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A Comparison of Nicotine and Cocaine Self-Administration in the Dog: Fixed-Ratio and Progressive-Ratio Schedules of Intravenous Drug Infusion

MARCUS E. RISNER and STEVEN R. GOLDBERG

National Institute on Drug Abuse, Division of Research, Addiction Research Center, Lexington, Kentucky (M.E.R.) and Baltimore, Maryland (S.R.G.)

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ABSTRACT

Beagle dogs pressed a lever under a 15-response fixed-ratio schedule of i.v. nicotine or cocaine infusion or water presentation. A 4-min time-out period followed each fixed-ratio trial and each daily session ended after 16 successive fixed-ratio trials. Both nicotine and cocaine were self-administered above saline levels, with the maximum number of infusions occurring at a dose of 30 μg/kg of nicotine and 100 μg/kg of cocaine. Rates of responding first increased, reaching a maximum at 10 to 30 μg/kg/infusion and then decreased, as the dose of nicotine or cocaine was varied between 3 and 300 μg/kg/infusion. The rate of responding and number of infusions obtained per session were higher under the schedule of cocaine self-administration than under the schedule of nicotine self-administration. Presession treatment with the nicotinic antagonist, mecamylamine (1.0 mg/kg i.v.), for seven consecutive sessions, decreased nicotine-maintained responding to levels not unlike those seen when saline was substituted for drug. Neither cocaine- nor water-maintained responding was affected by presession treatment with mecamylamine. A second group of beagle dogs pressed a lever under a schedule of i.v. nicotine (50–400 μg/kg/infusion) or cocaine (200–1600 μg/kg/infusion) infusion in which the fixed-ratio requirement was increased daily (*i.e.*, a progressive-ratio schedule). The maximum fixed-ratio value at which responding was maintained first increased as the dose per infusion increased and then, at the highest dose, either remained the same or decreased. Cocaine maintained considerably higher fixed-ratio values than did nicotine, but maximum fixed-ratio values for nicotine were well above those seen with saline. The effects of i.v. nicotine (3, 30 or 300 μg/kg) or mecamylamine (1.0 mg/kg) on heart rate, rectal temperature and pupillary diameter were measured in a third group of beagle dogs. Nicotine produced dose- and time-related changes in all three physiological parameters; the effects of mecamylamine were considerably greater than those seen with nicotine.

The role of nicotine in the maintenance of tobacco smoking by humans has been questioned because of difficulties in demonstrating consistent reinforcing effects in controlled laboratory studies (see reviews by Dougherty *et al.*, 1981; Goldberg and Spealman, 1982). Although i.v. infusion of nicotine has been found to maintain self-administration behavior of rats and monkeys, levels of responding usually have been very low compared with those maintained by other drugs such as cocaine or morphine (Deneau and Inoki, 1967; Clarke, 1969; Lang *et al.*, 1977; Latiff *et al.*, 1977; Yanagita, 1977; Singer *et al.*, 1978; Hanson *et al.*, 1979; Dougherty *et al.*, 1981). In most of these studies, each response or every few responses produced an infusion of nicotine and frequency of infusion depended on the rate of responding. As response rate increased, infusions occurred in more rapid succession, resulting in high cumulative doses which possibly altered the rate of subsequent responding.

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In recent studies with squirrel monkeys (Goldberg *et al.*, 1981; Goldberg and Spealman, 1982; Spealman and Goldberg, 1982), consistent reinforcing effects of nicotine were found when lever-pressing responses by monkeys only intermittently produced i.v. infusions of the drug. Under a fixed-interval schedule, the first response to occur after 5 min elapsed produced an i.v. infusion of nicotine; overall rates of responding of about 0.1 response per sec were maintained by 30 to 100 μg/kg i.v. infusions of nicotine. Under a second-order fixed-interval schedule with FR units, every 10th response produced a brief light and the first 10 response component completed after a 1- to 5-min interval elapsed produced both the light and nicotine infusions; very high overall rates of responding, ranging from 0.8 to 1.6 responses per sec, were maintained by 10 to 30 μg/kg i.v. infusions of nicotine. With both of these schedules, the maximal frequency of infusion was specified by the schedule parameters (once every 4–6 min); thus, frequency of infusion was relatively independent of response rate.

In the present experiments, the effectiveness of nicotine as a

ABBREVIATION: FR, fixed-ratio.

reinforcer of self-administration behavior was explored in another species under two different schedule conditions. The subjects were beagle dogs, a species in which self-administration data, generally similar to that seen with monkeys and rats, have been obtained with a variety of other drugs, including morphine (Jones and Prada, 1973), psychomotor stimulants (Risner and Jones, 1975) and sedative-hypnotics (Jones, 1977). In one experiment, a 15 response FR schedule of drug infusion (FR 15) was used. In order to limit the maximal frequency of infusion, a 4-min time-out period followed each nicotine infusion. The dose of nicotine per infusion was varied over a wide range to determine the optimal conditions for maintaining the highest rates of responding. For comparison, responding maintained by i.v. cocaine infusion or water presentation was studied under identical FR schedules in the same subjects. Also, the effects on nicotine-, cocaine- or water-maintained responding of daily treatment with the nicotinic antagonist mecamylamine were studied.

To further assess the reinforcing properties of nicotine, dogs were studied under a progressive-ratio schedule in which the number of responses required to produce one infusion was increased systematically until responding ceased; *i.e.*, until a "break point" was reached. Because cocaine generally maintains higher FR values under progressive-ratio schedules of drug infusion than a variety of other psychoactive drugs (*e.g.*, Griffiths *et al.*, 1978; Risner and Silcox, 1981), nicotine and cocaine were compared directly in the present experiments.

Finally, the direct physiological effects (including changes in heart rate, rectal temperature and pupillary diameter) of i.v. doses of nicotine and mecamylamine were measured in unanesthetized beagle dogs. The doses were identical to those used under the FR schedule of drug infusion.

