Pharmacology Biochemistry & Behavior, Vol. 30, pp. 227–234. Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Reinforcing Effects of Nicotine in Humans and Experimental Animals Responding Under Intermittent Schedules of IV Drug Injection

S. R. GOLDBERG[1] AND J. E. HENNINGFIELD

Addiction Research Center, National Institute on Drug Abuse
P.O. Box 5180, Baltimore, MD 21224

GOLDBERG, S. R. AND J. E. HENNINGFIELD. *Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of IV drug injection.* PHARMACOL BIOCHEM BEHAV **30**(1) 227–234, 1988.—The self-administration paradigm is an experimental model of drug dependence in which the reinforcing properties of drugs can be directly assessed. This paradigm avoids the possible confounding influence of nonpharmacologic factors which may contribute to drug taking in the nonlaboratory environment. When animals serve as subjects, social and cultural factors unique to humans may also be eliminated as confounding influences. Most drugs of abuse are self-administered by animals and humans under such conditions. Until 1981, laboratory studies of nicotine self-administration suggested that nicotine, in its own right, was only a marginally effective reinforcer. As will be shown in the present review, a study by Goldberg and his co-workers in 1981 [13] demonstrated clearly that nicotine could serve as a highly efficacious reinforcer in laboratory animals. There are several parameters which can function to substantially strengthen the behavior which leads to nicotine ingestion. These include the following: (1) intermittent availability of nicotine, (2) intermittent presentation of nicotine-paired stimuli, and (3) concurrent schedules of food reinforcement. Initial findings from a human IV nicotine self-administration study were consistent with those from the animal studies. Together these results confirm that nicotine can function to control behavior by serving as a reinforcer for animals and humans. The results also suggest that commonly used tobacco products function as ideal nicotine delivery systems for controlling behavior since they provide discrete nicotine-paired stimuli and lend themselves to intermittent nicotine delivery.

Drug self-adminstration Drug abuse Tobacco Nicotine Mecamylamine

ALL concepts of drug dependence have as a central focus the persistent maintenance of behavior that leads to drug self-administration [5, 20, 25]. Nicotine has long been considered the primary pharmacologic factor responsible for persistent tobacco smoking behavior. However, its functional role in the maintenance and regulation of tobacco smoking remained in question until 1981 because of difficulties in demonstrating strong and consistent reinforcing effects of the isolated drug under controlled laboratory situations. Reviews of a number of laboratory studies in animals led to the conclusion that nicotine was either ineffective or only marginally effective as a reinforcer to maintain self-administration [4, 14, 17].

Many of the effects of drugs as reinforcers are determined by the immediate contingencies relating responses and consequent injections of drug, contingencies which are termed schedules of reinforcement [6]. Until 1981, most studies of nicotine self-administration by animals involved continuous reinforcement schedules in which each response by an individual subject resulted in IV injection of nicotine (e.g., [3, 15, 21]). Rates of responding maintained by nicotine injections in these studies were all very low, ranging from about 0.008 to 0.005 response per second in different studies. Rates of responding also were relatively insensitive to changes in nicotine dose or to pretreatment with the centrally-active nicotine antagonist, mecamylamine. However, nicotine did appear to maintain higher response rates than saline in most of the studies, although there seldom were satisfactory controls for nonspecific activity-enhancing efforts of nicotine that may have contributed to the higher rates of responding with nicotine.

Many of the most interesting characteristics of drugs as reinforcers are only revealed when they are scheduled more intermittently. From 1981 to 1987, a series of laboratory studies demonstrated that high rates of responding could be consistently maintained by consequent injections of nicotine under certain intermittent schedules of reinforcement. However, nicotine appeared to maintain high rates of responding

[1]Requests for reprints should be addressed to Dr. S. R. Goldberg, Preclinical Pharmacology, NIDA Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224.

under a more limited range of conditions than other drugs of abuse such as cocaine. This paper will review a series of studies in which IV nicotine was shown to function as an effective reinforcer, maintaining overall rates of responding ranging from 0.1 to over 1.0 response per second. These increases in the amounts of behavior maintained by nicotine were obtained without the use of food deprivation or inducing schedules of food delivery. The schedules of reinforcement that maintained higher rates of responding had the common characteristic of limiting the frequency of nicotine injection. This was accomplished interposing timeout periods between successive injections or by using time-base schedules of reinforcement.

METHOD

General Method

In the laboratory, the potential reinforcing effects of a drug can best be evaluated by assessing its ability to strengthen and eventually maintain behavior that leads to its presentation. For example, the IV injection of cocaine following a lever-pressing response by a rat or monkey can increase the rate of lever pressing and can maintain this increased rate on subsequent occasions. Although drugs can be self-administered by various routes (intravenous, intramuscular, intraperitoneal or intracerebral injection by inhalating or by mouth), the intravenous route has been studied most extensively with nicotine in experimental animals and is the focus of this review. Several aspects are common to most studies of intravenous drug self-administration. A chronic venous catheter is implanted, often by way of jugular vein. The subject is usually fitted with a jacket or a harness to protect the catheter and is often restrained during study. Drugs then can be delivered rapidly through the catheter by an injection pump operated by automatic programming equipment.

If a drug appears to function as a reinforcer, there are several criteria that are commonly applied to assess its effectiveness. These are as follows:

(1) The absolute rates of responding maintained by the drug in question, expressed as responses per unit time, are of a similar magnitude to those maintained by known drugs of abuse and by non-drug events such as food presentation.

