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Nicotine Self-Administration in Baboons

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ATOR, N. A. AND R. R. GRIFFITHS. *Nicotine self-administration in baboons.* PHARMACOL BIOCHEM BEHAV 19(6) 993–1003, 1983.—Two experiments were conducted in which responding maintained by nicotine and cocaine was studied under two different schedules of drug delivery. In Experiment 1, nicotine (0.01–0.32 mg/kg IV) was available under a fixed-ratio 2 timeout 15 sec reinforcement schedule. When nicotine was substituted for cocaine or saline, dose-dependent differences in self-administration were evident across the first five sessions, resulting in an inverted U-shaped dose-effect curve. With continued exposure to each nicotine dose, however, number of injections generally stabilized at levels not very different, if at all, from saline; and the terminal dose-effect functions generally were low and flat. In Experiment 2, nicotine (0.01–0.56 mg/kg IV) was available under a fixed-interval 5 min timeout 60 sec reinforcement schedule. Response rates were considerably lower and response patterning was less likely to be scalloped than when responding was maintained by either cocaine or food, but number of injections was higher than those maintained by saline. When fixed-interval value was varied, number of nicotine reinforcements remained low and virtually constant, but number of food reinforcements increased as the fixed interval decreased. The present results, along with those from previous studies, suggest that the ability of nicotine to serve as a reinforcer appears to be strongly influenced by the conditions of drug availability, perhaps more so than for other drugs of abuse.

Nicotine Cocaine Self-administration Drug reinforcement Baboons

WHEN laboratory animals have been provided the opportunity to produce intravenous (IV) injections of nicotine by operating a lever, it has sometimes been concluded that nicotine is eminently capable of serving as a reinforcer, yet other studies have prompted the conclusion that nicotine is not particularly reliable or robust in its reinforcing efficacy [4, 7, 10]. Both species and schedule of nicotine reinforcement emerge as salient, potentially important variables in accounting for these differing conclusions. Studies in squirrel monkeys [8,19] and dogs [17] have successfully demonstrated that nicotine can maintain responding comparable to that maintained by other reinforcing events with an inverted U-shaped function describing the relationship between dose and response rate. Those studies employed schedules of intermittent reinforcement in which a specified minimum interinjection interval was imposed such that rate of lever pressing could vary relatively independently of rate of self-injection. In contrast, studies in rats and rhesus monkeys [3, 4, 11, 12, 23] have found relatively low rates of self-injection with only small differences in rate of self-injection as dose was varied, and rates of nicotine self-administration have been highly variable within and across subjects. These latter studies employed schedules of continuous reinforcement in which rate of responding was essentially equivalent to rate of self-injection.

In an effort to clarify those conditions under which nicotine reinforcement will be demonstrated, the present investigation first studied nicotine self-administration under a schedule of relatively continuous nicotine reinforcement and then compared those results with nicotine self-administration when rate of self-injection was more constrained. Under both conditions responding maintained by nicotine was compared with that maintained by cocaine and by saline.

EXPERIMENT 1

Experiment 1 characterized rate of nicotine self-administration both within and across sessions in which IV nicotine was available under a schedule of relatively continuous reinforcement and also examined whether immediate history of drug self-administration would affect responding maintained by nicotine. Nicotine doses were substituted for: (1) a cocaine dose that maintained a high rate of responding, (2) saline, after responding was occurring at low rates, and (3) another dose of nicotine. In addition, because food deprivation has been shown to increase intravenous and oral self-administration of a variety of drugs [1, 2, 16, 21], nicotine self-administration was studied in the context of restricted food intake to determine whether this variable would increase number of nicotine injections obtained.

METHOD

Subjects

Four male baboons (*Papio anubis*), weighing 20 to 30 kg, served as subjects. Baboon RF had a history of self-injection of methohexital and cocaine; baboons MS and GI had brief histories of self-injection of chlordiazepoxide; baboon RA was experimentally naive. The baboons had unrestricted access to 1 g food pellets, except as noted below, and were also fed two pieces of fresh fruit daily. Water was continuously available. Each baboon was surgically prepared with a silastic catheter in the internal jugular, femoral, or axillary vein

[13]. Injections of ketamine (Ketaset®) were given periodically in order to weigh the baboons and conduct physical examinations.

Apparatus

Each baboon was seated in a restraint cart [6], which protected the catheter by restricting the extent of lateral and vertical movement of the arms. The catheter was attached to a valve system through which infusions could occur via each of three separate peristaltic pumps. Heparinized saline (5 units/ml) was continuously administered via one pump (100 ml/24 hr) to maintain catheter patency. Drug could be infused into the system by means of a second pump and flushed into the animal with saline from a third pump. The cart was housed in a sound-attenuating chamber with the baboon facing an intelligence panel. A water spout protruded into the chamber from the ceiling in front of and to the left of the baboon. A 7 W houselight was mounted on the ceiling behind the baboon in the right corner. Either a specially modified Micro Switch lever (No. BZE6-2RN18) with a 0.5×3.5 cm stainless steel extension (baboons RF, GI, RA) or a Lindsley operandum (Gerbrands G6310, baboon MS) could be operated only with the left hand. An identical lever was positioned opposite the right hand. Jewel lights over the levers served as discriminative stimuli for food or nicotine availability. A 5×5 cm white translucent panel above the left lever was transilluminated during infusion, flush, and timeout. Food pellets were delivered into a tray to the right of the right hand lever. White noise masked extraneous sounds.

Procedure

Onset of a period of drug availability was accompanied by a 5-sec tone and illumination of a blue jewel light over the left lever. Two responses on the left lever, fixed ratio (FR) 2, produced a 1 ml injection of the drug solution (or saline) over 5 sec, followed by a 3 ml saline flush over 10 sec. At the beginning of the injection, the blue jewel light was turned off, the panel over the lever was transilluminated, and remained so for a 15 sec timeout following the saline flush. Therefore, the minimum possible interval from the beginning of one injection to the beginning of the next was 30 sec. Experimental sessions lasted for 2 hr or 50 injections, whichever came first, and were conducted once a day 7 days a week. Except as noted below, the stability criterion for changing a dose condition was that it had been in effect a minimum of 7, usually 10, sessions and until there were no increasing or decreasing trends in number of injections over the last five sessions.

