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# Effects of *d*-Amphetamine on Temporal Distributions of Schedule-Induced Polydipsia

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FLORES, P. AND R. PELLON. *Effects of* d-*amphetamine on temporal distributions of schedule-induced polydipsia.* PHARMACOL BIOCHEM BEHAV **57**(1/2) 81–87, 1997.—Food-deprived rats were divided into four groups according to the equal interval and time durations of a multiple fixed-interval, fixed-time schedule (15, 30, 60, and 120 s). Fixed-time components were signaled by a tone and lever withdrawal. *d*-Amphetamine (0.25–4.0 mg/kg) produced similar dose-dependent reductions in the drinking and licking induced by fixed-interval and fixed-time schedules. These dose-dependent decrements were a function of the interfood interval length. More licks occurred early in the interfood intervals with doses of *d*-amphetamine. Dose-dependent shifts to the left were observed in the distribution of licking, and there were dose-dependent decreases in the quarter-life, which were a function of fixed-interval and fixed-time lengths. The maximum lick rate within interfood intervals occurred at about the same absolute time in schedules up to 60 s; therefore, the effects of *d*-amphetamine were not mediated by its effects on temporal discrimination. © 1997 Elsevier Science Inc.

Schedule-induced behavior Drinking Temporal distribution *d*-Amphetamine Rats

WHEN food-deprived rats are exposed to procedures in which food is delivered intermittently, they drink large amounts of water if given the opportunity (3). It has been suggested that this schedule-induced polydipsia is an example of a more general class of behavior, adjunctive behavior, different from emitted operant and elicited respondent behavior (5). Schedule-induced polydipsia has also been termed interim behavior, distinguishable from facultative and terminal behaviors on the basis of their relationship to reinforcement (22). The view that adjunctive behavior such as schedule-induced polydipsia represents a distinct functional class of behavior remains equivocal, however (23).

The effects of stimulants such as amphetamines on schedule-induced polydipsia may differ from those shown with schedule-dependent operant behavior. For example, it has been shown that amphetamines either have no effect on or decrease schedule-induced polydipsia at small or moderate doses which simultaneously increase operant behavior maintained by the same schedule (1,20,21,25). However, the effects of amphetamines on adjunctive and operant patterns of behavior can be accounted for by the same basic principle of rate dependency (7). Thus, it may not be necessary to conclude that the drug has fundamentally different effects on schedule-induced and operant behavior or that the apparent differences force the view that schedule-induced polydipsia is a member of a functionally different class of behavior.

Similar effects of amphetamines have been reported on the patterning of schedule-induced polydipsia and schedule-controlled operant behavior within interfood intervals (15,20,25). The drug shifted to the left the distributions of adjunctive licking and operant behavior, increasing the probability that both behaviors would occur in earlier parts of the interfood intervals. This occurred despite the different temporal distributions of schedule-induced and operant behavior in interfood intervals. The higher rates of schedule-induced polydipsia are normally located just after food presentation, whereas operant lever pressing occurs predominantly before food reinforcement. *d*-Amphetamine produces similar displacements in the temporal distribution of schedule-induced polydipsia when no operant response is required for the delivery of food (18,20).

As a supplement to a study of the effects of *d*-amphetamine on different overall rates of schedule-induced polydipsia and schedule-controlled lever pressing (7), the present study investigated the effects of *d*-amphetamine on the distribution of schedule-induced licking in the equal interfood intervals of

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various multiple fixed-interval (FI), fixed-time (FT) schedules of food presentation which varied in their reinforcement frequency. FT components, in which operant responding did not occur, were used to evaluate the potential influence of operant behavior or its modification by *d*-amphetamine on schedule-induced polydipsia. It has been reported that the increases in operant behavior after some doses of *d*-amphetamine resulted from an increase in the rate of responding earlier in the interfood interval (25). This change in operant behavior may reduce the proportion of the interfood interval in which schedule-induced polydipsia normally occurs, and therefore could account in part for the displacement of schedule-induced polydipsia within interfood intervals. Similar effects of *d*-amphetamine on FI and FT 1-min schedules have been reported (20), but these effects remain to be investigated with shorter and longer interfood intervals.

