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Modelling Drug Kinetics With Brain Stimulation: Dopamine Antagonists Increase Self-Stimulation

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LEPORE, M. AND K. B. J. FRANKLIN. *Modelling drug kinetics with brain stimulation: Dopamine antagonists increase self-stimulation.* PHARMACOL BIOCHEM BEHAV 41(3) 489–496, 1992.—The rewarding effects of brain stimulation and drugs are believed to depend on a common neural system. However, the pattern of responding produced by drug reinforcers is different from the pattern produced by conventional brain stimulation. Furthermore, pharmacological antagonists of reinforcement increase the rate of drug self-administration but depress self-stimulation. To test the hypothesis that the differences in the characteristics of brain stimulation and drugs as reinforcers are due to differences in the kinetics of drugs and brain stimulation, we modelled drug kinetics with frequency-modulated trains of brain stimulation. We report that animals will self-administer such brain stimulation in a manner that resembles drug self-administration and that, under these conditions, dopamine antagonists can increase the rate of self-stimulation.

Self-stimulation Reward Reinforcement Drug kinetics Dopamine Pimozide *cis*-Flupenthixol

SINCE Olds and Milner (34) discovered animals would learn to perform a task to obtain trains of electrical pulses delivered to the brain, the study of self-stimulation has been at the centre of attempts to map the neural substrate of reinforcement.Myelinated fibres descending in the MFB, and the ascending dopamine projections from the ventral tegmentum to the ventral striatum, appear to be important components of the putative neural substrate of brain stimulation reward (21,26,53). The neural substrate of drug self-administration includes some of the same structures that have been implicated in self-stimulation. It is hypothesized that drugs are self-administered because they pharmacologically activate the neural systems that are activated electrically in self-stimulation (4,26).

However, brain stimulation and drugs have very different characteristics as reinforcers that are not easily reconciled. Typically, a train of reinforcing brain stimulation consists of a series of square-wave pulses (0.1–0.5 ms pulse width) 2–20 ms apart (50–500 Hz) or 60 Hz sine wave current. The train has an abrupt and immediate onset following a response, and lasts 1 s or less. Trains as long as 20 s have been used (10,24,30), but with long trains stimulation often appears to become aversive and animals will work to turn the stimulation off (2,42).

In contrast, even the most rapidly acting drugs, such as heroin or cocaine, have a time course of action more than an order of magnitude longer than the maximally effective brain stimulation trains. Animals will respond reliably for drug reinforcement when the time course of the effect of a single dose lasts for many minutes or even hours (47,48). When the dose of drug is above the threshold dose for reinforcement, animals appear to regulate the amount of drug in the blood in that the rate of drug self-administration is inversely related to the dose or duration of the drug effect (26,47–49,52,54). Under these circumstances, administration of a pharmacological antagonist of the drug results in an increase in the rate of drug self-administration (15,47,51,55). In contrast, drugs that are believed to block the reinforcing effect of brain stimulation depress the rate of self-stimulation or lead to extinction of the response (13,16,18,46).

Taken at face value, these differences between drugs and brain stimulation as reinforcers suggest that the neural substrate of drug self-administration has properties very different from those established for self-stimulation. Alternatively, these differences may be due to technical constraints that have determined how brain stimulation and drugs are delivered to the brain, that is, to the differing kinetics of brain stimulation and drugs. To explore this possibility, we have developed a brain stimulation model of drug self-administration using prolonged brain stimulation trains that rise and fall in strength in a manner analogous to the absorption and elimination of a drug. This report describes the behavioral characteristics of

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self-administration of brain stimulation (SABS) and the influence on it of antagonists of brain stimulation reward.