(2) The temporal patterns of responding maintained by the drug are similar to those characteristically maintained under the particular schedule of reinforcement by other drugs of abuse such as cocaine or by non-drug events such as food presentation.

(3) Rates of responding show systematic changes as the dose of drug is varied.

(4) The rate of responding maintained by the drug is appreciably greater than that maintained by the saline vehicle alone.

(5) Rates of responding maintained by the drug are reduced to near vehicle levels after pretreatment with specific antagonists.

(6) Sufficient amounts of drugs are self-administered to produce gross behavioral or physiological effects..

These criteria provide a uniform basis for comparing results of studies performed in different species and under a variety of conditions.

Schedules of Reinforcement

Nicotine self-administration has frequently been studied using either continuous reinforcement schedules (described earlier) or fixed-ratio schedules in which completion of a specified number of responses (most frequently 10 or 30) by an individual subject results in injection of nicotine. Unfortunately, as this small number of responses may be made quickly, injections can occur in rapid succession resulting in cumulative doses of nicotine that may decrease subsequent responding. The cumulative effects of successive injections can be limited, however, by interposing timeout periods between successive injections during which responses have no scheduled consequences or by using time-based schedules of reinforcement in which reinforcement follows the first response that occurs after a given period of time has elapsed (fixed-interval schedules). Under these conditions, the maximal frequency of drug injection is limited by the timeout or fixed-interval value and is relatively independent of the rate of responding.

Training Procedures

In evaluating the potential reinforcing effects of nicotine there are two general approaches for initially exposing the subject to response-contingent availability of nicotine. One approach is to train the subject to self-administer a known drug of abuse such as cocaine. Once self-administration behavior is well established with this baseline drug, either a saline vehicle or different doses of other drugs including nicotine are substituted for the periods of time ranging from one session to several months. In some studies of this type, each test dose of nicotine or saline vehicle is followed by restabilization on the baseline drug, a technique often referred to as a substitution procedure and most often used when a number of drugs, in addition to nicotine, are to be tested. In other studies of this type, subjects are initially trained to self-administer a drug such as cocaine but, once stable behavior develops, saline and a range of doses of nicotine are tested without further exposure to the training drug.

A second approach to evaluating the potential reinforcing effects of nicotine is to attempt to establish it as a reinforcer using various training procedures in drug-naive subjects. Training procedures have varied from one to 24 hour a day access to nicotine with occasional priming doses of nicotine, to concurrent scheduling procedures in which scheduled availability of nicotine injections occurred concurrently with scheduled automatic injections of the drug or presentations of food at fixed time intervals. Using such procedures, the training doses are often lower than those doses which are subsequently most effective at maintaining self-administration.

RESULTS AND DISCUSSION

Interval Schedules of Nicotine Injection

In one series of experiments with squirrel monkeys, Goldberg and Spealman [12] and Spealman and Goldberg [26] utilized a fixed-interval schedule in which the first response to occur after a 5-minute interval of time elapsed produced an IV injection of nicotine followed by a one-minute timeout. Responses during the 5-minute intervals had no specified consequences and daily sessions ended after 10 intervals or 2 hours. Of the six squirrel monkeys studied, four had responded previously under various schedules of food presentation or IV cocaine injection while the other two were untrained at the beginning of the study. Before the study of nicotine self-administration began, responding by the previously-trained monkeys was extinguished, either by

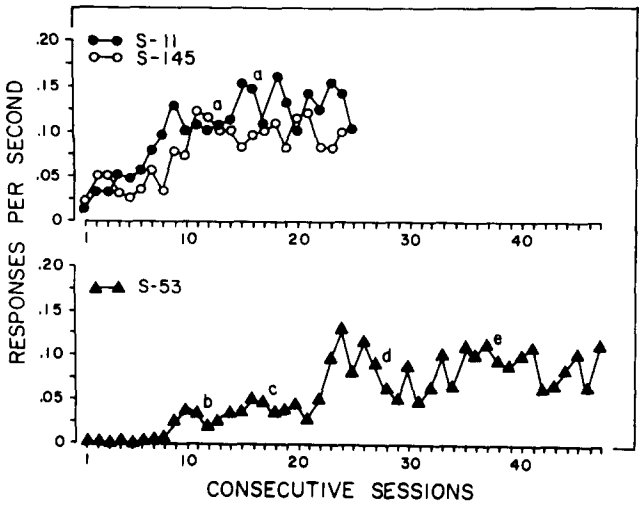

FIG. 1. Acquisition of responding under the 5-min fixed-interval schedule of IV nicotine injection. Abscissas: consecutive sessions; ordinates: response rates. Monkeys S-11 and S-145 (top panel) had responded previously under a fixed-interval schedule of food presentation, but responding was extinguished before exposure to nicotine. Money S-53 (bottom panel) was experimentally naive at the beginning of the study. See text for details. (From Goldberg and Spealman [12] with permission.)

