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Sensitization to the Behavioral Effects of Cocaine: Modification by Pavlovian Conditioning

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HINSON, R. E. AND C. X. POULOS. *Sensitization to the behavioral effects of cocaine: Modification by Pavlovian conditioning*. PHARMAC. BIOCHEM. BEHAV. 15(4)559–562, 1981.—Sensitization to the behavioral effects of cocaine was more pronounced following drug administration in the presence of cues previously associated with cocaine administration than in their absence. Furthermore, sensitization was attenuated by repeated presentations of the usual predrug cues followed only by saline, i.e., sensitization was extinguishable. These findings indicate that Pavlovian conditioning contributes to sensitization, and have implications for treatment of stimulant abuse.

Sensitization Pavlovian conditioning Stereotypy Extinction Cocaine

COCAINE produces dose-dependent behavioral effects in many species, including humans, which range from slight activation of normal behaviors to the elicitation of repetitive, ritualistic behaviors [7, 8, 13]. With repeated administrations the behavioral effects of a given dose of cocaine are shifted, as if the dose had been functionally increased [7,8]. This augmentation in the behavioral effects of cocaine with repeated administrations is termed sensitization. Chronic administration of cocaine has been reported in some cases to lead to a syndrome that resembles some forms of clinical psychoses [6]. Hence, a determination of mechanisms involved in cocaine sensitization may be important to the understanding of drug-induced psychoses.

Most accounts of cocaine sensitization have implicated neurochemical and neurophysiological changes which occur as the result of repeated cocaine administrations [15]. A potential factor in sensitization which has received less attention is the contribution of conditioning which may occur over repeated drug experiences. Pavlov [5] suggested that the administration of a drug usually conforms to the operational specifications of a classical conditioning trial because the pharmacological stimulation (the unconditional stimulus, UCS) is almost always preceded by a set of cues (the conditional stimulus, CS) consistently present when the drug is administered. These cues consist of the procedures, rituals, and other environmental stimuli that regularly precede drug receipt. The occurrence of conditioning involving a pharmacological UCS is revealed by presenting the usual predrug cues, but now followed by a placebo instead of the drug.

Conditioning with cocaine was reported as early as 1929 in an experiment demonstrating that dogs, with a history of cocaine injections, displayed conditional increases in activity to a placebo injection [16]. There have since been a number of reports of similar conditioned behavioral effects with cocaine [1, 10, 17, 18]. However, while these studies demonstrate that some cocaine-like behaviors can be conditioned, they provide no direct evidence that such conditioning contributes to the occurrence of sensitization. The present experiments were designed to test whether Pavlovian conditioning procedures might modify the occurrence of cocaine sensitization.

EXPERIMENT 1

If conditioning between predrug cues and cocaine's effects contributes to sensitization, then the occurrence of the sensitized response should vary with the presence and absence of the predrug cues; specifically, the sensitized response should be more fully expressed when tested in the presence of the usual predrug cues than when the drug-related cues are absent.

METHOD

Animals

The animals were 24 male Sprague-Dawley rats (Canadian Breeding Farms, St. Constant, Quebec), 7–8 weeks old at the beginning of the experiment. They were individually housed in a colony area maintained on a 12 hr light-dark cycle where food and water were freely available.

Design and Procedure

The experiment used two groups of 12 rats each. One group of rats received 13 cocaine and 13 saline intraperitoneal injections on an alternating schedule with an injection occurring every other day. Each substance was injected in a different environment. Cocaine injections (the first at 30

mg/kg, and the remaining 12 at 40 mg/kg) were given in a distinctive room environment characterized by noise at 75 dB above 20 $\mu N/m^2$ and dim red-light illumination. For each cocaine injection, each rat was transported to the distinctive room in its home cage from the animal colony room where it was usually housed. It was then placed in a clear Plexiglas observation box (27×27×39 cm), injected with cocaine 15 min later, and 50 min following injection removed from the box and returned to the colony room. Saline injections for this group were given in the animal colony room: Each rat was removed from its home cage, injected, placed in the observation box for 50 min, and then returned to its home cage. There was no extraneous noise provided in the colony room which was well-illuminated. Temperature in both environments was 21.5°C±0.5°C.

The second group of rats received the same experience with the two injection environments and procedures, but, in all cases, the substance injected was physiological saline.

Finally, all rats received a single test session in which they were administered a 30 mg/kg dose of cocaine. During this test session, a random half the cocaine-experienced rats received the drug in the distinctive room, i.e., in the presence of the cues previously associated with drug receipt (Cocaine-Distinctive Room, C-DR). The remaining half the cocaine-experienced rats received the test administration of the drug in the colony room, i.e., in the absence of the drug-related cues (Cocaine-Colony Room, C-CR). In order to determine whether nonassociative aspects of the two different injection environments might differentially affect cocaine's behavioral effects during testing, a random half the saline-experienced rats received the test dose of cocaine in the distinctive room (Saline-Distinctive Room, S-DR) and half in the colony room (Saline-Colony Room, S-CR).

