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Behavioral Antecedents of Cocaine-Induced Stereotypy

JEREMIAH P. COLLINS, HENRY LESSE, AND LORI A. DAGAN

Department of Psychiatry and Biobehavioral Sciences, The Neuropsychiatric and Brain Research Institutes, School of Medicine, University of California, Los Angeles, Los Angeles, CA 90024

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COLLINS, J. P., H. LESSE AND L. A. DAGAN. *Behavioral antecedents of cocaine-induced stereotypy.* PHARMAC. BIOCHEM. BEHAV. 11(6)683–687, 1979.—The effect of cocaine on discriminative behavior was determined in a study in which the subjects' ongoing behavior at the time of drug administration was manipulated. Cats were trained in a discrimination task where bar-pressing when a tone was present (S+) resulted in milk reinforcement. When the tone was absent (S−) milk was not delivered. The duration of these periods varied randomly during 30-min sessions and responses during S− delayed the next trial. Once a high level of discrimination was achieved, drug testing was begun. Ongoing behavior was manipulated by scheduling either a 5-min S+ or S− period immediately after cocaine injection (1 mg/kg). When S+ followed cocaine, stereotyped bar-pressing developed with markedly increased responding during the remainder of the session. In contrast, when S− followed cocaine, suppression of bar-pressing developed. The effect could be reversed in most subjects when stimulus conditions were later reversed. A similar experiment using rats yielded similar results. These results indicate that ongoing behavior and stimulus conditions are critically important in determing the behavioral effects of cocaine.

Cocaine Cats Rats Stereotyped behavior Discrimination

STEREOTYPED behaviors occur in a number of diverse situations. These behaviors have in common the following characteristics; they occur repetitively with little response variation, there is no apparent source of reinforcement sustaining the behaviors, and they are associated with decreased responsivity to ambient stimuli [9,16]. Examples of stereotyped behaviors are seen in schizophrenic patients, in confined animals and, most strikingly, in humans and animals following administration of certain drugs, primarily the psychomotor stimulants. The behaviors may consist of repetitive orienting reactions, head bobbing, sniffing, grooming movements; or in man, highly idiosyncratic behaviors involving complex response trains including speech, cognition and emotional reactions [13]. An understanding of the behavioral factors contributing to the development of these often bizarre response patterns may be helpful in elucidating the central actions of stimulant drugs.

While studying the electrophysiologic effects of cocaine, we observed idiosyncratic stereotyped reactions that apparently emerged from ongoing responses. For example, if cats were sniffing some part of the testing chamber or head bobbing near the observation window immediately following cocaine administration, then this behavior became stereotyped and continued with little variation for over an hour, completely eliminating a previously established operant response for food reinforcement. The food-deprived subject, when removed from the test chamber and placed on the laboratory floor with milk, would briefly drink, then jump back into the chamber and resume stereotyped behavior. Although stereotypies described in the experimental literature have consisted primarily of arousal reactions (sniffing, gnawing, etc.), there are also observations suggesting that components of operant responses may be incorporated into the drug reaction pattern, at least transiently [1, 5, 6, 15, 18]. If conditioned as well as unconditioned responses may become stereotyped, then this is a critically important factor in investigating behavioral effects of stimulants. In order to assess the role of ongoing responses in the development of stereotypies, it was necessary to control the animal's behavior immediately following drug administration. We employed a discrimination task requiring the bar-press response and manipulated behavior by controlling the discriminative stimulus, so that animals were bar-pressing or engaging in some other behavior when the drug effects occurred. Thus, if subjects were engaged in pressing, we would predict that bar-pressing or some component of this response would become the stereotyped behavior. Alternatively, if subjects were not pressing, then some other stereotyped pattern should appear which competes with bar-pressing resulting in a diminution of presses.