Methods

Behavioral Studies

Subjects. Subjects were five male (10.2–12.4 kg) and three female (8.0–8.8 kg) purebred beagle dogs obtained from commercial suppliers (Bar-Wan Farms, Crocker, MO and Ridglan Farms, Mt. Horeb, WI). Four dogs (D-3880, D-4123, D-4219 and D-4220) with no experimental histories were trained to respond under a FR schedule of nicotine or cocaine infusion. Two dogs (D-2968 and D-3070) were studied under a progressive-ratio schedule of nicotine or cocaine infusion; they had histories (11 and 20 months, respectively) of i.v. drug self-administration and had recently been used in experiments to assess the relative reinforcing properties of several psychomotor stimulant drugs (Risner and Silcox, 1981). Finally, three dogs (D-3254, D-4217 and D-4220) were trained to respond under a FR schedule of water presentation. Dog 4220 had first been studied under the FR schedule of nicotine or cocaine infusion; the remaining two dogs had brief histories (6 and 2 months, respectively) of i.v. psychomotor stimulant self-administration under a continuous reinforcement schedule. All eight dogs lived in individual stainless-steel canine cages (Advanced Industries, Odessa, MO) located in a well ventilated room that was maintained at an ambient temperature of 20–22°C and artificially illuminated between 6:00 A.M. and 8:00 P.M. The cages were neither visually isolated nor sound attenuated. Water and dry food (Purina Dog Chow) were continuously available to the dogs, except for the three dogs studied under the FR schedule of water presentation; their water intake was restricted to that received during each daily session and to a supplement of about 200 ml received within 1 hr after each session. Physical examinations and clinical procedures (including a complete blood count, blood chemistry analysis, urinalysis and fecal examination) were obtained for each dog before and at regular intervals throughout the experiments.

The six dogs studied under schedules of drug infusion were surgically fitted with chronic venous catheters. While anesthetized with a mixture of methoxyflurane, nitrous oxide and oxygen, one end of a silicone catheter (outside diameter, 2.16 mm; inside diameter, 1.02 mm) was positioned in the external jugular and terminated in the cranial vena cava. The other end of the catheter passed s.c. to the nape where it exited through a short incision. The exit site was protected with a rubber flap attached to a leather walking harness which the dog wore at all times.

Apparatus. The living cage of each dog was equipped to serve as an experimental chamber. Attached to the inside of the front door of the chamber was a response lever which measured 6.6 × 10.7 cm. The lever was mounted on a rod which protruded between 10 and 15 cm into the chamber. A minimum force of 80 g (0.78 N) was required to activate the lever. Two stimulus lights (25 w, 115 V a.c. bulbs) were positioned immediately above the top of the chamber; one at front center and one at rear center. Both lights were clearly visible to the dog. For the studies involving i.v. drug infusion, a custom-built fluid swivel was also mounted atop the chamber. One end of a flexible, stainless-steel tether (6.4 mm diameter × 61 cm length) was attached to the swivel and the other end was attached to the harness on the dog. The tether protected a piece of plastic tubing which connected the catheter to the swivel, yet allowed the dog to move freely within the chamber except for rolling over. Outside the chamber the swivel was connected to an infusion pump (model AL-2-E, Sigmamotor, Inc., Middleport, NY) and a graduated drug solution reservoir. For the studies involving water presentation, a water delivery system, including a water reservoir, drinking receptacle and remotely controlled electric solenoid valve, was affixed to the door of the chamber. Located in a nearby room was a computerized control system (SCAT 3002/DEC-PDP8E, Grason-Stadler Co., Inc., Concord, MA) used to program the experimental contingencies and record the data.

Procedure. FR schedule of drug infusion. Under the FR schedule of drug infusion, experimental sessions were conducted once a day Monday through Friday with four dogs. Each daily session consisted of 16 trials which were signalled by illumination of the rear stimulus light. Each trial lasted a maximum of 10 min to prevent the session from continuing indefinitely if responding did not occur. The dogs initially were allowed to self-administer cocaine HCl (30 μg/kg/infusion) under a continuous reinforcement schedule (only one response was required to produce a drug infusion; FR 1) with a brief time-out of 15 sec between successive infusions. After acquisition of lever-pressing behavior, both the FR requirement and time-out duration were gradually increased. Under the final schedule conditions, the 15th lever-pressing response (FR 15) produced a 15 sec i.v. infusion of drug, accompanied by illumination of the front stimulus light. There was a 240 sec, unsignalled time-out period between successive trials. Responses during the first 225 sec of the time-out were counted, but had no programmed consequences; responses during the last 15 sec of the time-out postponed trial onset by 15 sec. The dogs then were tested with five doses of cocaine (3, 10, 30, 100 and 300 μg/kg/infusion), five doses of nicotine (3, 10, 30, 100 and 300 μg/kg/infusion) and saline (0.1 ml/kg/infusion). Each dose was tested for seven consecutive sessions and, as shown in table 2, a mixed order of treatment presentations was used for each dog.

Upon completion of the FR 15, time-out 240 sec dose-effect curves, the effects of presession treatment with mecamylamine on nicotine and cocaine self-administration behavior were assessed. Mecamylamine (1 mg/kg i.v.) was given 30 min before the start of each session for seven consecutive days. For two of the dogs, the effects of mecamylamine were first tested on behavior maintained by nicotine (30 μg/kg/infusion) and then on behavior maintained by cocaine (30 μg/kg/infusion). The order was reversed for the other two dogs.

FR schedule of water presentation. Under the FR schedule of water presentation, daily experimental sessions were conducted Monday through Friday with three dogs. The schedule parameters were identical to those used to study drug self-administration, described above. Thus, during each of 16 trials, the rear stimulus light was illuminated and the 15th lever-pressing response produced 10 ml of water accompanied by illumination of the front stimulus light for 15

sec. A 240 sec, unsignalled time-out separated successive trials; responses during the last 15 sec of the time-out postponed trial onset by 15 sec. After behavior was stable, mecamylamine (1 mg/kg i.v.) was given 30 min before the start of each session for five to seven consecutive sessions.

