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Control of Behavior by Intravenous Nicotine Injections in Human Subjects

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HENNINGFIELD, J. E. AND S. R. GOLDBERG. *Control of behavior by intravenous nicotine injections in human subjects*. PHARMACOL BIOCHEM BEHAV 19(6) 1021–1026, 1983.—Results are summarized from a series of studies in which procedures used to assess the reinforcing and aversive properties of drugs in animals, were extended to a human paradigm. Human volunteers were tested using drug self-administration and avoidance procedures, whereby pressing a lever under a fixed-ratio schedule resulted either in the IV injection of nicotine or in the avoidance of programmed IV injections of nicotine, respectively. Nicotine was found to maintain responding that *produced* its injection under certain conditions, and to maintain responding that *avoided* its injection under other conditions. Nicotine produced the same constellation of stimulus properties whether functioning as a positively or negatively reinforcing event. These functional properties of nicotine may be determined by schedule of access to nicotine, dose of nicotine, and past history of the subject.

Nicotine Human studies Self-administration Avoidance Cigarette smoking Drug abuse Reinforcement schedule

NICOTINE, delivered via tobacco smoke, or intravenously, is well absorbed and provides discrete stimulus properties by its actions in the central nervous system [7, 16, 18]. In human subjects, the onset of nicotine's stimulus effects is within seconds, and the offset within a few minutes of an intravenous injection; the subjective effects include reports of lightheadedness, nausea, respiratory distress, sweating, feeling of fear, and numbing or burning at the injection site [7,13]. The fast onset and offset of the effects of nicotine should make it an ideal stimulus to control behavior; indeed, the "nicotine bolus effect" has been raised as a major determinant of patterns of cigarette smoking behavior [18]. With regard to operant behavior, nicotine could serve as either a discriminative stimulus that sets the occasion for a particular response to occur, a positive reinforcer that strengthens behavior leading to its presentation, or a negative reinforcer that strengthens behavior leading to its removal or postponement.

All three such properties of nicotine have been evaluated in animal studies. In drug discrimination paradigms, nicotine produces dose-related stimulus effects which are blocked by the centrally and peripherally acting antagonist, mecamylamine, but not by the peripherally acting antagonist, hexamethonium [16,24]. In drug self-administration paradigms, several investigators [6] have now demonstrated that nicotine can serve as a reinforcer, and that this property, too, is blocked by mecamylamine pretreatment. In punishment [2] and drug avoidance [21] paradigms, it has been demonstrated that nicotine may also produce noxious effects which function to suppress behavior maintained by food and to maintain behavior leading to postponement of scheduled nicotine injections, respectively; these effects of nicotine are also blocked by mecamylamine pretreatment.

In studies with human subjects, these properties of nicotine have only been assessed in a preliminary fashion. In the human analogue of a drug discrimination study, nicotine was shown to produce dose-related stimulus effects, which were blocked by pretreatment with mecamylamine [9]. Human subjects were also found to self-administer intravenous injections of nicotine [10]; however, some subjects showed decreased rates of nicotine-maintained responding relative to saline-maintained responding, suggesting that nicotine served as a punishing stimulus for these subjects. Experimental studies of punishment or avoidance with intravenous nicotine injections have not been conducted with human subjects.

The present paper describes studies in which the control of human behavior by intravenous nicotine injection was studied using both schedules of drug injection and schedules of avoidance of drug injections. Some of the findings relating to the reinforcing properties of drugs with laboratory animals were replicated in human subjects. Finally, some of the subjective concommitants of the functional properties of nicotine were assessed using a variety of psychometric instruments.

