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Effects of Drugs on the Temporal Distribution of Schedule-Induced Polydipsia in Rats

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PELLON, R. AND D. E. BLACKMAN. *Effects of drugs on the temporal distribution of schedule-induced polydipsia in rats.* PHARMACOL BIOCHEM BEHAV 43(3) 689–695, 1992.—Drinking was induced in food-deprived rats by a fixed-time 1-min schedule of food presentation. With three rats, *d*-amphetamine (0.25, 0.5, 1.0, and 2.0 mg/kg) led to a dose-related increase in licking early in the interfood intervals, the peak of the temporal distribution of licking being shifted to earlier values. These effects were seen even when *d*-amphetamine had no effect on overall rates of licking and drinking. With another three rats, however, diazepam (0.5, 1.0, 2.0, and 4.0 mg/kg) did not shift the peak of the temporal distribution of licks in interfood intervals, even at doses that produced small increases in overall rates of licking and drinking. However, diazepam did reduce the peak of the distributions of licks at doses that did not decrease water intake and licks per minute.

Schedule-induced behavior Drinking *d*-Amphetamine Diazepam Rats

IF food-deprived rats are exposed to procedures in which food is delivered intermittently, they will drink large amounts of water if given the opportunity to do so, a behavioral phenomenon termed schedule-induced polydipsia (4,5). It has been suggested (6) that schedule-induced polydipsia is an example of a more general class of behavior, adjunctive behavior, functionally different from emitted operant and elicited respondent behavior. Schedule-induced polydipsia has also been interpreted (21) as an example of a class of behavior termed interim behavior that differs from other classes of behavior, facultative and terminal, on the basis of the relationships of these classes of behavior to reinforcement and by reason of their temporal distributions in interreinforcement intervals. Despite extensive theoretical debate, the nature of schedule-induced drinking remains uncertain, but the behavior itself stands as a robust phenomenon in situations of intermittent food delivery (23).

A review of experimental studies of the effects of drugs on schedule-induced behavior (15) suggested that "behavioral pharmacologists . . . have much to gain by focusing more of their attention on these often overlooked but potentially important effects of intermittent reinforcement" (p. 280). Drugs exert orderly effects on schedule-induced behavior, but these effects may differ from those shown with schedule-dependent operant behavior. For example, it has often been shown that stimulants such as amphetamines either have no effect on or decrease schedule-induced drinking at small or moderate doses that simultaneously increase operant behavior maintained by the same schedule (3,20,22,24,25). The effects of anxiolytics have also been investigated with schedule-induced drinking. For example, increases in this behavior have been found after doses of the benzodiazepine chlordiazepoxide (1). It has also been reported (14) that small or moderate doses of ripazepam and diazepam increased some measures of schedule-induced drinking, although other investigators (9) have found that similar doses of diazepam reduced schedule-induced drinking.

As a supplement to a study of the effects of drugs on schedule-induced polydipsia in punished and nonpunished conditions (11), the present study investigated the effects of *d*-amphetamine and diazepam on the distribution of schedule-induced licking in the interfood intervals of a fixed-time (FT) schedule. It has been reported (8,24) that doses of amphetamine increased the probability of licks in the early parts of interfood intervals. However, both these experiments also investigated the effects of the drug on concurrent operant behavior controlled by the schedule of reinforcement, and this operant behavior was also affected by the drug. In the FT schedule used in the present experiment, there was no response requirement for the delivery of food. It has been reported, however, that some doses of diazepam that reduced overall

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water intake did not shift the within-interval distribution of schedule-induced licking, although the peak of the distribution was less marked (9).

METHOD

Subjects and Apparatus

Six male Sprague-Dawley rats served as subjects. They were experimentally naive and approximately 150 days old at the start of the experiment, with a mean body weight of 365 g (range: 340–383 g). Rats were housed individually in an environmentally controlled room (20°C temperature and 8:00 a.m./8:00 p.m. light/dark cycle). Before training, rats were gradually reduced to 85% of their free-feeding weights by controlled feeding. Each rat was then maintained at that weight: It was weighed before its daily experimental session, and at least 15 min after the session it was given an appropriate supplement to the food it had obtained in the experiment. Water was always continuously available in the home cages.