## METHOD

### *Subjects and Apparatus*

Sixteen male Wistar rats served as subjects. They were experimentally naive and approximately 90 days old at the start of the experiment, with a mean body weight of 420 g (range 368–486). Rats were housed individually in an environmentally controlled room (22°C temperature, 60% relative humidity, and 0800 L:2000 D cycle). Before training, rats were gradually reduced to 80% 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 not $<$ 15 min after the session it was given an appropiate supplement to the food it had obtained in the experiment. Water was continuously available in the home cages.

The experiment was conducted in four identical Letica Instruments (Barcelona, Spain) LI-836 test chambers, 29 $\times$ 24.7 $\times$ 35.5 cm. Each chamber was contained inside a ventilated sound-attenuating chest. The left operant lever was present in the test chambers during FI components, but at all other times it was withdrawn. Each retractable lever required a force of approximately 15 g for switch closure and was located 4.8 cm to the right of the food receptacle and 4.7 cm from the grid floor. A calibrated water bottle was mounted on the outside of the right wall of the chambers, with its spout accesible to the rat through a hole 3.2 $\times$ 3.9 cm situated 20 cm from the front wall and 7 cm above the grid floor. The spout was positioned 2 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 photocell beam situated in the hole 1–2 mm from the spout. Two 3-W lights illuminated the test chambers during each experimental session. The ambient noise produced by the ventilation fan was 60 dB, which served as masking noise. A Letica Instruments pellet dispenser delivered 45-mg pellets of standard rat food (Bio-Serv Inc., Frenchtown, NJ). The scheduling and recording of experimental events was achieved by means of a BBC microcomputer programmed in SPIDER (Acorn Computers Ltd., Cambridge, U.K.).

### *Procedure*

The subjects were randomly distributed into four groups ($n$ = 4/group), according to the equal interfood interval durations of a multiple FI, FT schedule. The values of the FI and FT schedules were 15, 30, 60, and 120 s for the different groups.

When each rat had stabilized at 80% of its free-feeding weight, a water-ingestion test was given on 2 successive days. Then 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. The number of food pellets was different for each group: 240 for the 15-s group, 120 for the 30-s group, 60 for the 60-s group, and 30 for the 120-s group. This measure provided a baseline against which to assess the degree of any schedule-induced polydipsia subsequently observed in the experiment, in which each animal received individually over a period of 60 min a number of food pellets identical to that given during the water-ingestion test (17).

On the next day the rats were adapted to the test chambers for 60 min and allowed to eat 20 food pellets that had previously been placed in the food receptacles. The subjects were subsequently trained to press the lever to obtain food reinforcers according to a fixed-ratio 1 (FR 1) schedule in which each bar-press was followed by one food pellet. Each subject could obtain 60 food pellets in a maximum 60-min session. The schedule of reinforcement was then changed to FI during 60-min sessions, in which a single 45-mg food pellet was scheduled to be delivered after the first response made after a specified period of time had elapsed since the delivery of the previous reinforcer. All subjects were first exposed to a FI 15-s schedule for one session. The FI schedule was extended to 30 s for another session for all animals except the 15-s group. FI values were progressively increased on subsequent sessions to FI 60 s and FI 120 s, with one group of subjects being held in succession to each of these values.

After this pretraining, the experiment proper began. The water bottles were filled with 100 ml of fresh tapwater and installed immediately before each experimental session. FI and FT components alternated in a multiple schedule. During the FT components a single pellet of food was delivered at regular intervals independently of the rat's behavior; these components were signaled by the presentation of a tone (70 dB, 40 Hz) and by lever withdrawal. Each session began with the illumination of both 3-W lights, and there was an equal probability that a session would start with the FI or the FT component. Component durations were 5 min for the groups of 15-, 30-, or 60-s schedule duration, and 10 min for the 120-s group. Each session ended 60 min after the start of the session. The following measures were recorded for each rat during each session: (a) the amount of water (ml) removed from the bottle; (b) the total number of licks during FI and FT components, which allowed the calculation of the number of licks per minute; (c) the number of licks in successive 2-s segments of the interfood intervals, which were summed to give a distribution of total licks and licks per minute in each segment across FI and FT components; and (d) the total number of lever presses.

