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Nicotine and Schedule-Induced Drinking in Rats[1]

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SANGER, D. J. *Nicotine and schedule-induced drinking in rats.* PHARMAC. BIOCHEM. BEHAV. 8(4) 343–346, 1978. – In the first experiment 4 rats developed schedule-induced water drinking during daily 1 hr sessions of a fixed-time 1 min schedule of food pellet delivery. Injections of a range of doses (0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg) of nicotine hydrogen tartrate were found to produce a dose related attenuation of water intake. The higher doses also reduced the numbers of entries into the food tray in three rats, while the lowest dose consistently facilitated this behavior in the same animals. In a second experiment schedule-induced water drinking developed in 4 other rats under a similar schedule. Substitution of nicotine solution (0.05 and 0.1 mg/ml) for the water reduced volumes of fluid consumed. However, schedule-induced drinking continued at a rate sufficient for the animals to ingest average doses of the nicotine salt of up to 8.5 mg/kg. It is concluded that schedule-induced drinking can be used successfully as a method of inducing self-administration of nicotine by rats.

Schedule-induced drinking Nicotine Rats

ALTHOUGH nicotine is widely self-administered by man, relatively few studies have appeared in the literature which have investigated the self-administration of this drug by laboratory animals. There have been reports that rats and primates can be induced to self-administer nicotine under some circumstances by drinking drug solutions [5,12], self-injecting solutions [1,2] or smoking cigarettes [6]. However, the relatively small number of such reports may be taken as an indication that these procedures have not provided completely satisfactory techniques for inducing self-administration of this drug.

Schedule-induced drinking [3] is a procedure which has been shown to provide a useful method for inducing drinking of drug solutions by rodents and primates. Thus, solutions of several drugs will be consumed in relatively large amounts if they are made available to animals which are concurrently receiving intermittent presentations of small portions of food. Drugs which have been investigated under such circumstances include ethanol [4], opiate narcotics [8], barbiturates [9] and chlordiazepoxide [10]. The present study was an attempt to use schedule-induced drinking for the self-administration of nicotine by rats. However, since a number of drugs can affect levels and patterns of schedule-induced drinking [11] an experiment was also carried out in which the actions of injections of several doses of nicotine on schedule-induced water consumption were studied.

GENERAL METHOD

Animals

The animals were 8 experimentally naive female hooded rats. They were approximately 120 days old at the beginning of experimentation and weighed between 160 and 190 g. During the experiments they were individually housed and maintained at approximately 85% of their preexperimental body weights. Water was freely available in the home cages.

Apparatus

The experiments were carried out in standard operant test chambers sized 8 × 9 × 9 in. (Campden Instruments Ltd.) housed in sound-attenuating 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 approximately 1–2 mm behind 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

[1] This work was carried out at the Department of Psychology, University of Birmingham, U.K. while the author was supported by an I.C.I. Research Fellowship.

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 (45 mg standard formula, Campden Instruments Ltd.) was carried out using standard electromechanical equipment. The volumes of fluid consumed during each session were also recorded.

EXPERIMENT 1

Procedure

Four rats served as subjects in this experiment. After adaptation to the test chambers the animals were given daily 60 min sessions during which 45 mg food pellets were delivered at a rate of one each minute independently of each animal's behavior (fixed-time 1 min: FT 1 min). This procedure was continued until the animals showed consistent schedule-induced drinking during each session (approximately 20 sessions). The effects of several doses of nicotine hydrogen tartrate were then assessed by administering the drug by subcutaneous injection approximately 5 min before a session. The doses used were 0.25, 0.5, 1.0, 2.0 and 4.0 mg/kg, expressed as the salt. Each dose was given to each animal on two occasions and at least three nondrug days intervened between successive drug administrations. Doses were given in a mixed order which was different for each animal. Saline (0.9%) injections were given on all nondrug days and saline was also used for preparing the drug solutions. Injection volumes were 2 ml/kg.

Results

Shortly after injection of the higher doses of nicotine the animals appeared to be sedated. However, recovery from this condition appeared to be complete within approximately 10 min of the injection. The effects of the drug on schedule-induced water consumption are shown for individual rats in Fig. 1. The figure shows that nicotine produced a dose-related decrease in the volumes of water consumed. However, even at the highest dose used (4.0 mg/kg) drinking was not completely eliminated and when drinking did occur it showed the characteristic pattern of a rapid burst of licking following pellet delivery. The effects of nicotine on numbers of licks were similar to its effects on volumes of water consumed and are thus not presented.

Also shown in Fig. 1 are the effects of nicotine injections on numbers of entries into the food tray. The figure shows that numbers of tray entries were reduced by the higher doses of nicotine in 3 animals. However, in the fourth rat (R 3) this measure was unaffected by the drug. Also, the lowest dose (0.25 mg/kg) consistently increased numbers of tray entries in three animals.

