Pharmacology Biochemistry and Behavior, Vol. 64, No. 3, pp. 507–512, 1999

0091-3057/99/$–see front matter

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PII S0091-3057(99)00109-4

Evidence for Opponent-Process Actions of Intravenous Cocaine

AARON ETTENBERG, MARY A. RAVEN, DEBORAH A. DANLUCK AND BRIAN D. NECESSARY

Behavioral Pharmacology Laboratory, Department of Psychology, University of California, Santa Barbara, CA 93106

Received 13 November 1998; Revised 12 March 1999; Accepted 25 March 1999

ETTENBERG, A., M. A. RAVEN, D. A. DANLUCK AND B. D. NECESSARY. *Evidence for opponent-process actions of intravenous cocaine.* PHARMACOL BIOCHEM BEHAV **64**(3) 507–512, 1999.—The present experiment was devised to test a prediction of the Opponent-Process Theory of drug action. This theory presumes that the initial affective experience of a subject treated with cocaine would be diametrically different immediately after administration compared to some point later in time when the positive impact of the drug had subsided. A conditioned place-preference procedure was employed in which a novel environment was paired with the effects of cocaine either immediately after, 5 min after, or 15 min after an intravenous injection of 0.75 mg/kg cocaine. It was hypothesized that animals would come to prefer environments associated with the immediate positive effects of cocaine and avoid environments associated with the drug's subsequent negative effects. The results confirmed this hypothesis. While the 0-min delay and 5-min delay groups exhibited conditioned preferences for the cocaine-paired environment, the 15-min delay group came to avoid the side of the preference apparatus paired with cocaine. These data, therefore, serve as additional support for an Opponent-Process account of cocaine's actions. © 1999 Elsevier Science Inc.

Cocaine Conditioned place preference Conditioned aversions Opponent-process theory Drug reward Anxiety Stimulant drugs

RESEARCHERS investigating the affective properties of cocaine in laboratory animals have historically concentrated on the drug's positive or reinforcing actions. There are, for example, numerous published reports describing the effects of cocaine in self-administration, conditioned place preference, and brain-stimulation reward studies [e.g., see reviews (5,7,16, 25,31,34,55,58)]. Inherent in this approach is the reasonable assumption that the reinforcing actions of cocaine likely account for much of the users' initial attraction to and use of the drug [e.g., (48,56)]. However, in studies of human drug users, the self-reported cocaine-induced "high" is often followed by a profound aversive affective state characterized by feelings of depression, anhedonia, agitation, and anxiety (1,21,30,32,37,41,46,52,54).

The results of clinical observations and reports from cocaine users have prompted researchers to more closely examine the possibility that cocaine may produce a similar aversive state in laboratory animals. This work is motivated by the hope that an animal model would provide investigators with the means of elucidating the underlying neurobiology of the drug's negative actions. In this regard, several years ago our laboratory reported that, although rats will learn to run a straight arm runway for a reward of IV cocaine, over trials they develop a highly distinctive "approach-avoidance" behavior regarding entry into the goal box (12,13). It was hypothesized that this apparent conflict behavior stemmed from the animals' concurrent positive (reinforcing) and negative (anxiogenic) associations with the goal box. Indeed, the animals' ambivalence about entering a goal box for IV cocaine was virtually identical to that observed in other animals running the same alley for a reward of food paired with the delivery of a mild footshock (18). In both the cocaine and the food+shock studies, the putative anxiogenic approach-avoidance behavior was dose dependently attenuated by pretreatments with the anxiolytic agent, diazepam (12,18). Others have reported that cocaine, or stimuli associated with cocaine, heightens the anxiogenic response of animals tested in an elevated-plus maze where anxiety is assessed by the subjects' ti-

Requests for reprints should be addressed to Professor Aaron Ettenberg, Department of Psychology, University of California, Santa Barbara, CA 93106.

midity about entering and remaining in the "open" arms of an elevated maze (9,36,57). Simon, Dupuis, and Costentin (40) have similarly shown that rats treated with cocaine and placed directly into an open field, exhibit more thigmotaxic behavior than control subjects. Thigmotaxis is the tendency of animals' to remain close to the walls, as opposed to venturing into the central open areas, of a large open field. The behavior's utility as a measure of anxiety has been validated in that known anxiogenic agents increase thigmotaxis while anxiolytic agents reduce it (40). Cocaine has also been shown to exacerbate the effects of punishment in a conflict test (17) and to potentiate animals' avoidance of an inherently aversive environment (8). In a recent and highly novel study, Mantsch and Goeders (27) have shown that the intereoceptive cues produced by exposure to restraint stress, generalize to the discriminative stimulus effects of cocaine in a two-choice food-reinforced drug discrimination test.

