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Cocaine Preexposure Sensitizes Conditioned Fear in a Potentiated Acoustic Startle Paradigm

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BOROWSKI, T. B. AND L. KOKKINIDIS. *Cocaine preexposure sensitizes conditioned fear in a potentiated acoustic startle paradigm.* PHARMACOL BIOCHEM BEHAV **49**(4) 935-942, 1994. – The consequences of chronic cocaine administration on fear-potentiated startle were evaluated in two experiments. Cocaine treatment (40 mg/kg) for 7 days prior to fear acquisition (light + shock pairings) had an attenuating influence on the ability of the conditioned stimulus (CS) to increase acoustic startle. When cocaine was administered in the context of the CS, following fear conditioning, a marked enhancement of potentiated startle was observed. In contrast, an extinction of the fear response was seen in saline and procaine animals repeatedly exposed to the nonreinforced CS. The results from control subjects injected with cocaine either in the shock chambers (contextual cues) or in their home cage environment, suggest that the systemic effects of this stimulant served to intensify the fear-eliciting properties acquired by the CS during fear conditioning. These findings demonstrate a cocaine sensitization of conditioned fear, and were related to the emotional and psychological disturbances associated with long-term cocaine use.

Cocaine Fear conditioning Sensitization Acoustic startle Acquisition Extinction

COCAINE preexposure enhances its acute locomotor-activating properties (4,21,24,37,43), and a sensitization of cocaine's rewarding effects has been demonstrated in self-administration (22), intracranial self-stimulation (30), and place conditioning (34) paradigms. The evolution of psychomotor sensitization has theoretical implications concerning the drug's potential for influencing emotional and psychological processes. It is known, for example, that cocaine use in humans is associated with an increased risk of anxiety and panic attacks (1,2,42), and after high doses or chronic intake, suspicious and paranoid behavior is often observed (36,40,42). Although stimulant-induced sensitization has been presented as a mechanism for drug addiction and craving (38), it is not clear whether a similar process is involved in precipitating the psychiatric disturbances associated with long-term exposure to cocaine.

To evaluate the consequences of cocaine treatment on fear motivation, the present study determined the effects of this stimulant on the acquisition and the extinction of a conditioned emotional response. In Pavlovian fear conditioning, a CS is paired with foot shock and the conditioned response to the previously neutral CS is assessed. The CS elicits behavioral and autonomic nervous system changes similar to the fear and defensive responses ordinarily produced by innate threatening stimuli (6,7,16,32,33).The potentiated acoustic startle task provides a reliable measure of conditioned fear (10-12,31). Following the pairing of a CS (light) with foot shock, the presentation of the CS increases the amplitude of the acoustic startle reflex (9,14). Fear-potentiated startle is modulated by the amygdaloid complex (19,35), and is sensitive to extinction procedures (15) and to anxiolytic compounds (5,13). The relevance of this paradigm in assessing anxiety associated with fear conditioning has been demonstrated in humans. The eyeblink component of the startle reflex is enhanced by a CS previously associated with shock (39,41), and by anticipatory anxiety arising from the threat of shock exposure (18). The present experiments examined the effects of chronic cocaine administration on conditioned fear as measured by potentiated acoustic startle.

METHOD AND MATERIALS

Subjects

Eighty-one male Wistar rats (Charles River, Quebec) served as subjects in this study. Animals weighed approximately 250 g at the beginning of the experiments, and were housed individually with free access to food and water. Experimental sessions were conducted during the light portion of a 12 L : 12 D cycle.

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Apparatus

The shock apparatus involved two identical styrofoam compartments (39 cm × 39 cm × 34 cm; outside dimensions) enclosing a circular stainless steel cylinder (27.5 cm diameter), with a floor made of stainless steel bars spaced 1 cm apart. A 6.3 volt Spectro miniature lamp located in the center of the styrofoam top of each shock chamber, 24 cm above the grid floor, served as the CS. The unconditioned stimulus (UCS) consisted of 400 μA of scrambled foot shock that was produced by a constant current generator (Schnabel Electronics, Saskatoon).

Acoustic startle was assessed in two cages (15 × 9.5 × 8 cm) constructed from wire mesh on a Plexiglas frame, each housed separately in a sound-attenuated styrofoam chamber (33 × 26 × 27 cm; inside dimensions). The cages were suspended 4 cm above the center of a strip of Piezo film (29 × 23 cm). The Piezo was insulated by cardboard, covered by a thin plate of glass, and was protected by a mylar sheath. A light (6.3 volt Spectro miniature lamp) was situated 4 cm above the wire mesh cage, and embedded in the side-wall of each styrofoam box was a high-frequency speaker (10 cm diameter). The acoustic stimulus was produced by a Grass-Stadler 901E white-noise generator, and consisted of a 100 ms white-noise burst that had a rise-decay time of 5 ms. Background noise in the chambers was 55 dB and was determined by a Simpson (model 860) sound level meter (A scale).