After 28 sessions, when inspection of the data revealed no systematic within-subject variation, rats were exposed to administrations of *d*-amphetamine sulphate at doses of 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg. The salt was dissolved in a 0.9% saline solution and administered in the form of a 1-ml IP injection 10 min before an experimental session. Drug doses were given in a random order. A further randomized sequence was then given, thus providing two determinations of the effects of each dose with each rat. Successive drug administrations were separated by three nondrug sessions, 10 min before each of which a 1-ml, IP, saline injection was given. The saline sessions immediately preceding each drug session were taken as the saline control condition. Testing of the drug required 40 experimental sessions. The measures described above were still recorded, but in addition the 2-s segment of the interfood

intervals containing the maximum licks per minute across FI and FT components was also recorded for each rat each session. These data were transformed for each rat to the percentage of the interfood interval which had elapsed at the time of the peak in the rate of licking, except when very low rates of licking were recorded. This occurred after the administration of *d*-amphetamine at doses of 4.0 mg/kg in all groups and of 2.0 mg/kg in the 120-s group, in two rats of the 30-s group, and in one rat under the FI 60-s schedule (because of the small number of subjects left, the dose of 2.0 mg/kg was statistically analyzed only in the FI 15-, FT 15-, and FT 60-s conditions).

### *Statistical Analyses*

Within-group comparisons of the water consumed between saline injections and the home-cage test were performed by paired *t*-tests. The effects of *d*-amphetamine on water consumption and lick rates were analysed by a repeated-measures analysis of variance (ANOVA) (24), with drug dose as a within-subject factor. Posthoc comparisons between *d*-amphetamine doses and the saline control sessions were calculated by Dunnett's *t*-test. The effects of FI and FT length on the percentage of the elapsed interfood interval at the time of the maximum lick rate were also submitted to an ANOVA, with group as a between-subject factor comprising four levels. Between-group comparisons were performed by Newman–Keuls' test. All these analyses were computed by the SPSS statistical package (Cary, NC). The significance level was set at a minimum $p < 0.05$ (two-tailed) for all comparisons.

A linear regression technique was used to calculate the dose of *d*-amphetamine that decreased to 50% ($ED_{50}$) the quarter-life of control sessions, measured as a percentage of change over control values for each rat in FI and FT components. This was done by means of standard parallel line bioassay techniques (6). The quarter-life measure (11) quantifies the percentage of the interfood interval which had elapsed when 25% of the responses had been emitted (10), and this was used to calculate the degree of temporal patterning of licking within the FI and FT schedules. The number of licks in each consecutive 2-s segment were summed until the cumulative total equalled one quarter of the total licks produced in the interval. The number of such segments was divided by the total number of 2-s segments in each interfood interval to calculate the quarter-life. A lower value of the quarter-life indicates that more licking occurred early in the interval. Quarter-life values are unreliable when response rates are very low, and therefore were not calculated at the highest dose of *d*-amphetamine in all groups, at the dose of 2.0 mg/kg in the 120-s group, and with the rats which showed a very small rate of licking in FI 30-, FT 30-, and FI 60-s schedules after being given the 2.0-mg/kg dose (see above).

## RESULTS

Figure 1 shows the effects of *d*-amphetamine on overall water consumption and licks per minute during FI and FT components for all groups of the experiment. Each panel in Fig. 1 represents a multiple FI/FT schedule with the duration at the top right of each panel.

Exposure to multiple FI FT 15-, 30-, 60-, and 120-s schedules resulted in an overall water intake higher than in the home-cage ingestion test, as can be seen by the water consumed during saline sessions. This difference reached statistical significance in the first three groups: [$t(3) = 3.37$, $p < 0.05$], [$t(3) = 5.83$, $p < 0.01$], and [$t(3) = 9.8$, $p < 0.01$], respectively, but was not significant in the 120-s group ($p > 0.05$). *d*-Amphetamine produced dose-dependent reductions in water consumption in each group of the experiment ($p < 0.0001$): $F(5, 15) = 15.01$ for the 15-s group, $F(5, 15) = 29.36$ for the 30-s group, $F(5, 15) = 30.27$ for the 60-s group, and $F(5, 15) = 12.49$ for the 120-s group. Dunnett's *t*-tests revealed significant decreases in water intake ($p < 0.01$) at the doses of 2.0 and 4.0 mg/kg in all groups, and at the dose of 1.0 mg/kg in the 30-s group.

