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Self Administration of Nicotine With and Without a Food Delivery Schedule

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LANG, W. J., A. A. LATIFF, A. MCQUEEN AND G. SINGER. *Self administration of nicotine with and without a food delivery schedule.* PHARMAC. BIOCHEM. BEHAV. 7(1) 65–70, 1977. — Rats have been shown to self administer a range of narcotic drugs using self injection procedures. However, studies of self administration of nicotine have been less successful in inducing rates of self injection comparable to that with narcotics. In this study different methods of self administration of nicotine by naive rats are evaluated. In the three series of experiments reported, rats self injected nicotine or saline through the jugular vein under normal body weight and reduced body weight conditions and also when the injections were adjunctive to a food delivery schedule. In a fourth series of experiments, oral intake of nicotine by rats under the condition of a food delivery schedule was investigated. The rates of self injection of nicotine by rats over a continuous 90 hr session were similar to saline injection rates. At reduced body weight the rate of self injection of nicotine was greater than saline. On a fixed interval 60 sec food delivery schedule for two hr a day, the rate of self injection of nicotine was significantly greater than the rate of self injection of saline under the same conditions and also significantly greater than that for nicotine injections at reduced body weight without the schedule. The oral intake of nicotine under the same conditions was similar to the intake of nicotine by schedule induced injections. Schedule induced self injections provide a paradigm for testing drug and environmental interactions.

Self administration of drug Nicotine

FOR THE STUDY of certain drug effects voluntary intake by animals of non-flavoured drug solutions is considered advantageous. Reports indicate that naive rats will self administer a range of opiates [4, 5, 8, 11] and cocaine [5, 10, 11] using self injection techniques. The aim generally of such experiments is to induce high levels of drug intake for the study of dependence, tolerance and withdrawal of the drug.

Another method of voluntary drug intake by animals is based on schedule-induced polydipsia (SIP). Animals at reduced body weight presented with a variety of intermittent food delivery schedules will drink excessive quantities of tap water as well as drug solutions which are normally rejected because of their aversive taste. SIP has been widely used to induce rats to drink ethanol (e.g. [7]) and solutions of narcotic analgesics (e.g. [9]).

Studies of intravenous self administration of nicotine have been less successful in inducing high levels of drug intake. In Deneau and Inoki's [3] study, the monkeys self injected only negligible doses of nicotine base which were not sufficient to induce tolerance or withdrawal symptoms.

In the present experiments different methods of self administration of nicotine by naive rats were investigated. In Experiment 1, the rates of self injection of two doses of nicotine and saline were compared when these drugs were available over a continuous 90 hr session. Since body weight reduction is an important variable in determining the level of schedule induced behavior, rats in Experiment 2 were reduced to 80% of their normal body weight. Rates of self injection of the higher dose of nicotine and saline were again compared over a continuous 90 hr session. In Experiment 3, oral intake of two concentrations of nicotine solutions under conditions of schedule induced food delivery was investigated in a two hr period per day and in Experiment 4, the rate of self injection of nicotine under the same conditions of schedule induced food delivery was compared with that of a saline control.

METHOD

Animals

Four naive Wistar white rats weighing approximately

400 g and 56 Lister hooded rats weighing 250–300 g were housed individually in a room with a 12 hr light-12 hr dark cycle. Food and water were available ad lib. In experiments requiring rats at 80% of their body weight these were reduced prior to surgery and then maintained at that weight, with water available ad lib.

In Experiments 1, 2 and 4, the rats were fitted with lightweight harnesses designed to support the implanted venous cannulae with a swivel system to allow relatively unrestricted movement. At surgery, a cannula of SP28 polyethylene tubing was inserted into the jugular vein. Rats were allowed three days to recover from surgery before being assigned to an experimental group.

Apparatus

The experimental chamber consisted of a Skinner box (35 × 32 × 32 cm) with a bar which when pressed, triggered a timing device set for a fixed interval of 5 sec. During this time a Palmer infusion pump delivered 0.07 ml of drug through the cannula and further bar presses during the 5 sec infusion were not rewarded with drug injections. All animals in Experiments 1, 2 and 4 were on a continuous reinforcement (CRF) schedule, that is, for each bar press, one dose of drug solution was delivered with the exception of a 5 sec fixed interval during drug infusion where bar presses did not result in a further infusion. For Experiments 3 and 4 a pellet dispenser was fitted to the box which delivered a 45 mg Noyes pellet on a FI 60 sec schedule. In Experiment 3, a lickometer tube, 10 cm from the pellet dispenser, recorded the number of licks during each session whereas in Experiment 4, the numbers of bar presses and self injections were recorded on a cumulative recorder. Each experiment commenced by priming the rat with an initial dose of drug solution or saline.

