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Review

Opponent process properties of self-administered cocaine

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Abstract

Over the past decade, data collected in our laboratory have demonstrated that self-administered cocaine produces Opponent-Process-like behavioral effects. Animals running a straight alley once each day for IV cocaine develop over trials an approach–avoidance conflict about re-entering the goal box. This conflict behavior is characterized by a stop in forward locomotion (usually at the very mouth of the goal box) followed by a turn and 'retreat' back toward the goal box. The results of a series of studies conducted over the past decade collectively suggest that the behavioral ambivalence exemplified by rats running the alley for IV cocaine stems from concurrent and opponent positive (rewarding) and negative (anxiogenic) properties of the drug—both of which are associated with the goal box. These opponent properties of cocaine have been shown to result from temporally distinct affective states. Using a conditioned place preference test, we have been able to demonstrate that while the initial immediate effects of IV cocaine are reinforcing, the state present 15 min post-injection is aversive. In our most recent work, the co-administration of IV cocaine with either oral ethanol or IV heroin was found to greatly diminish the development and occurrence of retreat behaviors in the runway. It may therefore be that the high incidence of co-abuse of cocaine with either ethanol or heroin, stems from the users' motivation to alleviate some of the negative side effects of cocaine. It would seem then that the Opponent Process Theory has provided a useful conceptual framework for the study of the behavioral consequences of self-administered cocaine including the notion that both positive and negative reinforcement mechanisms are involved in the development and maintenance of cocaine abuse.

Keywords: Drug reinforcement; Reward; Conditioned place preference; Drug self-administration; Ethanol; Speedball; Heroin; Runway

Contents

Human users of cocaine describe two distinct affective consequences of drug administration: an initial and profound euphoria typically followed by a state characterized by anxiety, fatigue, agitation, depression, and oftentimes cravings for more cocaine [1,73,82,88,89]. Clinical studies report that while the euphoric effects of cocaine remain stable over time, the negative properties of the drug appear to increase with time and can even precipitate episodes of panic attack and other related anxiogenic states. Indeed, there is a large and rapidly growing literature on the relationship between anxiety and cocaine in human drug users [14,18,34,38,51,52,68,87]. The notion that cocaine has negative or aversive side effects has also been suggested by the results of animal research studies. For example, over two decades ago, Spealman [85] reported that monkeys trained to lever-press for intravenous cocaine, also chose to press a second lever that terminated drug availability. In more recent studies, cocaine has been observed to decrease punished responding in a rodent conflict test [29], to have anxiogenic effects in the pentylenetetrazol discrimination test [71], induce anxiogenic-patterns of exploratory behavior in the mouse elevated plus-maze [75], and to increase animals' latency to enter an open field (thought to be a measure of anxiety) [81,93]. The relationship between cocaine and anxiety is also consistent with reports of cocaine-induced changes in brain benzodiazepine receptors [35,36] and increases in the secretion of adrenocorticotropin

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(ACTH) and corticotropin-releasing factor (CRF) [36,37, 67,74]. Together, these studies provide clinical, behavioral and neurochemical evidence suggesting that cocaine administration induces two distinct and powerful affective states—the first a strong positive euphoric reaction, followed temporally by a negative anxiogenic state whose onset occurs as the drug levels in plasma begin to fall.

