Pharmacology Biochemistry & Behavior, Vol. 13, pp. 657–662. Printed in the U.S.A.

Effects of Psychotropic Drugs on FI Responding and Adjunctive Drinking in Rats

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Received 21 July 1980

KURIBARA, H. AND S. TADOKORO. *Effects of psychotropic drugs on FI responding and adjunctive drinking in rats.* PHARMAC. BIOCHEM. BEHAV. 13(5) 657–662, 1980.—Effects of d-amphetamine (AM), chlorpromazine (CPZ) and diazepam (DZ) on schedule controlled responding (lever-pressing) and adjunctive drinking under a fixed interval (FI) 1.5 min schedule of food reinforcement in rats were investigated. The drinking was measured with a drinkometer and a lickometer. AM 0.13–1.0 mg/kg SC increased the total responses, and decreased the total amount of drinking and licking counts dose-dependently. A marked response increase in the early portion (0–30 sec component of the FI) and mid portion (30–60 sec component), and decrease of the drinking in the mid portion and terminal portion (60–90 sec component) occurred. CPZ 0.25–2.0 mg/kg SC decreased responses, drinking and licking in proportion with the doses. After CPZ, a response decrease in the mid and terminal portions was observed, but not in the early portion. Higher doses of CPZ decreased the drinking and licking in the whole range of the interval. A small dose of DZ (0.25 mg/kg SC) produced a significant response increase. Higher doses of DZ also increased responding, but the change was not significant. The drinking and licking were suppressed by DZ. A dose-related response increase in the mid portion was observed after DZ, but not in the early and terminal portions except after 0.25 mg/kg. Higher doses of DZ (more than 0.5 mg/kg) decreased drinking and licking throughout the whole range of the FI. The present results suggest that the interpellet distribution of responding, drinking and licking, as well as their total values, yield important information when assessing drug effects on FI responding and adjunctive drinking in rats.

FI 1.5 min schedule Interpellet distributions Fixed interval Drinking Adjunctive
d-Amphetamine Chlorpromazine Diazepam Rats

WHEN a food deprived rat is exposed to an intermittent food delivery situation, it sometimes shows a characteristic drinking pattern after each food delivery, and consumes a large amount of water. This behavior has been called "schedule-induced drinking" or "adjunctive drinking" [9,10]. A fixed interval (FI) schedule of food reinforcement is one of the representative situations in which small food pellets are delivered intermittently. Many investigators have reported the effects of various psychotropic drugs on the FI responding and on the adjunctive drinking [3, 4, 10, 11, 13, 15, 17, 18]. On the other hand, it is known that responding and drinking under the FI schedule are not uniformly distributed in the interpellet interval. We [11] reported for the FI 1.5 min schedule that most responding occurred in the terminal portion (60–90 sec component) of the interval, while most of the drinking occurred in the early portion (0–30 sec component). We also suggested the importance of taking into consideration not only total changes in responding, drinking and licking, but also their interpellet distributions to assess the effects of drugs on the behaviors. This is because it has been commonly observed after various psychotropic drugs that the behavior with a high frequency is more easily suppressed than that with a lower frequency, and *vice versa*, that is, the "rate-dependent effect of drugs" [6–8]. Many investigations concerning the rate-dependent effect of drugs on FI responding have been performed [6–8, 14], while there are very few on adjunctive drinking.

In the present experiment, we examined the interpellet distributions both of the FI responding (lever-pressing) and the adjunctive drinking which developed in rats under the FI 1.5 min schedule of food reinforcement, and investigated the effects of d-amphetamine, chlorpromazine and diazepam on them. In particular, the drinking behavior was observed continuously and quantitatively with a drinkometer [12] and a lickometer.

