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# Nicotine self-administration in rats

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**Abstract** Considering the importance of self-administration models in determining mechanisms of drug maintained behavior, we attempted to replicate the findings of nicotine self-administration by Corrigall and Coen. Male, Sprague-Dawley rats, trained on food reinforcement, acquired relatively high and stable rates of self-administration of IV nicotine bitartrate (0.03 mg/kg, free base). Extinction and reacquisition followed substituting saline and then nicotine, respectively. Responses, infusions and intake decreased at 0.003 mg/kg, while intake increased at 0.06 mg/kg. This model of nicotine self-administration provides a reliable alternative to experimenter-administration models for examining the effects of nicotine.

**Key words** Nicotine self-administration · Rats · Drug-reinforcement

## Introduction

The strength and persistence of self-administration of a drug is perhaps the hallmark of its abuse liability, or ability to produce dependence. Animal models of self-administration have been critical in characterizing the abuse liability of many drugs (Yokel 1987), and have served as valuable tools for investigating the neurobiological and environmental determinants of drug-seeking behavior (Carroll and Boe 1982; Bozarth et al. 1989; Glick et al. 1994).

Both human (Henningfield et al. 1983) and non-human primate (Goldberg et al. 1981) models of nicotine self-administration which demonstrate nicotine's ability to reinforce behavior have been reported. Past attempts at establishing a rodent model of nicotine self-administration, however, have had limited success. These models have produced either relatively low levels of drug intake (Cox et al. 1984) or self-administration dependent on conditions such as food deprivation combined with the use of a concurrent food delivery schedule (Lang et al. 1977; Latiff et al. 1980), or pretreatment with nicotine (Hanson et al. 1979). These types of results have led some researchers to conclude that nicotine is a relatively weak reinforcer restricted to very limited circumstances (Robinson and Pritchard 1992).

In 1989, however, Corrigall and Coen reported a method of nicotine self-administration in Long-Evans rats which resulted in relatively high, stable, and dose dependent rates of responding without the use of concurrent reinforcement, nicotine pretreatment, or food deprivation schedules that reduced body weight. Self-administration rates decreased with either saline substitution or administration of the central nicotinic blocker mecamylamine, but not with the peripheral blocker hexamethonium. To date, however, other laboratories have had difficulty in obtaining reliable self-administration using IV nicotine in rats, and some controversy has arisen regarding its usefulness (Dworkin et al. 1991; Corrigall, personal communication). Given the potential importance of such a model, we attempted to replicate the findings of Corrigall and Coen in Sprague-Dawley rats. We examined nicotine's ability to act as a reinforcer by using a partial extinction and reacquisition procedure, established a dose range that will support self-administration in our animals and started to characterize the drug-maintained behavior both within and across sessions.

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## Materials and methods

Twenty-two adult, male Sprague-Dawley rats 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.) with unlimited access to food and water. After a 7-day habituation period, animals were food deprived for 24 h, then trained in a single session to respond on an active lever for 45 mg food pellets on a CRF. For the remainder of the study, subjects received 20 g of food ev-

ery day at approximately 5 p.m. This feeding schedule is identical to that reported by Corrigall and Coen (1989) and therefore was used in this replication. Animals weighed between 225 g and 300 g at surgery and gained approximately 100 g over the next 6 weeks, which compares with an increase of approximately 230 g over the same period in free-feeding rats (unpublished observation).

Trained subjects were anesthetized with Equithesin (3 ml/kg IP) and implanted with jugular catheters similar to those described by Corrigall and Coen (1989). After surgery, they were injected with ampicillin (100 mg/kg SC) and given 3–8 days to recover before self-administration sessions began. Catheters were flushed prior to and after self-administration sessions with 0.1 ml heparinized saline.

