penicillin treatment were obtained from EPSP's with peak amplitudes varying from 10 to 15 mV. Before the addition of penicillin the half-amplitude durations of the orthodromically evoked EPSP's did not show any obvious relation to the amplitudes of the EPSP's. This result would be expected if the decay phase of the event was influenced by the occurrence of the succeeding IPSP. After penicillin treatment, however, the durations of the EPSP's varied monotonically with their amplitudes, suggesting a passive decay.
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* Present address: Department of Physiology and Biophysics, Louisiana State University Medical Center, Shreveport 71130.

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Behavior Maintained by Termination of a Schedule of Self-Administered Cocaine

Abstract. *Squirrel monkeys self-administered cocaine by pressing a lever while under a variable-interval schedule of reinforcement. At the same time, they terminated the availability of self-administered cocaine by pressing a second lever while under a fixed-interval schedule of reinforcement. The maintenance of behavior by scheduled drug injections and by termination of scheduled drug injections, usually considered to be processes associated with different classes of drugs, can occur simultaneously when behavior is controlled by different contingencies associated with a single drug.*

Some unexpected effects of drugs that are self-administered by laboratory animals have recently been observed (*1*). Under suitable conditions, both *d*-amphetamine and apomorphine have been found to maintain responding that leads to their injection; yet, these same drugs also suppress drinking of flavored solutions associated with their injection (*2*). Other drugs, such as pentazocine, propiram, nalorphine, and naloxone can maintain responding that either leads to or postpones their scheduled injection depending on the physiological state of the subject and the environmental conditions under which the drugs are administered (*3*). Such disparate effects suggest that factors other than the inherent properties of drugs can be critical in determining how drugs affect behavior. The identification of such factors should have important implications for the control of drug-taking behavior.

In the experiment reported here, separate responses by individual squirrel monkeys were maintained simultaneously when presses on one lever produced injections of cocaine and presses on a second lever terminated the schedule of cocaine injection. The maintenance of behavior by scheduled drug injections and by termination of scheduled drug injections, usually considered to be processes involving different classes of drugs, can occur simultaneously when behavior is controlled by different contingencies involving a single drug.

Four mature male squirrel monkeys (*Saimiri sciureus*) that had no previous experience with drugs were studied. Throughout the experiment, the monkeys had unrestricted access to food and water in their individual home cages. During daily experimental sessions, the monkeys were seated in a restraining chair equipped with a red stimulus light and two response levers (*4*); the chair was enclosed in a sound-attenuating chamber. Injections of cocaine were delivered through venous catheters (*5*) from an infusion pump located outside the chamber.

Initially, responses on a single lever produced intravenous injections of cocaine (*6*) on the average of once every 3 minutes (3-minute variable-interval schedule of cocaine injection). When responding was stable from day to day (18 to 24 sessions), a second lever was introduced to the left of the existing lever. The first response on the left lever occurring 3 minutes after the start of the session terminated the schedule of cocaine injection and started a 1-minute time-out period (3-minute fixed-interval schedule of termination). During the time-out, the stimulus light that normally illuminated the chamber was turned off, the schedules associated with each lever were stopped, and responses on the levers had no programmed consequences. At the end of the time-out, the stimulus light again illuminated the chamber and the schedules associated with each lever were restarted. This cycle was repeated 20 times per session.

Under the concurrently arranged schedules, distinctly different response rates and temporal response patterns

Table 1. Overall response rates (responses per second) on each lever for individual monkeys. Data are means based on the last three sessions of each condition; ranges are in parentheses. Protocol A: responses on the right lever initially produced injections of cocaine under a VI (variable-interval) schedule, while responses on the left lever terminated the schedule of cocaine injection under an FI (fixed-internal) schedule. The schedules associated with each lever were reversed twice. Protocol B: responses on the right lever produced injections of either cocaine or saline under a VI schedule, while responses on the left lever either terminated the schedule of injection under an FI schedule or had no programmed consequences (extinction).