METHOD

Subjects

The animals used were 16 adult, male rats of the Wistar strain. They were obtained from the breeding colony of Gunma University, Medical School. The animals were moved to the breeding room of our department at an age of 4 weeks, and groups of 4 rats were housed in stainless steel wire mesh cages of 25 (W)×40 (D)×20 (H) cm. A solid diet of MF (Oriental Yeast Co., Tokyo) and tap water were given freely to the rats until the start of the experiment. When the rats reached an age of 15 weeks and weighed about 350 g, a food deprivation program was started. Here, by a limitation of daily food intake to 12–15 g/rat/day, the rats were reduced to 80–85 % of their free-feeding body weight. Water was freely available. This condition was maintained thereafter. When rats readily ate each 45 mg food pellet (Clea Japan Co., Tokyo), training under the FI 1.5 min schedule was started.

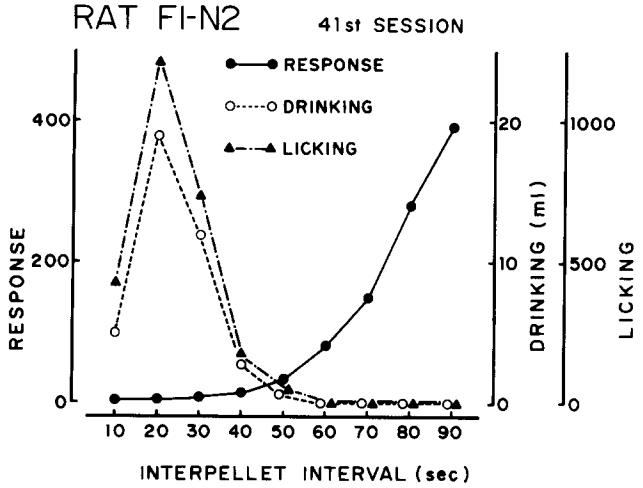

FIG. 1. Representative interpellet distribution patterns of responding, drinking and licking under the FI 1.5 min schedule of food reinforcement. The responding, drinking and licking are classified into 9 segments of 10 sec each.

Apparatus

Four experimental chambers of the same type were used. They were made of aluminium and acrylfiber boards with a size of 25 (W)×20 (D)×19 (H) cm. The floors consisted of stainless steel rods. A lever was set 5 cm above the floor and a food tray in the right side wall. To activate a microswitch attached to the lever and to be recorded as the response, the rat had to press the lever downward with a force of more than 15 g. A food dispenser (MODEL D-1, Ralph Gerbrands Co.) for the delivery of food pellets was set outside of the chamber. In the front wall 5 cm above the floor was a drinking spout (SE TV-15, O'hara and Co. Ltd., Tokyo). Water could be consumed freely throughout experimental sessions. The experimental chamber was contained in a wooden sound-attenuating box. The inside of the box was illuminated with a 10 W fluorescent lamp, and fresh air was circulated throughout the experimental sessions. The room temperature was controlled at 23 ± 2 °C, but the humidity was not controlled. The drinkometer and the lickometer were mounted outside of the sound-attenuating box. Water intake was measured continuously and quantitatively with the drinkometer for small animals (MODEL LA-1, O'hara and Co. Ltd., Tokyo). The principle of the device and the method of measurement have been described previously [11,12].

The experiment was controlled with an online minicomputer PDP 8/f (Digital Equipment Corp., Maynard) and was programmed in SKED language [16]. By this system, the control and recording of 4 rats' behaviors could be accomplished.

Drugs and Experimental Procedure

Drugs used and their doses were d-amphetamine sulfate (AM; 0.13, 0.25, 0.5 and 1.0 mg/kg), chlorpromazine hydrochloride (CPZ; Contomin Inj., Yoshitomi, 0.25, 0.5, 1.0 and 2.0 mg/kg), and diazepam (DZ; Cercine Inj., Takeda, 0.25, 0.5, 1.0 and 2.0 mg/kg). Doses are expressed in terms of the free bases. AM and CPZ were dissolved in a physiological saline vehicle and DZ in a 20% propylene glycol vehicle. In all cases, a single dose volume of 1.0 ml/kg was prepared in such a way as to contain the above mentioned amounts.