GENERAL METHOD

Subjects were male cigarette smokers, ages 21–50, who gave their informed consent to reside on the research unit and to participate in the studies. Their histories of recreational drug use ranged from light social drinking to polydrug abuse and dependence. Three-hour experimental sessions were run three days per week, during the six to twelve-week stay of subjects. An operant test panel with two levers and attendant stimulus lights were located near the subject's reclining chair. Before a session, the subject was catheterized

in a forearm vein using a standard intravenous infusion set. Automatically activated syringe pumps were used for injections. Drug dose volume was 1 ml and injection duration was 9.2 sec. Under concurrent schedules, two pumps were available to give drug and saline injections. To ensure that all drugs delivered reached the vein immediately following the operation of one of these pumps, a third pump delivered 0.5 ml of saline over 4.8 seconds. Additionally, a gravity-fed dextrose solution was infused at a rate of 12 ml per hour to maintain the patency of the catheter. During sessions the subjects sat in a reclining chair in isolation and had access to a radio and magazines. Cigarette smoking was not permitted for 1 hour prior to or during sessions.

Before and after each session, basic vital signs were collected by the research staff. Subjects then also completed three questionnaires: (1) A short form (40 items) of the Addiction Research Center Inventory (ARCI) which contains empirically derived scales sensitive to the effects of several classes of psychoactive drugs [12]. (2) The Single Dose Questionnaire (SDQ) which contains a scale of drug liking and a drug identification list with the street names of 10 common psychoactive drugs [12]. (3) A newly developed form with rating scales of drug dose strength and desire to smoke a cigarette. Additionally, one minute after each injection the liked and disliked effects of the injection were rated by the subject on 100 mm visual line analogue (VLA) scales.

Prior to the study, the safety of the nicotine dose levels was verified by injecting the subjects with each of the possible doses at one hour intervals in an ascending sequence. They were told that only doses from among this sequence, or placebo, would be available during the self-administration study, but they were given no information regarding the specific nicotine dose available during any session. In some studies, sessions were preceded by oral administration of mecamylamine. Subjects were told that any lever pressing or drug taking was voluntary; they were not asked or encouraged to take injections.

Studies were conducted following review and approval of the study plan by the Institutional Review Board. To further ensure the safety of subjects, (a) a one-minute time-out, during which no injections were available, followed each injection, (b) there was a programmed maximum limit on the number of injections available during successive thirty-minute intervals, (c) a research nurse observed the subject and the subject's continuous electrocardiogram display and was free to abort the session at his or her discretion, and (d) the subject was free to abort the session at any time.

CONTROL OF BEHAVIOR BY NICOTINE INJECTION (SELF-ADMINISTRATION)

Self-Administration of Nicotine

Six subjects were studied under a simple fixed-ratio schedule of nicotine or saline injection. During each session, ten responses on one lever produced an injection of nicotine or saline (FR 10); responding on the other lever (activity lever) had no programmed consequence [10]. Figure 1 shows cumulative records of lever pressing and injections from one subject. Subjects self-administered both nicotine and saline; however, nicotine injections occurred in regular patterns whereas saline injections occurred with wide variability in pattern and frequency both within and across subjects. Patterns of nicotine self-administration were similar to those of humans smoking cigarettes and to animals self-administering psychomotor stimulants [4]. In some of the subjects, nicotine

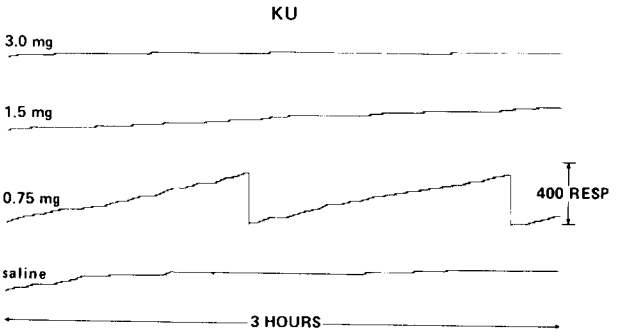

FIG. 1. Cumulative records from subject (KU) showing patterns of lever pressing and injections during sessions under a simple fixed-ratio schedule of drug injection. Every tenth lever press produced an IV injection of nicotine or saline. Responses are indicated by vertical increments and injections by diagonal slash marks. Subject KU was studied at each dose once during a 3-hour session. An alternate lever was present but responding on that lever had no scheduled consequences and seldom occurred and the records are not shown. (Reprinted with permission; [10].)