The experimental test chambers were three identical Campden Instruments (London, England) C140 rodent test chambers, 24.5 × 23.5 × 20 cm. Each chamber was mounted inside a ventilated sound-attenuating chest, with a small observation window in one wall. No operant levers were mounted in the test chambers in this experiment. A calibrated water bottle was clipped on the outside of the acrylic wall of the chamber, with its spout accessible to the rat through a hole 1 cm in diameter situated 18 cm from the front wall and 8 cm above the grid floor. The spout was positioned 0.5 cm behind the hole so that the rat could lick it but could not maintain permanent contact with it. Licks at the spout were sensed by a modified contact relay and associated pulse former, one side of the relay being connected to the spout and the other to all 16 parallel stainless steel bars of the grid floor. A 10-W houselight illuminated the test chamber during each experimental session. The ambient noise produced by the ventilation fan was 68–70 dB, which served as masking noise. A Campden Instruments pellet dispenser delivered 45-mg pellets of standard rat food (P. J. Noyes Co., Lancaster, NH). The scheduling and recording of experimental events was achieved by means of a microcomputer located in an adjacent room.

Procedure

When each rat had stabilized at 85% of its free-feeding weight, a water ingestion test was given on two successive days. Sixty 45-mg food pellets were placed together in a dish in the home cages and the amount of water consumed by each rat in 60 min was measured. This measure provided a baseline against which to assess the degree of any schedule-induced drinking subsequently observed in the experiment, in which 60 food pellets were delivered individually over a period of 60 min. On the next day, rats were adapted to the test chambers for 1 h.

After this pretraining, the experiment proper began. The water bottles were now filled with 100 ml fresh tapwater and installed immediately before each daily experimental session. Each session began with illumination of the houselight and delivery of one 45-mg pellet of food to the receptacle. Single pellets were then delivered at regular intervals of 1 min (FT 1 min) independently of the rat's behavior. Each session ended 1 min after the 60th pellet delivery, that is, 60 min after the start of the session. The following measures were recorded for each rat each session: a) the amount of water (ml) removed from the bottle; b) the total number of licks per session, which allowed the mean number of licks per interfood interval to be calculated; c) the number of licks in successive 5-s segments of the interfood intervals, which were summed to give a distribution of licks in each segment across each session.

After 45 sessions, when inspection of the data revealed no systematic within-subject variation rats were allocated to two groups that were approximately matched with respect to overall measures of drinking. Rats in the first group (now numbered 11–13) were exposed to administrations of *d*-amphetamine at doses of 0.25, 0.5, 1.0, and 2.0 mg/kg. The salt was dissolved in a 0.9% saline solution and administered in the form of a 1-ml IP injection 20 min before an experimental session. Rats in the second group (21–23) were exposed to administrations of diazepam. The drug was dissolved in a 0.9% saline solution together with two drops of Tween-80 and administered as a 1-ml IP injection at doses of 0.5, 1.0, 2.0, and 4.0 mg/kg. Injections of diazepam were given 20 min before an experimental session. The order of the doses of both drugs was randomized and differed between animals. A further two randomized sequences were then given, thus providing three determinations of the effects of each dose with each rat. Successive drug administrations were separated by four nondrug sessions, before each of which a 1-ml saline injection was given. The saline sessions immediately preceding each drug session were taken as the saline control condition in this experiment. Testing of the drugs required 60 experimental sessions.

RESULTS

In the home cage ingestion tests, the mean water intake obtained from the six rats per 60-min session was 4.1 ml (range 3.5–4.5 ml). The saline control data shown in Fig. 1 show that the mean water intake per experimental session ranged from 15–27 ml (overall mean: 21 ml). All six rats therefore showed the high levels of drinking in the experiment that are the defining characteristic of schedule-induced polydipsia.