Drugs

Nicotine hydrogen (+) tartrate (B.D.H. Ltd.) was prepared for intravenous administration by dissolving it in sterile saline (0.9% NaCl). The anaesthetic used for the surgery consisted of a combination of methohexitone and amylobarbitone and the solution was injected intraperitoneally.

EXPERIMENT 1: RATE OF SELF INJECTION OF NICOTINE AT NORMAL BODY WEIGHT

In this experiment, the rate of self injections of nicotine at two doses was compared with the rate of self injection of saline over a continuous 90 hr session.

Procedure

Ten Lister hooded rats with venous cannulae were placed in the Skinner boxes for a continuous 90 hr session with nicotine available through bar pressing. For nine control rats, saline was available through bar pressing. The pump delivered 0.07 ml of the solutions per infusion. The nicotine solution was available for self administration by the rats at doses of 0.05 and 0.1 mg/kg for each bar press. Food and water were available ad lib.

Results

Those rats that bar pressed for nicotine injections displayed active and passive period during the 90 hr session. Three or more responses per hour was considered to be an active period.

Six rats were given an initial priming dose of 0.05 mg/kg but only three bar pressed for nicotine during the session. By averaging the total number of bar presses per session, a frequency of 1–2 presses per hour was obtained. During the active periods, rats bar pressed for nicotine from 3–16 times per hour, which is equivalent to 0.15–0.8 mg/kg/hr. The remaining three rats did not bar press at all during the first 48 hr of the session and were classified as negative. Three of the other four rats given an initial 0.1 mg/kg dose of nicotine continued to bar press at an average rate of 0.3–1 reinforcement per hour. During the active periods these rats bar pressed at rates varying from 3–7 injections per hour, which was equivalent to 0.3–0.7 mg/kg of nicotine per hour (see Fig. 1A).

Of the nine saline control rats, three recorded a similar number of bar presses to the nicotine rats, while the remaining six rats displayed negligible responses similar to the negative nicotine rats (see Fig. 2).

In summary, the rats that self injected nicotine, did so at a very low average response rate which was not different from the response rate of rats injecting saline.

EXPERIMENT 2: RATE OF SELF INJECTION OF NICOTINE AT A REDUCED BODY WEIGHT

The rates of self injection of nicotine at the higher dose of 0.1 mg/kg were compared with the rates of self injection of saline over a continuous 90 hr session in animals maintained at 80% of their body weight.

Procedure

Nine Lister hooded rats at 80% body weight were cannulated, allowed to recover and then placed in the Skinner boxes as in Experiment 1. Nicotine was made available for self administration to three rats while the six controls had saline available.

Results

All three rats on an initial dose of 0.1 mg/kg bar pressed for nicotine at a rate greater than those that bar pressed for this dose of nicotine in Experiment 1. An average frequency of 4–9 bar presses per hour was observed in the three rats. However, during the active periods rats bar pressed for injections 10–35 times an hour, which was equivalent to an intake of 1.0–3.5 mg/kg of nicotine per hour. The other six rats bar pressed for saline but the total number of bar presses over the 90 hr session was similar to the bar presses for nicotine and saline by rats at 100% of their body weight. This is shown in Fig. 2 where the total reinforced responses over the 90 hr session for rats at 80% and 100% body weight for saline and nicotine at a dose of 0.1 mg/kg have been compared. Figure 1B, on the other hand, presents the mean number of bar presses per hour during the active periods of self administration of nicotine and saline. The mean nicotine intake over the 90 hr session in this experiment was 0.27 mg/kg/hr compared with a mean intake of 0.04 mg/kg/hr in the rats during Experiment 1.

In summary then, the mean nicotine intake of rats at reduced body weight was approximately seven times greater than that of the free feeding body weight rats.

