Pharmacology Biochemistry & Behavior, Vol. 5, pp. 123- 128.

The Role of Reinforcement Loss in Tolerance to Chronic Δ⁹-tetrahydrocannabinol Effects on Operant Behavior of Rhesus Monkeys

TIMOTHY F. ELSMORE[1,2]

Walter Reed Army Institute of Research, Washington, D.C. 20012

(Received 9 January 1976)

ELSMORE, T. F. *The role of reinforcement loss in tolerance to chronic Δ-9-tetrahydrocannabinol effects on operant behavior of rhesus monkeys.* PHARMAC. BIOCHEM. BEHAV. 5(2) 123 128, 1976. – Two monkeys were trained on a multiple fixed-interval (FI) 120 sec, differential reinforcement of low rate (DRL) 120 sec schedule of food reinforcement for lever pressing in which the two schedules, each correlated with a distinctive cue, alternated throughout an experimental session. Under chronic daily treatment with Δ-9-tetrahydrocannabinol in a dose of 7 mg *per os* (1 mg/kg), for 40 consecutive days, responding increased in both schedules. Performance on the DRL schedule was affected less dramatically than that on the FI schedule. Even though reinforcement frequency on the DRL schedule remained suppressed and FI reinforcement frequency was unaffected during chronic drug treatment, DRL performance showed greater tolerance than FI performance.

Δ-9-Tetrahydrocannabinol Chronic administration FI schedule DRL schedule Rhesus Tolerance

THE EFFECTS of chronic administration of Δ-9-tetrahydrocannabinol (Δ-9-THC) on behavior have been the subject of considerable research in the recent past. There have been many reports of tolerance development to a variety of effects of the drug [e.g. 3, 9, 13, 14], and a few reports of sensitization to the drug effects [10,19]. Reconciliation of these diverse responses to chronic THC administration is yet to come. It has been suggested [4,16] that an important determinant of the behavioral reponse to chronic drug administration is the way in which the initial drug effect interacts with the contingencies controlling the behavior. Schuster *et al.* [16] administered d-amphetamine to rats that had been trained on a multiple fixed-interval (FI), differential reinforcement of low rate (DRL) schedule of reinforcement, and observed that tolerance occurred to drug effects on responding in a particular component of the schedule only when the initial drug effect produced a reduction in reinforcement frequency in that component. In a second experiment, these investigators found no tolerance to response-rate-increasing effects of d-amphetamine in rats working on an undiscriminated shock avoidance schedule [17], when the drug effect resulted in the animals receiving fewer shocks than in non-drug conditions. On the basis of these results, Schuster *et al.* [16] proposed that, "Behavioral tolerance will develop in those aspects of the organism's behavioral repertoire where the action of the drug is such that it disrupts the organism's behavior in meeting the environmental requirement for reinforcement. Conversely, where the actions of the drug enhance, or do not affect the organism's behavior in meeting reinforcement requirements we do not expect the development of behavioral tolerance," [p. 181]. A similar explanation has been suggested for the development of behavioral tolerance to Δ-9-THC [7, 12, 18]. This explanation will be called the "reinforcement loss" hypothesis of behavioral tolerance.

The present experiment is similar to the Schuster *et al.* experiment in that it employed a multiple FI DRL reinforcement schedule for investigation of chronic drug effects. The utility of such a schedule in the investigation of interactions between behavioral and pharmacological variables in the control of behavior, is that the relatively rapid alternation of the behavioral contingencies represented by the different components of the schedule takes place in a constant pharmacological environment. Thus, any differential effects between the schedule components may be attributed to differences in the interaction between the behavioral requirements made by the schedules and the drug effect rather than to pharmacological or other variables.

It has been demonstrated that at intermediate doses, Δ-9-THC often produces an increase in the rate of response under various appetitive schedules of reinforcement [2,6].

