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Acquisition of nicotine self-administration in rats: the effects of dose, feeding schedule, and drug contingency

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Abstract The studies presented here were designed to further clarify the nature of nicotine self-administration (SA) based on a limited access model in which rats are food restricted, receive operant training using food reinforcement, and are then tested in daily 1-h drug sessions. We examined the effects of dose, feeding schedule, and contingency of drug delivery on acquisition of nicotine SA. Two doses of nicotine bitartrate, 0.03 and 0.06 mg/kg per infusion (free base), supported the transition from food-reinforced to drug-reinforced responding, although the pattern of behavior differed between these doses. In contrast, 0.01 mg/kg per infusion failed to maintain nicotine SA. In a second study, animals were divided into three groups according to feeding schedule. Rats that were both weight restricted and food deprived showed the highest level of SA behavior, although neither food deprivation nor weight restriction was necessary to establish SA. In the third experiment, rats that were switched from food to nicotine as the response-dependent reinforcer maintained higher response rates throughout a 9-day period than animals switched to response-independent (i.e., yoked) nicotine which showed minimal responding after day 1. Furthermore, the differences between self-administering and yoked animals emerged during the first session, suggesting that nicotine may serve as a reinforcer during the first drug exposure in naive animals. These results indicate that acquisition of nicotine SA can be influenced by both dose of nicotine and feeding schedule and that, in animals previously trained on a food-reinforced operant, active lever pressing is maintained only when nicotine delivery is contingent upon responding.

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Introduction

The reinforcement provided by nicotine is a necessary component of the processes that drive smoking behavior (USDHHS 1988). This observation has stimulated the development of animal models useful in determining the psychopharmacological parameters and neurobiological basis of nicotine's reinforcing effects. These models differ along several important dimensions. For example, nicotine has been found to reinforce operant responding in a variety of species, including non-human primates (Goldberg et al. 1981; Wakasa et al. 1995), dogs (Risner and Goldberg 1983), rats (Corrigall and Coen 1989; Corrigall 1992; Donny et al. 1995, 1996; Smith and Roberts 1995; Tessari et al. 1995; Chiamulera et al. 1996; Shoaib et al. 1996, 1997; Valentine et al. 1997) and mice (Martellotta et al. 1995). The range of species, including humans (Henningfield et al. 1983), that find nicotine reinforcing speaks to the generality of the phenomenon.

Animal models differ in several other ways, including whether an intravenous (IV) or oral route of administration is used, whether the schedule of access to the drug is continuous or limited and intermittent, whether animals are maintained on free feeding or restricted feeding schedules, and whether animals receive prior operant training and/or drug exposure before the first self-administration (SA) session. Reliable SA of nicotine has been reported under all of the above conditions. Each variation confers unique advantages for asking specific questions about the reinforcing properties of nicotine, but each must be interpreted within the constraints of the parameters chosen. For example, limited, intermittent access, such as 1–2 h per day, leads to more rapid acquisition and higher and more stable rates of drug-maintained behavior (Goldberg et al. 1983; Henningfield and Goldberg 1983; Carroll et al. 1990). It also minimizes the toxicity which can result from an overdose during continu-

ous access (Fitch and Roberts 1993), and enables the use of experimental designs which require large groups of animals or high temporal resolution. On the other hand, questions regarding chronic, continuous drug exposure or patterns of administration can more readily be addressed with a continuous access model.

The present paper deals with a model for nicotine SA in rats developed by Corrigall (Corrigall and Coen 1989; Corrigall 1992) and recently employed by other laboratories (Tessari et al. 1995; Chiamulera et al. 1996), including this one (Donny et al. 1995, 1996). In this model, rats are initially trained to bar press on an FR1 schedule for food reinforcement. All subsequent experimental sessions last 1 h/day, during which bar pressing results in nicotine infusions rather than food. Throughout, animals are maintained on a feeding schedule of 20 g per day, given immediately following each SA session. A unique advantage of prior operant training and the restricted feeding schedule, two features which have frequently been used in studies of drug reinforcement, is that high operant rates and drug infusions are achieved very rapidly, i.e., in the first session. This permits an examination of the acute effects of response-contingent nicotine in drug-naive animals, before those effects can change as a result of more extended, chronic exposure. The strategy is based on the assumption that chronic effects of response-contingent nicotine, and adaptations such as tolerance or sensitization, can be more accurately gauged by first establishing the acute effects. The disadvantage of this procedure is that it is unclear when, in the first several sessions, control of the operant response is transferred from food reinforcement to drug reinforcement. The purpose of the present study was to further characterize some of the features of this limited access model.

Dose-response functions for this model exist only for the maintenance phase, after rats acquire stable SA under a single dose regimen (Corrigall and Coen 1989; Corrigall 1992; Donny et al. 1995; Tessari et al. 1995). Under these conditions, a relatively flat, inverted U-shaped function has been reported, with peak responding at a nicotine dose between 0.01 and 0.03 mg/kg per infusion (free base). The first aim of the present study was to establish a dose-response relationship during the acquisition phase of SA.