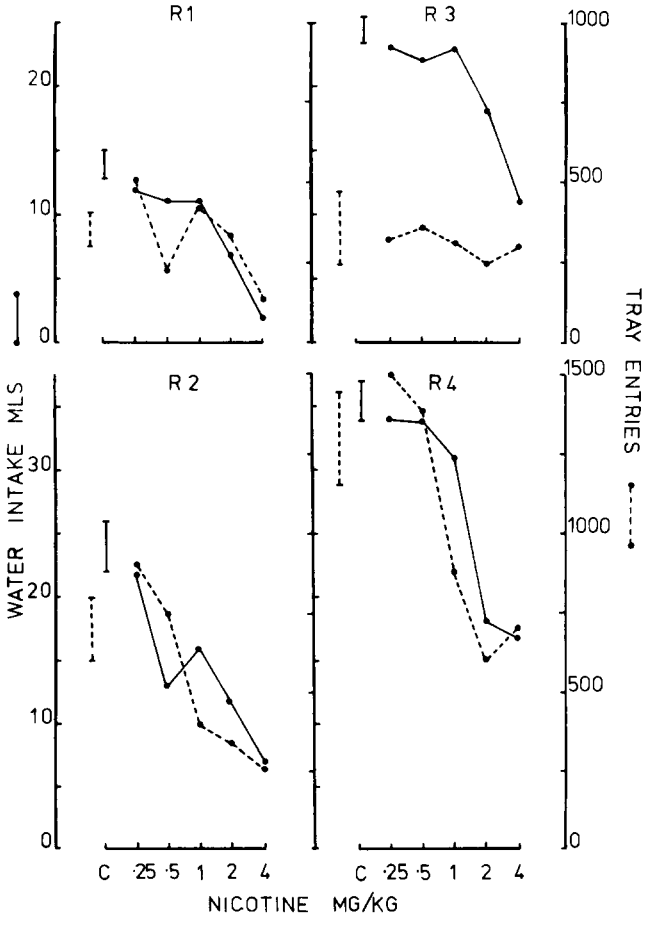

FIG. 1. Dose response curves showing the effects of injections of nicotine hydrogen tartrate on schedule-induced water drinking and entries into the food tray in four individual rats. Each point is the mean of two administrations of each dose. The vertical lines at C show the complete range of 10 control values taken from the sessions immediately preceding drug sessions.

EXPERIMENT 2

Procedure

Four rats served as subjects in this experiment. Initially the procedure was similar to that used in Experiment 1 so that a FT 1 min schedule was used during daily 60 min sessions to develop schedule-induced water drinking. After 20 sessions the water was removed and a solution of nicotine hydrogen tartrate in tap water at a concentration of 0.05 mg/ml was substituted. This solution was presented for the next 10 sessions after which water was returned for 10 sessions. Then, 10 sessions with a higher nicotine concentration (0.1 mg/ml) were given, followed by a further 5 sessions of water availability. One rat died during the course of the experiment and thus only 3 animals received the higher drug concentration. Water remained the available fluid in the home cages throughout the experiment.

Results

The volumes of fluid consumed during the various stages of the experiment are shown in Fig. 2. Initially daily water consumption during the sessions was between 20 and 30 ml. When water was removed and the lower concentration of nicotine (0.05 mg/ml) presented, volumes of fluid consumed decreased to between 10 and 20 ml although the pattern of postpellet drinking remained. Consumption increased when water was returned and declined again when the higher drug concentration was presented, although again patterns of drinking remained similar. Finally, fluid consumption again increased when water was presented during the final stage of the experiment.

