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Control of Behavior by Intravenous Nicotine Injections in Laboratory Animals[1]

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GOLDBERG, S. R., R. D. SPEALMAN, M. E. RISNER AND J. E. HENNINGFIELD. *Control of behavior by intravenous nicotine injections in laboratory animals.* PHARMACOL BIOCHEM BEHAV **19**(6) 1011–1020, 1983.—A series of recent studies are reviewed which demonstrate that behavior can be controlled by nicotine injections in different ways depending on the behavioral history of the subject and the schedule of reinforcement under which nicotine is administered. Lever-pressing responses by squirrel monkeys and beagle dogs were maintained well above saline-substitution levels by injections of 10 to 30 μg/kg of nicotine under fixed-ratio schedules of nicotine injection. Lever-pressing responses by squirrel monkeys also were well maintained by injections of 30 to 300 μg/kg of nicotine under a fixed-interval schedule of nicotine injection. The highest rates of responding were maintained by injections of 10 to 30 μg/kg of nicotine under second-order schedules in which responding by squirrel monkeys produced brief-light presentations which were only occasionally paired with nicotine injection. Under other conditions, however, response-produced injections of these same injection doses of nicotine (10 to 30 μg/kg) suppressed food-maintained fixed-ratio responding by squirrel monkeys during the punishment component of a multiple schedule. Finally, under a schedule of nicotine postponement, injection doses of 30 to 56 μg/kg of nicotine maintained responding that prevented, rather than produced, nicotine injections. These findings indicate that nicotine may control smoking behavior of humans in very complex and divergent ways depending on prevailing environmental conditions.

Nicotine Schedules of reinforcement Squirrel monkeys Dogs Self-administration

NICOTINE is believed to be the major constituent of tobacco responsible for the maintenance of persistent smoking behavior. Until recently, however, it had been difficult to demonstrate consistent reinforcing effects of nicotine in controlled laboratory situations. A number of investigators had found that nicotine maintained very low rates of responding leading to its injection by laboratory animals under conditions in which injection of other drugs maintained high rates of responding [13]. On the basis of laboratory studies with human subjects, it had even been suggested that nicotine might have aversive properties that limit rather than maintain smoking behavior [16]. Recently, several studies have demonstrated that nicotine can function effectively as a reinforcer of IV self administration behavior under certain intermittent schedules of reinforcement in laboratory animals [5, 9, 11, 22]. Under other conditions, however, nicotine either suppressed responding leading to its injection [9,10] or maintained responding that postponed its scheduled injection [21].

The purpose of the present paper is to review these recent studies on the control of behavior by nicotine injections in laboratory animals. These studies indicate that behavioral history and the current schedule conditions relating responding and injections are fundamental determinants of the ways in which nicotine controls behavior.

GENERAL METHOD

Monkeys

Mature male squirrel monkeys surgically prepared with chronic venous catheters were studied under various schedules of IV nicotine injection. Short experimental sessions, lasting 60 to 120 min were conducted once a day, Monday through Friday. Between experimental sessions monkeys lived in individual home cages with food and water freely available. During the sessions monkeys sat in Plexiglas chairs and were placed in ventilated, sound-attenuating chambers provided with white noise to mask extraneous

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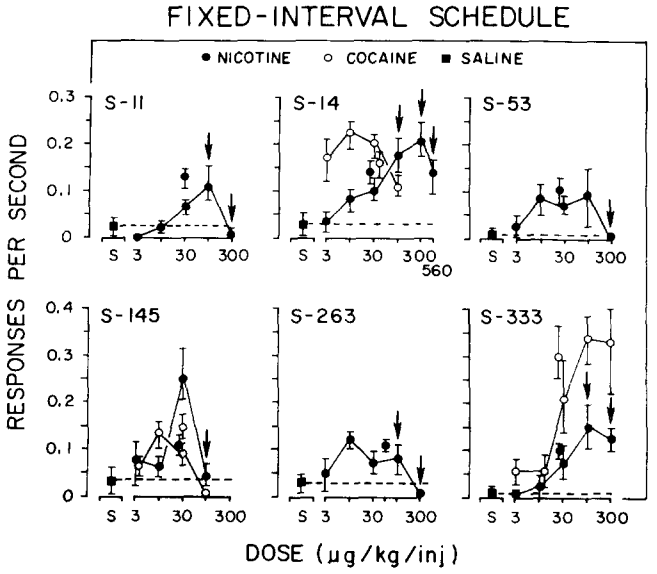

FIG. 1. Effects of dose on responding maintained by IV injections of nicotine or cocaine under the 5-min fixed-interval schedule in squirrel monkeys. Abscissas: dose, log scale; ordinates: overall rate of responding. Points are means based on the last three sessions at each dose or when saline was substituted for the drugs (points at S and dashed horizontal lines); brackets show ranges except where contained within the point. Unconnected circles show responding maintained by nicotine or cocaine during initial exposure to these doses. Arrows indicate doses of nicotine that produced vomiting during or shortly after the experimental session. (From Spealman and Goldberg [22] with permission).

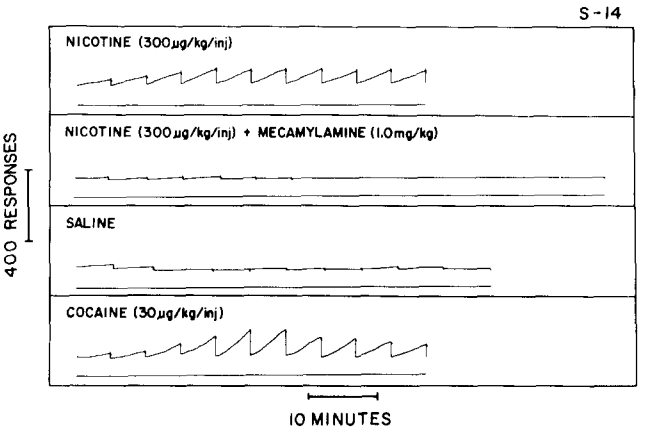

FIG. 2. Representative performances maintained by IV injections of nicotine or cocaine under the 5-min fixed-interval schedule in a squirrel monkey (S-14). Abscissas: time; ordinates: cumulative lever-pressing responses. Short diagonal strokes on the cumulative record and the resetting of the recording pen indicate injections of 300 µg/kg of nicotine (top record) or 30 µg/kg of cocaine (bottom record). After each injection there was a 1-min time-out period during which the recorder was stopped. Each record is taken from one of the last 3 days at the condition shown. The record in the second panel (nicotine + mecamylamine) shows approximately the first 1.5 hr of the session during which seven fixed-interval cycles were completed; no further responses occurred and the session ended after 2 hr. Each of the other records shows a complete session that ended after 10 fixed-interval cycles. Note that presession treatment with 1.0 mg/kg of mecamylamine or substitution of saline for nicotine (middle records) markedly reduced responding (From Goldberg and Spealman [9] with permission).

sounds. A response lever was mounted on a transparent wall in front of the monkey and different colored bulbs above the lever served as visual stimuli when illuminated. Injections were delivered through venous catheters connected by Teflon tubing to automatic syringe pumps located outside the chambers. The volume of each injection was 0.2 ml, infused over 200 msec.