EXPERIMENT 1

Conventional brain stimulation trains are constant-frequency trains with instantaneous onset and offset. In contrast, self-administered drugs are absorbed and eliminated at rates that vary widely for different drugs. From the point of view of stimulation, it is the effect of drugs on neural activity that can be modelled by brain stimulation, not the drug concentration itself. However, there is limited information concerning the kinetics of the effects of drugs on the brain since in most cases the neural substrate of drug action is not established. Since drugs that are rapidly absorbed are thought to be more readily self-administered, we attempted to model the effects of hypothetical drugs with kinetic characteristics that varied between those of conventional self-stimulation at one extreme and cocaine at the other. Following an intravenous injection, the effects of cocaine on the CNS of the cat are detectable within 30 s by electrographic recording (12). In humans, cardiovascular effects peak within 2–7 min (7,33, 39,40). Subjective effects in humans also peak within the first 10 min (25,40), and recent studies have found maximal ratings of "rush" and "good" at 2–3 min (27,33). Although the half-life of cocaine in plasma in humans may be as long as 48 min (7,25), the effects of cocaine after a bolus injection dissipate more rapidly (25,27). The half-life in the rat is estimated at 20 min (32), but the dopamine (DA)-releasing effect of cocaine dissipates with a half-time closer to 12–15 min (37). Since the DA-releasing effect is critical for reinforcement, we assumed, for the purpose of stimulation, that the reinforcing effect of cocaine in the rat would have an absorption half-time of 32 s and an elimination half-time of 1000 s (16.7 min).

One consequence of slow absorption of a drug is that it imposes a delay of reinforcement that would be expected to make acquisition of self-administration more unreliable as the absorption half-time increases (36). To determine if SABS performance was stable over a range of absorption half-times, we tested spontaneous acquisition of SABS with half-times of 2, 8, and 32 s in comparison with spontaneous responding for no reinforcement.

METHOD

Subjects

These experiments were carried out in accordance with the guidelines for the ethical use of animals in research approved by the Canadian Council on Animal Care and McGill University.

Adult, male Long-Evans rats (Charles River, St. Constant, Quebec) were anesthetised with pentobarbital (60 mg/kg) and a bipolar stainless steel electrode, aimed at the lateral hypothalamus, was implanted in the brain of each rat. Stereotaxic coordinates (35) were 0.5 mm posterior to the interaural line, ±1.5 mm lateral to the midline, and 8.3 mm below the skull surface. The correct placement of electrodes was confirmed histologically. Rats were allowed at least 1 week to recover before testing.

Apparatus

Animals were tested in a conventional Skinner box (Coulbourn Instruments, Lehigh Valley, PA) modified for delivery of brain stimulation (44) and equipped with a lever on which the rat pressed to obtain stimulation. Brain stimulation was delivered by an electrically isolated constant current stimulator. Trains of 0.15 ms square-wave pulses were generated by a variable-frequency oscillator. Oscillation frequency was controlled by a digital to analogue converter and the frequency could be changed in 4-Hz steps. A PC-XT microcomputer monitored the animals' responses, recorded data, and set the appropriate frequency of brain stimulation. The computer polled the lever press detectors and reset the brain stimulation frequency four times per s.

Computer Control of Brain Stimulation

(Full details of the program and hardware are available on request.) The frequency of continuously available brain stimulation was modulated by the animal's behavior. When the animal pressed the lever, the computer began to increase the frequency of the brain stimulation train from the existing level (initially 0 Hz) toward some specified increment in frequency (e.g., 200 Hz). The computer reset the stimulation pulse frequency four times per s. The rate of change of the frequency of the brain stimulation train was controlled by varying the interval between the application of successive steps of 4 Hz. These intervals were determined by a kinetic equation (linear or exponential) for "absorption." The outputs of the kinetic equations were rounded to the nearest whole integer to be fed to the digitally controlled oscillator. The minimum interval was 250 ms. The frequency attained at the end of the absorption phase represented the "peak plasma drug concentration," or "peak concentration at receptors," by analogy with drug self-administration. Once the specified increment in frequency was reached, the frequency of the stimulation train diminished according to a kinetic equation for elimination (linear or exponential) so that the frequency of stimulation decayed gradually in steps of 4 Hz (see Fig. 1). The envelope of frequencies, from the beginning of the rise in frequency through to maximum frequency and back toward 0 Hz, modelled the effect of a single dose of a drug. When the rat again executed a response that was to be reinforced, another "dose" was algebraically added onto whatever portion of the first

