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Schedule-Induction of Nicotine Self-Administration

BARBARA L. SLIFER[1]

Department of Pharmacology, Medical College of Virginia, Richmond, VA 23298

SLIFER, B. L. *Schedule-induction of nicotine self-administration.* PHARMACOL BIOCHEM BEHAV 19(6) 1005–1009, 1983.—Nicotine, although assumed to be an important factor in maintaining the use of tobacco products, has produced equivocal results when tested in drug self-administration studies using standard procedures with laboratory animals. Several recent studies however, have demonstrated nicotine self-administration using a procedure of schedule-induction. Schedule-induced behaviors occur as an adjunct to behavior controlled by an intermittent schedule of reinforcement and are thus not under control of the scheduled contingencies. Using schedule-induction procedures; oral, intravenous and inhaled self-administration of nicotine has been shown in rats, both rats and rhesus monkeys, and humans respectively. Although the self-administration of some doses of nicotine occurred without a concurrent schedule of intermittent reinforcement, schedule-induction results in responding maintained by lower doses of the drug and much more rapid initiation of self-administration. The result of such studies suggest an interaction between environmental factors, such as an intermittent schedule of other reinforcers, and nicotine's pharmacological effects. This interaction may be important in understanding the etiology and maintenance of human tobacco use.

Nicotine Self-administration Schedule-induction

DURING an operant conditioning procedure, intermittent presentation of reinforcers often results in excessive amounts of behavior which are not under control of the schedule contingencies. It has been suggested that the intermittent reinforcement in the controlling schedule increases the reinforcing efficacy of other stimuli that are present in the immediate environment [1]. These potentiated reinforcing properties then maintain the excessive behavior directed towards these stimuli. Such behaviors are called schedule-induced behaviors.

The first of this type of behavior to be characterized was polydipsia. Falk [4] reported the excessive drinking of water by rats during sessions of intermittent food delivery. Since then, several types of schedule-induced behaviors have been reported in a variety of species, from wheel-running in rats [15] to motor activity and polydipsia in humans [9,29].

Schedule-induced polydipsia has been useful in the initiation and maintenance of the oral ingestion of drugs by animals. For example, by schedule-induction, rats will drink excessive amounts of ethanol solutions over extended periods of time and in large enough quantities to produce physical dependence [6, 7, 14]. Schedule-induced oral self-administration of amphetamine [21], barbiturates [18], opiates [12, 13, 17] and phencyclidine [1] have since been reported. In addition, researchers have studied the schedule-induction of intravenous self-injection of opiates, CNS stimulants, and delta-9-THC [23].

The self-administration of drugs by laboratory animals has provided a valuable model for the abuse liability assessment of new and existing drugs. A decade of research has demonstrated a positive correlation between drugs which are abused by humans and those drugs that are self-administered by animals in the laboratory. For example, animals will readily self-administer injections of cocaine, and cocaine use/abuse among the human population is widely recognized. Conversely, there is no significant human abuse of the neuroleptic chlorpromazine, nor does the drug function as a positive reinforcer in laboratory animals. There are some drugs however, which are exceptions to this. Nicotine, for example, is a widely abused drug by humans in the form of tobacco products, yet it has been difficult to demonstrate the reinforcing efficacy of nicotine in most commonly used animal drug self-administration models.

Inherent in any model of drug abuse is the demonstration of voluntary rather than forced drug intake and schedule-induction is a procedure that can successfully be used to achieve this (see above). Schedule-induction has, in fact, been successfully used to demonstrate nicotine self-administration both orally in humans and laboratory animals, and intravenously in rats and rhesus monkeys. This paper will review some of these schedule-induction procedures and the results of these studies with nicotine.

SCHEDULE-INDUCED ORAL NICOTINE SELF-ADMINISTRATION

The first report of schedule-induced drinking of nicotine solutions was by Lang *et al.* [10]. In this study, food deprived rats received food pellets (apparently noncontingently) every 60 sec and the animals showed polydipsic water drinking. When nicotine solutions were substituted for

[1]Present address: Department of Psychology, University of North Carolina, Chapel Hill, NC 27514.