Dogs

Male and female purebred beagle dogs prepared with chronic venous catheters lived in individual cages that were neither visually isolated nor sound attenuated. Food and water were continuously available. Short experimental sessions were conducted daily, Monday through Friday. The front door of each dog's living cage contained a response lever. Two white bulbs, one positioned above the front center and one above the rear center of the cage, served as visual stimuli when illuminated. Venous catheters were protected by harnesses which were connected by flexible cables to fluid swivels above the cages; the catheters were connected by plastic tubing which passed through the cables and swivels to automatic injection pumps outside the cages. The volume of each injection was 0.1 ml/kg b.wt., infused over 15 sec.

Drugs

Nicotine(+)-hydrogen tartrate and the hydrochloride salts of cocaine and mecamylamine were dissolved in 0.9% saline solution. All doses are expressed as the salts.

MAINTENANCE OF BEHAVIOR BY NICOTINE INJECTIONS

Fixed-Interval Schedules

With fixed-interval schedules of drug injection, the maximal frequency of injection is limited by the temporal parameters of the schedule and is independent of the rate of responding. In a recent series of experiments [9,22], squirrel monkeys responded under a 5-min fixed-interval schedule of IV nicotine or cocaine injection. In the presence of a green light, the first response to occur after five min produced an injection of drug followed by a one-min timeout period. During the timeout, the chamber was dark and responses had no programmed consequences. Sessions ended after the completion of 10 fixed intervals or two hr, whichever occurred first.

Figure 1 shows dose-response curves for six monkeys under the 5-min fixed-interval schedule of nicotine or cocaine injection. Each dose was studied for at least five consecutive sessions. In all monkeys, responding was well maintained by most doses of nicotine or cocaine. As the dose per injection was varied from 3 to 300 µg/kg, the overall rate of responding first increased and then decreased; when saline was substituted for drug, responding occurred irregularly and at very low rates. Of the three monkeys studied with both nicotine and cocaine, only one monkey (S-333) showed overall rates of responding that were higher with cocaine injections than with nicotine injections. Most intermediate doses of nicotine or cocaine maintained patterns of responding within the interval that were characteristic of fixed-interval schedules of reinforcement; a pause in responding at

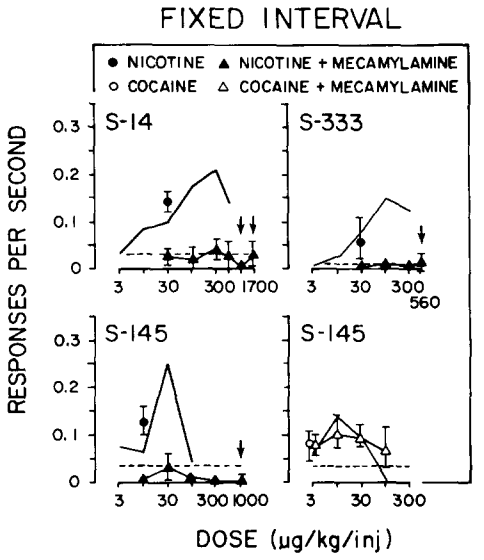

FIG. 3. Effects of daily treatment with mecamylamine (1.0 mg/kg, IM) on responding maintained by IV injections of nicotine or cocaine under the 5-min fixed-interval schedule in squirrel monkeys. Abscissas: dose of nicotine, log scale; ordinates: overall rate of responding. Unconnected circles show responding maintained by nicotine or cocaine alone; triangles show responding maintained by nicotine or cocaine after treatment with mecamylamine. Points are means based on the last three sessions at the doses specified; brackets show ranges except where contained within the point. Arrows indicate doses of nicotine in combination with mecamylamine that produced tremors during or shortly after experimental sessions. Solid lines without points show average response rates when the dose of nicotine or cocaine was varied before treatment with mecamylamine was begun; (replotted from Fig. 1) dashed horizontal lines show average response rates during saline substitution. (From Spealman and Goldberg [22] with permission).

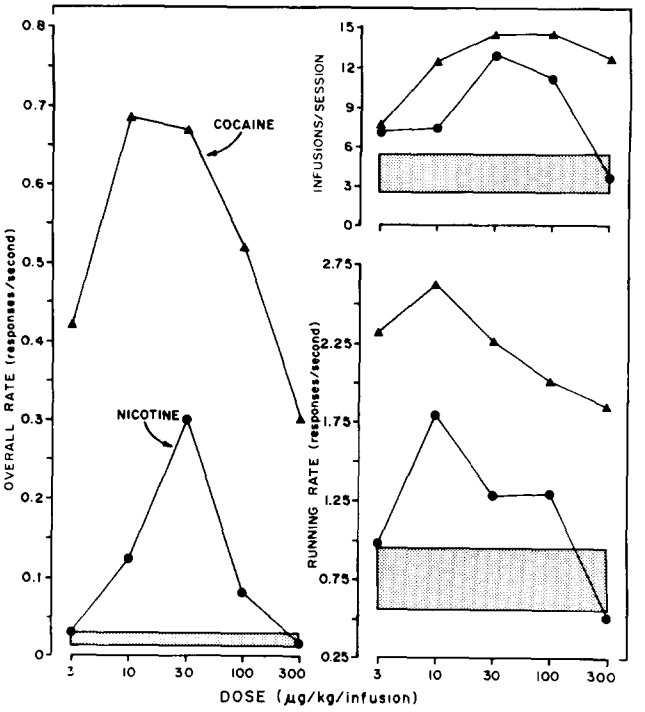

FIG. 4. Effects of dose on responding maintained by IV injections of nicotine (●) or cocaine (▲) under the 15-response fixed-ratio schedule in beagle dogs. Abscissas: dose, log scale; ordinates: number of infusions self-administered per session (upper right panel), overall rate of responding (left panel) and running rate of responding (i.e., the rate during the last 12 responses of the ratio; lower right panel). Point are means based on 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. (From Risner and Goldberg [15] with permission.)

the beginning of the interval was followed by acceleration of responding to a rate that was sustained until the end of the interval (Fig. 2). Although doses of nicotine above 30 μg/kg produced vomiting during experimental sessions, as indicated by arrows in Fig. 1, one or more of these high doses continued to maintain responding above saline-control rates in four of the six monkeys studied.

