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RAPID COMMUNICATION

Effects of Cocaine on Conditioning of the Rabbit Nictitating Membrane Response

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MARSHALL-GOODELL, B. AND I. GORMEZANO. *Effects of cocaine on conditioning of the rabbit nictitating membrane response*. PHARMACOL BIOCHEM BEHAV **39**(2) 503–507, 1991.—Two experiments were conducted to determine cocaine's (0, 1, 3, and 6 mg/kg) effects on associative, nonassociative, and motor processes in classical conditioning of the rabbit's nictitating membrane response (NMR). In Experiment 1, acquisition training consisted of tone- and light-conditioned stimuli (CSs) each paired on separate trials with a shock unconditioned stimulus (UCS). Cocaine injected prior to each session significantly impaired acquisition of conditioned responses (CRs). In Experiment 2, rabbits received cocaine injections prior to each training session involving explicitly unpaired CS-alone and UCS-alone presentations. Cocaine had no significant effects upon: base rate of NMRs; frequency of NMRs during presentations of the CSs; and frequency, amplitude, and latency of the UCRs. Consequently, cocaine's impairment of CR acquisition could not be attributed to its effects upon the nonassociative processes of base rate, sensitization, and pseudoconditioning, nor upon the sensory processing of the UCS and/or motor functioning of the UCR. Rather, cocaine's effects upon CR acquisition were mediated by the drug's effect upon associative processes. It appears likely that the drug affected the ability of the CS to enter into the associative conditioning process.

Cocaine Classical conditioning Nictitating membrane response Rabbit

THE purpose of the present investigations was to determine the effects of cocaine upon associative and nonassociative processes, and the unconditioned response (UCR) in classical conditioning of the rabbit's nictitating membrane response (NMR). In particular, the current investigations determined the dose-dependent effects of cocaine (0, 1, 3, 6 mg/kg) on: (a) rate and asymptotic level of acquisition of conditioned responses (CRs) (Experiment 1); and (b) base rate, sensitization, pseudoconditioning, and UCRs (Experiment 2).

The stimulant, cocaine, has a long and well-documented history as a drug of abuse (32,44). Moreover, its subjective effects have been extensively characterized to consist of alterations in: (a) perception of stimuli; (b) energy level; (c) intellectual functioning; and (d) mood (4,41). The experimental analysis of these subjective effects can be readily undertaken by operationalizing them to involve alterations in: (a) sensory; (b) motor; (c) learning; and (d) motivational processes. Yet few studies have been directed at determining the role of cocaine upon these processes. The vast majority of experiments on the behavioral effects of cocaine have been directed at determining the drug's addictive potency by relating drug dosage to its efficacy of reinforcement of operant behavior across a range of reinforcement schedules [e.g., (10, 19, 33, 35, 39)] and species [e.g., (25, 31, 41, 46)]. Cocaine has also been shown to disrupt: operant responding over a range of FI and FR schedules [e.g., (5, 9, 18, 43, 47)]; conditioned suppression of bar pressing (28); and accuracy and rate of completing complex operant chains (3,42). Furthermore, cocaine has been reported to enhance locomotor activity [e.g., (20,34)], augment conditioned avoidance (21,26), facilitate retention of one-trial passive avoidance (24), and reinforce conditioning of place preference [e.g., (2,29)], taste (7,23) and odor aversion (40). Finally, cocaine has been demonstrated to have stimulus properties capable of exercising discriminative control over operant responding [e.g., (1, 6, 48)].

Unfortunately, the above studies have provided few, if any, unconfounded determinations of cocaine's effects upon basic sensory, motor, learning and motivational processes. In particular, the absence of appropriate control groups in those studies purporting to reveal cocaine's effects upon learning and memory precludes concluding the drug's effects were upon learning rather than upon such nonassociative factors as base rate, sensitization, and pseudoconditioning. Moreover, all previous studies of cocaine's behavioral effects have employed paradigms whose methodological characteristics have not permitted assessing the drug's effects uniquely upon sensory or motor processes. On the other hand, a number of rabbit studies have amply documented the ability of the NMR preparation to localize a drug's effects upon the acquisition of CRs to associative learning processes or to nonassociative, sensory, and motor processes [e.g., (8, 13, 14, 37, 38)]. Accordingly, the present investigations sought to de-

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termine cocaine's effects uniquely upon associative learning processes. To our knowledge, the present studies are the first to determine if cocaine will unequivocally affect learning.