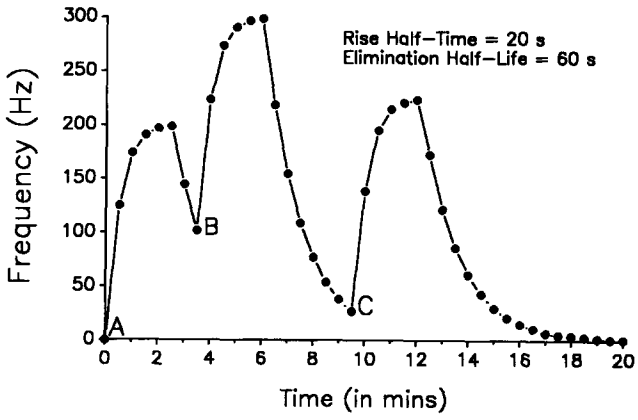

FIG. 1. Time course of the changes in pulse frequency of a hypothetical brain stimulation train generated by the SABS program. This train is designed to mimic the effect of an hypothetical drug with an absorption half-time of 20 s and an elimination half-life of 60 s. Data points are stored by the computer at 30-s intervals. A, B, and C indicate the time when a reinforced response occurred. For further explanation, see text.

dose was still present at the time of the response. An example of an hypothetical series of 200-Hz doses is shown in Fig. 1. At A, the rat responded to initiate the first train, which rose to 200 Hz with a 20-s half-time and then decayed with a 60-s half-time. At B, the frequency of the first train had decayed to 100 Hz when the rat against pressed the lever. The frequency rose from 100 Hz toward a new peak frequency, approximately 300 Hz. If the rat allowed the frequency to fall to 25 Hz, the next reinforced response at C would cause the frequency to peak around 210 Hz and then fall to 0 Hz if the rat did not respond again. Thus, the rat's response rate determined the average frequency of a stimulation train that fluctuated in frequency according to the kinetic equations. Since the frequency increased gradually following a lever press, an animal might administer several doses in rapid succession before the consequences of any single response were apparent, thus driving the peak frequency to undesirably high frequencies. To prevent this, lever presses were not reinforced during the absorption phase of a dose.

Normally, drug absorption and elimination occur simultaneously so that the peak concentration of drug is higher when a drug is eliminated slowly than when it is eliminated quickly. In the program, this characteristic could be modelled by simultaneously applying the equations for absorption and elimination.

Procedure: Spontaneous acquisition. Three groups of four rats were tested to see if they would spontaneously acquire SABS for brain stimulation reinforcements with absorption half-times of 2, 8, and 32 s. Elimination half-times were kept constant at 100 s. In this experiment, the "dose" was set at 200 Hz except that four rats were tested but no brain stimulation was applied (dose = 0 Hz). Animals not previously exposed to the apparatus, or to brain stimulation, were placed in the apparatus and left for 2 h each day for 10 days. Stimulation current was set at 75 μA.

RESULTS

All 12 animals acquired SABS when the SABS program was instituted de novo. Once SABS was established, performance remained stable in tests carried out up to 3 months. Table 1 shows the median performance of these animals over the first 5 days of training. The responding (on day 1 and summed over 5 days) of all three stimulated groups was significantly greater than the unstimulated group (Mann-Whitney $U = 0$, $p = 0.014$ in each case). There was no significant trend for response rates to increase over days of training. This indicates that most of the increase in response rate over the operant rate took place within the first session. Although rats in the 2-s and 8-s half-time groups seemed to have higher response rates than those in the 32-s group, individual variability was greater than the differences between groups. Response rates ranged from 6–188 responses per session for stimulated rats, while no unstimulated rat emitted more than 3 responses in a session.

TABLE 1

MEDIAN PERFORMANCE OF GROUPS OF FOUR RATS OVER FIRST 5 DAYS OF TRAINING

Rise Half-Time	Day 1	Day 2	Day 3	Day 4	Day 5
No stimulation	2.5	1.0	0.5	0.5	0.0
2 s	25.0	25.0	49.0	59.5	41.0
8 s	24.0	34.5	38.0	30.5	57.5
32 s	14.0	18.5	19.5	25.5	12.0

The values shown are the median number of stimulation trains self-administered per daily 2-h session during acquisition of self-administration behavior for groups of four rats receiving frequency-modulated brain stimulation trains that exponentially increased in frequency with half-times from 2–32 s and decayed in frequency with a half-time of 100 s.

DISCUSSION

The results confirm that the SABS performance is readily acquired without any pretraining or previous experience of brain stimulation, even when the stimulation frequency takes several minutes to reach its maximum (32-s half-time). The frequency threshold for self-stimulation under these conditions is not known, but studies of the frequency threshold for brain stimulation reinforcement in other paradigms suggest that, with a current of 75–100 μA, the threshold for a 1-s train would be above 100 Hz (11,19). The "absorption" half-times tested in this experiment thus imply that self-administration behavior is acquired with delays of reinforcement ranging from as little as 0.5 s to 15 s or more. This, and the fact that no attempt was made to optimize the stimulation current for each rat, may explain the high interindividual and session-to-session variability in response rate during acquisition. Whatever the explanation, SABS performance is similar to drug self-administration, which also shows considerable individual and session-to-session variability in rates of self-administration (1,29) during acquisition.