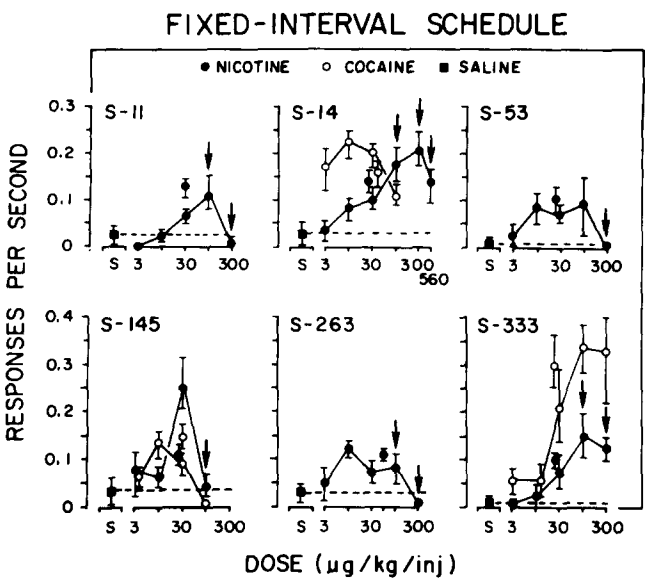

FIG. 2. Effects of dose on responding maintained by IV injection of nicotine or cocaine under the 5-min fixed-interval schedule in squirrel monkeys. Abscissas: dose, log scale; ordinates: overall rate of responding. Points are means based on the last three sessions at each dose or when saline was substituted for the drugs (points at S and dashed horizontal lines); brackets show ranges except where contained within the point. Unconnected circles show responding maintained by nicotine or cocaine during initial exposure to these doses. Arrows indicate doses of nicotine that produced vomiting during or shortly after the experimental session. (From Spealman and Goldberg [26] with permission.)

eliminating food presentations or by substituting saline for drug presentations.

Figure 1 shows the development of responding under the fixed-interval schedule of IV nicotine injection (30 µg/kg/injection) in three monkeys with no drug self-administration history. When monekys were initially exposed to the fixed-interval schedule of nicotine injection, a contingency was added that if a response did not occur within 2 minutes after the 5-minute interval elapsed, nicotine was injected automatically (technically an alternative 5-min fixed interval, 7-min fixed-time schedule). At the points labeled "a," automatic injections were discontinued, leaving only the 5-min fixed-interval schedule which subsequently maintained responding at overall rates of about 0.1 response per second. Monkey S-53 (bottom panel) was experimentally naive at the beginning of the study. Initially the fixed-interval value was 30 sec and the fixed-time value was 5 minutes. At the points labeled "b" and "c," the fixed-interval value was increased to 1 and 3 minutes, respectively. At the point labeled "d," the fixed-interval value was increased to 5 minutes and the fixed-time value was increased to 7 minutes. At the point labeled "e," automatic injections were discontinued leaving only the 5-minute fixed-interval schedule. Again, responding was maintained at an overall rate of about 0.1 response per second by 30 µg injections of nicotine.

Figure 2 shows curves obtained from the six monkeys under the final 5-minute fixed-interval schedule when nicotine dose was varied. For comparison, dose-response curves obtained earlier when three of the monkeys were studied with cocaine under the fixed interval schedule are also shown. Each dose was studied for at least five consecutive sessions. In all monkeys, nicotine functioned as an effective reinforcer: (1) peak rates of responding maintained by nicotine ranged from about 0.1 to 0.3 responses per second and were similar to those maintained by cocaine; (2) patterns of responding within the interval showed a characteristic pause in responding at the beginning of the interval followed by acceleration of responding to a rate that was sustained until the end of the interval; (3) as nicotine dose per injection was increased from 3 to 300 µg/kg rates of responding first increased and then decreased; (4) rates of responding maintained by nicotine were about 4 to 8 fold higher than those maintained during saline substitution; and (5) injection doses of nicotine above 30 µg/kg produced vomiting during the session, but one or more of these higher doses continued to maintain near maximal rates of responding in four of the six monkeys studied. Particularly striking was the finding that daily IM treatment with 1 mg/kg of mecamylamine reduced rates of responding maintained by nicotine to saline-control levels but had no effect on responding maintained by cocaine. Thus, nicotine satisified all the criteria discussed earlier for an effective reinforcer.

Ator and Griffiths [1] used a similar 5-minute fixed-interval schedule of IV nicotine injection with one-minute timeout periods in baboons. Figure 3 shows curves obtained from thee baboons when nicotine dose was varied. Peak rates of responding were low, ranging from about 0.007 to 0.02 responses per second in three baboons, but were higher than rates maintained during saline substitution. However, rates of responding maintained by nicotine were much lower than those maintained by IV injections of cocaine or by food presentation. Also, as injection dose of nicotine was increased from 10 to 560 µg/kg, rates of responding first increased then decreased at the highest doses in one baboon. With the other two baboons, rates of responding either showed little change or decreased as injection dose was increased. Ator and Griffiths subsequently varied the fixed-interval value from 30 seconds to 11 minutes, but rates of responding