The relationship between cocaine and anxiety has also been suggested on the basis of neurochemical studies. For example, cocaine administration has been shown to alter benzodiazepine receptor binding in discrete regions of the rat brain (19) and stimulate the release of the hormones corticosterone and ACTH, both of which are also released during periods of stress and anxiety (29,33,57). Several investigators have, in fact, hypothesized that cocaine's anxiogenic actions may be attributable to drug-induced increases in levels of corticotropin-releasing factor (CRF) that activates the hypothalamic–pituitary–adrenal axis, and has been implicated in the behavioral and immune response to various environmental and pharmacological stressors (9,11,20,22,38). Together, these studies provide ample evidence for the notion that, in addition to its well-known positive properties, cocaine administration is responsible for producing a profound negative affective state in the subject.

The demonstration that cocaine appears to produce a dual set of actions—one positive, and the other negative in nature—has renewed interest in the Opponent-Process Theory of motivated behavior [see original descriptions by Solomon and Corbit, (44,45) and Solomon (42,43), as well as more recent variations of the theory, e.g., (2,23,24)]. Central to this thesis is the notion that once the initial affective experience produced by a stimulus peaks and declines, a second affective state, opposite in nature to the first, is realized. Solomon (43) has described this view of two opponent processes as follows:

> First, when the stimulation begins, there is a rapid departure from baseline affect, which peaks in a few seconds (State A). Next, the affect intensity or magnitude starts to decline, even while the precipitating stimulus is present. The decreased State A affect then approaches a relatively stable steady level. When the stimulus event is terminated, there is a quick, phasic decrease in the affect level until the baseline is crossed, and then new, contrasting affective state (State B) emerges . . . (43), p. 694

Clearly, if one views cocaine's initial euphoric effect as "State A" and its subsequent aversive effect as "State B," then the events observed in the animal and human clinical literature appear to be consistent with the Opponent-Process Theory. The present experiment was, in essence, devised to test a prediction of the Opponent-Process model with respect to the acute effects of cocaine. Namely, that the affective experience of the subject would be diametrically different immediately after IV cocaine administration (State A) compared to a point in time several minutes afterwards when the drug "high" had subsided (State B). The test was accomplished using a conditioned place preference procedure in which a novel environment was paired with the effects of cocaine either immediately after, 5 min after, or 15 min after an IV injection of cocaine. The place conditioning paradigm is particularly well suited for examining this question because it makes use of the fact that rats will readily learn to approach or avoid distinctive environments respectively paired with either rewarding or aversive events (5,39). It was hypothesized that animals would come to prefer environments associated with the immediate positive effects of cocaine and avoid environments associated with the drug's subsequent negative effects.

METHOD

Subjects

Thirty-six male Sprague–Dawley rats weighing 300–350 g (at the time of surgery) served as subjects. The animals were housed in individual wire-hanging cages within a temperature-controlled (32° C) vivarium maintained on a 12 L:12 D cycle (lights on 0700 h). Animals were removed from the vivarium daily and brought to the laboratory where they were each handled (5–10 min) by the experimenters. This served to habituate them to the daily test procedure and to gentle them during the week prior to the onset of the study.