[1] Thanks are expressed to G. V. Fletcher for help in conducting the experiment, D. R. Rhodus for help in the data analysis, and W. Taylor for typing the manuscript.

[2] In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", DHEW Publication No (NIH) 73-23, as Prepared by the Institute of Laboratory Animal Resources, National Research Council.

If this were the case for both FI and DRL reinforcement schedules, the reinforcement loss hypothesis would predict opposite results of chronic THC administration on performances under the two schedules. With an FI schedule, a single response following the end of a fixed time period is the only requirement for reinforcement and responses occurring prior to the elapse of the fixed time period are without effect. The consequences of a drug-induced acceleration in responding in such a situation would be twofold; more responses would go unreinforced, and there would be little effect, or perhaps a slight decrease in the average interreinforcement interval as a result of the higher rate of response producing a decrease in the average time between reinforcement availability and the occurrence of a response. The reinforcement loss hypothesis would predict little tolerance to such a drug effect.

A DRL schedule requires that a fixed time period pass without the occurrence of a response before a response will produce reinforcement. Responding that occurs prior to the elapse of the interval resets the timer, delaying the opportunity for reinforcement. A drug-induced increase in responding in such a situation would increase both the number of unreinforced responses, and the average interval between reinforcements. Thus, the reinforcement loss hypothesis would predict tolerance to such drug effects under chronic administration conditions. A multiple FI DRL schedule thus provides a means for assessing the role of reinforcement rate reduction in producing tolerance to the behavioral effects of Δ-9-THC.

METHOD

Animals

Two adult male rhesus monkeys were used. Both had served in a variety of prior experiments with Δ-9-THC, but had been drug-free for the five months prior to the present experiment. The animals weighed approximately 7 kg at the beginning of the experiment and were maintained on Noyes 750 mg food pellets earned during experimental sessions (maximum of 96 per day) and ¼ piece of fruit (apple, orange, or banana) given at 0800 hrs each day. Water was available from a solenoid-operated drinking spout for a press on a lever on the right side of the cage when experimental sessions were not in progress.

Apparatus and Procedure

Each animal lived in a separate experimental cage with one barred wall facing a large laboratory. One side wall contained a 1 cm dia. lever protruding 2.5 cm into the cage, 15 cm from the front of the cage, and 30 cm high. A white jeweled pilot light was mounted 6 cm above the lever. Pellets were delivered into a food hopper 10 cm to the right and 10 cm below the food lever. The hopper could be illuminated with white light. A speaker was mounted in the cage for delivering auditory stimuli. Overhead houselights and room lights were on from 0800 to 2400 hrs daily, and off from 2400 to 0800 hrs. Experimental procedures and data recording were automated with solid-state logic modules, electromechanical counters, printing counters, and cumulative recorders. Data were later punched onto paper tape for computer analysis.

Prior to the experiment described here, both animals had been performing under a procedure similar to the one described below for about 3 months. Experimental sessions were run 4 times daily at 1000, 1600, 2200, and 0400 hrs. Each session consisted of 12 exposures each to an FI 120 sec and a DRL 120 sec schedule. White noise accompanied the FI schedule and a 1500 Hz tone accompanied the DRL schedule. The two schedules alternated in 5 min blocks of time, during each of which a single pellet could be obtained. At the start of each 5-min block, the pilot light over the lever and the auditory stimulus appropriate to the schedule currently in effect came on. Each press on the lever produced a 1 sec dimming of the pilot light, and a 1 sec illumination of the hopper light. When the requirements for reinforcement were met, the pilot light went off, and a food pellet was delivered during the one sec hopper light, following which the auditory stimulus, and all panel lights remained off until the remainder of the 5 min block of time had passed. If the requirements for reinforcement were not met within 5 min, the auditory stimulus changed automatically, and the other schedule was put into effect. This procedure was in effect for 34 days prior to the initiation of Δ-9-THC administration.