Baboons RF, GI, and MS first were studied under conditions of cocaine availability (0.001–0.1 mg/kg/injection) to determine a dose likely to maintain self-administration at 50 injections in 2 hr or less that could serve as a baseline dose for nicotine substitution. Next, all four baboons were studied under conditions of nicotine availability (0.01–0.1 for RF, GI, MS and 0.01–0.32 for RA). Each nicotine dose generally was studied more than once (RA was the exception) in mixed order with conditions of cocaine or saline availability intervening. Data have been grouped for presentation according to the drug condition prevailing, i.e., either cocaine, saline, or another dose of nicotine, when nicotine or saline was substituted. When cocaine was the baseline, cocaine (0.01 mg/kg/injection) was available until the baboon obtained 50 injections in three consecutive sessions, and then either saline or nicotine was substituted in the next session. When saline was the baseline, saline was available until mean number of injections across three consecutive sessions was less than 5 and then a dose of nicotine was substituted in the next session. On some occasions, nicotine itself was the baseline in that each dose of nicotine (or saline) was substituted for another dose of nicotine after responding met the stability criterion stated above.

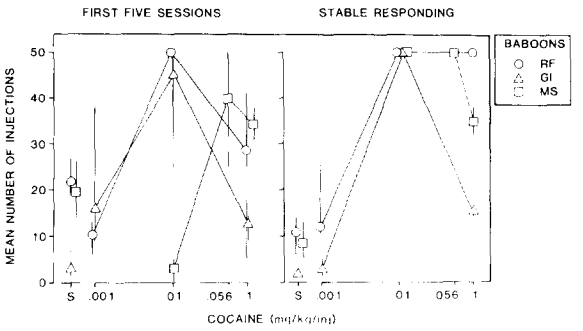

FIG. 1. Number of injections of cocaine or saline (S) in daily sessions under an FR 2 timeout 15 sec schedule of reinforcement. Points in the left panel generally represent the mean of the first five sessions at a given dose, and points in the right panel generally represent the mean of the last five sessions at each condition after number of injections met the stability criterion. Vertical bars indicate ranges unless they were encompassed within the point. Sessions ended after 2 hr or 50 injections, whichever came first. All points at 50 injections represent sessions that were less than 2 hr long.

Between drug sessions, the green jewel light above the right lever was illuminated and 1-g food pellets were available continuously under an FR 10 schedule of reinforcement on the right lever. Responses on the right lever were counted but had no programmed consequences during the drug sessions.

In a final condition, self-administration of a single dose of nicotine was studied in the context of restricting food intake. After number of injections of the dose to be studied (0.032 mg/kg for baboons MS anf RF and 0.056 mg/kg for GI) was stable, food pellet availability under the FR 10 schedule of reinforcement was decreased to a 2-hr period beginning 20 hr before the next drug session.

Drugs

Nicotine tartrate obtained from ICN K & K Labs (Plainview, NY) was used initially. This nicotine was reported by the company to be 92–98% pure nicotine tartrate (with the remainder being cotinine). During the food restriction condition, the source for the nicotine tartrate was changed to Pfaltz and Bauer (Stanford, CN) and this batch was independently analyzed to be 94.4% nicotine tartrate. No change in nicotine self injection could be attributed to the change in source. The nicotine tartrate was dissolved in 0.9% saline, and quantitative analysis revealed that nicotine solutions in the range of concentrations used in this study remained stable for at least 5 days. Cocaine hydrochloride (obtained from the National Institute on Drug Abuse) also was dissolved in normal saline and solutions were changed after 5 days or less. Drug doses are expressed as the salt.

RESULTS

When cocaine was available, an inverted U-shaped func-

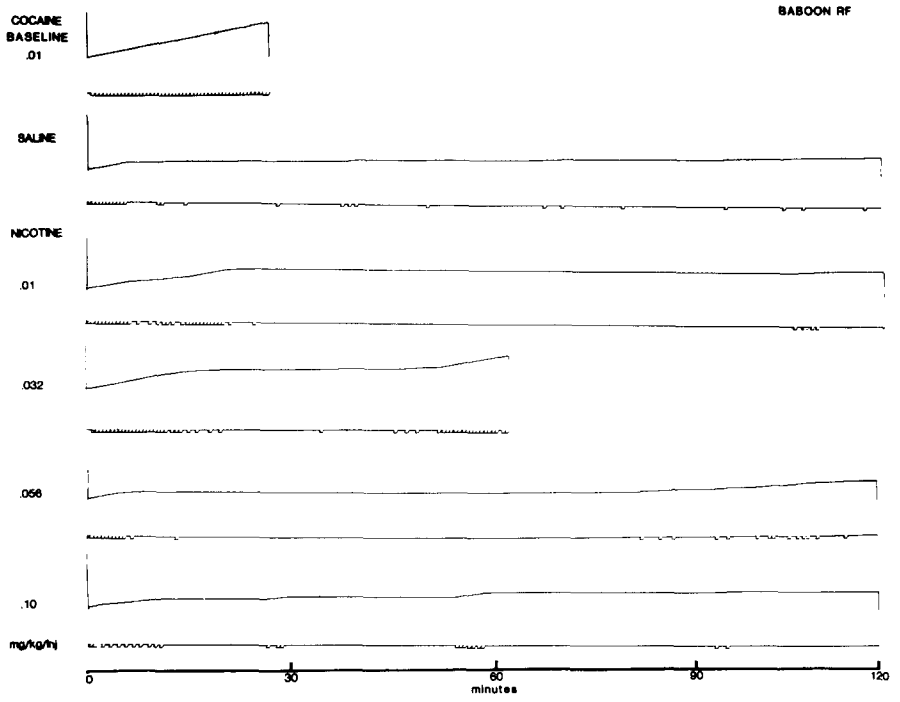

FIG. 2. Cumulative records from a representative cocaine baseline session and from the first session in which saline or each dose of nicotine was substituted for cocaine for Baboon RF. The paper moved continuously throughout each session. In each record, the upper pen stepped with lever presses and reset at the end of the session; the lower pen deflected during injection, flush, and the 15-second timeout which followed. Sessions ended after 2 hr or 50 injections, whichever came first.

tion generally characterized the relationship between cocaine dose and number of injections for both initial and stable sessions (Fig. 1). Responding under each cocaine dose condition met the stability criterion after a mean of 10.0 sessions (range=6–16). Because all baboons reliably produced 50 injections of the 0.01 dose in less than 2 hr, this dose was selected as a baseline for nicotine substitution.