Schedule		Responses per second		Sessions	Responses per second		Sessions
Left	Right	Left	Right		Left	Right	
Protocol A		*Monkey S-146*			*Monkey S-153*		
FI (termination)	VI (cocaine)	0.37 (0.33–0.41)	0.13 (0.10–0.17)	60	0.23 (0.22–0.26)	0.16 (0.14–0.17)	54
VI (cocaine)	FI (termination)	0.16 (0.14–0.18)	0.34 (0.24–0.45)	16	0.10 (0.09–0.13)	0.20 (0.18–0.23)	23
FI (termination)	VI (cocaine)	0.29 (0.24–0.37)	0.16 (0.11–0.19)	15	0.16 (0.15–0.17)	0.10 (0.08–0.11)	16
Protocol B		*Monkey S-154*			*Monkey S-332*		
FI (termination)	VI (cocaine)	0.20 (0.19–0.23)	0.14 (0.12–0.15)	62	0.18 (0.16–0.22)	0.30 (0.29–0.31)	36
FI (termination)	VI (saline)	0.06 (0.03–0.09)	0.05 (0.03–0.07)	13	0.02 (0.01–0.04)	0.04 (0.03–0.06)	5
FI (termination)*	VI (saline)	0.04 (0.02–0.06)	0.04 (0.03–0.05)	9	0.05 (0.03–0.07)	0.07 (0.03–0.10)	17
FI (termination)	VI (cocaine)	0.16 (0.15–0.17)	0.13 (0.10–0.15)	10	0.17 (0.16–0.19)	0.26 (0.25–0.27)	19
Extinction †	VI(cocaine)	0.04 (0.01–0.07)	0.18 (0.11–0.22)	18	0.02 (0.00–0.04)	0.28 (0.21–0.32)	7

*Cocaine infused before each session (*8*). †Sessions ended after 60 minutes.

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were maintained on each lever (Fig. 1). Responding on the right lever, which produced injections of cocaine (Fig. 1, upper record in each panel), occurred at a fairly constant rate throughout each session, typical of performances under variable-interval schedules (*7*). Responding on the left lever, which terminated the schedule of cocaine injection (Fig. 1, lower record in each panel), was characterized by low response rates at the beginning of the fixed interval, followed by higher response rates as the interval progressed, typical of performances under fixed-interval schedules (*7*).

The modifiability of responding was investigated in two monkeys by reversing the schedules associated with each lever (Table 1, protocol A). When the variable-interval schedule of cocaine injection was switched to the left lever and the fixed-interval schedule of termination was switched to the right lever, response rates on each lever changed in accordance with the new schedules. In each case, the response rates under the fixed-interval schedule of termination were higher than those under the variable-interval schedule of cocaine injection regardless of the particular lever associated with each schedule. These effects were reversible and related unequivocally to the schedules in effect on the two levers.

The sensitivity of responding was investigated in two additional monkeys by selectively eliminating the consequences of responding on each lever (Table 1, protocol B). When responding on the right lever no longer produced cocaine injections (that is, when saline was substituted for cocaine under the variable-interval schedule), response rates declined on both levers. Infusions of cocaine shortly before experimental sessions (*8*) temporarily increased response rates on the two levers but failed to reinstate sustained responding during successive sessions. These results show that responding under the variable-interval schedule was maintained by self-administered cocaine. More important, the results show that responding under the fixed-interval schedule was maintained by terminating the schedule of cocaine injection rather than by the change in visual stimulation per se (the change from a lighted to a dark chamber). This was true regardless of the presence or absence of the psychomotor-stimulant effects of cocaine (*9*). The original performances on the two levers were restored when presession infusions were discontinued and cocaine was again self-administered during the sessions.

When responding on the left lever no longer terminated the schedule of cocaine injection (that is, when the fixed-interval schedule was changed to extinction), response rates on that lever declined markedly. However, responding under the variable-interval schedule of cocaine injection (right lever) continued to be maintained. Thus, responding under the fixed-interval schedule was neither the result of a nonspecific increase in activity produced by cocaine nor the result of an adventitious chain of left- and right-lever responses.

In this study, responding was maintained simultaneously by scheduled injections of cocaine and by termination of the schedule of cocaine injection. Such disparate effects of a single drug are probably not restricted to cocaine; apparently related effects have been reported with *d*-amphetamine and apomorphine (*2*), and with several narcotic antagonists (*3*). Similar effects also have been reported with other environmental events. Under conditions analogous to those of the present study, for example, responding can be maintained simultaneously by delivery of electric shocks and by termination of the schedule of electric-shock delivery (*10*). Furthermore, responding can be maintained by either delivery or postponement of the same intensity and frequency of electrical stimulation of the brain (*11*), and by either delivery or postponement of food to food-deprived animals (*12*). These findings emphasize the importance of factors other than the inherent properties of environmental events, including the administration of drugs, in determining the way those events control behavior. A single drug can control behavior in distinctly different ways when administered according to different contingencies, and the behavioral effects of drugs cannot be predicted simply on the basis of a priori considerations of their pharmacological nature.

