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Acute and Chronic Nicotine Effects on Multiple-Schedule Behavior: Oral and SC Routes

CHYAN E. LAU, DEBRA J. SPEAR AND JOHN L. FALK[1]

Department of Psychology, Busch Campus, Rutgers University, New Brunswick, NJ 08903

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LAU, C. E., D. J. SPEAR AND J. L. FALK. *Acute and chronic nicotine effects on multiple-schedule behavior: Oral and SC routes.* PHARMACOL BIOCHEM BEHAV **48**(1) 209–215, 1994.—For rats responding on a 3 h FI 4 min FR 20 schedule of food reinforcement, presession SC nicotine doses (0.1–0.8 mg/kg) produced depression in all responding followed by stimulation of FI responding that was dependent upon both time and dose. With daily presession 0.8 mg/kg SC nicotine injections for 9 days, no tolerance to the depressive or stimulatory effects of nicotine occurred. When nicotine solutions were orally self-administered by presession exposure to 3 h of schedule-induced polydipsia, the subsequent FR responding was unaffected, but the degree of FI response stimulation and its duration occurred in a dose-related fashion (1.18–4.10 mg/kg). Prolonged daily sessions of oral nicotine self-administration provide a technique for investigating the effects of chronic exposure to nicotine. The postingestive effects of nicotine reveal stimulatory effects that last for at least 3 h.

Nicotine Multiple schedule Schedule-induced polydipsia Fixed-interval schedule Fixed-ratio schedule Nicotine tolerance

THERE has been little incentive to use the oral route of administration in the investigation of nicotine. Nicotine is well absorbed in the small intestine, but its oral bioavailability is only about 45%, owing to first-pass hepatic metabolism (1). However, the oral-buccal route remains of interest because it is used to self-administer smokeless tobacco recreationally and nicotine gum therapeutically. Recent evidence indicates that both the oral and oral-buccal routes are quite effective routes of nicotine administration for the production of changes in behavior. Smokeless tobacco improved performance in humans on complex performance tasks (9) and nicotine gum enhanced psychomotor performances of regular smokers (13). When exposed to drinking water adulterated with nicotine, rats developed tolerance to the effects on activity of challenge doses of IP nicotine (15). Rats trained to discriminate nicotine from saline following PO gavage in a drug-discrimination procedure reached training criterion just as rapidly and showed ED_{50}s comparable to values found when given nicotine by SC and IP routes (2). The latter study indicated that first-pass metabolism does not present a significant impediment to the investigation of the behavioral pharmacology of orally administered nicotine. One of the aims of the present study was to use a schedule-induced polydipsia procedure (5) that permitted oral self-administration of nicotine solutions to evaluate the effects of daily, 3 h sessions of nicotine drinking on an ensuing daily 3 h session of multiple-schedule behavior.

A second aim was to determine the effects of acute and chronic SC injections of nicotine on multiple-schedule behavior to compare these effects with those obtained after oral self-administration conditions. The SC injection procedure imposed the complete dose of nicotine just prior to the start of the multiple-schedule session, while in the schedule-induction procedure nicotine was orally self-administered over a preceding 3 h period. The latter procedure might yield a pattern of exposure to nicotine more like that produced by employing smokeless tobacco or nicotine gum than does an SC injection. It also may simulate the sustained serum nicotine levels produced by smoking, although it would lack the pulsatile exposure pattern resulting from smoke inhalation.

A third aim was to administer SC nicotine chronically prior to the multiple-schedule session to evaluate the possible development of tolerance.

[1] To whom requests for reprints should be addressed.

METHOD

Animals

Four male albino rats of the Holtzman strain (Madison, WI) were used. As a condition of an immediately preceding experiment, they had been maintained at 80% of their free-feeding, adult body weights, and they were held to these weights (mean = 308 g; range: 306–310 g) for the duration of the present experiments. They were housed individually in stainless steel cages in a temperature-controlled room, illuminated 12 h daily, with water freely available. In the preceding experiment, all rats had a history of caffeine, midazolam, and caffeine-midazolam combination injections under the presently used schedule of reinforcement (mult FI 4 min FR 20), but had not been exposed to nicotine. At the end of each daily, operant session, an animal was returned to its home cage and given a food supplement (Purina Lab Chow) sufficient to maintain the 80% weight level. All aspects of the experiment were executed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1985).