All sessions lasted for 1 h each day during which animals were removed from their home cage, placed into an operant chamber (BRS/LVE model #RTC-020; 10″×12″×11″) in the testing room, and attached to the drug delivery system which allowed virtually unrestricted movement throughout the chamber. All sessions ran between 9 a.m. and 5 p.m. (from hours 2 to 10 of a 12-h dark cycle). Responding on an active lever was reinforced with 0.03 mg/kg per infusion nicotine bitartrate (all doses are reported as free base) delivered in a volume of 0.1 ml/kg in approximately 1 s (IITC model 100 pneumatic syringe pump), while responding on an inactive lever had no consequence. A CRF was used for days 1–5, an FR2 for days 6–8, and an FR5 for the remainder of the study. Active and inactive responses and infusions were recorded 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. Animals were considered to have acquired self-administration if responding on the FR5 resulted in five or more infusions per session for at least three consecutive sessions. Stable response rate was defined as no increasing or decreasing trends over the last three sessions before extinction or dose-response analyses were initiated (Carroll et al. 1989). Of the original 22 rats, 18 acquired stable nicotine self-administration by the end of the 15th session.

After responding stabilized on an FR5, five rats in one experiment were given self-administration sessions in which nicotine was available, while six had saline substituted for nicotine for 3 days before nicotine was again made available. All other conditions remained constant, including the illumination of the cue light after an active lever response. A single priming injection was given in the reacquisition phase if the responding completely extinguished in the 3 days of extinction. Because all five rats in the no extinction group maintained stable rates throughout the "extinction" sessions, only two animals were continued through the reacquisition phase. The other three animals, and one rat from the extinction group (after reacquisition at 0.03 mg/kg) were then used in the dose response study described next. In the dose response experiment, after stabilizing at the acquisition dose of 0.03 mg/kg per infusion, five animals were switched to a dose of 0.003 mg/kg per infusion and five others to 0.06 mg/kg per infusion and given 3–5 days to stabilize at the new dose. The 18th rat developed a catheter block after initial stabilization and could not be used in dose response or extinction phases.

## Results

The data from an initial cohort of eight rats were used to describe the acquisition period. The number of active lever responses per hour for the last 3 days on the FR5 ranged from 46 to 214 with a mean of 121.5. Infusions per hour ranged from 9 to 37 with a mean of 20.9 for this time period (Fig. 1). Increasing the fixed ratio during the acquisition period resulted in increased responding, maintaining a rate of approximately 18 infusions per session over the 3 weeks (Fig. 1).

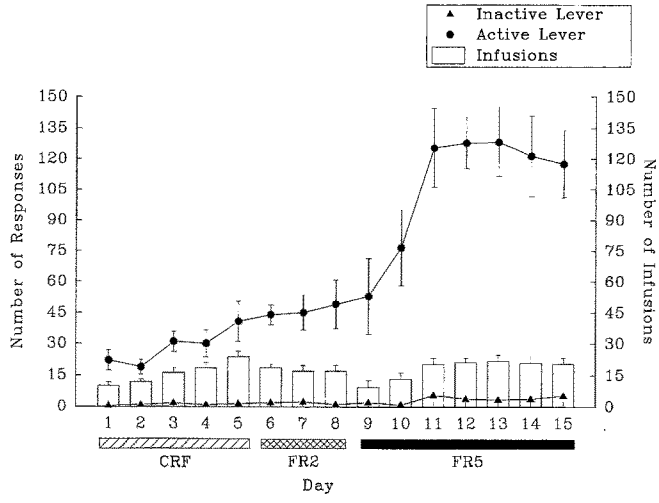


**Fig. 1** Total number of active lever responses, inactive lever responses, and infusions given during the acquisition of nicotine (0.03 mg/kg per infusion) self-administration. Values=means±SE. $n$=8. Changes in schedule indicated by *bars* below the abscissa