Δ-9-THC was administered at 0800 hrs daily by injecting it into the animal's ration of fruit. The daily dose was 7 mg (0.5 ml of a 14 mg/ml solution), or approximately 1 mg/kg. Dosing was done on an absolute basis because of the difficulty of weighing the animals frequently enough to accurately adjust dosage. Drug solutions were prepared by diluting an ethanol solution of Δ-9-THC (200 mg/ml) with propylene glycol to achieve the desired concentration. Drugging continued for 40 consecutive days.

RESULTS

Only data from the 1000 session will be reported. Drug effects occurred in the other 3 sessions of the day, and were generally in the same direction, but of smaller magnitude than the effects at 1000 hrs. The baseline schedule maintained quite low absolute rates of responding in both schedule components. The average baseline response rates for the FI schedules were 1.90 responses per min for Pete, and 0.44 responses per min for Max. Baseline DRL rates were 0.50 responses per min for Pete, and 0.34 responses per min for Max.

Changes in response rates under both the FI and DRL schedules under chronic drug treatment are presented in Fig. 1. These data exclude the first exposure to each schedule in each session, as well as exposures in which no responses occurred. Data for a given schedule for a session were also excluded if the animal failed to respond in at least 2 of the 12 scheduled exposures to that schedule in that session. Data were also unavailable for occasional sessions due to failure of recording apparatus. These exclusions also applied to all other data presented in the paper. To obtain the data of Fig. 1, the response rate (responses per min) was determined for each of the 11 analyzed exposures to each schedule in each session, and the median of these response rates was determined. These medians were then converted to percentages of the median response rates for the 10 predrug sessions (i.e. the median of the daily medians for the baseline sessions). Initial drug effects on median response rates were remarkably similar for both animals. Both the FI and DRL rates were elevated, with the DRL rate rapidly falling back towards baseline. Pete's FI rate continued to increase for about the first 10 days of drug administration, and Max's rate increased for the first 5 days of drug administration. For the remainder of the chronic

