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# Evidence for opponent-process actions of intravenous cocaine and cocaethylene

Lori A. Knackstedt, Max M. Samimi, Aaron Ettenberg*

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

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**Abstract**

The affective response to cocaine (COC) has been suggested to follow a time-course and pattern that adheres to the prediction of opponent-process models of drug actions. While the initial impact of the drug is positive, within a few minutes that effect wanes and is replaced by an aversive state characterized by anxiety and drug craving. We have demonstrated this phenomenon in animals by showing that rats prefer distinctive environments associated with the immediate effects of intravenous COC (1.0 mg/kg) but avoid environments associated with the state present 15-min postinjection. Human addicts have reported taking ethanol with their COC as a means of attenuating the negative aftereffects of COC administration. The combination of ethanol and COC results in the production of cocaethylene (CE), a metabolite of COC having psychostimulant properties. The current study was devised to assess whether the immediate and delayed affective responses to CE might account for the self-medication strategy of COC addicts pretreating themselves with ethanol. Rats developed conditioned place preferences for environments paired with the immediate effects of a 1.44-mg/kg intravenous dose of CE (equimolar to a 1.0-mg/kg dose of COC). While no aversive effects were observed at 0, 5, or 15 min postinjection, reliable place avoidance was detected for an environment paired with the internal state present 30-min post-CE. These data are consistent with the view that the development of CE may account for efficacy of ethanol to delay and weaken the aversive aftereffects of COC. 

*Keywords:* Cocaine; Conditioned place preference; Conditioned aversions; Opponent-Process Theory; Drug reward; Anxiety; Stimulant drugs

## 1. Introduction

Human cocaine (COC) users report that the initial euphoric state produced by the drug is often followed by unpleasant effects, such as anxiety and paranoia (Anthony et al., 1994; Smith, 1986; Williamson et al., 1997) that are exacerbated by chronic use (Anthony et al., 1994). Early studies using laboratory animals demonstrated the reinforcing nature of COC but failed to report any evidence of the aversive properties commonly reported by humans. However, this failure may have been due to the types of behavioral tests and methodologies used and not to the absence of aversive side effects in animals. For example, conditioned place preference (Nomikos and Spyraki, 1988; Spyraki et al., 1987) and self-administration (Griffiths et al., 1979; Pickens and Thompson, 1968) studies indicated that acute administration of COC was reinforcing. However, these tests were conducted in a manner that served to assess only the immediate, positive effects of the COC experience and not the temporally delayed negative effects that human drug users describe.

In recent years, a considerable body of evidence has been generated showing that COC administration does produce anxiety-like behaviors in laboratory animals. For example, in rodents, acute COC has been shown to produce more thigmotaxic behavior (hugging the walls) in the open field compared to controls (Simon et al., 1994), to enhance the anxiogenic response in an elevated plus maze (Rogerio and Takahashi, 1992; Yang et al., 1992), to increase defensive behaviors such as withdrawal (Yang et al., 1992), and to increase the startle reflex to a conditioned fear stimulus (Borowski and Kokkinidis, 1994; Willick and Kokkinidis, 1995).

Work done in our laboratory (Ettenberg and Geist, 1991) has examined the concurrent positive and anxiogenic effects of COC by training animals to run a straight alley once a day for intravenous drug reinforcement. While subjects

* Corresponding author. Tel.: +1-805-893-3682; fax: +1-805-893-4303.

*E-mail address*: ettenber@psych.ucsb.edu (A. Ettenberg).

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learned to run the alley for COC, an unusual "approach–avoidance" pattern of behavior developed (i.e., retreats) that appeared to be related to the mixed association (reward and anxiety) that animals formed with the goal box. Indeed, the "retreat" behavior was qualitatively identical to that observed in rats running an alley for concurrent food and shock (Geist and Ettenberg, 1997; Miller, 1944) and was alleviated by treatment with the anxiolytic drug, diazepam (Ettenberg and Geist, 1991).

The dual rewarding and anxiogenic effects associated with COC administration are consistent with the Opponent-Process Theory of drug action in which the initial positive affective experience produced by a drug is temporally followed by an opposing negative consequence (Koob et al., 1997; Solomon, 1980; Solomon and Corbit, 1974). To test this notion more directly, Ettenberg et al. (1999) treated rats with intravenous COC and then placed them in a distinctive environment either immediately after, 5 min after, or 15 min after drug administration. On alternate days, animals received intravenous vehicle solutions followed by exposure to a second unique environment. The animals were found to prefer the environment paired with the immediate positive effects of COC and avoid the environment associated with the drug state present 15-min postinjection (Ettenberg et al., 1999). The results of this experiment indicated that COC exhibits biphasic properties: an initial positive "euphoric" effect that is followed by a negative "dysphoric" effect at some later time.

