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Intravenous Self-Administration of Nicotine: With and Without Schedule-Induction[1]

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SLIFER, B L AND R L BALSTER. *Intravenous self-administration of nicotine With and without schedule-induction* PHARMACOL BIOCHEM BEHAV 22(1) 61–69, 1985 —In Experiment I, rhesus monkeys were trained to lever press on a concurrent fixed-interval 5-min (food pellets) fixed-ratio 1 (IV nicotine-injection) schedule of reinforcement All three monkeys self-administered nicotine (0 1–100 μg/kg/injection) at two or more doses during the concurrent conditions (Concurrent I or II) at rates that exceeded saline control or rates of nicotine-maintained responding on a simple fixed-ratio 1 schedule (No Food condition) At least one dose of nicotine did maintain FR 1 responding which was greater than saline rates on the single component schedule and these rates were not increased by the addition of a concurrent schedule of food reinforcement During the concurrent schedule, nicotine-maintained responding occurred throughout the 60-min session in contrast to the No Food (FR 1) condition where most injections of nicotine were self-administered during the initial segments of the session In general, nicotine injections occurred during the early portions of the interval, although this varied between individual animals In Experiment II, rhesus monkeys were trained to lever press for intravenous injections of cocaine (50 μg/kg/injection) on a fixed-ratio 10 schedule of reinforcement During testing, doses of nicotine (1–300 μg/kg/injection) or saline were substituted for cocaine. Nicotine maintained FR 10 responding at rates that exceeded saline self-administration at one or more doses in all four monkeys These doses were similar to those that functioned as positive reinforcers in Experiment I These two experiments demonstrate that nicotine can function as a positive reinforcer to maintain FR 1 or FR 10 responding Experiment I also showed schedule-induction by a concurrent food reinforcement schedule of the self-administration of low doses of nicotine which did not maintain responding on the simple FR 1 schedule, indicating an interaction between environmental factors (schedule of food reinforcement) and pharmacological properties of a drug

Nicotine Intravenous Self-administration Concurrent Fixed-ratio Schedule-induced Substitution Lever press Rhesus monkeys

RESEARCH in the behavioral pharmacology of drugs of abuse has shown that, in addition to intrinsic reinforcing properties of a drug, a number of variables including historical and present environmental factors are important in determining a drug's behavioral effects [11,25]. One such environmental factor may be the concurrent presence of the intermittently scheduled presentation of another reinforcer Falk [10] suggested that intermittent reinforcement increases the reinforcing efficacy of other stimuli that are present in the environment resulting in the schedule-induction of excessive amounts of behavior maintained by the reinforcing properties of the other stimuli. Schedule-induction procedures have been useful in the initiation and maintenance of the oral self-administration of several drugs by laboratory animals including: ethanol [24], amphetamine [31], opiates [22, 23, 27], barbiturates [28] and pencyclidine [2]. In addition, there is evidence for schedule-induction of intravenous self-injection of several of these drugs in rats [33] We recently reported preliminary findings of schedule-induced IV self-administration of nicotine by rhesus monkeys [34].

Typically, there has been found to be a good correspondence between the drugs which are self-administred by laboratory animals and those subject to human abuse [13, 19, 32] Yet, while nicotine in tobacco products is a widely abused drug by humans, experiments on the maintenance of self-administration behavior by nicotine using standard procedures in the animal laboratory have produced equivocal results. Some studies have shown that nicotine fails to serve as a reinforcer for responding leading to an intravenous injection of the drug [7,14], while others report nicotine-maintained responding in rats and monkeys, although usually at low rates relative to other reinforcing drugs such as cocaine [4, 5, 12, 16].

In humans, the self-administration of nicotine, via tobacco, is thought to be an important variable in maintaining smoking behavior. Nevertheless, although manipulations in the dose of nicotine change the reported subjective effects of the drug, such dosage changes often do not significantly alter human smoking behavior [15]. It is apparent from both controlled behavioral analysis and anecdotal reports on the per-

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sistence of the behavior, that smoking is a complex phenomenon which may be the result of an interaction between pharmacological and environmental factors and subject to schedule-induction [3, 15, 17].

