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Nicotine as a Reinforcer in Human Subjects and Laboratory Animals

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HENNINGFIELD, J. E. AND S. R. GOLDBERG. *Nicotine as a reinforcer in human subjects and laboratory animals.* PHARMACOL BIOCHEM BEHAV 19(6) 989–992, 1983.—Results are summarized from 17 studies in which intravenous nicotine was evaluated in self-administration paradigms. Six species, ranging from the albino rat to the human, have been tested under a variety of schedules of reinforcement, and as a function of several pharmacologic manipulations. Under certain environmental conditions, it is clear that nicotine can serve as a reinforcer. However, nicotine differs from many other drugs of abuse in that the range of environmental conditions under which it serves as a reinforcer appears to be more restricted.

Nicotine Self-administration Drug abuse Cigarette smoking Reinforcement schedule Behavioral pharmacology

THE self-administration paradigm has been widely used as a procedure to directly assess the reinforcing efficacy of drugs, and thereby to quantitate their abuse liability. In the self-administration paradigm, the range of variables which confound interpretation of phenomena in the nonlaboratory environment (e.g., dose, schedule of availability, pharmacologic interactions), can be systematically studied as independent variables in their own right. A finding of wide generality is that drugs of abuse serve as reinforcers in drug self-administration paradigms. Therefore, if the role of nicotine in tobacco abuse is the same as the role of ethanol in alcoholism or of morphine in opioid dependence, then nicotine should serve as a robust reinforcer in self-administration paradigms. Previous data, however, have left this hypothesis in question.

Among drugs of abuse, nicotine, in the form of cigarettes, appears to rival opioids and psychomotor stimulants in its abuse liability [11]. In contrast to these observations, it has been difficult to identify nicotine as the critical pharmacologic substrate of tobacco abuse and most of the evidence has been circumstantial [8,9]. Particularly problematic, are the results of nicotine studies involving drug self-administration paradigms. In brief, the consensus from two prior reviews of this literature, is that nicotine is a less robust reinforcer than other drugs of abuse [7], and that compared to other drugs of abuse, the range of environmental conditions under which nicotine so serves is much more restricted [3].

These conclusions provide a challenge for self-administration paradigms as procedures to quantitate abuse potential. Have they failed with respect to nicotine? Or is nicotine, in fact, not the critical pharmacologic substrate of tobacco abuse? Another possibility is that nicotine may differ from other drugs in ways that require special procedures to study.

Table 1 is a summary of previously reviewed and new studies, in which nicotine was tested in self-administration paradigms. As shown in the table, intravenous nicotine self-administration studies have been conducted in six species, using both simple and complex schedules of reinforcement, and as a function of pharmacologic, behavioral and neurologic manipulations. A casual analysis of the results of these studies would suggest that nicotine shares much in common with other, similarly tested, drugs of abuse; it serves as a reinforcer for several species, its reinforcing efficacy is enhanced by food deprivation, behavioral performance on reinforcement schedules is similar in pattern to that maintained by other drugs, manipulations of dose produce changes in rate of self-administration, blockade of the receptor results in saline-like self-administration performance, and nicotine, like cocaine, can also serve as punisher. Closer scrutiny of the data, however, reveals some important qualifications concerning the generality of these observations. Foremost, is that the conditions under which nicotine can be established as a reinforcer are much more limited than those for other drugs; a corollary is that, frequently, the same procedures used to establish other drugs as reinforcers are ineffective with nicotine. Furthermore, as a reinforcer, the efficacy of nicotine seems peculiarly dependent on the temporal pattern of its availability; it maintains behavior much more effectively on fixed-interval and second order schedules of reinforcement than on simple ratio schedules. Finally, dose-response data are somewhat anomolous; self-administration behavior tends to be rather insensitive to dose except at very high dose levels.