The demonstration that COC appears to exert opponent-process actions in laboratory animals is consistent with the subjective reports of human COC users. Clinical studies (Higgins et al., 1993) and epidemiological reports (Anthony et al., 1994; Smith, 1986; Williamson et al., 1997) have indicated that COC can induce anxiogenic side-effects that some "treat" through concurrent self-administration of alcohol (Brady et al., 1995; Gawin and Kleber, 1986; Magura and Rosenblum, 2000). Studies have estimated that anywhere from 50% to 90% of COC users coabuse alcohol (Anthony et al., 1994; Brookoff et al., 1996; Carroll et al., 1993; Grant and Harford, 1990; Magura and Rosenblum, 2000; Rounsaville et al., 1991; Weiss et al., 1988) and clinical studies have reported that the concurrent use of alcohol and COC prolongs the COC "high" while reducing the anxiety and other acutely dysphoric physical and psychological effects that characterize the COC "crash" (McCance-Katz et al., 1993; McCance et al., 1995; Perez-Reyes and Jeffcoat, 1992; Higgins et al., 1993). In animal studies, the combination of COC and ethanol similarly produced an enhancement of brain stimulation reward at doses that were otherwise ineffective when administered alone (Lewis and June, 1994).

A possible pharmacological mechanism for the reduction in COC-related anxiety upon coadministration of alcohol lies in the production of cocaethylene (CE), the ethyl ester of the COC metabolite benzoylecgonine. CE is a metabolite of COC that is only formed when alcohol is concurrently present with COC in the liver (Dean et al., 1991; Farre et al., 1993; McCance-Katz et al., 1993). Unlike the other COC metabolites, CE has the unique property of being pharmacologically active (Pan and Hedaya, 1999). Behavioral studies using animals have shown that, like COC, CE possesses psychomotor stimulant qualities (Jatlow et al., 1991), maintains self-administration (Jatlow et al., 1991; Raven et al., 2000), serves as a discriminative stimulus (Woodward et al., 1991), and produces a conditioned place preference (Schechter, 1995). In humans, CE has been reported to provide the same euphoric effects as COC and cannot be reliably distinguished from COC (McCance et al., 1995).

Consistent with the similar behavior patterns produced by COC and CE is the fact that both substances inhibit the dopamine transporter and are equipotent at increasing extracellular dopamine in the basal ganglia in rats (Jatlow et al., 1991) and nonhuman primates (Iyer et al., 1995). COC also blocks serotonergic uptake and, in fact, has a higher affinity for the serotonin transporter than for the dopamine transporter (Ritz et al., 1987). It has been suggested that serotonin pathways have a role in the neural basis of anxiety (Andrews et al., 1997; Graeff et al., 1996) and thus may be responsible for the dysphoric effects of COC. Because CE has a weaker effect on the serotonin transporter (Bradberry et al., 1993; Nobiletti et al., 1994), it may be less anxiogenic than COC. Indeed, results from our own laboratory confirm that the anxiogenic side-effects observed in rats working for intravenous COC reward are greater than those observed for CE (Raven et al., 2000). In addition, the half-life of CE is longer than that of COC as measured in humans (McCance-Katz et al., 1993; McCance et al., 1995; Perez-Reyes et al., 1994) and in rats (Pan and Hedaya, 1999). Theoretically, the delayed onset of the metabolite's action (relative to that of the parent compound, COC), combined with its longer duration of action and weaker anxiogenic effects, could serve to blunt or mask the onset of COC's anxiogenic actions. Such an explanation would obviously account for the high incidence of alcohol and COC coadministration. If this notion is correct, then one would predict that the immediate effects of CE would be rewarding and that the anxiogenic effects would be weaker and delayed relative to COC. The current study was devised to test these hypotheses using the conditioned place preference as an assay for the positive and negative actions of intravenous CE.