EXPERIMENT 1

METHOD

Subjects and Apparatus

Subjects were four adult female cats weighing 2.5 to 3 kg. Animals were maintained at approximately 90% of their ad lib weight and were 23 hours food deprived at the time of daily training and test sessions. Training and testing were conducted in a sound-attenuating chamber equipped with bar-press and milk delivery apparatus and one-way viewing

window. The food cup was located approximately 5 cm from the bar enabling simultaneous bar-pressing and milk drinking. Electronic programming and recording equipment was located in an adjacent room. White noise was present at all times.

Procedure

Cats were trained to bar-press and received daily 30-min training sessions using continuous reinforcement (0.1 ml milk/bar-press).Non-discrimination training was continued until a response rate of at least 50 responses/min was attained. A discrimination training schedule was then begun which provided reinforcement only for responses occurring when a 5 KHz tone was present (S+). When the tone was absent (S−), milk was not delivered. The duration of S+ and S− periods varied randomly. Initial values of 30-sec to 1-min were gradually increased to 1 to 5 min. To insure a high degree of discrimination, a 1-min DRL requirement was added such that bar-presses occurring in the last 1-min of each S− period delayed the following S+ period for 1 min. Thirty minute training sessions continued daily until a discrimination ratio of at least 85% (S+ responses/total responses) was obtained over three successive sessions.

Saline was then administered intramuscularly (hind limb) immediately before each session. If no disruption in task performance occurred in two successive sessions, drug testing was begun. Cocaine hydrochloride was injected (1 mg/kg, as the base; at a concentration of 50 mg/ml) in a manner identical to that of the saline injection. For two subjects, a 5-min period of bar-pressing (S+) began each saline and cocaine test session. A 5-min S− period initiated sessions for the remaining two. For all subjects, the remainder of the 30-min session consisted of random S+ and S− periods varying from 1 to 5 mins in duration. The selection of an initial 5-min period was based on previous studies indicating that the onset of cocaine-induced behavioral and electrophysiological changes occurred within this period [4,12]. Following the initial cocaine test all subjects were returned to saline control sessions until bar-press rate and discrimination was again stable. A second series of saline and cocaine test sessions were then conducted under the reversed stimulus conditions, i.e., if the first test began with S+, the second began with S−. A minimum period of 1 week was allowed between drug administrations.

RESULTS

The effect of cocaine on bar-pressing during the session differed significantly dependent upon whether the initial stimulus period resulted in bar-pressing or non-bar-pressing behavior. Perseverative bar-pressing developed when the S+ period followed cocaine administration while, in contrast, marked suppression of bar-pressing resulted when S− followed the drug. Cummulative response records for two typical subjects are shown in Fig. 1. Cat 85, exposed to an S+ period 10 sec. after cocaine injection, reacted to the tone offset with a brief slowing in response rate. Bar-pressing quickly resumed, however, and persisted throughout the remainder of the session, despite the absence of the discriminative stimulus and milk reinforcement. Note, that due to the DRL contingency, no further S+ periods occurred,

