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NICOTINE AS A POSITIVE REINFORCER FOR RATS: EFFECTS OF INFUSION DOSE AND FIXED RATIO SIZE

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ABSTRACT

Lever pressing by rats was established and maintained by intravenous nicotine infusions. The rate of lever pressing was reduced by substituting saline for nicotine infusions or by giving the rats response independent nicotine infusions. The rate of lever pressing was sensitive to both dose and fixed-ratio size. These results show that nicotine can function as a positive reinforcer for rats in the absence of other inducement or weight reduction procedures. In addition, the present results extended previous work showing that termination of prolonged exposure to nicotine does not result in a physiological dependence.

Nicotine is one of the most widely used compounds, however, it is only recently that the effects of nicotine on scheduled-controlled behavior have been systematically studied (1,2). In rats, nicotine increases responding maintained under fixed-interval (FI), variable-interval and differential-reinforcement of low rate schedules of food or water presentation and under-schedules of electrical shock postponement (1). Nicotine decreases responding under fixed ratio (FR) schedules of food or water presentation. Qualitatively similar results on responding have been reported in squirrel monkeys maintained under a multiple FI-FR schedule of either presentation of food or termination of a stimulus associated with electric shock (2). In addition it has been shown that intravenous injections of nicotine will maintain high rates of lever-pressing by squirrel monkeys under a second order schedule. Under this schedule responding results in the presentation of a visual stimulus that is intermittently associated with response contingent nicotine injections (3).

Many compounds from different pharmacological classes can increase and maintain behavior that leads to self-administration of those compounds (4). However, there is little evidence that rats will intravenously self-administer nicotine unless self-administration is induced by a food delivery schedule (5) or they are given programmed nicotine infusions for several days (6). The levels of responding maintained by intravenous nicotine following programmed infusions have been low (6). The present study demonstrates that intravenously delivered nicotine functions as a positive reinforcer in the absence of food inducement or programmed infusion conditions. Nicotine self-administration was studied under different FR values and across a range of infusion doses. In addition, the present results extend previous findings (1) by showing that termination of prolonged access to nicotine under conditions in which it functions as a positive reinforcer does not result in physiological dependence.

Ten male hooded rats each implanted with an venous catheter (7) were maintained in standard operant conditioning chambers with food (20-30g/ day) and water always available. Each chamber was enclosed in a sound-attenuating box. Responding on one lever activated an infusion pump for 4-5 seconds, delivering an infusion of 0.13 ml of solution. Responses on the other lever (activity lever) were recorded but had no programmed consequence. The rate of activity lever responding was recorded throughout all experimental manipulations and was compared to the rate of responding recorded from the lever resulting in nicotine infusions. The houselight provided illumination and blinked at a rate of 10 Hz during an infusion. First, nicotine self-administration was established in the rats at 32 µg/kg/infusion (all doses are expressed as the free base). Access to nicotine was unlimited (24 hours), with one response required for each infusion (FR 1). Then changes were made in the nicotine delivery procedure to determine if lever pressing was being maintained by the contingency established between lever pressing and nicotine delivery (4). Changes included substitution of saline for nicotine, systematic changes in dose and programmed nicotine infusions at intervals of 30, 45, 60 and 90 minutes. All rats were tested with the saline substitution procedure and three rats were given programmed infusions. In the seven rats not receiving programmed infusions the effect of infusion dose was determined on the number of infusions delivered and the total nicotine intake (mg/kg/24 hour) under an FR 1 schedule. Infusion doses (64.0, 32.0, 16.0, 8.0 and 4.0 µg/kg/infusion) were presented in descending order for a minimum of 7 days each. Under each infusion dose lever pressing was allowed to stablize before changes were made. In the three rats that received programmed infusions the effects of FR size (1-8 responses/32 µg/kg/infusion) on the number of lever presses and the number of infusions were studied. Ratios were presented in ascending

order and the rats were maintained under each ratio for a minimum of 7-10 sessions.

All rats initiated and maintained nicotine self-administration (Figure 1, left panel). Generally, 10-20 sessions were necessary for the acquisition and stablization of responding on the nicotine lever. Stability was defined as 3-5 sessions with no increasing or decreasing trends in the number of infusions. The within session pattern of nicotine-reinforced responding under the FR 1 schedule was typically a series of closely spaced infusions (2-4/minute), followed by a pause (30-90 minutes) during which time no infusions were taken. Nicotine self-administration was shown to be maintained by the response-nicotine contingency, rather than by other behavioral effects of nicotine. Substitution of saline for nicotine solution failed to maintain lever pressing (Figure 1). Saline substitution produced a temporary (3-6 hours) increase in lever pressing which rapidly declined to less than 12 infusions during the following 24 hour session. When nicotine was reintroduced (32.0 µg/kg/infusion) the number of nicotine infusions increased to previous levels (Figure 1). Periodic observation of the rats when nicotine was available and during the saline substitution failed to reveal any signs of physical dependence (8). When nicotine was available lever pressing occurred almost entirely on the lever delivering nicotine infusions. Activity-lever responses were less than 10% of the total number of responses for all rats.

