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# Behavioral Tolerance to Stimulating Effects of Pentobarbital: A Within-Subject Determination

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BRANCH, M. N. *Behavioral tolerance to stimulating effects of pentobarbital: A within-subject determination.* PHARMACOL BIOCHEM BEHAV **18**(1) 25–30, 1983.—Squirrel monkeys were trained to press a lever under a multiple schedule of food presentation. In one stimulus condition responses that terminated interresponse times greater than 28 sec were followed by food presentation. In the other stimulus condition, an interval schedule of food presentation was presented that provided approximately the same frequency and distribution of food delivery as that observed under the interresponse-time schedule. Except when it was administered for the first time, 5.6 mg/kg sodium pentobarbital produced reliable increases in responding during the interresponse-time schedule. Behavioral tolerance to the rate-increasing effect was assessed in individual subjects by first administering the drug daily following each session, and then giving it daily before each session. Following post-session drugging, the effects of 5.6 mg/kg were not changed, but tolerance developed when the drug was administered pre-session. The way in which tolerance developed was consistent with the reinforcement-loss hypothesis.

Barbiturates Tolerance Behavioral tolerance IRT schedules Interval schedules Multiple schedules Reinforcement-loss Squirrel monkeys

BEHAVIORAL tolerance is a subvariety of functional tolerance that can be distinguished by the demonstration that behavioral (or environmental) factors are important determinants of the rate and/or degree of tolerance development to a drug's behavioral effects [9]. The standard method for demonstrating that tolerance has a behavioral component is to compare the effects of repeated pre-test drug administrations to those of an equal number of post-test administrations [4]. The logic of such a comparison is that pre-test drug administrations allow the subject to engage in the measured behavior while drugged, during which time some sort of behavioral compensation may develop. Post-test administrations, by contrast, result in the same amount of exposure to the drug but do not allow the subject to engage in the task while under the drug's influence. Typically, two groups of subjects are used. One is exposed to a series of pre-test administrations, and the other is given an equal number of post-test treatments. Comparisons are then made of effects of pre-test administration. Tolerance is said to be behavioral if the pre-test group shows more tolerance than the post-test group. The basic behavioral-tolerance procedure has been used to examine environmental contributions to tolerance development for a variety of drugs across a range of behavioral tasks. Behavioral tolerance has been found for amphetamines [1, 3, 20], ethanol [4, 5, 16, 17, 26, 27], LSD and mescaline [18], barbiturates [13,25], cocaine [28,29], and $\Delta^9$-tetrahydrocannabinol [2,19].

One of the weaknesses of the traditional behavioral-tolerance procedure is that group means are often used to characterize effects, and consequently precise quantitative estimates of the contribution of environmental factors to the development of tolerance in individual subjects are not obtained. When behavioral effects of drugs are examined, quantitative differences among subjects are usually observed which will result in a group mean not being representative (cf. [3]). To characterize properly the contribution of behavioral factors to the development of tolerance in individual subjects, then, a method that allows determination of behavioral tolerance in individuals is required. The main purpose of the present experiments was to see if behavioral tolerance can be observed in a within-subject design. Post- and pre-test drug administrations were made in the same subject during different parts of the study and differences in effects were noted. An auxiliary purpose was to determine if behavioral factors can contribute to tolerance to stimulating effects of pentobarbital.

## METHOD

### *Subjects*

Two adult male squirrel monkeys (*Saimiri sciureus*) were studied. Between daily performance sessions they were housed individually with continuous access to vitamin-enriched water. A food-deprivation regimen kept each at about 85% of its free-feeding weight. (The 85% weights were 720 g for M501 and 765 g for M509). Both subjects had extensive operant-conditioning histories, and both had been exposed to daily administrations of $\Delta^9$-tetrahydrocannabinol. Neither monkey, however, had received the drug for over a

year. Shortly (3 months) before the present study, both had received occasional administrations of chlordiazepoxide.