Fluctuations in voltage output resulting from movement on the Piezo strip were measured and amplified by a specially designed sample-and-hold circuit interfaced to a PC 386 computer. Frequencies higher than 12 Hz were filtered out. The peak voltage amplitude was recorded for the 100 ms interval immediately prior to the presentation of the acoustic stimulus (prestartle movement amplitude), and for 100 ms following the onset of the white-noise burst (acoustic startle amplitude).

Procedure

Experiment 1—cocaine administration prior to fear conditioning. All subjects were tested for acoustic startle [20 white-noise presentations with a 20 s interstimulus interval (ISI)] on each of 2 days. During these sessions, noise intensities (90–105 dB) were adjusted such that the peak startle response for each animal was in the 200–300% range of their respective prestartle movement amplitudes. Forty-eight hours later, subjects were assigned to two drug treatment groups (n = 9) based on equalized average startle scores, and received an intraperitoneal (IP) injection of either saline or cocaine hydrochloride (40 mg/kg) once-daily for 7 consecutive days.

The fear-conditioning procedure was initiated 24 h following the last drug administration. On each of 3 successive days, animals were placed in the shock chambers and exposed to 30 CS/shock pairings with an ISI of 56.5 s for a total of 90 conditioning trials. The duration of the CS was 3.5 s, and foot shock was delivered during the last 500 msec of the CS interval.

Two days after fear conditioning animals were tested for potentiated startle. They were presented with 40 noise bursts (20 s ISI) in the acoustic startle chambers using each rat's predetermined dB level, and 40 trials of the light + white noise. The duration of the CS was 3.5 s and the noise pulse was introduced during the last 100 ms of the CS interval. The order of the 40 noise and CS + noise trials was counterbalanced between animals in each drug treatment group.

Experiment 2—cocaine administration following fear conditioning. Subjects were screened for acoustic startle and assigned to three experimental groups (n = 18) based on similar startle means. Forty-eight hours later they received 30 CS/shock pairings on each of 3 successive days (90 conditioning trials). The chronic drug administration phase of the experiment was initiated 24 h after the last fear conditioning session. For 7 consecutive days, one-half of the rats in each group (n = 9) received a daily IP injection of cocaine hydrochloride (40 mg/kg), and the remaining half were administered saline. The drug treatments were delivered in one of three environments. Animals were injected either in their home cage, were placed in the shock chamber for 30 min after drug administration, or were treated in the shock chamber and received 30 presentations of the CS (3.5 s duration with a 56.5 s ISI). Rats were not exposed to foot shock during drug treatment in the shock chamber and shock chamber + light environments, and 48 h after the last drug injection subjects were tested for potentiated startle using the procedure described in Experiment 1.

RESULTS

Experiment 1—Cocaine Administration Prior to Fear Conditioning

Prestartle movement and acoustic startle amplitudes were analyzed separately using a 2 (drug treatment) × 2 (stimulus condition) analysis of variance (ANOVA) with repeated measures on the latter factor.

The left panel of Fig. 1 shows the mean (+SEM) prestartle amplitude recorded during the 100-ms interval immediately prior to the presentation of the acoustic stimulus. This measure provides an index of the possible startle-like effects elicited by the CS. Movement during the CS was comparable to that seen in the noise-alone condition, and was not significantly influenced by cocaine preexposure.

Acoustic startle as a function of CS presentation and drug administration is depicted in the center panel of Fig. 1, and ANOVA of these data yielded a significant main effect for stimulus condition, $F(1, 16) = 48.95$, $p < 0.001$. Newman-Keuls analysis ($\alpha = 0.05$) showed that both saline and cocaine pretreated animals exhibited an enhanced startle reflex when the CS was presented together with the white noise.

The difference score [(light + noise) − (noise)] represents the magnitude of fear-potentiated startle (12) and is shown in Fig. 1 (right panel). Animals preexposed to cocaine demonstrated a marginally significant decrease in conditioned fear, $t(16) = 1.83$, $p < 0.09$.

Experiment 2—Cocaine Administration Following Fear Conditioning

The prestartle and acoustic startle results are depicted in Figs. 2–4. Analysis of the prestartle amplitude data found significant main effects for drug environment, $F(2, 48) = 7.48$, $p < 0.002$, drug treatment, $F(1, 48) = 9.44$, $p < 0.004$, and stimulus condition, $F(1, 48) = 7.16$, $p < 0.01$. A reduction in movement during the CS was observed, and cocaine treated rats showed an overall decline in prestartle amplitudes. As well, movement levels of animals injected in their home cage were lower relative to the other environmental conditions.