Surgery

One week after their arrival at UCSB, the animals underwent surgery during deep anesthesia for the chronic implantation of an intravenous silastic jugular catheter. Anesthesia was induced by a single 55 mg/kg intraperitoneal (IP) injection of pentobarbital (Nembutal). A supplemental injection of chloral hydrate (100 mg/kg IP) was provided if required to induce anesthesia, and all animals received a 0.4-mg/kg IP injection of atropine to reduce possible complications resulting from respiratory congestion. All IP injections were administered in a volume of 1.0 ml/kg of body weight. During anesthesia, one end of the catheter was passed subcutaneously to a threaded stainless steel guide cannula (Plastic Products Company; item C313G), which in turn, was affixed to a polyethylene assembly mounted on the animal's back. For behavioral testing, an internal cannula (Plastic Products Company; item C313I) connected by PE 20 tubing to a 10-ml drug-filled syringe, was screwed into the 0.6-cm exposed end of the guide cannula on the animal's back. Between tests, a cap was screwed down over the open end of the guide cannula. On the first day after catheterization the system was flushed once with heparinized (1000 IU/ml) physiological saline to help protect against the formation of embolisms in the vein. This procedure was repeated daily beginning 4 days after surgery. The first training day commenced 7–10 days after surgery.

Apparatus

The place conditioning apparatus was essentially a large rectangular box (94L × 43W cm) with sides 61 cm high and an open top. Two removable walls could be set in place to divide the box into three distinct compartments: on one side (measuring 42L × 43W × 61H cm) was a white chamber with a floor covered with wood chips; the opposite side of the apparatus consisted of a compartment of equal size, painted black, and having a smooth Plexiglas floor. Separating the white and black compartments was a narrow central "neutral" gray compartment (10L × 43W × 61H cm) that had a wooden floor. Prior to each test, the walls of the black chamber were wiped with a diluted solution of acetic acid. As a result, the three

compartments (white, black, and central gray) differed in color, texture, and odor.

Procedure

Ten days following surgery, each animal was individually placed into the central gray portion of the apparatus with the separating walls removed. The subjects' were free to explore all three compartments of the apparatus during a single 15-min baseline. Between each baseline, the entire apparatus was thoroughly washed with warm water, the wood chips replaced on the white side, and a fresh scent of acetic acid laid down on the black side. The location of the animals within the apparatus was recorded and timed by an observer who was blind to the treatment conditions of the subjects. An animal was defined as "within" a particular compartment when its rear paws were inside that compartment. Baseline data consisted of the time each subject spent within each of the three compartments of the preference apparatus. Based on these numbers, animals were assigned to one of three groups corresponding to a 0-min delay, 5-min delay, or 15-min delay condition. Assignments were made in a manner that ensured equivalent mean baseline performance for each group.

Beginning on the day following baseline, animals in a "0-min delay" group ($n = 12$) were administered an intravenous injection of either cocaine hydrochloride (0.75 mg/kg) or physiological saline (0.9%), and immediately placed into either the white ($n = 6$) or black ($n = 6$) sides of the apparatus for 5 min (with the dividing walls in place). This dose of cocaine was selected because we and others have found it to be highly effective as a reinforcer in studies of IV self-administration [e.g., (6,14,35)]. Injections were applied via a motorized Razel A infusion pump that delivered drug or saline in a volume of 0.1 ml over a 4-s interval. Upon completion of their baseline trials, the subjects were removed from the apparatus and returned to their home cages inside the animal vivarium. Twenty-four later, another trial was conducted in the same manner as the previous day's trial with two important exceptions: 1) those Ss that had received cocaine the previous day now received saline (and vice versa), and 2) those that had been placed in the white box on the previous trial were now placed into the black box (and vice versa). This alternating procedure continued each day for 8 days, after which each animal had experienced four cocaine pairings with one side of the apparatus and four saline pairings with the alternate side of the apparatus. The remaining two groups of animals were treated in the identical manner as just described, except that a delay (5 min or 15 min) was instituted between the completion of the cocaine or saline infusion and placement into the apparatus. During the delay conditions, subjects were held in a plastic holding cage. This procedure was, therefore, intended to examine the associations formed between a distinct environment and the "state" produced by cocaine either 0, 5 or 15 min postinjection.

Upon completion of the 8 days of place conditioning, a single 15-min place preference test was conducted in the identical manner as that described for the initial baseline.

