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BRIEF COMMUNICATION

Sustained Ingestion of Δ^9-Tetrahydrocannabinol and the Operant Behavior of Stump-Tailed Macaques[1]

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SNYDER, E. W., E. G. LEWIS, R. E. DUSTMAN AND E. C. BECK. *Sustained ingestion of Δ^9-tetrahydrocannabinol and the operant behavior of stump-tailed macaques.* PHARMAC. BIOCHEM. BEHAV. 3(6) 1129–1132, 1975. – Three stump-tailed macaques were trained to press a lever for liquid reinforcement on a tandem schedule which required the animal to delay responding for at least 30 sec after each reinforcer. If the animal responded during that interval, a clock was reset thus re-establishing the delay requirement. If he delayed responding appropriately, the monkey was shifted to a fixed-interval schedule of 135 sec duration. The FI component was terminated with a drop of flavored liquid at which point the delay requirement began anew. Following a stable baseline performance, two monkeys received 2 mg/kg of THC orally every third day for 90 days with the placebo administered on intervening days. The third animal received the placebo throughout testing. Each monkey's performance was described in terms of response rate and response patterning between reinforcers. Despite the sustained ingestion of THC, neither animal showed appreciable change in test behavior attributable to tolerance to the drug. Although the drug continued to have a powerful effect throughout testing on the days it was administered, there was no evidence of any consistent or cumulative drug effect on placebo-day performance.

Sustained THC ingestion Tandem schedule Response patterning

WHILE the acute behavioral effects of marijuana have been extensively studied in animals [16] the effects of sustained ingestion of this drug, such as behavioral tolerance, cumulative drug effects, or an abstinence syndrome, have received less attention. Studies with primates have begun to define some of the behavioral effects of sustained marijuana ingestion. These studies have demonstrated that monkeys develop behavioral tolerance to marijuana in fewer than 10 administrations [1, 7, 12]. There is also evidence for cumulative drug effects and for an abstinence effect when dosing is discontinued [7, 20].

There is one notable exception to the evidence for behavioral tolerance [5]. In this study chimpanzees performing on a matching to sample task did not become behaviorally tolerant to the effects of 42 daily doses (4 mg/kg) of Δ^9-trans-tetrahydrocannabinol (THC). The authors hypothesized that behavioral tolerance develops only when the animal is performing on a simple go, no-go task. This study also indicated that the drug was having a cumulative or toxic effect on behavior in that accuracy of performance decreased with repeated administrations of THC.

Briefly stated, daily administrations of THC apparently result in rapid behavioral tolerance unless the animal is performing a rather complex task. In addition, there is evidence for cumulative drug effects and for abstinence effects when dosing is discontinued.

Studies of sustained THC ingestion typically involve daily drug administration and daily testing. However, since many people consume marijuana intermittently over extended periods, it is important to investigate what happens to behavior, during a period of repeated THC ingestion, on days when no drug is administered as well as on those days when the drug is ingested.

The purpose of the present study was to monitor operant behavior for 3 months both on days when the drug was administered, and on 2 intervening days when the animals received only a placebo (henceforth referred to as placebo days). The behavior under study was controlled by a tandem schedule of positive reinforcement, combining schedule components which have been shown to be individually sensitive to many drugs including THC [2, 4, 6, 8, 13, 21]. Pilot work indicated that the tandem schedule was sensitive to the acute effects of THC.

METHOD

Animals

Three adolescent stump-tailed macaques (*Macaca arc-*

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toides), a 4.6 kg female (D1), and 8.7 kg male (D2) and an 8.5 kg male (C1), were studied.

Apparatus

The monkeys were secured in restraining chairs throughout testing except for one 16 hr exercise period per week when the animals occupied individual cages. The restrained monkeys were enclosed within sound-attenuated, lighted and vented isolation booths. White noise, played into each isolation booth throughout testing, masked outside noises. A commercial orange-flavored drink was delivered (1 ml per reinforcer) through a tube to the monkey's mouth by a solenoid valve liquid dispenser mounted on the restraining chair. The dispenser was activated by a lever attached to the front of the restraining chair.

