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Schedule-Induced Drinking of Chlordiazepoxide Solutions by Rats[1]

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SANGER, D. J. *Schedule-induced drinking of chlordiazepoxide solutions by rats.* PHARMAC. BIOCHEM. BEHAV. 7(1) 1–6, 1977. – Schedule-induced drinking developed in rats during daily 60 min sessions in which a food pellet was delivered to each rat every 60 sec (FT 1-min). For four rats the drinking fluid was tap water, for three rats it was a solution of chlordiazepoxide in water at a concentration of 0.1 mg/ml, and for three other rats a solution of chlordiazepoxide at a concentration of 0.4 mg/ml was available. All animals showed a rapid burst of licking shortly after the delivery of a food pellet, and this was followed by entries into the food tray, the rate of this behavior showing an increase in rate up to the delivery of the next food pellet. The average volumes of fluid consumed by the rats with the low drug concentration were slightly higher than the average volumes consumed by the rats with water available, and when water was substituted for the drug, volumes consumed decreased in all three rats. In contrast, less of the higher concentration of chlordiazepoxide than of water was consumed, and when water was substituted for this concentration of the drug drinking increased. Injections of relatively low doses of chlordiazepoxide (2.5, 5.0 mg/kg) increased both the volumes of water consumed and the number of tray entries in the rats which were consuming water, while higher doses (20, 40 mg/kg) decreased the rate of these behaviors. No consistent facilitation of either drinking or tray entries was produced in the chlordiazepoxide-consuming rats by injections of this drug. Injections of a range of doses of d-amphetamine (0.125–2.0 mg/kg) produced a dose-related decrease in drinking in all rats, and a similar decrease in tray entries in the water consuming rats. Marked increases in numbers of tray entries were produced by d-amphetamine in the rats consuming the lower concentration of chlordiazepoxide.

Schedule-induced drinking Chlordiazepoxide d-Amphetamine

IT IS possible to induce rats and other experimental animals to consume large volumes of water if they are deprived of food and food is delivered intermittently in small portions [3]. Falk [3] has called this behavior schedule-induced or adjunctive drinking, and such drinking will generalize to other fluids if they are presented in place of water. Thus, schedule-induced drinking can provide a useful laboratory technique for inducing animals to consume solutions of behaviorally active drugs.

The second published report of schedule-induced drinking showed that rats would consume significant volumes of an ethanol solution while obtaining food reinforcers on a variable-interval schedule [13]. This finding has been replicated and elaborated upon in a number of reports (e.g., [4,17]). It has also been shown that solutions of drugs other than ethanol will be ingested by rats during schedules of intermittent food delivery. Rats will consume large volumes of solutions of morphine and other narcotic analgesics [11, 12, 14], and ingestion of solutions of barbiturates has also been reported [10,16].

Rats whose lever pressing was maintained by a schedule of intermittent food presentation ingested large quantities of chlordiazepoxide when this solution was substituted for water during experimental sessions [8]. These observations have been confirmed in the present author's laboratory, and it was the purpose of the experiment reported here to carry out further analyses of schedule-induced chlordiazepoxide drinking in rats. In the present study solutions of this drug were available from the first session of the experiment in order to investigate whether schedule-induced drug consumption would occur without previous schedule-induced water consumption. The effects of presession injections of chlordiazepoxide and of d-amphetamine on both water and chlordiazepoxide consumption were also studied. Previous research has shown that administration of both these drugs can markedly affect levels of schedule-induced drinking [1, 2, 19, 20, 22, 25].

METHOD

Animals

The animals were 10 experimentally naive female hooded rats. They were approximately 130 days old at the beginning of the experiment and weighed between 180 and

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220 g. Throughout the experiment they were individually housed and maintained at approximately 85% of their pre-experimental body weights. Water was freely available in the home cages.

Apparatus

The experiment was carried out in standard operant test chambers (Campden Instruments Ltd.) housed in sound and light proof outer cubicles. In each chamber the lever and stimulus light to the left of the food tray were removed. The opening produced by the removal of the lever was covered by a sheet of steel, and a plastic 100 ml cylinder was hung outside the chamber so that the metal spout was just behind (approximately 1–2 mm) the hole left by the removal of the stimulus light. A rat placed in the chamber could lick the spout through the hole and licks were recorded by means of a lickometer connected to the spout and the grid floor of the chamber.