When nicotine or saline was substituted for cocaine (0.01 mg/kg), dose-dependent changes in responding were apparent in the first session of substitution for all four baboons. The top cumulative record in Fig. 2 shows that all 50 cocaine injections typically were produced with little or no pausing between injections. The records from the first sessions of saline and nicotine substitution show that there was a high rate of self-injection early in the session, with lengthy pausing between injections or groups of injections following the initial burst of responding. The duration of the initial burst was inversely related to dose i.e., the longest bursts were at 0.01 and 0.032 mg/kg while shorter bursts occurred at 0.056 and 0.1 mg/kg. At the highest nicotine dose, pausing between injections began with the second injection. Very similar dose-dependent changes occurred in the first session of substitution for the other three baboons.

The left panels of Fig. 3 present the mean number of injections of each nicotine dose in the first five sessions off the cocaine, saline, and nicotine baselines; for the sake of clarity in the figure, the ranges are presented in Table 1. An inverted U-shaped function generally related number of injections to dose in the first five sessions under all baseline procedures. Peak number of nicotine injections was highest in the cocaine and nicotine baseline conditions, but under the saline baseline condition mean number of injections at 0.032 mg/kg nicotine was higher than the saline baseline itself within the first five sessions of nicotine substitution for two baboons (RF, MS). In the nicotine baseline condition, one dose of nicotine was substituted for another. Over the first five sessions at the new dose the number of injections taken generally fell above or below the range of injections taken in the last five sessions at the preceding dose (data not shown), but there was no apparent systematic relationship between whether dose had been increased or decreased and the direction of change in number of injections. Overall, number of injections at a given nicotine dose was not found to be related to number of previous exposures to that or other doses of nicotine.

Responding under each saline or nicotine dose condition met the stability criterion after a mean of 14.7 sessions (range=7–39). The three right panels of Fig. 3 show that with extended exposure to each nicotine dose the function relating nicotine dose and number of injections generally became lower and flatter, and mean number of injections in the last five sessions was only marginally distinguishable, if at all, from saline. Only baboon MS reliably produced all 50 available nicotine injections in less than 2 hr at any nicotine dose. Total session nicotine intake was either an increasing function or a flat function of nicotine dose. Highest mean nicotine intake (mg/kg/session) was: GI, 0.86; RF, 1.48; RA, 1.24; and MS, 2.80.

Under conditions of stable responding, all four baboons generally produced a third to a half of the injections in the first 30 to 40 min of the session under at least one of the higher nicotine doses, but, except for baboon MS, these in-

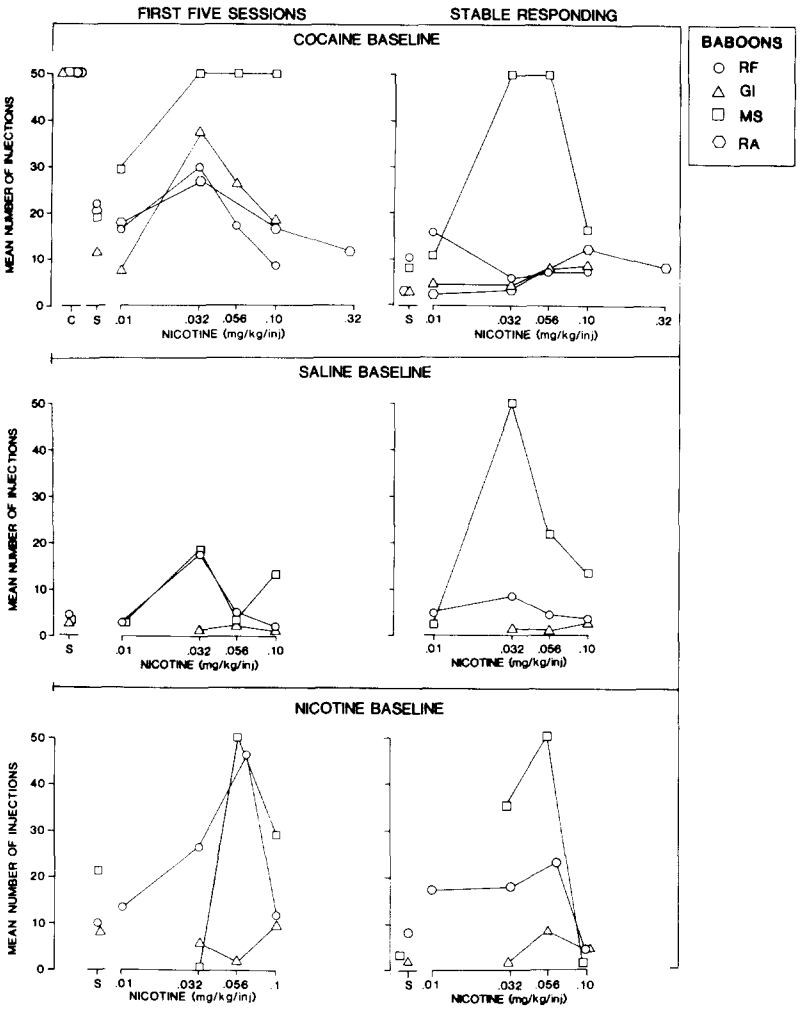

FIG. 3. Number of self-administered IV injections under the cocaine, saline, and nicotine baseline conditions for each baboon. Left panels generally show the means for the first five sessions of substitution, and right panels generally show the means for the last five sessions of each dose condition after number of injections met the stability criterion. Ranges around these points are presented in Table 1. Points above C in the cocaine baseline condition represent mean number of cocaine (0.01 mg/kg) injections in all three-session periods which preceded substitution of nicotine or saline. Points above S in the saline baseline condition represent mean number of saline injections in all the three-session periods which preceded substitution of nicotine. Points above S in the cocaine and nicotine baseline conditions represent mean number of saline injections after substitution for cocaine and nicotine, respectively. Other details are as for Fig. 1.