The nicotinic antagonist, mecamylamine, has been shown to block the direct effects of nicotine on schedule-controlled behavior [23,25]. After the dose-response curves shown in Fig. 1 were determined, the effects of presession treatment with mecamylamine were studied. The results are shown in Fig. 3. When 1.0 mg/kg mecamylamine was administered IM 30 min before each session, responding maintained by nicotine injections under the fixed-interval schedule fell to saline-control levels. Mecamylamine blocked the reinforcing effects of all doses of nicotine that previously had maintained responding in these monkeys. In contrast, mecamylamine had no effect on responding maintained under similar conditions by cocaine injections (Fig. 3; monkey S-145) or by food or electric shock [23]. Thus, mecamylamine appeared to be an effective and relatively specific antagonist of the reinforcing actions of nicotine.

Fixed-Ratio Schedules

With fixed-ratio schedules of drug injection, each injection follows the completion of a constant number of responses. Because the maximal frequency of injection under these conditions depends on the rate of responding, injections can occur in rapid succession. Overall rates of responding maintained by nicotine injection under these conditions have generally been either very low or indistinguishable from those maintained by saline injections [13].

In recent experiments [15], dogs responded under fixed-ratio schedules of nicotine or cocaine injection in which a long timeout period followed each injection, thus limiting maximal frequency of injection. In the presence of one stimulus light, the 15th lever-pressing response produced an injection of drug accompanied by illumination of a second stimulus light. Each injection was followed by a 4-min timeout. Responses during the timeout had no consequences, except during the last 15 sec when each response postponed onset of the next fixed-ratio trial by 15 sec. If a fixed-ratio trial was not completed within 10 min, it ended automatically without injection. Sessions ended after 16 fixed-ratio trials.

Figure 4 shows dose-response curves for four dogs under the fixed-ratio schedule of nicotine or cocaine injection. Each dose was studied for seven consecutive sessions. In all dogs, responding was well maintained by injection doses of 10 to 100 μg/kg of nicotine or 3 to 300 μg/kg of cocaine. As the dose of either drug was increased, the overall rate of responding, as well as the running rate of responding (average rate calculated from the 3rd to the 15th response in each

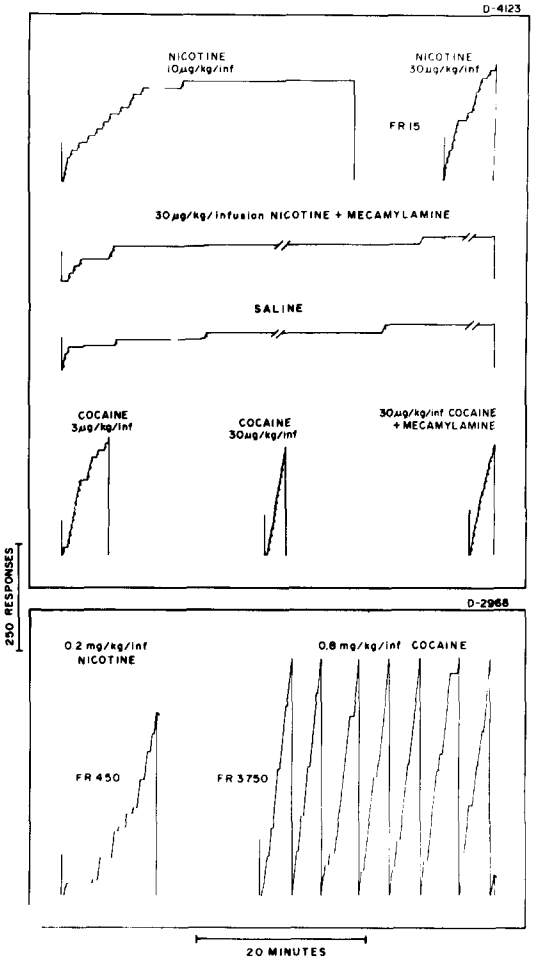

FIG. 5. Representative performances maintained by IV injections of nicotine or cocaine in beagle dogs under the fixed-ratio schedule (upper panel, dog D-4123) or progressive-ratio schedule (lower panel, dog D-2968). Abscissas: time; ordinates: cumulative lever-pressing responses. Short diagonal marks on the cumulative records indicate drug injections. After each injection there was a timeout period during which the recorder did not operate. Pairs of diagonal hash marks represent deleted segments of the records during which no responding occurred. From Risner and Goldberg [15] with permission).

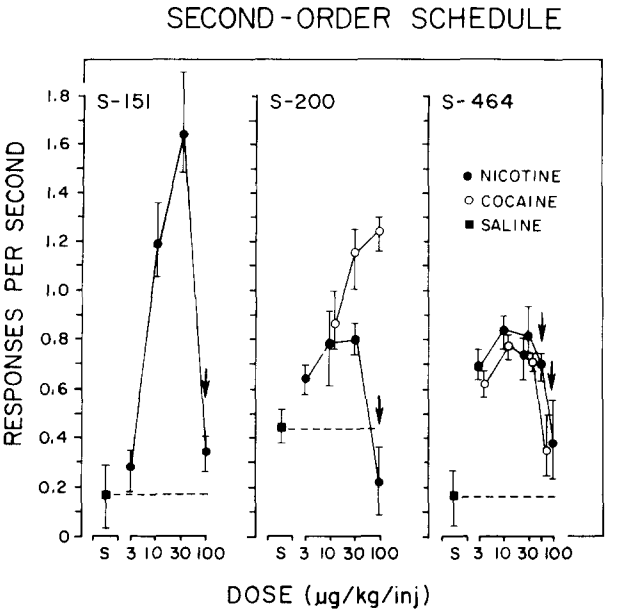

FIG. 6. Effects of dose on responding maintained by IV injections of nicotine or cocaine under the second-order fixed-interval schedule in squirrel monkeys. Abscissas: dose, log scale; ordinates: overall rate of responding. Points at S are means based on the last session of each of three saline-substitution periods (monkeys S-151 and S-200) or on the last three sessions of a single substitution period (monkey S-464); other points are means based on the last three sessions at the doses specified. Brackets show ranges. The 30 μg/kg injection dose of nicotine was studied twice in monkey S-464; the unconnected point shows responding during the first exposure to this dose. Arrows indicate doses of nicotine that produced vomiting during or shortly after experimental sessions. (From Spealman and Goldberg [22] with permission.)