Apparatus

Operant chamber. Each of four operant chambers (20 × 26 × 26 cm) had stainless steel grid floors, front and back panels of aluminum, and side panels of Plexiglas. A response lever (Ralph Gerbrands Co.) was mounted on one wall, 3 cm above the grid. Depression of the lever produced the audible click of a microswitch. To the left of the lever (11 cm), a stainless steel food pellet receptacle was located into which 45 mg dustless pellets (BioServ, Frenchtown, NJ) could be delivered. Each chamber was controlled by an IBM-type XT computer (Multi-Industry Technology, Edison, NJ). Sessions were programed and data recorded using QuickBasic. A fan provided ventilation and masking noise for each chamber. Mounted outside each chamber were houselights, consisting of two lamps (GE 306), that were illuminated during experimental sessions. Each chamber was enclosed in a sound-attenuating shell (69 × 71.5 × 76 cm).

Polydipsia chamber. For the oral self-administration of nicotine solution, animals were given sessions in individual polydipsia chambers. Each was a Plexiglas chamber (30 × 26 × 23 cm) containing a pellet receptacle and, on the opposite wall, a source of fluid. This source consisted of a Nalgene graduated cylinder to which was attached a stainless steel, ball-bearing drinking spout.

Drugs

Nicotine, (−)-nicotine di-[+]tartrate salt, obtained from Sigma Chemical Co. (St. Louis, MO), was dissolved in 0.9% NaCl solution for SC injections. For oral self-administration, the nicotine salt was dissolved in distilled water or a compound solution of 1.5% glucose and 0.08% saccharin made with distilled water. Doses are specified in terms of the base.

Procedure

A 3 h operant session was conducted daily. Animals responded under a mult FI 4 min FR 20 schedule. Under the FI 4-min contingency, the first lever press emitted 4 min following either the beginning of a session, or the delivery of a previous pellet, produced delivery of a pellet. Under the FR 20 contingency, a pellet was delivered after the 20th lever press. During an FI component, a Sonalert (P. R. Mallory, Indianapolis, IN) mounted behind the lever panel was pulsed once per s, producing audible beeps. No auditory stimulus was presented during the FR component. FI and FR components alternated in a semirandom order, with the constraint that no more than two components of the same type followed each other. For drug- and vehicle-injection sessions, the following 16-unit component sequence was repeated over the session: FI, FR, FI, FI, FR, FR, FI, FI, FR, FI, FR, FR, FI, FI, FR, FR. This permitted the between-session comparison of successive 15 min blocks across the 3 h session duration. The duration for which an FI component was presented was determined either by a lever press satisfying the FI 4 min contingency, or the elapse of 5 min since the last pellet had been earned. The duration for which an FR component was presented was determined either by the completion of three FR 20s, or the elapse of 5 min since the last pellet had been earned. Pellet presentation was accompanied by a 1 s darkening of the houselights.

The effect of acute administration of nicotine SC was determined first. Injections were given immediately before the start of a session. At least three baseline sessions preceded each injection, which was given only when visual inspection of an animal's data showed no consistent trend. Doses were administered in an ascending order: vehicle, 0.1, 0.2, 0.6, and 0.8 mg/kg nicotine.

After completion of the acute-injection series, a chronic dosing regimen with 0.8 mg/kg nicotine was begun. Animals were injected immediately prior to a session for nine consecutive sessions. Then vehicle was administered for three consecutive sessions.