The following experiments were conducted to further study the schedule-induction of intravenous self-administration of nicotine by rhesus monkeys using a concurrent food reinforcement schedule Schedule-induced intravenous drug administration has several advantages over schedule-induced oral drug self-administration which include the elimination of confounding factors such as gustatory components, delay of onset of drug effects via the oral route, and accurate quantification of the actual amount of drug intake In addition, we tested the reinforcing properties of intravenous nicotine injections using a standard substitution procedure [19]

GENERAL METHOD

Subjects

Six adult male rhesus monkeys *(Macaca mulatta)* were used as subjects in this study Three of the animals (M570, M232, M432) were experimentally naive at the start of the study while the remaining three monkeys (4173, 3018, M233) had prior histories of IV drug self-administration with other compounds Each animal wore a stainless steel restraint harness [6] and a spring arm which was attached to the rear of an experimental cubicle (0.8×0.8×1.0 M) in which the animals lived during the experiment The monkeys had continuous access to water except during the experimental sessions and were fed Purina Monkey Chow and a chewable multiple vitamin during daily afternoon feedings which followed the conclusion of all daily experimental sessions Fresh fruit supplements were given at least once a week

Apparatus

Each cubicle had a clear Plexiglas front on which was mounted two response levers, 30 cm above the floor Each lever had three corresponding 28V jewel lights above it A food bin was centered between the levers into which the externally mounted pellet feeder delivered 1 gram banana flavored Noyes pellets (P J Noyes Co , Lancaster, NH) Drug injections were delivered at a rate of 1 ml/10 sec by peristaltic pumps (Masterflex, Cole-Parmer Instrument Co , Chicago, IL) Events within the cubicles were controlled and recorded by solid-state programming equipment located in an adjacent room.

Procedure

The animals were prepared with chronic indwelling venous catheters under phencyclidine-pentobarbital anesthesia A silicon catheter (0.79 mm internal lumen, Ronsil Rubber Products, Belle Mead, NJ) was surgically implanted into a major vein (e g , internal or external jugular or femoral) If a catheter became nonfunctional during the experiment, a new catheter was implanted and the animal was returned to the study The catheter, when implanted, was passed subcutaneously to an exit point on the animal's back and through the spring arm and attached to the pump outside the cubicle Following a brief recovery period the three animals in Experiment I were put on a food restriction regimen and gradually reduced to approximately 85% of their free-feeding weights When the desired weight was obtained, training of the animals began

Drugs

Nicotine tartrate was obtained from Pfaltz and Bauer, Inc (Stamford, CN) Cocaine hydrochloride was obtained from the National Institute on Drug Abuse Drug solutions were prepared with physiological saline and doses were based on the salt

EXPERIMENT I
CONCURRENT FI (FOOD) FR (NICOTINE)

Procedure

All three monkeys (3018, M232, M570) in this experiment required training on the fixed-interval (FI) schedule of food presentation During daily 60-min sessions the three lights above the right lever and two of the three lights above the left lever were illuminated The two experimentally naive monkeys (M232, M570) were trained to press the right lever by baiting it with a raisin. Initially each lever-press response on the right manipulanda resulted in delivery of a food pellet At the same time responses on the left lever produced an injection of saline on a fixed ratio 1 (FR 1) schedule of reinforcement. During the infusion the center light above the left lever was illuminated while the two other lights were extinguished Following acquisition of the response, lever pressing on the right lever was reinforced on a FI schedule where the first response after 30 sec had elapsed delivered a food pellet (FI 30 sec) The interval value was gradually increased over 6–10 sessions to a final fixed interval of 5 minutes Because of the development of a pattern of switching responding between the two levers, a 3-sec changeover delay between left-lever responses and reinforcement on the right lever was instituted to eliminate adventitious reinforcement of left-lever responses by food-pellet delivery Responses on each lever were collected cumulatively during quarters of each 5-min interval Responses during the changeover delay and total infusions were also recorded When stable FI 5 min responding occurred and the animals consistently earned 11–12 food reinforcers per session, doses of nicotine (0 1–100 μg/kg/injection) were substituted for saline for 11 consecutive sessions on the concurrent FI 5 min FR 1 schedule The order of dosage presentation was different for each of the three monkeys, with the exception of the low dose (0 1 μg/kg/injection) which was tested last in all three conditions (see below)

Following completion of the dosage regimen with the concurrent fixed-interval (food) schedule (the Concurrent I phase of the study) the nicotine doses were again made available on a FR 1 schedule but the fixed-interval food schedule was removed During this No Food condition the FI stimulus lights were not illuminated and although responses were counted, the feeder was inoperative At the start of these daily sessions, the pellet feeder was manually operated to deliver 12 banana pellets into the food bin When the nicotine dosage regimen was again completed, the food reinforced fixed-interval contingency and corresponding stimuli were reinstated and saline and nicotine doses tested for a third time in the Concurrent II phase