maintained higher overall rates of lever-press responding than saline suggesting that nicotine was serving as a positive reinforcer. In other subjects overall rates of responding during sessions, when nicotine was available, were lower than those when saline was available, suggesting that nicotine was serving as a punishing stimulus relative to saline. Nicotine produced dose-related increases in scores on a drug liking scale, and was identified as cocaine in subjects with histories of cocaine abuse. Nicotine also produced noxious effects including nausea, feelings of fear, coughing, and pain at the injection site. These effects occurred regardless of whether nicotine appeared to be maintaining or suppressing behavior.

Acquisition of Nicotine Self-Administration

Two of the subjects tested in the above-described study were without histories of drug abuse. In both of these subjects, nicotine suppressed self-administration rates to levels well below those maintained by saline. Over seven consecutive sessions of access to nicotine, however, self-administration rates gradually increased (e.g., Fig. 2). These patterns of acquisition are similar to those reported in a study of drug-naive squirrel monkeys by Goldberg and Spealman [2]. When saline was substituted for nicotine, lever pressing rates first increased and then decreased across subsequent sessions to values lower than those ultimately obtained with nicotine (Fig. 2). The subject reported no change in dose strength across nicotine sessions as might be expected if the increase simply reflected tolerance to the effects of nicotine. These data suggest the possibility that the functional effect of nicotine had changed with time and repeated exposure from that of punishing to a reinforcing stimulus.

In another subject (OG), nicotine initially functioned as a negative reinforcer under a fixed-ratio schedule of avoidance of drug injections (data reported in the next section, Fig. 5). That subject was readmitted to the research unit for an additional study in which he was tested under a concurrent schedule of drug or saline injection. Under this schedule, ten responses on one lever produced an IV injection of nicotine, and ten responses on a second lever produced an IV injection of saline (a concurrent FR 10, FR 10 schedule of drug

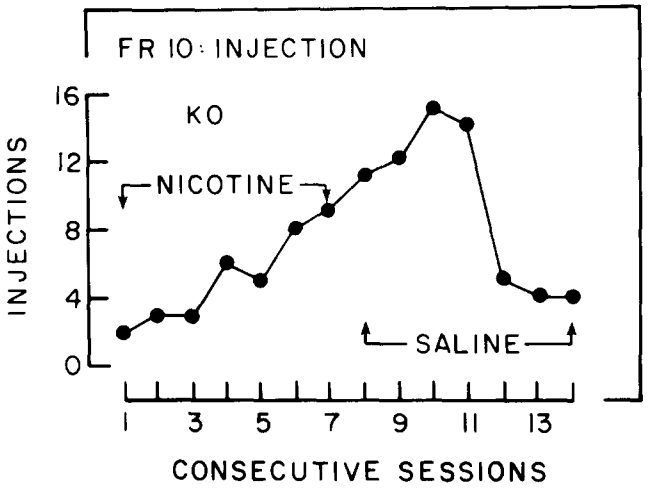

FIG. 2. Subject KO was a cigarette smoker without a history of drug abuse. He responded under the simple fixed ratio schedule of nicotine or saline injection. Nicotine was available (1.5 mg nicotine per injection) during seven consecutive sessions; then saline was substituted for an additional seven sessions. Number of injections per session are shown on the y-axis [10].