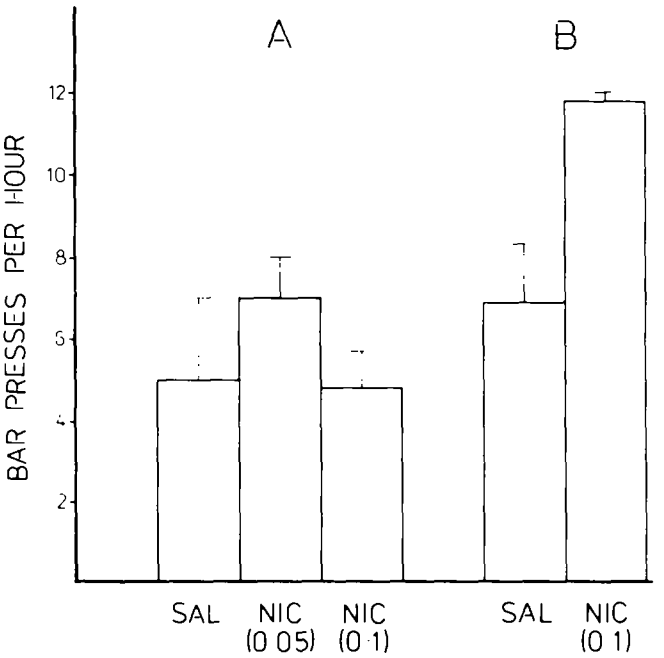

FIG. 1. Presents the mean number of bar presses per hour (+SD) during the active periods in Experiment 1(A) and 2(B) for rats self injecting nicotine and saline. The rates of self administration of nicotine at 0.1 mg/kg/ infusion are compared for rats at 100% body weight in Experiment 1 and 80% body weight in Experiment 2.

EXPERIMENT 3: ORAL INTAKE OF NICOTINE USING SIP METHOD

It has been shown that animals at 80% body weight when placed on an FI 60 sec food delivery schedule will voluntarily drink large volumes of water, or of a drug solution which they normally reject. In Experiment 3, this SIP paradigm was used to examine nicotine intake at two concentrations.

Procedure

Four Wistar rats were reduced to and maintained at 80% of their body weight, with water available ad lib. The rats were placed in the Skinner boxes for one hour on a FI 60 sec schedule. When lick rates and water intakes had stabilized over a few days, the water was replaced by nicotine solutions in concentrations of either 32 or 64 μg/ml. Lick rates and nicotine intakes were recorded for each session. After three days on nicotine the rats were returned to water and the usual recordings taken.

Results

An individual baseline for lick rate and water intake for each rat was established after a few days. When a nicotine solution of 32 μg/ml replaced water, the lick rates remained stable for two rats but slight increases were displayed by the others. A 64 μg/ml solution of nicotine in a lickometer tube for three days generally reduced lick rates and fluid intake in all rats. When water replaced the nicotine solution the original lick rate and water intake was re-established over the next few days. Figure 3 presents the pattern of lick rates of two rats representative of the group.

The mean nicotine intake of the four rats over the one hr session ranged from 0.90 - 1.35 ($\bar{x}$ = 1.32 ± 0.09) mg/kg at the higher concentration, which was similar to that consumed at the lower concentration, 0.96 - 1.38 (x = 1.08 ± 0.10) mg/kg.

In summary, the data show a large voluntary intake of nicotine which varied slightly with the concentration, but which was much higher when compared to the mean nicotine intake per hour over the 90 hr session in both Experiments 1 and 2.

EXPERIMENT 4: RATE OF SELF INJECTION OF NICOTINE ON A FOOD DELIVERY SCHEDULE

In the previous experiments, continuous self injections over long periods of time were used in an attempt to maximise nicotine intake. A pattern of active and non-active periods of self injection emerged with most of the nicotine intake occurring during the active periods. In Experiment 4, the animals on an FI 60 sec food delivery schedule at 80% body weight were allowed to self inject nicotine for two hr per day. This rate was compared with the rate of self injection of saline under the same scheduled conditions and with the rate of self injection of nicotine and saline of animals at 80% and 100% body weight without the food delivery schedule.

Procedure

The first two groups consisted of 12 Lister hooded rats with eight self injecting nicotine at 0.1 mg/kg/infusion for each bar press and the other four injecting saline. These rats at 80% body weight were placed on an FI 60 sec food delivery schedule during the two hr session. The remaining groups of eight rats at 80% and eight at 100% body weight were introduced into the Skinner boxes without the food delivery schedule; four rats in each group received nicotine for each bar press and four received saline. Thus, in total, three groups of rats self administered nicotine and three groups, saline.

Results

The mean number of bar presses for nicotine during each session for the three groups self injecting nicotine is shown in Figure 4A. The mean number of bar presses for the three saline groups is shown in Figure 4B. The mean number of bar presses during the two hour test period for the six groups is presented in Table 1.