1. Dual actions of cocaine in a runway model of cocaine self-administration

In our own work at UCSB, we came upon these dual opponent actions of cocaine somewhat inadvertently as part of our efforts, started in the early 1990s, to develop a means of reliably assessing an animal's motivation to seek reinforcing psychoactive drugs. We conceptualize motivation as the state or process that results in the *initiation* of goal-seeking behavior and hence is an antecedent condition of behavior. In contrast, reinforcement, is defined as a *consequence* of operant behavior that serves to increase the probability that an organism will repeat successful goal-directed responses. It seemed to us at the time, that research on drug reinforcement was conducted almost exclusively in operant chambers in which drugged animals were lever pressing to maintain their drugged state. While this work has proven remarkably important as a means of identifying the underlying neurobiology of drug reinforcement (e.g. see Reviews [79,80,91,92]), it was unclear whether or not such studies would shed much light on the antecedent motivational state that presumably led to the initiation of the operant responding in the first place (although see Ref. [27]). We therefore decided to leave our operant boxes in favor of the straight-alley which has a long history of use as a model for assessing the motivational state of the subject [6,13,53]. In this work, Run Times (from start box to goal box) are used as a measure of the subjects' motivation to seek reinforcing stimuli that on previous trials had been presented in the goal box. Over the course of a 2 year period, we developed an automated system that permitted animals fitted with intravenous catheters to traverse a six-foot runway and enter a goal box where infrared sensors detected their presence, closed the goal-box door, and activated a syringe pump that infused the reinforcing drug into the subject's bloodstream (see Ref. [31] for a detailed description of the apparatus). In our protocol, rats are typically run on a single trial per day and so their Run Times are not confounded by the inherent motoric side effects (some excitatory and some inhibitory) of the drug reinforcers that we are studying.

While we observed that rats run the alley faster each day for food [11,20,44,64], water [21,24], sex [54,55,56], amphetamine [19], or heroin [25,63], qualitatively different results were observed with cocaine. Although cocaine-reinforced animals continued to initiate each successive trial with statistically 'normal' start latencies, they take progressively longer to actually reach the goal box on each successive trial (beginning about 10–14 days into the experiment). Closer examination of the animals' runway behavior revealed that the elevation in Run Times was not because the animals were running more slowly, but rather because of the increased occurrence of a unique stop-and-retreat behavior as the experiment progressed [22,23,33]. Over trials, animals running the alley for IV cocaine, develop a tendency to quickly approach the goal box entry, stop their forward locomotion, peek their nose into the goal box, then turn and scamper all the way back to the start box. We refer to this as 'retreat behavior' and modified our runway with sets of infrared emitters and detectors along its entire length in order to create a clearer and more objective measure of the subjects' intra-alley behavior. With real-time location data and the help of our own custom software, we were able to produce computer-generated *spatio-temporal records* of each trial—a pictorial representation of the precise route that the animal took from start box to goal box on any given trial. Fig. 1 provides a representative example of an animal's spatio-temporal record after 14 trials of cocaine. Time is represented along the abscissa and location in the alley (with position '1' being in the start box and position '10' being the threshold of the goal box—photocells 11 and 12 are actually located inside the goal box; subjects must break the infrared beam at position 11 for the computer to automatically close the goal box door behind them and deliver the drug reinforcer). In these records, the slope of the curves is representative of the speed with which the animals are running (gentle slopes would be indicative of slower running) and horizontal lines represent

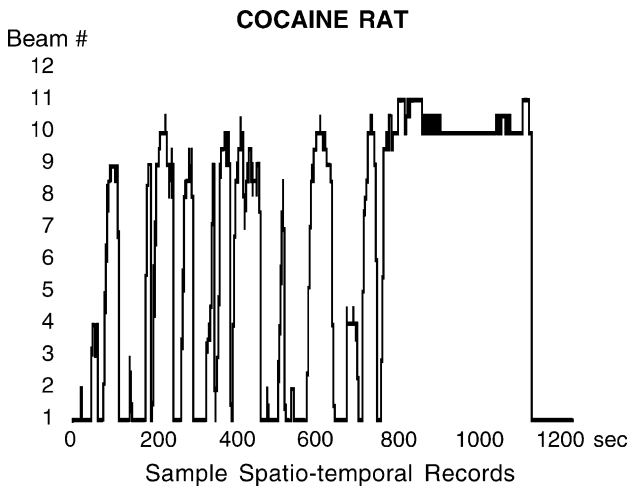

Fig. 1. A representative spatio-temporal record from a single trial of an experienced animal running a straight alley once a day for IV cocaine. The record illustrates the path that the subject took to reach to the goal box and earn the drug reinforcer. The locations in the runway are represented by the numbers on the ordinate, with '1' being an infrared sensor in the start box and 9 being one just outside the goal box entry. Positions 10–12 are inside the goal box. In the sample shown, the rat made numerous approach–avoidance 'retreats' (stopping forward movement and returning back toward the goal box) which are representative of mixed positive and negative associations with the cocaine goal box.

pauses in the subject's movement. Finally, the number of peaks serves as a measure of the retreat frequency for a given animal on a given trial. As one can see in Fig. 1, this subject ran quickly toward the goal but stopped and retreated multiple times before he actually entered the goal box (and received an IV injection of cocaine).