EXPERIMENT 2

Experiment 1 showed rats will spontaneously self-administer brain stimulation when responses modulate the brain stimulation frequency so that it rises and falls in a manner analogous to the rise and fall of a drug effect on the brain. In drug self-administration, rats seem to maintain the drug concentration at a level selected by the animal and rarely allow the drug effect to cease. The rate of responding, and the drug concentration maintained, are strongly influenced by the duration of action of each drug infusion. In general, the response rate declines with increases in the unit dose or with decreases in the rate of elimination of the drug (3,8,38,47,51). To see if this property of drug self-administration behavior could be modelled by self-administration of brain stimulation, Experiment 2 examined the effects on performance of changing the unit dose or the elimination half-time. Since in Experiment 1 performance was similar at different rates of absorption, a short absorption half-time (1 s) was used in Experiment 2 to facilitate training and ensure that changes in elimination times would be the dominant feature in discrimination between conditions.

METHOD

Subjects

Subjects were 12 rats prepared as described in Experiment 1.

Procedure

Effect of dose. Animals were first screened for self-stimulation using 1-s trains of 200 Hz stimulation, and the current was adjusted to produce a moderate rate of responding (500–750 responses per hour). They were then placed on the SABS

program with a dose of 200 Hz, absorption half-time 2 s and elimination half-time 330 s. In this experiment, absorption and elimination equations were applied simultaneously. When responding had stabilized (10 sessions in most rats), the effect of altering dose was tested. Each dose was tested on two consecutive sessions. The first day was used to accustom the rat to the new conditions, and the second day provided the data. Half the animals were tested with doses of 100, 200, and 400 HZ in that order, and the other half of the group received the doses in the reverse order.

Effect of elimination time. Animals were screened for self-stimulation as above and then placed on the SABS program. Short (1 s) absorption half-times were used, and the increment in frequency for each reinforcement ("dose") was kept constant at 200 Hz. So peak frequency produced by any stimulation would not vary with the elimination half-time, the elimination subroutine was locked out until absorption was completed. Animals were initially allowed to self-administer trains with an elimination half-time of 20 s. When performance was stable, which required about five sessions, they were allowed to respond for trains of 2000-s elimination half-time until stable performance was obtained. Each rat was then tested for three consecutive sessions with elimination half-times of 2, 20, 200, and 2000 s. The order of testing the different half-times was randomized for each rat. Preliminary trials indicated the pattern of responding stabilized during the first session on each half-time. The data from the last two sessions at each half-time were taken for analysis. For comparison, an additional group of four rats with similar training were tested with 1-s trains of 200-Hz brain stimulation in a conventional self-stimulation paradigm.

RESULTS AND DISCUSSION

The rate of SABS was inversely related to both dose and elimination half-time. As can be seen in Fig. 2, the response rate declined linearly with the log dose over the range tested, $F(2,6) = 13.53, p < 0.01$. The regression of response rate on log dose yielded $r = 0.98$. The strength of this relationship may seem extraordinarily high, but it is similar to the relationship between the rate of self-injection of cocaine or heroin and the unit dose of the drug (26). Moreover, the fact that response rate is linearly related to log dose is consistent with

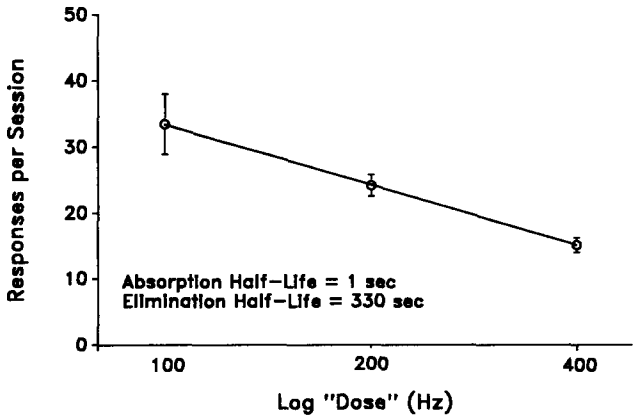

FIG. 2. Relationship between the size of the increment in frequency of a brain stimulation train ("dose") and the self-administration response rate for rats self-administering trains with a rise half-time of 1 s and decay half-life of 100 s. Vertical bars are standard errors.