*Apparatus*

The monkeys were studied in a Plexiglas restraining unit (chair) similar in design to one described previously [12]. The chair restrained the subject in a sitting position by means of a waist lock. Free movement of the entire upper body and of the legs was afforded. The chair was equipped with a response lever, colored stimulus lights and a pellet feeder that could deliver 190-mg banana-flavored food pellets (P. J. Noyes Co.) into a food cup recessed into the wall next to the lever. During sessions the restraining chair was placed in a ventilated, light- and sound-attenuating enclosure in a room where white masking noise was continuously present. Experimental events were monitored and controlled by a PDP-8/f minicomputer that was located in an adjacent room and operated under the SuperSKED software system [24]. Data were also collected on a cumulative response recorder (R. Gerbrands Co.)

*Behavioral Procedure*

The monkeys had been trained to press a lever under a multiple schedule of food presentation [10]. When blue stimulus lights were illuminated, lever presses resulted in presentation of a food pellet according to an interresponse time greater than 28-sec (IRT>28 sec) schedule. That is, lever presses that followed the immediately preceding press by 28 sec or more resulted in delivery of a food pellet. When white stimulus lights were on, lever presses resulted in food presentations according to a modified random-interval (RI) schedule. The schedule was arranged such that the probability that a lever press could result in food delivery was zero for the first 28 sec following presentation of a pellet. Subsequently, every second there was a fixed probability that food presentation would be made available. Once the schedule arranged availability, the next lever press resulted in delivery of the food pellet. The schedule was arranged in this fashion so as to result in comparable frequencies and distributions of food pellets in the two schedule components. (A more detailed description of the results of this RI procedure can be found in Galbicka, Lee and Branch [11]). Components lasted five min, alternated, and were presented four times each in a session. Each session began with the IRT component. At the time the present study began the subjects had been responding under the procedure for over three years, and performance was quite stable.

*Drug Procedures*

Pentobarbital sodium was dissolved in 0.9% sodium chloride solution. Dosages were determined as the salt, and injection volume was held constant at 0.5 ml/kg body weight. Injections were made into either the thigh or calf muscle (No effect of varying injection location was ever noted).

Acute effects of a range of doses (1.0–10.0 mg/kg) were determined initially by injecting the drug immediately before sessions at four-day intervals. Doses were arranged in an ascending, then descending, then ascending order. Because the effects of 5.6 mg/kg changed following the first determination, the effects of this dosage were redetermined four more times, during which dose spacing and magnitude of the preceding dose were varied. Altogether, the numbers of determinations of each dosage were as follows: Saline vehicle—5; 1.0 mg/kg—3; 3.0 mg/kg—3; 5.6 mg/kg—7; 10.0 mg/kg—4.

The chronic effects of 5.6 mg/kg pentobarbital were examined by first injecting the subjects once per day for twenty consecutive days immediately after the daily test session. On the 21st day, the daily injection was moved to immediately before the session. Pre-session injections continued for 30 days, after which ten daily sessions were preceded by injections of the saline vehicle.

## RESULTS

Under non-drug conditions different patterns and rates of responding were engendered in the two components of the multiple schedule. The IRT schedule produced low rates of lever pressing with a preponderance of IRTs greater than 28 sec. The RI schedule controlled a higher rate. Frequency of food delivery was about the same in both components. Quantitative data regarding control performance can be found in the figures that follow.

Administered acutely, pentobarbital had differential effects on rates of lever pressing in the two components, and effects of 5.6 mg/kg changed after the initial administration of this dosage. When first given, 5.6 mg/kg decreased response rates by about 2/3 during the RI schedule and left response rates unaffected during the IRT schedule. When administered subsequently, however, this dosage resulted in essentially no change during the RI but substantial increases in response rate during the IRT schedule.

Dose-effect curves for response rates and for numbers of food pellets per session during the two components are presented in Fig. 1. Data from the initial administration of 5.6 mg/kg were not included in the analyses. The drug had no appreciable effect on responding during the RI schedule unless the largest dose was administered, following which response rates and rate of food presentation decreased. By contrast, large reliable increases (at least 100% and in one case as high as 1000%) in response rate during the IRT schedule were observed following administration of 5.6 mg/kg. Accompanying these rate increases were corresponding decreases in the frequency of food pellet delivery.