METHOD

Subjects

Experiments 1 and 2 employed 48 and 36 New Zealand White albino rabbits, respectively. All rabbits weighed approximately 2 kg on arrival from Knapp Creek Rabbitry (Amana, IA). Animals were housed individually with free access to tap water. In Experiment 1, subjects were given 60 g of Teklad Rabbit Chow during their first week of stay and 90 g thereafter. In Experiment 2, subjects were given free access to Teklad Rabbit Chow, and the daily intake was recorded. Consistent with their rearing conditions, animals were kept in constant light.

Apparatus and General Procedure

The apparatus and procedure used in conditioning of the rabbit NMR have been described in detail (11,14). In brief, a 2-mm loop of surgical nylon (Ethilon 6-0) was sutured into the right NM, the surrounding hair was removed and two stainless steel wound clips (Autoclip) were attached to the skin over the paraorbital region at a distance of 10 mm posterior to the canthus and 7.5 mm above and below the midline to the canthus. One day later, the rabbit was placed in a Plexiglas restrainer and fitted with a headmount that supported a photoresistor assembly for recording NMRs by attaching to the nylon loop in the NM (12). The rabbit was then positioned in a ventilated, sound-attenuated conditioning chamber containing an 11.4-cm speaker, positioned above and in front of the animal and two 6-W, 24-V DC houselights, mounted on each side of the speaker. During the course of Experiments 1 and 2, three stimuli were employed: 1) an 800-ms, 75 dB (re: 20 $\mu N/m^2$), 1-kHz tone delivered through the speaker; 2) an 800-ms flickering light produced by interruption of the houselights at 10 Hz to yield a change in illumination, measured at the eye level of the animal, from 32.0 lux to 8.0 lux; and 3) a 100-ms, 3-mA 60-Hz shock delivered to the two woundclips in the paraorbital region by a constant current shock generator. A photoresistor assembly on the headmount converted nictitating membrane movements to electrical signals which were subjected to an analog-to-digital (A/D) conversion using a 5-ms sampling rate and a resolution of 62.5 μm of actual membrane extension. Experimental control of the presentation and duration of stimuli, A/D conversion, and response analysis were all accomplished by an Apple II/FIRST operating system (36). A response was defined as an NM extension of at least 0.5 mm, and the onset latency, amplitude and frequency of each response was recorded. Responses occurring in the CS-UCS interval were classified as CRs, whereas in the absence of CRs and on UCR-alone trials, responses occurring within 100 ms after shock-UCS onset were recorded as UCRs. During each session, baseline responding was assessed in the 800-ms interval preceding each CS onset.

Drugs

Cocaine hydrochloride was dissolved in sterile, nonpyrogenic 0.9% sodium chloride saline solution. The saline vehicle (0 mg/kg) or cocaine (1, 3, or 6 mg/kg) was injected on alternate days into the left- or right-marginal ear vein with a 25-gauge needle via a Harvard infusion pump (Model No. 975) in a volume of 0.4 ml/kg at a rate of 3 ml/min. Over the 8 consecutive days of training, the daily injections were initiated at the top of the marginal ear vein and subsequent injections were positioned at approximately equal points along the length of the vein from the tip to the base of the ear. The injections were administered to each animal approximately 30 min before each experimental session.

Adaptation

In both experiments, rabbits were given an adaptation session which was equal in length to subsequent sessions. No stimuli were presented and no drug was injected during these adaptation sessions. Base rate responding was assessed in the 800-ms interval that preceded CS onset in the subsequent acquisition sessions.

Experiment 1: Paired CS-UCS Training Under Cocaine

On the day following adaptation, rabbits were randomly assigned to one of four drug conditions ($n=12$), and received injections of either vehicle (0 mg/kg) or cocaine (1, 3, and 6 mg/kg) prior to each of 8 daily (60 min) conditioning sessions. In each conditioning session, all subjects received 60 CS-UCS paired trials at a CS-UCS interval of 800 ms. The conditioning trials were composed of 30 tone-CS and 30 light-CS pairings with the UCS. The sequence of tone-shock and light-shock trials was randomized within each 10-trial block with the restriction that no more than three consecutive presentations of the same CS could occur. Trials were presented at an intertrial interval of 60 ± 10 s, with a mean of 60 s.