jections were not closely spaced as during the first five sessions (cf., Fig. 2). At the lower nicotine doses and with saline, the few injections taken were spaced irregularly across the 2-hr period, although at least one injection usually was produced during the first 30 min of the session.

Mean response rates under conditions of stable responding for the cocaine baseline conditions are given in Fig. 4. Only baboon MS responded at rates higher than those maintained by saline at any nicotine dose, and, at 0.032 and 0.056 mg/kg nicotine, response rates were higher than those maintained by the baseline cocaine dose.

Each baboon was returned to a peak dose of nicotine (0.032 mg/kg for RF and MS; 0.056 mg/kg for GI) until number of injections met the stability criterion, and food availability was restricted to a 2-hr period each day. Food intake decreased by 50–58% and, over a month, body weights decreased (MS by 9%, GI by 6%, RF by 16%). During this time, mean number of nicotine injections in the 2-hr session increased for approximately 15 sessions for baboons RF (from 14.8 to 35.6) and GI (from 7.8 to 11.4) before stabilizing at the original (RF=14.7) or lower (GI=2.2) values; mean number of injections decreased for baboon MS (from 50 to 41.6).

DISCUSSION

With an immediate history of responding maintained at high rates by cocaine, a moderate to high number of nicotine

TABLE 1

RANGES FOR MEAN NUMBER OF INJECTIONS IN THE FIRST AND LAST FIVE SESSIONS WHEN SALINE OR NICOTINE WAS SUBSTITUTED FOR COCAINE (0.01 mg/kg), SALINE, OR ANOTHER DOSE OF NICOTINE*

	Dose (mg/kg/injection)											
	Saline		0.01		0.032		0.056		0.1		0.32	
Baboon	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last
						Cocaine Baseline						
RF	19–27	6–14	8–36	8–24	15–50	4– 9	5–31	6– 9	2–25	5–10		
GI	0–21	1– 9	2–12	2– 7	6–50	2– 6	14–49	6–10	7–39	7–11		
MS	9–29	3–13	13–50	6–13	—	—	—	—	—	1–17		
RA	5–48	0– 7	4–26	0– 5	4–50	1– 7			12–24	12–15	10–14	7–11
						Saline Baseline						
RF			1– 6	3– 8	5–28	5–15	5– 6	3– 6	0– 5	2– 6		
GI					1– 3	1– 2	1– 5	0– 2	1– 3	1– 5		
MS			1– 5	0– 4	4–34	—	2– 5	18–27	8–18	10–16		
						Nicotine Baseline						
RF	8–12	6–10	10–17	12–22	16–33	12–31	40–50	15–27	4–26	1– 7		
GI	7– 9	0– 5			5– 9	0– 4	1– 4	3–14	6–12	3– 6		
MS	7–42	2– 4			0– 1	11–50	—	—	14–50	0– 4		

*Dash indicates no variability.

injections occurred in the initial sessions after nicotine substitution, with an inverted U-shaped function relating nicotine dose to number of injections for all four baboons. With continued exposure to each dose of nicotine, the terminal dose-effect function generally became lower and flatter. With an immediate history of responding maintained at very low rates by saline, substitution of nicotine also resulted initially in inverted U-shaped dose-effect functions with peak number of injections increasing slightly above saline levels for two of the three baboons, but number of injections was lower than in initial sessions under the cocaine baseline condition. Continued exposure again resulted in low, flat dose-effect functions, with number of injections only slightly, if at all, above saline levels. Thus, immediate history did not influence final levels of self-administration, but did influence number of injections in early sessions of exposure to a nicotine dose.

Food deprivation has been shown to increase IV and oral self-administration of a variety of drugs [1, 2, 21] including nicotine [12]. In the present study, decreasing food availability and concomitantly decreasing body weight, increased nicotine self-administration in the two baboons not already receiving the maximum number of injections, but this increase was not sustained, and number of nicotine injections actually decreased below the predeprivation level. The ultimate weight loss for these baboons did not reach the 70–80% levels that have been studied with IV self-administration of etonitazene [2] and a single dose of nicotine [12] in rats, and it is unclear whether specific body weight, species, dose, or some other procedural variable might have produced a sustained increase in nicotine self-administration.

One baboon differed from the others in that, regardless of the baseline procedures used for introducing individual

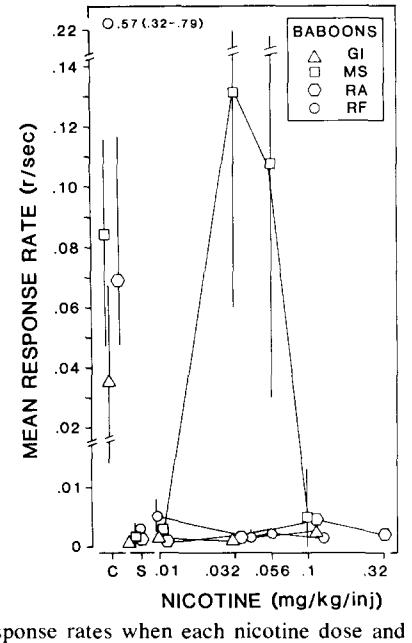

FIG. 4. Response rates when each nicotine dose and saline were substituted for cocaine (0.01 mg/kg) and number of injections was stable. The points represent the same sessions shown in Fig. 3 (upper right panel). The injection and timeout periods and any lever presses during them were excluded from the calculations. Vertical bars indicate ranges unless they were encompassed within the point.

nicotine doses, levels of self-administration were maintained that were clearly higher than those maintained by saline. This baboon (MS) was the only one for which nicotine reinforcement was convincingly demonstrated under the conditions of Experiment 1. The behavioral and drug history and time of arrival in the laboratory of this baboon was virtually identical to that of baboon GI, the baboon that showed the least responding maintained by nicotine. Thus, the possible determinants of the idiosyncratic nicotine self-administration of baboon MS were not readily apparent.