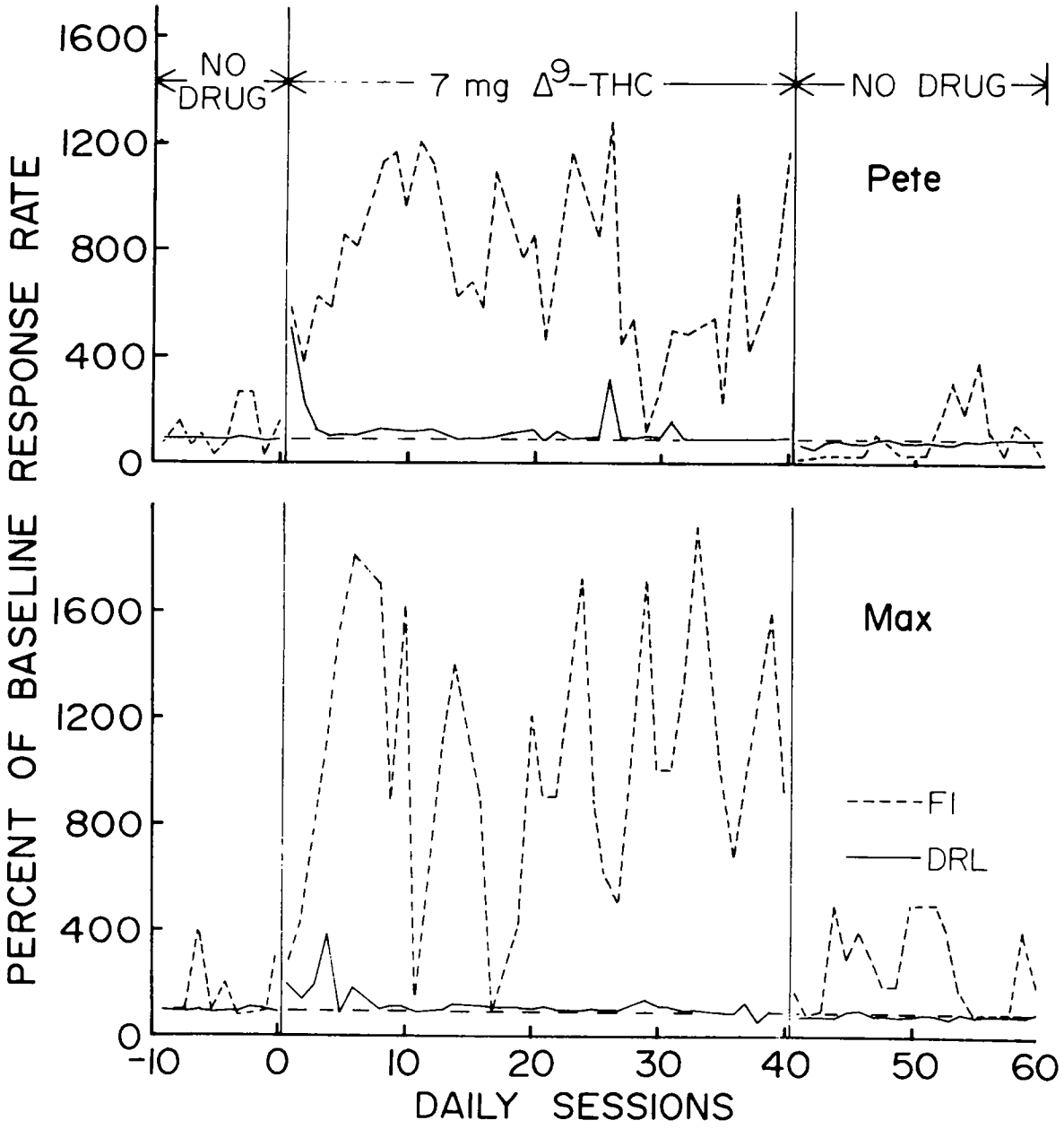

FIG. 1. Median FI and DRL response rates are shown as a percentage of the respective baseline median response rates for each schedule, before, during and after chronic daily treatment with Δ-9-THC. The drug was administered orally 2 hr presession, in a total dose of 7 mg (approximately 1 mg/kg).

drug regimen, FI rates were generally greatly elevated above baseline levels, with a good deal of variability. DRL rates continued at or very slightly above baseline during this period. When drugging was discontinued, baselines were recovered within 10 15 days, with some tendency for rates particularly for Pete, to be lower than baseline during the initial postdrug period. Thus, there appears to have been tolerance to the rate-increasing effect of Δ-9-THC on DRL responding, but no tolerance to the effect on FI responding. However, this was only partially true. When the response rate data were plotted as means rather than medians, the DRL responding, while still showing greater tolerance than FI responding, remained clearly above baseline for the duration of the drug treatment due to occasional infrequent episodes of relatively high-rate responding under the DRL schedule. These aberrations, with a few exceptions (e.g. Pete in sessions 26 and 31), did not occur frequently enough to affect the medians, but they did occur more frequently than during the baseline period.

Effects of the drug on reinforcement rates under the two schedules were as predicted. That is, FI reinforcement rates were either increased or unchanged, and DRL rates were suppressed. These data are presented in Fig. 2. For each session, mean reinforcement rates were computed for each schedule by dividing total reinforcements for the schedule by the total time the schedule was in effect. The data are

plotted as percentages of the mean of the 10 predrug sessions. Medians showed similar but less marked effects. It can be seen from this figure that DRL reinforcement rate remained suppressed for most of the chronic drug treatment period, although Pete appeared to show some consistent recovery towards the end of the treatment. Comparison of Figs. 1 and 2 shows that it would be difficult to account for the recovery in DRL response rate by the effect such recovery might have on reinforcement rate, since the time courses of the two effects are quite different.