Table I shows the effect of programmed infusions delivered independently of responding on nicotine maintained lever pressing. The percent decrease in the number of response contingent infusions was inversely related to the programmed interinfusion interval. The sum of response contingent infusions plus response independent programmed infusions was stable across sessions (Table 1), suggesting that the daily level of nicotine self-administration is at least in part under control of some circulating blood level.

The effect of varying nicotine dose on the number of infusions under an FR1 schedule is shown in the right panel of Figure 1. As the dose of nicotine was decreased the number of infusions first increased then decreased. In contrast, session intake (mg/kg of body weight) increased as a function of nicotine dose (Figure 1). Similar functional relationships have been found with other reinforcers (4). The 8 µg/kg/infusion dose did not maintain lever pressing above saline levels.

These results demonstrate that intravenously delivered nicotine can increase and maintain lever pressing that results in its delivery. The changes in the nicotine delivery procedure showed that lever pressing was maintained by the nicotine-response contingency. There were four indications of the positive reinforcing effects of nicotine: 1) a greater number of lever presses when nicotine was response-contingent than when saline was response-contingent; 2) a greater number of responses on the nicotine lever than on the activity lever; 3) a systematic decrease in the number of contingent infusions when nicotine was delivered noncontingently; and 4) systematic changes in lever pressing as a function of the nicotine dose.

The effect of increasing the ratio size on the number of lever presses and infusions is shown in Figure 2. Increases in FR size up to FR 5 resulted in substantial increases in the number of lever presses. At ratio of 6 and 7 the number of lever presses remained relatively stable. A further increase in ratio size to FR 8 resulted in a decrease in the number of lever presses. The number of infusions remained relatively stable across several ratios (1-6), then decreased at ratios of 7 and 8. Although intravenously delivered nicotine maintained ratio performance, these overall rates of responding compared to other intravenously delivered reinforcers (4) are low, suggesting that nicotine may be a weak reinforcing agent.

Previous attempts to establish nicotine as an intravenously delivered reinforcer for rats have shown that only under conditions of reduced body weight and/or concurrent fixed time food presentation will nicotine self-administration occur at rates above vehicle control levels (5). The present results show that nicotine can function as an intravenously delivered positive reinforcer for rats in the absence of such conditions, and that the level of responding can be maintained across several ratio schedules.

A detailed profile of the behavioral effects of nicotine has been emerging from several laboratories (1,2); however, there has been a continuing need for a systematic evaluation of the reinforcing effect of nicotine in the rat. In this study the maintenance of lever pressing was unequivocally the result of consequent nicotine infusions. Furthermore, the behavior was shown to be sensitive to both dose and response contingency manipulations.

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7. Venous catheters were implanted [J. R. Weeks, in Methods in Psychobiology, R. D. Myers, Ed. (Academic Press London, 1972), 2 pp 155]. Under pentobarbital and ketamine anesthesia and under aseptic conditions. One end of the catheter (inside dimension, 0.3 mm outside dimension, 0.62 mm)

was passed by way of the external jugular vein into the superior vena cava at the level of the right atrium. The distal end of the catheter was passed subcutaneously and out through the skin in the middle of the scapula of the rat's back. The catheter was connected to a stainless steel back plate. Each animal was allowed 10 days recovery before being placed in a test chamber.

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Table 1

The percent decrease in the number of self-administered nicotine infusions and the total number of infusions as a function of the interval between response independent programmed nicotine infusions.

Interinfusion Interval (minutes)	Mean (± standard error), % decrease in the number of self-administered infusions	Mean total infusions (± standard error) programmed plus response contingent
Control		76 (±3.8)
30	79 (± 4.3)	81 (±3.0)
45	56 (± 5.0)	75 (±4.3)
60	40 (± 3.4)	79 (±8.1)
90	29 (± 1.5)	74 (±2.6)

Figure 1. Effects of substituting saline for nicotine on the number of infusions (left panel). Each bar represents a mean of 30 sessions (10 rats x 3, 24 hour sessions). The vertical lines show the standard error. The right side of the figure shows the effect of varying the dose of nicotine on both the number of infusions (solid lines) and session intake (mg/kg/session, dashed lines) under an FR 1 schedule. Each point is a mean of 21 sessions (7 rats x 3 sessions each) and the verticle lines show the standard error.

Figure 2. The number of Lever presses and infusions (32 µg/kg) is shown as a function of the FR size. The ratios were presented in an ascending order. Each point is a mean of 9 observations (3 rats x 3 sessions) and the vertical lines show the standard error.

We thank Yvonne Dragan and Lisa Carron for their technical assistance.