A second experiment explored the effect of chronic, oral self-administration of nicotine solution on behavior in the multiple schedule. To produce oral nicotine self-administration, a 3 h schedule-induced polydipsia session immediately preceded each of the daily, multiple-schedule sessions. An animal was placed into a polydipsia chamber and exposed to a fixed-time 1 min schedule (FT 1 min), which noncontingently delivered a food pellet once per min. First, water was the fluid available in the chamber (19 days), and then a series of nicotine solutions, the concentration of which was increased every 3–7 days: 0.004, 0.006, 0.008, 0.01, 0.012, to a final concen-

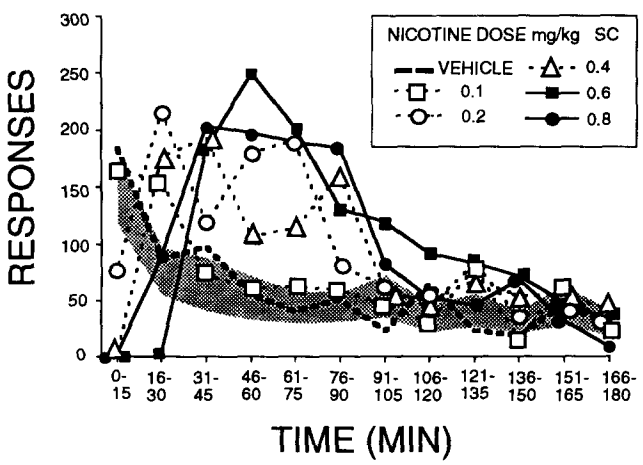

FIG. 1. Mean of total FI responses for consecutive 15 min blocks for sessions following acute nicotine administration (SC). Shaded area indicates ± SE for sessions preceding all nicotine injections. Schedule was mult FI 4 min FR 20, 3 h sessions. n = 4 animals.

tration of 0.015 mg/ml. The effect of oral nicotine self-administration on behavior occurring in the 3 h multiple schedule session immediately following each polydipsia session was evaluated. To attain a greater self-administered dose of nicotine, the drug (0.015 mg/ml) was dissolved in the glucose-saccharin solution vehicle for eight sessions. One animal (rat W2), although in seeming good health, lever pressed at low, unreliable rates on the multiple schedule after schedule-induction sessions were introduced. This animal's second-experiment data have been excluded.

RESULTS

Experiment 1: Acute and Chronic Effects of SC Nicotine on Multiple-Schedule Behavior

Figure 1 shows the effect of acute doses of nicotine (SC) on mean responding in the FI component for consecutive 15 min blocks across the 3 h session times. For baseline and vehicle-injection sessions, FI responding was greatest during the first 15 min, and decreased to a lower, stable rate for the remainder of each of these sessions. This effect is evident in the sample session record shown at the top of Fig. 2. The

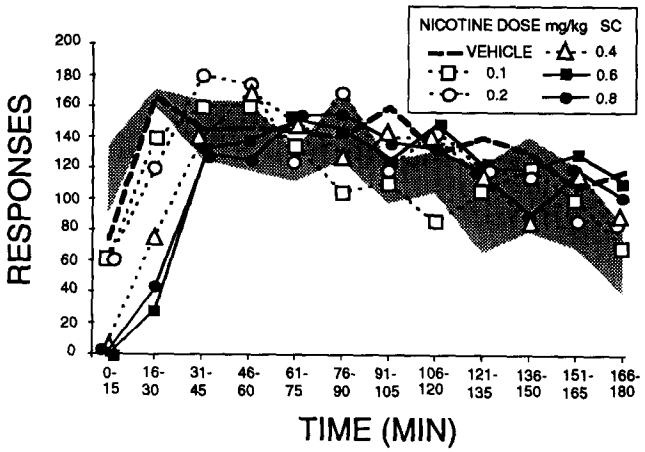

FIG. 3. Mean of total FR responses for consecutive 15 min blocks for sessions following acute nicotine administration (SC). Schedule was mult FI 4 min FR 20, 3 h sessions. Shaded area indicates ± SE for sessions preceding all nicotine injections.