## 2. Methods

### 2.1. Subjects

Seventy-four male albino Sprague–Dawley rats (375–450 g.) were obtained from Charles River Laboratories (Wilmington, MA). Rats were housed individually in metal wire cages located within a temperature-controlled

23 °C vivarium. Rats were maintained on a 12-h L:12-h D cycle with lights on at 0700 h (testing occurred between 1200 and 1500 h). All animals were allowed free access to food (Purina Rat Chow) and water throughout the experiment and were gentled for a period of 7 days prior to surgery. The animals' care and all experimental procedures were reviewed and approved by the University of California at Santa Barbara's Institutional Animal Care and Use Committee for compliance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

### 2.2. Surgery

Each rat was implanted with an indwelling chronic silastic jugular catheter under deep anesthesia induced using 2.5% isoflurane gas administered via inhalation (VetEquip). Within 5 min of the commencement of isoflurane administration, all rats were administered atropine (0.04 mg/kg im) to reduce respiratory congestion. During the surgery, animals were also administered the nonopiate analgesic, flunixin meglumine (Banamine, 2.0 mg/kg sc), to reduce discomfort upon emerging from anesthesia. One end of the intravenous catheter was inserted into the jugular vein and secured in place by suture. The other end was passed subdermally to an incision on the animal's back where it was attached to a fixed stainless steel guide cannula (Item C313G, Plastics One) that then protruded from the incision. The cannula was affixed using dental acrylic to a 3-$cm^2$ of Mersilene Mesh (Ethicon) that was laid flat and subcutaneously on the rat's back so that tissue could grow through the mesh and secure the cannula in place. The guide cannula was threaded so that an internal cannula could be inserted and removed. Administration of intravenous heparin or drug was accomplished with an internal cannula (Item C313I, Plastics One) connected by PE 20 tubing to a fluid-filled syringe. The internal cannula was screwed into the exposed end of the guide cannula in the animal's back. Between intravenous test sessions, a cap (Item C313DC, Plastics One) was screwed onto the shaft of the guide cannula to protect the integrity of the catheter. Catheter patency was maintained by daily injections of 0.05 ml heparin (1000 IU/ml) prepared in 0.9% physiological saline. Rats were allowed to recover for 5 to 10 days prior to behavioral training.

### 2.3. Drug administration

COC was administered in a dose of 1.0 mg/kg/injection and CE was administered in an equimolar dose of 1.44 mg/kg/injection. All doses were prepared in a vehicle solution of 0.9% physiological saline and delivered intravenously in a volume of 0.1 ml/injection over a 4.6-s duration via a motorized Razel A infusion pump. On nondrug conditioning days, 0.9% physiological saline was delivered intravenously in the same manner.

### 2.4. Conditioned place preference apparatus

Place conditioning was conducted in a rectangular wooden [94 cm ($L$) × 43 cm ($W$) × 61 cm ($H$)] enclosure. Two removable walls could be put in place to create three separate compartments: on opposite ends of the apparatus were a black and a white compartment that were equal in size ($42 \times 43 \times 61$ cm) and were separated by a central "neutral" gray compartment ($10 \times 43 \times 61$ cm). The black side of the apparatus had a smooth Plexiglas floor and was wiped prior to each trial with 1.0 ml of a 2% acetic acid solution. Wood chips were spread on the floor of the white side prior to each trial. The central gray region had a painted gray wooden floor. Thus, each environment had distinct olfactory, visual, and textual characteristics.

Fifteen infrared emitter–detector pairs were evenly spaced along the two longer walls of the apparatus 1.0 cm above the floor. Input from these infrared sensors was recorded in real time by a 486 Pentium PC desktop computer equipped with an I/O board and running custom software. A 55-W lamp was placed on the floor of the soundproof test room and served as the sole source of illumination.

### 2.5. Procedure

Approximately 1 week following surgery, each animal completed a single baseline trial that involved placing the subject individually in the apparatus with the dividing walls removed. The amount of time spent in each of the three compartments was then recorded over 15 min. Between each subject, the entire apparatus was wiped down with a damp cloth, the wood chips were replaced on the white side, and fresh acetic acid was laid down on the black side. Baseline data were used to assign each rat to one of six groups: CE 0-min delay ($n = 12$), CE 5-min delay ($n = 14$), CE 15-min delay ($n = 10$), CE 30-min delay ($n = 13$), COC 0-min delay ($n = 12$), and COC 15-min delay ($n = 13$). Assignments were made so that mean baseline performance within each group was approximately equal.