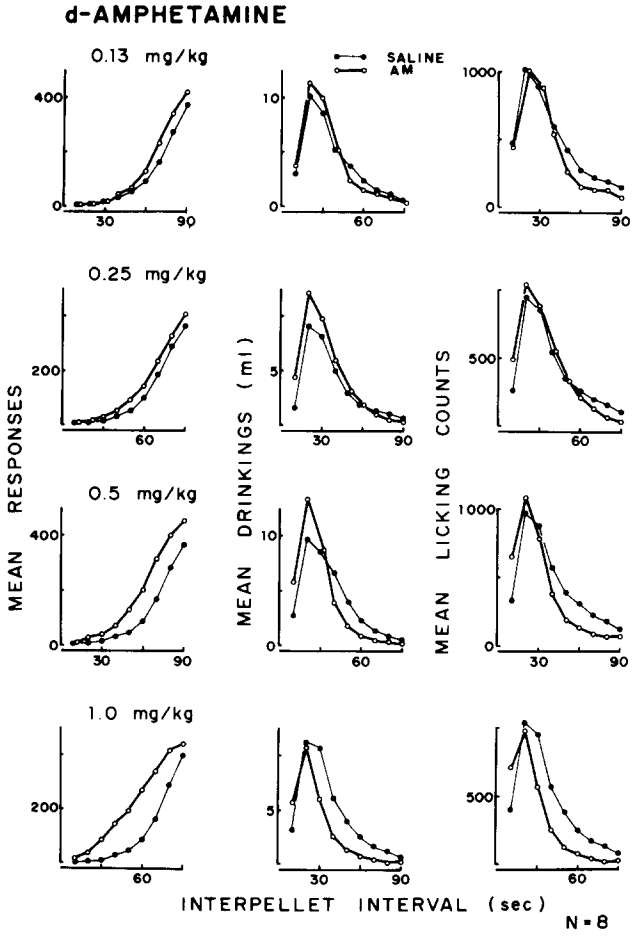

FIG. 2. Changes of the interpellet distributions of responding (left 4 panels), drinking (middle 4 panels) and licking (right 4 panels) under the FI 1.5 min schedule of food reinforcement with water available after SC administration of d-ampetamine 0.13, 0.25, 0.5 and 1.0 mg/kg. The open circles indicate the distribution patterns of the drug administered sessions, and the filled circles indicate the distribution patterns of the saline administered preceding sessions.

Each dose was administered SC immediately before start of the session. Sessions lasted for 1 hr. Drugs were given once a week, and on the day before, the same volume of saline or propylene glycol vehicle alone was given as a control session. On the other days, the animals were tested in the same way without injection of drugs or vehicles. The order of the drug tests was AM, CPZ and DZ. The doses administered progressed from the lower to the higher.

RESULTS

Baseline Performance

After 15 or more training sessions, 8 rats out of 16 showed typical adjunctive drinking after each food delivery, and consumed a large amount of water during the session (more than 20 ml). At that time, mean total responses, amount of drinking and licking counts of the 8 rats were about 1000, 35 ml and 3300 per session, respectively, and were maintained thereafter without marked change. Figure 1 shows representative interpellet distribution patterns of the responding, drinking and licking (Rat FI-N2 at the 41st session). A great