FI and FT schedules induced a similar rate of licking within a multiple schedule, except with the 15-s FI/FT, where rats licked slightly more during FT components. This difference was not statistically significant, however. *d*-Amphetamine produced similar dose-dependent decreases in the rate of licking during FI and FT schedules; these decreases were more apparent at 30 s, followed by 15 and 60 s. These effects on rates of licking are very similar to those reported for volume of water consumed. Statistical analyses revealed significant effects of *d*-amphetamine on the licking induced by FI components for the 15-s group [$F(5, 15) = 7.09$, $p < 0.01$], the 30-s group [$F(5, 15) = 44.42$, $p < 0.0001$], the 60-s group [$F(5, 15) = 15.36$, $p < 0.0001$], and the 120-s group [$F(5, 15) = 7.06$, $p < 0.01$], as well as on the licking induced by FT components in all groups: [$F(5, 15) = 10.91$, $p < 0.001$], [$F(5, 15) = 46.37$, $p < 0.0001$], [$F(5, 15) = 16.44$, $p < 0.0001$], and [$F(5, 15) = 9.08$, $p < 0.001$], respectively. Dunnett's *t*-tests showed a significant decrease ($p < 0.01$, unless indicated) after the administration of 2.0 and 4.0 mg/kg of *d*-amphetamine in all groups, both for FI and FT components ($p < 0.05$ for FI 15 s and for FI 120 s at the dose of 2.0 mg/kg), and after *d*-amphetamine at 1.0 mg/kg in the 30-s group both in FI and FT components.

Figure 2 shows the effects of *d*-amphetamine on the quarter-life of licking expressed as the percentage of change from control values, both for FI (closed circles) and FT (open circles) components. Each panel represents a multiple FI/FT schedule with the duration at the top right of each panel. The horizontal dotted line passing through 100 on vertical axes denotes no effect of the drug.

*d*-Amphetamine resulted in dose-dependent reductions in the quarter-life of all groups at any schedule, which were more marked as the FI and FT lengths increased. $ED_{50}$ values (see Method) were 2.61 mg/kg (95% CL: 1.96–3.27), 5.02 mg/kg (95% CL: −0.39–10.44), 2.04 mg/kg (95% CL: 1.1–2.99), and 1.05 mg/kg (95% CL: 0.58–1.52), respectively for FI 15-, 30-, 60-, and 120-s schedules. The obtained $ED_{50}$ values for FT 15-, 30-, 60-, and 120-s schedules were 3.66 mg/kg (95% CL: 2.09–5.23), 2.78 mg/kg (95% CL: 1.11–4.46), 2.04 mg/kg (95% CL: 1.34–2.75), and 1.13 mg/kg (95% CL: 0.68–1.58), respectively.

Figure 3 shows the time within interfood intervals that contained the peak in the rate of licking as a function of FI and FT length, represented as the mean percentage of total duration of the corresponding interfood intervals. The panel on the left represent the performance on FI components, and the panel on the right the performance on FT components. Also shown in Fig. 3 are the effects of the different doses of *d*-amphetamine.

In the saline condition it is possible to observe how the elapsed percentage of the interfood interval containing the peak in response rate decreased as the FI and FT length increased to 60 s, and how it was then maintained or was slightly increased in the 120-s group. There was a main effect of interfood interval length both on FI [$F(3, 12) = 4.93$, $p < 0.05$] and FT schedules [$F(3, 12) = 7.62$, $p < 0.01$]. Newman–Keuls comparisons showed significant differences between FI