Effects of chronic drugging are summarized in Fig. 2. When 5.6 mg/kg was administered daily immediately after each session, no effect was observed. Response rates and food-pellet frequencies typically fell within the range of effects observed under non-drug conditions. The initiation of daily pre-session administration revealed that very little if any tolerance had developed to pentobarbital's effects during post-session drugging. Response rates following the first pre-session injection fell within the ranges of values obtained when 5.6 mg/kg had been administered acutely. The rate during the IRT component for M509, however, was near the bottom of this range, suggesting that perhaps a modest amount of tolerance had developed. It should be noted, nevertheless, that the drug's effects on overall frequency of food presentation during the IRT component during the first session which was preceded by pentobarbital were unchanged from those seen during acute administration of 5.6 mg/kg.

In contrast to the absence of effects that resulted from daily post-session treatments, daily pre-session injections resulted quickly in tolerance to the response-rate-increasing and pellet-delivery-decreasing effects of pentobarbital during the IRT component of the multiple schedule. Following about 20 days of pre-session treatments, response rate dur-

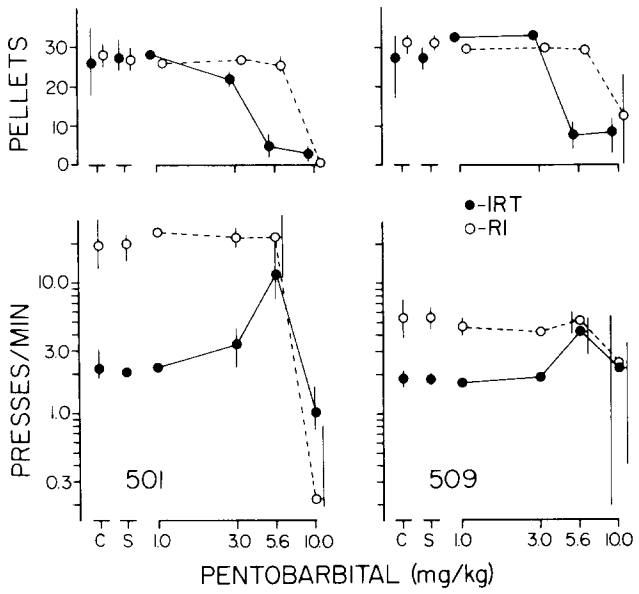


FIG. 1. Effects of pentobarbital on rate of lever pressing (lower graphs) and number of food pellets earned per session (upper graphs) for monkeys 501 (left) and 509 (right). Filled circles display data from the IRT>28-sec schedule, and open circles those from the RI schedule. Points above C are means from sessions that immediately preceded those in which injections were given. Points above S are from sessions that were preceded by injection of the saline vehicle. Vertical bars display ranges. Note that the Y-axes on the lower graphs and the X-axes are logarithmic.