For the acoustic startle results, the ANOVA revealed a significant 3 (drug environment) × 2 (drug treatment) × 2 (stimulus condition) interaction, $F(2, 48) = 7.14$, $p < 0.002$. Newman-Keuls multiple comparisons ($\alpha = 0.05$) indicated that the CS enhanced the amplitude of the acoustic startle

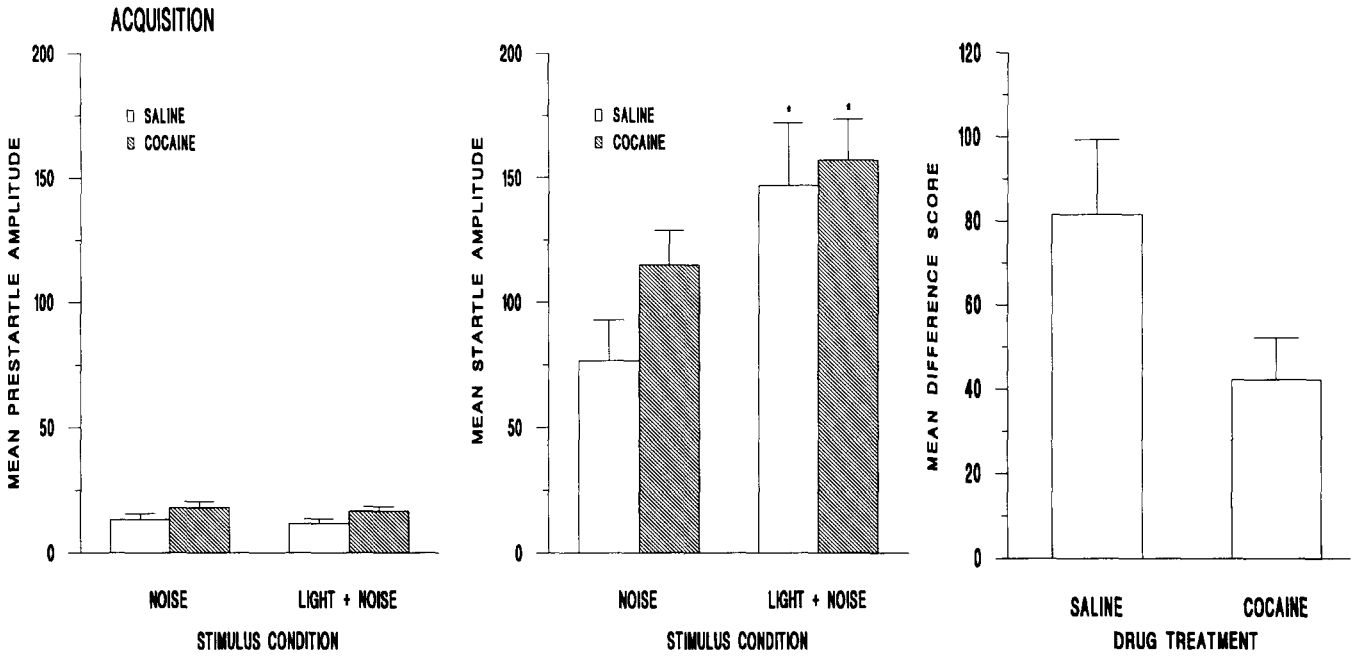

FIG. 1. Mean (+SEM) prestartle startle (left panel) and acoustic startle (centre panel) amplitudes as a function of noise-alone and CS + noise presentation. Animals received chronic exposure to saline or cocaine prior to fear conditioning. Mean (+SEM) difference scores [(CS + noise) − (noise)] are depicted in the right panel of the figure ($*p < 0.05$).