Data Analyses

Only the data from the last six days of each treatment were used in data analyses The data was collected as the number of fixed-interval or fixed-ratio responses per quarter

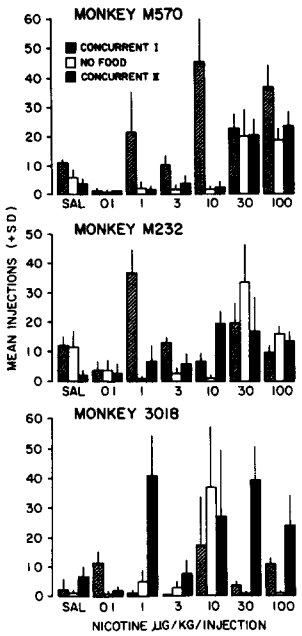

FIG 1 The mean number of injections (± S D) of saline or each dose of nicotine self-administered during the three separate conditions of the experiment Data are based on the last six days of each treatment

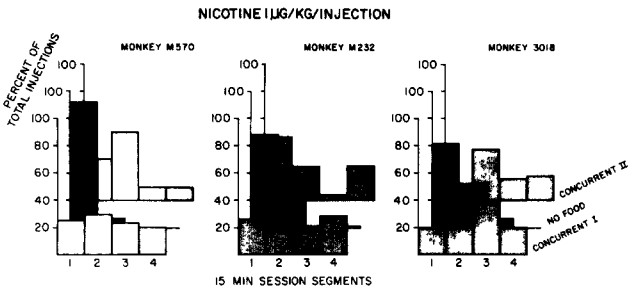

FIG. 2 The distribution of injections of 1 µg/kg/injection of nicotine across the 60-min sessions for the three conditions of the experiment Each bar represents the percent of the total number of injections which occurred in each 15-min segment. Data are based on the last six days of each treatment

of the 5-min interval. The mean number of injections for each treatment at each dose of nicotine or saline and mean per session intake of nicotine were determined for each monkey. The overall mean rates of responding for the three animals was calculated as a function of total session dose

RESULTS

The three monkeys rapidly acquired characteristic FI performance with increasing percentages of responses occurring in the last quarter of the FI, however the one monkey (3018) with an experimental history had a pattern of responding which included pauses followed by bursts of responding. Within 20 sessions all three monkeys earned 11–12 pellets per session on the FI 5 min schedule.

The mean number of injections self-administered during the three conditions (Concurrent I, No Food, Concurrent II) for the individual monkeys are presented in Fig. 1. When saline was available on the FR 1 schedule during the first concurrent condition the monkeys averaged from 2–12 infusions. During the following No Food condition each animal responded less for saline and in two animals (M232, M570) the second concurrent condition resulted in even lower rates of saline self-administration The third monkey (3018) showed slightly increased saline reinforced responding during the Concurrent II testing.

During the first concurrent schedule treatment (Concurrent I) rates of self-administration exceeded saline rates at one or more doses of nicotine and were greater than during the No Food condition at three to four doses in all three monkeys (Fig. 1). Two of the monkeys (M232, M570) responded for nicotine at higher rates during the concurrent I schedule than during the No Food condition across a similar range of doses of nicotine (1–10 µg/kg/injection and 1–10 and 100µg/kg/injection, respectively). These monkeys differed with respect to doses of nicotine that were self-administered at rates that exceeded Concurrent I saline, however. While the same range of nicotine doses maintained rates that exceeded saline self-administration rates in monkey M570, only one dose (1 µg/kg/injection) was self-administered at a rate that exceeded saline control by monkey M232. The third monkey (3018) had higher rates of nicotine self-administration during the Concurrent I schedule at doses of 0 1, 30 and 100 µg/kg/injection with nicotine self-administration rates greater than the corresponding saline control at doses of 0.1 and 100 µg/kg/injection.