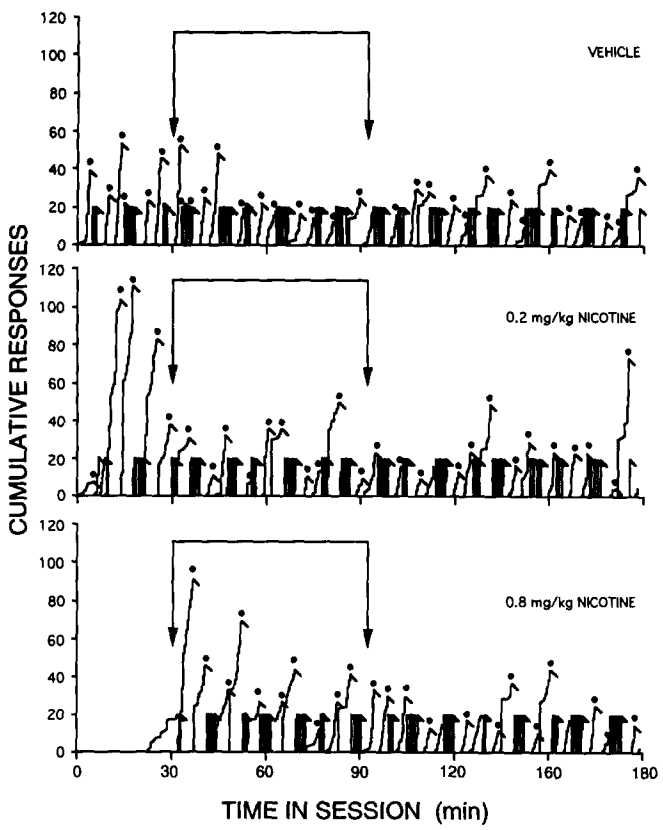

FIG. 2. Sample cumulative response records of complete sessions for animal V16 under mult FI 4 min FR 20 schedule for the session before the first nicotine dose, and the sessions following 0.2 and 0.8 mg/kg nicotine (SC). The response pen increments with each lever press. Pellet delivery is indicated by a slash and pen reset. Each FI component reinforcement is indicated by a dot above the pellet-delivery reset line. The arrow-bracketed period (30–60 min) indicates the period during which nicotine typically produced the most evident increases in FI responding.

lowest nicotine dose (0.1 mg/kg) had little effect on responding. After producing an initial 15 min depression in responding, the 0.2 mg/kg dose elevated responses for the next hour [Figs. 1 and 2 (middle)]. For the 0.2 mg/kg dose shown in Fig. 2 (middle), this animal (V16), after a short initial depression in responding, exhibited an ensuing FI response increase that began before 15 min had elapsed. Larger doses depressed responding fo'r at least 15 min. This was followed by elevated responding that returned to baseline levels at about the second hour of the session [Figs. 1 and 2 (bottom)]. The 0.6 mg/kg dose led to the greatest peak in responding, and the increased rate endured until about the last 0.5 h of the session. The sample session records (Fig. 2) illustrate the dual effect of acute nicotine doses (0.2–0.8 mg/kg): initial response depression followed by marked FI response stimulation. The arrow-bracketed period in Fig. 2 (30–60 min) indicates the period during which nicotine typically produced the most evident increases in FI responding.

The effect of acute doses of nicotine on the FR 20 component of the multiple schedule is shown in Fig. 3. In contrast to FI-component responding, FR responding during the first 15 min of undrugged sessions was lower than responding during the remainder of the first hour. There was a dose-related decrease in FR responding during the first 30 min. The apparent decrease in responding at 76–120 min following the 0.1 mg/kg nicotine dose was due to the unusual behavior of one animal (rat W2).

The effect of acute nicotine dose on schedule component responding within each 15 min block was analyzed by one-way ANOVA (df = 3, 5) for the first half of each session (90 min) and the results, along with individual animal values, are shown in Fig. 4. As described above, an early depression in all responding was produced by nicotine administration followed by an increase in FI responding that was dependent upon both dose and time. In general, the figure confirms an early stimulatory effect on FI responding for the lower doses, with depression by the larger doses, followed by the delayed stimulatory effect on FI responding for the larger doses. The depressive effect of nicotine on FR responding was significant only during the first 0.5 h.