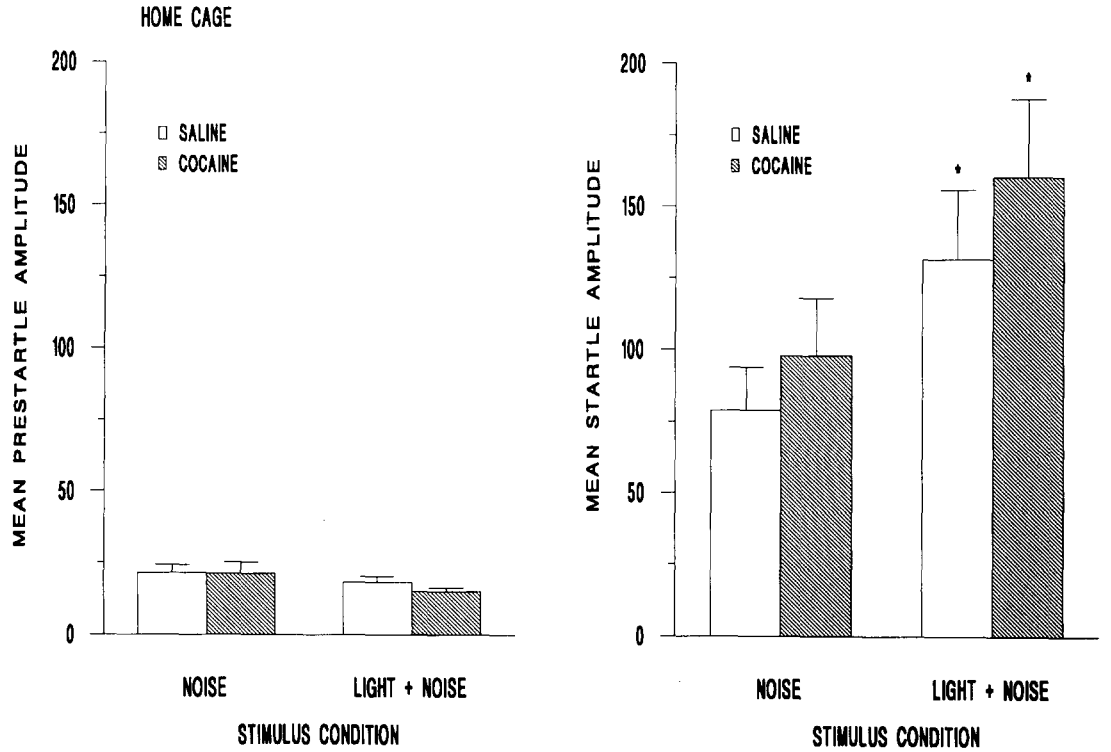

FIG. 2. Mean (+SEM) prestartle and acoustic startle amplitudes as a function of chronic saline and cocaine treatment in the home cage environment following fear conditioning and stimulus condition during testing ($*p < 0.05$).

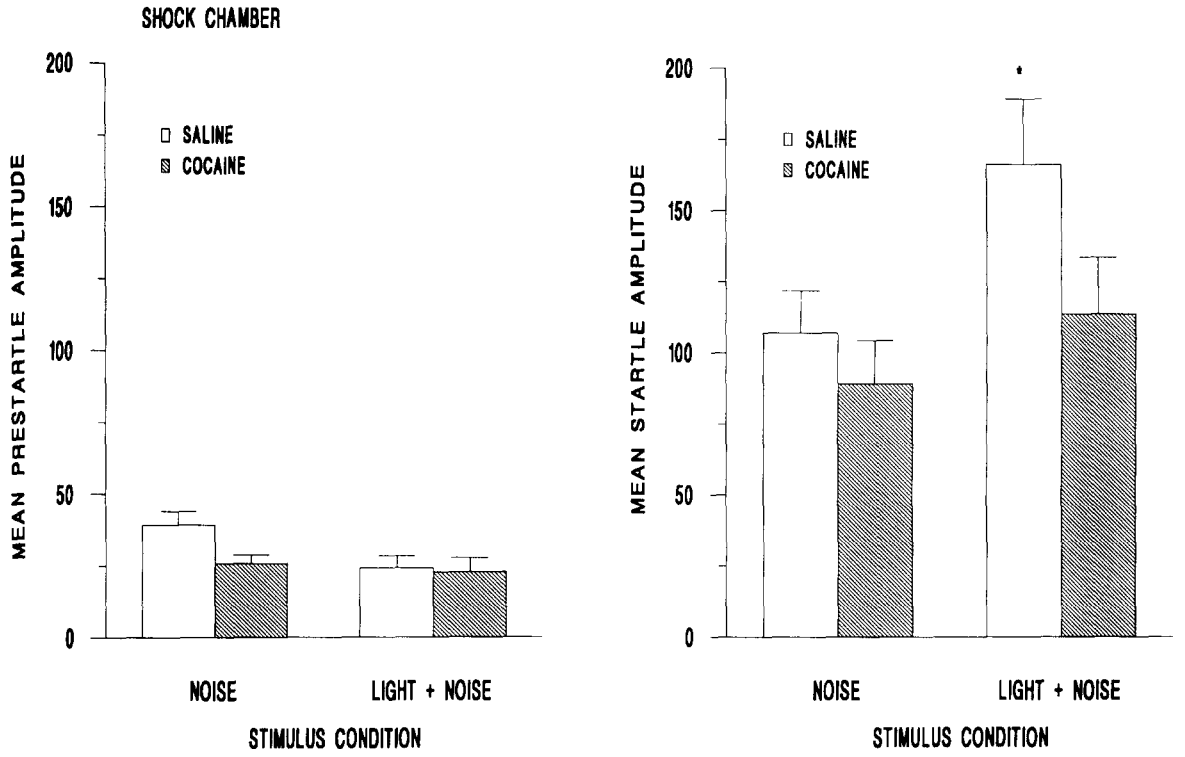

FIG. 3. Mean (+SEM) prestartle and acoustic startle amplitudes as a function of chronic drug treatment in the shock chambers following fear conditioning and stimulus condition during testing (*$p < 0.05$).