Data Analysis

During the test session, each rat's behavior was videotaped for 3 min at 10 min intervals for 50 min following drug injection. These video-tapes were subsequently randomly scored by one of two observers blind as to the subject's condition. Behavior was scored using a modified version of a rating scale developed for assessing the behavioral effects of amphetamine [2]. Briefly, there were 5 mutually-exclusive behavioral categories: (a) normal, inplace; (b) normal, alert, active; (c) slow patterned locomotor activity; (d) fast patterned locomotor activity; (e) stereotyped behaviors. Categories (a) and (b) were designed to reflect normal modes of behavior, while categories (c), (d) and (e) were designed to reflect increasingly more intense levels of drug-induced behavior. The amount of time each rat exhibited behavior in each of the different categories was recorded.

RESULTS AND DISCUSSION

Since all animals received a 30 mg/kg dose of cocaine during testing, it was expected that all would exhibit some degree of cocaine-induced behavior. The previously drug-naive animals (S-DR and S-CR) displayed cocaine behaviors during about 30% of the time; virtually all of which was slow patterened locomotor activity (category "c"). In contrast, the drug-experienced rats (C-DR and C-CR) showed cocaine-induced behaviors during a much larger proportion of the test session (99% and 68%, respectively). Furthermore, the cocaine behaviors displayed by the drug-experienced rats involved a more intense form of cocaine-induced behavior, stereotypy (category "e"). Results are presented and discussed only for stereotyped behaviors (category "e"), although identical conclusions are reached if all categories of cocaine-induced behavior are analyzed.

TABLE 1

MEAN PERCENT TIME (±1 SEM) STEREOTYPY EXHIBITED DURING COCAINE TEST SESSION: EXPERIMENT 1

	Substance Injected During Pretest Session	
Place of Testing	Cocaine	Saline
Distinctive Room	92.9 (± 2.0)	3.6 (±2.4)
Colony Room	47.1 (±12.8)	3.6 (±1.7)

The mean percent (±1 SEM) of time rats in each group evidenced stereotyped behavior collapsed over all five scoring intervals is presented in Table 1. The test dose of cocaine produced virtually no stereotypy in either of the drug-naive groups (S-DR and S-CR). The finding that the effects of the drug did not differ in the two drug-naive groups injected in the different environments indicates that there were no differential nonassociative influences of the two environments on cocaine's effects.

Both cocaine-experienced groups (C-DR and C-CR) displayed more stereotypy than the drug-naive groups at each of the five scoring intervals. However, cocaine-experienced rats tested in the absence of the usual predrug cues (C-CR) showed less stereotypy relative to that of rats tested in the presence of the cues previously associated with cocaine (C-DR), at each of the five scoring intervals. The difference in the level of stereotypy between Groups C-CR and C-DR increased over the five successive scoring intervals, due mostly to a diminishing level of stereotypy in animals in Group C-CR.

An analysis of variance of the data summarized in Table 1 revealed an overall group effect, $F(3,20)=37.48$, $p<0.001$, and subsequent analyses (Newman Keul's, p's <0.05) indicated that all pairwise differences were significant, except that between the two drug-naive groups.

The results of this experiment demonstrate that the display of cocaine stereotypy is directly modulated by the associative history of situational stimuli present at the time of drug administration: Stereotypy was substantially more pronounced in the presence of the usual predrug cues than in their absence despite identical pharmacological histories of the two cocaine-experienced groups. The results of a recent experiment(7) support the present results in demonstrating that sensitization to cocaine-induced hyperactivity (measured with an automated motility meter) is most pronounced following drug administration within an environmental context previously associated with cocaine.

EXPERIMENT 2

The results of Experiment 1 show that Pavlovian conditioning factors are involved in the manifestation of cocaine sensitization. If conditioning is a central factor in sensitization, then conditioning processes should also affect the loss of sensitization following termination of chronic drug experience. Sensitization to cocaine has been reported to persist with little decrement over extended drug-free periods

[11,14]. Such retention of sensitization is consistent with the suggestion that conditioning contributes to the phenomenon since conditioned responses are also well-retained unless extinguished [4]. If sensitization is in part attributable to conditioning, then it should also be decremented by extinction. That is, repeated presentations of the usual predrug cues without the drug should weaken conditioning, and thus attenuate sensitization. This expectation was evaluated in an experiment using the subjects from the previous experiment.

METHOD

Animals

The animals were the same 24 rats used in Experiment 1. Housing conditions were as described for Experiment 1.