Analysis and investigation of the retreat phenomenon revealed several important features. For example, the retreats were extremely uncommon in unconditioned animals and in animals reinforced with other natural or drug reinforcers. For example, we compared the runway behavior of subjects traversing the alley for single injections of either IV cocaine or IV heroin [23]. Both groups behaved comparably at the outset, exhibiting faster start latencies and faster Run Times over trials; however, by the second week of testing the cocaine subjects behaved in a manner comparable to that exhibited by the animal represented in Fig. 1, while the heroin animals behaved like more traditional reinforcers and continued to run more and more quickly over trials [23]. It would seem then, that the motivational state underlying drug-seeking behavior is qualitatively different for heroin- and cocaine-reinforced animals. A second unique feature of retreat behavior, is that the locations in the alley where the animals stop their forward movement and turn back toward the start box are not randomly located, but rather occur in close proximity to the goal box entryway (see Fig. 1; also Refs. [22,23]). This tendency to stop just outside the goal and then turn and retreat is a situation reminiscent of Neil Miller's classic description of approach–avoidance behavior [66] almost 60 years ago and suggested that the ambivalence we were observing in our cocaine animals about entering the goal box, was a consequence of mixed positive and negative associations with that location. Indeed, like other forms of conflict behavior [8,12,16] retreat behavior was found to be dose-dependently reversed by pretreatment with the benzodiazepine agonist, diazepam [22,33]. In other experiments we have shown that these same animals that produce retreat behavior in the alley, develop reliable preferences for a cocaine-paired environment, thereby demonstrating that the cocaine has still maintained its inherent reinforcing action [22] in such animals.

If retreat behavior truly reflects the presence of an approach–avoidance conflict then the pattern of behavior observed in our cocaine-reinforced animals ought to be comparable to those observed in rats experiencing more traditional positive + negative goal box events. We therefore trained hungry rats to traverse an alley for food reinforcement and then added a mild foot-shock upon their entry into the goal box [33]. While the food-reinforced animals continued to enter the goal box with normal latencies and exhibited no retreat behavior, those animals that earned food coupled with foot-shock made progressively more retreats over trials. Animals for whom food reinforcement was completely replaced with foot-shock, initially exhibited retreat behavior (they continued to enter the goal box where they had learned food would be located) but soon came to avoid the goal box all together. Additionally, as was the case for the cocaine-reinforced animals [22], the retreat behavior in the food + shock group occurred in close proximity to the goal box entryway and was dose-dependently decreased by the anxiolytic agent diazepam [33]. Finally, in a separate experiment, animals whose retreat behavior had extinguished over a 2 week period (the food reinforcer was continued without the foot-shock), demonstrated a reinstatement of that behavior when pretreated with the anxiogenic benzodiazepine inverse agonist FG7142 [32]. Two aspects of these results are relevant here: first, the nature and frequency of the retreat behavior exhibited by the food–shock group was virtually identical to that of subjects running an alley for IV cocaine reinforcement; and second, the continued demonstration of retreat behavior over trials required the concurrent presentation of *both* food and shock stimuli. Thus, while the shock only group did initially exhibit some retreats, these animals quickly learned to completely avoid the goal box. Therefore, taken together, our data again suggest that retreat behavior occurs as a consequence of an approach–avoid conflict that stems from concurrent positive (reinforcement) and negative (anxiogenic) associations with the goal box.

2. Opponent process actions of cocaine in a conditioned place preference test

The demonstration that cocaine appears to produce a dual set of actions—one positive and the other negative in nature, has naturally renewed interest in the Opponent Process Theory of motivated behavior (see original descriptions by Solomon and Corbit [84]), as well as more recent variations of the theory [3,49,50]. Central to this theory is the notion that the consequences of any stimulus that induces a change in affective state is 2-fold—an initial experience (State 'A') is activated, peaks and eventually wanes, upon which a second experience (State 'B') that is opposite in affective valence to the first, becomes predominant. Solomon [83] has described this conception 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 state. When the stimulus event is terminated, there is a quick, phasic decrease in the affect level until the baseline is crossed, and then a new contrasting affective state (State B) emerges…[83] p. 694.