water during 1 hr sessions the rats consumed over 1 mg/kg nicotine. The authors reported that the rates of licking during nicotine presentation differed from rates of licking for water only at the higher concentration of nicotine 0.64 μg/ml, where lick rates were reduced. Sanger [22] also found that nicotine would be self-administered orally by rats. Under a similar schedule of food presentation (FT 1 min), food-deprived rats exposed to nicotine solutions for ten daily sessions drank less total fluid volume than water but consumed an average of 4–6 mg/kg nicotine in a low concentration solution (0.05 mg/ml) and 6–9 mg/kg in a more concentrated solution (0.1 mg/ml). Since absolute intake volumes or lick rates are not reported by Lang *et al.* [10], these two studies can only be compared on the bases of quantity of drug consumed. The larger quantities of nicotine consumed by the rats in Sanger's study may be the result of more extensive exposure to the experimental conditions. These animals were pre-exposed to water for 20 days prior to 10 days of nicotine solutions, in contrast to four days water and three days nicotine as in Lang *et al.* [10]. It is not atypical for schedule-induced drinking to develop or increase over a number of sessions which might explain the higher overall intakes reported by Sanger [22]. In both studies however, significant levels of drinking were maintained when nicotine solutions were substituted for water. Further suggestion that this drinking was schedule-induced was provided by Sanger who reported that when nicotine was substituted for water the characteristic post-pellet pattern of drinking was maintained, a temporal characteristic of schedule-induced behaviors.

While these studies demonstrate that it is possible to induce the oral self-administration of nicotine in rats, this procedure has a drawback in that the drug solutions may have aversive gustatory effects which may then limit the quantities of the solution consumed. Schedule-induction of the intravenous self-administration of a drug eliminates the possible confounding taste factors.

SCHEDULE-INDUCED INTRAVENOUS NICOTINE SELF-ADMINISTRATION

Animals, prepared with intravenous catheters, can be trained to perform an operant task to receive an injection of a drug which is a positive reinforcer. In schedule-induction procedures, the animal receives scheduled food presentations which may or may not be contingent upon an operant response, while the response which produces a drug injection is the schedule-induced response. One necessary assumption with this procedure is that the drug or the dose of the drug, whose self-administration is to be induced, would not initially function as a positive reinforcer to maintain responding.

While studies of schedule-induced self-injection of several drugs have been conducted [16, 19, 20, 23, 27, 28], nicotine was one of the first studied in this paradigm and has since been studied in numerous other experiments [10, 11, 24, 26]. In Lang *et al.*'s original study [10], food-deprived rats received food pellets every 60 sec during 2 hr sessions. During these sessions single responses on a response lever produced an intravenous infusion of nicotine (0.1 mg/kg/injection). When compared to food-deprived and nonfood-deprived animals that did not receive scheduled food deliveries, the food-deprived rats established nicotine self-administration responding at rates that exceeded those of the animals without concurrent food schedules. Additionally, matched groups of animals which had access to saline rather than nicotine injections did not acquire schedule-induced saline self-administration. A study by Smith and Lang [26] further demonstrated the effectiveness of combined food deprivation and a concurrent food delivery schedule in the rapid acquisition of IV nicotine (0.1 mg/kg injection) self-administration by rats. Once self-administration responding is established by schedule-induction however, it has been shown that the food schedule can be removed or the body weights returned to free-feeding weights without significantly affecting nicotine self-administration responding [24,26].

Smith and Lang [26] also found that when given longer exposure to the experimental conditions (up to 28 days) animals at 80% of their free-feeding weight gradually acquired nicotine self-administration responding without a concurrent food schedule, and the rates at the end of 28 days did not differ from the rates of animals in a schedule-induced group. Rats at 100% free-feeding weight did not acquire nicotine self-injection behavior without schedule-induction. It is likely that the reason IV nicotine self-administration was not reported for the rats in the 80%-no food schedule group in the original report [10] is the shorter duration of the experiment (i.e., 6 days).

These studies suggest then, that although food deprived animals will gradually develop nicotine self-administration responding on a simple FR 1 schedule over a period of several weeks, a concurrent schedule of intermittent food delivery induces a much more rapid acquisition so that nicotine-maintained responding was acquired in one-fourth to one-half the amount of exposure to the drug.