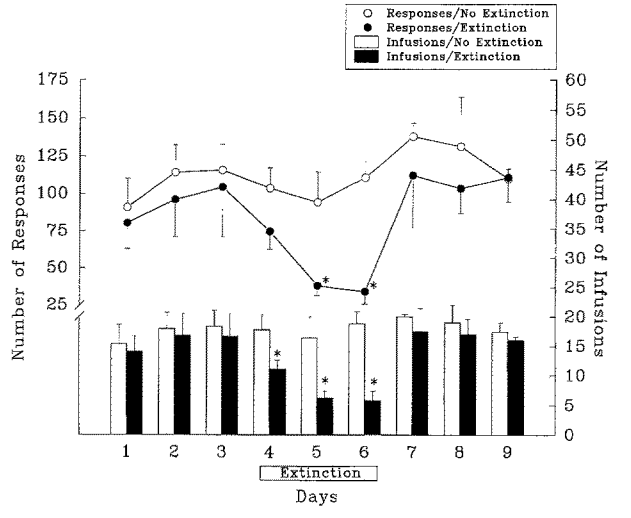


**Fig. 2** Responses and infusions decreased when saline was substituted for nicotine, and increased when nicotine was again made available. Values=means±SE. $n$=6 for Extinction group. $n$=5 for No Extinction group, except for days 7–9: $n$=2. *Significantly different from No Extinction group ($P$<0.05)

Analysis of the distribution of infusions taken within a single session after stabilization on a FR5 revealed more infusions taken in the first 30 min compared to the last 30 min (59.5% versus 40.5%). Overall, however, animals responding throughout the 1-h session, with 20.2% of the infusions occurring in the last 15 min. Responding on the inactive lever was virtually absent throughout the experiment.

Mixed ANOVAs followed by preplanned contrasts, revealed the following results. When compared to no extinction controls, rats receiving saline substitution showed a decrease in response rate on days 2 and 3 of extinction [$F$s(1, 8)=6.10 and 31.20; $P$s=0.04 and 0.001, respectively; Fig. 2] and a decrease in infusion rate on all 3 days of extinction [$F$s(1, 8)=6.26, 6.31 and 24.93;

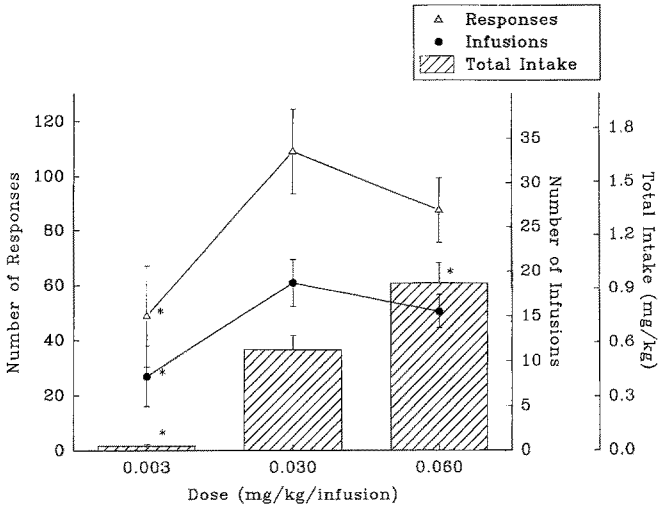


**Fig. 3** Decreasing the dose from 0.03 to 0.003 mg/kg per infusion resulted in a decrease in responses, infusions, and total intake for one group ($n$=5), while for five other rats, increasing the dose from 0.03 to 0.06 mg/kg per infusion led to an increased total intake. Values (means±SE) for 0.03 mg/kg per infusion represent the average of both groups ($n$=10) at that dose. Responses, infusions and total intake for each group separately at 0.03 mg/kg were: 116.5 19.8 and 0.594 for the first group and 101.5, 17.6 and 0.528 for the second group. *Significantly different ($P$<0.05) from 0.03 mg/kg per infusion, based on repeated measures comparison within groups