The effects of *d*-amphetamine and diazepam on schedule-induced drinking and overall licking are shown in Fig. 1. The data points for each dose represent the mean of three administrations of that dose. The control data (C) are the means and standard deviations of the 12 saline sessions immediately preceding the sessions in which a drug dosage was given. These overall data have been reported previously (11) in a different format and are presented in this manner here to provide an overall background against which the effects of the drugs on the temporal distribution of licking may be evaluated.

With rats 11–13, there is little evidence of consistent or marked effects on the amount of water consumed or on the overall number of licks per interval following administration of low doses of *d*-amphetamine. The larger doses of the drug, however, led to clear decreases in the amount of water consumed and number of licks with two of the three rats (11 and 12). With rats 21–23, there was a dose-related effect of diazepam on drinking: Low doses produced small but reliable increases, an effect that decreased with larger doses and gave way to a decrease in drinking with rat 23 at the 4.0-mg/kg dose. The effects of diazepam on licks per interval tended to be similar to, but less marked than, its effects on drinking.

Figure 2 shows for rats 11–13 the mean number of licks in successive 5-s segments of the interfood intervals after saline and after doses of *d*-amphetamine (these data were obtained

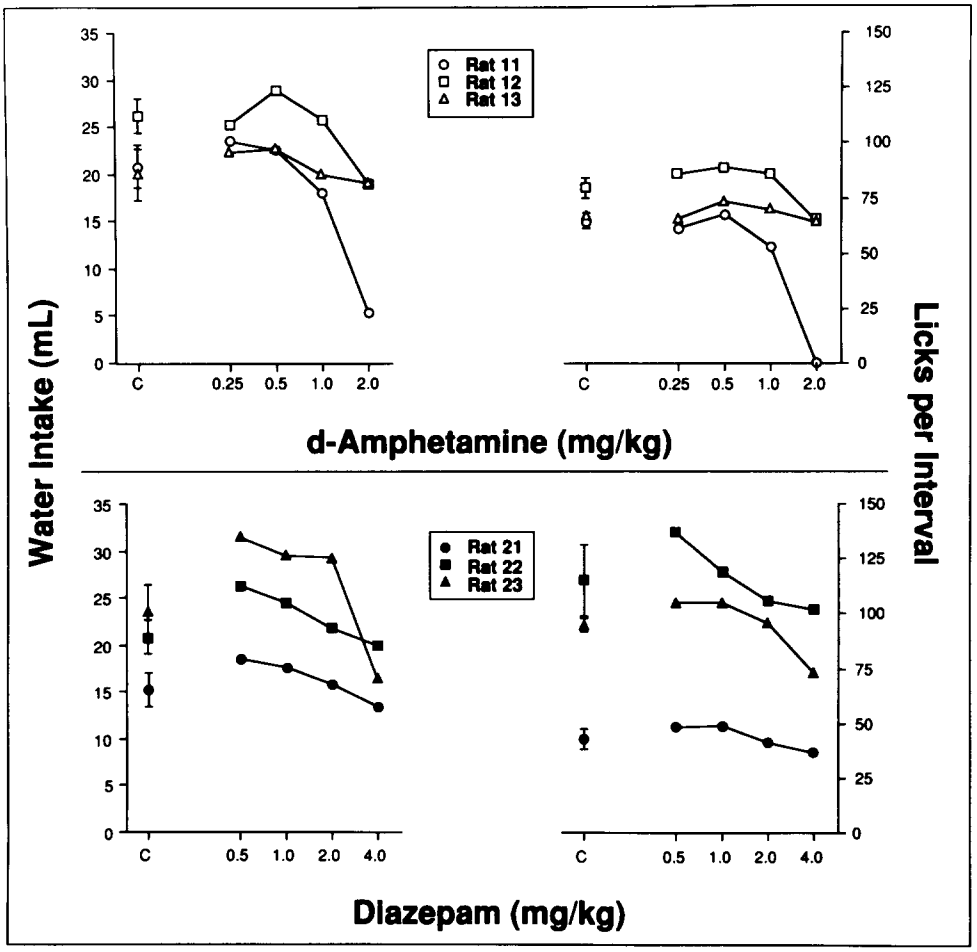

FIG. 1. Effects of *d*-amphetamine and diazepam on schedule-induced polydipsia. Control data (C) are the means and standard deviations of the 12 saline sessions that immediately preceded the drug sessions. Drug data are the means of three administrations of each dose. Left panels: mean water intake (ml); right panels: mean licks per interfood interval. These data have been presented previously in a different format [(11), Figs. 1 and 2, nonpunished condition].