The hatched bars in Fig. 4 indicate the mean FI responses

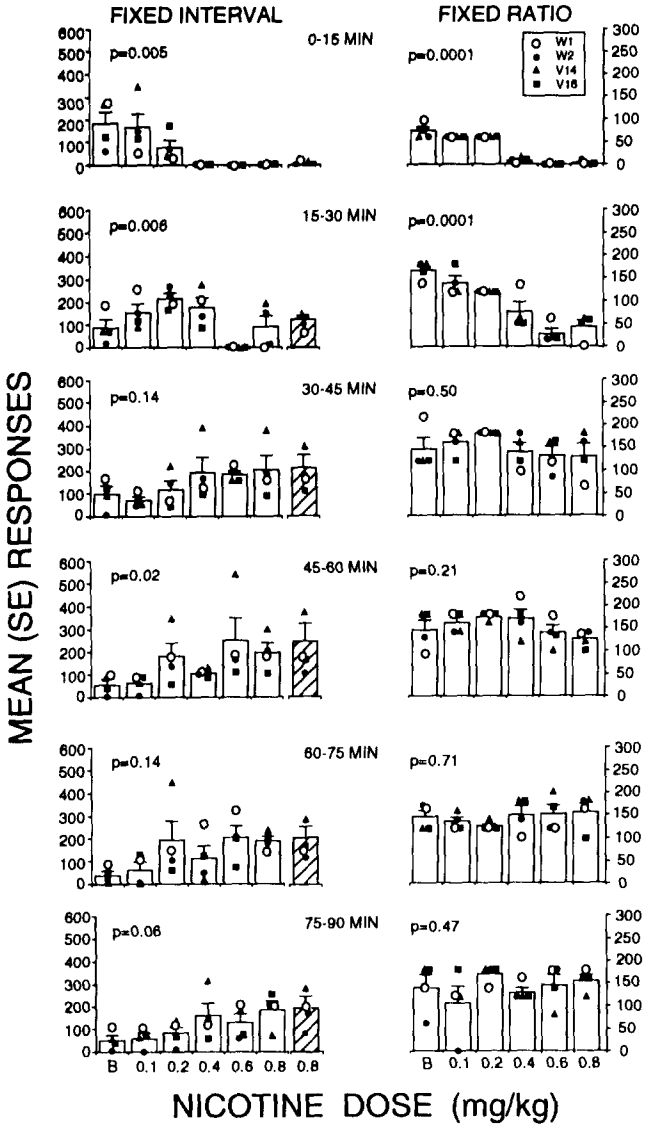

FIG. 4. Mean (SE) responses as functions of acute nicotine doses for FI (left) and FR (right) responding in 15 min blocks for the 1st 90 min of 3 h sessions. Individual animal data are indicated by unique symbols. B = the mean from the sessions immediately preceding each dose. The hatched bars show the FI response mean for the nine-session exposure to 0.8 mg/kg nicotine (SC) doses. ANOVA *p*-values are indicated for the open-bar data at each 15 min block.

for the 9 days of chronic nicotine (0.8 mg/kg, SC). There was no change in responding with chronic exposure compared to the values shown for this dose when nicotine was administered acutely. Responding under the FR component was similarly unchanged by chronic exposure when compared to the effect of this dose given acutely (not shown in figure).

Figure 5 shows the effects of chronic presession injections of 0.8 mg/kg (SC) nicotine on total session FI and FR responding for each animal. Following the acute injection series, there were four baseline sessions (last three of these shown as open symbols in Fig. 5 on left side of each quadrant), followed by daily presession nicotine (0.8 mg/kg, SC) injections. During chronic nicotine administration, FR responding showed only occasional small unsystematic variations across sessions for all animals. In contrast, FI responding increased considerably, although it occurred in a different temporal sequence for each animal. Three animals (W1, W2, and W14) showed increased FI responding with the initial dose. For V16, responding increased progressively over chronic sessions 2-5 and remained at this elevated level for the remainder of the chronic series. V14 also showed a progressive increase over sessions 1-5, thereafter decreasing somewhat. The sequences for W1 and W2 did not show the progressive-increase pattern, although both animals maintained considerably elevated FI response outputs throughout the chronic injection series. The open symbols on the right side of each quadrant of Fig. 5 show the result of substituting the injection of vehicle for nicotine. All animals returned to baseline levels of FI responding except V14, and this animal subsequently retained this baseline shift.