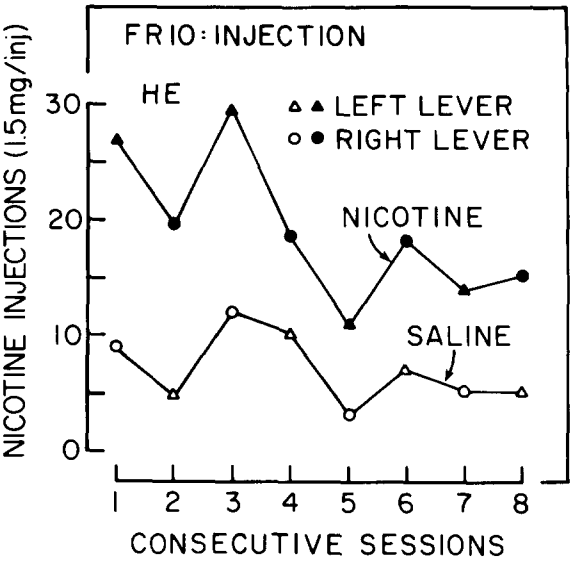

FIG. 3. Subject HE had a history of alcoholism and had been previously tested over a range of nicotine doses. In this study, he was given concurrent access to both nicotine (1.5 mg/injection) and saline during three-hour sessions. Ten responses (FR 10) were required to produce an injection and the levers which were associated with nicotine and saline injections reversed each day. Number of injections per session are shown on the y-axis. As an additional pilot procedure, a mecamylamine capsule was given one hour before each session. The mecamylamine doses were: 0 mg, sessions 1, 3 and 8; 2.5 mg, sessions 2 and 6; 5 mg, sessions 4 and 5; 10 mg, session 7. Mecamylamine attenuated self-reported liking of the nicotine injections and appeared to have decreased rate of nicotine-maintained responding but this may simply have been a trend across sessions.

and saline injection). Each injection was accompanied by a tone and stimulus light and was followed by a one-minute timeout. Sessions were one hour in duration. Initially, the subject's rates of nicotine self-administration were low and number of injections per session equalled those of saline (mean=3.9, range=3–5, for nicotine). After nine sessions of access to 1.5 nicotine and saline under the concurrent FR 10, FR 10 schedule, the schedule was changed to a second-order schedule of drug injection in which only nicotine was available. Under the second-order schedule, ten lever presses (FR 10) on the left lever produced a one-second presentation of the light and tone stimuli which normally accompanied injections; the completion of ten lever presses after a 30-minute interval (FI 30) had elapsed, produced both the stimuli and a 1.5 mg nicotine injection. Responding on the right lever had no scheduled consequences. Under this second-order schedule, number of injections per session increased somewhat from that of the concurrent schedule and averaged 5.7 (range=4–8). However, response rates increased sharply: Under the concurrent schedule, response rates on the nicotine lever averaged 0.24 responses per minute (range=0.18–0.31, n=9); under the second order schedule, response rates on the nicotine lever averaged 0.67 responses per minute (range=0.52–1.03, n=6).

Assessment of the Reinforcing Properties of Nicotine

A procedure that has been used in animal studies to demonstrate the reinforcing efficacy of a drug relative to saline is to increase the fixed-ratio response requirement. This was done in studies of ethanol and pentobarbital drinking by rhesus monkeys [8,14]. In those studies water intake exceeded drug intake at low fixed-ratio values; but when the fixed-ratio value was increased, drug, and not water, maintained performance. In a study by Goldberg and Henningfield (manuscript submitted for publication), using a concurrent FR 10, FR 10 schedule of IV nicotine or saline injection, one subject consistently responded at higher rates for saline than for nicotine. Over a number of consecutive sessions, the fixed-ratio value for both nicotine and saline was increased gradually to 400 and then decreased once again to 10. This resulted in a shift in responding under the final FR 10 condition to nicotine maintaining higher rates of responding than saline.

Concurrent schedules of drug and saline injection are useful for studying the reinforcing efficacy of a drug in human subjects, since rates of responding maintained by both drug and placebo, as well as the relative rate of responding (preference), can be determined within a single session. Figure 3 shows data from one subject (HE) who was given concurrent access to nicotine (1.5 mg per injection) and saline. Each was available following ten lever presses and the levers which produced either nicotine or saline were alternated each day. As shown in the figure, regardless of whether responses on the right or left lever produced nicotine, nicotine injections always exceeded saline injections.