When nicotine was available on the simple FR 1 schedule (No Food condition), self-administration rates were maintained above the corresponding saline baseline by at least one dose of the drug (10–100 µg/kg/injection) in all three subjects (Fig. 1). Reinstatement of the concurrent schedule (Concurrent II) produced somewhat different results than those obtained during the initial concurrent experiment (Fig. 1). Monkey 3018, with the exception of the lowest dose (0.1µg/kg/injection), had higher rates of nicotine-maintained responding during Concurrent II treatment than the Concurrent I and these rates were greater than during the No Food condition at all doses except 10 µg/kg/injection Re-exposure to the concurrent schedule in monkey M232 resulted in increases in nicotine-maintained responding above the previous No Food condition over the same dose range as during the Concurrent I schedule (1–10 µg/kg/injection), although the rates were lower than in the original concurrent condition. Monkey M570 had very low rates of responding for nicotine on the Concurrent II schedule at the lower doses (0.1 to 10 µg/kg/injection), while responding at doses of 30 and 100 µg/kg/injection did not differ from the rates during testing without the food schedule.

The pattern of nicotine-reinforced responding within the session differed between conditions. Figure 2 shows a representative example from each condition of the injection distributions across the 60-min session at a dose of 1 µg/kg/injection. All three monkeys self-administered nicotine throughout the 60-min concurrent sessions while the injections occurred predominantly in the first half of the session during the No Food condition. This was typically the case even though rates differed markedly between concurrent conditions.

The distribution of nicotine-maintained responding within the fixed-interval was determined by calculating the percentage of the injections which occurred within each interval

TABLE 1

INTERVAL DISTRIBUTIONS OF FIXED-INTERVAL AND FIXED-RATIO RESPONDING
MEAN PERCENT OF TOTAL FIXED-INTERVAL AND FIXED-RATIO RESPONSES
PER INTERVAL QUARTER

	Monkey No M570							
	Concurrent I Interval Quarters				Concurrent II Interval Quarters			
Treatment	1	2	3	4	1	2	3	4
Saline								
FI responses	9	12	30	49	9	7	25	59
FR responses	38	35	27	0	30	30	30	10
Nico 0 1 μg/kg/inj								
FI responses	6	10	24	60	8	12	28	52
FR responses	43	14	43	0	0	14	43	43
Nico 1 0 μg/kg/inj								
FI responses	4	12	34	50	10	8	27	55
FR responses	46	39	12	3	20	30	20	30
Nico 3 0 μg/kg/inj								
FI responses	6	6	28	60	13	10	24	53
FR responses	19	46	27	8	13	16	55	16
Nico 10 0 μg/kg/inj								
FI responses	10	12	29	49	4	6	30	60
FR responses	27	28	27	18	31	46	23	0
Nico 30 0 μg/kg/inj								
FI responses	7	8	20	65	9	12	29	50
FR responses	38	27	20	15	23	27	31	19
Nico 100 0 μg/kg/inj								
FI responses	6	10	29	55	19	16	24	41
FR responses	23	37	27	13	17	34	32	17

quarter Table 1 gives the intrainterval distribution of nicotine injections and FI responses for each dose of nicotine tested during the two concurrent conditions In general, a large portion of the nicotine infusions occurred within the first three quarters of the interval, typically prior to the majority of FI responding

The patterning of fixed-interval responding was not changed by nicotine intake The positively accelerated response patterns for each monkey were maintained across all doses of nicotine tested (Table 1) Likewise, rates of fixed-interval responding were unaffected by nicotine intake Figure 3 shows overall FI response rates as a function of total dosage of nicotine self-administered in the 60-min sessions One monkey (3018) showed increased FI rates with nicotine self-administration These increases were seen at total dosages of 201–500 μg/kg during the first concurrent schedule condition and at 51–200 μg/kg during the Concurrent II phase, however these intake levels occurred only during three and two sessions respectively Another animal (M570) showed decreases in FI rates at two dosage levels (201–500 and 1001–4000 μg/kg) during the Concurrent I phase, but again these data are based on three sessions at each total dosage