fixed-ratio trial), first increased and then decreased. When saline was substituted for nicotine or cocaine, responding occurred at very low rates. Vomiting sometimes occurred during or shortly after sessions at the two highest doses of nicotine. Recently, nicotine also has been reported to maintain responding by squirrel monkeys under a 10-response fixed-ratio schedule of IV drug injection with one-min timeouts following each injection [5]. Responding was maintained above saline substitution levels by injection doses of 3 to 30 μg/kg of nicotine in three of four monkeys studied.

In contrast to the generally similar overall rates of responding maintained by nicotine and cocaine injections under fixed-interval schedules in squirrel monkeys [9,22], overall and running rates of responding in the dog were consistently much higher under the fixed-ratio schedule of cocaine injection than under the comparable schedule of nicotine injection. Differences between nicotine and cocaine also were found when they were compared in other dogs under a progressive ratio schedule [15]. Under this schedule, the fixed-ratio requirement was increased daily until responding was no longer maintained. Cocaine maintained considerably higher fixed-ratio values than did nicotine under the progressive-ratio schedule (e.g., Fig. 5; lower panel), although maximum fixed-ratio values for nicotine were well above those for saline. Although cocaine was more effective than nicotine in maintaining high rates of responding in the dog, fixed-ratio patterns of responding maintained by nicotine and cocaine were similar (Fig. 5). A pause in responding at the start of each fixed-ratio trial was followed by a change to steady responding at a high rate until nicotine or cocaine was injected.

After the dose-response curves shown in Fig. 4 were completed the effects of presession IV treatment with 1.0 mg/kg of mecamylamine were determined in the dogs. When mecamylamine was administered IV 30 min before each session for seven consecutive sessions, nicotine-maintained responding rapidly fell to saline-control levels while cocaine-maintained responding was not changed. Representative results with one of the dogs are shown in the upper panel of Fig. 5. Again, mecamylamine was an effective and relatively specific antagonist of the reinforcing effects of nicotine.

Second-Order Schedules

Behavior maintained by drug injections often can be en-

hanced by using simple schedules such as fixed-ratio schedules as components of more complex second-order schedules of drug injection [2, 4, 8]. Under second-order schedules, completion of an individual component (or unit) schedule, rather than an individual response, produces the drug injection according to another overall schedule. Each component schedule terminates with the brief presentation of a light that has been associated with drug injection. In a series of recent experiments, this second-order scheduling technique was applied to the study of behavior maintained by nicotine injections. In these experiments [11,22], squirrel monkeys responded under a second-order fixed-interval schedule of IV nicotine or cocaine injection with fixed-ratio components of brief-light presentation. At the beginning of each experimental session a green light was turned on, and every tenth lever-pressing response (fixed ratio 10) during a 1-, 2- or 5-min fixed interval of time changed the light from green to amber for one sec; the first fixed-ratio component completed after the interval elapsed turned off the green light and produced both the one-sec amber light and an IV injection of nicotine or cocaine. A one- or three-min timeout period, during which the chamber was dark and responses had no programmed consequences, followed the injection. Each session ended after the 10th or 12th timeout or 90 min, whichever occurred first.

Figure 6 shows dose-response curves for three monkeys under second-order schedules of nicotine or cocaine injection. The temporal parameters of the schedule varied in the different monkeys as shown in Table 1. Each dose was studied for at least five consecutive sessions. Under the second-order schedules, intermediate doses of nicotine (10 to 56 μg/kg/injection) maintained high overall rates of responding in each monkey. At the high 100 μg/kg dose of nicotine, however, responding was poorly maintained and vomiting occurred as indicated by arrows. Comparison of nicotine and cocaine showed that the two drugs maintained similar rates of responding over a range of doses in one monkey (S-464) but that cocaine maintained higher overall rates of responding than did any dose of nicotine in a second monkey (S-200).

Representative cumulative-response records are shown for one monkey (S-464) in Fig. 7. Injections of nicotine and cocaine maintained similar patterns of responding. At intermediate doses, characteristic fixed-ratio patterns of responding were maintained throughout each interval. There was a short pause after most brief-light presentations followed by an abrupt change to a high response rate that continued until the ratio was completed and the brief light was presented again. At the high 100 μg/kg/inj dose of nicotine or cocaine, patterns of responding were disrupted and rates of responding decreased as the session progressed.

Although the frequency of nicotine injection was about the same under the second-order schedules and under the fixed-interval schedule described earlier, overall rates of responding were much higher under the second-order schedule. These differences are probably attributable to the repeated presentations during the interval of the brief light, which was intermittently paired with nicotine injection at the end of each interval. Figure 8 shows the effects of substituting saline for nicotine injections in three monkeys and of omitting brief-light presentations during the interval with two monkeys under the second-order schedule of nicotine injection. Overall response rates exceeding 0.8 responses/sec were maintained by 30 μg/kg injections of nicotine in all the monkeys. When saline was substituted for nicotine injections, rates of responding quickly decreased to low levels in two monkeys, but high rates of responding persisted during saline substitution in a third monkey (S-156); rates of responding were decreased during saline substitution in this monkey by omitting the brief stimulus lights during the interval for several sessions. When responding was maintained at high rates by nicotine injections, omitting the brief-light stimuli during the interval decreased overall rates of responding to about half those maintained previously (Fig. 8, lower panels); reinstating the brief lights during the interval returned rates of responding to the previous high levels. These findings demonstrate that although responding ultimately depended on injections of nicotine, the brief-stimulus presentations played an important role in the maintenance of high rates of responding under the second-order schedule.