In an effort to reconcile the varied findings from studies of nicotine self-administration, a symposium was held at the annual meeting of the American Psychological Association in 1982. The papers which follow are the proceedings of that symposium. In the recent experiments reviewed in these papers, the conditions of nicotine availability were modified in attempts to determine optimum conditions for mainte-

TABLE 1

SUMMARY OF REPORTS IN WHICH NICOTINE WAS AVAILABLE UNDER INTRAVENOUS DRUG SELF-ADMINISTRATION (S-A) PROCEDURES

Study	Species	Reinforcement Schedule	Main Finding	Comment
Deneau and Inoki (1967) [2]	Rhesus Monkey	Fixed-ratio 1 (FR 1). Several doses of nicotine were tested.	Two monkeys initiated S-A, the others required a priming procedure.	Currently accepted criteria to assess reinforcing efficacy were not achieved.
Yanagita, Ando, Oinuma and Ishida (1974) [22]	Rhesus Monkey	Experiment 1: FR 1. Several doses of nicotine, and lefetamine and saline were tested.	Nicotine did not serve as a reinforcer when compared to saline or lefetamine.	
		Experiment 2: FR 1. Several doses of nicotine were continuously available for at least 4 weeks.	Stable rates of nicotine S-A occurred in most subjects, but were not clearly related to dose.	No direct test of reinforcing efficacy was done.
		Experiment 3: Progressive ratio (PR) procedures. Two doses of nicotine, and saline, and three doses of cocaine were tested.	At 0.2 mg/kg nicotine, response rates slightly exceeded those maintained by saline or the lowest cocaine dose (0.03 mg/kg).	Nicotine was marginally reinforcing when compared to cocaine.
Lang, Latiff, McQueen and Singer (1977) [13]	Hooded Rat	FR 1. Nicotine and saline were tested in food-sated and food-deprived rats.	In food-deprived (but not food sated) rats, nicotine was a reinforcer, when compared to saline.	
Singer, Simpson and Lang (1978) [18]	Hooded Rat	Concurrent [(FR 1:Nicotine) (Fixed-time 1 min: food pellet)] in food-deprived rats. Subsequently, the rats were food-sated.	Food satiation decreased rate of nicotine S-A, however, nicotine was a reinforcer in both conditions.	Results were similar to those obtained when rats were similarly tested with ethanol [15].
Griffiths, Brady and Bradford (1979) [7]	Baboon	FR 160 followed by 3-hr time-out. Several doses of nicotine, and saline, were substituted for cocaine.	Number of nicotine injections per day did not exceed that of saline.	Caffeine, ephedrine, and a variety of other similarly tested stimulants, did serve as reinforcers, relative to saline, in this paradigm.
Hanson, Ivester and Moreton (1979) [10]	Albino Rat	FR 1. Several doses of nicotine and saline were tested.	Mecamylamine (centrally acting antagonist) but not pentolinium (peripherally acting antagonist) altered S-A behavior.	Group data suggest that nicotine was a reinforcer. However, there was no clear dose-effect curve.
Latiff, Smith and Lang (1980) [14]	Hooded Rat	CONC [(FR 1: injection) (FT 1 min: food pallet)]. Several doses of nicotine and saline were tested.	Nicotine was a reinforcer, relative to saline. Urine pH manipulations had mild effects on rate of S-A only during initial exposure to nicotine.	Rate of S-A was inversely related to dose during initial exposure to nicotine but not after nicotine S-A was established.
Smith and Lang (1980) [20]	Hooded Rat	FR 1. One dose of nicotine and saline were tested.	Nicotine was established as a reinforcer both with and without a concurrent food delivery schedule in food-deprived, but not food-sated rats.	
Goldberg, Spealman and Goldberg (1981) [6]	Squirrel Monkey	Second Order Schedule FI 1 or 2 min (FR 10: stimulus) followed by 3-min time-out. One dose of nicotine and saline were tested.	Nicotine maintained high rates of responding. Rates decreased markedly when (1) saline replaced nicotine, (2) the brief stimuli were omitted, (3) subjects were pretreated with mecamylamine.	Demonstrated the importance of ancillary environmental stimuli in maintaining high rates of responding.
Ator and Griffiths (1981) [1]	Baboon	FR 2 followed by 15 sec time-out. Several doses of nicotine, and saline and cocaine, were tested.	Nicotine was marginally reinforcing, compared to saline across a narrow dose range.	Initial dose-response curve was inverted-U shaped, and final dose-response curve was flat. (From abstract of study.)