The bar press data for this experiment were analysed by means of two way analysis of variance for drug effect and weight with food schedule conditions during the two hour session. The rate of bar pressing for nicotine by the three groups was significantly different from that of the three groups pressing for saline, $F(1,22) = 6.78$, $p < 0.05$. The rate of bar pressing between the three different body weight/ schedule conditions as shown in Table 1 was significant, $F(2,22) = 6.18$, $p < 0.01$. The interaction between the drug effect and the body weight conditions was not significant, $F(2,22) = 3.01$, $p > 0.05$.

A Scheffe post hoc analysis showed that bar pressing rates for nicotine were significantly higher under the food delivery schedule when compared to 80% body weight reduced rats without the schedule, $F(2,22) = 3.90$, $p < 0.05$ and hence the 100% body weight rats, $F(2,22) = 7.70$, $p < 0.01$. Also saline self injection rates were significantly lower than nicotine self injection rates in a comparison of

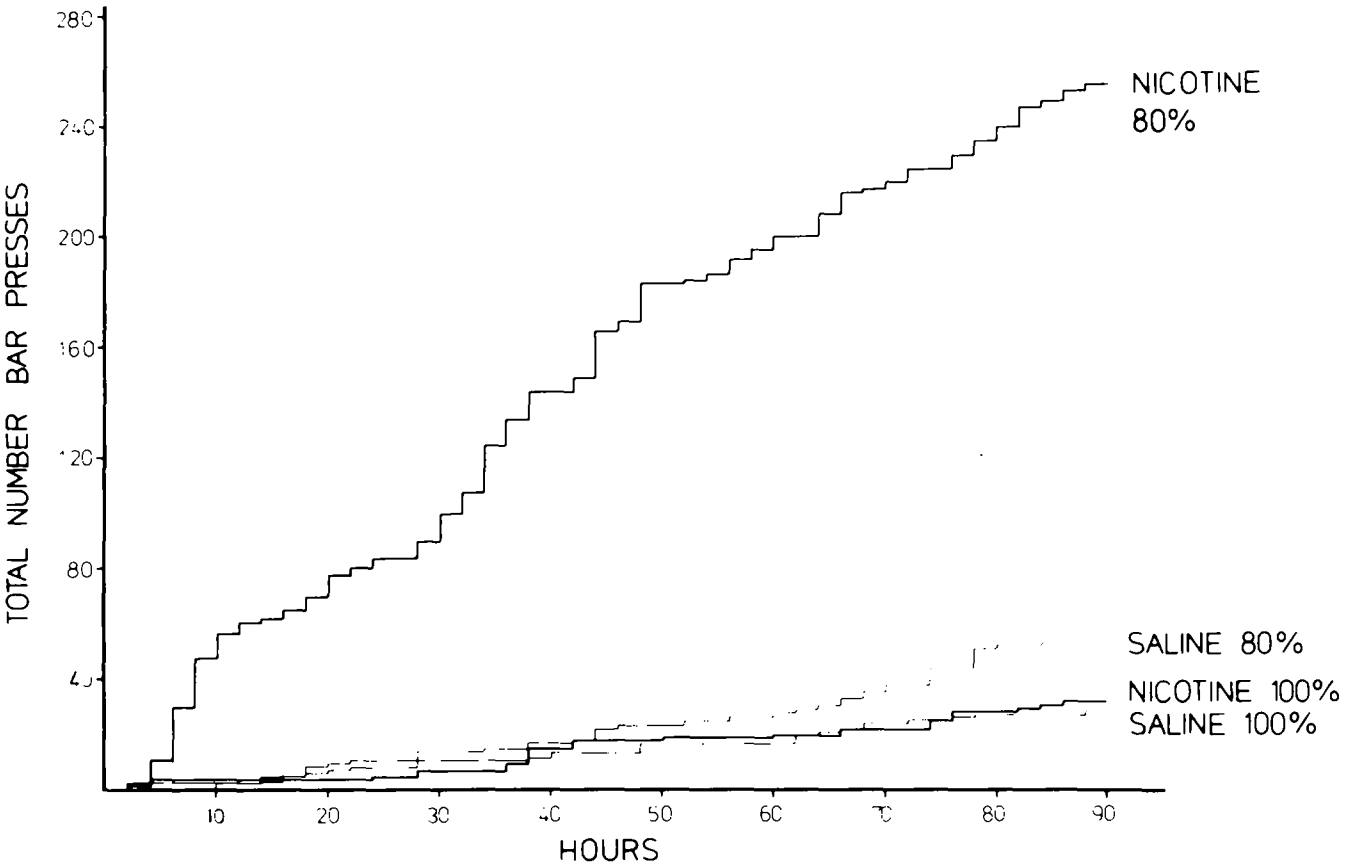

FIG. 2. Presents the total number of bar presses over the 90 hour session of one rat representative of each of the 100% body weight rats self administering nicotine (0.1 mg/kg/infusion) and saline. One rat from each of the 80% body weight rats self administering nicotine (0.1 mg/kg/infusion) and saline is also shown.