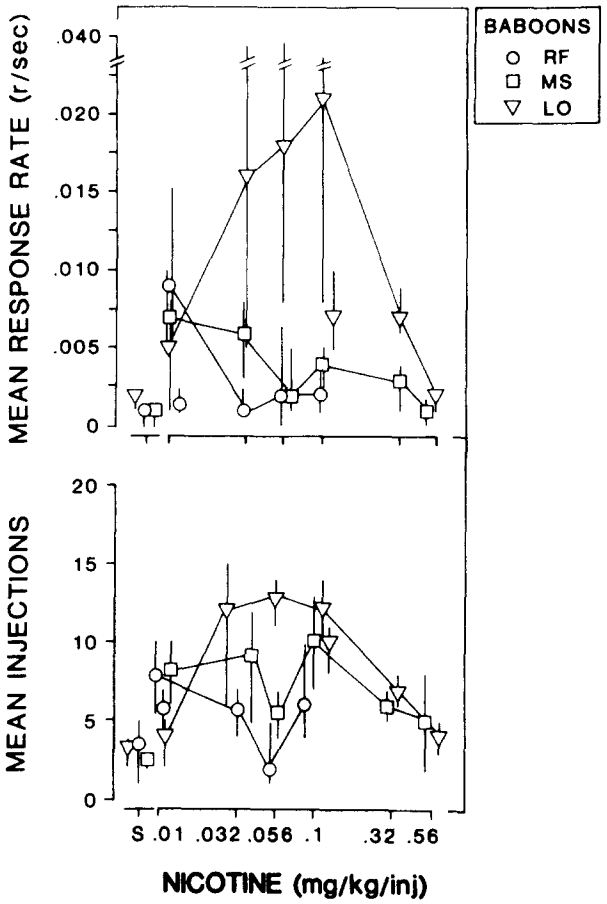

FIG. 3. Response rates (top panel) and number of injections (bottom panel) in daily 2-hr sessions under an FI 300 sec timeout 60 sec schedule of saline (S) or nicotine delivery. Points generally represent the mean of the last five sessions at each condition after number of injections met the stability criterion. Unconnected points represent replications of a dose condition. Vertical bars indicate ranges unless they were encompassed within the point. (From Ator and Griffiths [1] with permission.)

showed little change over this range of conditions. They considered nicotine only marginally effective as a reinforcer in the baboon.

The different levels of effectiveness of nicotine as a reinforcer in the studies by Ator and Griffiths and Goldberg and Spealman may be related either to different species (squirrel monkey vs. baboon) or to differences in the training histories of the subjects. In the Ator and Griffiths study [1], baboons were initially exposed to nicotine under the fixed-interval schedule when a low dose of nicotine (10 μg/kg/injection) was directly substituted for cocaine (32 μg/kg/injection). In contrast in the studies by Goldberg and Spealman [12,26], squirrel monkeys were initially exposed to a higher dose of nicotine (30 μg/kg/injection) after any previously-reinforced responding had been extinguished by substitution of saline for cocaine or by elimination of food presentations. Also, during initial exposure to nicotine, automatic injections of nicotine were scheduled to occur if a response by the squirrel monkey did not occur within 2 minutes after the 5-minute interval elapsed. Thus, frequency of nicotine injection and dose per unit time were greater during initial exposure to nicotine in the studies by Goldberg and Spealman.

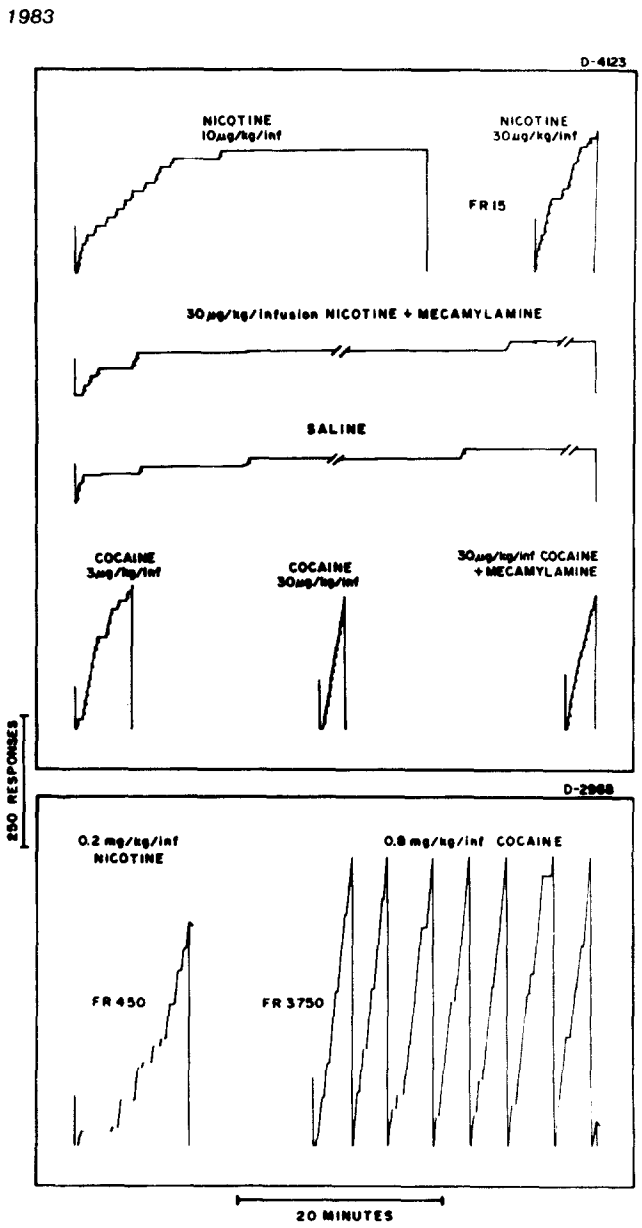

FIG. 4. Representative cumulative-response records depicting the temporal patterns of responding maintained by IV infusions (inf) of nicotine or cocaine under the multiple FR 15, timeout 240 sec schedule (upper panel) or progressive-ratio schedule (lower panel). Short diagonal marks on the cumulative records indicate drug infusions. After each injection there was a timeout period during which the recorder did not operate. Pairs of diagonal hash marks represent deleted segments of the records during which no responding occurred. (From Risner and Goldberg [23] with permission.)

