyweight. Drugs were administered via a polyethylene feeding tube inserted through the mouth to the stomach. The drug was injected into the cannula and washed down with 1 ml of water. The oral route was used because chronic intraperitoneal administration of THC has been shown to produce considerable peritoneal irritation [9].

Apparatus

The apparatus was an elevated zig-zag runway 129.5 cm long and 7.6 cm wide with a start box 27.9 cm long and 10.2 cm wide and a goal box 30.5 cm long and 10.2 cm wide. The apparatus rested on wooden pillars which raised the floor level to 35.6 cm above ground. The floor was covered with medium gauge sandpaper. The start and goal boxes each had walls 10.2 cm high and were covered with clear plastic lids; there were no walls lining the runway. Two guillotine doors, one painted flat black and the other clear plastic, separated the start box from the runway. One flat black guillotine door separated the runway from the goal box. The runway consisted of a straight starting section, 6 alternating left–right turns, each with an outside radius of 15.2 cm, and a straight finishing section. All interiors and the floor were painted flat white. A round food cup 3.8 cm in dia. and 1.3 cm deep was fastened to the end wall of the goal box and rested on the floor. Emergence from the start box was measured by a photocell placed 7.6 cm beyond the start box door, across the runway. Entry into the goal box was recorded by a photocell in the goal box, 15.2 cm beyond the entrance from the runway.

Procedure

Pretraining lasted for 4 sessions, one every second day. One hr before each session, animals were given 0.25 cc of propylene glycol orally. On the first two pretraining days, each animal received two 10 min placements in the goal box and was allowed to eat Noyes pellets from the food cup. Animals that failed to eat in these sessions were returned to the goal box and left there until they ate.

On the last two pretraining days the animals were allowed to explore the start box for five min. They were then placed in the goal box until they ate 5 food pellets or until 5 min had elapsed.

Training continued on an every second day schedule, for a total of 23 sessions. The first session had 2 trials, the second session, 3 trials, and all of the other sessions had 4 trials. On each trial the goal box was baited with 4 food pellets.

Animals were randomly divided into 2 groups on Day 1. The 10 animals in Group M_1 received 6.0 mg/kg THC, 1 hr before the training session, beginning on the first day of training and throughout the experiment. The 20 animals in Group P received a control volume of propylene glycol 1 hr before the session.

On Day 5, animals in Group P were divided into two groups of 10 animals each, M_5 and P. Animals were matched on the mean total time to travel the runway on Day 4. Animals in Group M_5 received 6.0 mg/kg THC before the session, continued throughout the remaining session. Animals in Group P continued as before, with

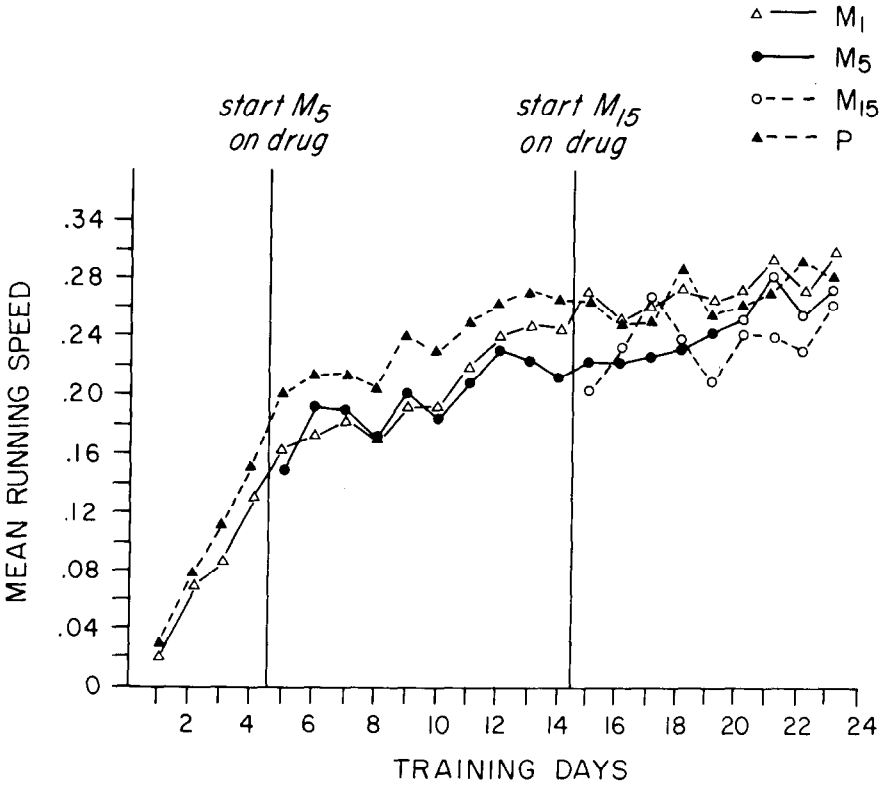

FIG. 1. Group mean running speeds for 23 days of training.