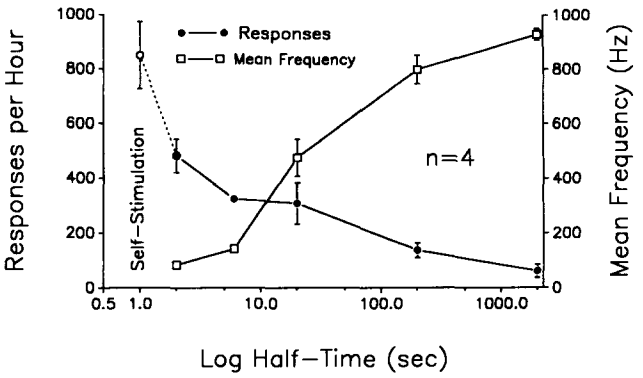

FIG. 3. Hourly rate of responding for SABS and the mean pulse frequency of stimulation maintained over 3-h sessions for different rates of decay of the frequency of the brain stimulation train. The rate of responding for conventional brain stimulation trains (1 s at 200 Hz) is shown for comparison. Vertical bars are standard errors.

the pharmacokinetic principle that, in the middle range of effective doses (20–80% effect), the duration of effect should be linearly related to log dose (45).

The relationship between duration of effect and self-administration behavior is very clearly shown when elimination half-time is varied. Figure 3 shows the relationship between elimination half-time and response rate and the mean frequency maintained by that response rate. The maintained frequency here is analogous to the mean plasma concentration of a drug in a drug self-administration experiment. The mean frequency maintained increased with the elimination half-time, $F(4,12) = 10.45, p < 0.001$, and regression of frequency on dose yielded $r = 0.81$ ($p < .0001$). Higher-order regressions did not significantly improve the fit.

Figure 4 shows the records of responding for one rat. With short half-times (<20 s), performance was similar to that observed in conventional self-stimulation. Animals spent most of the time responding, and the stimulation frequency fell to zero after each reinforcement. The mean frequency of brain stimulation maintained was in the range of frequencies used in conventional self-stimulation (75–250 Hz). With longer elimination half-times (>20 s), the rats' behavior more closely resembled drug self-administration in that the response rate was low and responses occurred at intervals that seemed to top-up the stimulation frequency when it fell too low (Fig. 4). Although response rate fell as the elimination half-time increased, the compensation was incomplete and mean frequency continued to rise. Similarly, in drug self-administration, though the rate of self-administration falls as unit dose increases, the total drug intake continues to increase (48,49,52).

In drug self-administration, interresponse times are short at the beginning of a session and become longer and relatively uniform as drug concentration increases (54). Likewise, rats self-administering brain stimulation took several doses in rapid succession at the beginning of the session and the average frequency was then raised to a level maintained by bouts of responding at regular intervals (Fig. 4). Not all subjects respond as regularly as the one shown in Fig. 4. In particular, some subjects (e.g., see Fig. 6) responded more slowly during the second and third hour of the session. In either case, the pattern of responding was consistent from one session to the next. Rats showed no signs of aversion or distress during