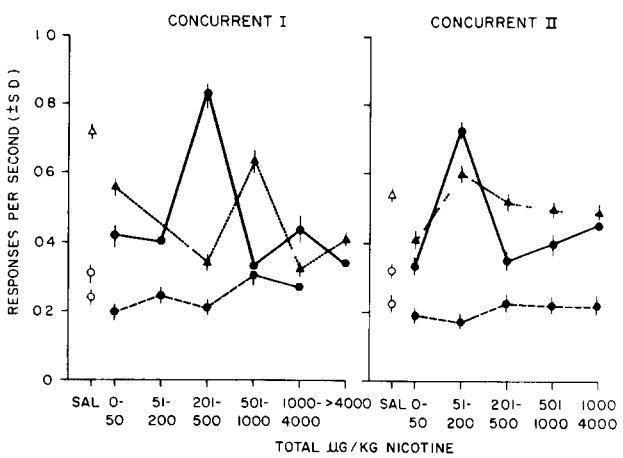

FIG 3 Rates of fixed-interval responding for each monkey during the concurrent I and concurrent II conditions at several levels of nicotine intake Nicotine levels were determined as total μg/kg nicotine self-administered within the 60-min sessions Rates of responding during sessions where saline injections were available are represented above the SAL point Data points are based on the mean rates of responding which occurred during sessions at each of the levels of nicotine The individual monkeys are represented by the following symbols triangle—M570 circle—3018 hexagon—M232

DISCUSSION

The lack of schedule-induction of saline self-administration in the present study is in marked contrast to studies involv-

TABLE 1

INTERVAL DISTRIBUTIONS OF FIXED-INTERVAL AND FIXED-RATIO RESPONDING
MEAN PERCENT OF TOTAL FIXED-INTERVAL AND FIXED-RATIO RESPONSES
PER INTERVAL QUARTER (Continued)

Monkey No M232								Monkey No 3018							
Concurrent I Interval Quarters				Concurrent II Interval Quarters				Concurrent I Interval Quarters				Concurrent II Interval Quarters			
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
2	2	24	72	3	6	23	68	4	5	26	63	5	9	28	58
3	37	59	1	15	16	54	15	42	58	0	0	38	31	18	13
5	5	20	70	4	3	19	74	9	11	26	54	8	9	28	55
25	54	17	4	14	52	33	1	58	23	9	10	90	0	0	10
4	7	24	65	4	5	23	68	2	8	33	57	4	8	32	56
11	18	44	27	14	37	39	10	94	0	6	0	14	24	45	17
3	6	26	65	4	4	29	63	3	11	40	46	5	10	29	56
9	28	54	9	8	30	54	8	0	0	0	0	29	46	22	3
4	5	26	65	5	8	31	56	5	10	35	50	4	9	31	56
4	37	47	12	14	41	34	11	6	27	52	15	15	18	35	32
3	4	28	65	4	7	28	61	1	7	35	57	5	10	29	56
5	33	46	16	8	33	36	23	56	28	16	0	17	32	30	21
3	6	29	62	4	5	29	62	4	14	31	51	7	15	29	49
4	41	47	8	8	33	49	10	46	30	14	10	28	32	22	18

ing schedule-induced oral drug self-administration. Such studies typically report that, although rates of drinking of drug solutions may exceed rates for water, a significant amount of schedule-induced water consumption also occurs [2,31] The present results, on the other hand, are consistent with other reports of schedule-induced IV drug self-administration [20,33] which show no increase in saline-maintained responding by the addition of a concurrent food delivery schedule It is possible that the consummatory response (i e , drinking) may be an important factor in schedule-induced drinking studies and because such a consummatory response does not occur in the present study, the IV self-administration of a pharmacologically inert solution (saline) was not increased by schedule induction

The induction of IV self-administration of low doses of nicotine by the addition of the concurrent fixed-interval food schedule was demonstrated in all three monkeys The individual animals, however, had a somewhat different course of development of schedule-induced behavior and different dose-response curves. The two experimentally naive monkeys (M570, M232) typically responded more during the first concurrent schedule treatment (Concurrent I) than during the Concurrent II condition. In the third animal (3018) the schedule-induction of nicotine self-administration only emerged upon re-exposure to the concurrent schedule following the No Food condition. It is possible that this monkey's previous experience with an FR 10 schedule of drug self-administration in earlier experiments may have influenced the induction of the concurrent behavior in the present experiment Further suggestion of behavioral history interference was seen in this monkey's pattern of responding during the fixed-intervals which resembled fixed-ratio patterns

In general, when nicotine did function as a reinforcer to maintain responding at rates greater than for saline in the absence of a concurrent food schedule (FR 1), the addition of the concurrent food schedule did not induce higher rates of self-administration. Similar results have been reported for the schedule-induction of *d*-amphetamine and cocaine self-administration in rats [29,37]. In one experiment [37], under conditions similar to the present, intravenous self-injection by rats of *d*-amphetamine at a dose that maintained responding on a simple FR 1 schedule was not increased by the addition of a concurrent fixed-time food schedule although the rates during the concurrent schedule with these doses still exceeded saline control rates.