Experiment 2: Unpaired CS and UCS Training Under Cocaine

Experimentally naive groups of rabbits ($n=9$) received IV injections with either saline (0 mg/kg) or cocaine (1, 3, and 6 mg/kg) approximately 30 min prior to each of 8 daily (60 min) conditioning sessions. Each daily session consisted of 120 trials composed of 30 tone-alone, 30 light-alone, and 60 shock-alone trials, so that the total number of tone-CS, light-CS, and shock-UCS presentations, and the duration of the session (60 min) was equal to that employed in the paired CS-UCS procedure. These three trial types were presented in a randomized sequence within 20-trial blocks with the restriction that no more than three of the same stimuli were presented consecutively. The intertrial interval was 30 ± 10 s, with a mean of 30 s.

Data Analysis

Repeated measures analyses of variance were performed on the data for each experiment with follow-up analyses to localize significant sources of variation carried out by the method of Tukey (45). Unless otherwise specified, levels of significance were set at the $p<0.01$ level for all analyses in each experiment.

RESULTS

Experiment 1: Paired CS-UCS Training Under Cocaine

Panels (a) and (b) of Fig. 1 present the effect of cocaine dosage (0, 1, 3, and 6 mg/kg) on the mean percentage of CRs to tone- and light-CSs, respectively, across the 8 days of acquisition training, whereas panels (c) and (d) present cocaine dosage effects on the mean number of acquisition trials required to observe the occurrence of 1 through 5 consecutive CRs to the tone- and light-CSs, respectively. A comparison of panels (a) and (b) reveals a higher overall level of responding to the tone- than

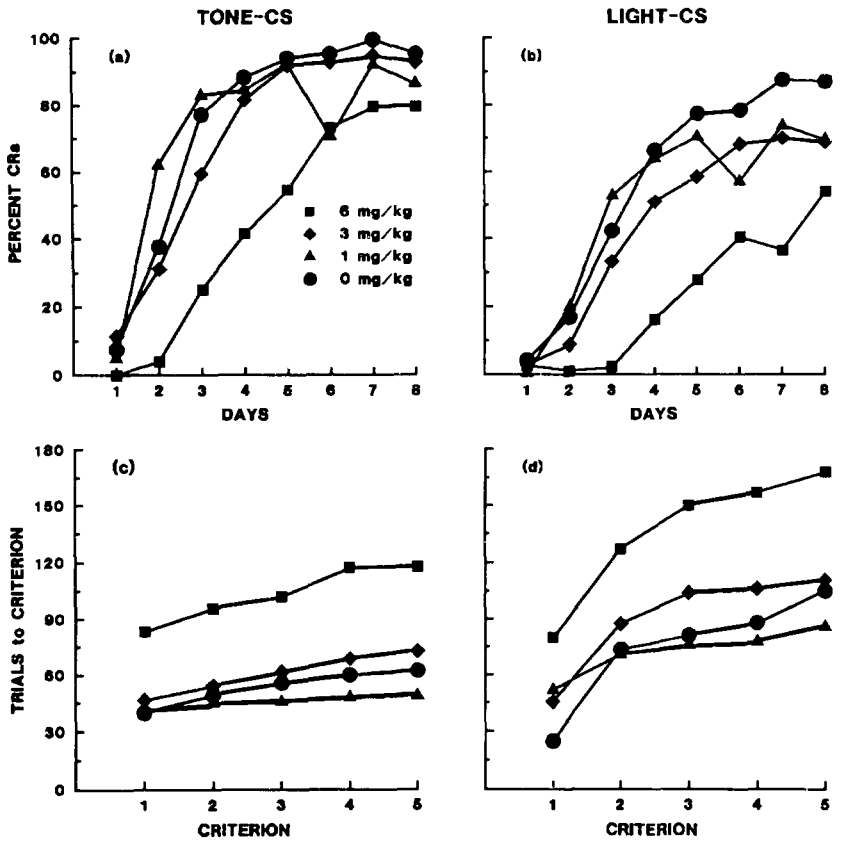

FIG. 1. Effects of cocaine on acquisition of CRs during the paired CS-UCS training. In panels (a) and (b), data are expressed as the mean percentage of CRs during each of the 8 acquisition days for (a) tone- and (b) light-CSs. Panels (c) and (d) present the mean number of trials required to reach the criteria of 1 through 8 CRs in a row for (c) tone- and (d) light-CSs.