Dougherty *et al.* [4], suggested that flat dose-response curves for nicotine self-injection might be the result of averaging injection frequency over entire sessions or days. They found that behavior in the early parts of 3-hr sessions under short (16 and 60 sec) fixed-interval (FI) schedules changes systematically with nicotine dose, but that responding in the later part of these sessions was similar to that maintained by saline. Although our findings were similar to those of Dougherty *et al.* [4] for initial sessions of nicotine substitution, continued exposure to a nicotine dose over days generally resulted in a low total number of injections per session, and these few injections were generally irregularly spaced over the session.

Under schedules of relatively continuous nicotine reinforcement comparable to that of the present study, similar results have been obtained: rates of self-injection have been low and interdose differences have been relatively small whether nicotine was available 24 hr per day [11, 12, 23] or for restricted periods of time each day [4]. Marked intersubject differences in nicotine self-injection have been reported previously [3, 4, 11, 12] and were found also in Experiment 1. Overall, the low rates of self-injection and variability across animals in this and other studies of relatively continuous nicotine reinforcement might be taken to indicate that nicotine is only marginally reinforcing under these conditions.

EXPERIMENT 2

Under the FR 2 schedule of reinforcement in Experiment 1, responding maintained by nicotine was, for most baboons, only transiently higher than that maintained by saline. Under schedules of intermittent nicotine reinforcement, a different picture of the ability of nicotine to maintain responding has emerged [4, 8, 17, 19]. Rates of responding clearly higher than those maintained by saline were obtained across a range of doses. Response rates did not uniformly decrease over time, and an inverted U-shaped dose-effect function was the rule. In addition, these studies found patterns of lever pressing characteristic of the intermittent reinforcement schedules employed. Taken together, these studies indicated that responding was similar to that maintained by a variety of other reinforcers.

The purpose of Experiment 2 was to determine whether more intermittent nicotine reinforcement would be able to sustain stable levels of responding higher than those maintained by saline. Schedule parameters under the fixed interval (FI) schedule of reinforcement were chosen initially to be similar to those successfully employed by Goldberg and Spealman [19] with nicotine-maintained responding in squirrel monkeys. Subsequently, FI value was manipulated in order to determine the effect of interreinforcement interval on responding maintained by nicotine. For comparison, sessions were conducted using the same FI values with responding maintained by food instead of nicotine.

METHOD

Subjects

Baboons RF and MS from Experiment 1 and an experimentally naive baboon (LO) served as subjects (baboons RA and GI no longer could be catheterized). Baboon LO was prepared with an IV catheter as described above. Between Experiment 1 and Experiment 2 baboons RF and MS were studied under the FR 2 schedule of nicotine self-administration under conditions of concurrent food availability (results not to be reported here). The baboons were fed a daily ration of monkey chow and a piece of fresh fruit 3 hr after the food session and 5 hr prior to the daily drug session.

Apparatus

The apparatus was similar to that described in Experiment 1, except that the food lever and associated jewel light for baboon RF was moved to a position 8.6 cm to the right of the drug lever. Thus, both levers were operated with the left hand. For baboon LO, the levers were Lindsley operanda as for baboon MS.

Procedure

The injection volumes and durations, the stimulus conditions, and the stability criterion for changing conditions were the same as for Experiment 1.

Nicotine (0.032 mg/kg) first was made available for all three baboons under an FR 2 timeout 300 sec schedule of reinforcement in the daily 2-hr drug session until responding was stable. Further study of timeout duration and of delivering nicotine independently of lever pressing was made. These manipulations did not yield changes in nicotine self-administration and will not be further described. Next, the schedule was changed to an FI 300 sec schedule of drug delivery in which the first operation of the left lever after 300 sec produced an injection followed by a timeout of 60 sec. Initially, responding was maintained by cocaine (0.032–0.32). Nicotine (0.01 mg/kg) then was substituted for 0.032 mg/kg cocaine; additional nicotine doses (0.032–0.56 mg/kg) were studied in ascending order. Saline was studied for baboon MS after 0.56 mg/kg, for baboon RF after a return to 0.01 mg/kg, and for baboon LO after a return to 0.1 mg/kg. Food sessions also were conducted each day, in which 1-g food pellets were available under the FI 300 sec timeout 60 sec schedule on the right lever. These sessions were also 2 hr long and ended 8.5 hr before the drug session.

Following the nicotine dose manipulations, baboons RF and LO were returned to 0.1 mg/kg nicotine and FI value was manipulated in both the drug and food sessions. The order of FI values for baboon LO was FI 300, 420, 540, 660, 300, 180, 120, 60, 30 sec; for baboon RF the order of FI values was FI 300, 180, 60, 30, 300, 420, and 660 sec. Food session FI values were generally changed at the same time, although there were some deviations from this in order to assess possible interactions with drug session responding; none were seen.