Self-administration studies in animals and humans with opioid agonists (e.g., morphine) have shown that pretreatment with antagonist drugs (e.g., naltrexone) decrease the reinforcing efficacy of the opioid, relative to placebo [4]. Similar findings were obtained after mecamylamine pretreatment in animal studies of nicotine self-administration (e.g., [23]). The effects of mecamylamine treatment on nicotine self-administration by human subjects was evaluated in a preliminary fashion by giving subject HE a dose of mecamylamine or placebo, orally, one hour before each of the sessions shown in Fig. 3. As shown in the figure, mecamylamine did not produce clear behavioral effects. However, subjective effects were altered and the procedure

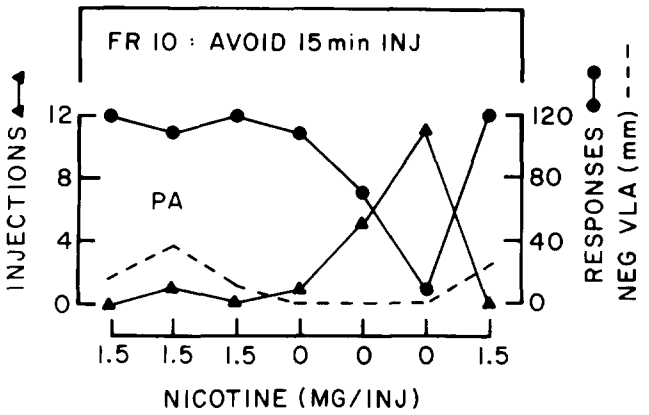

FIG. 4. Subject (PA) was tested during 3-hour sessions on a concurrent schedule in which pressing the right lever (FR 10) produced nicotine injections and pressing the left lever extinguished the left lever light and avoided the next programmed injection (12 injections were programmed at 15-min intervals). The subject did not press the right lever. The number of programmed injections and number of responses (left lever) per session are shown for seven consecutive sessions. The negative VLA scores are the number of mm away from the neutral point on a 100 mm visual line analogue scale; the instructions on the scale are to place a mark on the line that "indicates the strength of any bad or negative effect which you don't like." The score shown is the mean of that produced by the first 3 injections, including the 15 min presession injection.

was shown to be safe and viable. The subject described the nicotine dose as "very mild" following sessions in which mecamylamine was given and as "moderately strong" following sessions in which placebo was given before nicotine. In a subsequent study, another subject (OG) was given either 10 mg of mecamylamine or placebo one hour before sessions, and mecamylamine was given over consecutive sessions. Nicotine and saline were concurrently available under fixed-ratio 10 schedules, and the nicotine-delivering lever was alternated each day. During each of the four consecutive sessions following mecamylamine pretreatments, number of saline injections equalled number of nicotine injections (mean=4.3, range=4–5, for both nicotine and saline), and scores on both the positive and negative visual line analogue scales were zero (neutral). When mecamylamine was replaced with placebo for two sessions, number of nicotine injections increased, exceeding number of saline injections (nicotine, mean=5.0; saline, mean=3.5). Both negative and positive visual line analogue scale scores increased to the levels at which they had been at before mecamylamine was given. These results, though preliminary, are not inconsistent with those obtained in studies with animals (e.g., [2]).

A subsequent study examined the effects of systematic, within-subject manipulations of nicotine dose in human and squirrel monkey subjects when ten lever presses were required per intravenous nicotine injection (manuscript submitted for publication). With the human subjects, nicotine and saline were presented concurrently; with the animal subjects, saline and nicotine were presented sequentially across sessions. A one-minute timeout followed each injection, and each session lasted 100 minutes (monkeys) or 180 minutes (humans). The results of the study were similar in both species. All subjects self-administered both nicotine and saline. Number of nicotine injections exceeded number of saline injections in three of the four humans and three of the four monkeys tested, indicating that nicotine was serving as a positive reinforcer for these subjects. With the human subjects, as injection dose increased from 0.75 to 1.5 mg, there was little change in number of injections taken per session. However, when dose was increased to 3.0 mg, number of injections per session decreased. This is interesting since studies of the effects of nicotine yield in cigarettes on cigarette smoking behavior have shown little effect on rate of cigarette consumption except when nicotine yield of the cigarettes was in excess of 2 mg per cigarette [5].