Computation of FR response rates. Overall rates of responding under the FR schedule were computed for each session by dividing total responses in each FR trial by the total time the trials were in effect each session. Responses that occurred and time that elapsed during time-out periods and during the first FR trial of each session were not included in computations. For analysis of local patterns of responding within FR trials, running rates of responding also were computed from the 3rd to the 15th response in each FR trial and averaged for the entire session.

Progressive-ratio schedule of drug infusion. The progessive-ratio schedule has been previously described in more detail (Risner and Silcox, 1981). Two dogs had access to a single response-contingent drug infusion during each of three 1-hr trials per day (Monday through Saturday) beginning at 10:30 A.M., 1:30 P.M. and 4:30 P.M. These trials were signalled by illumination of the rear stimulus light. Initially, 30 responses were required to produce a drug infusion and end the trial. If a dog failed to complete the response requirement within 1 hr, the trial ended without drug infusion. If the dog completed at least one FR each day, the number of responses required to obtain one infusion each trial was increased the following day (see table 1). The response requirement was increased until the dog failed to complete any FR requirement for two consecutive days, *i.e.*, until they reached a break point. Four doses each of nicotine (50, 100, 200 and 400 μg/kg/infusion) and cocaine (200, 400, 800 and 1600 μg/kg/infusion) were tested. Drugs were delivered i.v. over 4 min while the front stimulus light was illuminated. The order of testing was randomly determined for both dogs and saline (0.1 ml/kg/infusion) was included in the treatment series.

Physiological Studies

Subjects. The subjects for the physiological studies were four male (10.6–12.2 kg) and two female (7.9 and 8.1 kg) purebred beagle dogs obtained from commercial suppliers. Housing conditions and animal care procedures were identical to those described for the dogs in the behavioral studies.

Procedure. The dogs were trained to rest quietly in a sling (Alice King Chatham Medical Arts, Los Angeles, CA) while loosely restrained. At weekly intervals they were given i.v. infusions of nicotine (3, 30 or 300 μg/kg), mecamylamine (1.0 mg/kg) or saline (0.1 ml/kg. The heart rate (determined by auscultation), body temperature (measured by a rectal thermistor probe inserted 15 cm) and pupillary diameter (determined photographically by the method of Marquardt *et al.*, 1967) were recorded at timed intervals after the infusion. Base-line observations on these same three parameters were made four times at 10-min intervals before drug administration. In addition to the physiologic measures, the general appearance and behavior of the dogs were noted throughout the experiment. All infusions were made *via* the cephalic vein over a period of 15 sec. Observations were made between 5 and 90 min after drug administration. At least three dogs were tested at each dose of nicotine or mecamylamine; all dogs were tested with saline. Order of treatment was randomly determined for each dog.

Drugs. Nicotine hydrogen (+)-tartrate (Pfaltz & Bauer Inc., Stamford, CT), cocaine hydrochloride (Mallinckrodt Chemical Works, St. Louis, MO) and mecamylamine hydrochloride (Merck Sharpe & Dohme, West Point, PA) were dissolved in 0.9% saline solution. Solutions were diluted so that doses could be infused in a volume of 0.1 ml/kg b.wt. i.v. (FR and physiological studies) or 0.4 ml/kg b.wt. i.v. (progressive-ratio studies). All doses are expressed as the salt.

TABLE 1

Progressive-ratio protocol used to assess the relative reinforcing efficacy of cocaine and nicotine

If the number of infusions was 1, 2 or 3, 0 (1 day) or 0 (2 consecutive days); then, the corresponding changes in the schedule were: increase FR to next step, no increase and lower FR to 30, respectively.

Step No.	FR Size	Step No.	FR Size
1	30	9	630
2	60	10	870
3	90	11	1110
4	150	12	1350
5	210	13	1830
6	270	14	2310
7	390	15	2790
8	510	16	3750

Results

FR schedule of drug infusion. Both nicotine and cocaine were self-administered above saline levels, with the maximum mean number of infusions occurring at a dose of 30 μg/kg of nicotine (13.2 infusions) and 100 μg/kg of cocaine (14.9 infusions). For both drugs, there was an inverted "U"-shaped relationship between dose per infusion and number of infusions per session (table 2; fig. 1, upper right panel). Overall response rates also varied systematically as a function of dose per infusion (table 2; fig. 1, left panel). With nicotine, mean overall rate reached a maximum of 0.29 responses/sec at 30 μg/kg, then decreased at higher doses. For cocaine, the maximum mean overall rate was 0.69 responses/sec at a dose of 10 μg/kg; higher doses were associated with lower rates of responding. The "running" rates of responding (*i.e.*, the rate during the last 12 responses of the ratio) reached a maximum of 1.90 and 2.66 responses/sec at a dose of 10 μg/kg of nicotine and cocaine, respectively (fig. 1, lower right panel). There was minimal, if any, responding by the dogs during the time-out intervals separating successive trials; the time-out response rate rarely exceeded 0.01 response/sec. Emesis was occasionally seen during or shortly after the sessions when the dogs were tested with the two highest doses of nicotine. Representative cumulative-response records depicting the temporal pattern of responding by one dog are shown in the upper panel of figure 2.

Presession treatment with mecamylamine altered behavior which was maintained under the schedule of nicotine infusion but not under the schedule of cocaine infusion (figs. 2 and 3). Under the schedule of nicotine infusion, the mean number of infusions per session dropped from 13.9 during the control period to 11.0 on the first session of mecamylamine treatment and continued to decline over the 7-day treatment period to 4.7 (fig. 3, upper panel). Similarly, the overall response rate dropped to 34.5% of control on the first session and continued to decline over the treatment period to 7.0% of control on the last day (fig. 3, lower panel). The temporal pattern of nicotine self-administration during mecamylamine treatment was much like that seen with saline (fig. 2, upper panel). The first two to three FR trials in each session were rapidly completed, resulting in infusions separated by the shortest possible time-out interval. Subsequent infusions, if they occurred, were separated by long periods of minimal, if any, responding. When responding was maintained by cocaine infusions, rather than nicotine infusions, 7 days of mecamylamine treatment had little effect on responding or on the number of infusions received each session.