Drugs

Drugs were the same as in Experiment 1, except that during the nicotine dose manipulations the source of the nicotine tartrate was changed to Gallard-Schlesinger Mfg. Co. (Carl Place, NY). This batch was independently

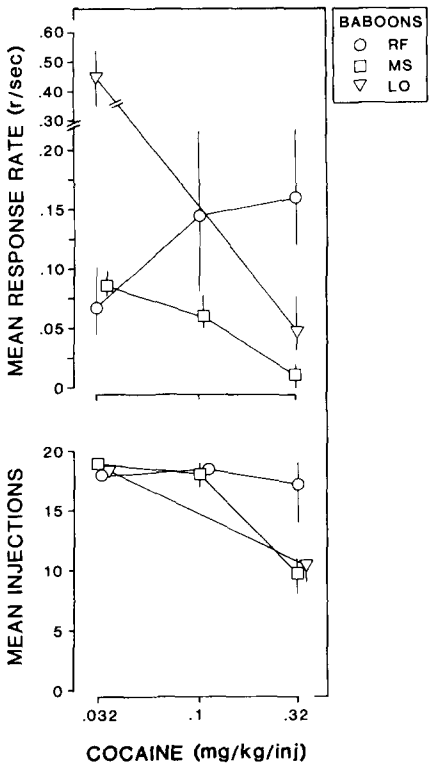

FIG. 5. Response rates (top panel) and number of injections (bottom panel) in daily 2-hr sessions under an FI 300 sec timeout 60 sec schedule of cocaine delivery. Points generally represents the mean of the last five sessions at each condition after number of injections met the stability criterion. Vertical bars indicate ranges unless they were encompassed within the point.

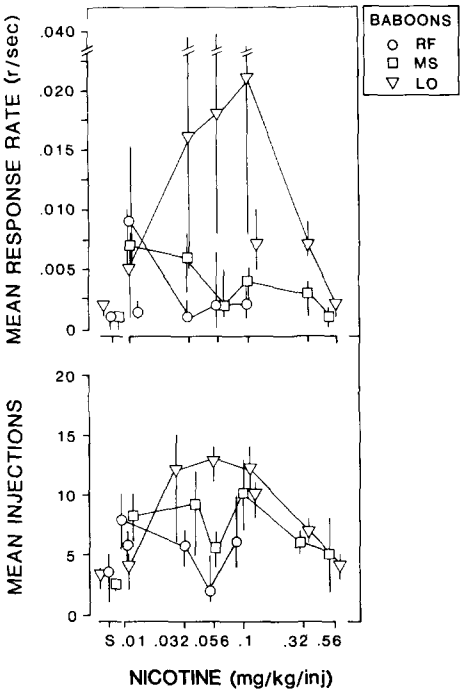

FIG. 6. Response rates (top panel) and number of injections (bottom panel) in daily 2-hr sessions under an FI 300 sec timeout 60 sec schedule of saline (S) or nicotine delivery. Points generally represent the mean of the last five sessions at each condition after number of injections met the stability criterion. Unconnected points represent replications of a dose condition. Vertical bars indicate ranges unless they were encompassed within the point.

analyzed to be 98% nicotine tartrate. No change in nicotine self-administration was apparent as a function of change in source of the nicotine tartrate.

RESULTS

When cocaine, 0.032 mg/kg, was available under the FI 300 sec timeout 60 sec schedule, virtually all possible injections were reliably produced by all three baboons; as cocaine dose increased, number of injections remained the same or decreased (Fig. 5). Likewise, all possible food reinforcements typically were produced under this FI schedule in the separate food sessions (data not shown). When nicotine was available under the FI 300 sec schedule no baboon ever produced the maximum available number of injections at any nicotine dose (Fig. 6). Mean number of injections in the first five sessions at each dose (and with saline) was generally higher than mean number of injections after the stability criterion was met; but ranges generally overlapped so that responding was not very different when initial and terminal phases of a dose condition were compared. Mean number of sessions until the stability criterion was met was 14.6 (range=9–26). An inverted U-shaped curve related dose to number of injections for baboon LO; the functions were relatively flat for baboons RF and MS, except for a dip in the function at 0.056 mg/kg for both baboons. Return to the 0.01 dose for baboon RF and to the 0.1 mg/kg dose for baboon LO resulted in mean number of injections that were slightly lower than, but within the range of, the values initially obtained (Fig. 6, unconnected points). The mean and range of the number of saline injections was below the range of number of injections at most of the nicotine doses studied. Nicotine intake was an increasing function of nicotine dose for all three baboons. Highest mean nicotine intake (mg/kg/session) in the sessions represented in Fig. 6 was: RF, 1.02; MS, 2.8; and LO, 2.35. At the dose of nicotine (0.032 mg/kg) at which a comparison could be made between the FI 300 sec timeout 60 sec schedule and the FR 2 timeout 300 sec schedule, more injections were produced under the FI (Fig. 6) than under the FR schedule (RF: mean=4, range=1–6; LO: mean=4.4, range=0–8; MS: mean=0.4, range=0–2).

Response rates under the FI schedule were lower at all doses of nicotine (Fig. 6) than at the cocaine doses studied (Fig. 5), but nicotine-maintained response rates generally were higher than those maintained by saline. In general, response rates maintained by nicotine were more different from those maintained by saline under the FI than they had been under the FR 2 schedule in Experiment (Fig. 4).

Representative patterns of stable intrasession responding under the FR 2 timeout 15 sec and FI 300 sec timeout 60 sec schedules can be compared for baboon RF in Fig. 7. For further comparison, a cumulative record from the food session at FI 300 sec is also included. Although the maximum number of reinforcements was obtained under the FI schedule in both the cocaine and food sessions, response rates clearly were higher in the food session. Response rates under the FI schedule at the nicotine dose condition were