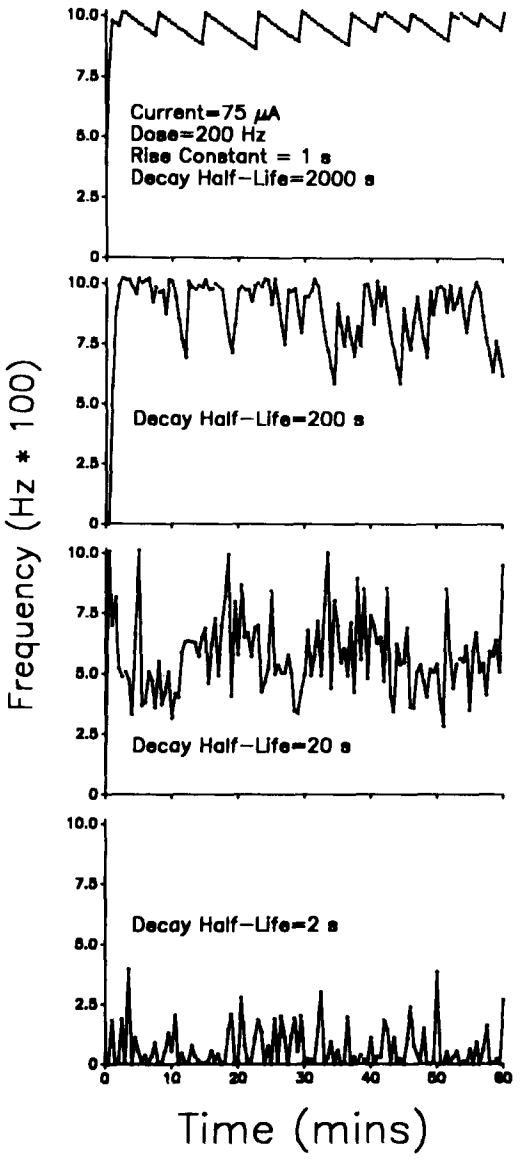

FIG. 4. Pulse frequency of continuous brain stimulation maintained over 1 h of self-administration of brain stimulation by a single rat during sessions of responding for trains with decay half-lives of 2000, 200, 20, or 2 s. Stimulation frequency is sampled every 30 s.

long-lasting trains of stimulation. At the beginning of a session, they were very active and spent most of their time in rearing and sniffing or locomotion. In the second and third hour, activity declined, and in some rats the rate of responding also slackened. At this time, rats were observed to be sitting quietly while stimulation continued at several hundred Hz. Periodically, the rat would get up and administer another dose.

It may be noted that with half-times of 200 or 2000 s the stimulation is maintained between 800 and 1000 Hz for most of the session. There have been few studies of self-stimulation with such high-frequency stimulation trains. Trains of 500–1000 Hz have been reported to be reinforcing (6,31), although the efficiency of high-frequency trains as activators of the reinforcement system is thought to reach a maximum at 200–300 Hz (30,31). Nevertheless, it has been suggested that the total reinforcing effect of an extended high-frequency train can continue to increase slowly up to approximately 1000 Hz (31). This is confirmed by our data for the 2000-s half-time where animals respond reliably to increase the frequency from 700–800 Hz to 900–1000 Hz (e.g., top panel, Fig. 4).

EXPERIMENT 3

Experiment 2 showed the operant behavior of rats self-administering brain stimulation resembles the behavior of animals self-administering drugs in several respects. In particular, animals appear to control the overall level of stimulation they receive, just as they maintain a relatively constant drug level. Another distinctive feature of drug self-administration is that animals increase the intake of a drug when the drug's effect is challenged by a dose of a pharmacological antagonist (15, 47,51,55). This is presumably because challenge with a pharmacological antagonist is functionally equivalent to reducing the dose. The reinforcing effects of brain stimulation can be also challenged by drugs that block DA receptors (13,16–18,20). To see if animals self-administering brain stimulation would compensate for pharmacological antagonism of reinforcement, we examined the effect of the DA antagonists cis-flupenthixol and pimozide on SABS.

METHOD

Subjects

Subjects were 21 rats operated as described in Experiment 1.

Procedure

Animals were screened for self-stimulation and given preliminary training as described in Experiment 2. A group of six rats were trained on conventional self-stimulation for 1-s trains of 100 Hz stimulation. The remaining rats were allowed to self-administer brain stimulation with the parameters listed below for 3 h every second day till responding was stable. Stability was defined as no more than 15% fluctuation in response rate over three consecutive sessions. SABS parameters were set at a dose of 200 Hz with an absorption half-time of 2 s, and elimination half-time of 330 s. To prevent accidental overdosing, once an increase in frequency was scheduled access to additional brain stimulation was locked out until the train reached its maximum frequency. During the lockout period, responses were recorded but not reinforced.

Drug tests were carried out over four consecutive sessions with drugs administered as follows: low dose of pimozide or *cis*-flupenthixol, vehicle, vehicle, high dose of pimozide or *cis*-flupenthixol. SABS was tested with both *cis*-flupenthixol and pimozide, conventional self-stimulation with pimozide only. The effect of *cis*-flupenthixol on SABS and pimozide on conventional self-stimulation were tested in 1-h sessions. The effect of pimozide on SABS was tested over 3-h sessions.