light-CS throughout training. A further examination of panels (a) and (b) indicates that across the 8 days of training: 1) all groups acquired CRs to both tones and lights; 2) the 6-mg/kg cocaine dose impaired acquisition of CRs to the tone- and light-CS; and 3) there was a slight tendency for the 1-mg/kg dose to enhance responding to the tone and light CSs. An inspection of panels (c) and (d) of the figure indicates that, relative to vehicle controls, cocaine, at the 6-mg/kg dose, substantially increased the number of training trials required to attain the successive 1–5 CR criteria to tone- and light-CSs while cocaine at the 1-mg/kg dose slightly decreased the number of trials to each criteria. Analyses of variance conducted on percent CRs revealed significant effects of dose, $F(3,42) = 13.43$, CS modality, $F(1,42) = 90.52$, days, $F(7,294) = 109.28$, Dose × Days, $F(21,294) = 3.07$, CS Modality × Days, $F(7,294) = 7.04$, and CS Modality × Dose × Days, $F(21,294) = 2.57$. Follow-up tests localized the effect of dose to the 6-mg/kg dose of cocaine acting to impair the occurrence of CRs (CD = 18.7%). Moreover, the analysis of variance on the number of trials to criterion revealed significant effects of dose, $F(3,42) = 10.27$, CS modality, $F(1,42) = 37.8$, criterion level, $F(4,168) = 50.18$, Dose × Criterion $F(12,169) = 3.6$, CS Modality × Criterion, $F(4,168) = 18.2$, and Dose × CS Modality × Criterion $F(12,168) = 2.35$. Follow-up tests of the significant main effect of dose and the Dose × Criterion interaction revealed that animals injected with the 6-mg/kg dose of cocaine took longer to initiate 1 through 5 consecutive CRs than all other groups (CD = 36.84), and that animals injected with 1 mg/kg of cocaine took slightly fewer trials to demonstrate 3, 4, and 5 consecutive CRs than those injected with 3 mg/kg (CD = 22.13%, $p<0.05$). Responding during the 800-ms baseline interval prior to each tone and light remained low throughout training (4.2%) and was not affected by cocaine dosage.

Experiment 2: Unpaired CS and UCS Training Under Cocaine

Figure 2 presents the effects of cocaine dosage during unpaired CS and UCS presentations on the percentage of NMRs occurring during the 800-ms duration tone-CS (panel a) and light-CS (panel b) and the 800-ms duration baseline measurement period preceding each presentation of tones (panel c) and lights (panel d). An examination of these panels reveals that, regardless of the cocaine dosage, the percentage of responses across days of unpaired stimulus presentations was low both during (4.0%) and before (3.3%) the tones and lights. Consistent with these descriptive aspects of the data, an analysis of variance revealed no significant effects of cocaine dosage upon responding during the tones and lights nor during the 800-ms baseline period before the tones and lights. Moreover, an examination of the frequency, latency, and amplitude of NM UCRs elicited by the 3-mA shock UCS-alone presentations across the 8 daily sessions (figure not shown) and analyses of variance revealed no systematic effects of cocaine dosage.

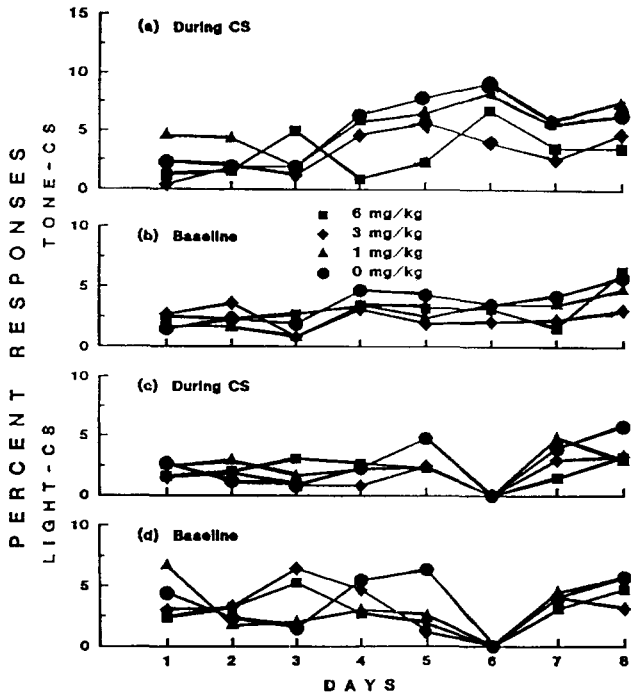

FIG. 2. Effect of cocaine on responding during the 8 days of unpaired CS and UCS training. In panels (a) and (c), data are expressed as the mean percentage of responses during the (a) tone- and (c) light-CSs. Panels (b) and (d) present the mean percentage of baseline responses during an 800-ms pre-CS period occurring immediately prior to the tone- and light-CSs, respectively.