The reason for the inability to re-establish schedule-induced nicotine self-administration following the simple FR 1 schedule at the levels originally obtained on the Concurrent I schedule in two monkeys (M570, M232) is not clear. It was not due to tolerance to the pharmacological effects of the drug because in certain cases doses later in the Concurrent II regimen were self-administered at levels which exceeded levels

of self-administration of previously tested doses and the effect was not dose related

The temporal occurrence of the nicotine injections seen here differed somewhat from that often seen with other schedule-induced behaviors. Schedule-induced polydipsia, for example, has been reported to occur primarily in the immediate post-pellet period [8,9] In general, the monkeys in this study made the majority of their responses on the FR lever during the first three quarters of the interval. Some FR responses however, also occurred later in the interval coincident with high rates of FI responding A similar pattern has been reported for schedule-induced drinking in rats when the animals could engage in both behaviors concurrently because of the spatial proximity of the manipulanda [26] Thus, the temporal pattern of FR responding is not entirely different from other reports of schedule-induced behaviors and may be related to the ease in making the schedule-controlled and schedule-induced responses concurrently

It might be expected that the repeated self-administration of active doses of nicotine would result in disruption of the concurrent fixed-interval responding Such a disruption should then result in limiting the induction of further self-administration behavior Direct effects of the drug on controlling schedule performance and induced behavior has been reported with schedule-induced oral opiate self-administration [22]. Such disruptions in overall FI rates did not occur in the present study (Fig 3) and thus was not the major variable in determining the levels of schedule-induced self-administration.

EXPERIMENT II
NICOTINE FR 10 SELF-ADMINISTRATION

This study was conducted to test the reinforcing properties of doses of nicotine that maintained responding on an FR 1 schedule in Experiment I, when these doses of the drug were available on an FR 10 schedule of reinforcement

Procedure

Four monkeys were used in this part of the study Monkey 3018 had been in the previous experiment while monkey 432 was experimentally naive The remaining two animals (4173, M233) were experienced with the substitution procedure and did not require training Following completion of the previous study (see above) monkey 3018 was rapidly trained to respond on the left lever for cocaine (50 μg/kg/injection) on a gradually incremented ratio to a final fixed ratio of 10 (FR 10)

The monkeys were housed in self-administration cubicles and wore restraint harnesses as described in Experiment I The animals were fed as previously described but were allowed free access to water during the sessions as well as during all other times

After catheter implantation and recovery from surgery, monkey 432 was trained to respond on the left lever for cocaine injections on an FR 1 schedule and gradually brought up to an FR 10. Daily sessions were 60 minutes When stable FR 10 responding for cocaine occurred in all four monkeys (less than 10% deviation from the mean for 3 consecutive days), doses of nicotine (10–300 μg/kg/injection) or saline were substituted for cocaine injections for four consecutive days Following each dosage substitution the animals were returned to cocaine for at least three days or until stable responding occurred

The four monkeys were tested with the following doses of nicotine in the following order: Monkey 3018 received 0, 30, 10, 100, 0 μg/kg/injection, monkey 432 was given 0, 10, 30, 100, 0 μg/kg/injection, monkey M233 was tested with 0, 10, 30, 100, 0 and 300 μg/kg/injection, and monkey 4173 received 0, 100, 30, 10, 300, 0 μg/kg/injection

Data Analyses

The mean number of injections of nicotine for the last three days of substitution was calculated for each dose for each monkey Injection rates for cocaine are based on all cocaine baseline days throughout the study. A dose of a drug was considered to be functioning as a reinforcer if mean rates of self-administration exceeded saline rates and the ranges did not overlap. The within-session distributions of injections for cocaine, saline and each nicotine dose were calculated as the mean percentages of the total number of injections per 15-min session segment for all four monkeys

RESULTS

The two monkeys (3018, 432) that needed to be trained on the fixed-ratio 10 schedule rapidly acquired responding, and cocaine injections (50 μg/kg/injection) maintained stable FR 10 performance in all four animals Characteristic fixed-ratio responding was demonstrated, with steady rates of responding leading to the injection delivery and small pauses following reinforcement.