It is well known that the schedule of feeding affects SA of a wide range of drugs, including nicotine; continuous access to food suppresses drug SA, whereas schedules that restrict food intake and weight gain facilitate drug SA (Lang et al. 1977; Carroll and Meisch 1984; Carroll et al. 1990). In the present model, rats are fed a daily ration of 20 g, which is equivalent to their daily nutritional requirement (CCAC 1980) after each SA session. This restricted feeding schedule is not a form of chronic food deprivation. In fact, this schedule results in modest weight gain, in contrast to the excessive weight gain produced by free feeding. It is important to note that unlimited feeding, while commonly used, is not necessarily the most healthy or natural diet for laboratory animals. Recent data indicate that laboratory rats are healthier and live longer under restricted, rather than unlimited feeding schedules (Abelson 1995; Hart et al. 1995). In the present study, we determined the effects of restricted food intake on the acquisition of SA. Since this schedule both restricts weight gain and presumably leads to a period of hunger prior to each SA session, we compared the acquisition of nicotine SA of rats receiving unlimited food with those given 20 g, 2 h prior to, or just after each session.

Prior training on a food-reinforced operant, bar pressing, is also used in this model to facilitate the acquisition of nicotine SA. To the extent that nicotine is reinforcing, it should substitute for food in maintaining bar pressing, but only if drug administration is contingent on that response. In order to better characterize this relationship, we compared bar pressing of rats that were switched from food to nicotine as the response-dependent reinforcer, with response rates of animals switched to response-independent (i.e., yoked) nicotine or saline.

Materials and methods

Subjects

Male, Sprague-Dawley rats (Zivic Miller), 41–44 days old and weighing between 200 and 225 g upon arrival, were individually housed in a temperature controlled environment on a 12-h reverse light/dark cycle (lights off from 7:00 a.m. to 7:00 p.m.). Prior to any experimental manipulation, animals were given a minimum of 7 days to habituate to the colony room, during which they were weighed, handled and received unlimited access to both food and water. All animals were then food deprived for 24 h and trained to lever press on the right (active) lever for 45 mg food pellets. Training consisted of a single 20-min habituation session, a 25-min magazine training session, hand shaping (during which animals received approximately 20 pellets as a consequence of responding on the active lever), and an FR1 session in which a maximum of 75 food reinforcements was given. Responding on the left (inactive) lever had no scheduled consequence. Unlimited access to water was available throughout all experiments. All animals received 20 g/day of food after each experimental session unless otherwise noted. In all experiments, subjects which were trained to lever press and implanted with catheters were randomly assigned to experimental groups.

Surgery

After acquiring the operant, all animals were anesthetized with Equithesin (3 ml/kg IP) and implanted with a catheter into the right jugular vein as described by Corrigall and Coen (1989). All animals received ampicillin (100 mg/kg SC) treatment which consisted of a single injection on the day of surgery, twice daily injections for the 3 subsequent days, and a single injection on the morning of day 4. Animals were allowed 4–8 days to recover from surgery, during which time their catheters were flushed twice a day for 3 days and then once daily with 0.1 ml sterile, heparinized saline (30 U/ml). Thereafter, catheters were flushed with 0.1 ml sterile, heparinized saline (30 U/ml) prior to and following each session throughout each study.

Experimental sessions

Experimental sessions began immediately following the recovery period. All sessions lasted for 1 h per day during which time the

subjects were connected to a drug delivery system which allows virtually unrestricted movement throughout the chamber. For all SA animals, responding on an active lever was reinforced with nicotine bitartrate (Sigma; all doses are reported as free base and detailed below) delivered in a volume of 0.1 ml/kg in approximately 1 s (IITC model 100, pneumatic syringe pump or Med Associates model PHM100-10 rpm), while responding on an inactive lever had no consequence. Active lever responses, inactive lever responses and infusions were recorded by an interfaced computer and software (Med Associates, MED-PC 2.0) throughout each session. All infusions were paired with a 1-s cue light and followed by a 1-min time-out period, during which the chamber light was turned off and responding was recorded, but not reinforced.

Effects of nicotine dose on acquisition of self-administration

Twenty-seven rats were allowed to self-administer nicotine at one of three doses, 0.01 (n=8), 0.03 (n=10), or 0.06 mg/kg per infusion (n=9), for 15 consecutive daily sessions. Schedule requirements progressed from an FR1 (days 1–5) to an FR2 (days 6–10) to an FR5 (days 11–15). Group sizes are unequal due to catheter failure.

Effects of feeding schedule on nicotine self-administration

Forty rats were run for 15 consecutive, daily SA sessions. Prior to the first SA session subjects were randomly divided into three groups. Animals in each group were fed 20 g after their first SA session; group differences in feeding schedules were not instituted until after the second session. The first group (20 g/After; n=13) continued on our normal feeding schedule of 20 g given after each SA session throughout the experiment. This feeding schedule results in both restricted weight gain and a deprivation state during SA sessions. The second group (20 g/Prior; n=12) was fed 10 g after their second session, 10 g 2 h prior to their third session and, starting on day 4, fed 20 g/day 2 h prior to each session for the remainder of the experiment. In almost all cases, 2 h was ample time for the animals to finish their daily allotment. The transition from 20 g given after the session to 20 g prior to the session in the second group was done in this way to avoid completely depriving this group of food on the second day while still restricting food intake to 20 g in between each session. This schedule restricted weight gain, but did not result in a state of food deprivation during the SA session. The third group (Unlimited; n=15) had continuous access to food beginning immediately following the second SA session, therefore experiencing neither weight restriction nor food deprivation. This group consumed approximately 38 g food per day. Groups did not differ until after the second session, in order to allow the initial transfer from food to nicotine reinforced lever pressing in rats that were still motivated to lever press. These feeding schedules resulted in a mean (±SEM) weight gain over the 15 SA days of 32.8±3.1 g, 27.3±8.1 g, and 139.0±5.9 g for 20 g/After, 20 g/Prior, and Unlimited, respectively. Each group was run on an FR1 for days 1–5, an FR2 for days 6–8, and an FR5 for days 9–15. All groups were reinforced for active lever pressing with 0.03 mg/kg per infusion delivered in approximately 1 s.

