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Concurrent Intracranial Self-Stimulation and Amphetamine Self-Administration in Rats[1]

ROY A. WISE, ROBERT A. YOKEL,[2] PETER A. HANSSON AND GARY J. GERBER

Center for Research on Drug Dependence, Department of Psychology, Concordia University Montreal, Quebec, Canada, H3G 1M8

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WISE, R. A., R. A. YOKEL, P. A. HANSSON AND G. J. GERBER. *Concurrent intracranial self-stimulation and amphetamine self-administration in rats.* PHARMAC. BIOCHEM. BEHAV. 7(5) 459–461, 1977. – In a two-lever testing chamber, rats had concurrent access to intravenous amphetamine and brain stimulation reinforcers. Responding for each reinforcer was generally increased above baseline rates taken when only one reinforcer was available. Amphetamine stereotypy was observed, but did not interfere with rapid lever-pressing for brain stimulation.

Drug dependence Self-stimulation Self-administration d-Amphetamine Concurrent schedule

THE VIEW that central catecholamines play a critical role in mediation of reward phenomena has recently received a good deal of attention. The data upon which this view is based are primarily from studies of brain-stimulation reward [1, 5, 8], but there is perhaps stronger evidence for catecholamine mediation of intravenous stimulant reward [3, 7, 10, 12]. The possibility that amphetamine pharmacologically activates the same reward substrate as is electrophysiologically activated by rewarding brain stimulation [6, 11, 12] makes it of interest to determine the behavior of animals offered the two rewards concurrently.

Two questions are of immediate interest: are animals capable of lever-pressing for brain stimulation during the period of vigorous stereotyped head movements that are seen between amphetamine responses, and, if so, does one of these rewards substitute for (decrease responding for) the other? To answer these questions we have begun a series of studies in which rats are given concurrent access to intravenous amphetamine and intracranial stimulation. It is clear from our initial observations that rats can concurrently maintain normal or supranormal response rates for both brain stimulation and ampetamine reinforcers, and that the delivery of one does not serve as a simple substitute for the other.

METHOD

Animals

Adult male Sprague-Dawley rats were used. Each was implanted with a lateral hypothalamic self-stimulation electrode and an indwelling venous catheter. Electrodes were stereotaxically implanted with the incisor bar 5.0 mm above the interaural line; coordinates were 0.4 mm posterior to Bregma, 1.5 mm lateral to the sagittal suture, and 8.2 mm ventral to the ependymal surface. Standard procedures for catheterization of the jugular vein were used [9], and the catheter exited through the head pedestal. Sodium pentobarbital (Nembutal) injected IP in doses of 40–60 mg/kg, was the anesthetic.

Apparatus

Rats were tested in a 23 × 23 cm box containing two response levers (Ralph Gerbrands G6312) mounted side by side on one wall, 10 cm above the grid floor. A cue lamp was located directly above each lever.

Stimulation was produced by a constant current stimulator which delivered a 0.5 sec train of 60 Hz sine wave stimulation after each lever press. Amphetamine infusions were delivered by a syringe pump (Razel Scientific Instruments) which injected 0.25 mg/kg of *d*-amphetamine sulfate in 0.25 ml of normal saline over a 28 sec injection time. Amphetamine dosage is expressed in terms of the salt.

Procedure

Each rat was tested under conditions of self-stimulation alone, amphetamine self-administration alone, and concurrent self-stimulation and self-administration. Five rats were tested in our preferred design which entailed at least five four-hr testing sessions under each condition. Both reinforcers were delivered on schedules of continuous reinforcement.

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[2] Current Address: Department of Pharmacology, University of Cincinnati, Cincinnati, OH.

Self-stimulation threshold was determined as the current necessary to sustain 10 responses per min for five min. Following threshold determination, rats were tested at stimulation intensities 5 μA above the estimated self-stimulation threshold; intensities ranged between 18 and 26 μA.

Each rat was tested separately for at least five consecutive days each with self-stimulation and self-administration reinforcers. Testing continued until responding was stable for each reinforcer, such that rates on four of the five preceding days were within 30% of the five-day mean response rate. At this point, rats were given concurrent access to self-stimulation and amphetamine self-administration levers. Drug and stimulation reinforcers were each uniquely associated with an arbitrarily assigned lever, except during tests of the lever specificity of the established self-administration and self-stimulation response patterns.

An additional seven rats were tested from between one to five days under each condition with low stimulation currents (20–25 μA) which maintained stable rates of responding; self-stimulation thresholds were not determined in these rats.

RESULTS

Rats tested for at least five days on self-stimulation and five days on self-administration showed stable responding for each reinforcer across days. Mean self-stimulation responding for individual rats for the four hr test period ranged between 300 and 3550 responses per hour. Mean *d*-amphetamine intake for individual rats ranged between 3.2 and 12.5 infusions per four-hr session. When tested under the concurrent self-stimulation, self-administration condition, rats alternated lever-pressing for the two reinforcers. Mean response rates for individual rats were between 1450 and 3900 responses per hr for stimulation, and 6.4 to 14.4 per four-hr session for *d*-amphetamine. Self-stimulation responding occurred in the intervals between responses for amphetamine. Mean response rates and variances under each condition are shown for each of five rats in Table 1, along with the number of sessions required to reach stability criterion during separate reinforcer testing. Changes in response rates during concurrent reinforcer testing as a percentage of response rates obtained during single reinforcer baseline testing are shown for the five rats in Fig. 1.