Experiment 2: Effects of Chronic Schedule-Induced Oral Self- Administration of Nicotine on Multiple-Schedule Behavior

Table 1 shows mean daily intakes for the 3 h polydipsia sessions when animals were drinking: a) water, b) nicotine solutions in water vehicle, and c) the terminal concentration of nicotine solution in glucose-saccharin vehicle. Individual water intakes are the means of the last three session intakes before animals were exposed to the first nicotine solution. Inasmuch as there were sizable individual differences in fluid intakes, the data for nicotine intakes are organized into a low, medium, and high dose range to facilitate dose-effect evaluation. For the medium and high self-administered dose ranges, this coincided well with the drinking fluid presented: 0.015 mg/ml nicotine in water and in glucose-saccharin vehicle, respectively (mean of three consecutive sessions for each). For the low dose range, two sessions for each animal were selected wherein the self- administered nicotine doses were as equivalent as possible. These were obtained from sessions presenting 0.006 mg/ml nicotine, except for one session for W1 when 0.004 mg/ml nicotine was presented (Table 1).

Immediately after each daily polydipsia session ended, animals were transferred to their operant chambers and exposed to the multiple schedule. Figure 6 shows the mean baseline FI response outputs across 3 h sessions when animals had drunk water in the polydipsia session preceding the operant session (shaded area). Under chronic nicotine solution polydipsia conditions, FI responding increased in a dose-related fashion. For the low self-administered dose level, slight increases occurred mainly during the first half of such sessions. Similarly, for the medium dose level, elevated responding predominated in the initial half of the session. For the largest dose, increased FI responding was sustained thoughout the session. FR responding was not affected (data not shown).

Sample cumulative records of two complete sessions for animal V16 show the last session for which water polydipsia preceded the performance (Fig. 7, top) and the last session for which 0.015 mg/ml nicotine solution made with water vehicle preceded the performance (Fig. 7, bottom). The self-administered dose of nicotine that preceded this session performance was 1.86 mg/kg, a dose that was at the low end of the medium dose range (Table 1). Comparing these records, nicotine effected an elevation in FI responding that was main-

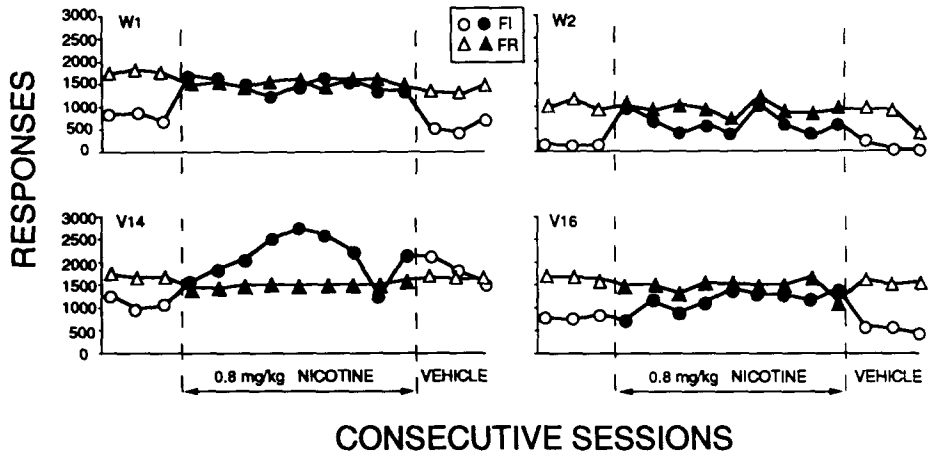

FIG. 5. Effects of chronic daily administration of nicotine (0.8 mg/kg, SC) on 3 h session responses for FI (circles) and FR (triangles) components of mult FI 4 min FR 20 schedule for four animals. Open symbols (left side of each quadrant) are three baseline sessions; open symbols (right side of each quadrant) are three drug-discontinuation vehicle sessions.

tained throughout the session. This contrasts with the effect of presession SC nicotine, which suppressed FI responding in the early portion of sessions.