TABLE 1

TEMPORAL PARAMETERS OF THE SECOND-ORDER FIXED-INTERVAL SCHEDULE OF IV NICOTINE OR COCAINE INJECTION FOR INDIVIDUAL MONKEYS*

Monkey	Duration of interval min	Duration of timeout min	Cycles per session
S-151	1	3	12
S-200	2	3	12
S-464	5	1	10

*From Spealman and Goldberg [22] with permission.

The effects of administering mecamylamine when responding was maintained under the second-order schedule of nicotine injection were similar to those previously described under the fixed-interval and fixed-ratio schedules of nicotine injection. When 1.0 mg/kg of mecamylamine was administered IM to two monkeys 30 min before each session, rates of responding fell rapidly to low levels, similar to the levels observed during saline substitution (Fig. 8; monkeys S-151 and S-200). When mecamylamine treatment was terminated, high rates of responding were restored.

SUPPRESSION OF BEHAVIOR BY NICOTINE INJECTIONS

The behavioral properties of a drug often depend on the conditions under which the drug is studied. For example, responding by squirrel monkeys can be maintained simultaneously by scheduled injections of cocaine and by termination of the schedule of cocaine injection [19]. Nicotine also can control behavior in very different ways depending on the conditions which it is injected. In the preceding experiments nicotine clearly functioned as a reinforcer to maintain responding in monkeys and dogs under various schedules of nicotine injection. In recent experiments [9,10] we explored the possibility that under certain conditions nicotine might function as a punisher to suppress rather than maintain responding.

Squirrel monkeys were studied using a punishment procedure similar to one used previously to study suppressant effects of other noxious stimuli, such as electric shock [20], pressurized air [20] or IV injections of histamine [3]. The monkeys were food-deprived and lever-pressing responses were maintained under a two-component, fixed-ratio schedule of food presentation. In one component (non-

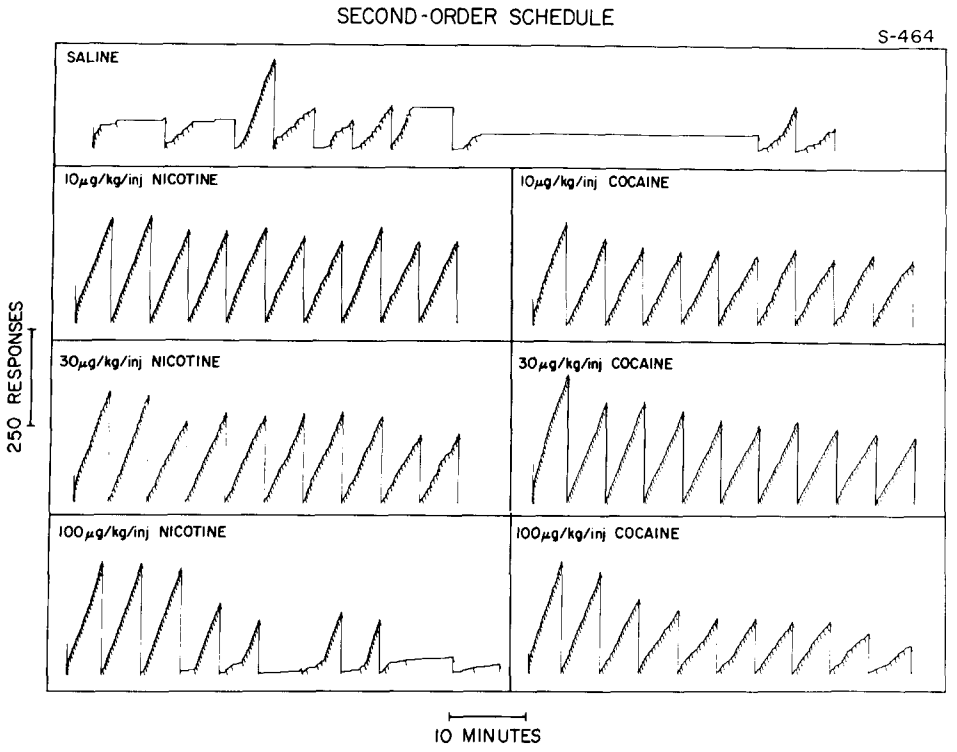

FIG. 7. Representative performances maintained by IV injections of nicotine or cocaine under the second-order fixed-interval schedule in a squirrel monkey (S-464). Abscissas: time; ordinates: cumulative responses. Diagonal marks show presentations of the 1-sec visual stimulus. The recorder reset after each injection and did not operate during the timeout period. Each panel shows a complete record at the doses specified or when saline was substituted for the drugs. (From Spealman and Goldberg [22] with permission).

punishment component), a green light was present and food was presented after every 30th response. In the second component (punishment component), a red light was present and food was also delivered after every 30th response but, in addition, the first response in each fixed ratio produced an IV injection of nicotine or saline. Each session began with a 5-min nonpunishment component, which was followed by a 10-min punishment component and another 5-min nonpunishment component. One-minute timeout periods separated the different components.

Figure 9 shows dose-response curves for three monkeys studied under this multiple schedule. Figure 10 shows representative cumulative-response records for one of these monkeys and, for comparison, another monkey studied under a comparable procedure with electric shock delivery rather than IV injections of nicotine. Each dose of nicotine was studied for at least six sessions.

When saline was injected during the punishment component of the multiple schedule, similar high rates and characteristic fixed-ratio patterns of responding were maintained in both the punishment and nonpunishment components and many injections occurred each session (Figs. 9 and 10). There was a brief pause in responding after each food delivery, followed by an abrupt transition to steady responding at a high rate until food was delivered again (Fig. 10). When responding in the punishment component produced injections of nicotine rather than saline, responding declined markedly in that component, but not in the alternating nonpunishment components, and the number of injections per session decreased. The degree of suppression depended on the dose per injection of nicotine, with 3 μg/kg having little effect, 10 μg/kg suppressing responding by about 70% and 30 μg/kg suppressing responding by over 80% (Fig. 9). With one monkey (S-18) responding was so severely suppressed by the 30 μg/kg dose of nicotine that during some sessions no injections occurred. Vomiting occurred occasionally at the 30 μg/kg dose of nicotine in two monkeys.