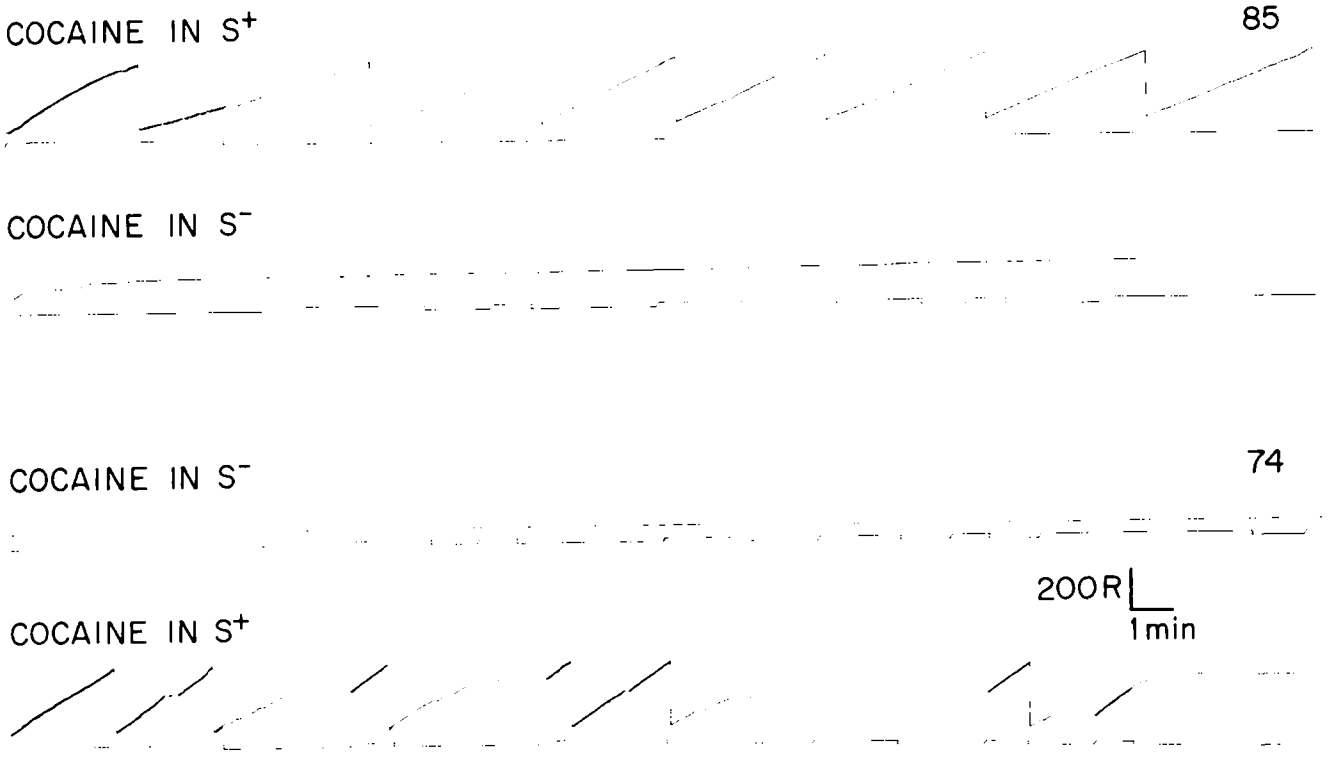

FIG. 1. Cumulative bar-presses for two cats administered identical (1 mg/k) doses of cocaine. Upward deflection of event marker indicates an S+ period. Subject 85 received an initial S+ period during the first test (upper tracing). The second tracing is of the same subject tested two weeks later but with an initial S− period. Subject 74 was treated identically except that the order of initial periods was reversed.

and no food was delivered for the succeeding 2000 bar-presses. After a series of saline sessions, a second test was conducted with an S− period following the drug. The effect of an identical dose of cocaine in the same animal now differed markedly from that of the previous test. Only a few scattered bar-presses occurred throughout the session although milk was available. During this test the stereotyped behavior consisted of repetitive head turning (an activity the cat was engaged in during the initial S− period). The results for a second subject (74) are also illustrated in Fig. 1. This cat was treated identically, except that the order of test sessions was reversed so that an S− period initiated the first cocaine test. This cat, sitting quietly, staring straight ahead toward the one-way mirror made one response during this first S− trial. With the onset of the tone the animal bar-pressed only once, quickly resumed its former immobile stance and failed to react again to presentations of the discriminative stimulus. During the subsequent S+ cocaine test conducted the following week, the animal responded normally during most S+ periods, consumed milk, but showed a marked increase in S− responding. A total of 656 S− responses were recorded as contrasted with only 40 S− presses in the preceding saline session. In addition, this cat was observed repeatedly touching the lever but with insufficient force to activate the microswitch.