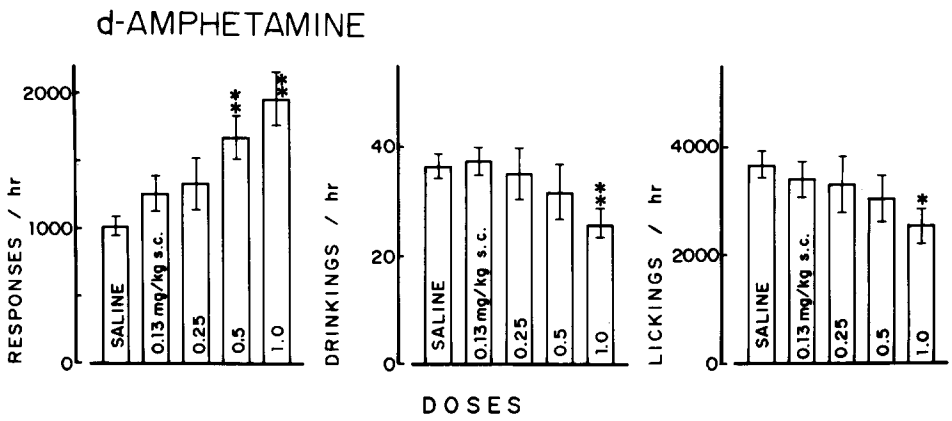

FIG. 3. Effects of d-amphetamine 0.13, 0.25, 0.5 and 1.0 mg/kg SC on the total responses, amount of drinking and licking counts under the FI 1.5 min schedule of food reinforcement with water available. *Significantly different from the saline administered control value ($p<0.05$, Student's t-test).
** $p<0.01$.

part of the responses was recorded in the terminal portion of the interpellet interval, and great parts of the drinking and licking were measured in the early portion. Moreover, there was a linear correlation between the amount of drinking and the licking counts (ca. 95 licks/ml).

The other 8 rats only drank slightly, and were excluded from the drug tests.

Effects of d-Amphetamine

Figure 2 shows changes of the interpellet distribution patterns of responding, drinking and licking after SC administration of AM 0.13–1.0 mg/kg. Figure 3 represents changes of mean total responses, amount of drinking and licking counts after AM.

AM increased the responses dose-dependently. The changes after more than 0.5 mg/kg were statistically significant compared with the saline administered control value ($p<0.01$, Student's t-test). A marked increase of the responses was observed in the early and mid portions of the interval, while it was not so marked in the terminal portion.

The total amount of drinking and licking counts were significantly suppressed by AM 0.5 and 1.0 mg/kg. The drinking and licking in the early portion, which were high rate at the control session, increased slightly after AM 0.13–0.5 mg/kg. However, those in the mid and terminal portions decreased. The linearity between the drinking and licking changed slightly after AM 0.25 and 0.5 mg/kg. Here, the drinking in the second segment (10–20 sec component) of the interpellet interval increased slightly without a marked change in licking.

Effects of Chlorpromazine

Figure 4 shows changes of the interpellet distribution patterns of responding, drinking and licking after SC administration of CPZ 0.25–2.0 mg/kg. Figure 5 represents changes of mean total responses, amount of drinking and licking counts after CPZ.

CPZ decreased the responses dose-dependently. The changes after 2.0 mg/kg were statistically significant. A marked decrease of the responses in the mid and terminal portions of the interpellet interval was observed, while it was not so marked in the early portion.