Design and Procedure

Following the test session of the previous experiment, the rats chronically treated with cocaine received one of two treatments. Half of these rats were simply left undisturbed in their home cages for the next 36 days (C-REST), while the remaining half received placebo extinction sessions in the distinctive room environment (C-EXT). Half the rats from each of Groups C-DR and C-CR of Experiment 1 were randomly assigned to each of these two groups. These placebo extinction sessions were given in an identical manner to cocaine sessions of the previous experiment except that saline was substituted for the drug. Finally, all rats received a single test session involving a 30 mg/kg dose of cocaine administered in the distinctive room. If conditioning contributes to sensitization, sensitization should be less in rats given the extinction procedure than in rats simply left alone.

The drug-naive control animals of the previous experiment were divided into two analogous treatment groups. That is, half of these rats were left undisturbed in their home cages (N-REST) while the other half received daily saline injections in the distinctive room environment (N-EXT). Finally, these animals received a single cocaine test session in the distinctive room. These control animals provide an assessment of whether the extinction procedure itself had any effects on responsivity to the drug during testing.

RESULTS AND DISCUSSION

The test session data, presented in Table 2, were treated identically to those of the previous experiment with regard to collection, presentation, and analysis. The two control groups (N-EXT and N-REST) displayed virtually identical levels of stereotypy during the test session, which indicates that the extinction procedure itself produced no differential effect on drug reactivity. However, it is worth noting that the level of stereotypy displayed by the control groups during testing in this experiment was substantially elevated relative to the level these control animals exhibited during the test session in the first experiment. This increased reactivity to cocaine is consistent with evidence [14] that cocaine has more of an effect in older and heavier rats than in younger and lighter rats.

For the cocaine-experienced groups, rats left undisturbed for 36 days (Group C-REST) displayed virtually ceaseless stereotypy during each scoring interval on the test session. In contrast, cocaine-experienced rats subjected to the extinction treatment (Group C-EXT) exhibited less stereotypy at each scoring interval during the test session. Thus, for rats with equivalent experience with cocaine, merely withholding the drug for 36 days produced no decrement in sensitization, whereas repeated saline injections in the context of the usual predrug cues produced attentuation of sensitization.

TABLE 2

MEAN PERCENT TIME (±1 SEM) STEREOTYPY EXHIBITED DURING COCAINE TEST SESSION: EXPERIMENT 2

Treatment During Drug-Free Period	Previous Drug Experience: Extensive Cocaine Exposure*	Previous Drug Experience: Single Cocaine Exposure*
Extinction	68.4 (±12.2)	49.3 (± 4.6)
Rest	97.7 (± 1.0)	48.1 (±10.4)

*Animals in the extensive exposure groups had 14 previous cocaine injections (13 during the pretest sessions and 1 during the test session of Experiment 1). Animals in the single cocaine groups had only the test session cocaine administration (30 mg/kg) from Experiment 1.

The impressions gathered from examination of Table 2 were confirmed by an overall groups effect, $F(3,20)=7.64$, $p<0.005$, with the only significant pairwise comparisons being those contrasting Group C-REST with all other groups.

GENERAL DISCUSSION

The present experiments demonstrate that cocaine sensitization is influenced by Pavlovian conditioning processes. The first experiment showed that the amount and intensity of cocaine behavior displayed by cocaine-experienced rats was controlled by the presence and absence of cues previously coincident with cocaine experience. The second experiment demonstrated the cocaine sensitization was attenuated if the usual predrug cues were subjected to Pavlovian extinction during a drug-free period.

As indicated previously, the administration of cocaine produces several neurochemical changes which have been suggested to underlie cocaine's behavioral effects. The present findings showing Pavlovian control of sensitization suggest that the neurochemical mediators of cocaine-induced behavior may themselves be under Pavlovian control.

The present findings have clinical implications for treatment of the effects of chronic cocaine use. An important facet of chronic cocaine use is that prolonged use may produce psychotic-like behavior. Reducing the capacity of drugs to produce such behavior should be an important aspect of treatment. The results of the extinction experiment indicate that merely withholding the drug does not diminish the capacity of subsequent drug administrations to produce intensified behavioral reactions. Rather, it is necessary for the stimuli normally associated with drug administration to be repeatedly presented without the drug in order to neutralize the sensitizing effects of the previous drug history.

The present research demonstrates that Pavlovian conditioning is involved in the augmented drug responsiveness that results from chronic cocaine administration, i.e., sensitization. Several recent reports [3,12] have shown that Pavlovian conditioning is involved in some instances of decreased drug responsivity following chronic drug exposure, i.e., tolerance. Hence, at a general level a consistent picture

emerges–Pavlovian conditioning is involved in altered drug effects which result from chronic drug experience, whether such alteration involves sensitization or tolerance. In spite of the pervasiveness of conditioning in altered drug responsivity demonstrated by this research, there remains the intriguing question of why some drug effects evidence sensitization while others show tolerance.

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