from the same sessions as were the drinking and overall licking data shown in Fig. 1). After saline, the distributions showed a peak in the first half of the interval with rats 11 and 12, but rather later in the case of rat 13. *d*-Amphetamine produced dose-related effects, shown (except in the case of rat 11 with the 2.0-mg/kg dose, which almost abolished licking) as increases in the number of licks in the early parts of the interfood intervals and a shift in the peaks of the distributions to the left (earlier in the intervals). These effects were detectable with doses that had little or no effect on overall numbers of licks per interval (e.g., after doses of 0.25, 0.5, and 1.0 mg/kg with rat 11, after doses of 0.25 and 1.0 mg/kg with rat 12, and after all doses of the drug with rat 13).

Figure 3 shows the effects of diazepam on the number of licks in successive 5-s segments of the interfood intervals. The distributions of licks showed a distinct peak in saline conditions, but although with some doses of diazepam these peaks became less marked (2.0 and 4.0 mg/kg with rats 21 and 22 and 4.0 mg/kg with rat 23) the drug did not shift the peaks or substantially change the number of licks before or after the peaks, except in the case of rat 23 at the 2.0- and 4.0-mg/kg doses.

DISCUSSION

All rats developed schedule-induced drinking and licking in the present experiment. The mean water intake in the saline condition of the experiment was five times greater than that in the home cage ingestion tests, and the drinking and licking of each rat was comparable with that reported from an identical experimental procedure (10). In the case of four rats (rats 12,13,22, and 24), the distributions of licks in interfood intervals were characteristic of schedule-induced polydipsia in that most licks occurred relatively early in the intervals. However, with rats 13 and 22 the licking in saline conditions occurred predominantly in the second half of the interfood intervals, a less typical effect that has nevertheless been reported before (18).

Low doses of *d*-amphetamine had no reliable effect on overall measures of schedule-induced behavior, while the