Effects of drug contingency on operant behavior

Animals were trained on the food-reinforced operant and placed on the food restricted schedule (20 g after), according to our standard procedure. Lever trained rats with patent catheters were then divided into triads with one member in each triad being assigned to one of three groups. The first group (SA/Nic) was allowed to self-administer nicotine bitartrate (0.03 mg/kg per infusion). Individuals in the second group (Yoked/Nic) received the same number of nicotine (0.03 mg/kg per infusion) infusions at identical times during each session as compared to their self-administering partner. Their infusions were contingent upon their self-administering partner's responding and not upon their own lever pressing. The third group (Yoked/Sal) was also yoked to individuals in the SA/Nic group, but received saline infusions instead of nicotine. Active and inactive lever pressing in the yoked groups were recorded, but did not result in any scheduled consequences. Only complete triads were included in the analyses (n=16 triads or 48 rats).

All animals were run for nine consecutive, daily, 1-h experimental sessions. For self-administering animals, responding on the active lever was reinforced on an FR1 for all 9 days. All changes in the cue light and house light were identical for all three groups and based on the self-administering animal's active lever responding. These data are derived from ongoing studies measuring nicotine's neuroendocrine effects. For this purpose, animals were habituated to the experimental chamber for 1 h on each of 2 consecutive days prior to the first session and for a 10-min period immediately before the first session. Lever access was prevented during these periods. Neuroendocrine data are not reported here.

Statistical analyses

For the first and second studies (i.e., dose and feeding), analyses were first performed using all animals which completed all 15 days of SA sessions. Analyses were then repeated using only the subset of animals which acquired nicotine SA, according to the following criterion: active lever responding greater than twice the inactive lever responding, with a minimum of ten active lever responses, for the majority of days on an FR5. This criterion was derived by setting a 95% confidence interval around active lever responding in animals receiving non-contingent (yoked) nicotine and determining a point (ten responses) which was greater than the upper limit for each of the last three of ten daily sessions. Requiring twice the inactive lever response rate assured that responding was specific to the active lever. Only analyses using rats which met the acquisition criterion are reported. However, the same pattern of results was found when all animals were included in the analyses, indicating that the results are not a function of an arbitrary acquisition criterion.

Analyses of active lever responding, inactive lever responding, infusions, and total drug intake consisted of MANOVAs with Group as a between subjects factor and Day as the within subjects factor. Preplanned group comparisons across days and for individual days were also performed and reported. For study 2 (i.e., feeding), only days 3–15 were included in the MANOVAs, since the experimental manipulation which differentiated groups did not occur until after day 2. For the third study (i.e., drug contingency) a MANOVA with Day as the within subjects factor and Group as the between subjects factor was run on active and inactive lever responses. Individual groups were then compared by preplanned contrasts across the 9-day period and on each of the 9 days. A statistical significance level of $P<0.05$ was used for all analyses.

Results

Effects of nicotine dose on acquisition of self-administration

Nicotine SA was obtained at the 0.03 and 0.06 mg/kg per infusion doses, but not at 0.01 mg/kg per infusion. Of the eight rats in the 0.01 mg/kg per infusion group, only one (13%) reached the acquisition criterion. Animals receiving 0.01 mg/kg per infusion as a group showed extinction of responding over the 15-day period, receiving approximately five infusions/day for the first 7 days, and then approaching zero during the second part of the acquisition period. When animals which met the acquisition criterion at the two higher doses were compared,