Programming and recording equipment located in an adjoining, sound-attenuated room controlled each monkey's behavior by a separate electromagnetic system. A positive voltage coincident with each lever press and a negative voltage coincident with each reinforcer were recorded on electromagnetic tape for subsequent computer analysis.

Procedure

Each animal was trained to lever press on a schedule which required the animal to delay responding for at least 30 sec following each reinforcer. If the animal responded during that interval a clock was reset thus reestablishing the 30 sec delay requirement. If the animal did not lever press for 30 sec after each reinforcer he was automatically shifted to a fixed interval schedule of 135 sec duration. Only the first response following the 135 sec fixed interval was reinforced with 1 ml of orange drink. No stimuli were associated with either component of the schedule or with the changeover, so the animal had to learn to withhold his responding with no assistance from external cues other than the momentary deliverance of the reinforcer.

All animals were deprived of liquid for 20 hr preceding the beginning of a session.

Drug procedure. The drug, Δ^9-tetrahydrocannabinol (THC), was supplied by NIMH in concentrated form. One gram of the 93 percent pure THC was dissolved in 25 ml of ethyl alcohol. The mixture was refrigerated and was exposed to light and room temperatures only during administration.

Two drug monkeys (D1 and D2) and one control monkey (C1) were given 67 days of training prior to testing. During the last two weeks of training all monkeys received the placebo daily at noon. Following baseline Monkeys D1 and D2 received THC (2 mg/kg) on 3 banana-flavored sugar cubes every third day at noon while the control animal (Monkey C1) received the placebo (banana-flavored sugar cubes) throughout the study. The placebo was administered to Monkeys D1 and D2 on the days between drug administrations. All monkeys were tested on the schedule for 3 hr a day, 7 days a week for 3 months. After 30 drug administrations the placebo was again administered daily for 2 weeks.

RESULTS

Figures 1 and 2 portray pre- and post drug baselines and data for three 18 day segments which encompass the beginning, middle and final stages of drug administration. Not shown are data for two intervening 18 day segments

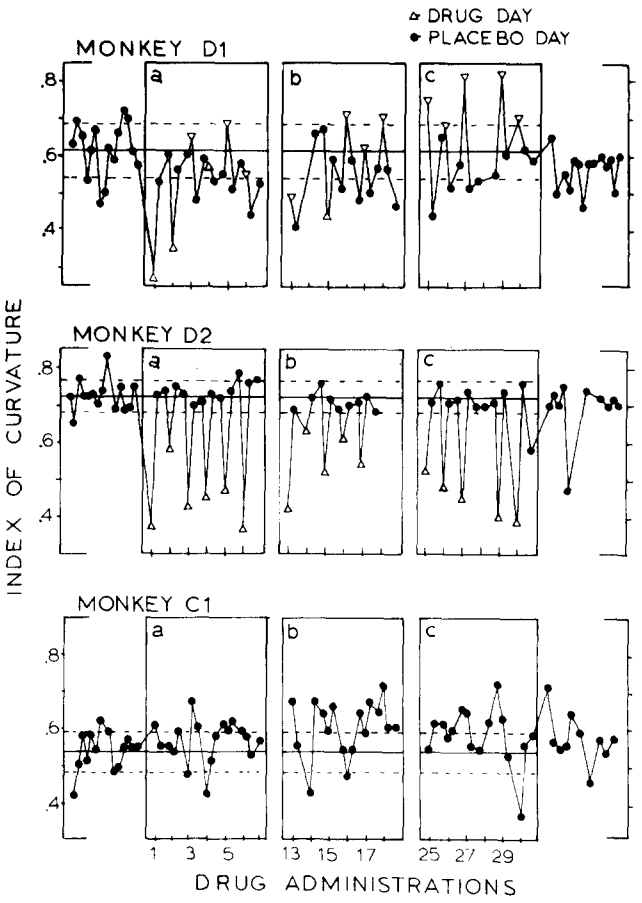

FIG. 1. Mean daily index of curvature. Each panel (a-c) represents 18 days of testing with 18 days omitted between panels. Drug was administered every third day for 90 days to Monkeys D1 and D2 while Monkey C1 received placebo throughout. Dashed lines indicate predrug baseline standard deviation.

which were highly consistent with graphed data. The analyses of variance described below are based on the placebo-day means of both baselines and all 18 day segments including those omitted in the figures.