Rats responded nearly continuously for brain stimulation. While it was difficult to determine if amphetamine stereotypy was normal in this interval, it was clear that vigorous sniffing-like head movement and general activity accompanied the self-stimulation. The differential response rates were reinforcer-specific; when response contingencies were reversed the rapid self-stimulation response pattern continued for only a few responses on the now wrong (amphetamine) lever before the animals began responding rapidly on the now right (brain-stimulation) lever.

Response rates in the concurrent reinforcement condition generally increased above single reinforcer baseline rates, although the degree of increase was variable (Fig. 1). Increases in self-stimulation and self-administration were each seen in 10 of 12 rats; such increased responding is statistically significant ($p<0.034$, binomial sign test, two-tailed). The increase in self-stimulation rate was not the result of perseverative behavior induced by high doses of amphetamine; rats stopped responding for stimulation in a normal extinction pattern if the stimulator was switched off during the concurrent schedule condition.

TABLE 1

RESPONSE RATES FOR INTRACRANIAL STIMULATION AND INTRAVENOUS AMPHETAMINE INFUSIONS PRESENTED SEPARATELY AND CONCURRENTLY

	Separate Testing Mean ± S.E.		Concurrent Testing Mean ± S.E.	
	Self-Stimulation Responses/Hour	Self-Administration Infusions/Session	Self-Stimulation Responses/Hour	Self-Administration Infusions/Session
Rat 8	238 ± 65	12.5 ± 1.0	1783 ± 193	14.4 ± 0.5
N	5	4	5	5
Days to Criterion	21	11		
Rat 13	309 ± 12	3.2 ± 0.9	1450 ± 277	6.4 ± 1.0
N	3	5	5	5
Days to Criterion	3	7		
Rat 17	1984 ± 352	10.0 ± 0.6	3544 ± 162	8.4 ± 0.7
N	5	5	5	5
Days to Criterion	18	5		
Rat 19	1815 ± 81	7.6 ± 1.1	3914 ± 285	11.2 ± 1.5
N	5	5	5	5
Days to Criterion	5	6		
Rat 20	3573 ± 192	12.5 ± 1.0	3798 ± 262	14.4 ± 0.5
N	5	4	5	5
Days to Criterion	5	5		

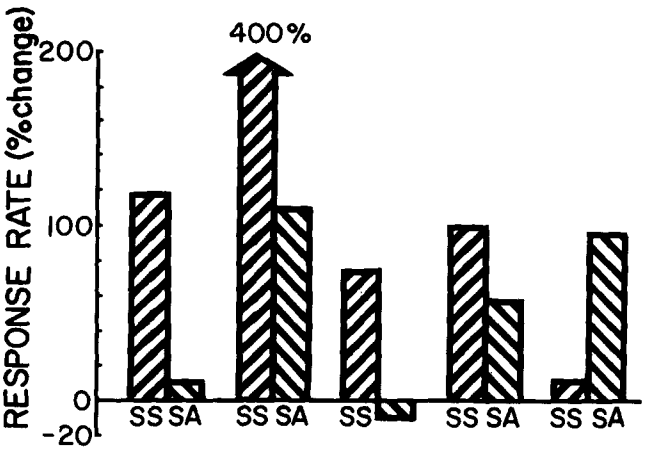

FIG. 1. Histograms showing percentage change in response rates for five rats tested in the concurrent self-stimulation, self-administration paradigm as compared with response rates obtained during single-reinforcer baseline testing. Changes from baseline are calculated using five-day mean response rates from Table 1, expressing mean responding during concurrent reinforcer testing as a percentage of mean responding during separate reinforcer testing. Similar results were obtained with seven additional animals that were tested for fewer sessions.

DISCUSSION

The maintenance of stable patterns of responding in rats given concurrent access to brain stimulation and amphetamine reinforcers establishes two important facts. First, it is

clear that rats are capable of initiating rapid and coordinated motor acts during the period of amphetamine-induced stereotypy seen between self-administered injections. It might have been thought that stereotypy would interfere with self-stimulation responding, since it was suggested at one time that the spacing of responses for stimulants themselves might be due to incapacitating high-dose effects of the drugs [10]. Our data clearly rule out this possibility: our animals made as many as 1900 lever presses between half-hourly amphetamine responses, despite vigorous stereotyped sniffing movements during this period. This observation fits nicely with observations indicating that amphetamine stereotypy is not an invariant drug-elicited motor pattern, but rather is a pattern that can be significantly controlled and modified by environmental conditions [4].

The second important fact is that amphetamine reward and brain-stimulation reward do not provide simple substitutes for one another. It is known that amphetamine generally facilitates self-stimulation, but if the hypothesis is valid that the two rewards activate a common catecholaminergic mechanism [6, 11, 12] then it is not clear why it should do so, at least for rewarding doses of amphetamine. If both rewards activate the same mechanism, why should animals work for both rewards concurrently? Why does experimenter-administered amphetamine not act a free reward and cause a period of reduced responding for earned reward in the form of stimulation? Why, in the present study, did not earned amphetamine reduce performance for earned stimulation reward?

It is too early to attempt to answer these questions from present data. Whatever the ultimate explanation, rewarding brain stimulation and rewarding amphetamine injections do not directly substitute for one another. Parametric studies are in progress to determine the ranges of current and dose parameters in which this relation holds. These studies, along with parallel studies with direct catecholamine receptor stimulants should further the understanding of the mechanism of interaction of these two rewards.

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