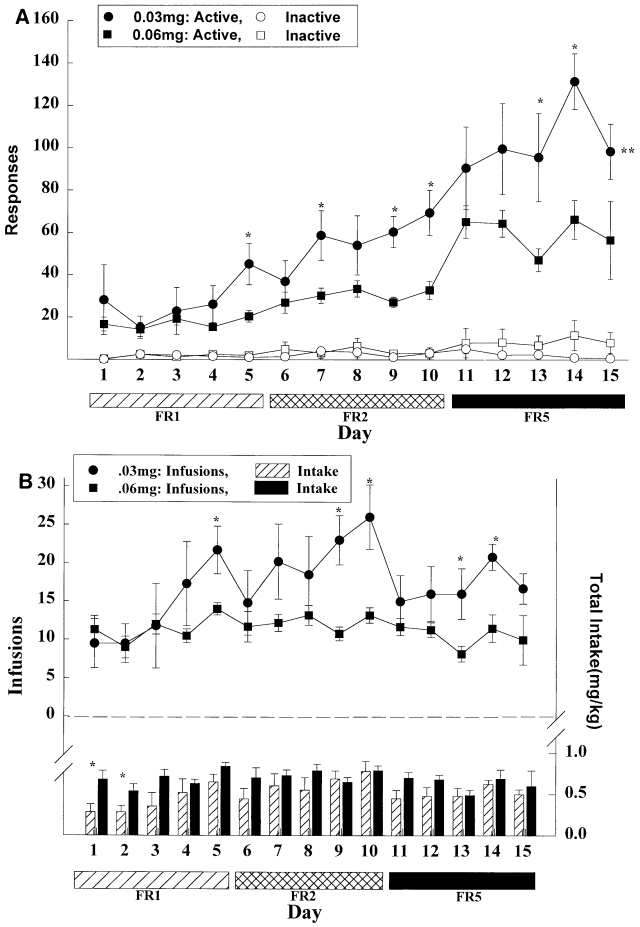


Fig. 1A, B Mean active and inactive lever response rates (**A**) and mean number of infusions and total drug intake (**B**) for animals which acquired stable SA during the 15 day period at 0.03 and 0.06 mg/kg per infusion. * 0.03 mg/kg per infusion significantly different from 0.06 mg/kg per infusion ($P<0.05$). *Single symbols* represent group differences for a single day, *double symbols* represent group differences across days 3–15

greater active lever response [$F(1, 10)=14.32$, $P<0.005$] and infusion [$F(1, 10)=4.89$, $P=0.05$] rates (i.e. number of responses and infusions per hour) were seen at 0.03 mg/kg per infusion, while there was little difference in total intake. There was a significant effect of Day for active lever responses [$F(14, 140)=14.24$, $P<0.001$], infusions [$F(14, 140)=2.85$, $P<0.005$], and total drug intake [$F(14, 140)=2.87$, $P<0.005$]. No interaction effects were observed. Day by day differences between groups can be seen in Fig. 1.

There was a tendency for 0.06 mg/kg per infusion to result in greater total intake of nicotine for a couple of days each time the schedule of reinforcement was changed, but this disappeared after the first few days under each schedule. To explore this observation further, the linear changes in infusions received per day over each 5-day period corresponding to a particular schedule of reinforcement were analyzed for group differences. Linear changes were determined by using polynomial contrasts for the linear effect of Day within regression analysis. Group was entered as a contrast coded variable and the interaction between Group and the linear effect of "Day" was used to determine if group differences in linear trends occurred. The results revealed a significant linear trend for both 0.03 [$F(1, 5)=11.97$, $P<0.05$] and 0.06 mg/kg per infusion [$F(1, 5)=6.23$, $P=0.05$] during the FR1 portion, only for 0.03 mg/kg per infusion during the FR2 [$F=(1, 5)=6.27$, $P=0.05$], and for neither group during the FR5 portion. A group difference in the linear trend was seen for the FR1 [$F(1, 10)=6.80$, $P<0.05$] and a strong trend for the FR2 [$F(1, 10)=4.56$, $P=0.06$] portion of the experiment with the 0.03 mg/kg per infusion groups showing a greater increase across days. This difference in intake appeared to be due to a temporary decrease in infusions, which occurred each time the schedule changed for rats self-administering 0.03 mg/kg per infusion and lasted for two to three sessions. This pattern was not seen in animals self-administering 0.06 mg/kg per infusion.

Effects of feeding schedule on nicotine self-administration

Nicotine self-administration was observed under all three feeding schedules, with the most robust active lever responding occurring in the 20 g/After animals (Fig. 2). Animals from all three feeding schedules acquired nicotine SA according to the criterion outlined above [nine of 15 Unlimited (60%), eight of 12 20 g/Prior(67%), and nine of 13 20 g/After (69%)]. Self-administration of nicotine, as indicated by active lever response rates and total number of infusions earned, was greater in the 20 g/After group than in either the 20 g/Prior or Unlimited groups, which showed few significant differences from each other (see Fig. 2). There was a significant effect of Group and Day on both active lever responding [Group: $F(2, 23)=6.48$, $P<0.01$; Day: $F(12, 276)=18.71$, $P<0.001$] and infusions [Group: $F(2, 23)=5.58$, $P<0.05$; Day: $F(12, 276)=3.32$, $P<0.001$], while the Group by Day interaction was only significant for active lever responses [$F(24, 276)=2.23$, $P<0.001$]. The 20 g/After group responded significantly more than both the 20 g/Prior and Unlimited group on the active lever across the 13 days. Day by day comparisons revealed significantly greater responding in the 20 g/After group as compared to the 20 g/Prior group, on 4 of 13 days, and as compared to the Unlimited group, on 8 of 13 days (Fig. 2). Active lever responding and infusions in the Unlimited group were significantly less than the 20 g/Prior group only on day 11 and days 10 and 11, respectively. The 20 g/After group self-administered significantly more infusions than the Unlimited group on days 3–13 as well as across the 13 days, and significantly more than the 20 g/Prior group on 4 of 13 days.