When the cocaine injection was followed by an S+ trial, the mean responses for all subjects in subsequent S− periods increased by over 2000% compared with the previous saline sessions (see Table 1). When the injection was followed by an S− period, responding in subsequent S+ periods decreased over 99%. These drug effects proved reversible for three of the four cats when the initial stimulus situation was altered. Moreover, in some subjects it was possible to obtain several additional reversals of the effects. Analysis of variance indicated that the treatment by drug interaction was significant, $F(1,3)=31$, $p<0.02$. The drug by stimulus interaction was also significant, $F(1,3)=22$, $p<0.02$. As indicated in Table 1, the predicted decrease in S+ responding when cocaine was followed by an S− period was significant ($p<0.001$) as well as the increase in S− responding when S+ followed the drug ($p<0.05$), Students t-test for paired observation). No significant differences due to the order of treatment were found.

TABLE 1

COMPARISONS OF THE EFFECT OF COCAINE ON BAR-PRESSING WHEN INJECTION WAS FOLLOWED BY AN INITIAL 5 MIN S+ OR S− PERIOD

	Mean Bar-Presses ± SEM		
	Saline	Cocaine	Percentage Change
Cocaine in S−			
Cats S+	1249 ± 67	4 ± 4	− 99.7‡
S−	71 ± 32	29 ± 22	− 59.2 NS
Rats S+	510 ± 68	35 ± 19	− 93.1‡
S−	49 ± 11	33 ± 20	− 32.7 NS
Cocaine in S+			
Cats S+	1265 ± 140	896 ± 268	− 29.2 NS
S−	39 ± 1	905 ± 422	+2220.5*
Rats S+	550 ± 40	405 ± 73	− 26.4 NS
S−	33 ± 12	186 ± 47	+ 463.6†

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ (Student's t-test).

EXPERIMENT 2

Since the majority of behavioral studies of psychomotor stimulants have utilized rodents as subjects, a second experment was conducted employing two groups of rats trained in a manner similar to the cats.

METHOD

Animals and Apparatus

Subjects were 14 male Sprague-Dawley rats approximately 75-days old at the beginning of training. Subjects were reduced to 85% of their normal body weight and trained to bar-press for food(45 mg. food pellets) in a standard operant chamber (Lehigh Valley Electronics). A 5kHz tone and a small light over the bar (2.8 W) served as the discriminative stimulus. A house light provided general illumination at all times and ventilation fans supplied masking noise.

Procedure

Subjects were shaped to bar-press and received two sessions of continuous reinforcement with the 5kHz tone and stimulus light present. Discrimination training was then begun which consisted of S+ periods (5 kHz tone plus stimulus light) during which bar-presses were reinforced and S− periods (absence of tone and light) during which food was not delivered. The durations of these periods varied randomly and were gradually increased to periods varying from 1 to 5 min with a one min DRL contingency in effect during S− periods. The schedule of reinforcement was also gradually changed from continuous reinforcement to an ultimate schedule of variable ratio 10 (VR 10). The initial period of each training schedule was either a 5-min S+ or 5-min S− period. Subjects continued training on this schedule until an 80% discrimination ratio was obtained over three successive sessions. The 14 subjects were then randomly divided into two groups. One group was injected with saline intraperitoneally and immediately placed in the chamber for the 30-min session which began with a 5-min S+ period. A second group also received saline but the initial period of the session was a 5-min S− period. The following day, all subjects were administered 12.5 mg/k of cocaine hydrochloride (12.5 mg/ml) intraperitoneally and immediately placed in the chamber. The schedule used on the preceeding saline test day was repeated.

RESULTS

The results of Experiment 2 were consistent with those of Experiment 1. When cocaine administration was followed by an S+ period, significantly greater responding occurred during the subsequent S− periods. When the drug was followed by S−, significantly less responding occurred during subsequent S+ periods. Analysis of variance revealed that the treatment by drug interaction was significant, $F(1,12)=32$, $p<0.001$, as well as the drug by stimulus interaction, $F(1,12)=38$, $p<0.001$. Mean responses for both treatment groups and paired t-statistic significance levels are shown in Table 1.