The suppression of responding by IV injections of nicotine was similar to that usually seen with other noxious stimuli. For example, suppression of responding comparable to that produced by 10 to 30 μg/kg injections of nicotine occurred when a second group of monkeys were studied under the identical punishment procedure with 200 msec electric shocks instead of nicotine injections [10]. At shock intensities of 1.0 to 5.0 mA, responding was suppressed by over 60% in the punishment components, but was not suppressed in alternating nonpunishment component, (e.g., Fig. 10, right panel). Chlordiazepoxide, an antianxiety agent with general rate-increasing effects on suppressed responding, had similar effects on responding suppressed by either nicotine injections or electric shocks. When 5.6 or 10 mg/kg of chlordiazepoxide was administered IM five min before the session, responding that had been suppressed either by nicotine injections or by electric shocks was increased by over 100% and the number of nicotine injections or electric shocks increased (Fig. 10, bottom panels). Mecamylamine, on the other hand, had specific effects on responding suppressed by nicotine injections (Fig. 10, middle panels). When 0.1 to 0.3

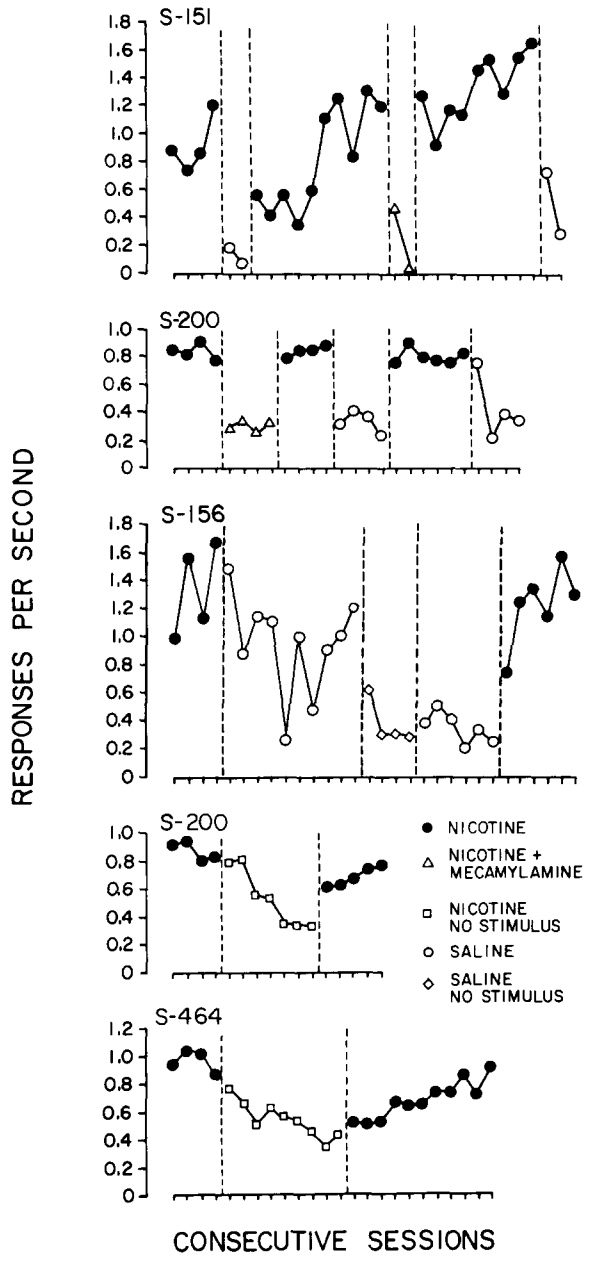

FIG. 8. Effects of substituting saline for nicotine injections (open circles), treatment with mecamylamine before the session (open triangles), or omitting the brief stimulus during the interval (open squares) on responding under the second-order schedule of IV nicotine injection for individual squirrel monkeys. Abscissas: consecutive sessions; ordinates: overall rate of responding. (From Goldberg, Spealman and Goldberg [11] with permission.)

mg/kg of mecamylamine was administered IM 30 min before the session, responding previously suppressed by nicotine injections was increased to high levels, similar to those observed when saline was injected. In contrast, responding suppressed by electric shock under the identical schedule was not increased by mecamylamine. Thus, mecamylamine had a specific effect on responding controlled by nicotine, rather than a general antipunishment effect.

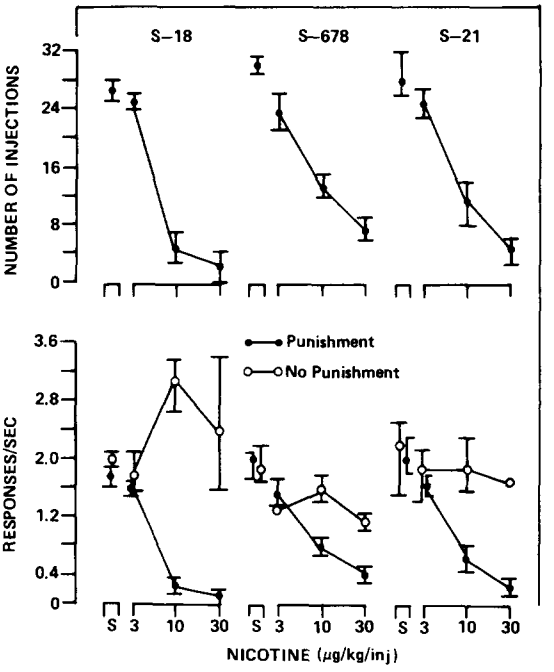

FIG. 9. Effects of dose of nicotine on rates of responding in punishment and nonpunishment components of the multiple schedule of food presentation and on number of injections per session with three squirrel monkeys (S-18, S-21 and S-678). Abscissas: dose, log scale (saline; S); ordinates: rate of responding (lower panels) and number of injections per session (upper panels). Each point is the mean of results from the last three sessions at a dose; bracketed vertical lines show the range. As the dose of nicotine was increased, the degree of suppression in the punishment component increased and the number of nicotine injections decreased. (From Goldberg and Spealman [10] with permission.)