DISCUSSION

The principal findings of the present series of investigations were that: (a) under paired CS-UCS presentations, cocaine impaired the rate of CR acquisition and overall occurrence of CRs to tone- and light-CSs (Experiment 1); and (b) under unpaired CS and UCS presentations, cocaine failed to reveal any systematic effects upon the occurrence of NMRs during the CS, the UCRs elicited by a single shock-UCS intensity, and the frequency of base rate NMRs (Experiment 2).

In Experiment 1, cocaine (0, 1, 3, and 6 mg/kg) significantly retarded the rate of acquisition and overall frequency of CRs. Although cocaine's effects upon CRs were manifested during the CS-UCS pairings of acquisition training, the pairing operation alone does not assure that the drug's effects were upon associative learning processes. Specifically, it remained to be determined if cocaine's effects upon CRs arose from its acting upon the associative CS-UCS contiguity process or from its effects upon nonassociative processes (i.e., base rate, sensitization, and pseudoconditioning), sensory processing of the CS and UCS, or motor functioning of the UCR. Experiment 2, involving the unpaired CS and UCS presentations, was principally directed at determining whether or not cocaine's effects were upon those associative processes governed by temporal contiguity of the CS and UCS under the CS-UCS pairing operations or upon nonassociative and sensory and/or motor processing of the UCS. The results of Experiment 2 indicated that cocaine affected the acquisition of CRs in Experiment 1 by operating upon associative learning processes. In particular, under unpaired CS and UCS presentations, and therefore, in the absence of CS-UCS contiguity, there was no evidence of CR acquisition nor, of course, of cocaine operating to affect the acquisition of CRs. Thus, under CS-UCS pairings, the differences in percent CRs between saline- and cocaine-treated rabbits could not be attributed to such nonassociative factors as alterations in the base rate of NMRs or differences in responsivity to the CSs due to repeated exposure to the CSs (habituation/sensitization) or the UCS (pseudoconditioning). Finally, the failure to detect any effect of cocaine upon the UCRs elicited by the 3-mA UCS-alone presentations suggests that cocaine's effects upon CR acquisition were not attributable to those mechanism(s) by which the UCS/UCR enter into the conditioning process. In sum, the present experiments unequivocally demonstrated that cocaine's effects were upon those associative learning processes by which CR acquisition occurs. In contrast, previous investigations of cocaine's effects upon conditioned avoidance (20,26), passive avoidance (24), conditioned place preference [e.g., (2,29)], and taste (7,23) and odor aversion (40), failed to demonstrate that the drug's effects were uniquely upon associative processes since no assessment was made of cocaine's effects upon nonassociative processes, sensory processing of stimuli, and motor functioning.

It should be noted that because the CS and UCS are the only components entering into the conditioning processes, the only remaining conditioning component by which cocaine could affect acquisition is the CS. However, such an assertion would require demonstrating cocaine's effects upon the sensory processing of the CS. In this regard, a number of previous NMR studies assessing the effects of drugs on learning have revealed that scopolamine's (17), haloperidol's (16), and morphine's (37,38) impairment of CR acquisition was localized to the drugs attenuating tone-CS intensity (16, 17, 37, 38). Moreover, consistent with expectations from behavioral theories of conditioning (16, 23, 29, 33), these earlier studies revealed that the rate of CR acquisition and postasymptotic levels of CRs were proportional to the drug-altered intensity of the CS. Accordingly, to the extent that cocaine's CR acquisition effects can be tentatively localized to the CS, behavioral theories of conditioning would also expect the drug to attenuate tone-CS intensity and, thereby, impair the tone-CS's entry into conditioning and the level of postasymptotic CRs. In a future series of investigations, we shall seek to determine cocaine's effects upon CS processing and, in particular, tone-CS intensity threshold and unconditioned excitatory effects of tone-CSs.

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