Fig. 2 provides a schematic representation of the Opponent Process Theory as described above by Solomon

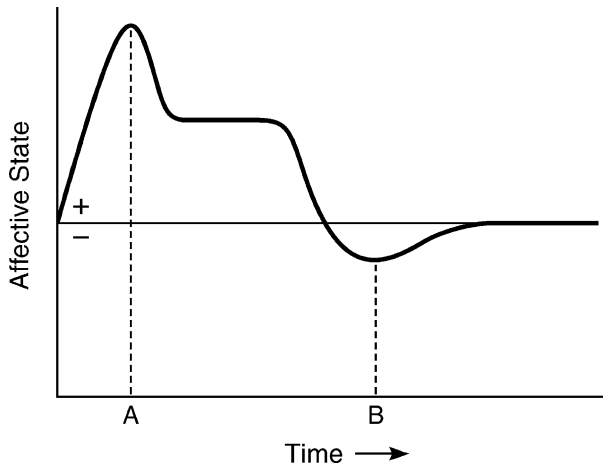

Fig. 2. A schematic representation of the affective response to an injection of cocaine as predicted from Opponent Process Theory. Following administration there is an initial positive reaction that rises quickly to a short-lived peak level (time point 'A'), and then decreases to a steady state level that eventually gives way and drops back toward initial baseline (neutral) levels. The delayed onset of a second opposing negative/aversive state is in part responsible for the reduction in positive affect and in time exerts a net negative impact on the subject's affective experience (time point 'B').

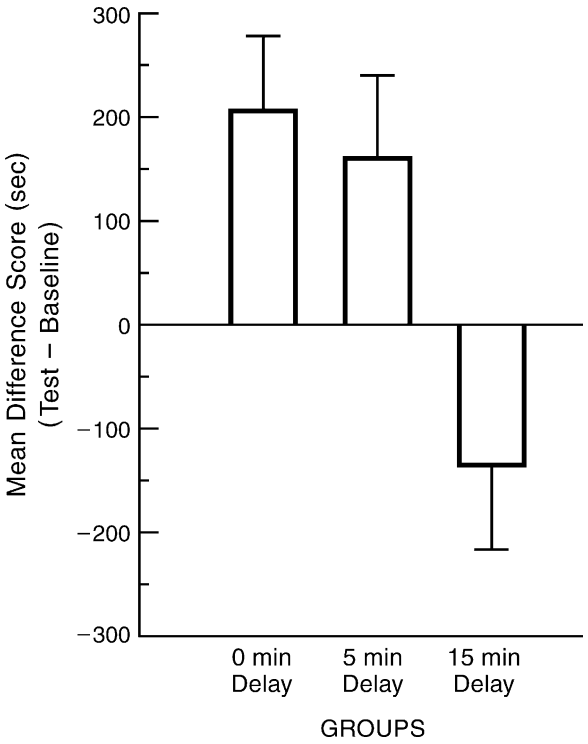

Fig. 3. Opponent process actions of cocaine as revealed in the conditioned place preference test. Time spent in the cocaine-paired environment is expressed as mean (±SEM) difference scores (in s): test day less baseline day performance. Values above the zero line indicate greater time spent in the cocaine-paired environment after conditioning while values below the line indicate a shift away from the cocaine-paired environment (place aversions) following conditioning. The 0-day and 5-min delay groups produced reliable shifts toward the cocaine environment (place preferences), while the 15-min delay group exhibited a conditioned aversion for that environment. Reprinted with permission from Ettenberg et al. [26].

[83]. In this context, the initial positive euphoric effects of cocaine are representative of State A, while the subsequent, negative opponent effects would represent state B. Thus, following cocaine administration, the initial affective experience (indicated in Fig. 2 by time point A) would be characterized as positive to the subject while the affective state at time point B would be diametrically opposite and occur only after the initial positive state had waned.