Place conditioning trials were conducted once daily for 8 days beginning on the day immediately following the baseline trial. The dividing walls were set in place and the subjects were restricted to either the white or black side of the apparatus after their daily intravenous injection. Each animal alternately received drug on one day and saline on the next, with half the animals in each group receiving drug on even days and the other half receiving drug on odd days. The conditioning schedule was also counterbalanced in that half the animals in each dosage group experienced drug on the side that was preferred during the baseline trial, while half experienced drug on the nonpreferred side. Following each injection, subjects were either placed directly into the apparatus (0-min delay groups) or into a plastic holding cage located outside the conditioning room for the appropriate delay (5, 15, or 30 min) and then placed into the white

or black side of the apparatus. Conditioning trials lasted 5 min for all groups. This procedure yielded four drug–place/A and four saline–place/B pairings for each animal. On the day following the completion of the 8-day place conditioning period, a final 15-min preference test was conducted with no preinjections and with the walls removed as described for the baseline trial (see above). After the final preference test, catheter patency was confirmed for each rat by means of an infusion of 0.2 ml methohexital sodium (Brevital sodium, 10 mg/ml iv).

## 3. Results

Place preferences and aversions were operationally defined as reliable shifts from baseline on test day. As a result, mean difference scores for the amount of time spent in the drug-paired side (test minus baseline) were computed for each group (see Fig. 1). The distribution of side preferences at baseline was similar for each group (46% preferred the white side; 54% preferred the black side). Catheter failure in several animals reduced final sample sizes for each delay group as follows: COC 0-min delay ($n=11$), COC 15-min delay ($n=10$), CE 0-min delay ($n=9$), CE 5-min delay ($n=10$), CE 15-min delay ($n=10$), CE 30-min delay ($n=11$). A one-way independent-group analysis of variance computed on the data and depicted in Fig. 1 revealed a significant main effect for Group: $F(5,56)=8.680$, $P<.001$. Directional one-tailed single-sample $t$ tests were then computed to assess whether the mean shift from baseline either toward the drug-paired side (preference) or away from the drug-paired side (aversion) was statistically different from the "no change" value of zero. Both COC delay groups had difference scores that deviated significantly from zero [0-min delay, $t(10)=3.081$, $P<.01$; 15-min delay, $t(9)=3.122$, $P<.01$). The CE 30-min delay group's difference score was also different from zero: $t(10)=2.532$, $P<.05$ as was the mean for the CE 0-min delay group: $t(8)=3.644$, $P<.01$. Because the mean difference score of one subject in the CE 0-min delay score showed an aversion that was more than three standard deviations from the mean, the data from this animal were not included in the data analysis. The remaining groups' scores on the test day did not reliably shift from baseline [their mean difference scores were not statistically different from zero: CE 5-min delay, $t(9)=0.741$, n.s.; CE 15-min delay, $t(9)=0.797$, n.s.].

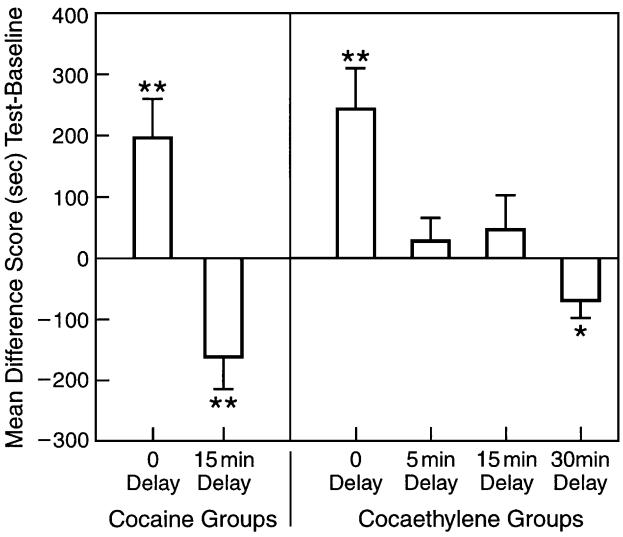


Fig. 1. Time spent in the COC- or CE-paired environment expressed as mean (+S.E.M.) difference scores (in seconds): test day less baseline day performance. Values above the zero line indicate greater time spent in the drug-paired environment after conditioning, while values below the line indicate a shift away from the drug-paired environment following conditioning. The COC 0-min delay and CE 0-min delay groups produced significant shifts toward the drug-paired environment, indicating a conditioned place preference for both groups (i.e., difference scores deviated reliably from zero; $^{**}P<.01$; $^{*}P<.05$). The COC 15-min delay and CE 30-min delay groups demonstrated significant shifts away from the drug-paired environment, indicating conditioned place aversions. The CE 5- and 15-minute delay groups did not reliably shift from baseline. These data are consistent with an Opponent-Process Theory for COC and CE action.