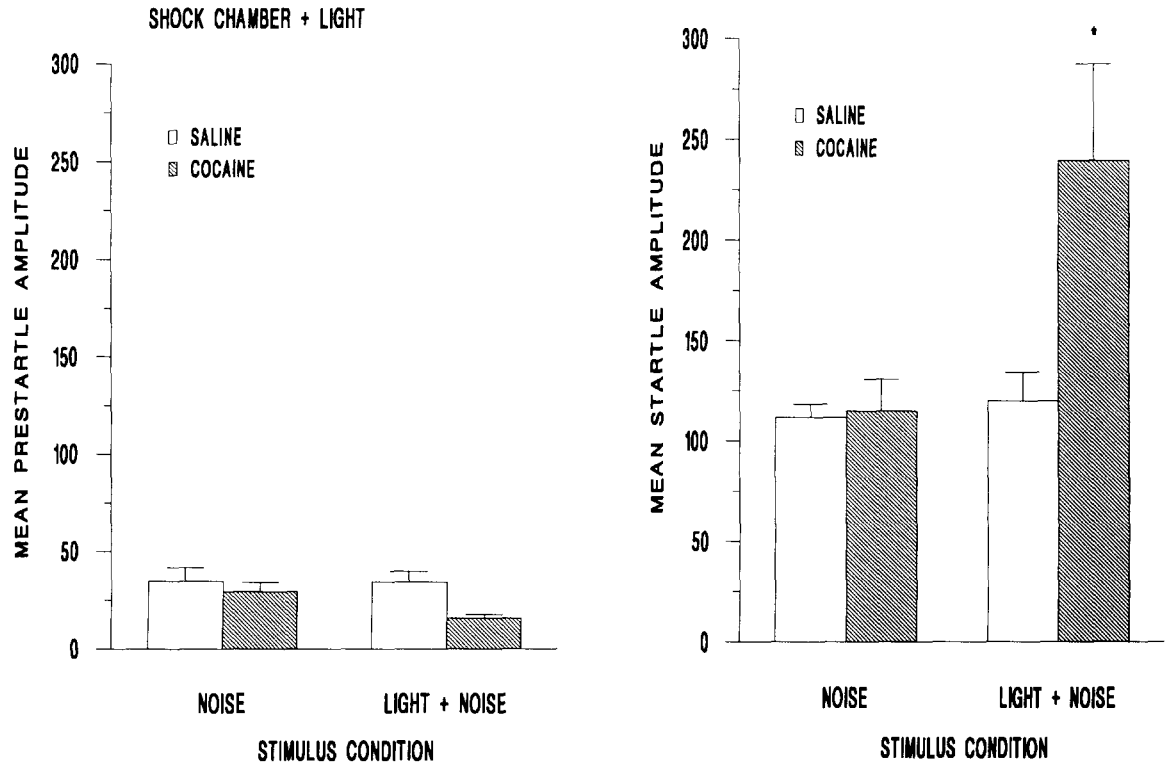

FIG. 4. Mean (+SEM) prestartle and startle amplitudes after repeated pairings of saline or cocaine with the CS during extinction and stimulus condition during the test session (*$p < 0.05$).

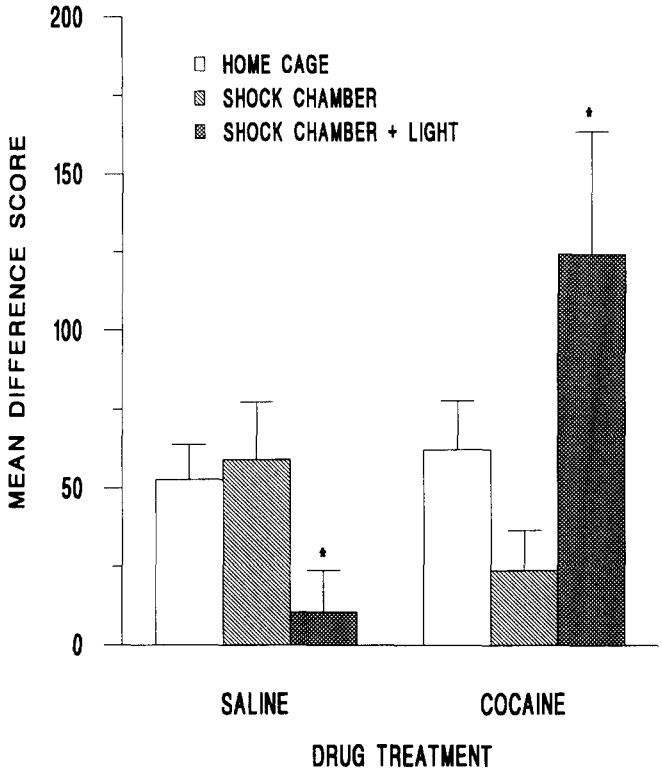

FIG. 5. The magnitude (difference scores) of the fear-potentiated startle response as a function of drug preexposure and drug treatment environment (*$p < 0.05$).

reflex of the home cage group, and no differences in fear-potentiated startle were evident as a function of drug administration (see Fig. 2).

A CS-induced increase in startle was also observed in animals that received saline in the shock chambers; however, a similar effect was not apparent in cocaine treated subjects (see Fig. 3).

Rats exposed to the nonreinforced CS during chronic saline treatment showed an extinction of fear-potentiated startle, whereas repeated daily cocaine/CS pairings augmented the effects of the CS on acoustic startle (see Fig. 4).