Drugs

Preliminary trials indicated that low doses (0.1–0.2 mg/kg) of *cis*-flupenthixol or pimozide would increase SABS, while after higher doses responding became unstable. Pimozide (0.1 or 1.0 mg/ml) was dissolved in 3% tartaric acid and 1 ml/kg of the appropriate solution was injected 4 h before the start of the test session. Flupenthixol (0.1 mg/ml) was dissolved in water and injected 1 h before testing. All drugs were administered IP.

RESULTS

Cis-flupenthixol

A dose of 0.1 mg/kg of the D_1/D_2 antagonist *cis*-flupenthixol increased SABS responding in five of six rats compared to a vehicle injection. Mean self-administration rates were increased from 55.6 to 69.8 per hour ($p < 0.05$, Wilcoxon test). The higher dose of *cis*-flupenthixol (0.2 mg/kg) did not alter response rate.

Pimozide

Figure 5 shows the effect of pimozide on SABS during a 3-h session and on conventional self-stimulation during a 1-h session. During the first hour, 0.1 mg/kg pimozide increased the rate at which rats self-administered brain stimulation ($p = 0.033$; Wilcoxon test) and raised the mean brain stimulation pulse frequency ($p = 0.021$). The rate of SABS in both groups fell over the 3 h, but at no time did rats consistently respond more slowly under pimozide than under vehicle condition. In fact, five of nine rats responded faster in the second hour and six of nine responded faster in the third hour, although the magnitude of the differences was variable. Pimozide 1 mg/kg severely depressed the rate of self-administration in the first hour ($p = 0.008$) and eliminated responding in the second and third hours. The compensatory increase in SABS under pimozide 0.1 mg/kg can be readily seen in individual cases, one of which is displayed in Fig. 6. As can be seen in the right panel of Fig. 5, the rate of conventional self-stimulation was depressed by both 0.1 mg/kg pimozide ($p = 0.028$) and 1 mg/kg ($p = 0.028$).

DISCUSSION

Pimozide and other dopamine antagonists have been reported to reduce the reinforcing effect of brain stimulation and drugs in several behavioral models (9,17,18,20,23,28,55). A dose of 0.1 mg/kg pimozide has previously been shown to raise the frequency threshold for brain stimulation reward (17,20,28) without causing significant disruption of performance, while doses over 0.5 mg/kg cause a general depression of performance (14). In the present experiment, 0.1 mg/kg pimozide depressed conventional self-stimulation in all animals tested, confirming that pimozide reduced the reinforcing effect of single brain stimulation trains. Under similar conditions, the rate of SABS was consistently increased. Thus, the increased rate of SABS produced by low doses of pimozide or cis-flupenthixol can be interpreted as a compensation for reduced effectiveness of the reinforcer. These findings provide strong support for the view (16) that antagonistic effects of neuroleptics on self-stimulation cannot be attributed simply to motor deficits.

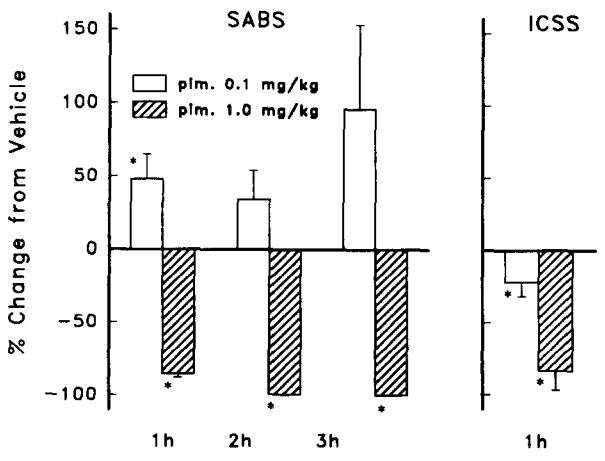

FIG. 5. Mean rates of self-administration of brain stimulation (left) and conventional self-stimulation (right) following injections of pimozide (0.1 or 1.0 mg/kg, IP) or its tartaric acid vehicle. Vertical bars are standard errors.