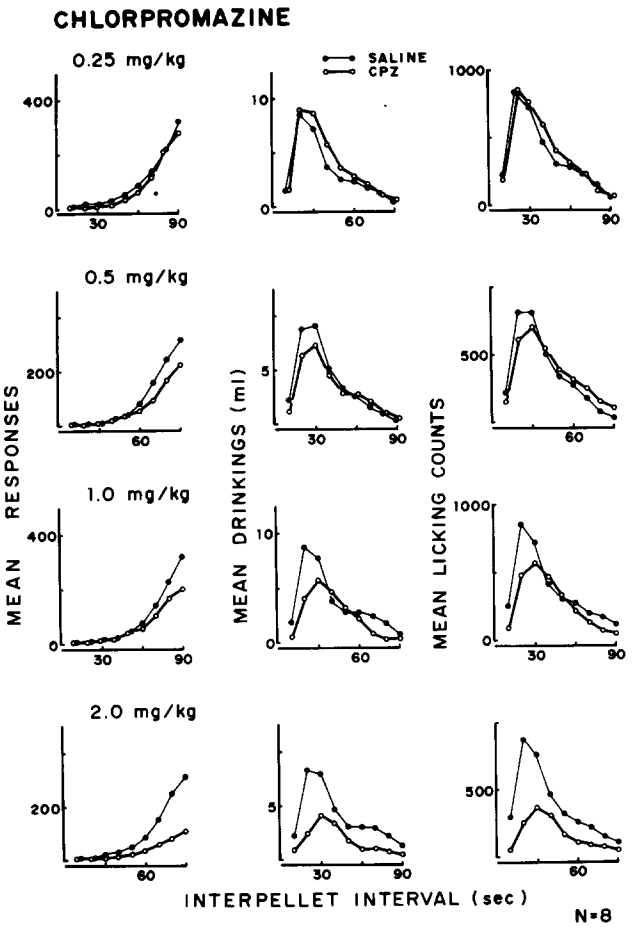

FIG. 4. Changes of the interpellet distributions of responding, drinking and licking under the FI 1.5 min schedule of food reinforcement with water available after SC administration of chlorpromazine 0.25, 0.5, 1.0 and 2.0 mg/kg. The data are expressed in the same way as in Fig. 2.

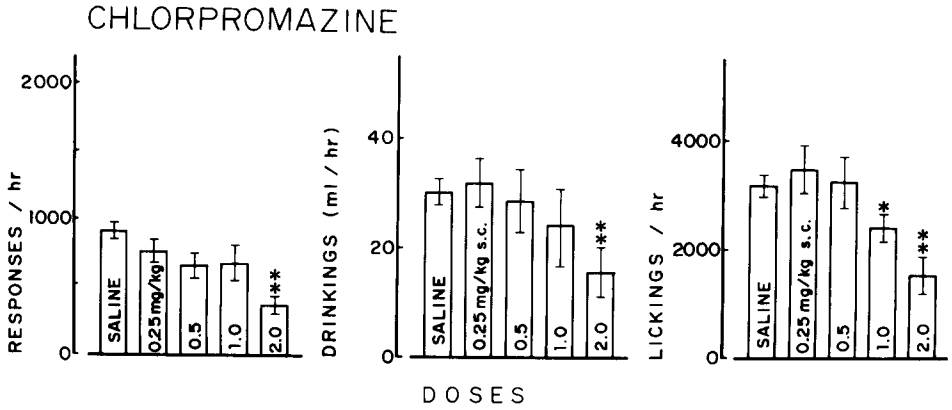

FIG. 5. Effects of chlorpromazine 0.25, 0.5, 1.0 and 2.0 mg/kg SC on the total responses, amount of drinking and licking counts under the FI 1.5 min schedule of food reinforcement with water available. The data are expressed in the same way as in Fig. 3.

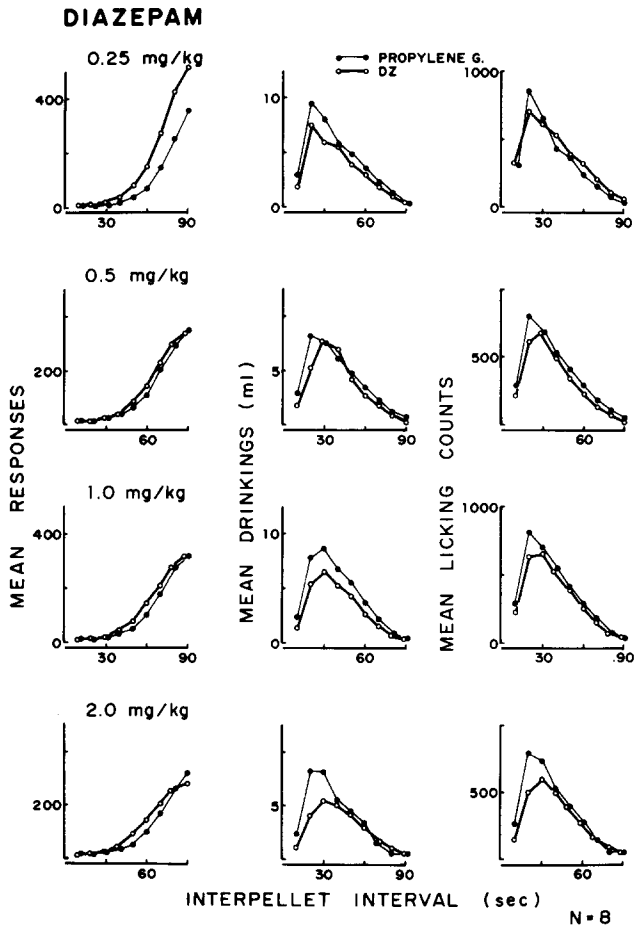

FIG. 6. Changes of the interpellet distributions of responding, drinking and licking under the FI 1.5 min schedule of food reinforcement with water available after SC administration of diazepam 0.25, 0.5, 1.0 and 2.0 mg/kg. The data are expressed in the same way as in Figs. 2 and 4.