RESULTS

Although there were originally 12 Ss assigned to each group, a catheter failure in one animal from the 5-min delay condition resulted in a sample of 11 in that condition. Because all three groups were matched for initial mean baseline performance, conditioned place preferences could be readily detected as reliable shifts in the time Ss spent in the drug-paired environment on test day relative to baseline. Mean difference scores (test day − baseline day) were, therefore, computed for each group with the results depicted in Fig. 1. Subjects in the 0-min delay condition spent, on average, 278 ± 73 more seconds in the cocaine-paired environment on test day than they did initially on baseline. The 5-min delay group demonstrated a somewhat smaller conditioned place preference for cocaine (mean difference score: 240 ± 80 s), while subjects in the 15-min delay condition spent less time in the cocaine-paired environment on test day than they did during baseline (mean difference score: −135 ± 82 s). A one-way independent groups analysis of variance computed on the data depicted in Fig. 1 confirmed reliable differences between the three experimental conditions: $F(2,32) = 6.51$, $p = 0.004$. Tukey HSD post hoc comparisons revealed significant differences in the behavior of the 0-min and 15-min delay conditions and the 5-min and 15-min delay conditions ($p < 0.05$). In addition, because conditioned place preference or place aversion is inherently defined as a reliable shift toward or away from a place relative to the preferences that were already there at baseline, mean difference scores for each group were compared to "zero" (i.e., to the "no change" value). One-

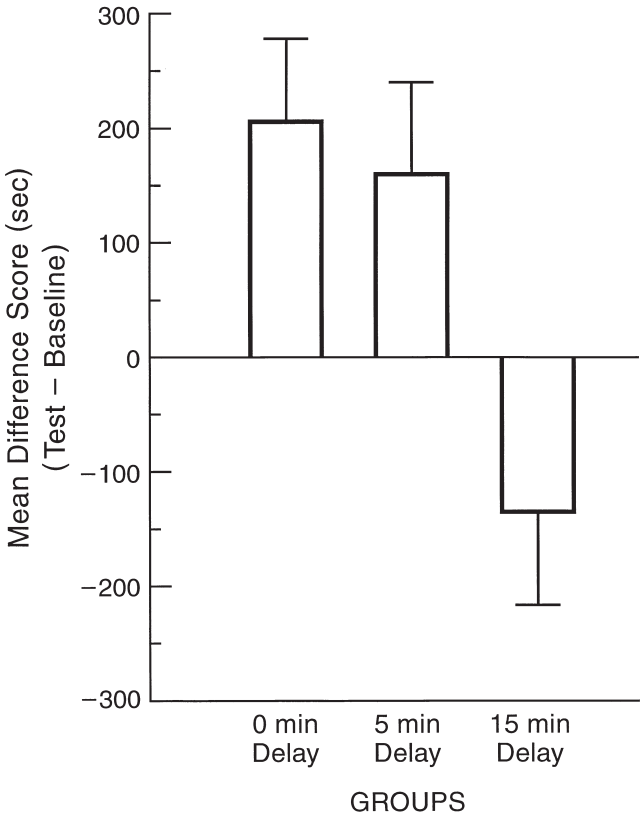

FIG. 1. Time spent in the cocaine-paired environment expressed as mean (+SEM) difference scores (in seconds): test day less baseline day performance. Values above the zero line indicate greater time spent in the cocaine-paired environment after conditioning, while values below the line indicate a shift away from the cocaine-paired environment following conditioning. The 0-delay and 5-min delay groups produced statistically significant shifts toward the cocaine environment (conditioned place preferences), while the 15-min delay group exhibited a conditioned aversion for that environment. These data are consistent with an opponent-process account of cocaine's actions.

tailed *t*-tests confirmed that each group's difference scores were statistically different from zero: 0-min delay, $t(11) = 3.185$, $p < 0.005$; 5-min delay, $t(10) = 1.89$, $p < 0.045$; 15-min delay, $t(11) = -1.86$, $p < 0.045$).