As shown in Fig. 5, the most striking results involved the shock chamber + light groups. ANOVA of the difference scores revealed a significant interaction between the drug treatment and drug environment variables, $F(2, 48) = 6.78$, $p < 0.003$. Saline + CS animals had lower difference scores as compared to the other treatment conditions with the exception of the cocaine-shock chamber group. Cocaine administration in the context of the CS, on the other hand, significantly increased the magnitude of the conditioned fear response.

Potentiated startle was not seen when animals were injected with cocaine in the shock chambers, and to better understand these results the data from the CS + noise test sessions were analyzed over 10 blocks of four trials. A drug treatment × drug environment × trial block interaction, $F(18, 432) = 2.30$, $p < 0.002$ was observed. A significant decrease in the fear-eliciting properties of the CS over trials was evident in all groups, with the exception of animals that were treated with saline in the shock chamber + light environment (see Fig. 6).

In the cocaine-home cage condition, startle amplitudes on trial blocks 2–4 were significantly higher than those of the saline-treated subjects. With respect to the cocaine-shock chamber group, a CS-elicited potentiation of startle, similar

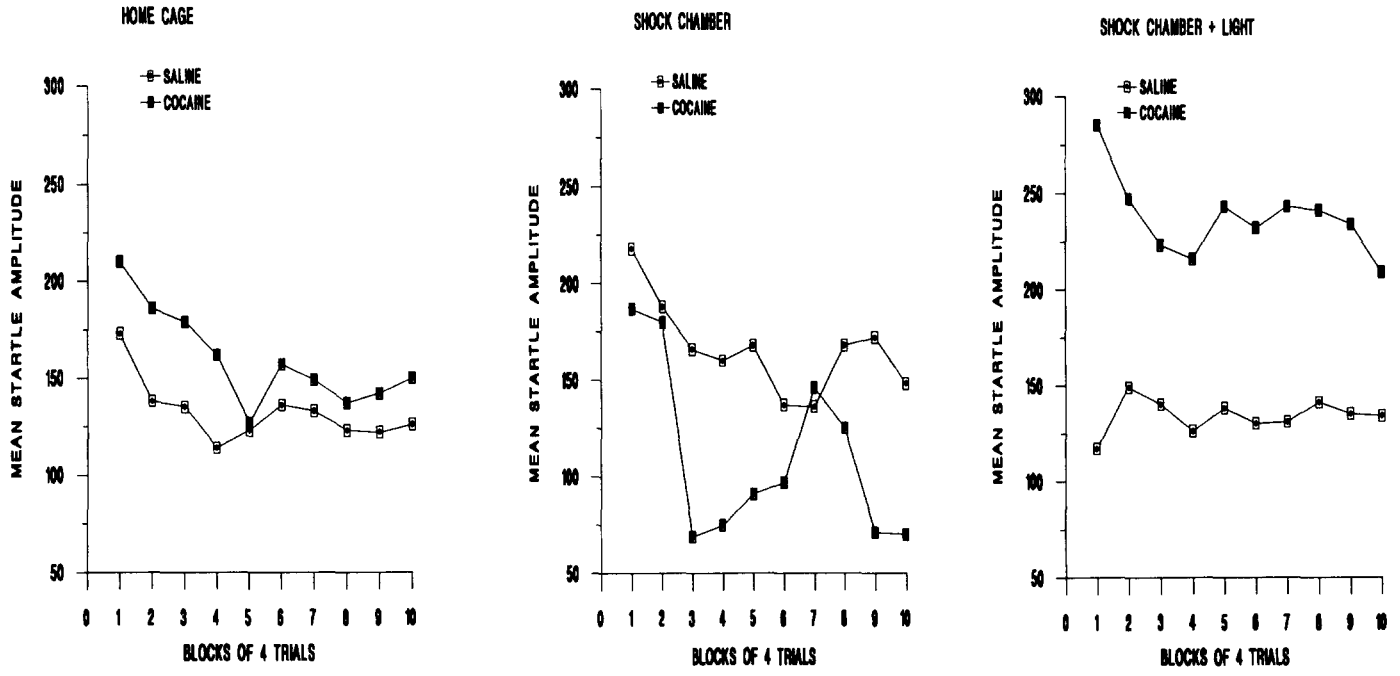

FIG. 6. Acoustic startle amplitudes during the CS + noise test sessions shown over 10 blocks of four trials following saline and cocaine treatment in the home cage, shock chamber, and shock chamber + light environments.

in magnitude to that of the saline controls, was apparent during the first two blocks of CS presentation. This was followed by a significant decrease in startle amplitudes on trial blocks 3-5, 9 and 10. Enhanced potentiated startle was observed on all trial blocks in animals preexposed to cocaine and the CS.

Factoring out baseline acoustic startle from the CS + noise data yielded a similar pattern of results ($F(18, 432) = 2.23$, $p < 0.003$ for the drug treatment × drug environment × trial block interaction). In addition to the extinction (saline + CS) and sensitization (cocaine + CS) effects, increased conditioned fear was apparent in the cocaine-home cage group (trial block 3), and cocaine-context animals showed a significant decline in the difference scores on trial blocks 3-5 and 9 (see Fig. 7).