The food tray was recessed behind the wall of the chamber and was covered by a clear plastic, hinged flap. A microswitch was attached to the flap and thus entries into the food tray were recorded. Recording of licking and tray entries and delivery of food pellets was carried out using standard electromechanical equipment. The volumes of fluid consumed during each session were also recorded.

Procedure

Throughout the experiment the rats were given daily 60 min sessions, 7 days a week, in the chambers with fluid available. For four animals (Rats 1, 2, 9, and 10) the fluid was tap water, for three (Rats 3, 4, and 5) it was a solution of chlordiazepoxide hydrochloride in water at a concentration of 0.4 mg/ml and for the other three (Rats 6, 7, and 8) the fluid was chlordiazepoxide solution at a concentration of 0.1 mg/ml. The concentrations of drug solution were chosen on the basis of preliminary experiments with other animals, which are not reported here. Fresh drug solutions were prepared every few days.

Before Sessions 1 and 2 of the experiment 60 food pellets (45 mg) were placed in the food tray for each animal, and the volumes of fluid consumed during these 60 min sessions were recorded. On subsequent sessions 60 pellets were delivered at a rate of one each minute independently of each animal's behavior (fixed time 1-min procedures: FT 1-min). This procedure was continued for over 130 daily sessions during which time dose-response determinations of the effects of pre-session injections of chlordiazepoxide and d-amphetamine on drinking were made. Finally, for the six rats which had the chlordiazepoxide solutions available, water was substituted for the drug, and water consumption was studied for a further 10 sessions.

Chlordiazepoxide hydrochloride in doses of 2.5, 5.0, 10, 20 and 40 mg/kg and d-amphetamine sulfate in doses of 0.125, 0.25, 0.5, 1.0 and 2.0 mg/kg were administered by IP injection approximately 5 min before the start of a session. Both drugs were dissolved in 0.9% saline to give injection volumes of 2 ml/kg body weight. Each animal received each dose on two occasions, and doses were given in a mixed order which was different for each animal. At least three non-drug days, on which injections of saline were administered, intervened between two successive drug injections.

RESULTS

During the first two sessions, when 60 pellets were presented together, each animal consumed only a small volume of its available fluid. On subsequent sessions, however, when the FT 1-min procedure was in operation, all 10 rats developed consistent schedule-induced drinking which had reached high levels of fluid intake by about the tenth session. Figure 1 shows the development of drinking over the first 22 sessions of the experiment. For convenience the data are presented for groups of animals. The rats which had either water or the lower concentration of chlordiazepoxide (0.1 mg/ml) available developed very high levels of fluid intake, individual animals drinking up to 40 ml in each 60 min session. The average intake of the three rats with the lower drug concentration available was slightly higher than the average intake of the four rats with water available. The three rats with the higher drug concentration (0.4 mg/ml) also showed consistent schedule-induced drinking although the volumes consumed were somewhat lower than those of the other fluids. However, as shown in Fig. 1, consumption of the high chlordiazepoxide concentration was sufficient for the rats to take doses of up to 40 mg/kg of chlordiazepoxide each day.

The effects of the substitution of water for the chlordiazepoxide solutions, at the end of the experiment, are shown in Table 1. This table presents average fluid intakes, for the six individual rats, over the last 10 sessions of chlordiazepoxide availability and for the final 10 sessions of the experiment when water was presented in place of the drug solutions. For the three rats which had been drinking the lower concentration of chlordiazepoxide, substitution of water for the drug led to slightly reduced levels of fluid intake. In contrast, for the three rats which had drunk the higher drug concentration substitution of water produced increases in the volume of fluid consumed.

The pattern of schedule-induced drinking during each session was similar in all 10 animals. It consisted of a rapid burst of licking immediately after almost every food pellet was obtained. Representative records of this licking are shown in Fig. 2. Early in the experiment the patterns of licking for the three rats which were consuming the higher drug concentration (Rats 3, 4, and 5) were similar to that shown in Fig. 2 for Rat 3. However, later in the experiment Rat 5 began to drink larger volumes of the solution and showed a somewhat different pattern of licking which consisted of a number of extended bursts of licking as well as shorter bursts. A record of licking for Rat 5 is also presented in Fig. 2.

Following the burst of schedule-induced licking after delivery of each food pellet, and during the remaining part of the time until the next pellet delivery, the rats were observed to be very active. A great deal of this activity was directed towards the food tray, although the delivery of each pellet was signalled by the clearly audible click of the pellet dispenser, and this behavior was recorded as high numbers of tray entries. Figure 3 presents cumulative records of these tray entries for three animals. These three rats showed particularly high rates of tray entry but the patterning of this behavior was similar in all 10 animals. There appeared to be no consistent differences in the numbers or patterning of tray entries between rats which were consuming the different fluids.