DISCUSSION

Animals placed into a distinctive environment either immediately or 5-min after IV injections of cocaine, come to develop reliable preferences for those environments. More specifically, animals treated in this manner produce statistically significant shifts in the time spent in the cocaine-paired environment postconditioning relative to the time spent there during the preconditioning baseline. The precise explanation for the development of such conditioned place preferences (CPPs) is necessarily open to some speculation. Nevertheless, there appears to be a considerable consensus in the literature that CPPs result from the positive or rewarding qualities of the stimuli paired with the preferred environment. For example, animals learn to prefer places where they have experienced sex (28), ingested food (47), consumed sucrose (53), or been administered rewarding brain stimulation (10) in addition to those places where they have experienced the effects of reinforcing drugs (5,39). Animals also come to avoid distinctive places explicitly associated with aversive events [e.g., (3,15, 49,51,53)]. Hence, the conditioned place test seems particularly well suited for examining the opponent-process actions of psychoactive drugs because it is sensitive to both the putative positive and negative aspects of drug administration. With respect to the current study, the effects of cocaine during the first 5–10 min after an IV injection appear to be sufficiently rewarding in nature to support the development of reliable CPPs. However, beyond that time interval the valence of the drug experience appears to diametrically change. The 15-min delay group that was administered the identical dose of cocaine that produced place preferences in the 0-delay and 5-min delay conditions demonstrated aversions for the cocaine-paired environment. Thus, animals came to avoid the place associated with the state present 15–20 min after an IV injection of cocaine.

It would appear then, that cocaine has dual or biphasic properties—an initial positive or rewarding action followed temporally by one that is negative or aversive in nature. Such a conclusion is, of course, consistent with descriptions of the drug's actions provided by human users. Cocaine addicts report that the drug produces an initial euphoric "high" that quickly wanes and is replaced by a profound sense of dysphoria, craving, and anxiety [e.g., (1,32,37,38,46,52,54)]. The present data provide an example of a comparable set of drug properties in laboratory animals. Additionally, the "high" that human users report following cocaine administration appears to occur during the time when brain and plasma levels are rising, while the dysphoria is associated with the drug's rapid clearance from these compartments (50). It is, therefore, interesting to note that the current place preference results are strikingly consistent with the known pharmacokinetics of IV cocaine. For example, Ma, Fang, and Lau (26) have recently reported that the distribution half-life ($t_{1/2\alpha}$) of cocaine following intravenous administration was 1.2 min, while the half-life for the elimination phase of the drug ($t_{1/2\beta}$) was 12.9 min. This work confirms the earlier results reported by Booze et al. (4). Thus, the place preferences exhibited by the 0-delay and 5-min delay groups were likely associated with peak or near peak brain levels of the drug while the aversion demonstrated in the 15-min delay group was associated with rapidly falling levels of cocaine. Such results clearly support an opponent-process account of cocaine action [e.g., (2,23,24,42–45)]. In its classical form, that account suggests that the acute application of a reinforcing drug results in an initial rewarding or euphoric "State A" that rapidly dissipates and is replaced by an opposing negative affective "State B" (42,43). In the present context, the initial State "A" would account for the conditioned place preferences observed in the 0-delay and 5-min delay groups, while the subsequent and aversive State "B" would be responsible for inducing the place aversions observed in the 15-min delay condition.

In both the original and more contemporary accounts of the opponent-process theory, the development of "drug addiction" is attributed to changes in States A and B, which are thought to occur with repeated exposure to the abused drug. For example, Solomon (43) hypothesized that with repeated drug administration "the positive reinforcer loses some of its power, but the negative reinforcer gains power and lasts longer" (p. 696). The present data involved but four injections of cocaine over an 8-day period, and hence, do not effectively address the predicted changes in subjective experience following chronic exposure to the drug. However, in previous work, we have shown that animals running an alley once a day for a reward of IV cocaine came to exhibit a strong approach–avoidance conflict about entry into the goal box (12,13). This ambivalence about entering a place associated with cocaine administration was not detected until day/trial 10–14, and subsequently grew stronger with continued testing—a result consistent with the notion that, with repeated testing, the strength of the underlying negative state is growing stronger relative to the positive state. Hence, in examining the motivation of individuals to self-administer drugs of abuse, it would seem that two types of reinforcement are likely to be in effect. The initial euphoria reported by users of cocaine would serve as a powerful positive reinforcing stimulus that undoubtedly accounts for the initiation and contributes to the maintenance of cocaine self-administration. In addition, the profound dysphoric, craving, and anxiogenic states that occur upon cocaine termination act as potent sources of negative reinforcement that ensure that cocaine self-administration is reinstated and maintained.

ACKNOWLEDGEMENTS

The authors wish to thank Brian Crook and Lisa Gatzke for their assistance in running this experiment. The work described was supported by NIDA Grant DA05041 awarded to Aaron Ettenberg, and an NSF predoctoral fellowship awarded to Mary Raven.

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