Ratio Schedules of Nicotine Injection

Intermittent schedules of nicotine injection either remain constant (fixed-ratio schedules) or increase systematically until responding is no longer maintained (progressive-ratio schedules) have been frequently studied with conflicting results. Griffiths, Brady and Bradford [14] used a fixed-ratio schedule in which baboons were required to make 160 lever

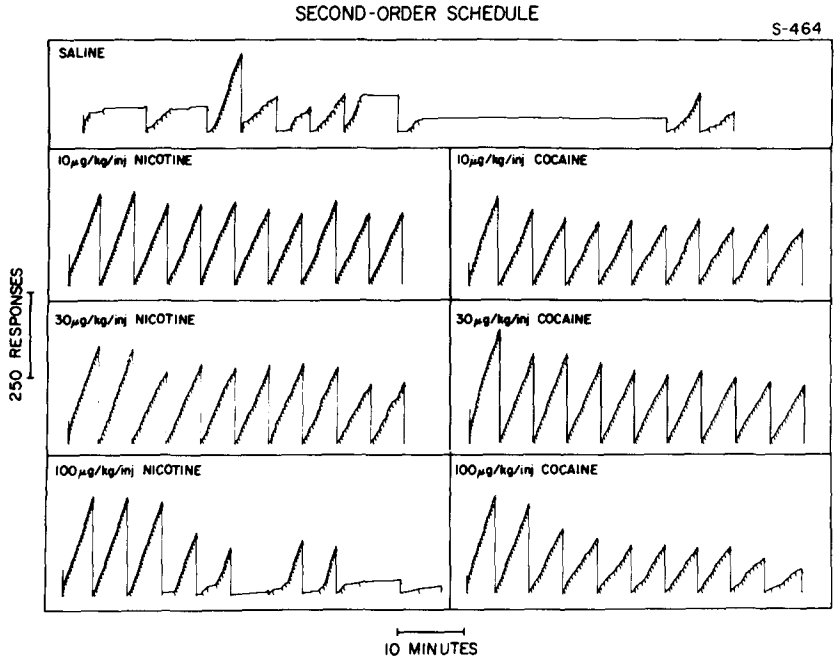

FIG. 5. Representative performances maintained by IV injections of nicotine or cocaine under the second-order fixed-interval schedule in a squirrel monkey (S-464). Abscissas: time; ordinates: cumulative responses. Diagonal marks show presentations of the 1-sec visual stimulus. The recorder reset after each injection and did not operate during the timeout period. Each panel shows a complete record at the doses specified or when saline was substituted for the drugs. (From Spealman and Goldberg [26] with permission.)

presses to produce each IV injection of nicotine and each injection was followed by a 3-hour timeout period. Baboons were trained to respond at high rates for cocaine and doses of nicotine ranging from 0.01 to 3 mg/kg per injection were then substituted for 12 days each, with restabilization on cocaine between doses. Regardless of dose, rates of responding maintained by nicotine did not exceed those maintained by saline. Ator and Griffiths [1] used a 2-response fixed-ratio schedule with a 15-second timeout in baboons tested in daily 20 hour sessions. Dose-related increases in responding were found during the initial five sessions when nicotine was substituted for cocaine, but continued availability of nicotine resulted in decreased rates of responding that were relatively insensitive to changes in dose. Although some doses of nicotine maintained higher rates of responding than saline, overall rates of responding seldom exceeded 0.01 responses per second. Similarly, Slifer and Balster [24] and De La Garza and Johanson [2] used a 10-response fixed-ratio schedule with no timeouts in rhesus monkeys tested in daily 1- or 3-hour sessions. When saline or different doses of nicotine were substituted for cocaine, some doses of nicotine maintained higher rates of responding than saline, but overall rates of nicotine-maintained responding did not exceed about 0.08 responses per second and were much lower than those maintained by cocaine.

Under certain conditions, high rates of responding can be maintained under fixed-ratio schedules of nicotine injection. Risner and Goldberg [23] used a 15-response fixed-ratio schedule of nicotine injection with 4-minute timeout periods following each injection in four beagle dogs. Nicotine was an effective reinforcer in all dogs: (1) peak rates of responding were about 0.3 responses per second at a dose of 30 μg/kg/injection but higher rates of responding were maintained by cocaine; (2) as injection dose of nicotine increased from 3 to 300 μg/kg, response rates first increased and then decreased at the highest two doses; (3) peak rates of responding maintained by nicotine were about 15-fold greater than those maintained by saline. Also, vomiting sometimes occurred at the 100 and 300 μg/kg doses of nicotine. Figure 4 (upper panel) shows representative cumulative-response records for one of the dogs at two different doses of nicotine or cocaine and illustrates the effects of substituting saline for nicotine or cocaine or pretreating the dogs with 1 mg/kg of mecamylamine. Although cocaine was more effective than nicotine in maintaining high rates of responding in the dog, fixed-ratio patterns of responding maintained by nicotine and cocaine were similar. A pause in responding at the start of each fixed ratio was followed by a change to steady responding at a high rate until nicotine or cocaine was injected. When saline was substituted for either nicotine or cocaine rates of responding decreased markedly. Rates of responding maintained by nicotine but not by cocaine were reduced by saline levels by treatment with mecamylamine.