The effect of cocaine on the behavior of rats appeared more variable and of shorter duration than that found in cats. In several cases this appeared due to the fact that more often only components of the bar-press response became stereotyped. For example, one subject was observed repeatedly touching the bar but with insufficient force to operate the microswitch while another was observed making pressing movements but missing the bar entirely.

DISCUSSION

The results of both the cat and rat experiments indicate that components of the behavior occurring immediately following cocaine administration became stereotyped. Stereotyped bar-pressing developed when the S+ period followed drug administration while other behaviors, which competed with bar-pressing, persisted when the S− period followed. Thus, an identical dose of cocaine administered to subjects trained on identical schedules produced markedly different behaviors dependent upon the response pattern occurring at the time of drug administration. A single administration of cocaine proved adequate for inducing either species-specific or bar-pressing stereotypies. The 1 mg/kg dose in the cat is relatively small and within the human use range [19]. The induction of the stereotyped behavior was accomplished rapidly, within 5 min. It is interesting to note that the behavioral effects of cocaine in most subjects could be reversed by altering stimulus conditions during a second administration of the drug.

The present results are not easily explained by several hypotheses advanced to account for the behavioral actions of psychomotor stimulants. For example, it has been proposed that stimulants potentiate the activity of brain reward mechanisms [17] or enhance the reinforcing effects of conditioned stimuli [8, 14, 15]. While these reward-enhancing hypotheses might correctly predict the increased responding when the S+ period followed cocaine administration, they would not account for the suppression of bar-pressing and the failure to respond to the discriminative stimulus in the S− treatment condition. Other hypotheses have emphasized the importance of rate-dependent effects in determining whether stimulants increase or decrease response rates [2,11]. However, the present results are not explained on this basis since either suppressed or increased bar-pressing was produced in subjects with similar baseline response rates and identical reinforcement schedules. Because of the reinforcing properties of stimulants, it has been proposed that "accidental" conditioning of ongoing responses may result in some on the stereotypy observed after chronic amphetamine intoxication [5,6] and following apomorphine [1]. This conditioning hypothesis would correctly predict the observed increased and decreased bar-pressing. However, if accidental conditioning were responsible for the different types of stereotyped behavior induced in the present experiments, then the temporal parameters for acquisition and subsequent extinction and reversal training were unusually brief. Several other pharmacological properties of cocaine are not capable of accounting for both the increase and the decrease in responding found under the two distinct treatment conditions. For example, the anorexic effects of the drug would explain a decrease but not an increase in responding. A cocaine-induced impairment in sensory function also is an unlikely explanation since either errors of commission or omission occurred.

The importance of the behavior occurring at the onset of the drug effect has not been recognized or controlled in many previous studies testing the behavioral effects of stimulants. These studies have employed procedures in which behavioral testing occurred immediately or was delayed for intervals as long as 30 min after drug administration. Consequently, the behavior occurring when the drug had its initial effect may have been some component of a response being measured (e.g. bar-pressing) or possibly a competing behavior which subsequently interferred with the response measured. This variation in procedures may account for some of the discrepant results which have appeared in the psychomotor stimulant literature, especially in studies involving discriminative behavior [3, 7, 10]. In many studies, however, it is unclear exactly what is happening to the subjects in the period immediately following drug administration.The present results clearly indicate that the stimulus situation as well as the behaviors occurring at the time cocaine takes effect may become powerful determinants of subsequent drug-induced behaviors. These findings may help to elucidate the origins of perserverative behaviors induced by cocaine and in addition, may account for some of the puzzling variations in responses to psychomotor stimulants observed in both laboratory and clincal situations.

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