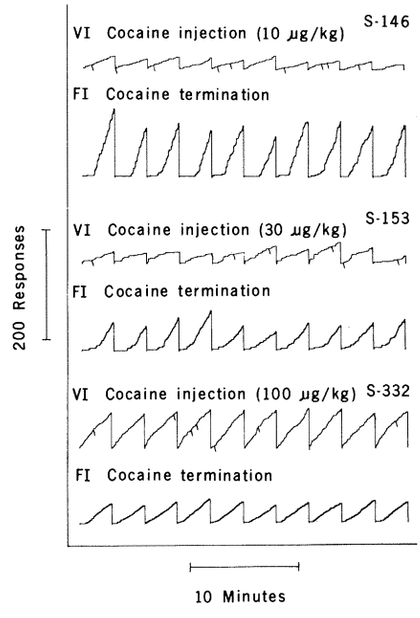

Fig. 1. Characteristic response rates and temporal response patterns maintained simultaneously by cocaine injections and by terminating the schedule of cocaine injection. Responses on the right lever (upper record in each panel) produced intravenous injections of cocaine under a variable-interval (*VI*) schedule; responses on the left lever (lower record in each panel) terminated the schedule of cocaine injection for 1 minute under a fixed-interval (*FI*) schedule. The abscissas show time, and the ordinates show cumulative lever-pressing responses. Diagonal marks of the upper record show injections of cocaine; each record was reset at the beginning of the 1-minute time-out periods, during which the recorders did not operate. Performances are shown for three monkeys that were studied with three different doses of cocaine. The performance on each lever was appropriate to the schedule associated with that lever for individual monkeys.

A pervasive concern of research on drug abuse is the development of techniques for reducing the frequency with which drugs are self-administered. The present results can be viewed in this context. During time-out periods, drug self-administration was precluded, and the occurrence of these periods was controlled by the subject's responding. Under these conditions, persistent responding was maintained when responding eliminated the opportunity to self-administer cocaine and hence reduced the overall frequency of cocaine injections. These findings suggest that the availability of suitable alternative behaviors, which themselves produce periods of drug abstinence, can play an important role in the self-management of drug-taking.

ROGER D. SPEALMAN
Harvard Medical School and
New England Regional Primate Research Center,
Southborough, Massachusetts 01772

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cording to published methods [J. A. Herd, W. H. Morse, R. T. Kelleher, L. G. Jones, *Am. J. Physiol.* **27**, 24 (1969)]. While the monkey was under halothane anesthesia and in aseptic conditions, one end of a polyvinyl chloride catheter (inside diameter, 0.38 mm; outside diameter, 0.76 mm) was passed by way of the left or right external jugular vein into the superior vena cava at the level of the right atrium. The distal end of the catheter was passed subcutaneously and exited through the skin in the middle of the monkey's back. Each monkey wore a leather jacket at all times to protect the catheter. Catheters were flushed daily with 0.9 percent saline solution and were sealed with stainless steel obturators when not in use.

6. Cocaine HCl was dissolved in 0.9 percent saline solution. The volume of each injection was 0.20 ml, infused over 200 msec. An amber feedback light was presented for 1 second before each injection. The doses (as the salt) per injection were as follows: 10 μg per kilogram of body weight (monkey S-146), 30 μg/kg (monkeys S-153 and S-154), and 100 μg/kg (monkey S-332). These doses were selected on the basis of preliminary observations and maintained responding throughout each session for individual monkeys.
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Norepinephrine Inhibits Calcium-Dependent Potentials in Rat Sympathetic Neurons

Abstract. *Norepinephrine reversibly antagonizes three calcium-dependent potentials recorded from rat postganglionic neurons. Norepinephrine inhibits the development of a shoulder on the action potential, the magnitude of the hyperpolarizing afterpotential, and the rate of rise and amplitude of the calcium spike. The action of norepinephrine is antagonized by the α-adrenergic antagonist phentolamine, but not by MJ 1999, a β-adrenergic antagonist. These results suggest that activation of an α-adrenergic receptor may antagonize a voltage-sensitive calcium current.*