Procaine Effects on Fear-Potentiated

To determine whether the cocaine sensitization of conditioned fear involved its anesthetic properties, experimentally naive rats ($n = 9$) were tested for fear-potentiated startle following chronic exposure to an equimolar dose of procaine hydrochloride (32 mg/kg) in the shock chamber + light environment. The procaine data were analyzed together with the saline and the cocaine difference scores from Experiment 2, and the one-way ANOVA yielded a significant drug treatment effect, $F(2, 24) = 6.92$, $p < 0.004$. As shown in Fig. 8, the difference values for the procaine subjects were comparable to that of the saline group, indicating an extinction of the conditioned fear response.

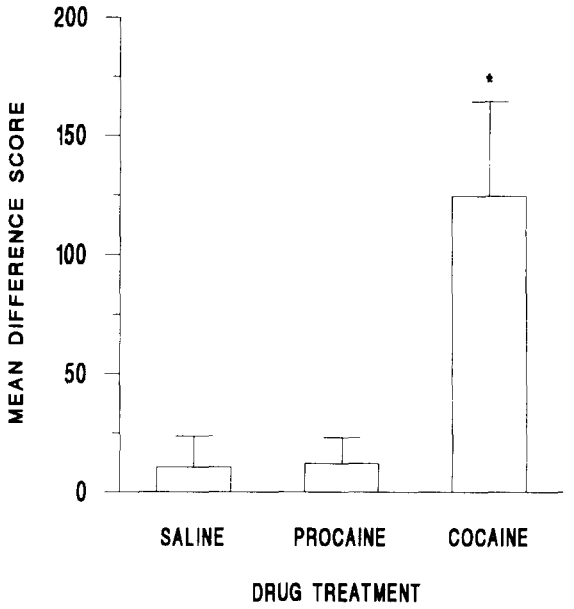

FIG. 8. Mean (+SEM) difference scores of procaine treated rats during extinction (procaine + CS) presented together with the saline and cocaine difference scores depicted in Fig. 5 (*$p < 0.05$).

DISCUSSION

The purpose of these experiments was to evaluate the effects of repeated cocaine administration on fear-potentiated acoustic startle. Animals exposed to CS/shock pairings exhibited an enhanced startle response when the CS was presented together with the white-noise burst. The CS did not augment prestartle movement amplitudes, suggesting that potentiated startle involves the interaction between the acoustic stimulus and the fear-eliciting properties of the CS (10,11,31).