The total amount of drinking and licking also decreased after CPZ, and were mainly due to marked decreases in the early portion. Nevertheless, after CPZ the linearity between the drinking and licking was maintained.

Effects of Diazepam

Figure 6 shows changes of interpellet distribution patterns of responding, drinking and licking after SC administration of DZ 0.25–2.0 mg/kg. Figure 7 represents changes of mean total responses, amount of drinking and licking counts after DZ. In the control sessions, propylene glycol vehicle was given.

Propylene glycol vehicle did not produce any marked changes in the responding, drinking and licking. DZ 0.25 mg/kg increased responding markedly. The change was caused by an increase of the responses in the terminal portion of the interpellet interval. DZ 0.5–2.0 mg/kg increased the responses in the mid portion without eliciting a marked change in the early and terminal portions.

The total amount of drinking decreased, dose-dependently, after DZ. More than 0.5 mg/kg of DZ also decreased licking. However, a clear dose-response relationship was not observed in the licking. DZ 0.25 mg/kg tended to increase the licking, but not significantly, without eliciting a marked change in the amount of drinking. Higher doses of DZ (0.5–2.0 mg/kg) decreased drinking and licking throughout the whole range of the interpellet interval.

DISCUSSION

The results demonstrated that, after about 15 sessions training under the FI 1.5 min schedule of food reinforcement, a typical, high rate of adjunctive drinking was produced in half of the 16 rats, and that great parts of the FI responding and the adjunctive drinking were measured in the terminal and early portions, respectively, of the interpellet interval. It is considered that the FI responding and the adjunctive drinking are opposing behavioral topographies, and that the interpellet distribution pattern of responding reflects temporal constraint under the FI schedule.

AM, in the dose range of 0.13–1.0 mg/kg, increased total responses in a dose-dependent fashion. Similar results were reported by Byrd [3], Segal *et al.* [15] and Wayner *et al.* [18]. The increase is considered to be elicited from the CNS-stimulating effect of the drug. Responding increased markedly in the early and mid portions of the interpellet interval, but not in the terminal portion, suggesting that this change after AM follows the rate-dependency relation [6–8]. The temporal discrimination of rats also may be impaired by the drug. Under a DRL schedule, in which a different temporal

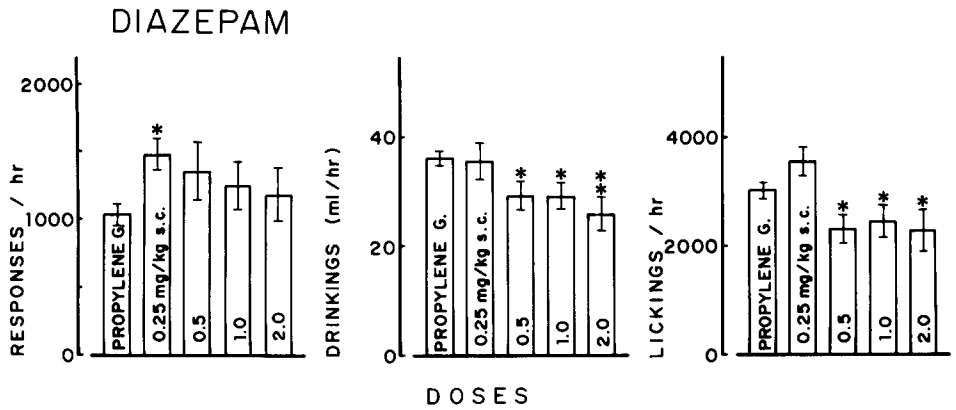

FIG. 7. Effects of diazepam 0.25, 0.5, 1.0 and 2.0 mg/kg SC on the total responses, amount of drinking and licking counts under the FI 1.5 min schedule of food reinforcement with water available. The data are expressed in the same way as in Figs. 3 and 5.

discrimination was required to obtain food, became disordered after AM [1].