The effects of pre-session injections of chlordiazepoxide on both the volumes of fluid consumed and the numbers of

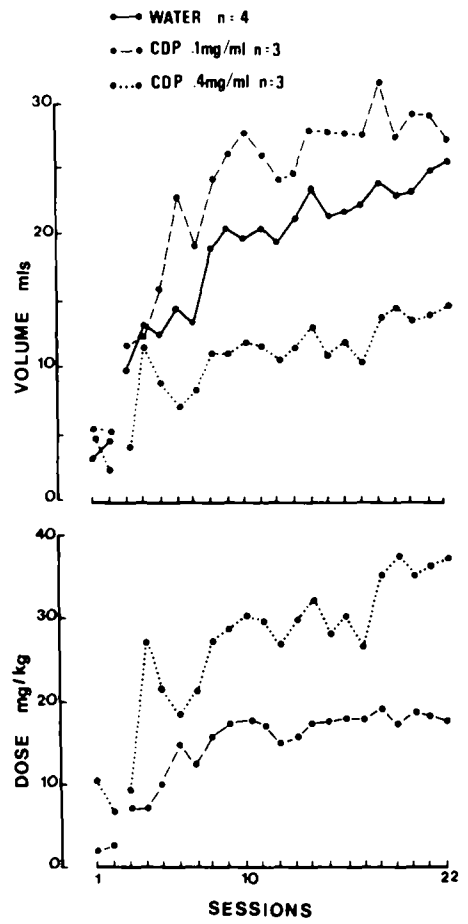

FIG. 1. The development of schedule-induced drinking in rats grouped according to the fluid available. The top graph shows the mean volumes of fluid consumed during daily 60 min sessions and the lower graph shows the mean dose of chlordiazepoxide ingested by the animals with solutions of this drug available. On Sessions 1 and 2 60 food pellets were presented to each rat at the beginning of the session while on all subsequent sessions individual pellets were delivered at 1 min intervals (FT 1-min).

TABLE 1

MEAN VOLUMES OF CHLORDIAZEPOXIDE AND WATER CONSUMED BY INDIVIDUAL RATS

Rat	CDP Concentration	Volume of CDP, ml	Volume of Water, ml
3	0.4 mg/ml	16.4 ± 1.3	20.8 ± 3.4
4	0.4 mg/ml	15.5 ± 1.7	22.7 ± 1.8
5	0.4 mg/ml	27.7 ± 1.2	32.0 ± 7.8
6	0.1 mg/ml	17.9 ± 2.2	14.3 ± 2.8
7	0.1 mg/ml	33.0 ± 1.5	31.4 ± 1.4
8	0.1 mg/ml	28.4 ± 1.3	21.4 ± 1.9

Each value is the mean ± SD of 10 sessions: the last 10 sessions when CDP was available and 10 further sessions on which water was presented in place of CDP.

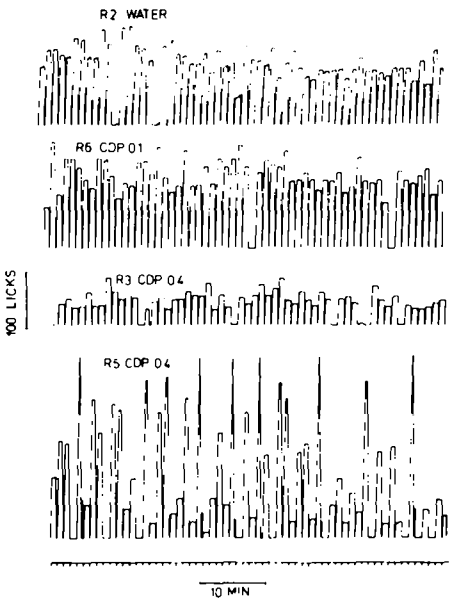

FIG. 2. Records of licking at the spout of the liquid tube in four individual rats. Rat 2 had tap water available, Rat 6 a solution of chlordiazepoxide at 0.1 mg/ml and Rat 3 and Rat 5 chlordiazepoxide at 0.4 mg/ml. Food pellets were delivered at 1 min intervals (shown as deflections of the bottom pen) and each pellet delivery reset the pens recording licking.