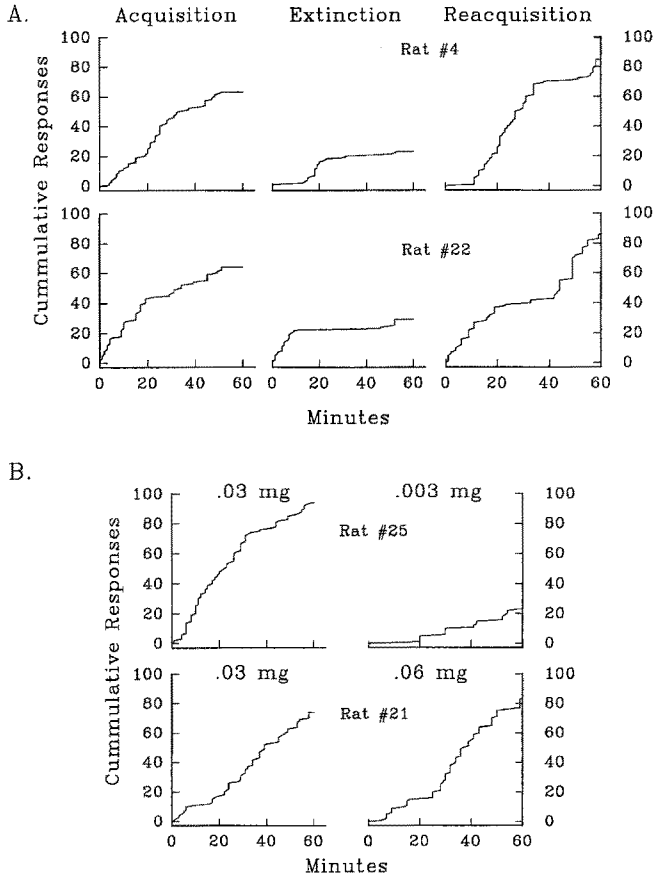


**Fig. 4** Cumulative response records for representative animals on the last day of acquisition, extinction, and reacquisition (**A**), and for each of the three doses used (**B**)

*Ps*=0.037, 0.036 and 0.001, respectively; Fig. 2]. None of these rats showed complete extinction; at least five responses and one infusion were obtained on each of the extinction days. All animals reacquired to pre-extinction levels when nicotine was again made available.

Comparisons for the effect of dose were made using the mean of the last 2 days at each dose. A change from the acquisition dose of 0.03 mg/kg per infusion to 0.003 mg/kg per infusion resulted in decreases of 55.3% in the number of responses, 55.6% in the number of infusions, and 95.4% in total intake [*Fs*(1, 4)=220.72, 82.66 and 63.56; *Ps*<0.001,=0.001, and <0.001, respectively; Fig. 3]. Two of the five rats switched to 0.003 mg/kg exhibited almost complete extinction by the last session at this dose, i.e., no infusions and only three and one responses, respectively. At 0.06 mg/kg per infusion, however, neither responses nor infusions were significantly changed as compared to 0.03 mg/kg per infusion [*Fs*(1, 4)=0.39 and 0.32; *Ps*=0.565 and 0.606, respectively], while total intake increased to 166.1% of the acquisition dose [*F*(1, 4)=15.14; *P*=0.018; Fig. 3]. Individual cumulative response records of representative animals at all three doses and extinction are illustrated in Fig. 4.

## Discussion

The results presented here replicate the essential features of Corrigall and Coen's 1989 report that stable rates of nicotine self-administration in rats can be obtained using a limited access schedule. Nicotine's control over behavior was shown by the partial extinction and reacquisition observed when saline and then nicotine were available. Both 0.03 mg/kg per infusion and 0.06 mg/kg per infusion maintained high levels of responding in our animals, while 0.003 mg/kg per infusion was less effective as a reinforcer. These findings support the work in other species, including nonhuman primates (Goldberg et al. 1981; Wakasa et al. 1995) and humans (Henningfield et al. 1983) in suggesting that nicotine has significant reinforcing properties.

Because our initial goal in this study was to determine whether the findings of Corrigall and Coen (1989; also see Corrigall 1992) could be replicated in our laboratory, we followed their procedures almost exactly. There were, however, two methodological differences. First, male, Sprague-Dawley rats were used here, whereas male, Long-Evans rats had been used by Corrigall and Coen (1989). This difference suggests that nicotine self-administration is not strain specific. Second, we used an 18- to 24-h, rather than a 36-h deprivation period before initial training for food reinforcement.