The nicotine dose-response curves and control rates are presented in Fig 4 The mean number of cocaine injections for individual monkeys ranged from 29 to 71 injections Saline substitution resulted in low levels of self-administration with average injection rates of 4 to 6 injections per session Substitution of doses of nicotine (10–100 μg/kg/injection) produced relatively flat, inverted "U" shaped dose-response functions with at least one dose in all monkeys maintaining responding above saline levels where the ranges did not overlap Maximal rates of self-administration were maintained by 30 μg/kg/injection of the drug in three of the four monkeys. The highest dose of 300 μg/kg/injection was tested in two animals In these monkeys (M233, 4173), 300 μg/kg/injection nicotine decreased responding to within the saline range

Total nicotine intake was related to dose. Maximal intake occurred at the highest dose tested (300 μg/kg/injection) resulting in an average of 1460 μg/kg/session Although these are high doses of nicotine, upon observation following the high-dose session the monkeys appeared somewhat hyperreactive but otherwise normal No signs of emesis were noted at any dose tested

The distribution of injections of cocaine, saline and nicotine are shown in Fig 5 Cocaine injections were evenly distributed throughout the 60-min session while saline substitution resulted in negatively accelerated patterns with 57–82% of the injections taken in the first 15 min of the session Nicotine, at doses of 10–300 μg/kg/injection, yielded patterns of self-administration which resembled saline in three of the monkeys The fourth monkey (432) however, self-administered one dose of nicotine (10 μg/kg/injection) throughout the session in a pattern that more closely resembled distribution patterns of cocaine than saline

DISCUSSION

Nicotine was shown to maintain fixed-ratio 10 responding in all four monkeys The results, however, suggest that

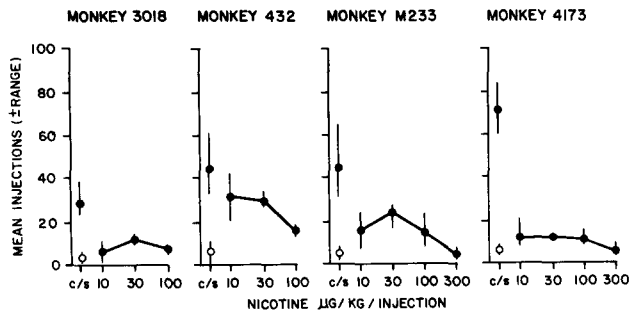

FIG 4 The mean number of injections of each dose of nicotine self-administered by each monkey Points above c/s represent the mean number of self-administered injections of cocaine and saline, respectively Nicotine and saline points are based on the last three days of each dosage substitution Cocaine data are based on all cocaine days throughout the study Verticle lines around each point represent the range

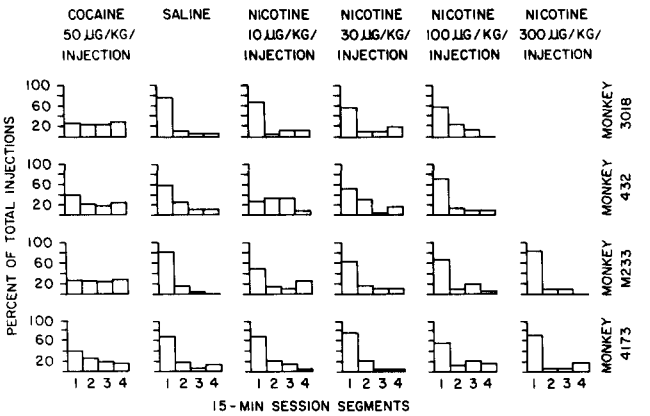

FIG 5 The distribution of injections for cocaine, saline and doses of nicotine Data are presented as the mean percent of the total number of injections per 15-min session segment Nicotine and saline data are based on the last three days of substitution at each dose of the drug Cocaine data are based on all cocaine days throughout the study

nicotine is a marginal reinforcer for a variety of reasons. First, with the exception of one animal (432) the rates of nicotine self-administration in the present study were below the range of cocaine-maintained responding.These results are consistent with a number of other reports of nicotine-maintained responding when compared to other reinforcing drugs. Griffiths *et al.*[14] for example, found that in baboons FR 160 rates of nicotine-maintained responding were much lower than cocaine self-administration rates. Additional reports of low rates of nicotine-reinforced responding have been published for the baboon [1], rhesus monkey [7,38], and rat [16,20].

Another characteristic of nicotine self-administration seen in the present study is the relatively flat dose-effect curves. Small interdose differences in responding for IV nicotine are a common occurrence in nicotine self-administration studies where different doses have been tested [7, 14, 21, 38] Also, in humans, measures of cigarette smoking behavior (presumably nicotine self-administration) were found to be unaffected by nicotine dose [15].