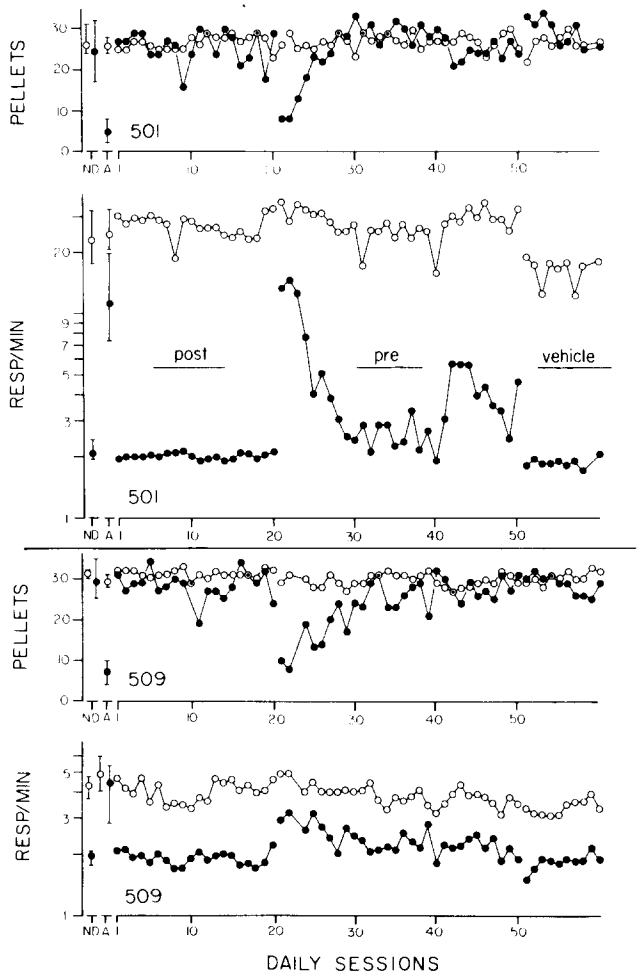


FIG. 2. Number of food pellets delivered per session (top and third graphs) and responses per minute (second and bottom graphs) over sessions of chronic drug administration and during withdrawal. Data for Monkey 501 appear in the upper two graphs, and those for Monkey 509 in the lower two. Y-axes for response rates are logarithmic whereas those for number of food pellets are arithmetic. Filled symbols are from the IRT schedule, and open symbols are from the random-interval schedule. Points and bars above "ND" show the means and ranges, respectively, of values obtained during the 15 daily sessions immediately preceding daily drug administration. Points and bars above "A" illustrate the means and ranges, respectively, of values obtained via acute administration of 5.6 mg/kg pentobarbital (each point is a mean of six determinations). The first 20 connected points are from sessions that were followed by injections of 5.6 mg/kg pentobarbital. The next thirty points are from session preceded by injections of the drug, and the last ten points are from sessions preceded by injections of the saline vehicle. Data points are missing from Day 23 for Monkey 509 and from Day 59 for Monkey 501 as a result of apparatus failures that prevented collection of valid data.

ing the IRT component became somewhat variable, but large reductions in the frequency of food pellet delivery during the component did not occur.

Discontinuation of daily pentobarbital resulted in a decrease in response rate, as compared to the no-drug baseline, in both components of the multiple schedule for Monkey 501 and in the IRT component for Monkey 509. Rates remained low for Monkey 501 over the last 10 sessions of the experiment, whereas those of Subject 509 recovered in a few sessions.

Other aspects of performance during chronic drugging are detailed in Figs. 3 and 4 which show cumulative response records and IRT distributions, respectively, from selected sessions. The IRT distributions labeled A–D are from the sessions from which the cumulative records of Fig. 3 were taken. The cumulative records in the top row of Fig. 3 and the IRT distributions labeled "A" in Fig. 4 are from the last session prior to the initiation of post-session drug administration. Performance in the two components tended to be consistent across a session. Most IRTs were longer than 28 sec and the mode of the IRT distributions fell in the 28–32 sec class interval. The cumulative records in the second row and the IRT distributions labeled "B" are from the last (M501) or second to last (M509) session during post-session drugging. Neither the IRT distributions nor the records indicate much change. Data in the next row of each figure are from the first session of the pre-session administration phase, and here changes are very apparent. Response rates during the IRT component were increased, resulting in a corresponding decrease in the number of food pellets obtained during this component of the multiple schedule. Modes of the IRT distributions were shifted to the left, and the shift was more pronounced for Monkey 501.

The bottom cumulative records and IRT distributions in row "D" are from the last session of the pre-session injection phase. By the end of this phase cumulative records