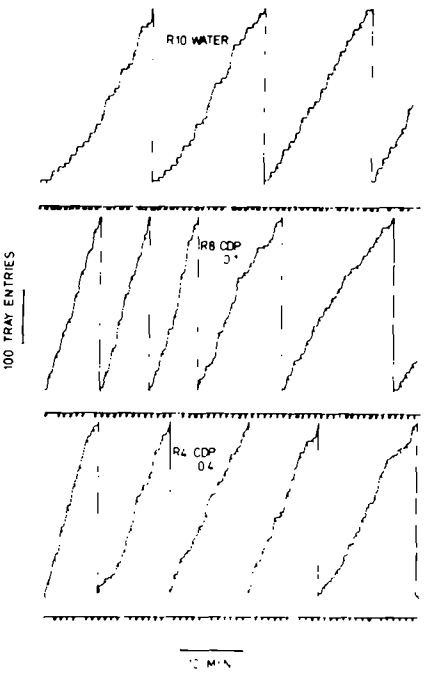

FIG. 3. Cumulative records of entries into the food tray in three individual rats. Rat 10 had water available, Rat 8 chlordiazepoxide solution at a concentration of 0.1 mg/ml and Rat 4 chlordiazepoxide at 0.4 mg/ml. Licks are shown as deflections of the event pens.

tray entries are shown in Fig. 4. For clarity of presentation the animals in each of the three conditions have again been grouped, and the effects of the drug are presented as percentages of control values. Thus the volume of fluid ingested and the number of tray entries after each drug administration were converted to a percentage of these measures on the immediately preceding session.

At the two lower doses of chlordiazepoxide (2.5 and 5.0 mg/kg) the four animals which were drinking water showed small but consistent increases in the volumes ingested. Higher doses produced a dose-related decrease in drinking. The rats which were consuming the chlordiazepoxide solutions did not show consistent increases in drinking after injections of the lower doses of chlordiazepoxide but decreases did occur after the higher doses (Fig. 4).

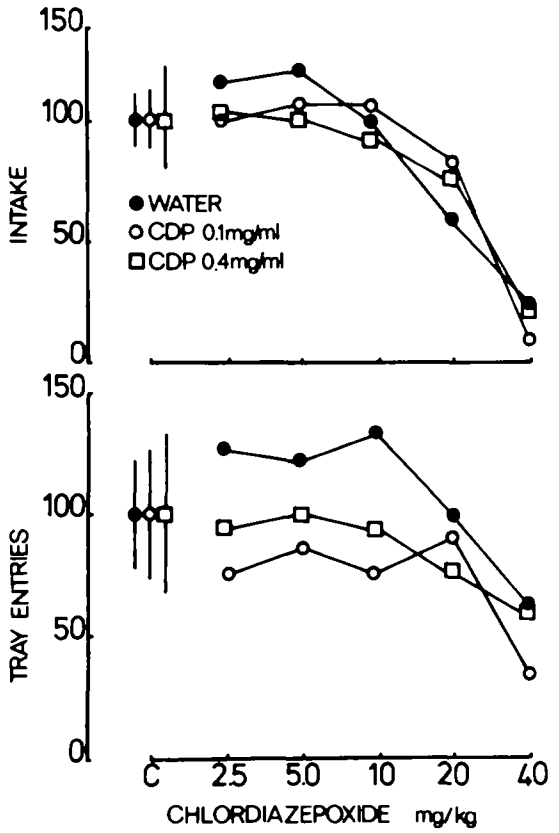

FIG. 4. Dose response curves showing the effects of injections of chlordiazepoxide on schedule-induced ingestion of water or chlordiazepoxide solutions and on entries into the food tray. Both measures are expressed as percentages of control values. Rats are grouped according to the fluid ingested: for water n = 4, and n = 3 for each of the two concentrations of chlordiazepoxide. Each point is the mean of 6 or 8 values (2 administrations of each dose to either 3 or 4 animals) except for the points at C which show the mean ± the standard deviation of 30 or 40 control sessions. Mean absolute numbers of tray entries were: water 690, CDP 0.1 mg/ml 636, CDP 0.4 mg/ml 861.

Figure 4 also shows the effects of chlordiazepoxide injections on the numbers of tray entries. This behavior was facilitated by the lower doses in the four water-consuming rats, but such an effect did not occur in the animals consuming the drug solutions. In fact, the three rats which were drinking the lower concentration of chlordiazepoxide frequently showed decreases in the numbers of tray entries after injections of lower doses of this drug. The highest injected dose of chlordiazepoxide decreased tray entries in all animals.