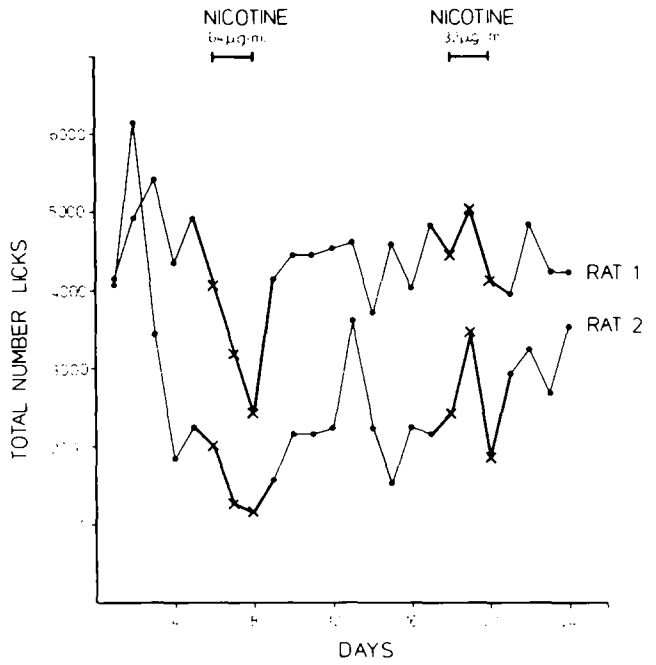

FIG. 3. Presents the total number of licks of two rats, representative of the group, over the days tested, when water and nicotine at concentrations of 32 and 64 μg/ml were available.

TABLE 1

MEAN OF TOTAL BAR PRESSES ± SDM FOR NICOTINE (0.1 MG/KG/INFUSION) AND SALINE BY THE THREE GROUPS OF RATS

Body Weight / Schedule Conditions	Nicotine	Saline
80% + FI60	22.64 ± 7.21	3.59 ± 0.90
80%	6.39 ± 2.62	2.33 ± 1.12
100%	2.22 ± 1.33	2.00 ± 1.56

the two groups on a food delivery schedule, $F(2,22) = 5.31$, $p < 0.05$. There were no other significant effects between the various comparisons of the remaining groups, $F(2,22) < 3.44$, $p > 0.05$).

The bar pressing was equivalent to a mean nicotine intake of 1.13 ± 0.36 mg/kg/hr for the food schedule group, 0.31 ± 0.13 mg/kg/hr for the 80% body weight reduced group and 0.11 ± 0.07 mg/kg/hr for the normal body weight group. The difference between the nicotine intake for the 80% body weight rats with and without the food delivery schedule was significant ($t = 5.20$, $df = 10$, $p < 0.01$). However, the nicotine intake of the 80% and