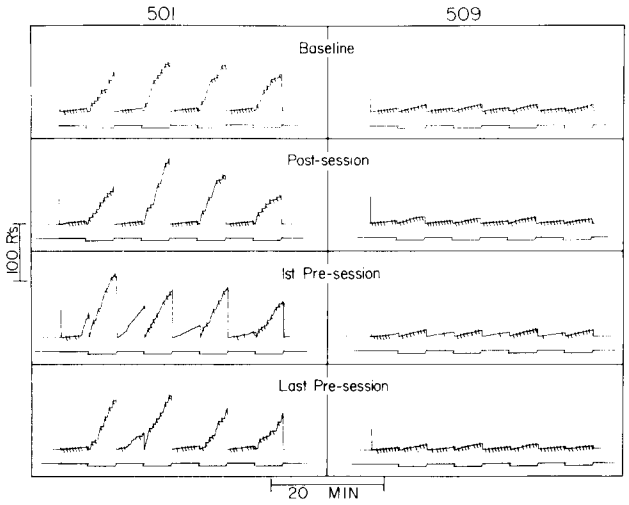


FIG. 3. Cumulative response records from selected sessions for Monkeys 501 (left) and 509 (right). Y-axes: cumulative responses. X-axes: time. Diagonal marks on the records indicate food-pellet delivery, and the response pen reset to baseline at the end of each five-min component. The event pen was deflected downward when the RI schedule was in effect. The records labeled "Baseline" are from the last session prior to initiation of daily post-session drugging. Those labeled "Post-session" are from the last (501) or second-to-last (509) session of post-session drugging. The records in the next row are from the first session of daily pre-session drugging, and those in the bottom row are from the last session of the pre-session series.

looked similar to those obtained under control conditions except that Subject 501 would occasionally respond at high rates for short periods during the IRT component. Interresponse-time distributions once again had modes in the 28–32 sec class interval.

The IRT distributions at the bottom of Fig. 4 illustrate effects of withdrawing daily pentobarbital. For both subjects the mode of the distribution shifted to the right when pre-session saline was substituted for pentobarbital. This effect disappeared in one session in Monkey 509 and in two sessions for Monkey 501. That is, after either one or two session the mode of the IRT distribution returned to the 28–32 sec category.

## DISCUSSION

The present experiments were successful in demonstrating that behavioral tolerance can be examined in individual-subject designs. Tolerance did not develop to pentobarbital's rate-increasing and reinforcement-frequency-decreasing effects during the IRT schedule when the drug was administered immediately after daily sessions, but did develop when it was administered before sessions. Thus, the tolerance observed can be considered behavioral tolerance [7]. Within-subject designs to study behavioral tolerance should be of considerable utility in providing quantitative estimates of the contribution of behavioral factors to the development of tolerance. It has been proposed, for example, that behavioral factors may simply augment the degree of tolerance that results from repeated drug administration [14]. It should be possible using variants of the procedures employed in the present experiments, simply by subtracting the amount of tolerance that results from post-test injections