In other studies Goldberg and Henningfield [8–10] used 10- to 30-response fixed-ratio schedules of IV nicotine injection in squirrel monkeys. When a 1-minute timeout followed each injection, nicotine maintained rates of responding higher than saline, but overall rates of responding were very low. When timeout value was increased to 4 minutes [10,22] making maximal frequency of nicotine (30 μg/kg/injection) injection comparable to earlier studies by Goldberg and colleagues, nicotine maintained high rates of responding that ranged from 0.3 to 2.4 responses per second in different monkeys. Also, nicotine maintained characteristic fixed-

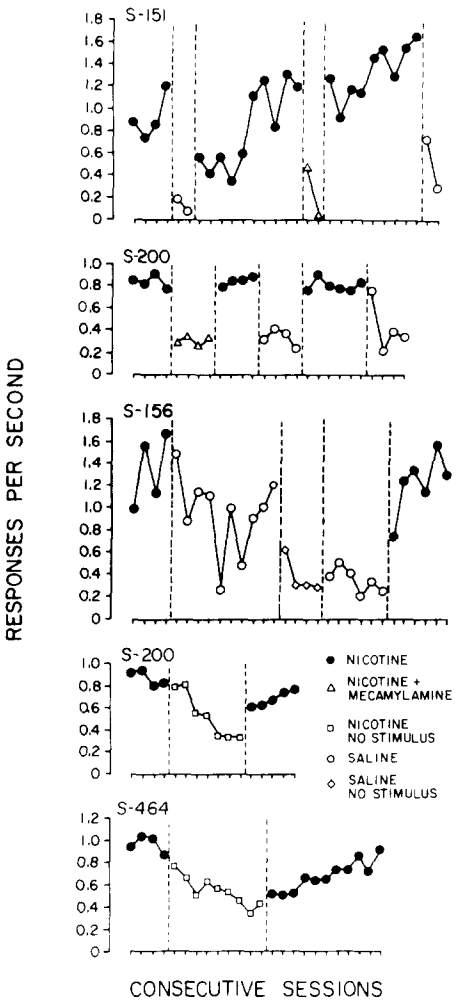

FIG. 6. Effects of substituting saline for nicotine injections (open circles), treatment with mecamylamine before the session (open triangles), or omitting the brief stimulus during the interval (open squares) on responding under the second-order schedule of IV nicotine injection for individual squirrel monkeys. Abscissas: consecutive sessions; ordinates: overall rate of responding. (From Goldberg, Spealman and Goldberg [13] with permission.)

ratio patterns of responding; a pause in responding at the start of each ratio was followed by steady responding at a high rate until nicotine was injected. Similar high rates and fixed-ratio patterns of responding were maintained by nicotine injections and by food presentation.

Pronounced differences between nicotine and cocaine have been found when the drugs are compared under progressive-ratio schedules. Risner and Goldberg [23] studied beagle dogs under a schedule in which the fixed-ratio requirement was increased daily until responding was no longer maintained. Cocaine maintained considerably higher fixed-ratio values than did nicotine under this progressive-ratio schedule (Fig. 4, lower panel) although maximal fixed-ratio values for nicotine were well above those for saline. Yanagita [27,28] obtained similar findings under a progressive-ratio schedule of IV nicotine or cocaine injection in rhesus monkeys.

Second Order Schedules of Nicotine Injection

Another demonstration that nicotine can have powerful reinforcing effects in squirrel monkeys was provided by Goldberg, Spealman and Goldberg [13] and Spealman and Goldberg [26] using a more complex type of schedule, termed a second-order schedule of drug injection [11]. Under this schedule, completion of each 10-response fixed ratio during a 1-, 3-, or 5-minute interval of time produced a brief visual stimulus; the first fixed ratio completed after the fixed interval of time elapsed produced both the visual stimulus and IV injection of drug and this was followed by a one- or three-minute timeout. Again, nicotine functioned as a powerful reinforcer: (1) peak rates of responding maintained by nicotine ranged from 0.8 to 1.7 responses per second and were similar to those maintained by cocaine in one monkey but lower than those maintained by cocaine in a second monkey; (2) as nicotine dose increased from 3 to 100 μg/kg rates of responding first increased and then decreased; (3) rates of responding maintained by nicotine were 2- to 8-fold greater than those maintained during saline substitution; (4) rates of responding maintained by nicotine were reduced to saline control levels by presession administration of 1 mg/kg of mecamylamine; and (5) injection dose of nicotine above 30 μg/kg produced vomiting during the session.

Representative cumulative-response records are shown for one monkey in Fig. 5. Injections of nicotine and cocaine maintained similar patterns of responding. At intermediate doses, characteristic fixed-ratio patterns of responding were maintained through each interval. There was a short pause after most brief-light presentations followed by an abrupt change to a higher response rate that continued until the ratio was completed and the brief light was presented again. At the high 100 μg/kg/injection dose of nicotine or cocaine, patterns of responding were disrupted and rates of responding decreased as the session progressed.

Although the frequency of nicotine injection was about the same under the second-order schedule and under the fixed-interval schedule described earlier, overall rates of responding were much higher under the second-order schedule. These differences are probably attributable to the repeated presentations during the interval of the brief light, which was intermittently paired with nicotine injection at the end of each interval. Figure 6 shows the effects of substituting saline for nicotine injections in three monkeys and of omitting brief-light presentations during the interval with two monkeys under the second-order schedule of nicotine injection. Overall response rates exceeding 0.8 responses/sec were maintained by 30 μg/kg injections of nicotine in all the monkeys. When saline was substituted for nicotine injections, rates of responding quickly decreased to low levels in two monkeys, but high rates of responding persisted during saline substitution in a third monkey (S-156); rates of responding were decreased during saline substitution in this monkey by omitting the brief stimulus lights during the interval for several sessions. When responding was maintained at high rates by nicotine injections, omitting the brief-light stimuli during the interval decreased overall rates of responding to about half those maintained previously (Fig. 6, lower panels); reinstating the brief lights during the interval returned rates of responding to the previous high levels.