Performance on the tandem schedule is described in terms of the index of curvature and the number of responses per reinforcer. The index of curvature describes the degree of departure from a steady state of responding between reinforcers [9]. The rate of response acceleration (scallop) near the end of an interreinforcer interval varies directly with the index of curvature.

Figure 1 portrays the mean daily index of curvature. During the 2 week predrug baseline the index of curvature showed no consistent changes for any monkey. However, following the first drug administration, Monkeys D1 and D2 had a reduced index (see Fig. 1, panel a) indicating a more even distribution of responses throughout the interreinforcer interval. Index of curvature scores returned to baseline on the two succeeding placebo days. A similar pattern was seen following the second drug administration.

Following the third drug administration there was a change in the index of curvature for Monkey D1. For that animal the index was usually higher on drug days as

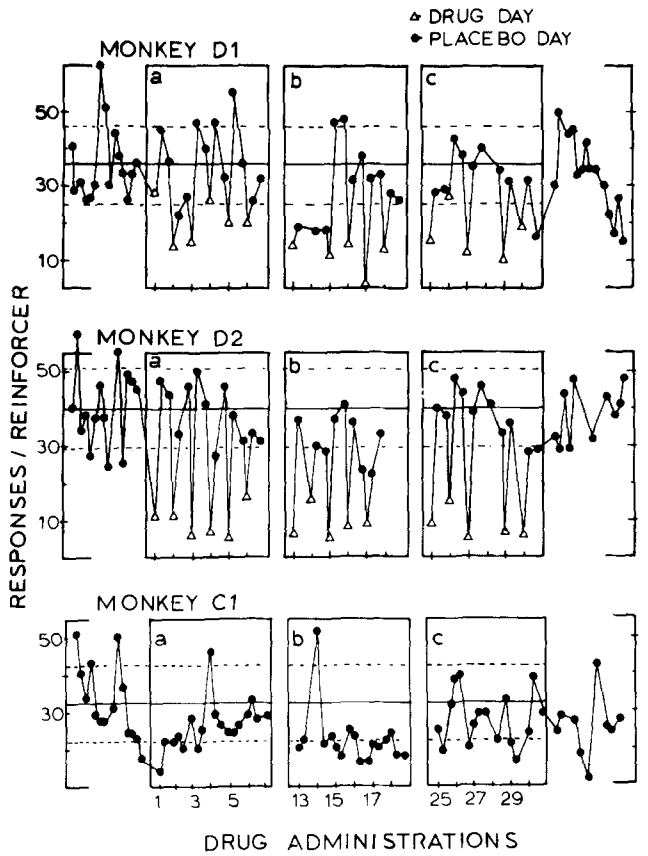

FIG. 2. Mean daily responses per reinforcer. Each panel (a-c) represents 18 days of testing with 18 days omitted between panels. Drug was administered every third day for 90 days to Monkeys D1 and D2 while Monkey C1 received placebo throughout. Dashed lines indicate predrug baseline standard deviation.

compared to placebo days while Monkey D2's index continued to be low on drug days.

Throughout the drugging period there was no lasting convergence of the drug and placebo-day values for either monkey. In fact, scores for the last 5 drug administrations for Monkey D1 (Fig. 1, panel c) indicated an increased divergence of drug and placebo-day values. Placebo-day scores did not change consistently over the three month period as evidenced in Fig. 1. The placebo day means of all time segments, including those omitted in Fig. 1, were subjected to analysis of variance using the randomized block design [11]. This analysis was based on a log-transformation which serves to reduce heterogeneity of variance in a condition, such as the present, where the distributions are likedly to be skewed [18]. The analysis indicates that, while the monkeys were significantly different from one another, $F(2,12) = 45.07$, $p<0.01$, there was no significant difference between the means of the time periods, $F(6,12) = 0.493$, $p>0.10$. In fact, a test for nonadditivity [18] indicates no interaction between subjects and treatments, $F(1,11) = 0.232$, $p>0.10$. That is, drug and control animals did not change differentially over time.