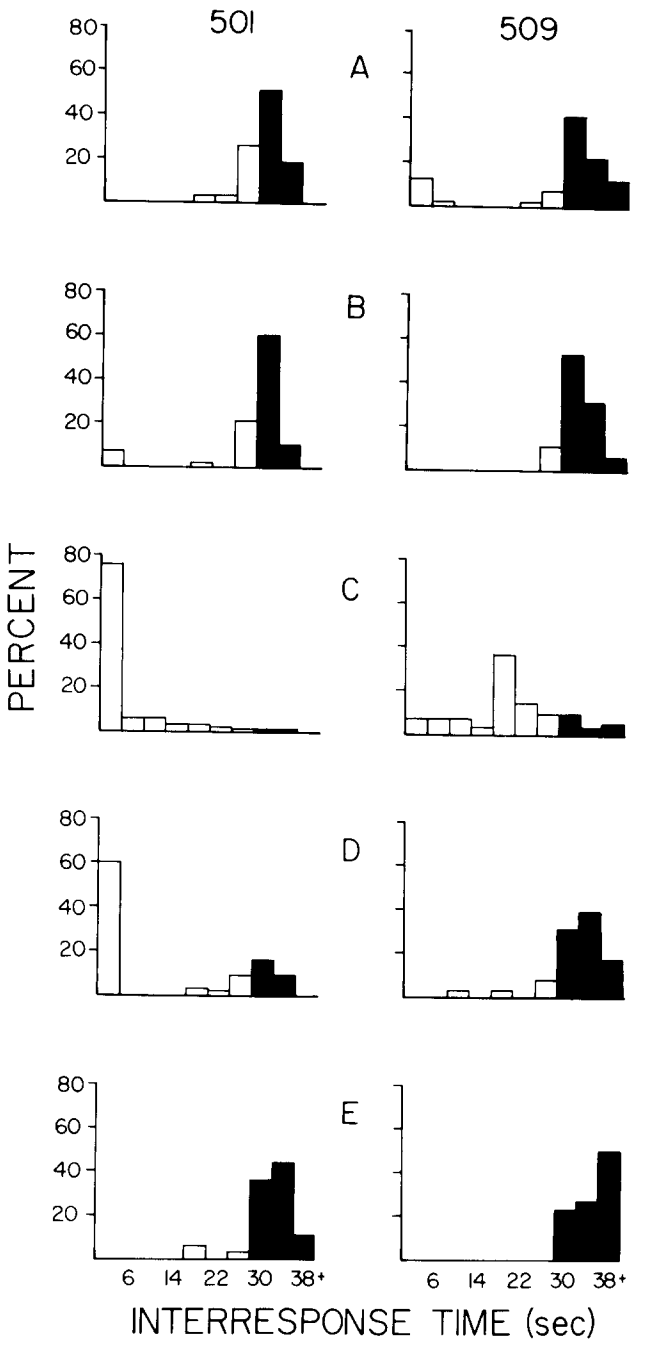


FIG. 4. Interresponse time (IRT) distributions from selected sessions. Y-axes: percentage of IRTs in a category, X-axes: IRTs in 4-sec class intervals (the last category includes all IRTs longer than 36 sec). Reinforced IRTs are shaded. Data in the left column are from Monkey 501 and those in the right from Monkey 509. Rows A-D correspond to the sessions displayed in Fig. 3, i.e., last baseline, late post-session, first pre-session and last pre-session. Row E shows data from the first session following withdrawal of daily pentobarbital.

from that observed when pre-test administrations are made, to determine precisely the contribution of behavioral factors. For example, in the present experiments it appears that virtually all the tolerance observed depended on behavioral factors since virtually no tolerance developed as a function of post-session administration.

The within-subject method should be preferable to between-groups comparisons because it allows more precise quantification of effects as they apply to individual subjects [23]. The technique, as employed here however, is not without its weaknesses. First, it is not known whether any sort of asymptotic state was reached during the phase in which post-session injections were made. It is possible that had more post-session injections been made tolerance would have developed. This problem could be overcome by determining dose-effects at various stages during post-test administrations and then beginning pre-session administrations only when such probes show that a steady state has been reached.

A second weakness is that post-test injections may change the rate at which tolerance develops once pre-test administrations begin. That is, a history of drug exposure may alter the rate at which tolerance develops once behavioral factors are allowed to play a role. If one is interested in the question of the influence of prior drugging on the rate at which behavioral tolerance develops then between-subject comparisons are necessary. If one, however, is interested mainly in the degree of tolerance that results from behavioral factors, then the present procedure is appropriate.

The present results are consistent with the "reinforcement-loss" hypothesis concerning the development of behavioral tolerance [7,22]. According to this notion, tolerance is more likely to develop if a drug's effect results in a decrease in reinforcement frequency. The present study, of course, did not provide a direct test of the hypothesis because reliable changes in response rate that were uncorrelated with changes in reinforcement frequency were not produced. Nevertheless, rate increases during the IRT schedule resulted in a decrease in the frequency of food delivery, and tolerance developed to the rate-increasing effect. Had tolerance not developed, the "reinforcement-loss" hypothesis would have been challenged. It is also interesting to note in Fig. 2 that towards the end of the pre-session drugging phase Monkey 501 exhibited response-rate increases. Rates for Monkey 509 also were slightly above non-drug control levels. These increases, however, were not associated with substantial decreases in the frequency of food presentation. (A feature of IRT>t schedules is that very short IRTs result in less of a decrease in frequency of reinforcement than do longer IRTs that are still short of the criterion length. As Fig. 4 shows, Monkey 501 either emitted very short IRTs or IRTs longer than the criterion at the end of the pre-session drugging phase). Thus, by the end of the pre-session drugging phase, tolerance to rate increases had developed in such a way that, although mean rates were not consistently at baseline levels, frequencies of reinforcement were very nearly at such levels. This finding, too, is consistent with the "reinforcement-loss" notion in that tolerance developed to rate increases only to the extent needed for baseline frequencies of reinforcement to be recaptured.