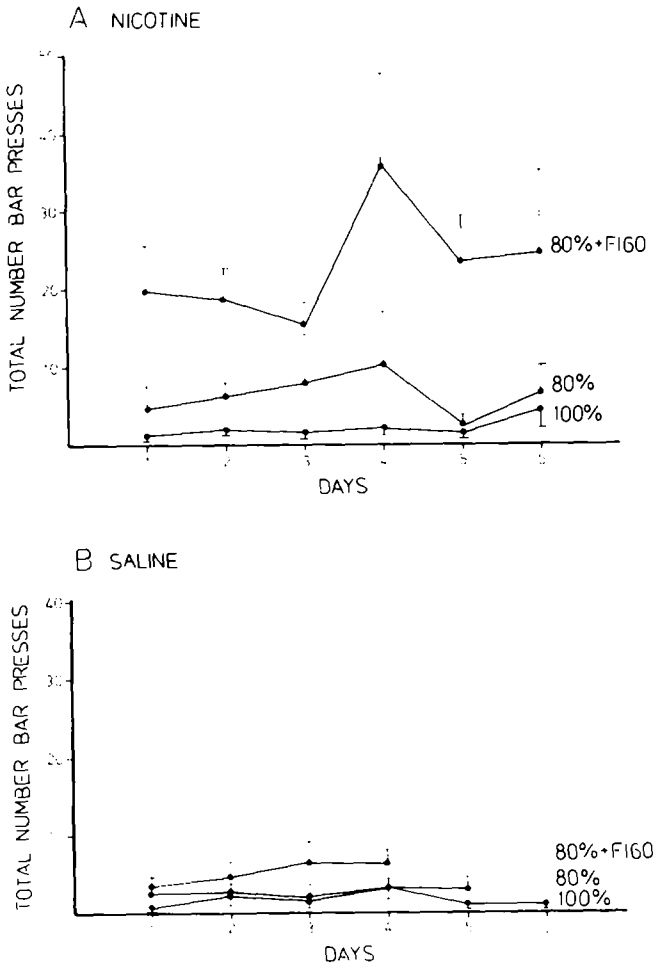

FIG. 4A. Presents the mean number of bar presses (±SE) for nicotine (0.1 mg/kg/infusion) for each session of the three groups of rats. 4B. Presents the mean number of bar presses (±SE) for saline by the three groups of rats.

100% body weight rats without the food delivery schedule was not significantly different ($t = 0.59$, $df = 10$, $p > 0.05$).

In summary, the 80% body weight rats on the food delivery schedule bar pressed for nicotine at a significantly higher rate than any of the other rats.

DISCUSSION

To our knowledge, this is the first report of schedule induced self injection of drugs by rats. When their body weight is reduced and food pellets are provided at 60 sec intervals, rats bar press at considerably higher rates to obtain injections of nicotine than they do to obtain saline injections. On the other hand, rats which can obtain nicotine injections by bar pressing without schedule control will normally do so at a rate little different to the rate of bar pressing to self administer injections of saline.

Previous attempts to study self administration of nicotine injections in rats by Clark [2] or in monkeys by Deneau and Inoki [3] showed that even with priming, only small amounts of the drug were administered, suggesting that nicotine had poor reinforcing capacity. In contrast, Pickens and Thompson [10] showed that rats would self administer injections of cocaine and that this was maintained over a range of doses. They concluded that cocaine served as a reinforcer of behavior. Other reports indicate similar patterns of self injection for narcotic drugs [4, 5, 8, 11].

The intake of nicotine under conditions of schedule induced self injections is similar to the intake under conditions of schedule induced polydipsia with solutions of nicotine over the same period. It therefore appears that for nicotine, taste aversion is not an important factor in reducing drug intake. However, studies by Clark [1] indicate that rats exhibit a preference for nicotine solutions over water at concentrations up to 64 μg/ml when a slight reversal appeared. It is interesting to note in our study that rats drinking low or high concentrations of nicotine solutions take in equivalent amounts of nicotine.

There was no significant increase in the rate of saline self injection by rats under conditions of schedule induced control compared to the rate without schedule control. This together with the data on nicotine intake suggests that there was an interaction of environmental and pharmacological factors leading to the development and maintenance of self administration of nicotine. Some pharmacological action of nicotine occurring under schedule induced conditions seems to be of more importance than is the case when bar pressing for nicotine injections is not schedule induced.

When nicotine was freely available on bar pressing, it was observed in our experiment that the rate of self injection of nicotine by rats was increased when their body weight was lowered to 80% by food reduction. This may mean that nicotine acted to suppress hunger or that hunger might have evoked the increase in activity. These possibilities are being investigated in additional experiments.

The use of schedule induced conditions to maintain self administration of drug injections provides a new means of studying voluntary drug intake in naive animals. This model has the advantage over similar techniques using schedule induced polydipsia to administer drugs, because it eliminates the problem of simultaneous large water intake. It is also a paradigm which will allow the study of psychological and physical factors in drug taking behavior and their interactions. Consideration of this interaction of the pharmacological and environmental factors has been neglected in previous studies. For the comparison of different drugs, schedule induced self injection seems to offer advantages over other experimental models in studying maintenance of self administration as well as drug dependence and withdrawal.

In these experiments, no formal testing for dependence or withdrawal was conducted. However, other studies in our laboratory indicate that withdrawal for nicotine is minimal or absent. This model could also be used for testing dependence or withdrawal symptoms of other drugs, for example, ethanol [6].

ACKNOWLEDGEMENT

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