Thus, second-order schedules allow one to study not only the reinforcing effects of a drug, but also the acquired reinforcing effects of environmental stimuli associated with the drug. This may be particularly relevant to tobacco smoking in which absorption of nicotine is accompanied by a host of visual, olfactory, taste and tactile stimuli which likely serve to greatly strengthen smoking behavior.

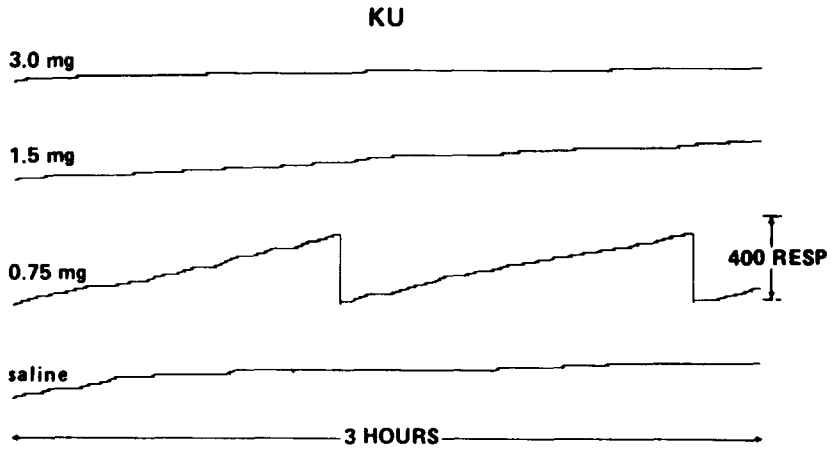

FIG. 7. Cumulative records from subject (KU) showing patterns of lever pressing and injections during sessions under a simple fixed-ratio schedule of drug injection. Every tenth lever press produced an IV injection of nicotine or saline. Responses are indicated by vertical increments and injections by 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. (From Henningfield, Miyasoto and Jasinski [19] with permission.)

Nicotine as a Positive Reinforcer in Humans

The methods developed in animal studies have been used to assess the reinforcing effects of IV nicotine injections in human volunteers in a series of studies by Henningfield, Miyasato and Jasinski [19], Henningfield and Goldberg [16] and Goldberg and Henningfield [8–10]. All subjects had histories of tobacco use and some had histories of abuse of a variety of other drugs. The subjects were not allowed to smoke before or during 3-hour sessions, in which every 10th lever press produced IV injection of either nicotine or saline followed by a 1-minute timeout. In one study [19], on some days nicotine was available while on other days saline was available. In the other studies [8–10, 16], nicotine and saline were concurrently available for responding on alternate levers. In both studies, all of the subjects initiated self-administration responding for nicotine. Figure 7 shows representative performance under the fixed-ratio schedule in one subject studied by Henningfield, Miyasato and Jasinski. Nicotine injections were regularly spaced throughout each session and rate of self-administration was inversely related to dose. When saline was substituted for nicotine or when it was available concurrently, rates of responding for saline were usually low and responding that did occur for saline occurred predominantly at the start of each session.

At the 1-minute timeout value employed in the preceding studies, rates of responding were generally higher for nicotine than for saline but were still very low (0.01 response per second or less). In a recent attempt to maintain higher rates of nicotine-maintained responding in both humans and squirrel monkeys, timeout value and number of responses required per injection (FR value) were systematically increased [10]. With humans, increasing timeout value in increments to a final value of 20 minutes produced more than a fourfold increase in response rates. When FR value was then increased to 100 at the 20-minute timeout value, rates of responding increased and ranged from 0.4 to 2 responses per second, similar rates to those seen with squirrel monkeys and dogs in the studies previously described. These studies of IV nicotine self-administration by humans were the first to establish that pure nicotine can serve as an effective positive reinforcer in humans.

CONCLUSIONS

The series of studies reviewed show that nicotine by itself can serve as an effective reinforcer for humans and experimental animals, but it does so under a more limited range of conditions than do other reinforcers such as IV cocaine injection or food presentation. It is plausible that tobacco vehicles for nicotine administration (e.g., cigarette, chewing tobacco) provide the analogous factors of paired stimuli (e.g., taste and smell of tobacco) and intermittent dosing (e.g., multiple cigarettes and mutiple puffs within each cigarette) which appear to strengthen the control of the drug over behavior (cf. [18]). Certain experimental parameters such as dose, minimum injection interval, repeated presentation of associated stimuli and concurrent schedules of food presentation may be critical for the acquisition of nicotine self-administration behavior. The application of intermittent schedules of reinforcement to studies of nicotine as a reinforcer in the animal laboratory and the extension of these methodologies to studies with human volunteers under controlled laboratory conditions has provided the most direct evidence to date that pure nicotine, separated from other tobacco constituents and from the host of olfactory, tactile and visual stimuli associated with smoking behavior, can function as an effective positive reinforcer to maintain persistent drug-seeking behavior.