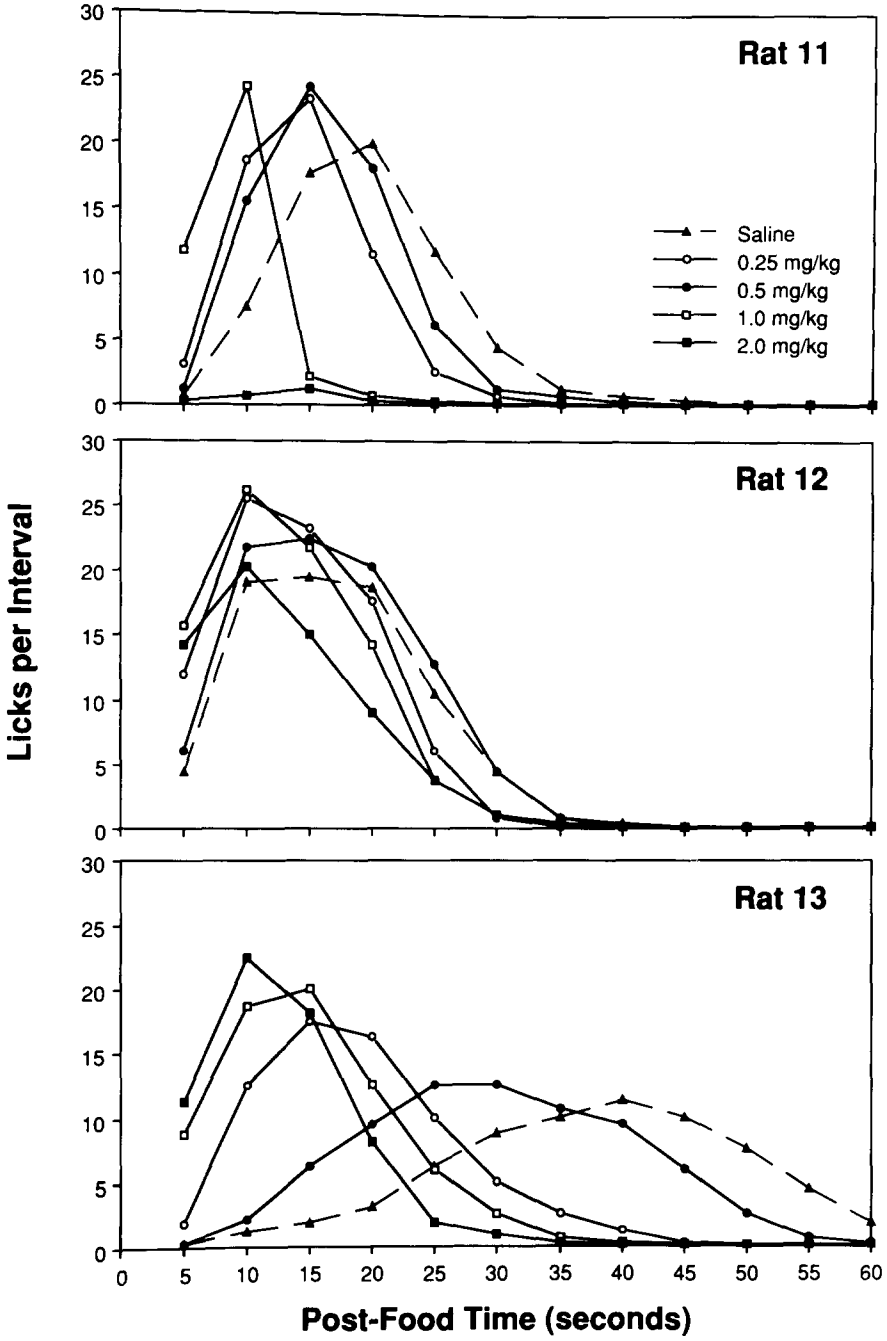

FIG. 2. Effects of *d*-amphetamine on the distribution of licks in successive 5-s segments of the interfood intervals. Each drug data point is the mean for each rat of 3 administrations of each dose of the drug and each saline data point is the mean of 12 saline injections.

highest dose decreased both drinking and licks per interval. These findings are consistent with earlier reports (3,5,8, 13,16,17,19,20,22,24,25).

d-Amphetamine produced dose-related changes in the distribution of licking within interfood intervals in the present study. It has been reported previously (8) that doses of 0.3 and 1.0 mg/kg methamphetamine increased the number of licks in the early parts of interreinforcement intervals, and it has also been found (24) that doses of 0.3 and 1.0 mg/kg *dl*-amphetamine increased the probability of licks in the early parts of interfood intervals while decreasing the probability of licks in the later parts. In the present experiment, effects were detected with doses of *d*-amphetamine that had little or no effect on the overall number of licks, a finding also reported in both studies cited above (8,24). However, both these earlier experiments also investigated the effects of the drug on

concurrent operant behavior that was also controlled by the schedule of reinforcement, and this operant behavior was also affected by the drug. The present experiment used an FT schedule in which there was no response requirement for the delivery of food, and thus potentially confounding effects of the drug on the distribution of licks were reduced. Similar effects of *d*-amphetamine have also been reported with an FT (and also with a fixed-interval) schedule (13), with dose-dependent decreases in the index of curvature as the measure of the temporal distribution of licking.