FR schedule of water presentation. Responding was well maintained by water presentation under the FR schedule. Mean overall response rates for the four control sessions preceding mecamylamine treatment were 0.61, 1.21 and 1.19 responses/sec for the three dogs studied and all dogs obtained the maximum of 15 water presentations each session. There was no

change in responding during the subsequent 5 to 7 days of mecamylamine treatment, with mean overall response rates during the last days of mecamylamine treatment of 0.66, 1.11 and 1.22 responses/sec for the three dogs, with all dogs obtaining 15 water presentations per session.

Progressive-ratio schedule of drug infusion. All doses of nicotine and cocaine maintained self-administration behavior at FR values above those obtained with saline (fig. 4). In general, there was a biphasic relationship between dose and break point. Thus, across the lower portion of the dose range, larger doses maintained higher FR values, but at the highest doses tested there was a downturn in the function. With both subjects, the highest FR values were maintained by cocaine, followed by nicotine and then saline. For example, dog D-2968 made as many as 3750 responses during a single 1-hr trial when the cocaine dose was 0.4 or 0.8 mg/kg (fig. 4, left panel; fig. 2, lower panel). When the same dog was tested with nicotine, the highest FR completed was 450 at a dose of 0.2 mg/kg (fig. 4, left panel; fig. 2, lower panel).

In addition to the considerable differences in maximum break points associated with cocaine *vs.* nicotine, there were other appreciable differences in the behavior maintained by these drugs. As seen in the cumulative-response records (fig. 2, lower panel), the temporal patterns of responding within each session were different for the two drugs. The rates of responding appeared to be lower and there were more pauses in responding

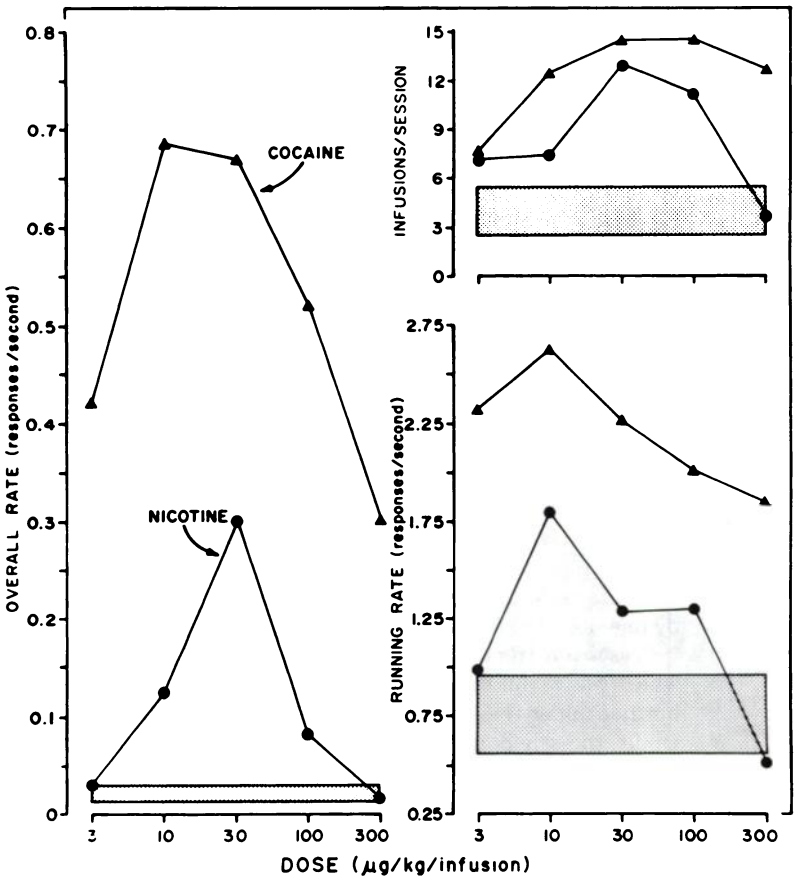

Fig. 1. Effects of nicotine (●) and cocaine (▲) dose per infusion on the number of infusions self-administered per session (upper right panel), overall response rate (left panel) and running response rate (*i.e.*, the rate during the last 12 responses of the ratio; lower right panel). Each point represents the mean of data from four beagle dogs obtained on the last 4 days of testing with each dose. The stippled band across the lower portion of each panel represents the effects of saline (±1 S.E.M.).

TABLE 2

Mean values of overall response rates and number of infusions per session (shown in parentheses) for individual dogs under the FR schedule of nicotine or cocaine infusion[a]

The treatment order is indicated by the numerical superscripts.

Dog	NaCl[a]	Size of Dose (µg/kg/infusion)				
		3	10	30	100	300
				Nicotine		
3880	0.000 (0.0)^{9}	0.025 (7.8)^{7}	0.006 (2.5)^{3}	0.05 (10.0)^{1}	0.024 (7.8)^{2}	0.004 (1.8)^{8}
4220	0.020 (6.5)^{4}	0.014 (5.3)^{9}	0.102 (5.3)^{7}	0.084 (13.8)^{6}	0.039 (10.5)^{5}	0.016 (6.8)^{8}
4123	0.021 (6.5)^{6}	0.040 (8.3)^{10}	0.340 (14.8)^{5}	0.920 (15.0)^{4}	0.190 (12.7)^{3}	0.004 (0.75)^{7}
4129	0.040 (10.3)^{7}	0.025 (8.0)^{9}	0.026 (7.3)^{6}	0.120 (13.8)^{4}	0.070 (13.3)^{5}	0.023 (5.5)^{8}
				Cocaine		
3880		0.004 (2.0)^{10}	0.022 (6.5)^{5}	0.13 (14.0)^{4}	0.78 (14.8)^{11}	0.048 (10.8)^{6}
4220		0.014 (5.5)^{11}	0.450 (14.8)^{3}	0.10 (15.0)^{2}	0.18 (15.0)^{1}	0.690 (14.8)^{10}
4123		1.240 (15.0)^{11}	2.020 (15.0)^{9}	2.06 (15.0)^{8}	0.65 (14.8)^{1}	0.037 (10.5)^{2}
4219			0.265 (13.7)^{3}	0.35 (14.7)^{2}	0.46 (15.0)^{1}	0.216 (14.7)^{10}

[a] The mean of results from the 4th to 7th sessions at each condition is shown.