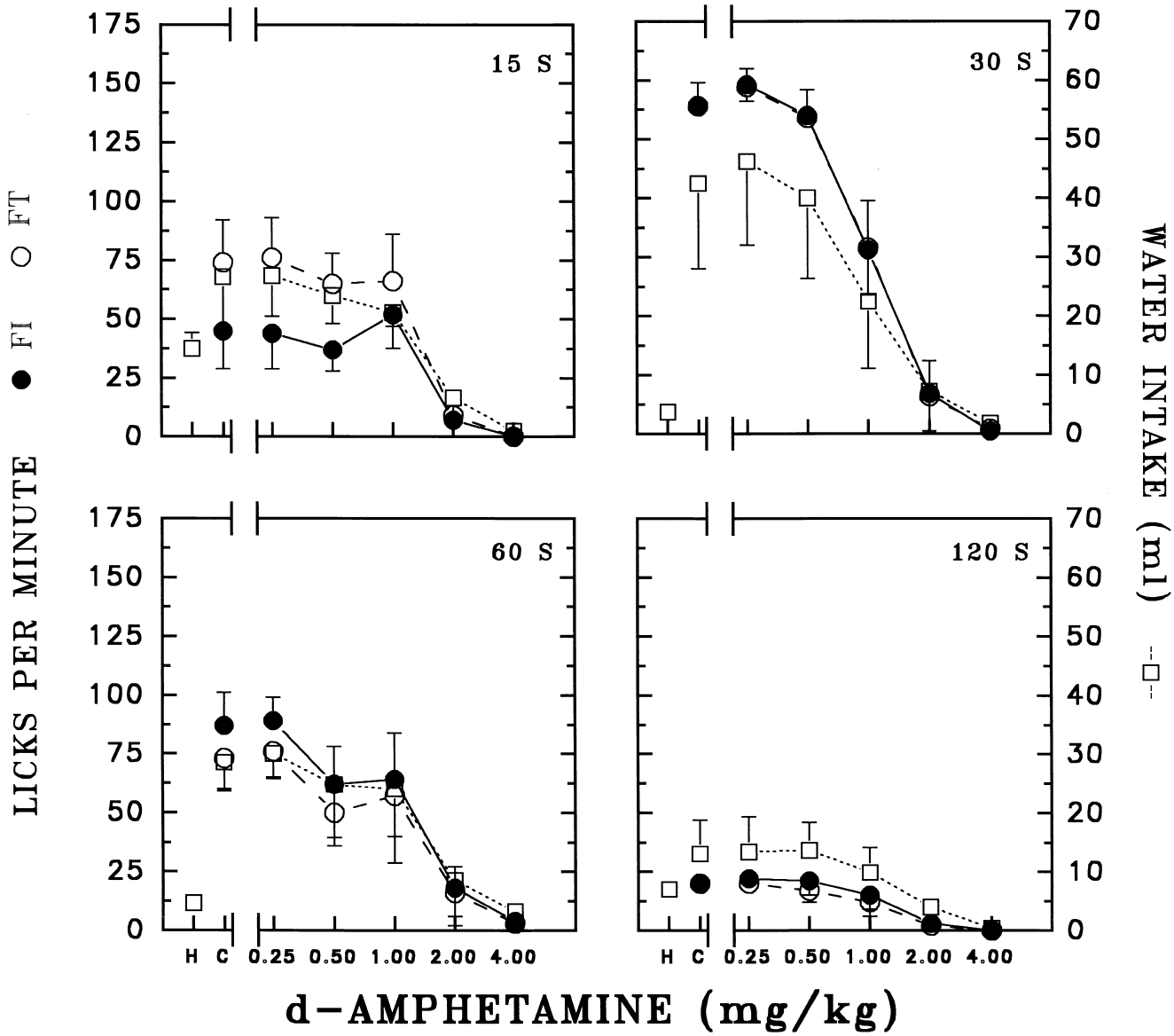


FIG. 1. Effects of *d*-amphetamine on drinking induced by different multiple fixed-interval, fixed-time schedules of food presentation. Home-cage data (H) are the means and standard errors of the two test sessions conducted before the experiment began. Control data (C) are the means and standard errors of the 10 saline sessions which immediately preceded the drug sessions. Drug data are the means and standard errors of two administrations of each dose. ●, ○ = rate of licking during fixed-interval and fixed-time schedules, respectively. □ = overall amount of water consumed (milliliters).

15- and 60-s schedules ($p < 0.05$), and between the FT 15-s schedule and FT 30- ($p < 0.05$), FT 60-, and FT 120-s ($p < 0.01$) schedules.