Continued

TABLE 1
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Dougherty, Miller, Todd and Kostenbauder (1981) [3]	Rhesus Monkey	FI 16 and second order FI 1 min (FR 4: stimulus). Several doses of nicotine, and saline, were tested.	Nicotine maintained higher rates of S-A than saline under the FI and second order schedules, but was only a marginally effective reinforcer when continuously available.	Establishment of nicotine as a reinforcer required several months using procedures that typically require only a few days to establish cocaine or codeine as reinforcers.
Goldberg and Spealman (1982) [5]	Squirrel Monkey	FI 5 min. Several doses of nicotine and cocaine, and saline were tested.	Nicotine and cocaine were qualitatively similar reinforcers, when compared to saline. Cocaine maintained higher rates of responding in one of two monkeys. Mecamylamine pretreatment reduced rates of nicotine S-A.	This study also showed that nicotine could serve as a punisher, similar to electric shock.
Singer, Wallace and Hall (1982) [19]	Long-Evans Rat	CONC [(FR 1: nicotine) (FT 1 min: food pellet)]. One dose of nicotine was tested.	A group of rats with 6-OHDA lesions in the nucleus accumbens S-A nicotine at lower rates than a sham-lesioned group.	Extended the range of scheduled-induced behaviors that are inhibited by such lesions.
Spealman and Goldberg (1982) [21]	Squirrel Monkey	Second order FI 1, 2, or 5 min (FR 10 stimulus), and FI 5 min schedules were tested. Several doses of nicotine and cocaine, and saline were tested.	Nicotine and cocaine maintained similar patterns of responding on the schedules. Nicotine, but not cocaine S-A, decreased to saline-like rates when animals were pretreated with mecamylamine.	Nicotine's reinforcing efficacy was comparable to that of cocaine.
Risner and Goldberg (1983) [17]	Beagle Dog	FR 15 followed by 4 min time-out. Several doses of nicotine, cocaine, and saline were tested. Progressive ratio schedule was used.	Nicotine and cocaine maintained qualitatively similar patterns of responding, and were reinforcers relative to saline. Mecamylamine pretreatment reduced nicotine, but not cocaine, S-A.	Cocaine maintained substantially greater response rates than nicotine.
Henningfield, Miyasato and Jasinski (1983) [12]	Human	FR 10 followed by 1 min time-out. Several doses of nicotine, and saline, were tested.	Number of nicotine injections generally exceeded number of saline injections, and were inversely related to nicotine dose. Post-session cigarette smoking was suppressed by nicotine.	Nicotine produced subjective effects similar to those produced by intravenous cocaine, and had both reinforcing and punishing effects.
Goldberg and Henningfield (1983) [4]	Human and Squirrel Monkey	FR 10 followed by 1 min time-out. Several doses of nicotine, and saline were tested.	Patterns of responding were qualitatively similar in both species. Number of nicotine injections exceeded number of saline injections in 3 of 4 human and 3 of 4 monkey subjects.	In both the human and monkey subjects, there was evidence that nicotine functioned with both reinforcing and punishing properties.

nance of self-administration behavior in squirrel monkeys, baboons, rhesus monkeys, and beagle dogs. The effects of: (1) a variety of training histories; (2) of different types and parameters of schedules of drug injection; (3) of concurrent availability of another reinforcer; and (4) of extensive dose manipulations are described.