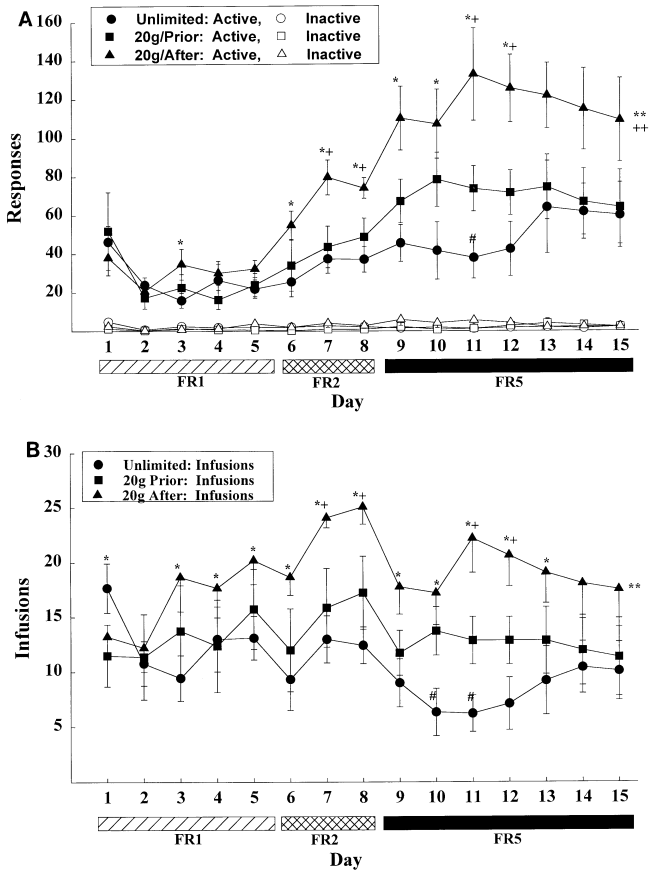


Fig. 2A, B Mean active and inactive lever response rates (**A**) and mean number of infusions (**B**) for animals which acquired stable SA during the 15 day period in each of the three groups: 20 g/After, 20 g/Prior, and Unlimited. +20 g/After significantly different from 20 g/Prior ($P<0.05$). * 20 g/After significantly different than Unlimited ($P<0.05$). *Single symbols* represent group differences for a single day, *double symbols* represent group differences across days 1–15. #Unlimited significantly different than 20 g/Prior ($P<0.05$)

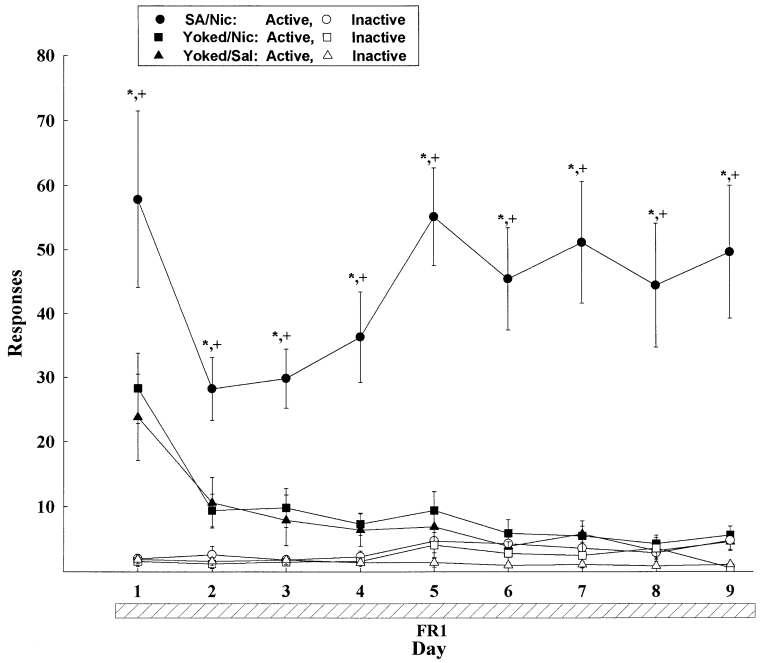
Fig. 3 Mean active and inactive lever response rates over a 9-day period for SA/Nic, Yoked/Nic and Yoked/Sal. +SA/Nic significantly different from Yoked/Nic ($P<0.05$). * SA/Nic significantly different from Yoked/Sal ($P<0.05$)

Effects of drug contingency on operant behavior

Response-dependent nicotine (SA/Nic) maintained active lever responding throughout the 9-day period, while response-independent nicotine (Yoked/Nic) and saline (Yoked/Sal) failed to support robust lever pressing behavior after day 1 (Fig. 3). Active lever responding was significantly greater than inactive lever responding for the SA/Nic group throughout the 9-day period. For both the Yoked/Nic and Yoked/Sal groups, active lever responding declined over the 9-day period, although it remained elevated over inactive lever responding on 3 and 5 of the last 5 days, respectively, indicating that complete extinction had not yet occurred. The MANOVAs resulted in a significant effect of Group on active [$F(2, 45)=32.73$, $P<0.001$], but not inactive lever responding. The effect of Day was only significant for active lever responding [$F(8, 360)=5.99$, $P<0.001$]. The Group by Day interaction was significant for active lever responding [$F(16, 360)=1.83$, $P<0.05$], but was not significant for inactive lever responding. Active lever responses were significantly greater in the SA/Nic group on every day as compared to Yoked/Nic and Yoked/Sal ($P<0.05$). There were no significant differences between Yoked/Nic and Yoked/Sal in either active or inactive lever responding. Self-administered nicotine produced greater inactive lever responding on the ninth day as compared to Yoked/Nic and Yoked/Sal. There were no other significant group differences.

Discussion

In the first experiment, 60% and 67% of animals acquired stable nicotine SA at 0.03 and 0.06 mg/kg per infusion, respectively, but only one rat (13%) met the crite-



rion for stable SA at 0.01 mg/kg per infusion. Although differences between reported studies in the criteria used for stable SA make direct comparisons difficult, these percentages for the higher two doses are comparable to those reported by Shoaib et al. (1997) but somewhat lower than the 82% we had previously reported using a more stringent criterion (Donny et al. 1995; 95% when recalculated using present criterion). These differences may be due to variability in responsiveness to nicotine between shipments of animals from a single supplier (unpublished observations).