Administration of *d*-amphetamine led to dose-dependent reductions in the percentage of the interfood interval with the maximum rate of licking, and so the peak of the response distribution occurred earlier as the dose of the drug was increased. At the FT 120-s schedule the doses of 0.25 and 0.5 mg/kg had little effect on, or slightly increased, the proportion of the interval where the peak of responding was located. The ANOVA showed that the dose-dependent decreases produced by *d*-amphetamine were statistically significant in the following groups and schedules: FI 15 s [$F(4, 12) = 6.52$, $p < 0.01$]; FT 30 s [$F(3, 9) = 4.87$, $p < 0.05$]; and FT 60 s [$F(4, 12) = 3.83$, $p < 0.05$]. Dunnett's *t*-tests showed significant decreases at the doses of 1.0 mg/kg ($p < 0.05$) and 2.0 mg/kg ($p < 0.01$) in the FI 15-s schedule, 1.0 mg/kg ($p < 0.05$) in the FT 30-s schedule, and 2.0 mg/kg ($p < 0.01$) in the FT 60-s schedule.

## DISCUSSION

Rats exposed to multiple FI FT 15-, 30-, 60-, and 120-s schedules drank larger amounts of water than in home-cage control conditions, although rats in the 120-s group did less so than the others. Schedule-induced drinking and licking in the present experiment was an inverted U-shaped function of