CONTROL OF BEHAVIOR BY AVOIDANCE OF NICOTINE INJECTIONS

The following are self-reported symptoms of a subject following a response-produced saline injection (right lever) and a response-produced 3.0 mg nicotine injection (left lever). These symptoms are typical of those reported by other subjects in earlier studies (e.g., [10])

9:55 a.m.	[I] pressed [the] right lever: Placebo.
10:42 a.m.	[I] pressed [the] left lever: Very strong dose. Respiratory problems, took breath at first. Tightness in chest. Lightheaded sensations lasted approximately 15–20 seconds. Would be willing to [pay] seventy-five dollars *not* to receive it.
10:50 a.m.	[I am] beginning to feel drowsy and sluggish.

This subject did not subsequently self-administer nicotine, but most of the other subjects, who also reported such effects, did. The implication is that the same constellation of effects produced by nicotine can serve as a positive reinforcer under some conditions, and as an aversive stimulus under others.

In subsequent studies, subjects who did not self-administer nicotine during initial sessions, were tested under a concurrent schedule of nicotine avoidance and nicotine self-administration. Injections were scheduled to occur at predetermined intervals (30 min for 2 subjects and 15 min for 1 subject). Pressing the left lever ten times before an injection was programmed to occur, turned off the left lever light and avoided the next injection. Pressing the right lever ten times produced an injection. Thus it was possible for a subject to avoid programmed injections of nicotine, to self-administer nicotine, or any combination thereof. The same dose was available under each schedule condition. A single injection of the dose to be studied was given to the subject 15 minutes before the start of a session.

One subject (PA) who had previously been studied for four sessions under the concurrent fixed-ratio schedule of nicotine or saline injection and had taken less than three nicotine and saline injections per session, was tested under the concurrent scheule of nicotine avoidance and nicotine self-administration. As shown in Fig. 4 either 11 or 12 of the 12 programmed nicotine injections were avoided by pressing on the left lever. Responding on the right lever, which would have produced nicotine injections, never occurred. When saline was substituted for nicotine, lever pressing declined until the third day when 11 programmed injections occurred.

When nicotine was reinstated on the following day, responding increased and all 12 programmed injections were avoided. The subject had then completed his term of study on the research unit and was discharged. Interestingly, as shown in Fig. 4, scores on the negative visual line analogue scale corresponded with the lever-pressing behavior of the subject: scores were higher in the presence of nicotine and declined to zero when saline was substituted for nicotine.

Two additional subjects tested were presented with a range of doses, each given four times in a randomized block sequence. Figure 5 shows the results of this procedure. As shown in the figure, higher doses of nicotine were accompanied by increased rates of lever pressing to avoid injections, and decreased numbers of programmed injections occurred. Neither subject completed the ten-responses on the alternate lever required to produce a nicotine or saline injection. Also, as with the previous subject, scores on the negative visual line analogue scale were directly related to nicotine dose.