Of interest is the fact that daily post-session injections of pentobarbital produced so little effect. It is widely documented that repeated barbiturate (except barbital) administration leads to the induction of liver microsomal enzymes that accelerate the degradation of the barbiturate, and such effects are measurable after only a few daily treatments [6,21]. Two possible explanations for the present failure to find an effect are (a) the dose employed in the present study was comparatively small and, as such, may not have produced the effect, or (b) chronic administration may have produced an accelerated rate of metabolism of pentobarbital but the 40-min daily session may have been too short to allow effects to be observed. Additional study on the determinants of enzyme induction may help clarify the issue.

The present findings also are in agreement with and extend previous findings concerning effects of barbiturates on schedule-controlled responding. Others [13], using between-groups comparisons, have reported behavioral tolerance to rate-decreasing effects of phenobarbital, and the present findings show that behavioral factors can play an important role in tolerance to rate-increasing effects of pentobarbital. The rate at which tolerance developed to pentobarbital's effects once pre-session injections were begun was also comparable to reports by others who have studied effects of repeated barbiturate administration on conditioned behavior [13,25]. This comparability suggests that in the present case post-session drugging did not alter the rate at which behavioral tolerance developed.

The present findings also support previous work (e.g. [8,15]) that emphasizes the important role that schedules of consequent event delivery can play in determining a drug's behavioral effects. Under conditions of acute administration, 5.6 mg/kg pentobarbital produced large changes in behavior under the IRT schedule while having little if any affect on responding under the RI schedule. This large difference occurred in spite of the fact that overall frequencies and temporal distributions of food delivery were very similar in the two components of the schedule. Oftentimes frequency of consequences and schedule type are confounded in experiments that purport to demonstrate schedule-dependent drug effects [8,15]. In the present study this confounding was minimized and still, large schedule-dependent differences in effects were found. Thus, the precise nature in which behavior and environment interact (i.e., the contingencies of reinforcement) can determine a drug's behavioral effects.

One puzzling but noteworthy aspect of the present data is the change in pentobarbital's effects following its first administration. Initially, no dose increased response rates during either schedule component. After initial determination of the dose-effect curve, however, 5.6 mg/kg consistently and reliably resulted in large increases in rate during the IRT schedule. It seems unlikely that the initial failure was due to a general drug "novelty" effect because both subjects had previous experience with behaviorally active compounds. Perhaps exposure to the largest dosage, 10.0 mg/kg, was necessary before the lower dose would result in rate increases. Upon initial determination of dose-effects, no effect was seen until 10.0 mg/kg was given, at which time rates were decreased. Perhaps exposure to the rate-decreasing dose was a prerequisite for observing rate increases at lower doses. In any event, these results serve to emphasize the importance of determining dose-effects more than once.

To summarize, the present experiments demonstrated that behavioral tolerance developed to rate-increasing effects of pentobarbital and in so doing showed that it is feasible to study behavioral tolerance in a within-subject design. It is hoped that further development and use of such designs will increase our understanding of behavioral tolerance as it applies to individual subjects.