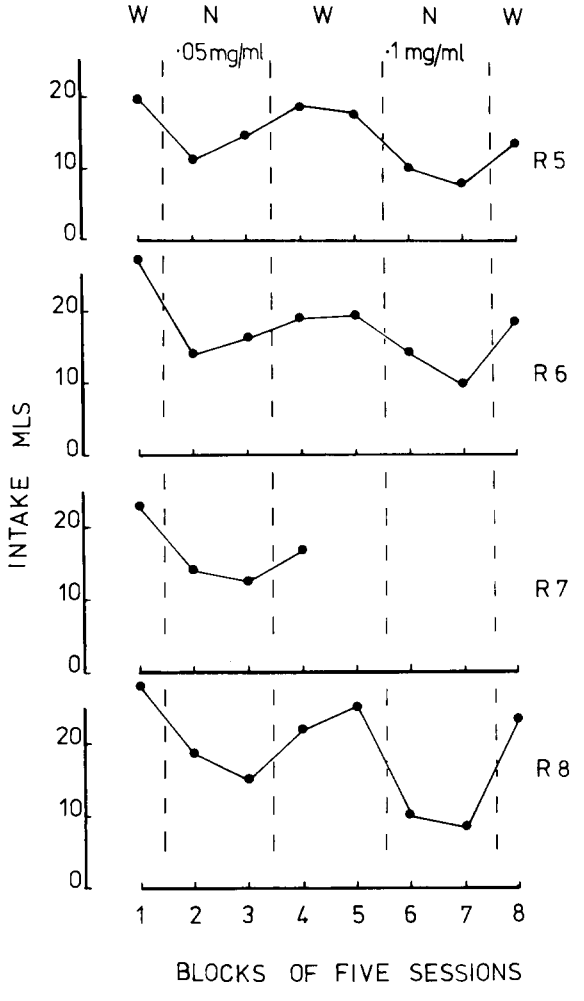

FIG. 2. Volumes of fluid consumed by individual rats during schedule-induced drinking of water or solutions of nicotine hydrogen tartrate in water. Each point is the mean daily fluid intake for a block of five consecutive daily sessions. W = water; N = nicotine.

The average doses of the nicotine salt ingested by individual animals during schedule-induced drinking of drug solutions are presented in Table 1. The table shows that even though the volumes of fluid consumed declined when nicotine was presented in place of water, the amounts of nicotine solutions consumed were sufficient for each animal to ingest doses higher than the highest dose administered by injection in Experiment 1.

TABLE 1

AVERAGE DAILY DOSES OF NICOTINE HYDROGEN TARTRATE CONSUMED BY INDIVIDUAL RATS DURING SCHEDULE-INDUCED DRINKING

Animal	Nicotine Concentration 0.05 mg/ml	0.1 mg/ml
R 5	4.6±1.0 mg/kg	5.6±1.8 mg/kg
R 6	5.3±1.1 mg/kg	8.5±2.3 mg/kg
R 7	4.4±1.0 mg/kg	—
R 8	5.9±1.1 mg/kg	6.3±2.0 mg/kg

Each value is the mean ± standard deviation of 10 sessions.

The numbers of entries into the food tray during the different phases of this experiment are shown in Table 2 in which these data are presented for 5 session blocks. In general tray entries increased when nicotine was presented but only in one animal (R 6) did this effect occur reliably throughout the experiment.

DISCUSSION

The results of the second experiment reported here showed that schedule-induced drinking may be used successfully as a technique for inducing the oral ingestion of solutions of nicotine by rats. In this experiment, individual rats consumed average doses of nicotine during daily 60 min sessions of up to 8.5 mg/kg although in the first experiment doses of 2.0 and 4.0 mg/kg, given by subcutaneous injection, were found to markedly reduce levels of schedule-induced water consumption. Other experimenters have also shown that similar doses of nicotine can exert depressant actions on other patterns of behavior [12]. It is interesting to note, however, that the lower doses of nicotine administered in the present Experiment 1, while slightly reducing the volumes of water consumed, did not consistently depress levels of tray entries, the other behavioral measure taken in this experiment. In fact, the lowest injected dose of nicotine (0.25 mg/kg) increased numbers of tray entries in 3 animals while in the other rat (R 3) tray entries were unaffected at any of the doses of nicotine used. Also, in Experiment 2 the substitution of nicotine solutions for water tended to increase the numbers of tray entries even though the doses of nicotine ingested

TABLE 2

NUMBERS OF ENTRIES INTO THE FOOD TRAY FOR INDIVIDUAL RATS DURING THE SUCCESSIVE PHASES OF THE EXPERIMENT

Animal	Phase Water	Nicotine 0.05 mg/ml		Water	Nicotine 0.1 mg/ml		Water
R 5	407	408	494	467	494	515	473	451
R 6	269	485	514	308	511	650	487	229
R 7	317	660	692	733	—	—	—	—
R 8	215	348	387	390	391	398	577	716

Each value is the mean tray entries/session for a block of five sessions.

were quite high in comparison to those administered by injection in Experiment 1. This is probably because the drug was consumed orally and over the period of 60 min while in Experiment 1 administration was by means of subcutaneous injection.

Since the present experiment was carried out, Lang *et al.* [7] have also reported the schedule-induced self-administration of nicotine solutions by rats. These researchers maintained rats on a fixed-interval schedule of food reinforcement and allowed the animals access to either nicotine solutions which could be consumed orally or to a lever, a depression of which produced an intravenous injection of nicotine. It was found possible to induce self-administration of nicotine by both schedule-induced drinking and schedule-induced self-injection. The presently reported experiments confirm and extend the findings of Lang *et al.* [7] in showing that, as with several other drugs, nicotine will be self-administered by rats subjected to a schedule of intermittent food delivery.

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