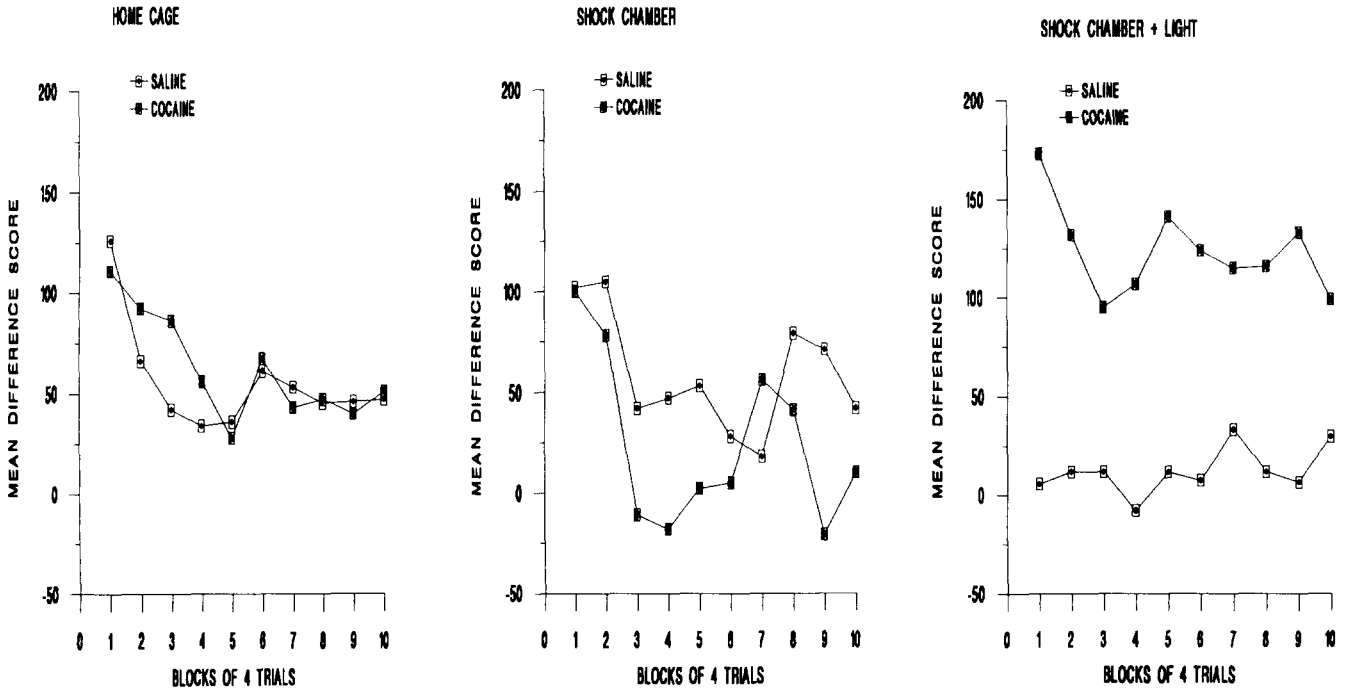

FIG. 7. Mean difference scores [(CS + noise) − (noise)] over 10 blocks of four trials as a function of drug treatment in the home cage, shock chamber, and shock chamber + light environments.

Following fear acquisition, cocaine administered in the context of the CS increased the magnitude of the conditioned fear response. The cocaine sensitization does not represent a general effect of the drug on emotional behavior, since 7 days of drug treatment prior to fear conditioning had an attenuating influence on potentiated startle. Exposure to the nonreinforced CS during procaine treatment resulted in the extinction of conditioned fear. This observation implicates the central neurochemical consequences of cocaine on the enhancement of fear motivation.

Relative to the substantial fear sensitization seen after cocaine/CS pairings, cocaine administration in the home cage environment produced a small rise in conditioned fear that was detected by the trials analysis, and in contrast to both of these drug treatment groups, cocaine injections in the shock chambers reduced the overall ability of the CS to potentiate startle. Together, these results demonstrate that once a fear response is established, cocaine can produce a modest increase in conditioned fear and this effect is magnified considerably by exposure to the nonreinforced CS.

In contrast to the cocaine data, the presentation of the CS without the UCS to saline-treated animals resulted in the extinction of potentiated startle (15). State-dependent extinction has been observed with benzodiazepines (8) and barbiturates (3), and a resistance to extinction was demonstrated after long-term amphetamine treatment (28). Because in the cocaine + CS group extinction evolved in the drugged state and behavioral testing occurred in the nondrugged state, the extinction memory may not have transferred to the acoustic startle test. Although we cannot rule out an extinction deficit, the results showing that cocaine/CS pairings augmented fear-potentiated startle above the level seen in the nonextinguished groups (home cage environment), suggest that cocaine is intensifying the fear-evoking qualities of the CS.

Cocaine administration in the shock chambers decreased the effectiveness of the CS to potentiate acoustic startle. Stimulus generalization during extinction has been shown for both classically (23) and instrumentally conditioned responses (20,27), and the finding that context-dependent extinction was apparent only in the drugged state indicates a relatively specific action for cocaine on this process. The mechanisms responsible for this effect are unclear, particularly because acoustic startle was assessed in a different environment than that used to condition fear. The observation that preexposure to the nonreinforced contextual stimuli of the shock chambers did not influence the excitatory strength of the CS on acoustic startle in saline animals, further illustrates the complexity of these results.

The effects of cocaine on contextual fear might have resulted from the counterconditioning of the stimulant and rewarding properties of the drug to the shock chamber environment. Weiss et al. (43) demonstrated context-dependent locomotor sensitization after high dose (40 mg/kg) cocaine administration, and an enhancement of place conditioning was reported following chronic cocaine treatment (34). The repeated pairing of the shock chamber cues with the psychomotor-activating effects of cocaine during extinction would serve to diminish, somewhat, the overall strength of the CS. Consistent with this hypothesis, fear-potentiated startle in the cocaine-context group was evident early in the test session, and a rapid rate of decline in startle responding was observed over trials.

Although this explanation of the data deserves consideration, it cannot account for the differential effects of cocaine delivered in the shock chamber and CS + shock chamber environments. In addition to the sensory modality-specific nature of the CS, a major distinction between these treatment conditions entails the intermittency of the CS presentation. Given the cocaine-shock chamber results, it would appear that the distinguishing feature of the fear sensitization might well involve the interrupted repeated occurrence of the CS. It is possible that cocaine administration together with a continuous 30-min CS would negate and not sensitize the expression of conditioned fear, and further research is necessary to better understand the relationship between the temporal parameters of the CS and cocaine's effects on fear motivation.

In conclusion, cocaine use can result in emotional and psychological disturbances characterized by anxiety and paranoia (1,2,36,40,42). The results of this study describe the conditions in which cocaine increases fearful behavior in animals and provide a framework for evaluating the processes underlying the cocaine fear sensitization. We can only speculate on the neurochemical and neuroanatomical correlates of this effect; however, it is known that the amygdala modulates conditioned fear (12,32), and is involved in stimulant-related sensitization (17,25,26,29). Presently, we are assessing the effects of intraamygdaloid injections of cocaine and amphetamine on fear-potentiated startle.

ACKNOWLEDGEMENTS

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