Injections of d-amphetamine produced a dose-related decrease in the volume of fluid consumed in every animal. Figure 5 shows the effects of this drug on drinking in rats grouped according to fluid consumed. Also shown in this figure are the effects of injections of d-amphetamine on tray entries. This drug produced a dose-related decrease in this behavior in the four water-consuming animals but its effects on this behavior in the rats which were drinking chlordiazepoxide solutions were quite different. Tray entries were decreased by higher doses of d-amphetamine in the three rats drinking the higher concentration of chlordiazepoxide. In the three rats consuming the lower drug concentration marked facilitation of tray entries was produced by every dose of d-amphetamine.

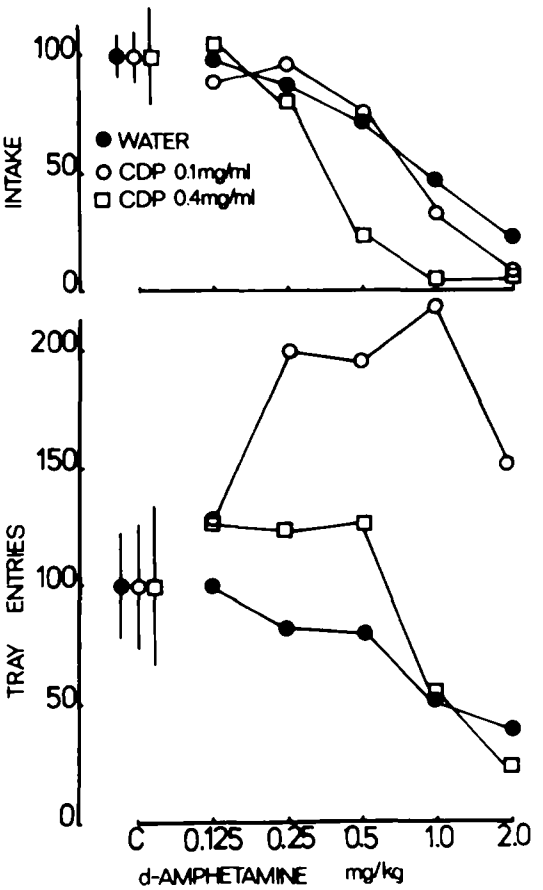

FIG. 5. Dose response curves showing the effects of injections of d-amphetamine on schedule-induced ingestion of water or chlordiazepoxide solutions. The data are expressed as in Fig. 4.

DISCUSSION

Recent research has demonstrated that schedule-induced drinking can be a useful experimental technique for inducing rats and primates to drink large volumes of solutions of ethanol and of narcotic analgesics [4, 11, 17]. The present experiment shows that rats will also ingest large

quantities of chlordiazepoxide solutions during a FT 1-min schedule of food pellet delivery. This schedule-induced drinking of chlordiazepoxide developed without a prior history of schedule-induced water consumption.

Self-administration of chlordiazepoxide and other minor tranquilizers in laboratory animals appears to have been studied much less frequently than has self-administration of drugs from other categories such as stimulants and narcotic analgesics [21]. However, it has been shown that monkeys will self-inject chlordiazepoxide [6], and there have also been several studies which have attempted to induce rats to drink solutions of this drug. Kamano and Arp [9] reported that when a solution of chlordiazepoxide (0.2 mg/ml) was the only fluid available to rats in their home cages the animals consumed an average of 27 ml/day. When both the drug solution and water were available, however, the volume of drug consumed was considerably lower. Stolerman *et al.* [24] also studied both the forced and choice consumption of a solution of chlordiazepoxide, although at a higher concentration (0.5 mg/ml) than that used in the present experiment, during the course of an experiment concerned with the consumption by rats of solutions of several drugs. These researchers found that their rats drank appreciable quantities of the drug under both forced and choice conditions although in the latter case considerably more water was consumed. Similarly, Harris *et al.* [7] reported that naive rats preferred water over a solution of chlordiazepoxide at a concentration similar to that used by Stolerman *et al.* [24]. The rats were subsequently deprived of food and trained to obtain food pellets by drinking the drug solution. This had the effect of producing substantial drug ingestion which remained at a relatively high level when the rats were again given a choice between water and the drug solution. The present experiment complements these previous findings in demonstrating that rats can be induced to consume relatively large doses of chlordiazepoxide without prior fluid deprivation and without making the delivery of another reinforcer contingent upon drinking.