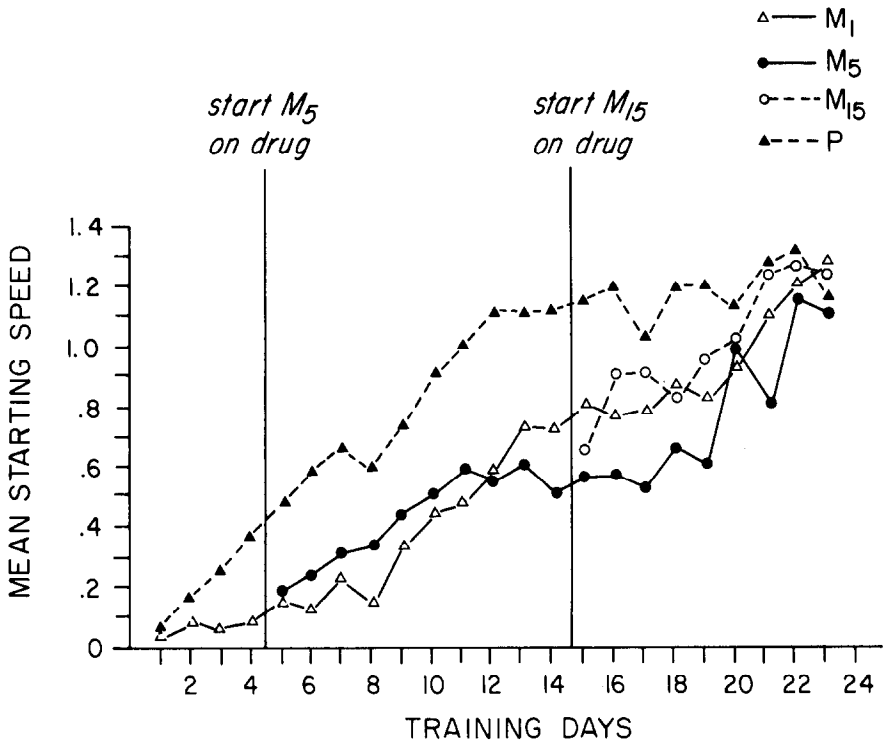

FIG. 2. Group mean starting speeds for 23 days of training.

propylene glycol.

On Day 15, the animals remaining in Group P were divided into 2 groups of five animals each, matched on the mean time to travel the runway on Day 14. Animals in Group M_{15} received 6.0 mg/kg THC now before each session. Animals in Group P continued with propylene glycol.

On each trial 3 times were recorded: Emergence time, the time from the opening of the start box to the emergence of the rat; starting time, the time from emergence to the traversing of the first 18 inches of the runway; and Running time, the time to traverse the rest of the runway to the goal box. The time scores were converted into reciprocals (speed scores) for analysis.

RESULTS

Group means were calculated for the speed scores on each of the three measures. Fig. 1 presents the mean running speed for the several groups over the 23 days of the experiment. It is clear that at the 6 mg/kg dose, marihuana produced a very small decrease in running performance. This decrease did not even reach statistical reliability, so that the question of tolerance to this effect does not arise. The running measure was apparently not very sensitive to the drug effect.

Figure 2 presents the mean starting speed for the several groups. Marihuana depressed starting speed more than running speed. The control group (P) reached asymptotic performance in about 11 days. Groups M_1 and M_5 improved very slowly and reached the level of the control group on Days 21 and 22 respectively. Group M_{15} showed a large depression of performance on the first administration of the drug but improved rapidly, reaching the level of the control group on Day 21.

Figure 3 presents the mean emergence speed for the several groups over the course of the experiment. This measure presents a picture similar to starting speed. Control animals showed a gradual increase in speed over the first 12 days, approaching an asymptote at that point. Group M_1, dosed with marihuana from the first trial, showed a much slower increase, reaching asymptote at about Day 23. Group M_5, dosed with marihuana from Day 5, also showed a low rate of increase, reaching asymptote at Day 22. Group M_{15}, dosed from the 15th day, rapidly increased to the level of the control group by Day 21. Thus, the figure reveals the pattern predicted: rats with more training develop behavioral tolerance more rapidly.

A separate one-way analysis of variance was carried out on the data for each day of testing for Days 5 through 23. On days that the analysis of variance indicated a signficant effect, Newman-Keuls tests were conducted to see which groups differed. None of the drug treated groups ever differed from each other. Group M_1 was significantly depressed from control ($p<0.05$ or better) on Days 5, 6, 12, 13, 14 and 15. Group M_5 was significantly depressed from control on Days 5, 6, 12, 13, 14 and 15. Group M_{15} was significantly depressed from control only on Day 15. It is apparent from these data that the drug-induced depression of performance is much more prolonged in those animals that receive the drug early in training, Groups M_1 and M_5, than in animals receiving the drug late in training, Group M_{15}.