The fact that the drug continued to affect DRL

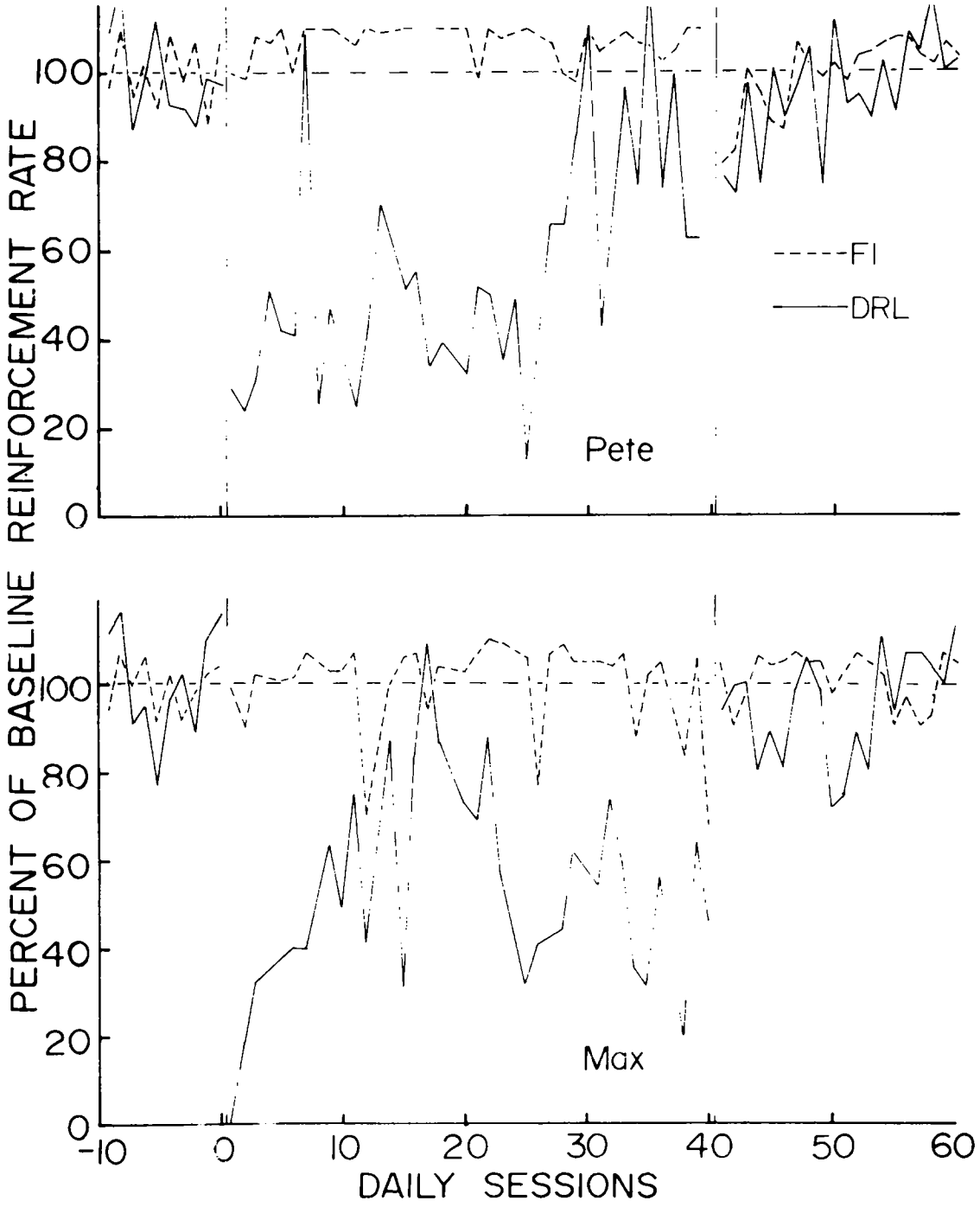

FIG. 2. Mean FI and DRL reinforcement rates are shown as a percentage of the baseline mean reinforcement rates for each schedule, before, during, and after chronic daily treatment with Δ-9-THC.