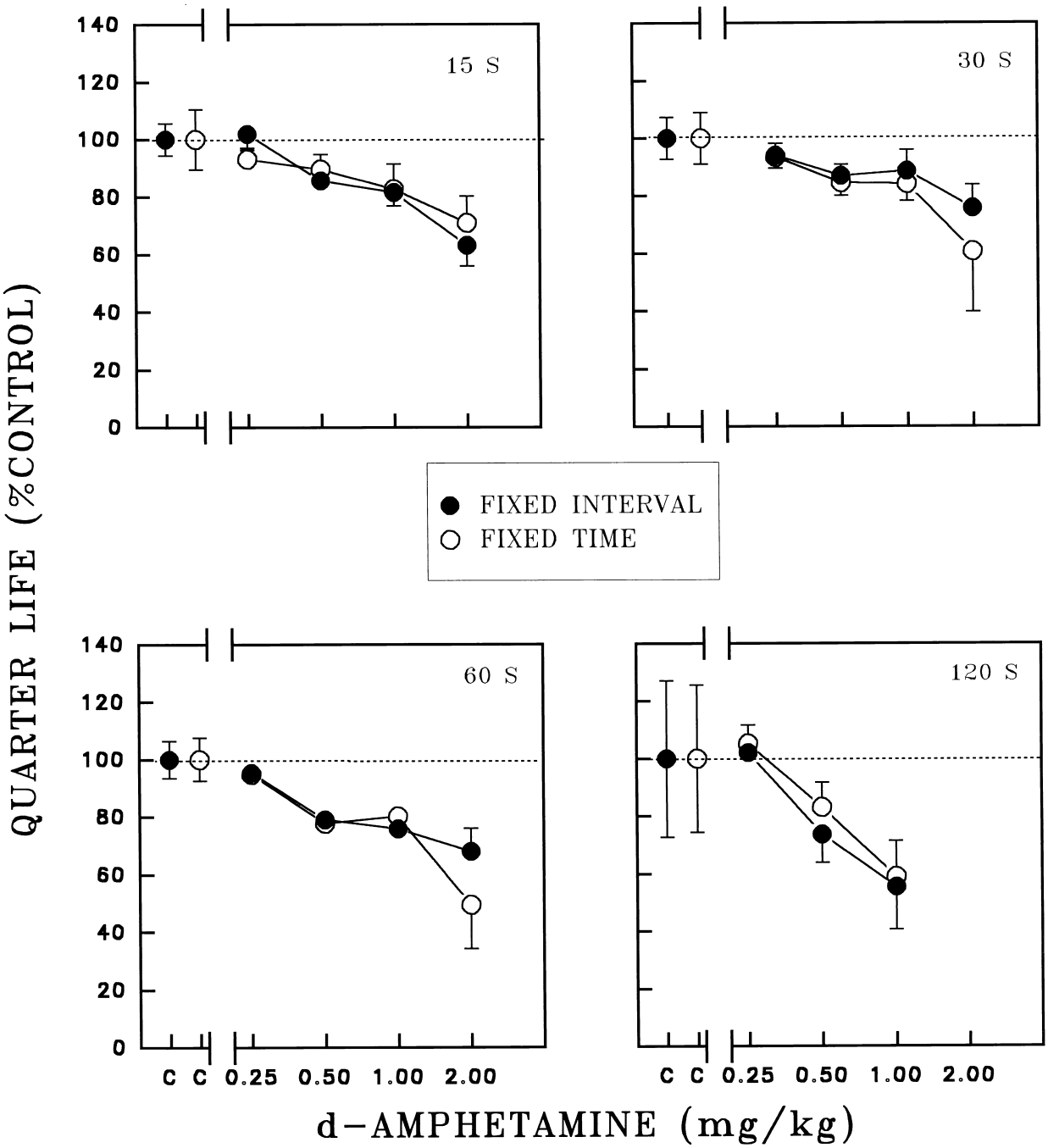


FIG. 2. Effects of *d*-amphetamine on the quarter-life of the licking induced by different multiple fixed-interval, fixed-time schedules of food presentation, represented as a percentage of change over control values. Each saline data point (C) is the mean and standard error for each group of eight saline injections. Each drug data point is the mean and standard error for each group of two administrations of each dose of the drug. With the 2.0-mg/kg dose, the data from two rats in the 30-s group and from one rat in FI 60 s were excluded from the calculations of the means.

FI and FT length (4,8), with greater polydipsia developed by animals in the 30-s group.

*d*-Amphetamine produced dose-related decrements in overall schedule-induced drinking and licking on FI and FT schedules, which are consistent with those reported by others (1,18,20, 21,25). These reductions in schedule-induced polydipsia were dependent on the interfood interval. For example, 1.0 mg/kg of *d*-amphetamine only slightly reduced the drinking and licking induced by the FI/FT 60-s schedule, whereas there were marked decreases in drinking and licking under the FI/FT 30-s schedule.

*d*-Amphetamine had virtually identical effects on drinking induced by FI and FT schedules. These results indicate strongly