Examination of individual records indicated that the averaged data was representative. Animals improved their performance under the influence of the drug more rapidly when drug administration was begun later in training. To specifically examine the rate of recovery of performance under the drug, a performance curve was plotted showing the mean emergence score for each day under the drug for each animal in Group M_1, M_5 and M_{15}. For each curve, a

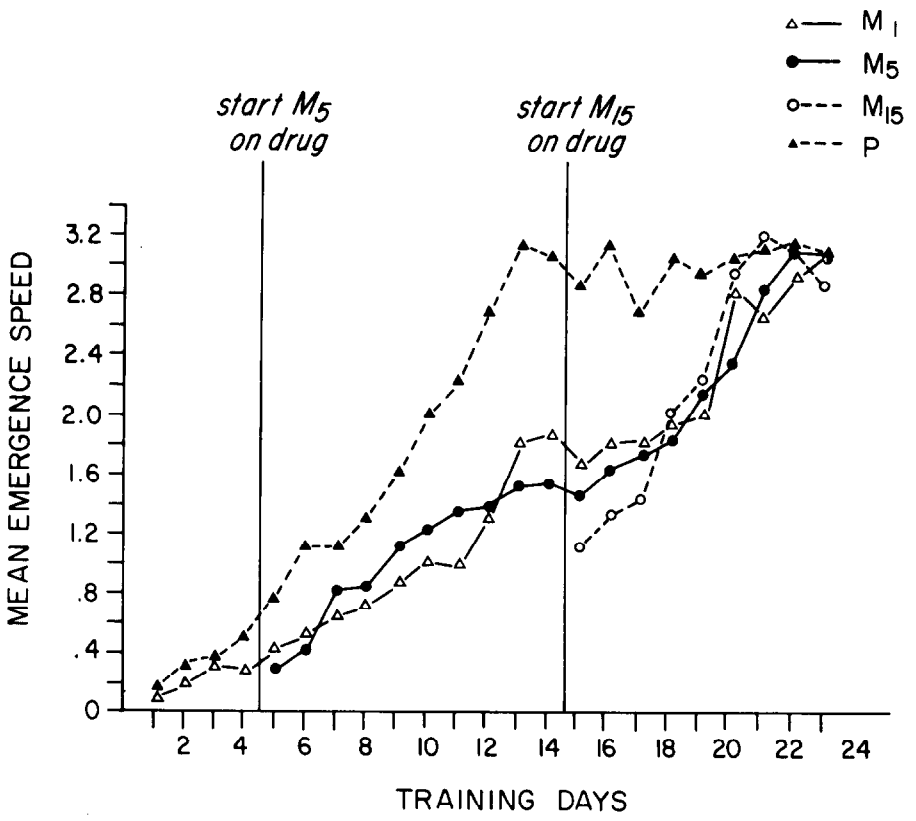

FIG. 3. Group mean emergence speeds for 23 days of training.

slope was calculated for the rate of improvement between the onset of drug administration and the attainment of asymtotic performance for that animal. Table 1 summarizes these scores. A one-way analysis of variance on these data confirmed the assertion that the amount of prior training influenced the rate of improvement under the drug. The effect of days of training prior to drug administration was highly significant ($F = 28.4$, $p<0.01$). Post hoc Sheffe comparisons indicated that Group M_1, differed significantly from M_{15} ($p<0.05$), while the M_1, M_5 difference and the M_5, M_{15} difference, though in the predicted direction, were not statistically reliable.

DISCUSSION

At the 6 mg THC/kg dose level employed in the study, running speed in the alley was not depressed. Emergence speed and starting speed were depressed, however. Why these latter measures should be more sensitive to the drug is not clear. It is possible that this resulted from a drug-induced increase in reaction time.

TABLE 1

RATE OF IMPROVEMENT OF EMERGENCE SPEED AS A FUNCTION OF DAY OF FIRST DRUG ADMINISTRATION

	M_1	M_5	M_{15}
Mean	1.82	2.26	3.86
S.D.	0.61	1.51	1.87

The development of tolerance on the starting and emergence measures was as predicted. Well trained animals improved most rapidly under the drug. This confirms a very recent report by Glick and Milloy [7] and is consistent with the view that behavioral tolerance involves a learned compensation for the debilitating effects of the drug. Thus behavioral tolerance can be compared to recovery from the effects of a distracting stimulus, or to the relearning of a response following an alteration of environmental conditions; disruption is less prolonged following increased amounts of training.

There is an alternative hypothesis, however. The analysis above assumes that marihuana depresses only performance. As soon as tolerance is developed, marihuana treated rats will perform at the level of controls. The alternative is that marihuana depresses both learning and performance. At least one report has demonstrated a marihuana produced learning deficit in rats [12]. If marihuana depresses both learning and performance, then a rat treated early in training would not reach the level of controls as soon as tolerance was established; it would still need to learn the task. A rat treated with the drug after training was complete would reach the level of controls as soon as tolerance developed, since this rat would already have learned the task.

Whichever hypothesis is correct, the present study indicates that learning can provide a useful model for the phenomena of behavioral tolerance to marihuana. Perhaps most important, the present data have significant practical

implications if they generalize to other drugs and other species: new behaviors may be very difficult to develop under the influence of drugs, even though previously acquired behaviors may rapidly return to a predrug level.

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