While there were no differences between 0.03 and 0.06 mg/kg in the percentage of animals that acquired SA, dose did affect the level of responding, number of infusions earned, and possibly the stability of behavior. Response and infusion rates were higher for 0.03 than 0.06 mg/kg per infusion, resulting in similar amounts of total drug taken over the 1-h period. These findings are consistent with previous reports that, within this dose range and limited access schedule, rats tend to maintain approximately equal intake of nicotine by adjusting response and infusion rates (Corrigall and Coen 1989; Corrigall 1992; Shoaib et al. 1997). Lower infusion rates at higher doses and equal total intake have also been reported for other drugs such as amphetamine and cocaine (Wise 1987; Carroll and Lac 1997). Our failure to find evidence of such compensation in our previous report (Donny et al. 1995), in which total intake was higher for 0.06 than 0.03 mg/kg, may have been due to the fact that, unlike the present study, in which animals had an extended period of time to learn to regulate total intake of nicotine at a single dose, the earlier report included rats that were trained on 0.03 mg/kg per infusion and switched to 0.06 mg/kg per infusion for only 3–5 days.

Animals self-administering 0.03 mg/kg per infusion showed decreases in response and infusion rates each time the operant schedule was changed and the number of responses necessary to earn an infusion was increased. In contrast, response rates at 0.06 mg/kg per infusion remained extremely stable throughout the experiment. This is consistent with a recent review of nicotine SA (Rose and Corrigall 1997) suggesting that lower doses may be more affected by changes in schedule of reinforcement.

The observation that infusion rates were lower and more stable at 0.06 than at 0.03 mg/kg may also relate to the suggestion that the decrease in response rates normally seen with higher doses for most drugs of abuse occurs because each dose is temporarily satiating with larger doses producing a more prolonged satiation (Wise 1987). An alternative view is that higher doses are less reinforcing and/or more aversive (Corrigall and Coen 1989; Rose and Corrigall 1997). The stability of infusion rates seen here, and the equal percentage of animals acquiring SA at the higher dose, suggest that the decrease in response rates may not be due to the aversive properties of nicotine, but instead to the duration of the reinforcing effect of each unit dose. The relationship between dose, level and duration of reinforcement should be further elaborated in future studies using designs that are more sensitive to relative changes in reinforcing properties, such as a progressive ratio schedule of reinforcement (Roberts and Richardson 1992). In addition to more stable response and infusion rates across days, there also appeared to be less within group variability for 0.06 as compared to 0.03 mg/kg per infusion. This suggests that the higher dose resulted in smaller individual differences in response and infusions rates and may be useful in reducing the error and increasing statistical power in future SA studies.

Our failure to find stable SA at 0.01 mg/kg contrasts with other reports of SA at 0.01 mg/kg per infusion (Corrigall and Coen 1989; Tessari et al. 1995) and 0.015 mg/kg per infusion (Shoaib et al. 1997). This difference cannot easily be accounted for by method of obtaining SA or rat strain, although differences in animal supplier and the criterion used to define SA cannot be ruled out.

The results of experiment 2 demonstrate the impact of feeding schedule on nicotine SA, but also show that in this model, SA is not dependent on deprivation and/or weight restriction (also see Shoaib et al. 1997). Some early reports failed to find convincing evidence of nicotine SA in free feeding rats. These studies did not show preference for nicotine over saline (Lang et al. 1977), did not demonstrate operant behavior which was specific to the active lever (Hanson et al. 1979; Cox et al. 1984), or reported very low rates of operant behavior (Hanson et al. 1979; Cox et al. 1984). Here, however, rats in all three feeding conditions demonstrated clear evidence of nicotine self-administration. In addition, this study is the first to distinguish between the effects of weight restriction and hunger on nicotine self-administration.

Animals that were fed 20 g prior to their SA session and therefore experienced restricted weight gain, but presumably were not in an acute state of deprivation during the SA session, acquired nicotine SA. Likewise, animals that were placed on an unlimited feeding schedule in which they were neither weight restricted nor in a state of deprivation, also acquired nicotine SA. While each group showed evidence of SA, the different feeding conditions did result in varying levels of drug intake. The greatest intake occurred in animals that were both weight restricted and food deprived. However, weight restriction in the absence of current food deprivation (20 g/Prior) also tended to increase self-administration, relative to the Unlimited rats. These findings confirm earlier reports (Lang et al. 1977; Singer et al. 1978; Dougherty et al. 1981) in indicating that the reinforcement produced by nicotine responds to the availability of other reinforcers, like food, in a manner similar to that of other drugs of abuse (Carroll et al. 1979, 1990).

It is of interest to note that there was little difference in the percentage of animals which acquired nicotine SA either at the two highest doses tested or between the feeding conditions. This suggests that above a threshold dose (between 0.01 and 0.03 mg/kg per infusion), and most likely, below an upper dose limit (Corrigall 1992), the acquisition of nicotine self-administration in drug na-

ive animals is a stable and robust process. The precise rate of behavior in animals acquiring nicotine self-administration, however, appears to be sensitive to manipulations of dose and feeding schedule, which reliably affect the self-administration behavior of other drugs of abuse (Carroll et al. 1979, 1990; Wise 1987; Carroll and Lac 1997).