MAINTENANCE OF BEHAVIOR BY POSTPONEMENT OF NICOTINE INJECTIONS

In the preceding experiments, both maintenance and suppression of responding by response-produced injections of nicotine were observed at equivalent doses per injection and each effect could be blocked by mecamylamine. The diverse effects of nicotine in these experiments indicate that the scheduled relations between responding and injections of nicotine are fundamental determinants of the ways in which nicotine controls behavior. In a recent series of experiments [21], the control of behavior by nicotine injections was further explored under schedules in which responding postponed injections that otherwise occurred at a specified rate.

Squirrel monkeys were trained to respond under a schedule of IV nicotine postponement similar to the schedule of electric-shock postponement originally described by Sidman [17,18]. In the presence of a red light, each lever-pressing response postponed an impending IV injection of nicotine for 60 sec; in the absence of responding, injections occurred every 20 sec. A 200 msec change in the stimulus light color from red to amber accompanied each injection. Experimental sessions ended after one hr or 30 injections, except at the highest dose of nicotine (100 μg/kg injections) when the maximum number of injections was reduced to 20 per session. After the experiments with nicotine were completed, two monkeys then were trained to respond under a

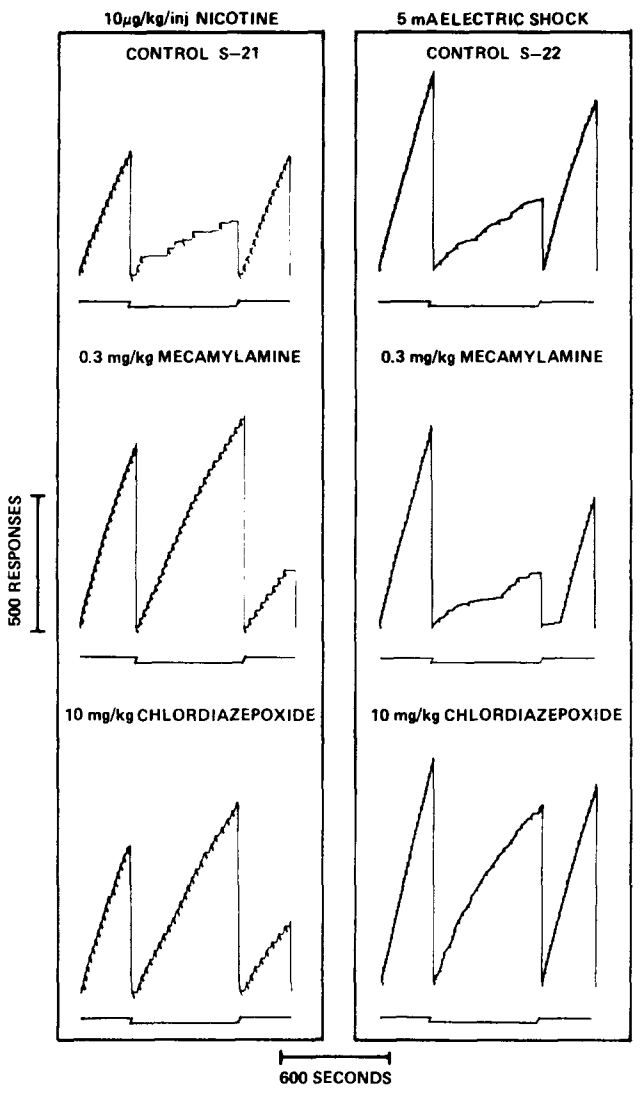

FIG. 10. Representative performances of squirrel monkeys under the multiple schedule of food presentation when responding in the punishment component was suppressed by 10 μg/kg injections of nicotine (monkey S-21) or by 5-mA electric shocks (monkey S-22). Each record shows a complete session. Abscissas: time; ordinates: cumulative lever-pressing responses. Short downward strokes on the cumulative records indicate food presentations. During the punishment component, a red light was on and the lower event pen remained down. The recording pen reset to the bottom of the cumulative record at the end of each component and the recorder did not operate during the 1-min timeout periods which separated punishment and nonpunishment components. Control performances (upper records), with marked suppression of responding during the punishment component, are representative of those obtained when the monkeys were not injected before the session or were injected with saline. Note that chlordiazepoxide (lower panels) produced large increases in responding that had been suppressed by either nicotine injections or electric shocks, whereas mecamylamine (middle panels) markedly increased responding that had been suppressed by nicotine injections but not by electric shocks. (From Goldberg and Spealman [10] with permission.)

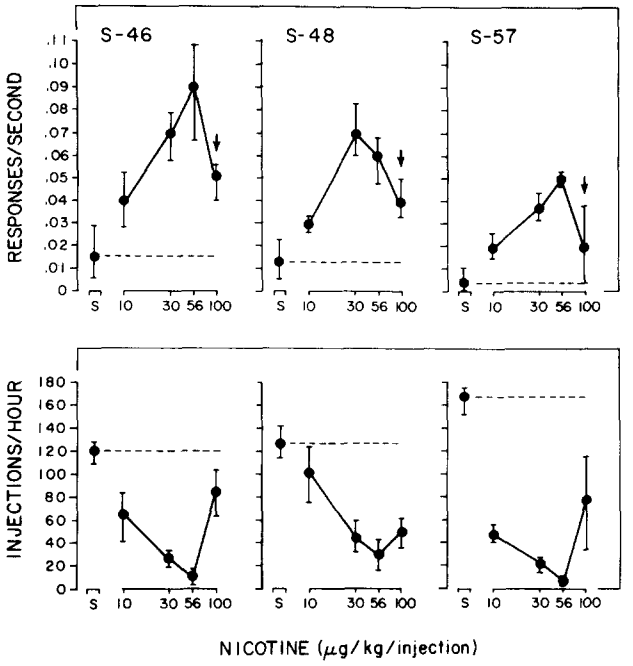

FIG. 11. Effects of dose on performances maintained by IV injections of nicotine under the postponement schedule for individual monkeys. Abscissas: dose, log scale; ordinates: rate of responding (top panels) or frequency of injections (bottom panels). Points are means based on the last three sessions with each dose or when saline was substituted for nicotine (points at S and dashed horizontal lines); brackets show ranges. Arrows indicate that vomiting was observed during or shortly after the experimental sessions. (From Spealman [21] with permission.)

schedule of electric shock postponement with schedule parameters identical to those used in the studies with nicotine.