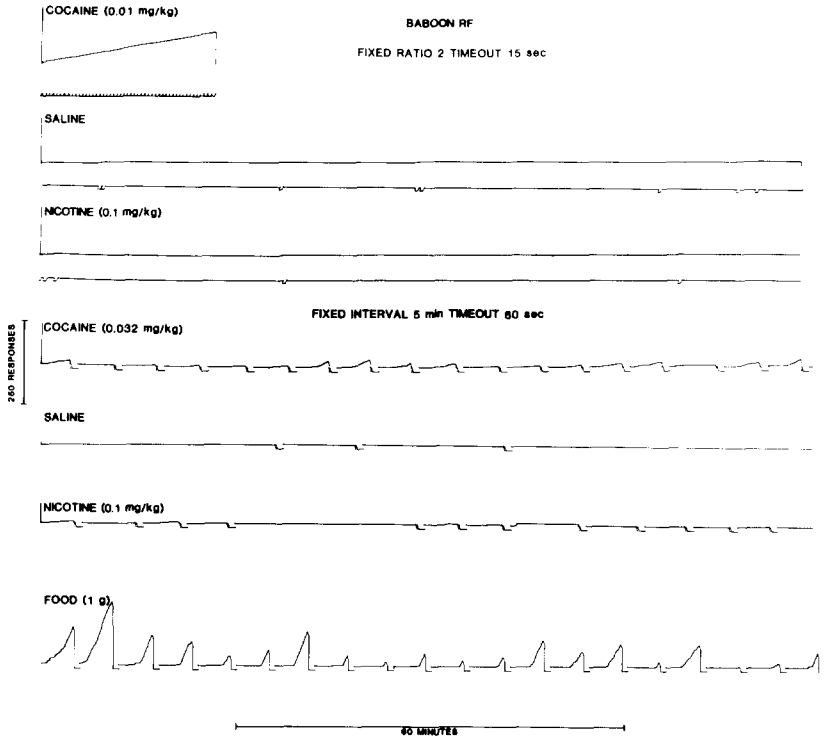

FIG. 7. Cumulative records representing stable responding in cocaine, saline, and nicotine sessions under the FR 2 timeout 15 sec (Experiment 1) and FI 300 sec timeout 60 sec schedules and in a food reinforcement session under the FI schedule. The top record is representative of cocaine-maintained responding under the FR 2 schedule. Each of the other records is for one of the last five sessions in that condition and was chosen for having response rates and numbers of reinforcements that were closest to the mean values of the last five sessions. The upper pen in each record stepped with lever presses. Under the FR 2 schedule, the lower pen deflected during the injection, flush and the timeout. Under the FI schedule, the upper pen reset at reinforcement and was deflected during the timeout.

low and FI patterning was minimal, but there was more regularity in responding across the 2-hr session than at the same nicotine dose under the FR 2 schedule. For baboon LO (Fig. 8), cocaine maintained high response rates and a generally scalloped pattern of FI responding. Nicotine maintained higher FI response rates for baboon LO than for either of the other two baboons (Fig. 5), but did not generally maintain the characteristic FI pattern, except in occasional intervals. It is noteworthy, however, that such patterning occurred only under stable responding in the nicotine conditions and never under stable responding in the saline condition for any of the three baboons.

When nicotine dose was held constant at 0.1 mg/kg and FI value was varied, response rates and number of injections changed relatively little across most of the FI values studied (Fig. 9). Under the same FI values in the food sessions, however, number of food deliveries was inversely related to FI value and approached or equalled the maximum available. Response rates maintained by food were clearly higher than those maintained by nicotine for both baboons. For baboon RF, the shape of the function for food reinforcement was similar to that for nicotine reinforcement; but for baboon LO, response rates in the food sessions generally were inversely related to FI value. When number of pellets per reinforcement were increased from one to three (at FI values of 300 sec for RF and at 300, 420, and 540 sec for LO) response rates increased markedly (data not shown).

DISCUSSION

Under the FI 300 sec schedule when responding was stable, number of injections per session was higher across a range of nicotine doses than for saline. Response rates in those nicotine dose conditions, while relatively low, were higher than those maintained by saline. In addition, the characteristic FI patterning of responses within intervals was occasionally present under nicotine dose conditions but never present under the saline condition. When FI value was manipulated across a wide range, both response rates and number of nicotine injections remained relatively invariant. This result contrasts with that for the food condition, in which response rates and/or number of reinforcements increased as FI value decreased. An inverse relationship between FI duration and response rate also has been reported for rats and pigeons with food [5, 18, 21] and for squirrel monkeys with shock [14] as the maintaining events.

GENERAL DISCUSSION

The results of Experiment 2 contrast with those obtained under the FR 2 schedule in Experiment 1. In Experiment 1,

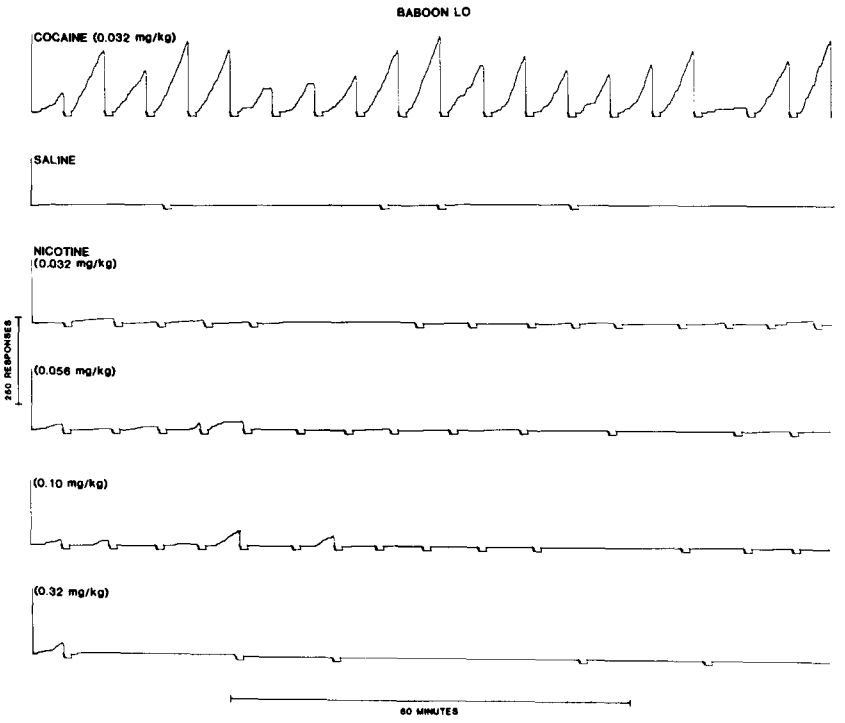

FIG. 8. Cumulative records for the representative sessions under an FI 300 sec timeout 60 sec schedule of reinforcement for cocaine, saline, and increasing nicotine doses. Other details are as for Fig. 7.

although number of injections initially was higher than that maintained by saline, it generally stabilized at levels that were not different from those maintained by saline. Also, between-subject variability in self-administration was more extreme under the FR 2 schedule in Experiment 1 than under the FI 300 sec schedule in Experiment 2. Finally, the FI schedule in Experiment 2 seemed to promote a patterning of nicotine injections at more regular intervals across the 2-hr session than was characteristic of stable responding under the FR 2 schedule of nicotine delivery in Experiment 1.