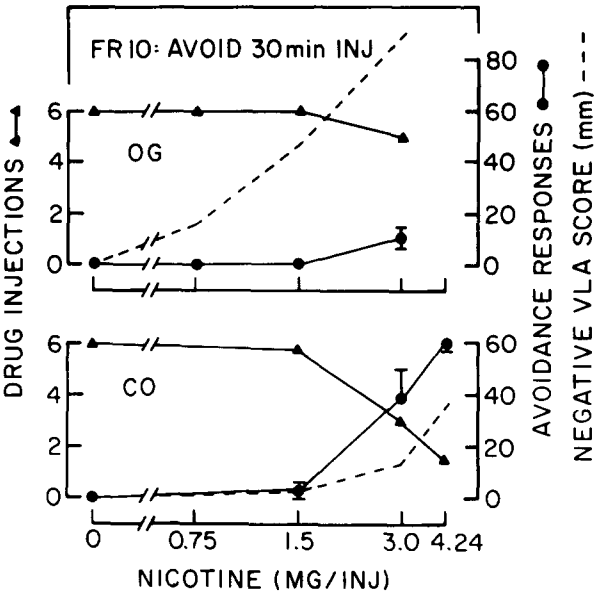

FIG. 5. Two subjects (OG and CO) were tested during 3-hour sessions on a concurrent schedule in which pressing the right lever (FR 10) produced nicotine injections and pressing the left lever (FR 10) extinguished the lever light and blocked the next scheduled injection (6 injections were scheduled at 30-min intervals). Neither subject pressed the right lever. The y-axis shows number of programmed injections that were taken, left-lever responses and negative visual line analogue (VLA) scores. The negative VLA scores are the number of mm away from the neutral point on a 100 mm visual line analogue scale; the instructions on the scale are to place a mark on the line that "indicates the strength of any bad or negative effect which you don't like." The score shown is the mean of that produced by the first 3 injections, including the 15 min presession injection.

GENERAL DISCUSSION

It is clear that many of the procedures which have been used to characterize the behavioral pharmacology of psychoactive drugs in laboratory animals may be applied to intravenous studies with human subjects. Furthermore, the results from these procedures are generally consistent with the results of clinical pharmacologic assessment (e.g., self-report data). In brief, procedures to quantitate reinforcing efficacy which have been described by others (e.g., [15,22]) were invaluable in the assessment of nicotine. These include (a) saline substitution, (b) manipulation of nicotine dose, (c) use of a pharmacologic antagonist, (d) concurrent nicotine-saline choice, (e) alternating the lever which produced nicotine injections, (f) use of a nonfunctional lever to control for general activity. Similarly, some of these same procedures were used in initial studies of the noxious properties of nicotine. The *direct effects* of nicotine may be described as follows: Effects are directly related to dose; the onset of effects is within seconds and offset is within minutes of injections; qualitatively, effects include sweating and reports of lightheadedness, nausea, respiratory distress, feeling of fear, and numbing or burning at the injection site. These characteristics do not vary as a function of whether the drug produces concomittant effects of liking or disliking, and whether the drug serves as a positive or a negative reinforcer. The *functional behavioral effects* of nicotine are diverse and the conditions under which they occur are only beginning to be understood: Nicotine can serve as either a positive or a negative reinforcer, and, in animal studies, it has been demonstrated to serve as a punisher that suppresses behavior maintained by other reinforcers. Preliminary data presented here, and data presented by others [1, 3, 6, 20], show that several factors are relevant in determining the functional properties of nicotine. These include (a) history of the subject, (b) schedule of reinforcement or temporal aspects of access, and (c) nicotine dose.

The prominence of these factors in determining the functional properties of nicotine may be greater than for other drugs of abuse. That nicotine may serve as a stimulus with multiple functional properties is well known by researchers and therapists who study and treat cigarette smoking. Johnston observed in 1942 [13], and Russell [17] has further discussed, the fact that nicotine can produce both pleasureable and aversive effects. Similarly, cigarette smoking can be treated by both a nicotine delivering chewing gum which produces some of the desired effects of smoking, or rapid smoking procedures which induce transient sickness and discomfort [11,19]. Clearly, the data are not consistent with descriptions of nicotine as consistently serving as a positive reinforcer or an aversive stimulus, or simply as a toxin lacking behavioral effects. Nicotine appears to be a particularly malleable stimulus. These findings are compatible with a large amount of animal literature showing that different types of drug and nondrug stimuli (e.g., cocaine, nalorphine, electric shock, brain stimulation) can maintain responding leading either to their presentation or their postponement, depending on the environmental conditions (cf., [21]). A challenge for future research is to identify the variables that determine the functional properties of nicotine.

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