The third experiment was designed to clarify the influence of prior, food-reinforced operant training on the acquisition of nicotine SA. In the present study, response patterns of rats switched from food to nicotine as the response-dependent reinforcer were compared with those of rats switched to response-independent (i.e., yoked) nicotine or saline. On day 1, animals in all three groups displayed high levels of active lever responding. However, animals receiving response-dependent nicotine were already demonstrating significantly higher active lever response rates than both yoked-nicotine and yoked-saline animals. The response rates for the self-administering animals on the first day were presumably a result of both prior food-reinforced training and the contingent delivery of nicotine while those of yoked animals reflected only prior food-reinforced training. The differences in response rates between SA/Nic and both yoked groups, therefore, suggests that nicotine SA may be present as early as the first session in drug naive rats and that nicotine's reinforcing properties are at least partially evident on first exposure and do not require more extended, chronic treatment, or prior exposure to nicotine, to emerge.

The drop in response rates in all three groups on day 2 may have been due to partial extinction of the food-reinforced operant. Self-administered nicotine, however, appeared to at least partially replace food as the reinforcer, since it maintained response rates which were significantly greater than both yoked nicotine and yoked saline on the second day and throughout the 9-day period. In contrast, non-contingent delivery of nicotine produced little effect on response rates and did not slow the progression of extinction. Active lever response rates for both the yoked groups approached those for the inactive lever, although there was some indication that extinction of the food-reinforced operant was not complete after 9 days.

Meisch (1987) outlined several criteria for demonstrating the reinforcing effects of a drug in the self-administration paradigm. Many of these criteria have already been met for nicotine in rodents including: 1) extinction of responding when vehicle is substituted for drug (e.g. Hanson et al. 1979; Corrigall and Coen 1989; Donny et al. 1995; Tessari et al. 1995; Chiamulera et al. 1996; Shoaib et al. 1997); 2) preference for the active over the inactive lever (e.g. Corrigall and Coen 1989; Donny et al. 1995; Tessari et al. 1995); 3) self-administration under intermittent schedules of reinforcement (Corrigall and Coen 1989; Donny et al. 1995); and 4) varied responding as a function of dose (e.g. Hanson et al. 1979; Corrigall and Coen 1989; Donny et al. 1995; Shoaib et al. 1997). The present report fulfills the final criterion outlined by Meisch (1987), that non-contingent delivery of drug presented in a manner similar to self-administered drug, does not maintain operant responding. Furthermore, nicotine SA is attenuated by administration of central, but not peripheral nicotinic antagonists, as well as by dopaminergic antagonists (Corrigall and Coen 1989, 1991; Shoaib et al. 1997). Finally, nicotine self-administration in rodents has also now been demonstrated using rapidly accelerating progressive ratio schedules of reinforcement (Chambers et al. 1997; Donny et al. 1997). Taken together, reports from a number of laboratories provide convincing evidence that nicotine functions as a reinforcer in rodents.

The results presented here indicate that nicotine SA, like SA of other drugs of abuse, is sensitive to changes in dose, feeding schedule, and contingency of drug delivery. Not surprisingly, parametric differences, which often exist between laboratories, can affect the level of operant behavior. Nonetheless, SA of nicotine was seen at multiple acquisition doses and different feeding conditions, indicating that within this model and the set of parameters tested, nicotine SA is only dependent upon the contingent delivery of nicotine within a given range of doses, and not on conditions such as a restricted feeding schedule (also see Shoaib et al. 1997). Nicotine SA has now been demonstrated using a variety of methods (Corrigall and Coen 1989; Tessari et al. 1995; Shoaib et al. 1997; Valentine et al. 1997). However, whereas each method may produce reliable SA, the nature of the behavior being studied may differ depending upon the conditions under which it is tested.

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References

Abelson PH (1995) Flaws in risk assessments. Science 270: 215

Carroll M, Lac ST (1997) Acquisition of IV amphetamine and cocaine self-administration in rats as a function of dose. Psychopharmacology 129: 206–214

Carroll ME, Meisch RA (1984) Increased drug-reinforced behavior due to food deprivation. In: Thompson T, Dews PB, Barrett JE (eds) Advances in behavioral pharmacology. Academic Press, New York, pp 47–88

Carroll ME, France CP, Meisch RA (1979) Food deprivation increases oral and intravenous drug intake in rats. Science 205: 319–321

Carroll ME, Stitzer ML, Strain E, Meisch RA (1990) The behavioral pharmacology of alcohol and other drugs. In: Galaner M (ed) Recent developments in alcoholism, vol 8. Combined alcohol and other drug dependence. Plenum Press, New York, pp 5–46

CCAC (1980) Guide to the care and use of experimental animals. Canadian Council on Animal Care, Ottawa, Ontario

Chambers LK, Rovetti CC, Mansbach RS (1997) Receptor mediation of the discriminative and reinforcing effects of nicotine. Paper presented June 15, 1997 at the College of Problems of Drug Dependence, Nashville, Tenn.