To test the concept of opponent processes in the lab, we directly compared the affective experience of subjects immediately after IV cocaine administration (State A; corresponding to time-point A in Fig. 2) with that present several minutes afterwards when the drug 'high' had subsided (State B; corresponding to point B in Fig. 2). This 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 [26]. The place conditioning paradigm is particularly well-suited for examining this question since 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 [4,78,86]. The results of this experiment are shown in Fig. 3. As the figure clearly illustrates, the initial effects of IV cocaine (either immediately after or 5 min after injection) were positive in nature and animals came to prefer a distinct environment associated with the effects of the drug present at that time point. However, animals exposed to the same distinct environment beginning 15 min after the same IV injection of cocaine, demonstrated a reliable aversion to that location during the test session. Note that these data cannot be explained by a weakening in conditioning produced by the insertion of a delay between the drug and place stimuli—such an account of the results might predict that the 15-min delay group would show no conditioning (because the CS-US interval was too long), but *not* a significant 'aversion' to the drug-paired side. Thus, while there are undoubtedly a myriad of different hypotheses that might be evoked to account for these results, they remain both intriguing and of course consistent with the notion that the 'state' present 15-min after IV cocaine may be qualitatively different than that immediately after, or 5 min after, cocaine administration.

3. Co-administration of alcohol or heroin as a means overcoming the anxiogenic properties of cocaine

Human drug self-administration is typically a polydrug phenomenon—human users rarely restrict themselves to a single drug over the course of time or even within the same self-administration session. In this context, the recognition that IV cocaine has adverse or negative consequences might account for why some human cocaine users choose to concurrently self-administer other psychoactive drugs along

with the cocaine. For example, epidemiological studies estimate that anywhere from 50 to 90% of those who chronically self-administer cocaine choose to concurrently ingest alcohol [1,2,9,10,40,58,76]. Some have suggested that a substantial subset of this population may be using alcohol as a means of self-medication to 'treat' the anxiogenic side effects of the cocaine [7,30]. The concurrent use of cocaine and alcohol has also been reported to prolong the initial cocaine-high while reducing the magnitude of the subsequent anxiety and other dysphoric reactions that characterize the cocaine 'crash' [43,62,70]. We tested this notion in the animal laboratory by training thirsty rats to run an alley for IV cocaine and then permitting them to drink various solutions of ethanol or water immediately after their removal from the goal box (i.e. 5 min post-cocaine injection). Cocaine-reinforced animals permitted to drink water after their runway trials, developed the normal pattern and frequency of approach–avoidance retreat behavior in the runway. However, animals permitted to drink ethanol immediately upon their removal from the apparatus, exhibited a dose-dependent reduction in the occurrence of retreat behaviors in the runway [46]. The delayed timing of the ethanol consumption relative to the cocaine infusion suggests that the ethanol may have acted to reduce the intensity or onset of the negative properties of the cocaine either via its own inherent reinforcing properties [15,39,41,48,60,65] or its well documented anxiogenic effects [5,57,90].

A possible pharmacological explanation for the effects of the cocaine + alcohol combination involves the production of cocaethylene—a psychoactive metabolite of cocaine that is only formed when both cocaine and alcohol are concurrently present in the liver [17,28,62]. Because cocaethylene is itself reinforcing [45,72,77] its delayed onset relative to that of cocaine may account for the 'prolonged high' that users describe when taking cocaine and alcohol in combination. Additionally, the longer half-life of the metabolite relative to that of its parent compound, cocaine [61,62,69] may serve to counteract or mask the onset of cocaine's anxiogenic actions. If this notion is correct, then one would predict that the immediate effects of cocaethylene would be rewarding and longer lasting than those of cocaine. To test this, Knackstedt et al. [47] recently compared the immediate positive and delayed negative properties of cocaine with cocaethylene using the conditioned place preference procedure as described earlier for cocaine alone [26]. Once again the rats demonstrated strong place preferences for an environment associated with the immediate effects of IV cocaine, and aversions for an environment paired with the effects of the same dose present 15 min after cocaine. However, animals treated with an equimolar dose of cocaethylene, produced comparable preferences in the no-delay condition, but no aversions for places associated with the effects present 15-min post-injection. A small place aversion was demonstrated in a 30-min delayed group. These place preference data are therefore consistent with the pharmacological data demonstrating that the metabolite has a longer half-life than cocaine; additionally, and perhaps most importantly, the negative properties of cocaethylene were delayed and reliably weaker than those observed following IV cocaine [47]. Thus, whether via its own positive effects, or through its role in the production of the cocaethylene metabolite, the addition of alcohol appears to offset the development of the negative state that would otherwise occur following cocaine administration.