In several previous studies of schedule-induced drug ingestion it has been observed that rats typically consume less of the drug solution than they do of water [11,15]. It has also been reported that the schedule of food delivery may lose control of drinking so that drinking ceases to occur in discrete post-pellet bursts [12,15]. These effects are presumably due to the acute pharmacological effects of the ingested drug and to the development of dependence, respectively. In the present experiment the rats which were drinking the lower concentration of chlordiazepoxide drank slightly larger volumes than did those which were consuming water, and when water was substituted for the drug intake decreased. In contrast, the animals with the larger drug concentration drank less fluid and their intake increased when water was substituted for the drug. There was little evidence for loss of control by the FT schedule during the course of the experiment. In only one animal (Rat 5) did the pattern of drinking change and even with this rat drinking remained generally post-pellet. This continuing control by the schedule, together with the observation that substitution of water did not lead to any gross disruption of behavior, suggests that dependence on chlordiazepoxide had not developed in this experiment. Similar observations have been made by previous experimenters [7,24].

Presession injections of both chlordiazepoxide and d-amphetamine modified levels of drinking in all rats. Low doses of chlordiazepoxide produced a small facilitation of water consumption while higher doses decreased water intake. Such effects have been reported on several previous occasions [1, 2, 19, 20]. No facilitation of chlordiazepoxide drinking was observed after injection of this drug although injections of higher doses decreased chlordiazepoxide intake. These effects were presumably due to a summation of the injected dose of the drug and the dose ingested through drinking. It is interesting to note that no tolerance appeared to have occurred to the depressant effects of chlordiazepoxide even though some of the rats had been ingesting relatively large doses of the drug for many daily sessions. d-Amphetamine produced a dose-related decrease in drinking in all animals. Similar decreases in schedule-induced drinking have been reported previously [22,25].

During each inter-pellet interval the rats placed their heads into the food trays many times as shown by the cumulative records of tray entries. The frequency of this behavior showed a gradual increase until a pellet was delivered, a pattern very similar to that maintained by fixed-interval schedules of reinforcement [5]. Indeed it may be possible to consider this behavior as an operant since a tray entry was obviously necessary before a food pellet could be consumed. However, since each pellet delivery was signalled by the click of the pellet dispenser it may be less contentious to place these tray entries in the more general category of terminal responses which are responses which emerge in close temporal proximity to food reinforcers when these are presented intermittently [23]. Similar temporal patterns of key pecking have been found in pigeons during intermittent response-independent presentation of food [26].

Numbers of tray entries were markedly changed by injections of both chlordiazepoxide and d-amphetamine. With the four rats which were drinking water, chlordiazepoxide increased tray entries at lower doses and decreased them at higher doses. d-Amphetamine, however, produced a dose related decrease in this behavior. It is interesting to compare these effects with previously reported actions of these drugs on fixed-interval responding in similar situations. Chlordiazepoxide has been reported to increase fixed-interval response rates while either increasing or decreasing schedule-induced drinking [1]. d-Amphetamine, however, increases fixed-interval responding while decreasing drinking [25]. It is worth pointing out that in the present experiment the actions of the injected drugs on tray entries in the water consuming rats closely parallelled their actions on drinking.

With the rats which were drinking the chlordiazepoxide solutions the effects of injections of chlordiazepoxide and d-amphetamine were quite different from their actions on the water-consuming animals. Injections of chlordiazepoxide produced only decreases in tray entries, presumably due again to a summation of the injected drug with the consumed drug. d-Amphetamine, however, produced increases in tray entries particularly in the rats consuming the lower concentration of chlordiazepoxide. This action may have been due to an interaction between the injected d-amphetamine and the consumed chlordiazepoxide since combinations of these drugs have been reported to exert synergistic effects on behavior in other situations (e.g., [8]).

The results of the present experiment demonstrate that

adjunctive drinking is a useful procedure for inducing rats to ingest relatively large doses of chlordiazepoxide by drinking solutions of this drug. This behavior was shown to develop without prior experience of schedule-induced water consumption. It was also found that levels of adjunctive drinking and entries into the food tray could be modified by injections of chlordiazepoxide and d-amphetamine although the effects of these drugs depended to some extent on whether water or chlordiazepoxide solutions were being consumed.

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