The present experiment was similar to a previous study (8) in that it measured changes in the number of licks in successive segments of interfood intervals, while other investigators (24) measured their effects in terms of changing probabilities of responding. The dose-related effects seen in the present study were more differentiated than those reported in the study that

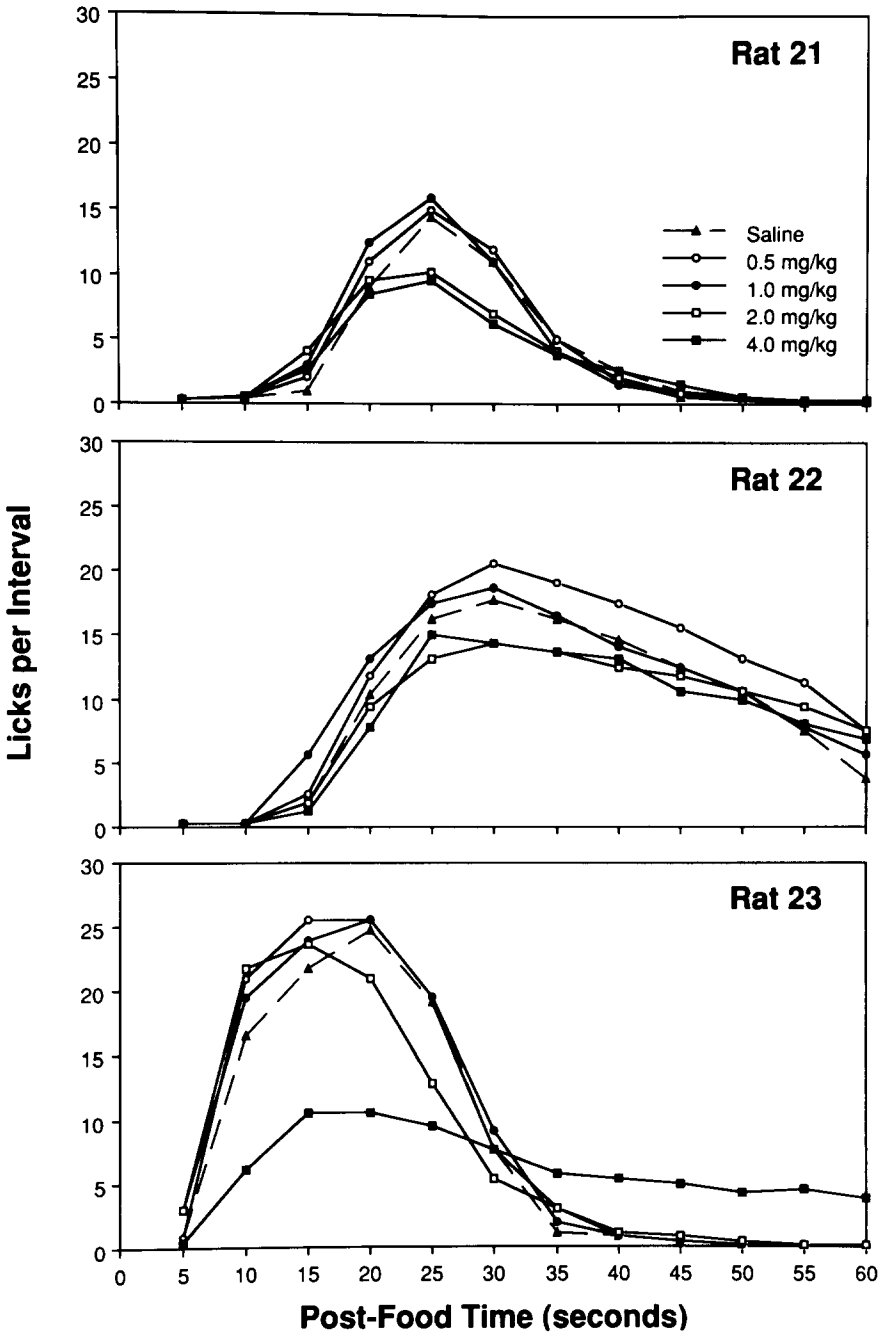

FIG. 3. Effects of diazepam on the distribution of licks in successive 5-s segments of the interfood intervals. Each drug data point is the mean for each rat of 3 administrations of each dose of the drug and each saline data point is the mean of 12 saline injections.

used the same type of measure (8), probably because the successive segments of interfood intervals were 5 s rather than 18 s as was used in the earlier study. Other experimenters (12) have found that *d*-amphetamine produced dose-related decreases in schedule-induced licking during the early parts of the interreinforcement intervals of a fixed-interval 60-s schedule, an apparently anomolous result that may also reflect the use of relatively long successive segments (10 s).