Chiamulera C, Borgo C, Falchetto S, Valerio E, Tessari M (1996) Nicotine reinstatement of nicotine self-administration after long-term extinction. Psychopharmacology 127: 102–107

Corrigall WA (1992) A rodent model of nicotine self-administration. In: Boulton AA, Baker GB, Wu PH (eds) Neuromethods 24: animal models of drug addiction. Humana, New Jersey, pp 315–344

Corrigall WA, Coen KM (1989) Nicotine maintains robust self-administration in rats on a limited access schedule. Psychopharmacology 99: 473–478

Corrigall WA, Coen KM (1991) Selective dopamine antagonists reduce nicotine administration. Psychopharmacology 104: 171–176

Cox BM, Goldstein A, Nelson WT (1984) Nicotine self-administration in rats. Br J Pharmacol 83: 049–055

Donny EC, Caggiula AR, Knopf S, Brown C (1995) Nicotine self-administration in rats. Psychopharmacology 122: 390–394

Donny EC, Caggiula AR, Rose C, Knopf S, McAllister CG, Sved AF, Perkins KA (1996) Self-administered nicotine may produce different effects than yoked nicotine. Neurosci Abstr 22: 70.2

Donny EC, Caggiula AR, Mielke MM, Strong S, Rose C, Ploskina TM, Jacobs KS, Shupanko CD (1997) Use of progressive ratio schedules in nicotine self-administration. Neurosci Abstr 23: 103.8

Dougherty J, Miller D, Todd G, Kostenbauder HB (1981) Reinforcing and other behavioral effects of nicotine. Neurosci Biobehav Rev 5: 487–495

Fitch TE, Roberts DCS (1993) The effects of dose and access restrictions on the periodicity of cocaine self-administration in the rat. Drug Alcohol Depend 33: 119–128

Goldberg SR, Spealman RD, Goldberg DM (1981) Persistent behavior at high rates maintained by intravenous self-administration of nicotine. Science 214: 573–575

Goldberg SR, Spealman RD, Risner ME, Henningfield JE (1983) Control of behavior by intravenous nicotine injections in laboratory animals. Pharmacol Biochem Behav 19: 1011–1020

Hanson HM, Ivester CA, Morton BR (1979) Nicotine self-administration in rats. In: Krasnegor NA (ed) NIDA Research Monograph 23: cigarette smoking as a dependence process. US-DHHS, Rockville, Md., pp 70–90

Hart RW, Neumann DA, Robertson RT (1995) Dietary restriction: implications for the design and interpretation of toxicity and carcinogenicity studies. ILSI, Washington, pp 127–140, 167–196, 213–228, 245–326

Henningfield JE, Goldberg SR (1983) Nicotine as a reinforcer in human subjects and laboratory animals. Pharmacol Biochem Behav 19: 989–992

Henningfield JE, Miyasato K, Jasinski DR (1983) Cigarette smokers self-administer intravenous nicotine. Pharmacol Biochem Behav 19: 887–890

Lang WJ, Latiff AA, McQueen A, Singer G (1977) Self-administration of nicotine with and without a food delivery schedule. Pharmacol Biochem Behav 7: 65–70

Martellota MC, Kuzmin A, Zvartau E, Cossu G, Gessa GL, Fratta W (1995) Isradipine inhibits nicotine intravenous self-administration in drug naive mice. Pharmacol Biochem Behav 52: 271–271

Meisch RA (1987) Factors controlling drug reinforced behavior. Pharmacol Biochem Behav 27: 367–371

Risner ME, Goldberg SR (1983) A comparison of nicotine and cocaine self-administration in the dog: fixed ratio and progressive ratio schedules of intravenous drug infusion. J Pharmacol Exp Ther 224: 319–326

Roberts DCS, Richardson NR (1992) Self-administration of psychostimulants using progressive ratio schedules of reinforcement. In: Boulton AA, Baker GB, Wu PH (eds) Neuromethods 24: animal models of drug addiction. Humana, New Jersey, pp 233–269

Rose JE, Corrigall WA (1997) Nicotine self-administration in animals and humans: similarities and differences. Psychopharmacology 130: 28–40

Shoaib M, Swanner LS, Prada J, Yasar S, Goldberg SR (1996) Caffeine potentiates both acquisition and maintenance of intravenous nicotine self-administration. Behav Pharmacol 7[Suppl 1]: 103

Shoaib M, Schindler CW, Goldberg SR (1997) Nicotine self-administration in rats: strain and nicotine pre-exposure effects on acquisition. Psychopharmacology 129: 35–43

Singer G, Simpson F, Lang WJ (1978) Schedule induced self-injection of nicotine with recovered body weight. Pharmacol Biochem Behav 9: 387–389

Smith A, Roberts DCS (1995) Oral self-administration of sweetened nicotine solutions by rats. Psychopharmacology 120: 314–346

Tessari M, Valerio E, Chiamulera C, Beardsley PM (1995) Nicotine reinforcement in rats with histories of cocaine self-administration. Psychopharmacology 121: 282–283

US Department of Health and Human Services (1988) The health consequences of smoking: nicotine addiction (1988 report of the Surgeon General). Public Health Service, Office on Smoking and Health, Rockville, Md.

Valentine JD, Hokanson JS, Matta SG, Sharp BM (1997) Acquisition of intravenous nicotine self-administration in rats allowed unlimited access to relatively low doses of the drug. Psychopharmacology 133: 300–304

Wakasa Y, Takada K, Yanagita T (1995) Reinforcing effect as a function of infusion speed in intravenous self-administration of nicotine in rhesus monkeys. Jpn J Psychopharmacol 15: 53–59

Wise RA (1987) Intravenous drug self-administration: a special case of positive reinforcement. In: Bozarth MA (ed) Methods of assessing the reinforcing properties of abused drugs. Springer, New York, pp 117–141