Simply exposing the rats to the experimental conditions for 28 days however, was not sufficient to establish schedule-induced self-injection responding. The pharmacological effects of nicotine are important to the acquisition and maintenance of self-administration responding. Several experimental findings support this conclusion [10, 11, 24, 26]. First, neither food-deprived nor nonfood-deprived animals acquired significant amounts of saline self-injection responding, even when tested during the 28-day protocol [10,26]. Furthermore, even with food deprivation and an intermittent food delivery schedule, optimal conditions which resulted in nicotine self-administration, saline self-administration was not induced [10,24]. Finally, when saline was substituted for nicotine following acquisition of nicotine self-administration the rates of schedule-induced self-injection significantly decreased [11,26].

Only one study of the acquisition of schedule-induced IV nicotine self-administration in rats has looked at the effects of different doses of nicotine. Latiff *et al.* [11] studied the development of food-schedule induced IV self-administration of three different doses of nicotine in rats. The rates of responding for nicotine during the initial six days of acquisition were dose related. The highest rates were maintained by the lowest dose (0.05 mg/kg/injection) and decreased as the dosage increased. Following the initial acquisition period, when the rats were tested on the other two doses it was reported that these initially established rates were not further affected by dosage changes.

Although the influence of an intermittent food delivery schedule on the initial, rapid induction of IV nicotine self-administration in rats has been demonstrated, it is unfortunate that the temporal location of the injections relative to food delivery have not been reported. Thus, the pattern of the induced behavior cannot be compared to other types of schedule-induced responses.

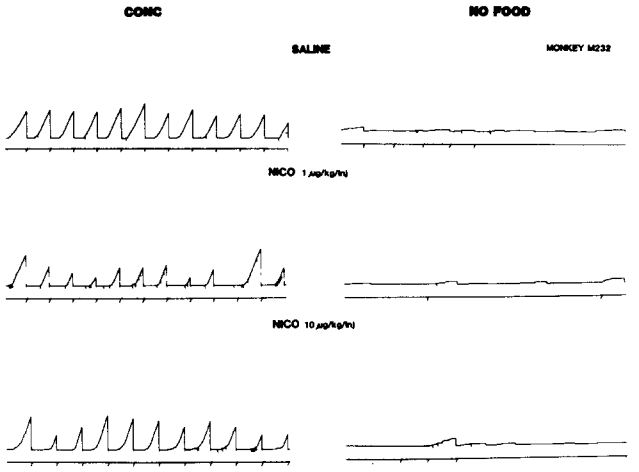

FIG. 1. Cumulative records from 30-min sessions when saline or nicotine (1 and 10 µg/kg/injection) was available on an FR 1 schedule. Records on the left are from sessions with the concurrent FI food schedule present. Records on the right are from sessions without the concurrent FI schedule. The upper pen represents cumulative reponses on the FI lever. The pen was reset following food pellet delivery and offset of this pen represent infusions. The lower event pen offset with food pellet delivery.

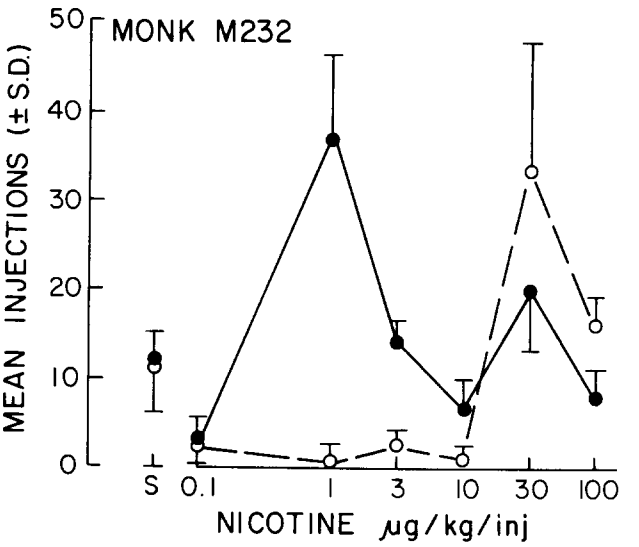

FIG. 2. Injections of nicotine on an FR 1 schedule with (●) or without (○) a concurrent FI (food) schedule of reinforcement. Data are from one subject (M232). Each point represents the mean (±S.D.) of the last six of eleven days at each dose for each treatment. The point above S represents saline control.

In our laboratory, we have conducted studies of schedule-induced intravenous nicotine self-administration with rhesus monkeys [25]. Adult, male rhesus monkeys were surgically prepared with indwelling intravenous catheters and outfitted with light-weight tubular stainless steel harnesses. The harnesses were attached to the rear of self-administration cubicles (0.8×0.8×1.0 M) by a spring arm which secured the animal yet allowed relatively unrestrained movement within the chamber. The animals were maintained at approximately 85% of their free-feeding weight by post-session feedings during the experiment.