Using fixed-interval schedules of reinforcement in which delivery of food was dependent upon the emission of operant behavior, it has been found (2,7) that amphetamine produces similar changes in the distribution of operant lever-presses which the fixed interreinforcer intervals as those seen with schedule-induced behavior in the present study.

Small doses of diazepam increased schedule-induced drinking and licking. These effects are similar to those reported previously with diazepam and with another benzodiazepine, ripazepam (14). In the earlier experiment, as in the present study, the effects of the drugs were seen principally in the form of increases in water intake after low doses. In a study that used squirrel monkeys as subjects, increases in the schedule-induced consumption of water (and of a 3% alcohol solution) were found after low doses of the benzodiazepine chlordiazepoxide (1). However, there have also been reports of reductions in drinking and licking after high doses of chlordiazepoxide (8,20) and also after diazepam (9), and none of these studies reported any increases in schedule-induced drinking or licking after low doses of the drug.

In the present study, diazepam did not change the distribution of licking in the interfood intervals except after 2.0- and 4.0-mg/kg doses with rat 23. Similar findings have been reported previously with diazepam (9). With chlordiazepoxide also, no effect of the drug on the distribution of schedule-induced licking within interreinforcement intervals has been reported (8). However, it has been reported (9) that doses of 3.0 and 5.0 mg/kg diazepam reduced overall water intake and also the peak of the distribution of licking within interfood intervals. The present results confirm that high doses of diazepam reduce the peak of the distributions, but these effects were not as large as those reported earlier (9) and were not necessarily accompanied in the present study by reductions in overall water intake (see rats 21 and 22 at the 2.0-mg/kg dose). The present results therefore suggest that diazepam may have distinctive effects in reducing the temporal regulation of licking in interfood intervals without producing systematic shifts in the temporal distribution of licking. More direct comparisons of the effects of the two benzodiazepine drugs—diazepam and chlordiazepoxide—may therefore be warranted.

The present results extend our knowledge of the effects of drugs on schedule-induced behavior. They confirm, but with a procedure that eliminates possible contaminating effects of drug-produced changes in concurrent operant behavior, that *d*-amphetamine may exert an effect on the temporal distribution of schedule-induced polydipsia in interfood intervals even at doses that do not affect overall drinking and licking. The distributions of licking were not shifted by diazepam in this study, however, even at doses that exerted an effect on overall licking and drinking. These findings are important in light of the theoretical emphasis on the temporal characteristics of schedule-induced behavior in comparison with those of schedule-dependent operant behavior.