DISCUSSION

The sequence of behavioral effects produced by the oral self-administration of nicotine in the present study differed from those observed when nicotine was imposed subcutaneously. Whereas SC administration produced a biphasic effect on behavior (e.g., Fig. 4), with a period of depression followed by stimulation, the daily periods of sustained exposure to nicotine produced by the schedule-induction condition resulted in a steady-state stimulation of FI responding for the ensuing 3 h multiple-schedule session. Under FR schedule values similar to the FR 20 used in the present study, the effects of SC nicotine administered to rodents were similar to those reported here: there were occasional increases in responses at low doses, but at 0.2 mg/kg and above mainly short-lived (about 30 min) response decreases occurred (6). For FI schedules, which contain periods of low responding, SC nicotine often produces an overall increase in responding even at relatively high doses (6). But upon closer inspection, such schedules typically illustrate the biphasic effect of SC nicotine we report: for doses of 0.4–0.8 mg/kg, there is an initial response depression lasting about 30 min, followed by a longer stimulatory phase (6,8,11,12).

As shown in Figs. 4 and 5, no tolerance developed to either the depressive or stimulatory effects produced by the chronic SC administration of 0.8 mg/kg nicotine. Although several studies on rodents indicate that chronic nicotine injection can produce tolerance, both the dose used and duration of chronic exposure are important factors determining the appearance of tolerance to nicotine. An early study indicated that with daily

TABLE 1

MEAN (SE) INTAKES OF WATER AND OF NICOTINE SOLUTIONS FOR 3-h SCHEDULE-INDUCED POLYDIPSIA SESSIONS FOR THREE ANIMALS

	H_2O Intake	Low-Dose Nicotine*		Medium Nicotine†		High Nicotine‡	
	ml	ml	mg/kg	ml	mg/kg	ml	mg/kg
Rat W1	107.6 (0.71)	92.0 (11.31)	1.43 (0.21)	70.0 (1.87)	3.38 (0.10)	102.7 (11.43)	4.86 (0.54)
Rat V14	41.3 (0.82)	59.0 (12.73)	1.10 (0.24)	37.3 (5.72)	1.76 (0.26)	96.0 (16.06)	4.33 (0.74)
Rat V16	139.3 (4.55)	52.0 (14.14)	1.01 (0.27)	44.3 (4.26)	2.16 (0.12)	64.7 (8.64)	3.12 (0.40)
Mean	96.1 (35.36)	67.7 (15.11)	1.18 (0.16)	50.5 (12.18)	2.43 (0.60)	87.8 (14.35)	4.10 (0.63)

*Low-dose nicotine: 0.006 mg/ml, except W1 (0.004 and 0.006 mg/ml); 2 day means.
†Medium nicotine: 0.015 mg/ml; 3 day means.
‡High nicotine: 0.015 mg/ml in compound solution of 1.5% glucose and 0.08% saccharin; 3 day means.

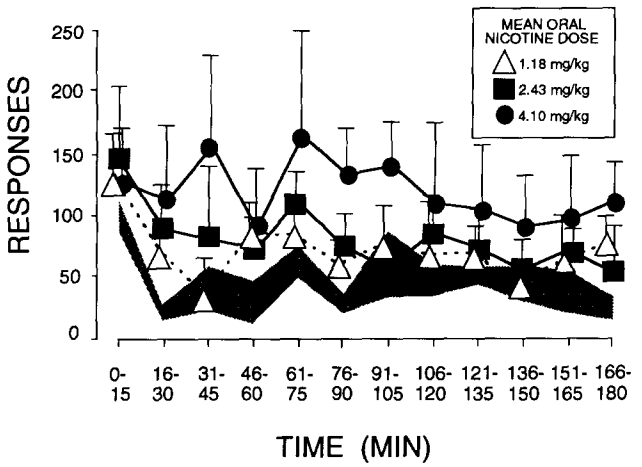

FIG. 6. Mean (± SE) FI responses (shaded area) for a mult FI 4 min FR 20 schedule for consecutive 15 min blocks following 3 h sessions of schedule-induced self-administration of water, as well as means for sessions preceded by schedule-induced self-administration of three dose levels of nicotine. n = 3 animals.