Figure 11 shows dose-response curves for three monkeys under the schedule of nicotine postponement. Figure 12 shows representative cumulative-response records for one of these monkeys under the schedule of nicotine postponement and, for comparison, under an identical schedule of electric shock postponement. Each dose of nicotine (or saline) was studied for at least five sessions. When saline was injected under the postponement schedule, rates of responding were very low and the frequency of injection was very high (Figs. 11 and 12). With the lowest dose of nicotine (10 μg/kg/injection), rates of responding were only slightly higher and injections occurred only slightly less frequently. With intermediate doses of 30 to 56 μg/kg/injection of nicotine, however, response rates increased markedly and the frequency of injection decreased. At the highest dose of nicotine (100 μg/kg/injection), responding was disrupted, the frequency of injections increased and vomiting occurred in each monkey. With intermediate doses, responding under the schedule of nicotine postponement was characterized by a relatively constant rate of responding throughout each session. These performances were similar to those maintained under an identical schedule of electric shock postponement (Fig. 12).

When 1.0 mg/kg of mecamylamine was administered IM 30 min before each session under the schedule of nicotine postponement, the nicotine dose-response curves were shifted about one log unit to the right and the vomiting

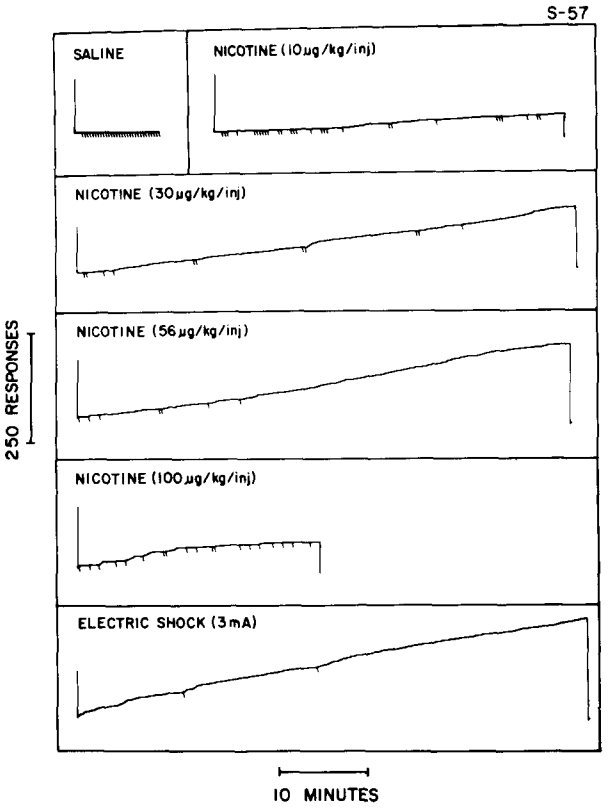

FIG. 12. Representative performances maintained by IV injections of either saline or nicotine or by delivery of electric shock under the postponement schedule in a squirrel monkey (S-57). Abscissas: time; ordinates: cumulative lever-pressing responses. Diagonal marks of the pen show injections or electric shocks. Each record shows a complete session. Session lengths varied depending on the dose and on the monkey's performance. Note that patterns of responding maintained by nicotine (30 and 56 μg/kg/injection) were similar to those maintained by electric shock. (From Spealman [21] with permission.)

produced by nicotine was blocked. With mecamylamine injected before each session, the dose of nicotine had to be increased to 560 to 1000 μg/kg/injection to maintain responding similar to that previously maintained by doses of 30 to 56 μg/kg/injection of nicotine. This antagonism of nicotine's effects was relatively specific, since presession treatment with 1.0 mg/kg of mecamylamine had no systematic effect on resonding maintained in the same monkeys under the schedule of electric-shock postponement.

SUMMARY

Nicotine controlled behavior of laboratory animals in many different ways in the studies reviewed. Under a variety of intermittent schedules of drug self-administration, nicotine functioned effectively to maintain lever pressing by squirrel monkeys and dogs. Doses of 10 to 100 μg/kg/injection of nicotine maintained moderate to high rates of responding by squirrel monkeys under fixed-interval and second-order schedules of drug self-administration, yet response-produced injections of these same doses of nicotine functioned effectively to suppress food-maintained responding by squirrel monkeys during the punishment component of a multiple schedule. Further, under the schedule of nicotine postponement, doses of 30 to 56 μg/kg/injection effectively maintained responding that prevented, rather than produced, scheduled IV injections. Nicotine shares this spectrum of diverse drug effects with a variety of other drug and nondrug environmental events, including cocaine, naloxone or nalorphine injection [6, 7, 20, 26], electric shock delivery [1,14] or brain stimulation [24].

The manner in which behavior is affected by environmental events such as nicotine injection depends on the behavioral history of the subject, the prevailing schedule of reinforcement and the ongoing behavior at the time the event is introduced. In the self-administration studies reviewed above, nicotine injections were introduced while responding was occurring at very low rates, a relatively long sequence of responses was required to produce each injection of nicotine and there was a specified minimum period of time between successive injections (four min or more) which did not depend on response rate. In the punishment studies, however, response-produced injections of nicotine were superimposed on high, ongoing rates of fixed-ratio responding maintained by food presentation, only a single response at the start of each fixed-ratio unit produced a nicotine injection and the time between possible injections was limited only by the monkey's rate of responding. Finally, in the postponement studies, nicotine was introduced at the start of training when responding occurred at very low rates, a single lever press was sufficient to postpone a scheduled injection of nicotine and the time between successive injections was determined both by the schedule parameter and by the subject's rate of responding. How nicotine functions to control behavior is likely determined by such differences in the subjects ongoing behavior and in the schedules of drug injection.

The findings reviewed in this paper indicate that nicotine may control smoking behavior of human subjects in very complex and divergent ways depending on prevailing environmental conditions. This is further emphasized by recent findings that in human subjects nicotine can maintain fixed-ratio responding that either produces [5,12] or prevents [12] its scheduled IV injection. Since nicotine can function either to maintain or suppress responding which *produces* its injection or to maintain responding that *prevents* its injection, it is not surprising that the precise effects of nicotine in the control of human smoking behavior have been difficult to determine. The nature of the control of smoking by nicotine is probably modified in response to changing environmental conditions. An increased understanding of how changing environmental conditions can alter the control of behavior by nicotine may allow the design of more efficient treatments for modifying smoking behavior.

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