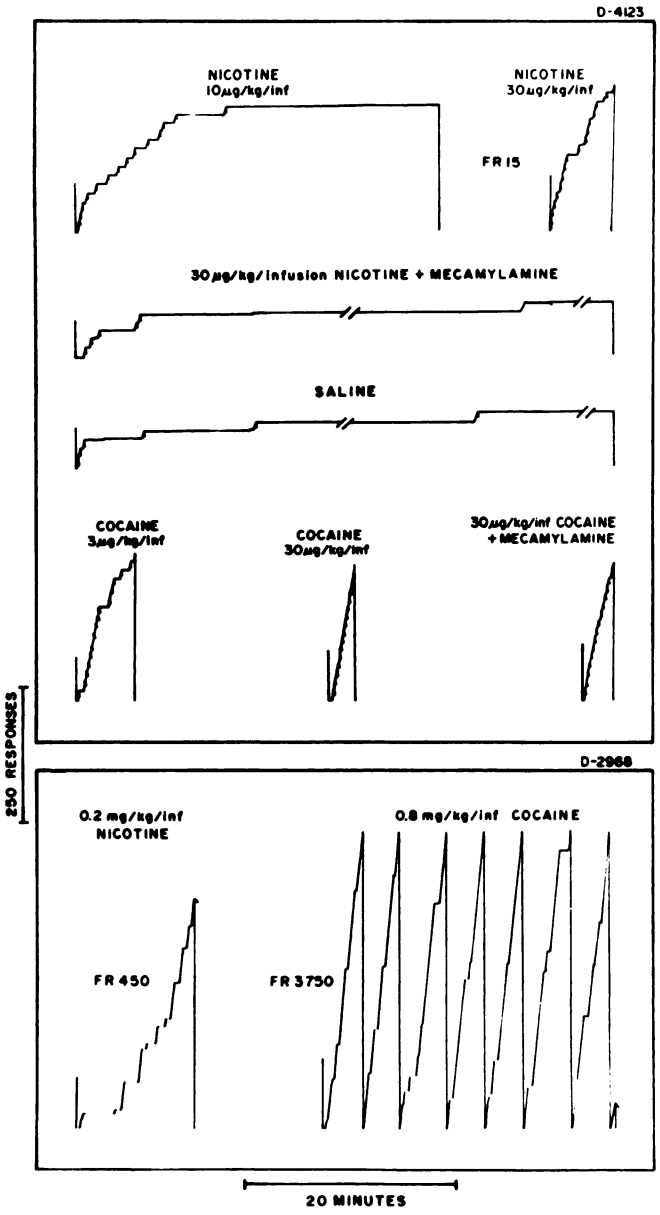

Fig. 2. Representative cumulative-response records depicting the temporal pattern of responding maintained by i.v. infusions (inf) of nicotine or cocaine under the multiple FR 15, time-out 240-sec schedule (upper panel) or progressive-ratio schedule (lower panel). Short diagonal marks on the cumulative records indicate drug infusions. After each injection there was a time-out period during which the recorder did not operate. Pairs of diagonal hash marks represent deleted segments of the records during which no responding occurred.

when the dogs were tested with nicotine rather than cocaine. The percentage of days on which all three of the available infusions were self-administered during each break point determination was consistently higher with cocaine than nicotine (table 3). The dogs self-administered three infusions per day, an average of 75.5% of the time when tested with cocaine, but only 38.8% of the time when tested with nicotine.

Physiological studies. Nicotine produced dose- and time-related changes in all three physiological parameters (figs. 5 and 6). For example, after the administration of 3 or 30 µg/kg of nicotine, rectal temperature was significantly elevated above that seen with saline throughout most of the 90-min observation period; 300 µg/kg initially produced an appreciable increase (+0.23°C) followed by a precipitous decrease (−0.5°C) and gradual return to levels similar to those seen with saline. The effects of nicotine on heart rate were qualitatively similar, regardless of dose. Five minutes after drug administration, there

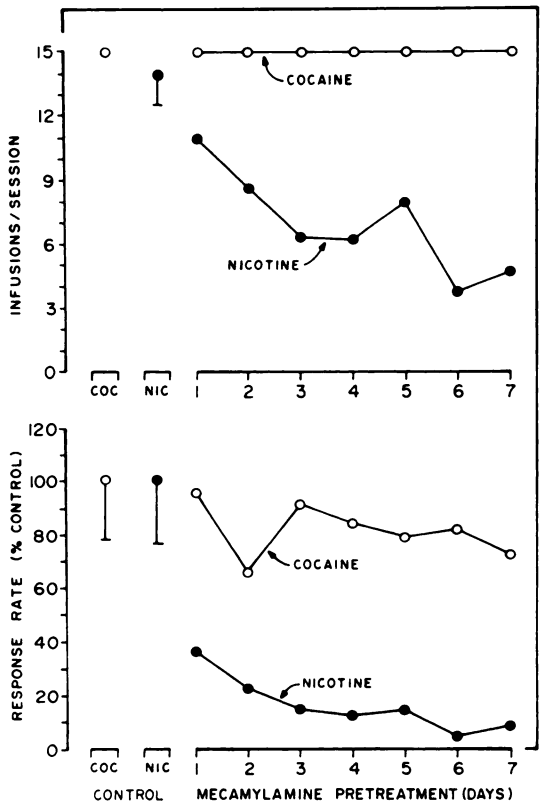

Fig. 3. Effects of mecamylamine on the number of nicotine (NIC) or cocaine (COC) infusions self-administered per session (upper panel) or the rate of responding (expressed as a percentage of control) maintained by NIC or COC infusions (lower panel). Control values shown at COC or NIC show the mean of data obtained during the four sessions preceding the start of mecamylamine treatment. Vertical lines drawn through the data points depict 1 S.E.M.