A final result that suggests that nicotine's reinforcing efficacy may differ from that of cocaine is the distribution of injections across the session. The negatively accelerated patterns at doses of nicotine which did maintain responding above saline control resembled the injection distribution seen with saline substitution and indicate extinction of responding through the session. It is possible that the negatively accelerated distribution might be the result of within-session tolerance to the reinforcing properties of the drug There is some evidence for the rapid development of tolerance to certain effects of nicotine [7, 18, 36]. Henningfield *et al* [18] found that human subjects self-administering IV nictotine reported that the maximal euphoric effects of the drug were produced by the initial injection and decreased with the following injection. The authors report that self-administration rates decreased when the euphoric effects became weak The present results may parallel these findings and indeed represent extinction of nicotine-maintained responding as the session progressed An alternative explanation,however, is a response-rate decreasing effect as a result of cumulative nicotine doses, which is somewhat supported by the greater negative acceleration seen at the higher unit doses of nicotine.

GENERAL DISCUSSION

The present study extends our previous findings [34] of nicotine self-administration at higher rates and lower doses during a schedule-induction procedure (concurrent schedule) than during a single component simple FR schedule. In Experiment I three types of behavior occurred : (a) Fixed-interval food maintained responding, (b) responding maintained by IV nicotine, and (c) responding for IV nicotine which was induced by the presence of a concurrent fixed-interval schedule of food reinforcement. Experiment II demonstrated that the doses of nicotine that functioned as reinforcers to maintain FR 1 responding in Experiment 1 were effective as postive reinforcers to maintain FR 10 responding in a standard drug self-administration substitution procedure.

The behavior which was induced by the concurrent FI FR schedule was particularly interesting because it was topographically similar to the schedule-controlled response (i.e., lever-pressing) and because it was an arbitrary response relative to the IV nicotine infusion. In this respect, the schedule-induced IV self-administration of nicotine differs from most types of schedule-induced behaviors which are typically behaviors inherently related to the environmental stimulus involved. The best example of this is schedule-induced drinking where the response of licking is intrinsically related to fluid consumption. Another schedule-induced behavior is the ingestion of nonfood substances, called pica behavior. In monkeys for example, wood shavings pica involves the tactile manipulation and direct oral ingestion of the shavings. In contrast, in the present study lever pressing is not inherently related to IV nicotine administration yet the response was schedule-induced It might be argued that the FI food schedule induced lever pressing *per se* which was directed towards the other lever This was not the case however, since the rates of FR 1 lever pressing were not changed (i.e., schedule-induced) by the presence of the food reinforcement schedule when saline was available on the FR lever. If the behavior of lever pressing was what was induced, it would be expected that rates would have been increased during this condition also.

Nicotine was found to be an effective reinforcer to maintain responding on both the FR 1 and FR 10 schedule of reinforcement at similar doses The highest rates of FR 10 self-administration responding occurred at a dose of 30 μg/kg/injection, a dose that maintained the highest rates of self-administration on the simple FR 1 schedule Total session intakes of nicotine were also similar at reinforcing doses (30 and 100 μg/kg/injection) in the two experiments (approximately 600 and 1200 μg/kg respectively). The doses that were effective in maintaining responding in the present study (30–100 μg/kg/injection) are consistent with doses reported by others to maintain IV self-administration responding on fixed-interval and fixed-ratio schedules in squirrel monkeys, baboons and dogs [1, 12, 30,35].

Relative to the rates of responding for doses of 3 and 10 μg/kg/injection, rates of self-administration of saline and the lowest dose of nicotine (0 1 μg/kg/injection) were not significantly increased during the concurrent schedules This implies the involvement of pharmacological factors This increase in self-administration of low doses by the addition of a concurrent fixed-interval food schedule is consistent with Falk's [10] proposal that schedule-induction results in an enhancement of the reinforcing properties of events whose inherent properties are not sufficient to maintain responding on a simple schedule On the other hand, the rates of nicotine-maintained responding at reinforcing doses were not sensitive to schedule-induction as demonstrated by the lack of increase in rates of responding for nicotine infusions

In summary, this study shows an environmental-pharmacological interaction between a schedule of intermittent food reinforcement presentation and the inherent reinforcing (pharmacological) properties of nicotine Furthermore, the environmental-pharmacological interaction was only apparent at low doses of the drug suggesting that pharmacological factors predominate and are not affected by the induction procedure at doses which have intrinsic reinforcing properties

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