The results of Experiments 1 and 2, taken together with the contrasting results from other studies of continuous and intermittent nicotine reinforcement cited earlier, suggest that imposing some minimum interinfusion interval may be important for demonstrating nicotine reinforcement. The most obvious effect of such a contingency is that it precludes the massing of injections within a short period of time. In Experiment 1, massing nicotine injections within a short period of time not only was possible but typical of early sessions of drug exposure, and self-injection decreased both within and across sessions. Although direct effects of nicotine on lever pressing, or even satiation, might be used as an explanation for suppression of responding after initial bursts of injections within sessions, it cannot explain decreased responding across sessions.

It has been suggested [4] that decreased nicotine self-injection, both within and across sessions may result from nicotine tolerance, but the results of Experiment 1 do not appear to be consistent with such an explanation. The typical pattern of self-administration, in both animals and humans, with reinforcing drugs that characteristically produce tolerance is one of increasing, not decreasing, numbers of injections [9]. If tolerance to the reinforcing effect of a nicotine dose were to make it functionally equivalent to saline, one might expect a marked increase in responding when higher nicotine doses were substituted for lower. In the nicotine baseline condition in Experiment 1, this result was not found.

A possible explanation for the low level of nicotine self-administration under conditions of continuous reinforcement is suggested by the findings of Goldberg and Spealman [7] that when the first lever press in each ratio under an FR schedule of food delivery produced an injection of nicotine, response rates decreased i.e., nicotine was functioning as a punisher. The doses which served as punishers were the same as those that maintained lever pressing under an FI schedule. These results suggest that, as with other events (e.g., electric shock [15], electrical brain stimulation [20]) the way in which events are arranged with respect to behavior plays an important role in determining the functional relationship of that event to behavior. With nicotine, it may be that when minimum interinjection intervals are very short, exposure to cumulative high nicotine doses, resulting from initial high rates of responding, may serve to suppress future responding, but that when interinjection intervals are longer, precluding exposure to cumulative high doses of nicotine, responding can be well maintained. Limitations on the ability of nicotine to maintain behavior when response requirements are relatively high and/or interinjection intervals are very long are suggested by a study in which doses of nicotine (0.001–3.2 mg/kg) were substituted for cocaine, but 160 responses per injection were required with a 3-hr timeout between injections. Number of injections in 24 hr was not higher than that maintained by saline [10]. In addition, the results of the FR 2 timeout 300 sec condition contrasted with the results of the FI 300 sec timeout 60 sec condition in

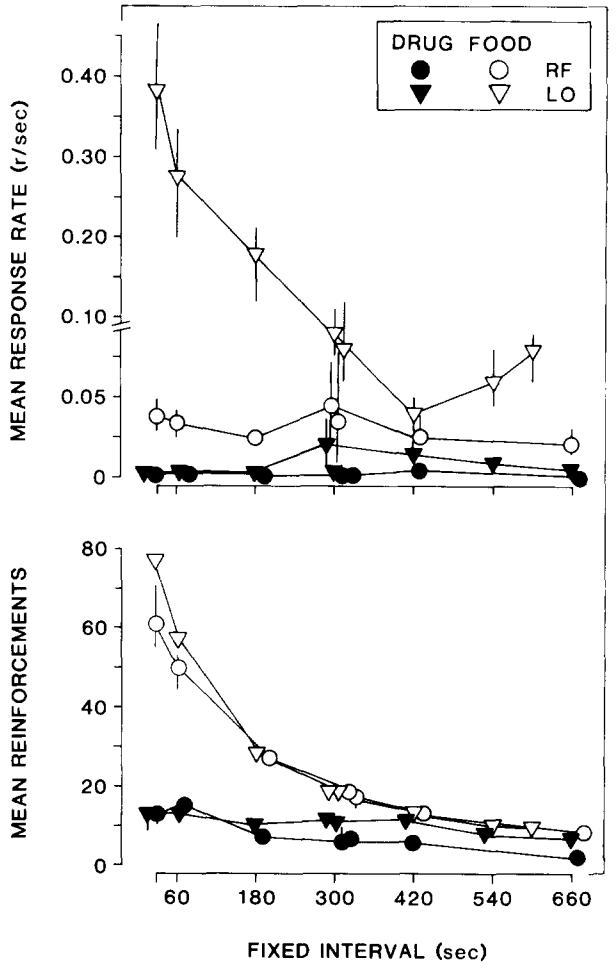

FIG. 9. Response rates (top panel) and number of reinforcements (bottom panel) in the nicotine (0.1 mg/kg) and food (a 1-g food pellet) maintained sessions. Each point represents the mean of the last five sessions at each FI value, and vertical bars indicate ranges unless they were encompassed within the point.

Experiment 2 suggests the importance of variables beyond interreinforcement interval alone (e.g., schedule of reinforcement).

In conclusion, nicotine appears to be somewhat unique among psychotropic drugs in that its ability to maintain high rates of responding across a range of doses appears to be more strongly influenced by conditions of availability than other drugs which have been extensively studied in infrahuman drug self-administration paradigms [9]. Future work which focuses on the role of schedule of nicotine reinforcement and interreinforcement interval may elucidate further the conditions under which nicotine reinforcement may occur and those under which nicotine will suppress responding which leads to its delivery.

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