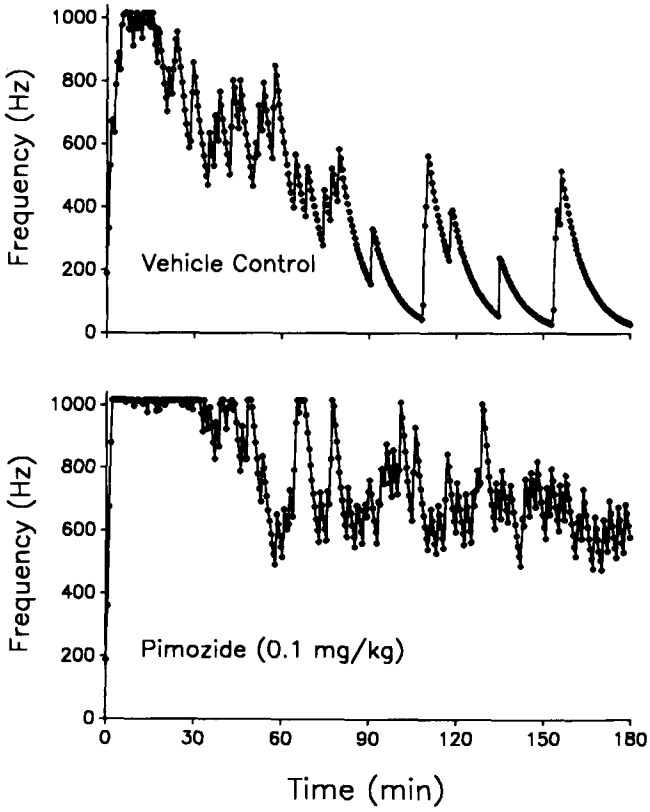

FIG. 6. Pulse frequency of continuous brain stimulation maintained over 1 h by a single rat 4 h after administration of tartaric acid vehicle (top) or 0.1 mg/kg pimozide (bottom).

Although the effect of DA antagonists on SABS is similar to their effect on drug self-administration, the increased rate of SABS is not reliable beyond the first hour or so. In comparison, the increase in psychostimulant self-administration produced by DA antagonists is more dramatic and lasts for several hours (41,50). There are several reasons why the parallel between SABS and drug self-administration might be incomplete. First, there was a ceiling to the increase in SABS due to the fact that most rats were maintaining the stimulation at pulse frequencies close to the physical limit of the frequency generator (800–100 Hz). Moreover, since these frequencies are probably near the physiological upper limit for summation of reinforcing effects (31), it is to be expected that further increases in pulse frequency would have relatively small effects on reinforcement magnitude. Thus, increasing SABS to overcome the DA antagonists would be only partially successful. Pharmacological considerations point to a similar conclusion. Amphetamine and cocaine overcome the pharmacological ef-

fects of DA antagonists so that increased self-administration not only restores the reinforcing effect but also overcomes other effects of DA antagonists. In comparison with psychostimulant drugs, DA release produced by brain stimulation is likely to be much more limited in quantity and anatomical distribution (22,43), again suggesting that increased SABS could only partially overcome the effect of a DA antagonist.

GENERAL DISCUSSION

The results of the three experiments show that when animals self-administer trains of brain stimulation that have a time course that resembles the time course of the effect a drug in the brain the pattern of responding is similar to that of drug self-administration. Animals control the level of brain stimulation and increase the rate of self-administration to compensate for decreases in the effect of stimulation caused by reduction of stimulation frequency or by drugs that reduce the reinforcing effect of stimulation.

Taken together, the results suggest that differences between the patterns of responding for brain stimulation and drugs can be largely accounted for by differences in the time course of the effects of these reinforcers on the brain. When the time course of brain stimulation is made to mimic the time course of a drug effect, there are remarkable similarities in the self-administration of brain stimulation and drugs. The fact that these similarities extend to the effects of DA antagonists on self-administration behavior supports the hypothesis that dopaminergic mechanisms play a similar role in the neural substrate of reinforcement in both paradigms (4,26).

Finally, the SABS paradigm confirms that the kinetic characteristics of a reinforcer are an important determinant of its properties as a reinforcer. This supports the view (5) that the pharmacokinetic characteristics of drugs may also be an important determinant of their properties as reinforcers of behavior. Computer control of brain stimulation allows the experimenter to mimic the effects of drugs that differ only in their kinetic characteristics or drugs that have unusual kinetic characteristics. This type of brain stimulation may, therefore, be a useful tool to study the determinants of drug self-administration and other behaviors produced by drugs.

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