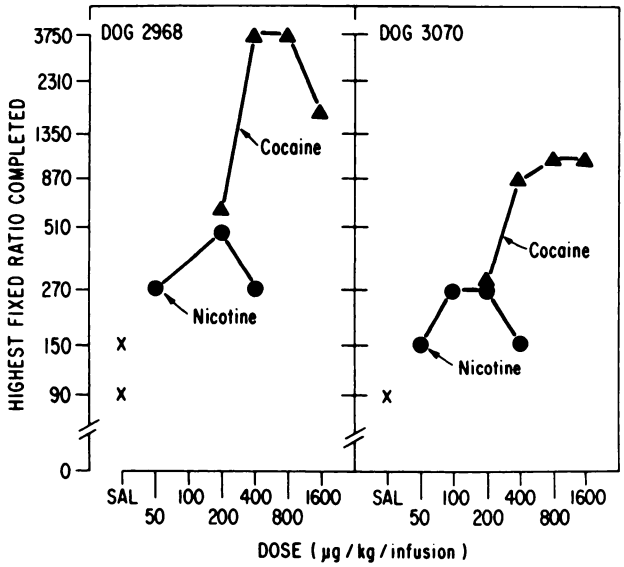

Fig. 4. The highest FR completed by two dogs for i.v. infusions of either nicotine (●), cocaine (▲) or saline (SAL) (×) under a progressive-ratio schedule. Each point represents a single determination at the selected dose and drug. Dog 2968 was tested twice with SAL. Note the logarithmic scale used for the ordinate.

TABLE 3

Comparison of cocaine and nicotine under the progressive-ratio schedule

Dog	Drug	Break Point		Before Break Point	
		Days[a]	All Infusions[b]	Days[c]	Infusions[d]
	(μg/kg/infusion)				
2968	Cocaine				
	200	9	7 (78)[e]	1	2
	400	18	15 (83)	2	3
	800	16	14 (88)	1	2
	1600	15	14 (93)	1	3
	Nicotine				
	50	7	4 (57)	2	3
	200	15	7 (47)	1	1
	400	12	9 (75)	1	3
3070	Cocaine				
	200	9	6 (67)	1	2
	400	10	5 (50)	1	1
	800	11	8 (73)	1	1
	1600	11	8 (73)	2	1
	Nicotine				
	50	4	1 (25)	2	2
	100	7	1 (14)	1	1
	200	5	1 (20)	1	2
	400	6	2 (33)	1	1

[a] Number of days to reach the break point.
[b] Number of days on which all three infusions were self-administered.
[c] Number of days at the FR value immediately before the break point.
[d] Number of infusions self-administered at the ratio before the break point.
[e] Numbers in parentheses give the percentage of days to reach the break point on which all three infusions were self-administered.

was an increase in heart rate that was positively correlated with dose. With 3 or 30 μg/kg, the increase lasted for only 10 to 20 min. In contrast, the increase in heart rate produced by 300 μg/kg was evident for 60 min after drug administration. Nicotine had a biphasic effect on pupil size. Regardless of dose, pupillary diameter increased by approximately 0.5 mm over base line within 5 min after drug administration. The mydriatic effect of nicotine was brief; pupillary size decreased between 10 and 30 min after nicotine infusion. With few exceptions, pupillary diameter was not appreciably different from saline for the remainder of the observation period.

The effects of an i.v. infusion of 1.0 mg/kg of mecamylamine were more marked than those seen with nicotine. At 20 min after drug administration, the average change in heart rate in the four dogs studied was +26 beats/min, the average change in pupillary diameter was +0.8 mm and the average change in rectal temperature was −0.3°C. The area under the time action curve for the first 20 min after mecamylamine infusion was +356 (±177.1 S.D.) for heart rate, +10.4 (±7.8 S.D.) for pupillary diameter and −2.9°C (±0.7°C S.D.) for rectal temperature.

Discussion

Under a FR schedule, lever-pressing responses by beagle dogs were consistently maintained by i.v. infusions of nicotine or cocaine when 4-min time-out periods separated successive FR trials. With infusions of saline or the lowest dose of nicotine or cocaine, rates of responding were very low and only about one-third of the 16 infusions possible each session was received. As the dose per infusion of nicotine or cocaine was increased, both overall and running rates of responding first increased, reaching a maximum at 10 to 30 μg/kg/infusion, and then decreased. Over the full range of doses studied, overall and running rates of responding were much higher under the schedules of cocaine