Acquisition of stable responding on the active lever for 0.03 mg/kg per infusion proceeded over 10–15 sessions as the schedule progressed from CRF to FR2 to FR5. The establishment of stable responding appeared to be slightly more rapid and at somewhat higher average response and infusion rates than in previous studies (Corrigall 1992), although it is difficult to determine whether these differences are reliable.

Substitution of saline for nicotine for three sessions produced a significant decrease in response and infusion rates, which was followed by reestablishment of stable responding when nicotine was reintroduced. The failure to obtain complete extinction within 3 days should not be surprising. The continued presentation of the cue light with responding on the active lever during extinction may have functioned as a secondary reinforcer. Moreover, Corrigall and Coen (1989) reported full extinction only after a 5- to 10-day period.

Two of the five rats showed some tendency to increase responding at the beginning of the first extinction session (49% and 54% of total responding for that session within the first 10 min), but otherwise, we did not see the "extinction-burst" pattern which is sometimes reported for other drugs (Yokel and Wise 1975; Ettenberg et al. 1982). Corrigall and Coen reported this pattern for only some of their rats.

One apparent difference between the two studies is in the dose-response analysis. Responding to 0.03 mg/kg per infusion produced very similar levels of total intake (approximately 0.4–0.6 mg/kg) over the session. However, reducing the unit dose from 0.03 to 0.003 mg/kg per infusion resulted in a much more substantial decrease in responding in our study than in Corrigall and Coen's (1989; Corrigall 1992). Similarly, switching from 0.03 to 0.06 mg/kg per infusion produced a slight, nonsignificant decrease in response and infusion rates, and actually increased total intake in the present experiment, whereas response rates decreased and total intake remained constant in the earlier work. Thus, it appears that our dose-effect curve is shifted to the right relative to that reported by Corrigall and Coen (1989). One possible explanation for the apparent discrepancies in the dose-effect function is that different strains were used in the two studies. However, such apparent differences in nicotine sensitivity and/or its reinforcing potency could also be due to a variety of other factors, including unplanned stress effects or differences between laboratory environments. For example, stress has been shown to modify several of nicotine's effects when the drug is experimenter-administered (Peck et al. 1991; Caggiula et al. 1993) and can enhance self-administration of several drugs (Piazza et al. 1990; Shaham and Stewart 1994). Finally, differences in the methods of determining dose-response functions used by the two studies may have contributed to the discrepancies noted above. Future experiments conducted in the same laboratory will be needed to determine whether one or more of these factors can alter the dose-response function for nicotine self-administration.

Our data also confirm Corrigall and Coen (1989), in demonstrating that food deprivation sufficient to produce a loss of body weight is not necessary to obtain stable nicotine self-administration. We followed their practice of providing 20 g/day, which maintained moderate weight gain over 5 weeks to approximately 133% of their starting weight. Nevertheless, since other studies have shown that the acquisition and maintenance of self-administration of other drugs is extremely sensitive to conditions of feeding, weight gain and, more generally, on the availability of other reinforcers (Carroll and Boe 1982; Carroll and Meisch 1984), the role of feeding schedule in nicotine self-administration will be systematically explored in future studies.

One important use of this model is in characterizing the behavioral and physiological effects of self-administered nicotine. Evidence from other psychoactive drugs has demonstrated that the effects of self-administering a drug may differ from those obtained when the drug is administered by the experimenter. For example, baboons allowed to self-administer midazolam showed an increase in sensitivity to the discriminative stimulus properties of midazolam, while the same pattern of infusions, if given by the experimenter, resulted in decreased sensitivity (Ator and Griffiths 1993). Moreover, Dworkin et al. (1995), using a yoked design, have reported that rats receiving response-independent infusions of cocaine showed increased mortality compared to rats self-administering exactly the same amount of drug. The model of nicotine self-administration described herein, and previously reported by Corrigall and Coen (1989), provides the opportunity to investigate such differences with regard to nicotine, as well as to further evaluate the factors which influence nicotine-maintained behavior.

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