The monkeys were trained to respond on a two-lever concurrent FI 5 min FR 1 schedule of reinforcement during daily 60 min sessions. Responses on the right lever in the chamber resulted in delivery of a banana-flavored pellet according to the FI schedule, while responses on the left lever activated an infusion pump which delivered a 1 ml/10 sec infusion of saline or nicotine solution.

The animals initially had access to saline on the left lever, followed by doses of nicotine tartrate (0.1 to 100 µg/kg/injection). Each dose of drug or saline was presented for 11 consecutive days. When all doses had been tested, the dosage regimen was repeated on a simple FR 1 schedule. During this phase of the experiment (No Food treatment) the FI schedule contingencies and corresponding stimuli were removed. Immediately prior to the start of the sessions during the No Food condition, the monkeys were given 12 banana pellets by manually operating the feeder. This feeding was equivalent to the number of reinforcements earned during the concurrent schedule.

Figure 1 presents one animal's cumulative records for single sessions during both the concurrent schedule (left column) and the No Food condition (right column) for saline and two doses of nicotine. The fixed-interval schedule maintained characteristic, positively-accelerated rates of responding throughout the five-minute interval. This monkey's control FI response rates averaged 15 responses per minute and were not affected by even high levels of nicotine intake. Although schedule contingencies and stimuli were removed during the No Food condition, some responses still occurred on the FI response lever. In contrast to the concurrent schedule, the lower rates and different pattern of FR 1 responding during the No Food condition can be seen from the response records.

The results of testing the range of doses of nicotine in the two conditions in monkey M232 are shown in Fig. 2. Doses of 0.1 to 10 µg/kg/injection nicotine did not maintain FR 1 responding when presented on a simple FR schedule during the No Food condition, while doses of 30 and 100 µg/kg/injection were self-administered above saline levels when tested on this schedule. When the FI food schedule was concurrently present, rates of self-administration of saline or the lowest dose of nicotine (0.1 µg/kg/injection) did not differ from the rates during the No Food condition. The rates of FR 1 responding for doses of 1–10 µg/kg/injection nicotine however, were higher during the concurrent schedule than on the simple FR schedule, although only at the dose of 1 µg/kg/injection did the rates of self-administration exceed saline control rates. At higher doses, those that were reinforcing on the simple FR schedule, the concurrent schedule did not increase rates of nicotine-maintained responding. Similar results were seen in the other two monkeys tested.

The FR 1 responses during the concurrent schedule most frequently occurred prior to the initiation of fixed-interval responding (Fig. 1). Figure 3 shows the intra-interval distribution of injections during the concurrent schedule for two doses of nicotine. The distributions are plotted for a dose at which self-administration was schedule induced (1 µg/kg/injection) and a dose at which the rates of self-administration were not significantly different (10 µg/kg/injection) between the two schedules. The greatest percentage of injections of 1 µg/kg/injection of nicotine (nearly 50%) occurred during the first quarter, nearly 40%

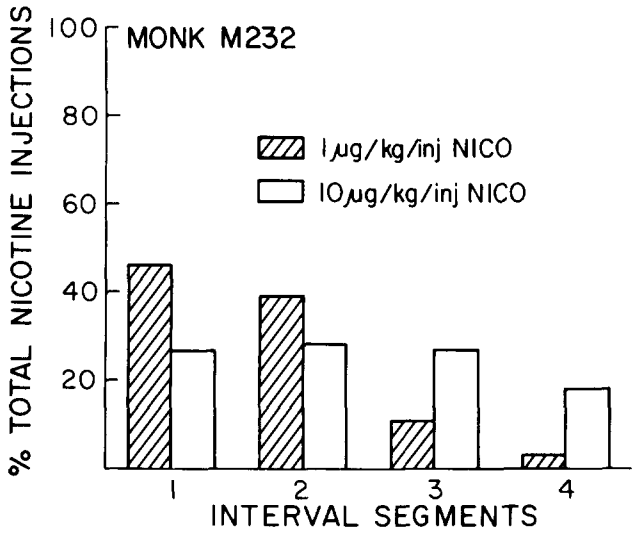

FIG. 3. Distributions of injections of two doses of nicotine (1 μg/kg/injection—slanted line column, and 10 μg/kg/injection—open column), across the five-minute fixed interval. Each bar represents the percent of the total session injections which were self-administered during each quarter of the interval. Data are based on the last six of eleven days at each dose.

occurring during the following quarter and very few for the remainder of the 5 min interval. In contrast to this pattern of nicotine injections, the dose of 10 μg/kg/injection resulted in injections which were equally distributed across the four quarters of the interval.