Experiments also are reviewed which demonstrate that nicotine can function as a noxious stimulus in squirrel monkeys under certain environmental conditions, either suppressing behavior leading to its injection or maintaining behavior that prevents its scheduled injection. Finally recent experiments with human volunteers in which nicotine functioned either as a reinforcer, to maintain intravenous self-administration behavior, or as a noxious stimulus, to maintain behavior that prevented its scheduled injection, will be reviewed. These papers demonstrate that the self-administration model can be an effective means of quantitating the behavioral pharmacology of nicotine, and that nicotine shares many salient features of other drugs of abuse. However, nicotine differs from other drugs in that the range of environmental conditions under which it serves as a reinforcer appears to be more restricted. These differences may be related to the shorter time-frame of the pharmacokinetic and pharmacodynamic properties of nicotine when compared to other drugs.

REFERENCES

1. Ator, N. A. and R. R. Griffiths. Intravenous self-administration of nicotine in the baboon. *Fed Proc* **40:** 298, 1980.
2. Deneau, G. A. and R. Inoki. Nicotine self-administration in monkeys. *Ann NY Acad Sci* **142:** 227–279, 1967.
3. Dougherty, J., D. Miller, G. Todd and H. B. Kostenbauder. Reinforcing and other behavioral effects of nicotine. *Neurosci Biobehav Rev* **5:** 487–495, 1981.
4. Goldberg, S. R. and J. E. Henningfield. Intravenous nicotine self-administration by squirrel monkeys and human volunteers. Submitted for publication, 1983.
5. Goldberg, S. R. and R. D. Spealman. Maintenance and suppression of responding by intravenous nicotine injections in squirrel monkeys. *Fed Proc* **41:** 216–220, 1982.
6. Goldberg, S. R., R. D. Spealman and D. M. Goldberg. Persistent high-rate behavior maintained by intravenous self-administration of nicotine. *Science* **214:** 573–575, 1981.
7. 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.
8. Griffiths, R. R. and J. E. Henningfield. Pharmacology of cigarette smoking behavior. *Trends Pharm Sci* **3:** 260–263, 1982.
9. Gritz, E. R. Smoking behavior and tobacco abuse. In: *Advances in Substance Abuse,* edited by N. K. Mello. Greenwich, CT: JAI Press, 1980, pp. 91–158.
10. 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. Washington, DC: U.S. Government Printing Office, 1979, pp. 70–90.
11. Henningfield, J. E., R. R. Griffiths and D. R. Jasinski. Human dependence on tobacco and opioids: Common factors. In: *Behavioral Pharmacology of Human Drug Dependence,* edited by T. Thompson and C. E. Johanson. Washington, DC: U.S. Government Printing Office, 1981, pp. 210–234.
12. Henningfield, J. E., K. Miyasato and D. R. Jasinski. Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav* **19:** 887–890, 1983.
13. 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.
14. Latiff, A. A., L. A. Smith and W. J. Lang. Effects of changing dosage and urinary pH in rats self-administering nicotine on a food delivery schedule. *Pharmacol Biochem Behav* **13:** 209–213, 1980.
15. Meisch, R. A. Ethanol self-administration: Infrahuman studies. In: *Advances in Behavioral Pharmacology,* vol 1, edited by T. Thompson and P. B. Dews. New York: Academic Press, 1977.
16. Meisch, R. A., D. J. Kliner and J. E. Henningfield. Pentobarbital drinking by rhesus monkeys: Establishment and maintenance of pentobarbital-reinforced behavior. *J Pharmacol Exp Ther* **217:** 114–120, 1981.
17. 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.
18. Singer, G., F. Simpson and W. J. Lang. Schedule induced self injections of nicotine with recovered body weight. *Pharmacol Biochem Behav* **9:** 387–389, 1978.
19. Singer, G., M. Wallace and R. Hall. Effects of dopaminergic nucleus accumbens lesions on the acquisition of schedule induced self injection of nicotine in the rat. *Pharmacol Biochem Behav* **17:** 579–581, 1982.
20. Smith, L. A. and W. J. Lang. Changes occurring in self administration of nicotine by rats over a 28-day period. *Pharmacol Biochem Behav* **13:** 215–220, 1980.
21. 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.
22. 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.