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REFERENCES

1. Barrett, J. E.; Weinberg, E. S. Effects of chlordiazepoxide on schedule-induced water and alcohol consumption in the squirrel monkey. Psychopharmacologia 5:635–640; 1975.
2. Branch, M. N.; Gollub, L. R. A detailed analysis of the effects of *d*-amphetamine on behavior under fixed-interval schedules. J. Exp. Anal. Behav. 21:519–539; 1974.
3. Byrd, L. Effects of *d*-amphetamine on schedule-controlled key-pressing and drinking in the chimpanzee. J. Pharmacol. Exp. Ther. 185:633–641; 1973.
4. Falk, J. L. Production of polydipsia in normal rats by an intermittent food schedule. Science 133:195–196; 1961.
5. Falk, J. L. Studies on schedule-induced polydipsia. In: Wagner, M. J., ed. Thirst: First International Symposium on Thirst in the Regulation of Body Water. New York: Pergamon Press; 1964:95–113.
6. Falk, J. L. The nature and determinants of adjunctive behavior. Physiol. Behav. 6:577–588; 1971.
7. McAuley, F.; Leslie, J. C. Molecular analyses of the effects of *d*-amphetamine on fixed-interval schedule performances in rats. J. Exp. Anal. Behav. 45:207–219; 1986.
8. McKearney, J. W. Effects of methamphetamine and chlordiazepoxide on schedule controlled and adjunctive licking in the rat. Psychopharmacologia 30:375–384; 1973.
9. Mittelman, G.; Jones, G. H.; Robbins, T. W. Effects of diazepam, FG 7142, and RO 15-1788 on schedule-induced polydipsia and the temporal control of behavior. Psychopharmacology (Berl.) 94:103–109; 1988.
10. Pellon, R.; Blackman, D. E. Punishment of schedule-induced drinking in rats by signaled and unsignaled delays in food presentation. J. Exp. Anal. Behav. 48:417–434; 1987.
11. Pellon, R.; Mas, B.; Blackman, D. E. Effects of *d*-amphetamine and of diazepam on non-punished and punished schedule-induced drinking in rats. Behav. Pharmacol. 3:75–81; 1992.
12. Robbins, T. W.; Roberts, D. C. S.; Koob, G. F. Effects of *d*-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxydopamine-induced lesions of the nucleus accumbens. J. Pharmacol. Exp. Ther. 224: 662–673; 1983.
13. Sanger, D. J. The effects of *d*-amphetamine and scopolamine on drinking induced by a multiple schedule. Psychopharmacology (Berl.) 58:311–315; 1978.
14. Sanger, D. J.; Blackman, D. E. Effects of diazepam and ripazepam on two measures of adjunctive drinking in rats. Pharmacol. Biochem. Behav. 5:139–142; 1976.
15. Sanger, D. J.; Blackman, D. E., eds. The effects of drugs on adjunctive behavior. In: Contemporary research in behavioral pharmacology. New York: Plenum Press; 1978:239–286.
16. Segal, E. F.; Deadwyler, S. A. Amphetamine differentially affects spaced bar pressing and collateral water drinking. Psychonom. Sci. 1:349–350; 1964.
17. Segal, E. F.; Oden, D. L. Concurrent facilitation of food-reinforced, spaced licking and depression of schedule-induced polydipsia drinking by amphetamine. Psychonom. Sci. 10:155–156; 1968.
18. Segal, E. F.; Oden, D. L.; Deadwyler, S. A. Determinants of polydipsia: IV. Free reinforcement schedules. Psychonom. Sci. 3: 11–12; 1965.
19. Segal, E. F.; Oden, D. L.; Deadwyler, S. A. Determinants of polydipsia: V. Effect of amphetamine and pentobarbital. Psychonom. Sci. 3:33–34; 1965.

20. Smith, J. B.; Clark, F. C. Effects of *d*-amphetamine, chlorpromazine, and chlordiazepoxide on intercurrent behavior during spaced responding schedules. J. Exp. Anal. Behav. 24:241–248; 1975.
21. Staddon, J. E. R. Schedule induced behavior. In: Honig, W. K.; Staddon, J. E. R., eds. Handbook of operant behavior. Englewood Cliffs, NJ: Prentice Hall; 1977:125–192.
22. Wayner, M. J.; Greenberg, I.; Trowbridge, J. Effects of *d*-amphetamine on schedule-induced polydipsia. Pharmacol. Biochem. Behav. 1:109–111; 1973.
23. Wetherington, C. L. Is adjunctive behavior a third class of behavior? Neurosci. Biobehav. Rev. 6:329–350; 1982.
24. Williams, J. L.; White, J. M. G. The effects of amphetamine and scopolamine on adjunctive drinking and wheel-running in rats. Psychopharmacology (Berl.) 82:360–367; 1984.
25. Wuttke, W.; Innis, N. K. Drug effects upon behavior induced by second-order schedules of reinforcement: The relevance of ethological analyses. In: Gilbert, R. M.; Keehn, J. D. eds. Schedule effects: Drugs, drinking and aggression. Toronto: University of Toronto Press; 1972:129–147.