That pharmacological factors are involved in the schedule-induced self-administration of low doses of nicotine (1–10 μg/kg/injection) is evident from the lack of schedule-induction of self-administration of saline and the lowest nicotine dose (0.1 μg/kg/injection). The fact that the rates of self-administration of doses of nicotine that maintained FR 1 responding during the No Food condition were not increased by schedule induction, suggests that the pharmacological effects of nicotine may predominate to control FR responding at these doses and that these effects may be less sensitive to schedule induction.

Studies which are analogous to the schedule-induced nicotine self-administration studies conducted with laboratory animals have been concerned with human smoking behavior.

SCHEDULE-INDUCED CIGARETTE SMOKING

It is assumed that self-administration of nicotine via smoking is the reinforcer that maintains much of smoking behavior. The reinforcing properties of nicotine in smoking are not entirely clear however, since smoking behavior has been demonstrated to be not totally related to the nicotine content of the cigarettes. It has been suggested that smoking behavior may be a type of schedule-induced behavior.

A variety of schedule-induced behaviors have been reported for humans responding under different schedules of reinforcement [2, 3, 8, 9, 29, 30]. Three studies report the induction of cigarette smoking behavior in humans by fixed-interval schedule control of other operant responses [2, 3, 29]. The rate of puffing was shown to be the behavior that was increased by schedule-induction. When button-pushing was maintained on a fixed-interval schedule of monetary reinforcement, Cherek [2] found that this behavior was sensitive to values of the fixed interval. Maximum rates of puffing occurred at an interval value of 120 sec and decreased with lower or high values. Unfortunately, no baseline data for puff rates were reported so, although rates were related to interval value it is not known how these rates compare with puff rates without the concurrent schedule-controlled behavior. Cherek [2] does report the pattern of the cigarette puffing behavior. It was found that the majority of the responses occurred within the first one-third of the interval, the portion following reinforcement presentation. The sensitivity of the behavior to interval parameters and the temporal patterning are consistent with reports of other types of schedule-induced behaviors.

SUMMARY

The studies reviewed above have demonstrated the schedule-induction of nicotine self-administration through ingestion, inhalation or intravenous injections. The addition of a concurrent schedule of intermittent stimulus presentation, whether as a reinforcer for an operant response or presented noncontingently, results in the relatively rapid acquisition of nicotine self-administration. This was especially evident when schedule-induction was compared to the prolonged development of nicotine-maintained responding when nicotine was available on a simple FR schedule of reinforcement.

The importance of the pharmacological properties of nicotine in the development of schedule-induced self-administration is also apparent. Self-administration of saline or doses of nicotine that were effective reinforcers on a simple FR schedule, were not affected by schedule-induction procedures; while rates of self-administration responding for low doses of nicotine were markedly increased by the addition of a concurrent schedule.

Schedule-induction also produced an increase in the rates of previously acquired nicotine self-administration. This was demonstrated by an increase in cigarette smoking behavior when human subjects performed an intermittently reinforced operant task.

The results of these studies of the schedule-induction of nicotine self-administration in a variety of species suggest an environmental-pharmacological interaction in the induction and maintenance of nicotine self-administration. Such an interaction may be an important variable in human smoking behavior, perhaps by the schedule-induced potentiation of the reinforcing properties of the small boli of nicotine self-administered with each puff of a cigarette.

REFERENCES

1. Carroll, M. E. and R. A. Meisch. Oral phencyclidine (PCP) self-administration in rhesus monkeys: Effects of feeding conditions. *J Pharmacol Exp Ther* **214:** 339–346, 1980.
2. Cherek, D. R. Schedule-induced cigarette self-administration. *Pharmacol Biochem Behav* **17:** 523–527, 1982.
3. Cherek, D. R. and J. T. Brauchi. Schedule-induced cigarette smoking behavior during fixed-interval monetary reinforced responding. In: *Quantification of Steady-State Operant Behavior*, edited by C. M. Bradshaw, E. Szabadi and C. F. Lowe. Amsterdam: Elsevier, 1981, pp. 389–392.