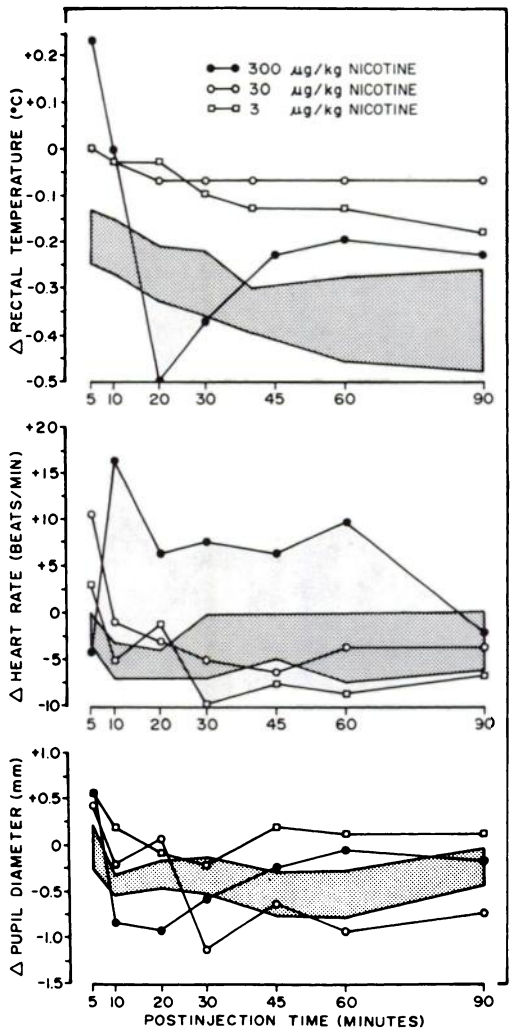

Fig. 5. Time-action curves for i.v. administered nicotine (3 to 300 μg/kg) or saline (stippled band; ±1 S.E.M.) on changes in rectal temperature (upper panel), heart rate (middle panel) or pupil diameter (lower panel). From three to five dogs were tested at each dose of nicotine; all of the dogs (N = 6) were tested with saline.

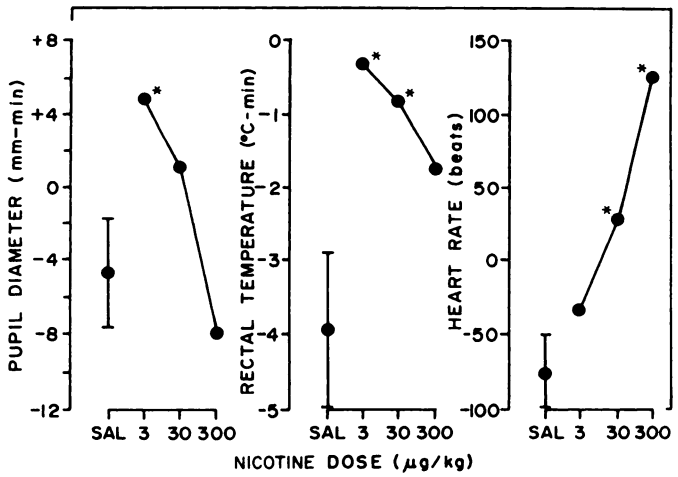

Fig. 6. Areas under the time-action curves for the effects of i.v. nicotine or saline (SAL) on pupil diameter (left panel), rectal temperature (center panel) and heart rate (right panel). Each point is the mean area under the time-action curve for the first 20 min after nicotine administration. From three to five dogs were tested at each dose; all of the dogs (N = 6) were tested with SAL. Vertical lines drawn through the SAL points depict ±1 S.E.M. Asterisks indicate $p < .05$ when compared with SAL.

infusion than under the schedules of nicotine infusion. Over a wide dose range, the number of cocaine infusions per session also was higher than the number of nicotine infusions per session. Although cocaine was more effective than nicotine in maintaining high rates of responding, FR patterns of responding maintained by nicotine and cocaine were similar. A period of no responding at the start of each FR trial was followed by a change to steady responding at a high rate until nicotine or cocaine was infused. At doses of 10 to 100 μg/kg/infusion, running rates of responding exceeded 1.0 response/sec with nicotine and 2.0 responses/sec with cocaine. Thus, both nicotine and cocaine functioned effectively as reinforcers to maintain self-administration behavior of beagle dogs under a FR schedule of i.v. drug infusion. When nicotine and cocaine were previously compared in squirrel monkeys under fixed-interval and second-order schedules of i.v. drug infusion, cocaine maintained higher maximal rates of responding in some subjects but patterns of responding maintained by the two drugs were highly similar (Goldberg and Spealman, 1982; Spealman and Goldberg, 1982).

The doses of nicotine that maintained FR responding by beagle dogs in the present experiment were similar to those previously reported to maintain responding by squirrel monkeys under fixed-interval and second-order schedules of i.v. drug infusion (Goldberg *et al.*, 1981; Goldberg and Spealman, 1982; Spealman and Goldberg, 1982). In those experiments, as in the present experiments, the schedule parameters imposed a maximum frequency of infusion of about once every 4 to 6 min and each session ended after 10 to 12 infusions. Responding by squirrel monkeys was poorly maintained by 3 μg/kg infusion of nicotine, was well maintained by nicotine doses ranging from 10 to 100 μg/kg and at higher doses of nicotine response rates decreased and emesis occurred. Under the fixed-interval schedule, appropriate doses of nicotine maintained a characteristic pattern of accelerated responding within each fixed-interval component; under the second-order schedule, brief light stimuli that were occasionally associated with nicotine infusions controlled characteristic FR patterns of responding and high running rates of responding. Thus, in different species and under various schedules of reinforcement, i.v. infusions of nicotine, or stimuli associated with infusions of nicotine, can maintain characteristic schedule-controlled rates and patterns of responding.

When nicotine and cocaine were compared under the progressive-ratio schedule in the present experiment, the maximum FR value at which responding was maintained (break point) depended on the dose. As the dose per infusion of nicotine or cocaine increased, the break point first increased and then, at the highest dose, either remained flat or decreased. Such relationships between dose per infusion and maximum FR value appear characteristic of responding maintained by drug infusion under progressive-ratio schedules (Yanagita, 1973; Griffiths *et al.*, 1978; Bedford *et al.*, 1978; Risner and Silcox, 1981). In the present study, the maximum FR values at which responding was maintained were much higher with cocaine than with nicotine, although nicotine maintained responding at higher FR values than saline. Nicotine break points were comparable to those seen when mazindol was tested under identical experimental conditions in a previous study (Risner and Silcox, 1981).