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## REFERENCES

1. Campbell, J. C. and L. S. Seiden. Performance influence on the development of tolerance to amphetamine. *Pharmac. Biochem. Behav.* **1:** 703–708, 1973.
2. Carder, B. and J. Olson. Learned behavioral tolerance to marijuana in rats. *Pharmac. Biochem. Behav.* **1:** 73–76, 1973.
3. Carlton, P. L. and D. L. Wolgin. Contingent tolerance to the anorexigenic effects of amphetamine. *Physiol. Behav.* **7:** 221–223, 1971.
4. Chen, C. S. A study of the alcohol-tolerance effect and an introduction of a new behavioral technique. *Psychopharmacologia* **12:** 433–440, 1968.
5. Chen, C. S. A further note on studies of acquired behavioral tolerance to alcohol. *Psychopharmacologia* **27:** 265–274, 1972.
6. Conney, A. H. Pharmacological implications of microsomal enzyme induction. *Pharmac. Rev.* **19:** 317–366, 1967.
7. Corfield-Sumner, P. K. and I. P. Stolerman. Behavioral Tolerance. In: *Contemporary Research in Behavioral Pharmacology*, edited by D. E. Blackman and D. J. Sanger. New York: Plenum Press, 1978, pp. 391–448.
8. Dews, P. B. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *J. Pharmac. exp. Ther.* **113:** 393–401, 1955.
9. Dews, P. B. Behavioral Tolerance. In: *Behavioral Tolerance: Research and Treatment Implications*, edited by N. A. Krasnegor. Washington, DC: DHEW, 1978, pp. 18–26.
10. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement*. New York: Appleton-Century-Crofts, 1957.
11. Galbicka, G., D. M. Lee and M. N. Branch. Schedule-dependent tolerance to behavioral effects of $\Delta^9$-tetrahydrocannabinol with matched reinforcement frequencies. *Pharmac. Biochem. Behav.* **12:** 85–91, 1980.
12. Hake, D. F. and N. H. Azrin. An apparatus for delivering pain shock to monkeys. *J. exp. Analysis Behav.* **6:** 297, 1963.
13. Harris, R. A. and D. Snell. Effects of acute and chronic administration of phenobarbital and *d*-amphetamine on schedule-controlled behavior. *Pharmac. Biochem. Behav.* **12:** 47–52, 1980.
14. Kalant, H., A. E. LeBlanc and R. J. Gibbins. Tolerance to, and dependence on, some non-opiate psycho-tropic drugs. *Pharmac. Rev.* **23:** 135–191, 1971.
15. Kelleher, R. T. and W. H. Morse. Determinants of the specificity of the behavioral effects of drugs. *Ergebn. Physiol.* **60:** 1–56, 1968.
16. Le Blanc, A. E., R. J. Gibbins and H. Kalant. Behavioral augmentation of tolerance to ethanol in the rat. *Psychopharmacologia* **30:** 117–122, 1973.
17. LeBlanc, A. E., H. Kalant and R. J. Gibbins. Acquisition and loss of behaviorally augmented tolerance to ethanol in the rat. *Psychopharmacologia* **48:** 153–158, 1976.
18. Murray, T. F., A. L. Craigmill and G. J. Fischer. Pharmacological and behavioral components of tolerance to LSD and mescaline in rats. *Pharmac. Biochem. Behav.* **7:** 239–244, 1977.
19. Olson, J. and B. Carder. Behavioral tolerance to marihuana as a function of amount of prior training. *Pharmac. Biochem. Behav.* **2:** 243–247, 1974.
20. Pearl, R. G. and L. S. Seiden. The existence of tolerance to and cross-tolerance between *d*-amphetamine and methylphenidate for their effects on milk consumption and on differential-reinforcement-of-low-rate performance in the rat. *J. Pharmac. exp. Ther.* **198:** 635–647, 1976.
21. Remmer, H. Drugs as activators of Drug Enzymes. In: *Metabolic Factors Controlling Duration of Drug Action*, edited by B. B. Brodie and E. G. Erdos. New York: McMillan, 1962, pp. 235–249.
22. Schuster, C. R., W. S. Dockens and J. H. Woods. Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia* **9:** 170–182, 1966.
23. Sidman, M. *Tactics of Scientific Research*. New York: Basic Books, 1960.
24. Snapper, A. G. and G. Inglis. *The SKED Software System: Time-Shared Super-SKED*. Kalamazoo, MI: State Systems Inc., 1978.
25. Tang, M. and J. L. Falk. Behavioral and Pharmacological components of Phenobarbital Tolerance. In: *Behavioral Tolerance: Research and Treatment Implications*, edited by N. A. Krasnegor. Washington, DC: DHEW, 1978, pp. 142–148.
26. Wenger, J. R., V. Berlin and S. C. Woods. Learned tolerance to the behaviorally disruptive effects of ethanol. *Behav. Neural. Biol.* **28:** 418–430, 1980.
27. Wenger, J. R., T. M. Tiffany, C. Bombardier, K. Nicholls and S. C. Woods. Ethanol tolerance in the rat is learned. *Science* **213:** 575–576, 1981.
28. Woolverton, W. L., D. A. Kandel and C. R. Schuster. Tolerance and cross-tolerance to cocaine and *d*-amphetamine. *J. Pharmac. exp. Ther.* **205:** 525–535, 1978.
29. Woolverton, W. L., D. A. Kandel and C. R. Schuster. Effects of repeated administration of cocaine on schedule-controlled behavior. *Pharmac. Biochem. Behav.* **9:** 327–337, 1978.