Figure 2 illustrates the mean daily responses per reinforcer. The baselines were stable in that no animal showed a continuous increase or decrease over the 2 week predrug baseline. There was also a stable relationship between the responses per reinforcer and the index of curvature as indicated by a high negative correlation between these scores during predrug baseline (Monkey D2, r = -.81, $df = 13$, $p<0.01$; Monkey D1, r = -.69, $df = 12$, $p<0.01$; Monkey C1, r = -.74, $df = 13$, $p<0.01$). In marked contrast to these negative correlations, Monkey D2's drug-day performance throughout testing was characterized by a simultaneous decrease in both measures (Figs. 1 and 2). Monkey D1's performance on the first two days of drug administration (Figs. 1 and 2) also showed a simultaneous decrease on both measures.

As with the index of curvature, the responses per reinforcer showed no lasting convergence of drug and placebo-day scores (Fig. 2). Although the animals' response rate did decrease significantly over time, $F(6,12) = 6.41$, $p<0.01$, the lack of a significant interaction [18] indicates that the animals' response rate did not change differentially over time, $F(1,11) = 0.854$, $p>0.10$.

Following the last (30th) dose of THC the responses per reinforcer for Monkey D1 increased markedly then decreased systematically to an unusually low rate of responding. During this time Monkey D2's rate of responding had a general upward trend. These unstable postdrug baselines are contrasted not only by Monkey C1's postdrug baseline (Fig. 2) but also by the stable indices of curvature (Fig. 1) during postdrug baseline.

DISCUSSION

Early Effects of THC

The first and second administrations of THC produced a simultaneous decrease in index of curvature and response rate for both monkeys in contrast to the baseline negative correlation between these measures. If the drug was producing simple behavioral depression one would expect the drug related decrease in response rate to be accompanied by an increase in index of curvature. Thus the drug apparently affected the animals' response patterning independently of their response rate as compared to baseline performance. These findings correspond to primate studies [4,10] which report a decrease in response output and a general disruption of temporal discrimination following acute administration of THC.

Effects of Sustained THC Ingestion

The monkeys did not develop behavioral tolerance even after 30 administrations of THC. That is, with few exceptions, drug and placebo scores remained divergent throughout testing. The lack of behavioral tolerance is in contrast to all but one recent study [5] in which chimpanzees did not become behaviorally tolerant to the effects of 42 daily doses of THC as measured by performance on a matching-to-sample task. The authors hypothesized that behavioral tolerance develops only when the animal is performing on a simple go, no-go task in which response consequences are immediate. For example, monkeys under the control of a schedule which delivers a reinforcer immediately following an appropriate pause (differential reinforcement of low rates or DRL), have been shown to develop tolerance after 5–8 daily sessions. The consequences of the tandem schedule used in the present study were not immediate as they are in a DRL schedule. Although the tandem schedule, like the DRL schedule, requires the animal to pause, an appropriate pause serves

only to activate the FI component; no stimulus is associated with either component of the tandem schedule or with the change from one component to the other. The demands of this tandem schedule may preclude the development of behavioral tolerance as the demands of a matching-to-sample task apparently did [5] even with daily ingestion of high doses.

Although the drug continued to have a substantial effect on days of drug administration, placebo-day indices of curvature did not change significantly over time indicating that the drug was having no additive effect on placebo-day performance. Although the response rate did change significantly over time, the drug and control animals did not show a differential change. Thus, if the drug was accumulating in the monkeys, as both behavioral and pharmacological evidence suggest it does [3, 14, 15, 17, 19], it was apparently not having an additive or cummulative effect on performance on those days when no drug was ingested.

While performance on placebo-days was apparently not affected by repeated drug ingestion, there was some evidence for an abstinence effect when dosing was discontinued. Thus both drug monkeys showed an unstable postdrug baseline (Fig. 2) in terms of their response rate. It is of interest that while the post-drug baseline response rate appeared to be changing over time, the indices of curvature (Fig. 1) remained relatively stable. These data suggest that THC withdrawal may have had a specific effect upon the rate of responding without affecting the temporal pattern of responding.

In summary, it is apparent that while THC continued to have a powerful effect on the days of administration, repeated intermittent administration did not produce obvious changes in placebo-day performance. These results must be interpreted in light of the limited sample size and single dose level.

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