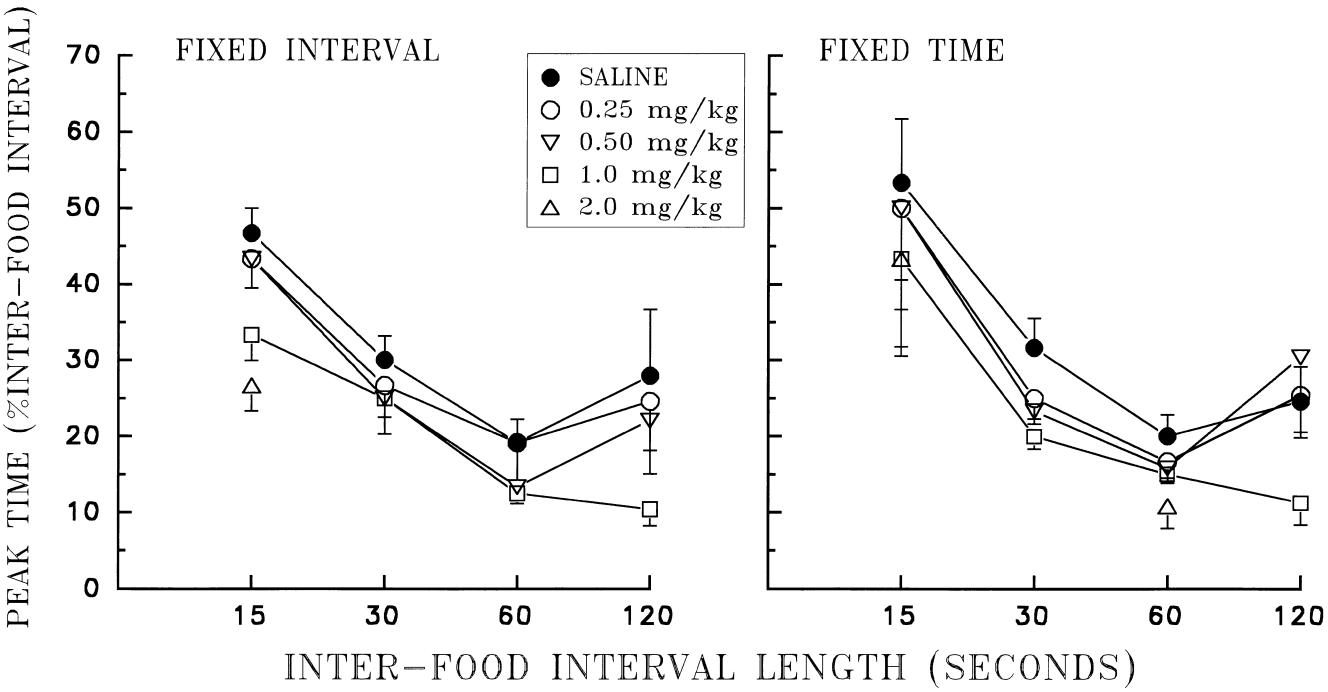


FIG. 3. Effects of *d*-amphetamine on the location of the peak of licks per minute within interfood intervals as a function of fixed-interval (left panel) or fixed-time (right panel) length. Data are the mean percentage of total interfood time which had elapsed at the time of the peak in response rate. Each drug data point is the mean and standard error for four rats of two administrations of each dose of the drug, and each saline data point is the mean and standard error of eight saline injections.

that the drug exerted direct effects on schedule-induced polydipsia rather than actions mediated indirectly by its effects on operant lever pressing. The present results, over a wide range of interfood intervals, are consistent with previous reports (20).

In general, *d*-amphetamine produced a dose-dependent shift to the left in the distribution of licking within interfood intervals. Increases in the dose of the drug led to reductions in the measure of the quarter-life in comparison to control values, and this effect occurred in all groups both in FI and FT schedules. However, the displacement to the left after *d*-amphetamine was dependent on the FI and FT lengths. As the frequency of reinforcement decreased (the FI and FT schedules increased), the dose required to reduce the quarter-life to 50% was smaller. This was a general effect, even though the dose required to reduce the quarter-life to 50% was the highest in the FI 30-s schedule. The conclusion that amphetamine acted by shifting to the left the distribution of licking within interfood intervals is further supported by the finding that *d*-amphetamine decreased the percentage of the interfood interval which had elapsed at the time of the peak in the rate of licking. This effect was not schedule dependent, however. The present results were obtained from groups of only four subjects, and this should be present when interpreting the results.

It has been reported previously that amphetamines increased the number or probability of licks in the early parts of the interfood intervals (15,18,25) and that *d*-amphetamine produces a dose-dependent decrease in the index of curvature as a measure of the temporal distribution of licking (20). Other experimenters (16,19) found that *d*-amphetamine produced dose-related decreases in schedule-induced licking during the initial parts of the inter-reinforcement intervals of FI schedules, probably because they divided the inter-reinforcement intervals in 10- or 18-s segments which were too long to capture adequately the effects of the drug on molecular aspects of behavior.

Using FI schedules of reinforcement in which delivery of food was dependent on the emission of operant behavior, it was found (2,14) that amphetamine produces similar changes in the distribution of operant lever-presses within interfood intervals as those seen with schedule-induced behavior in the present study.

Some investigators have suggested that amphetamines produce a shortening in time estimation (13), which gives rise to the leftward shift in the interfood interval distribution of responding. The findings that amphetamines affect both schedule-induced drinking and operant lever pressing in similar ways suggest that the effects of these stimulants on time perception are not restricted to operant behavior. However, our results also suggest that schedule-induced drinking is not a simple time-regulated behavior, because the elapsed percentage of the interfood interval with the maximum lick rate is a function of the duration of the FI and FT schedules [see also (12)]. Indeed, the within-interfood interval distributions of licking tended to peak at about the same absolute time regardless of FI and FT durations up to 60 s (at 8, 10, and 12 s for the 15-, 30-, and 60-s schedule durations). Operant lever pressing shows proportional timing (9), the location of the peak depending on the overall inter-reinforcement interval length. Because the effects of amphetamines on interfood interval distribution are very similar on a temporally regulated behavior (i.e., operant lever pressing) and on a nontemporally regulated behavior (i.e. schedule-induced drinking), the common effects of amphetamines on patterns of responding main-

tained by intermittent reinforcement schedules may not be mediated by temporal discrimination.

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