A second drug that is reported to be commonly co-administered with cocaine is the opiate agonist, diacetylmorphine (heroin). The self-administration of this drug combination is colloquially referred to as 'speedballing' and may act, like alcohol, to counteract the negative properties inherent in the cocaine crash. As is the case for alcohol, heroin may have its desired effects either through its own positive reinforcing properties or anxiolytic actions. For example, a recent clinical study [59] reported that men who used cocaine + opiates had significantly elevated indices of 'trait anxiety' compared to those who chose to use cocaine alone. It therefore seemed reasonable to hypothesize that cocaine users experiencing strong anxiogenic side effects might medicate themselves by adding heroin to 'take the edge off' of the aversive aspects of the cocaine experience. Our preliminary results [42] are consistent with this possibility. Animals were trained to run a straight alley for IV cocaine reinforcement once each day until retreat behaviors had developed (i.e. during the second week of testing). The rats were then assigned to groups that differed in the dose of heroin (0.0–0.1 mg/kg/injection) that was added to the standard 0.75 mg/kg/injection dose of cocaine that they had experienced each day in the goal box of the runway. The results clearly demonstrated that while the retreat frequency of the cocaine animals continued to increase over trials, the rats reinforced with a 'speedball' of cocaine + heroin showed no further increases in retreat frequency over another 2-week period of daily testing. Thus, as was the case with alcohol, the addition of heroin appeared to immunize the subjects from the negative properties of the IV cocaine and might therefore account for the motivation of cocaine addicts to engage in speedballing behavior.

4. Summary

Both the classic and more contemporary accounts of Opponent Process Theory, predict changes in the underlying States A and B during the addictive process [49,50,83,84]. For example, Solomon [83] explains that with repeated exposure to the drug "the positive reinforcer loses some of its power, but the negative reinforcer gains power and lasts longer" (p. 696). The conditioned place preference study described above (see Fig. 3) confirms what appears to be two diametrically opposing states that result from a single identical injection of IV cocaine—an immediate positive

state followed shortly thereafter by a negative/aversive state. The effects of repeated exposure to the drug were observed in runway experiments in which rats traversing a straight alley for IV cocaine exhibited a growing ambivalence about entering the goal box (retreat behaviors) beginning 10–14 days into testing and increasing with trials thereafter. The runway data are therefore also consistent with the predictions of Opponent Process Theory in that the occurrence and increased frequency of retreats with repeated testing might be reflective of the increasing strength of the underlying negative state relative to the positive state as drug exposure is increased. It would seem then that the motivation of individuals to self-administer cocaine likely involves two forms of reinforcement. The initial euphoria would serve as a powerful positive reinforcing stimulus that accounts for the initiation and contributes to the maintenance of cocaine self-administration; and the profound anxiogenic and dysphoric state that comes to accompany the cocaine crash would serve as a potent source of negative reinforcement that ensures that cocaine self-administration is reinstated and maintained. These dual opponent actions of cocaine might also account for why human users often combine their cocaine with other drugs. In the laboratory, the development and/or occurrence of runway retreat behaviors (reflective of the presence of dual positive and negative properties of cocaine) can be reliably attenuated by the co-administration of either alcohol or heroin. It would seem then that the combination of cocaine and alcohol or cocaine and heroin may represent attempts on the part of users to self-medicate against the delayed onset of the negative properties of the cocaine. In conclusion, the Opponent Process Theory has proven to be a valuable theoretical tool to help understand the behavioral consequences of cocaine administration in both human and animal subjects.

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