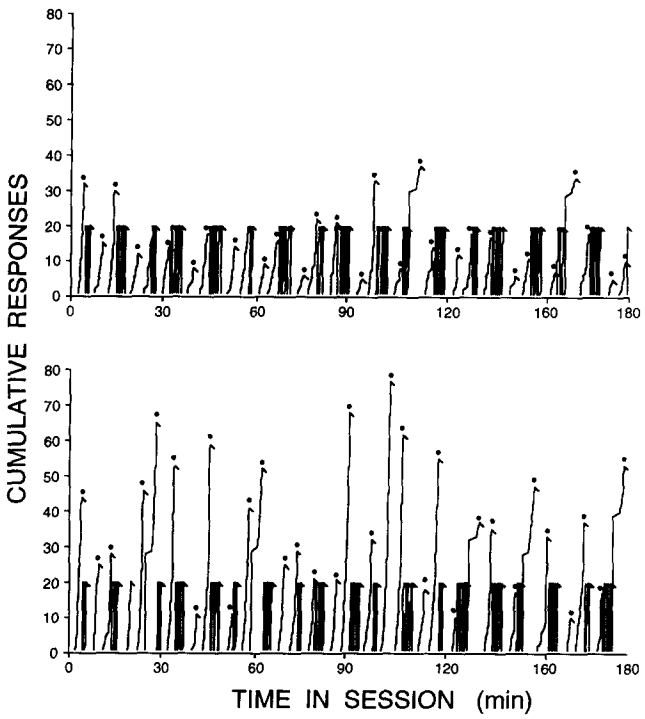

FIG. 7. Sample cumulative records of two complete sessions for animal V16 under mult FI 4 min FR 20 schedule show the last session for which water polydipsia preceded the performance (top) and a session for which nicotine solution polydipsia (self-administered dose = 1.86 mg/kg) preceded the performance (bottom). The response pen increments with each lever press. Pellet delivery is indicated by a slash and pen reset. Each FI-component reinforcement is indicated by a dot above the pellet-delivery reset line.

exposure to two injections of 0.25 mg/kg nicotine per day, rats developed tolerance to the depressant effect on FR 15 behavior of the first of the daily pair of injections after about 15 days of chronic exposure (3). Subsequent studies have indicated that tolerance occurs more readily when the unit exposure dose is in this low range. When the unit dose was 0.25 mg/kg (3 times per day for 8 days), tolerance to the activity decrement developed, but not when the unit dose was 0.50 or 1.0 mg/kg (14). For FR 50 behavior in rats, tolerance developed to the effects of low daily doses of nicotine, but not when the unit injection dose was increased to either 0.50 or 0.65 mg/kg for several days (4). However, tolerance can develop to the effects of administering such larger doses of nicotine chronically if the exposure period is prolonged. For example, mice responding on an FR 20 schedule developed tolerance to the effects of daily 1.2 mg/kg doses of nicotine after 30 days of dosing (7). Similarly, rats responding on a VI 15 s schedule developed tolerance to the effects of daily 0.8 mg/kg doses of nicotine after 14 days of dosing (16). The lack of tolerance development in the present study, then, was most likely due to the high dose chosen for chronic SC administration (0.8 mg/kg) and the relatively short time of chronic exposure (9 days).

Exposure to the 3 h session of schedule-induced oral self-administration of nicotine at a middle or high dose range produced a marked increase in FI responding that endured for the entire 3 h of the multiple-schedule session that followed the polydipsia session (Figs. 6 and 7). The efficacy manifested by moderate doses of oral gavage nicotine in producing behavioral effects (2) may call into question the importance of the hepatic first-pass effect in limiting the action of oral nicotine. Indeed, rats that had undergone portacaval anastomosis to prevent the liver first-pass effect and increase the bioavailability of oral nicotine did not differ from control animals in their plasma nicotine peak concentrations after intragastric nicotine loading (10). The daily, oral self-administration of nicotine in schedule-induction sessions provides a feasible technique for exposure to nicotine, the daily effects of which can be investigated in ensuing postingestive daily behavior sessions.

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