REFERENCES

1. Ator, N. A. and R. R. Griffiths. Nicotine self-administration in baboons. *Pharmacol Biochem Behav* **19:** 993–1003, 1983.
2. De La Garza, R. and C. E. Johanson. The effects of food deprivation on the self-administration of psychoactive drugs. *Drug Alcohol Depend* **19:** 17–27, 1987.
3. Deneau, G. A. and R. Inoki. Nicotine self-administration in monkeys. *Ann NY Acad Sci* **142:** 227–279, 1967.
4. Dougherty, J., D. Miller, G. Todd and H. B. Kostenbauder. Reinforcing and other behavioral effects of nicotine. *Neurosci Biobehav Rev* **5:** 487–495, 1981.
5. Eddy, N. B., H. Halbach, H. Isbell and M. H. Seevers. Drug dependence: Its significance and characteristics. *Bull WHO* **32:** 721–733, 1965.
6. Ferster, C. B. and B. F. Skinner. *Schedules of Reinforcement*. New York: Appleton-Century-Crofts, Inc., 1957.
7. Goldberg, S. R. The behavioral analysis of drug addiction. In: *Behavioral Pharmacology*, edited by S. D. Glick and J. Goldfarb. St. Louis: C. V. Mosby Co., 1976, pp. 283–316.
8. Goldberg, S. R. and J. E. Henningfield. Fixed ratio responding maintained by intravenous nicotine injections in humans and squirrel monkeys. *Pharmacologist* **25:** 219, 1983.
9. Goldberg, S. R. and J. E. Henningfield. Intravenous nicotine self-administration in humans and squirrel monkeys. *Neurosci Lett [Suppl]* **14:** 140, 1983.
10. Goldberg, S. R. and J. E. Henningfield. Nicotine as a reinforcer in humans and experimental animals. Paper presented at symposium on Progress in Understanding the Relationship Between the Pharmacological Effects of Nicotine and Human Tobacco Dependence, held at annual meeting of American Society for Pharmacology and Experimental Therapeutics, Baltimore, MD, August 1986.
11. Goldberg, S. R., R. T. Kelleher and W. H. Morse. Second-order schedules of drug injection. *Fed Proc* **34:** 1771–1776, 1975.
12. Goldberg, S. R. and R. D. Spealman. Maintenance and suppression of behavior by intravenous nicotine injections in squirrel monkeys. *Fed Proc* **41:** 216–220, 1982.
13. Goldberg, S. R., R. D. Spealman and D. M. Goldberg. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science* **214:** 573–575, 1981.
14. Griffiths, R. R., J. V. Brady and L. D. Bradford. Predicting the abuse liability of drugs with animal drug self-administration procedures: Psychomotor stimulants and hallucinogens. In: *Advances in Behavioral Pharmacology*, Vol 2 edited by T. Thompson and P. B. Dews. New York: Academic Press, 1979, pp. 163–208.
15. Hanson, H. M., C. A. Ivester and B. R. Morton. Nicotine self-administration in rats. In: *Cigarette Smoking as a Dependence Process*, edited by N. A. Krasnegor. National Institute on Drug Abuse Research Monograph Series No. 23. U.S. Department of Health, Education and Welfare. Washington, DC: U.S. Government Printing Office, 1979, pp. 70–90.
16. Henningfield, J. E. and S. R. Goldberg. Control of behavior by intravenous nicotine injections in human subjects. *Pharmacol Biochem Behav* **19:** 1021–1026, 1983.
17. Henningfield, J. E. and S. R. Goldberg. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacol Biochem Behav* **19:** 989–992, 1983.
18. Henningfield, J. E. and S. R. Goldberg. Stimulus properties of nicotine in animals and human volunteers: A review. In: *Behavioral Pharmacology: The Current Status*, edited by L. S. Seiden and R. L. Balster. New York: Alan R. Liss, 1985, pp. 433–449.
19. Henningfield, J. E., K. Miyasato and D. R. Jasinski. Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav* **19:** 887–890, 1983.
20. Jaffe, J. H. Drug addiction and abuse. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan, 1985, pp. 532–581.
21. Lang, W. J., A. A. Latiff, A. McQueen and G. Singer. Self-administration of nicotine with and without a food delivery schedule. *Pharmacol Biochem Behav* **7:** 65–70, 1977.
22. Prada, J. A. and S. R. Goldberg. Effects of caffeine and nicotine pretreatments on nicotine self-administration by the squirrel monkey. *Pharmacologist* **27:** 226, 1985.
23. Risner, M. E. and S. R. Goldberg. 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, 1983.
24. Slifer, B. L. and R. L. Balster. Intravenous self-administration of nicotine: With and without schedule-induction. *Pharmacol Biochem Behav* **22:** 61–69, 1985.
25. Spealman, R. D. and S. R. Goldberg. Maintenance of schedule-controlled behavior by intravenous injections of nicotine in squirrel monkeys. *J Pharmacol Exp Ther* **223:** 402–408, 1982.
26. Spealman, R. D. amd S. R. Goldberg. Drug self-administration by laboratory animals: Control by schedules of reinforcement. *Annu Rev Pharmacol Toxicol* **18:** 313–339, 1978.
27. Yanagita, T. Brief review on the use of self-administration techniques for predicting drug dependence potential. In: *Predicting Dependence Liability of Stimulant and Depressant Drugs*, edited by T. Thompson and K. R. Unna. Baltimore: University Park Press, 1977, pp. 231–242.
28. Yanagita, T., K. Ando, N. Oinuma and K. Ishida. Intravenous self-administration of nicotine and an attempt to produce smoking behavior in monkeys. Proceedings of the 36th Annual Scientific Meeting, Committee on Problems of Drug Dependence, National Academy of Sciences, 1974, pp. 567–578.