performance, though to a lesser extent than FI performance, is demonstrated in Fig. 3 which shows latency of responding (time to the first response) under each schedule throughout the experiment. These data were calculated in a manner similar to those of Fig. 1. Both animals showed shorter latencies in both schedules under treatment with △-9-THC. This effect was greater for both animals under the FI schedule than the DRL schedule, and persisted throughout the chronic drug treatment. It is important to note, however, that the decrease in DRL latencies did persist for the duration of the drug treatment. Thus, the apparent total tolerance in DRL response rate could only have been accounted for by an increase in the duration of interresponse times subsequent to the first response in each DRL component. When drug treatment was terminated, latencies immediately became longer for Pete under both schedules, returning rapidly to baseline. For Max, latencies under the DRL schedule appeared to remain elevated for 20 days postdrug.

Considered separately, the drug effects on the two schedules confirm other △-9-THC studies. Recovery in DRL response rate under chronic △-9-THC administration has

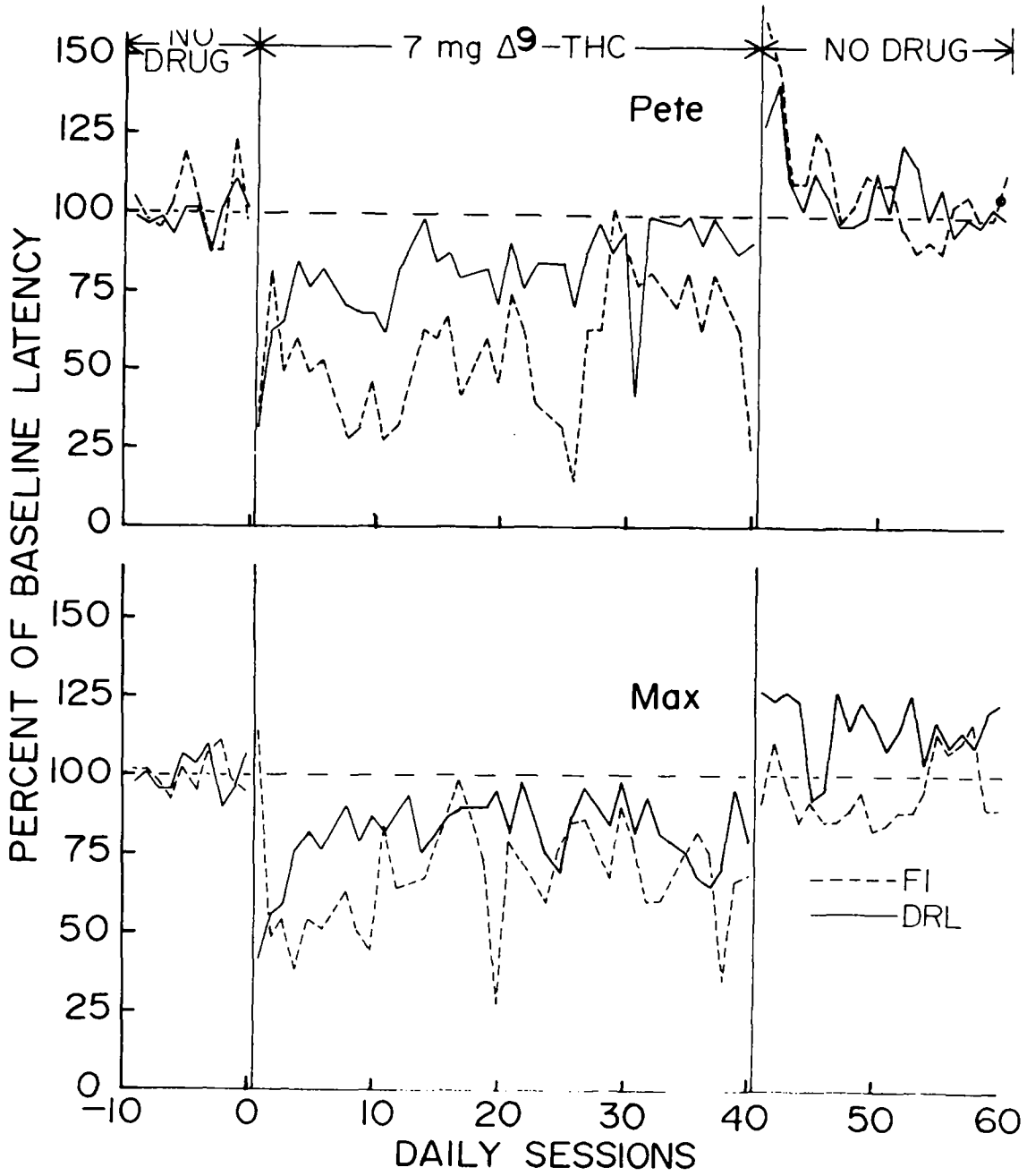

FIG. 3. Median latencies (time to the first response upon exposure to a given schedule) are shown as a percentage of the baseline median latencies for each schedule, before, during, and after chronic daily treatment with △-9-THC.

been reported by Sodetz [18] and Ferraro and Grisham [9]. These results are in contrast with those of Frankenheim [10] who found increased sensitivity to the rate-increasing effects of delta-8-THC on DRL performance of rats. This discrepancy remains to be clarified. In agreement with the present study, Newman, Lutz, and Domino [15] found tolerance to rate-depressing effects of THC on FI performance in rats to be extremely slow. Ferraro and Grilly [8] also found no tolerance to the drug in chimpanzees working under a matching-to-sample task. The finding in the present study of tolerance and lack of tolerance to different behavioral effects of Δ-9-THC in the same animal during the same series of chronic injections also replicates the data of Harris, Waters, and McLendon [11] and Elsmore [5] who found different degrees of tolerance in the same animals, depending on the behavioral requirements.