Cocaine has been compared directly under progressive-ratio schedules with a variety of other drugs, including amphetamine (Yanagita, 1973; Risner and Silcox, 1981), SPA (1,2-diphenyl-1-dimethyl-aminoethane) and methamphetamine (Yanagita, 1973), amphetamine derivatives such as diethylpropion, chlorphentermine and fenfluramine (Griffiths *et al.*, 1978; Risner and Silcox, 1981), methylphenidate and secobarbital (Griffiths *et al.*, 1975) and mazindol (Risner and Silcox, 1981). Although a wide range of doses were studied and schedule details were varied in many of these experiments, cocaine consistently maintained responding at higher FR values than any of the other drugs tested.

Mecamylamine appears to be an effective and relatively specific antagonist of the behavioral actions of nicotine. In previous experiments, mecamylamine antagonized both the rate-increasing and the rate-decreasing effects of nicotine when behavior was maintained in rats or squirrel monkeys under fixed-interval and FR schedules of food presentation, water presentation or termination of a stimulus associated with electric shock (Morrison *et al.*, 1969; Stitzer *et al.*, 1970; Spealman *et al.*, 1981); mecamylamine also antagonized the discriminative-stimulus effects of nicotine in rats (Morrison and Stephenson, 1969; Schechter and Rosecrans, 1972; Hirshhorn and Rosecrans, 1974; Meltzer *et al.*, 1980). When behavior of squirrel monkeys was maintained under fixed-interval schedules of i.v. drug infusion, presession treatment with 1.0 mg/kg of mecamylamine reduced responding maintained by nicotine infusions to saline-control levels, but had no effect on responding maintained by cocaine infusions (Spealman and Goldberg, 1982). Under other conditions, both i.v. infusion of nicotine and delivery of electric shock served as punishers to suppress food-maintained responding by squirrel monkeys (Goldberg and Spealman, 1982, 1983); presession treatment with 0.1 to 0.3 mg/kg of mecamylamine reversed the suppression of responding produced by nicotine infusions but failed to reverse the suppression of responding produced by electric shocks. In the present experiment, mecamylamine was also an effective and relatively specific antagonist of the behavioral effects of nicotine. When 1.0 mg/kg of mecamylamine was administered before every session, responding maintained by nicotine infusion under the FR schedule was reduced to saline-control levels within a few sessions. In contrast, responding maintained by either cocaine infusion or water presentation under the same FR schedule was not reduced by mecamylamine treatment.

Although the dose of mecamylamine used in the present experiment had no effect on responding maintained by water presentation or cocaine infusion, it did have marked physiological effects. After the i.v. administration of 1.0 mg/kg of mecamylamine to unanesthetized beagle dogs, heart rate and pupil diameter were markedly increased and rectal temperature was markedly decreased. These physiological changes are characteristic of autonomic ganglionic blockade (Taylor, 1980). The magnitudes of the physiological changes produced by 1.0 mg/kg of mecamylamine were greater than those produced by any of the doses of nicotine studied. For example, the maximum area under the time-action curve for the effect of the high dose of nicotine (300 μg/kg) on heart rate was +140 beats, whereas that for 1.0 mg/kg of mecamylamine was +356 beats.

The effects of nicotine on heart rate, temperature and pupil diameter are in general agreement with previous results from animal and human studies. When administered i.v. to unanesthetized beagle dogs, nicotine produced increases in heart rate and pupillary dilation followed by constriction. Nicotine has previously been reported to produce tachycardia and elevated blood pressure when administered i.v. in dogs (Gebber, 1969) and humans (Argue, 1974; Kumar *et al.*, 1976) and to produce increases in pupil size in humans when administered by inhalation as a component of tobacco smoke (Roberts and Adams, 1969). Even more marked effects of nicotine on heart rate and pupil size might have been found had observations been made earlier than 5 min after drug administration.

Nicotine also has been reported to produce hypothermia when administered i.v. or i.p. or i.c.v. to mice (Staib and Baudia, 1972) or i.c.v. to unanesthetized cats or rhesus monkeys (Hall, 1972; Hall and Myers, 1971). In the present experiment, nicotine produced an elevation in rectal temperature in unanesthetized beagle dogs at doses of 3 to 30 μg/kg. At a high dose of 300 μg/kg, nicotine had a biphasic effect consisting of an initial increase in temperature followed by a very marked but short-lasting hypothermia.

The effectiveness of i.v. nicotine infusion as a reinforcer of schedule-controlled behavior in the present experiment and in previous experiments by Goldberg and colleagues (1981, 1982) is in contrast to many previous reports that nicotine either was ineffective in maintaining responding (Griffiths *et al.*, 1979) or at best maintained only very low rates of responding that differed little from those maintained by saline infusion (Deneau and Inoki, 1967; Lang *et al.*, 1977; Latiff *et al.*, 1977; Yanagita, 1977; Singer *et al.*, 1978; Hanson *et al.*, 1979; Ator and Griffiths, 1981; Dougherty *et al.*, 1981). The similarities in the maximal frequency of infusion (every 4–5 min) specified by the temporal parameters of the schedules used in the present experiment with beagle dogs and in previous experiments with squirrel monkeys suggest that the factors controlling frequency of infusion may be important in determining the rates and patterns of responding maintained by nicotine infusion. In most previous experiments, every response or every few responses produced an infusion of nicotine and as response rates increased frequency of infusion also increased, resulting in relatively large cumulative doses within a short period of time. In one experiment with baboons (Griffiths *et al.*, 1979), frequency of infusion was limited by interposing 3-hr time-out periods between successive FR trials, yet nicotine was no more effective than saline in maintaining responding. The different results obtained in the present experiment and those by Griffiths *et al.* (1979) may be related to the markedly different time-out durations employed, a maximal frequency of infusion greater than once every 3 hr possibly being necessary for nicotine to function as a reinforcer. Although it is unlikely that beagle dogs and squirrel monkeys are uniquely sensitive to the reinforcing effects of nicotine, further studies with other species using schedule conditions similar to those used successfully with beagle dogs and squirrel monkeys are needed.

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Send reprint requests to: Dr. Marcus E. Risner, National Institute on Drug Abuse, Addiction Research Center, P. O. Box 12390, Lexington, KY 40583.