The decrease in total responses after CPZ is probably due to the CNS-depressing effect of the drug. The same result was reported by Canon and Lippa [4]. The responses decreased throughout the whole range of the interpellet interval when given at the higher doses. Clark [5] reported that, after 0.5–1.0 mg/kg IM, responses increased in the early portion and decreased in the terminal portion. The present results confirmed the data of Canon and Lippa [4], but not those of Clark [5]. One of the reasons for the discrepancy may be the difference between the schedule interval values. FI 1.5 min and FI 4 min schedules were used in the present and Clark's experiments, respectively. In addition, the rats could drink water during the session in the former case, but could not in the latter. The present results suggest that the change in the interpellet interval response distribution also follows the rate-dependency relation after CPZ, but it is not so marked as that after AM.

On the other hand, changes of responses after DZ 0.25–2.0 mg/kg differed from those after AM and CPZ. The lowest dose (0.25 mg/kg) of DZ increased the responses significantly. More than 0.5 mg/kg of DZ also produced a slight increase of the responses. Also, a change was observed in the interpellet response distribution. Here, an increase of the responses in the mid portion of the interval was marked after DZ. It has been reported by many investigators [2, 4, 6–8, 13] that not only DZ but also chlordiazepoxide increases FI responding. Canon and Lippa [4] demonstrated the response-increasing effect of DZ in the mid portion of the interpellet interval without marked change of the early and terminal portions.

AM, CPZ and DZ suppressed adjunctive drinking. The decreases after AM and CPZ also were reported by many investigators [3, 4, 13, 15, 18]. However, there were some discrepancies in the effect of DZ on adjunctive drinking. Canon and Lippa [4] reported that DZ 5.0–15.0 mg/kg PO elicited no marked change in the drinking, while Bacotti and Barrett [2] reported an increase in the drinking after chlordiazepoxide 1.0–5.6 mg/kg IP. The schedules used in their experiments were FI 1 min and MULT FR 80 FI 2 min in the former and latter, respectively. The differences between the results of the present experiment and the others may be due to the differences in schedules.

The effect of AM, CPZ and DZ on the interpellet distributions of the drinking and licking were quite different. AM produced marked decreases in drinking and licking in the mid and terminal portions without marked changes in the early portion. This suggests that the rate-dependent effect of AM, noted for responding, is not observed in the adjunctive drinking. After CPZ and DZ, the drinking and licking decreased at uniform rates in almost all the segments of the interpellet interval. However, the origins for these results may differ from each other. This is because a marked depression of the rat's behavior was observed following administration of CPZ, and was considered to be a main cause. Actually, the dose-effect relations of CPZ for the responses, drinking and licking run nearly parallel. After DZ, an increase of responses in the mid portion of the interpellet interval may produce the decrease in drinking and licking. Again, these results strongly suggest that the effects of psychotropic drugs on adjunctive drinking hardly follow the rate-dependency relation, and that the different changes of responding and drinking distributions after the drugs reflect the different behavioral topographies between schedule-controlled and adjunctive behaviors.

In the present experiment, we measured continuously the adjunctive drinking of rats under the FI 1.5 min schedule of food reinforcement by recording the amount of water intake as well as the licking counts, and observed that there was a linearity between the amount of drinking and licking counts in the control sessions. The correlation was maintained after CPZ. After AM and DZ, however, the correlation altered slightly. Sanger and Blackman [14] demonstrated that rats given a low dose of DZ showed differential changes in drinking and licking. These results suggest the importance of measuring both the amount of drinking and licking to investigate the drinking behavior of the rats. The drinkometer assembled by us may be used to advantage for this purpose [12].

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