The present results partially confirm predictions made by the reinforcement loss hypothesis regarding the development of behavioral tolerance to drug effects. Greatest tolerance to THC-induced increases in responding occurred only in those cases where the initial drug effect reduced reinforcement frequency. The exact nature of the mechanism, however, remains unclear. Biochemical mechanisms are effectively ruled out by the experimental design. A corollary that would seem to follow from the reinforcement loss hypothesis is that recovery from drug-induced reduction in reinforcement frequency would accompany and support observed behavioral tolerance. This did not occur in the present study. The DRL reinforcement rates of both animals remained suppressed throughout drug treatment, although Pete's DRL reinforcement rate appeared to be recovering towards the end of the series. Thus, although a clear difference in the rate of recovery from drug-induced increases in responding seems to have occurred in the present study, the recovery in DRL responding was not supported by a concurrent increase in reinforcement frequency.

An alternative behavioral mechanism may be proposed to account for the occurrence of tolerance. The increased DRL response rates produced a reduction in reinforcement frequency in only that component of the multiple schedule. It is well established that decreases in reinforcement frequency lead to corresponding reductions in response rate [1]. Thus, the reduction in DRL responding that appears to be tolerance to the drug effect may simply reflect a general weakening of the behavior in that component of the multiple schedule due to the reduction in reinforcement frequency under the DRL conditions. Since the reinforcement rate was unchanged or increased in the FI component of the multiple schedule, no reduction in response rate would be expected. The generality of this explanation is probably quite limited. What these results, and those mentioned earlier suggest, is that the degree of behavioral tolerance to Δ-9-THC effects is highly dependent upon the specifics of the interactions between the drug and the schedule of reinforcement maintaining the behavior.