4. Falk, J. L. Production of polydipsia in normal rats by an intermittent food schedule. *Science* **133:** 195–196, 1961.
5. Falk, J. L. The nature and determinants of adjunctive behavior. *Physiol Behav* **6:** 577–588, 1971.
6. Falk, J. L. and H. H. Samson. Schedule-induced physical dependence on ethanol. *Pharmacol Rev* **27:** 449–464, 1975.
7. Falk, J. L., H. H. Samson and G. Winger. Behavioral maintenance of high concentrations of blood ethanol and physical dependence in the rat. *Science* **177:** 811–813, 1972.
8. Frederiksen, L. W. and G. L. Peterson. Schedule-induced aggression in nursery school children. *Psychol Rec* **24:** 343–351, 1974.
9. Kachanoff, R., R. Leveille, J. D. McLelland and M. J. Wayner. Schedule-induced behavior in humans. *Physiol Behav* **11:** 395–398, 1973.
10. 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.
11. 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.
12. Leander, J. D. and D. E. McMillan. Schedule-induced narcotic ingestion. *Pharmacol Rev* **27:** 474–487, 1975.
13. Leander, J. D., D. E. McMillan and L. S. Harris. Schedule-induced oral narcotic self-administration: Acute and chronic effects. *J Pharmacol Exp Ther* **195:** 279–287, 1975.
14. Lester, D. Self-maintenance of intoxication in the rat. *Q J Stud Alcohol* **22:** 223–231, 1961.
15. Levitsky, D. and G. Collier. Schedule-induced wheel running. *Physiol Behav* **3:** 571–573, 1968.
16. Madden, C., T. P. S. Oei and G. Singer. The effect of schedule removal on the maintenance of heroin self-injection. *Pharmacol Biochem Behav* **12:** 983–986, 1980.
17. McMillan, D. E. and J. D. Leander. Schedule-induced oral self-administration of etonitazine. *Pharmacol Biochem Behav* **4:** 137–141, 1976.
18. Meisch, R. A. Self-administration of pentobarbital by means of schedule-induced polydipsia. *Psychon Sci* **16:** 16–17, 1969.
19. Oei, T. P. S. Reversal of schedule-induced self-injection of heroin by naloxone. *Pharmacol Biochem Behav* **13:** 457–459, 1980.
20. Oei, T. P. S., G. Singer and D. Jefferys. The interaction of a fixed-time food delivery schedule and body weight on self-administration of narcotic analgesics. *Psychopharmacology (Berlin)* **67:** 171–176, 1980.
21. Sanger, D. J. d-Amphetamine and adjunctive drinking. *Psychopharmacology (Berlin)* **54:** 273–276, 1977.
22. Sanger, D. J. Nicotine and schedule-induced drinking in rats. *Pharmacol Biochem Behav* **8:** 343–346, 1978.
23. Singer, G., T. P. S. Oei and M. Wallace. Schedule-induced self-injection of drugs. *Neurosci Biobehav Rev* **6:** 77–83, 1982.
24. Singer, G., F. Simpson and W. J. Lang. Schedule induced self injection of nicotine with recovered body weight. *Pharmacol Biochem Behav* **9:** 387–389, 1978.
25. Slifer, B. L. and R. L. Balster. Schedule-induced nicotine self-administration in rhesus monkeys. *Pharmacol Biochem Behav* **15:** 833, 1981.
26. 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.
27. Takahashi, R. N. and G. Singer. Self-administration of Δ-9-tetrahydrocannabinol by rats. *Pharmacol Biochem Behav* **11:** 737–740, 1979.
28. Takahashi, R. N., G. Singer and T. P. S. Oei. Schedule-induced self-injection of d-amphetamine by naive animals. *Pharmacol Biochem Behav* **9:** 857–861, 1978.
29. Wallace, M. and G. Singer. Adjunctive behavior and smoking induced by a maze solving schedule in humans. *Physiol Behav* **17:** 849–852, 1976.
30. Wallace, M., A. Sanson and G. Singer. Adjunctive behavior in humans on a food delivery schedule. *Physiol Behav* **20:** 203–204, 1978.