Ion conductance mechanisms enable neurons to regulate membrane potential and alter intracellular ion concentrations. Voltage-sensitive calcium conductances, $g\mathrm{Ca}_{(v)}$, and calcium-sensitive potassium conductances, $g\mathrm{K}_{(Ca)}$, have been observed in neurons from both invertebrate and vertebrate species (*1*). These conductances can play important physiological roles, including the control of repetitive firing of neurons, pacemaker activity, and neurotransmitter release (*2*). A related event is the hyperpolarizing afterpotential (HAP) of the rat postganglionic neuron. Yarowsky and McAfee (*3*) have shown that the HAP results from an increased $g\mathrm{K}$ which is largely dependent upon extracellular Ca^{2+}. In addition, postganglionic neurons support a regenerative Ca^{2+} action potential that is insensitive to tetrodotoxin (TTX), the Na^+ conductance antagonist. Analysis of the Ca^{2+} spike and HAP (*3*) indicates that these neurons possess both $g\mathrm{Ca}_{(v)}$ and $g\mathrm{K}_{(Ca)}$ and suggests that inward Ca^{2+} current triggers part of the HAP (*4*). We now report that norepinephrine reversibly antagonizes both the HAP and the Ca^{2+} spike, and propose that norepinephrine acts through an α-adrenergic receptor to inhibit Ca^{2+} current.

Superior cervical sympathetic ganglia isolated from mature Sprague-Dawley rats (150 to 250 g) were desheathed and perfused with oxygenated Locke solution for up to 12 hours in vitro (24° to 26°C). Intracellular recordings were made with glass microelectrodes from postganglionic cells visualized through a compound microscope. Membrane potential was controlled by current passed through the microelectrode. The composition of the perfusion medium was altered as indicated to apply drugs or to change extracellular ion concentrations (*3*, *5*).

We have identified three voltage responses in postganglionic neurons which are Ca^{2+}-dependent. Two, the HAP and a "shoulder," are seen during discharge in unmodified Locke solution. In this case, a single, brief depolarizing current pulse (100 to 1000 pA, 4 to 15 msec), applied through the recording microelectrode, resulted in action potentials that began with a rapid depolarization followed by a less rapid repolarization having a distinct inflection or shoulder (Fig. 1); the repolarization overshot the resting potential by 12 mV, producing a HAP lasting 300 msec (Fig. 1). This pattern was reproduced in all 75 cells studied. Both the shoulder and the HAP decreased in magnitude as extracellular Ca^{2+} concentration, $[Ca^{2+}]_0$, was reduced (Fig. 1). Divalent cobalt (0.5 to 3.0 m*M*), a Ca^{2+} antagonist in this and other preparations (*1*, *3*), also reduced the shoulder and the HAP with little or no change in the rising phase or duration of the action potential. These Ca^{2+}-dependent potentials appeared to be independent of the voltage-sensitive K^+ conductance [delayed rectification, $g\mathrm{K}_{(v)}$], inasmuch as tetraethylammonium (TEA), an antagonist of $g\mathrm{K}_{(v)}$, augmented both the action potential shoulder and the duration of the HAP. When TEA was used, the enlarged shoulder and HAP remained sensitive to low $[Ca^{2+}]_0$ or 3 m*M* Co^{2+}.

The third Ca^{2+}-dependent potential is the regenerative discharge produced by depolarization of postganglionic neurons bathed in Locke solution containing TTX (1 μ*M*) and TEA (5 m*M*) (Fig. 1). Yarowsky and McAfee (*3*) concluded that this action potential was a Ca^{2+} spike because its amplitude was proportional to $[Ca^{2+}]_0$ and antagonized by Co^{2+}. This spike was followed by a HAP with characteristics similar to the HAP in normal Locke solution.

Norepinephrine (10 μ*M*) reversibly inhibited all of these three Ca^{2+}-dependent potentials. It reduced the action potential shoulder and the magnitude of the HAP in all neurons studied ($N = 25$) (Fig. 1); the average attenuation of the HAP was about 40 percent. The membrane resistance decrease associated with the HAP was also reduced by norepinephrine. These effects occurred after less than 1 minute of exposure to norepinephrine, did not desensitize over a 15-minute period, and were reversed within 10 minutes of washing. A minimum detectable effect was produced at a concentration of 0.1 to 0.3 μ*M*. A 10-μ*M* concentration sometimes produced a slight hyperpolarization (0.5 to 4.0 mV) of resting membrane potential which was not accompanied by a detectable change in resting input resistance (*6*). The effects of norepinephrine on the action potential and the HAP were seen even when the

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