REFERENCES

1. Catania, A. C. and G. S. Reynolds. A quantitative analysis of the responding maintained by interval schedules of reinforcement. *J. exp. Anal. Beh.* **11**: 327–383, 1968.
2. Conrad, D. G., T. F. Elsmore and F. J. Sodetz. Δ-9-tetrahydrocannabinol: Dose-related effects on timing behavior in chimpanzee. *Science* **175**: 547–550, 1972.
3. Davis, W. M. and L. A. Borgen. Tolerance development to the effect of Δ-9-tetrahydrocannabinol on conditioned behavior: Role of treatment interval and influence of microsomal metabolism. *Archs Int. Pharm. Ther.* **213**: 97–112, 1975.
4. Dews, P. B. Psychopharmacology. In: *Experimental Foundations of Clinical Psychology*, edited by A. J. Bachrach. New York: Basic Books, 1962, pp. 423–441.
5. Elsmore, T. F. Effects of delta-9-tetrahydrocannabinol on temporal and auditory discrimination performances of monkeys. *Psychopharmacologia* **26**: 62–72, 1972.
6. Elsmore, T. F. and F. J. Manning. Time course and dose-response effects of orally administered delta-9-THC on interval schedule performance of the rat. *Life Sci.* **15**: 481–489, 1974.
7. Ferraro, D. P. Effects of Δ-9-trans-tetrahydrocannabinol on simple and complex learned behavior in animals. In: *Current research in marijuana*, edited by M. F. Lewis. New York: Academic Press, 1972, pp. 49–95.
8. Ferraro, D. P. and D. M. Grilly. Lack of tolerance to Δ-9-tetrahydrocannabinol in chimpanzees. *Science* **179**: 490–492, 1973.
9. Ferraro, D. P. and M. G. Grisham. Tolerance to the behavioral effects of marihuana in chimpanzees. *Physiol. Behav.* **9**: 49–54, 1972.
10. Frankenheim, J. M. Effects of repeated doses of 1-Δ^8-trans-tetrahydrocannabinol on schedule-controlled temporally-spaced responding in rats. *Psychopharmacologia* **38**: 125–144, 1974.
11. Harris, R. T., W. Waters and D. McLendon. Behavioral effects in rhesus monkeys of repeated intravenous doses of Δ-9-tetrahydorcannabinol. *Psychopharmacologia* **26**: 297–306, 1972.
12. Manning, F. J. Acute tolerance to the effects of delta-9-tetrahydrocannabinol on spaced responding by monkeys. *Pharmac. Biochem. Behav.* **1**: 665–671, 1973.
13. McMillan, D. E., L. S. Harris, J. M. Frankenheim and J. S. Kennedy. 1-Δ-9-trans-tetrahydrocannabinol in pigeons: tolerance to the behavioral effects. *Science* **169**: 501–503, 1970.
14. McMillan, D. E., W. L. Dewey and L. S. Harris. Characteristics of tetrahydrocannabinol tolerance. *Ann. N.Y. Acad. Sci.* **191**: 83–96, 1971.
15. Newman, L. M., M. P. Lutz and E. F. Domino. Delta-9-tetrahydrocannabinol and some CNS depressants: evidence for cross-tolerance in the rat. *Archs int. Pharmacodyn.* **207**: 254–259, 1974.
16. Schuster, C. R., W. S. Dockens and J. H. Woods. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia* **9**: 170–182, 1966.
17. Sidman, M. Two temporal parameters of the maintenance of avoidance behavior by the white rat. *J. comp. physiol. Psychol.* **46**: 253–261, 1953.
18. Sodetz, F. J. Δ-9-Tetrahydrocannabinol: Behavioral toxicity in laboratory animals. In: *Current research in marijuana*, edited by M. F. Lewis. New York: Academic Press, 1972, pp. 25–48.
19. Weil, A. T., N. E. Zinberg and J. M. Nelson. Clinical and psychological effects of marihuana in man. *Science* **162**: 1234–1242, 1968.