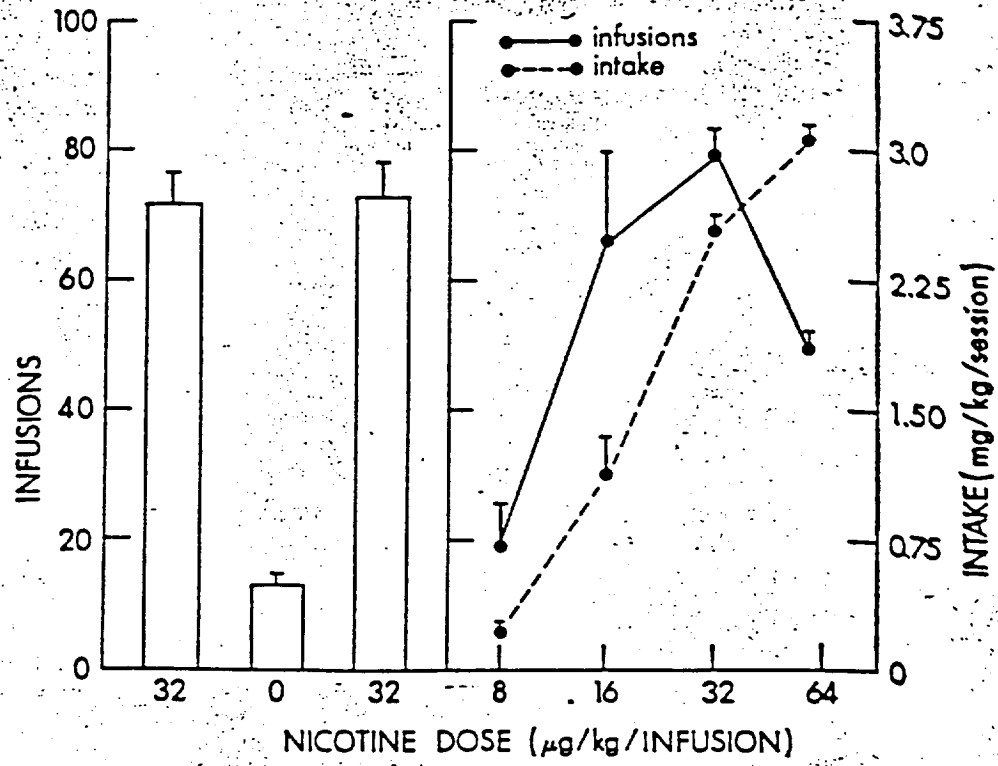

Figure 1

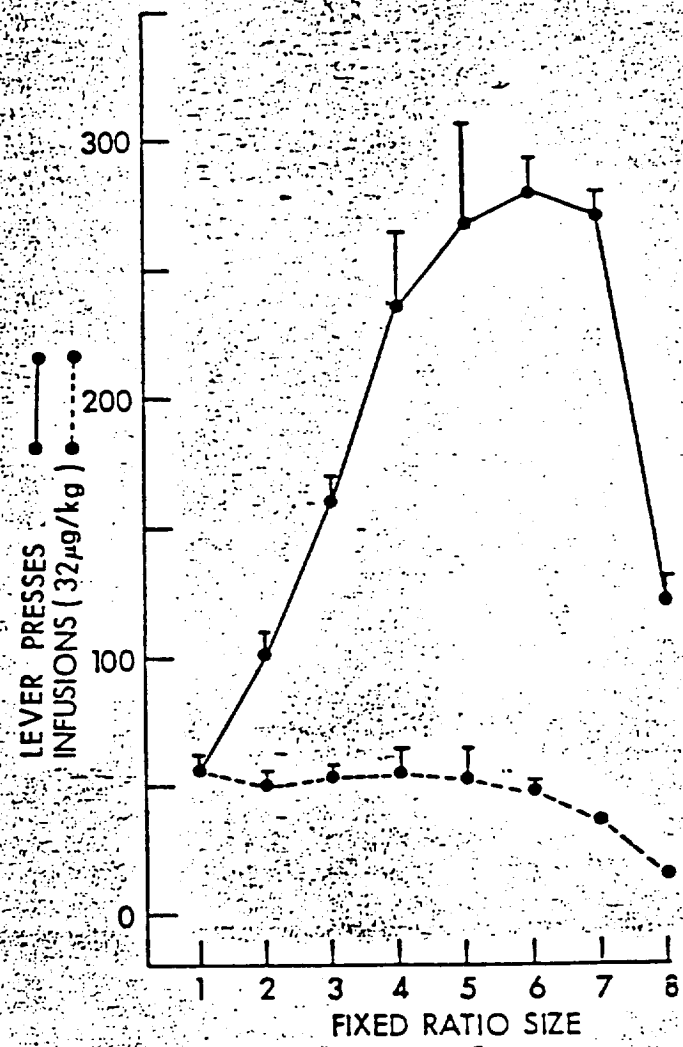

Figure 2