## 4. Discussion

Results of this experiment confirm the results of Ettenberg et al. (1999) demonstrating that animals placed into a distinctive environment immediately after intravenous injections of COC come to develop a reliable preference for that environment while animals having experienced a distinct environment paired with the effects of COC 15-min post-intravenous injection demonstrated reliable aversions to the drug-paired environment. The current study extends these findings to CE, which also has biphasic properties similar to the opponent-process actions of COC. Immediate CE–place pairings produced a place preference while delays in the drug–place pairings eventually resulted in place aversions. The question under study here was whether or not the aversive effects of CE would be temporally delayed (due to the drug's longer half-life) relative to those of COC. The answer to this question appears to be "yes." While COC produces a statistically significant place aversion in the 15-min delay group, animals given intravenous injections of CE only show reliable aversions in the 30-min delay condition. In fact, subjects in the CE 15-min delay group displayed slight preferences (not aversions) for the drug-paired environment (although they were not reliably different from zero). These patterns of aversions and preferences indicate that while both COC and CE produce biphasic drug effects, the onset of CE's negative actions is retarded relative to COC's. Furthermore, these results cannot be accounted for by differences in some direct but nonspecific behavioral side-effect of the drugs in question since all subjects were undrugged at the time of testing.

When used properly, the conditioned place preference paradigm produces a reliable index of the inherent affective properties of psychoactive drugs or other experimental manipulations. Animals have been shown to develop preferences for environments paired with the rewarding characteristics of such stimuli as food (Spyraki et al., 1982), sex (Miller and Baum, 1987), sucrose (White and Carr, 1985), rewarding brain stimulation (Duvauchelle et al., 1992), and psychoactive drugs (see review by Carr et al., 1989). Conversely, animals develop aversions for environments paired with aversive stimuli such as phencyclidine (Barr et al., 1985), radiation sickness (Garcia et al., 1957), and electrical stimulation of the dorsal gray (Roberts and Cox, 1987). The present study, along with that of Ettenberg et al. (1999), is unique in their demonstration that the identical intravenous injection of drug can produce preferences or aversions based upon the time postinjection that the place pairings occur. These data therefore provide strong support for the presence of opponent-processes in COC and CE actions (Koob et al., 1997). The present results are also consistent with the data of Pan and Hedaya (1999) on the half-life of COC and CE in rats after intravenous injection. Those investigators reported a plasma half-life of $15.8 \pm 1.5$ min for COC and $25 \pm 3.1$ min for CE, in both cases, these time points are associated with aversive or negative properties of the respective drugs. Additionally, the place aversion produced by CE (at 30 min delay) was of a lesser magnitude than that produced by COC (at 15 min delay). While this difference was not statistically reliable, it supports the results of Raven et al. (2000) who reported CE to be less anxiogenic than COC when used as reinforcers in an operant runway (Raven et al., 2000). Taken together, these data collectively suggest that in people taking COC and ethanol, the metabolism of CE with its own rewarding effects, longer duration of action, and weaker anxiogenic side-effects may serve to counteract some of the negative properties of COC that would otherwise appear at a time when CE remains positive.

In clinical studies, McCance-Katz et al. (1993) found that human subjects who followed intranasal COC with oral ethanol reported an enhanced and prolonged COC-like euphoria compared to subjects who did not receive ethanol. Perez-Reyes and Jeffcoat (1992) found a comparable effect when oral ethanol preceded intranasal COC. Similarly, Higgins et al. (1993) reported that subjects' ratings of "restlessness" following COC were attenuated by coadministration of ethanol. Once again, these results from clinical studies indicate that the concurrent consumption of COC and alcohol prolongs the euphoria produced by COC while reducing anxiety effects that are quite plausibly mediated by the longer-acting metabolite, CE.

By way of summary, the results of the present experiment show that CE is less anxiogenic and longer-acting than its parent compound, COC. When placed within the context of the clinical studies cited above, these results suggest that CE may act to prolong the initial "high" of the user while also ameliorating the anxiogenic effects of COC that occur as its plasma levels drop (and while CE levels remain high). Specifically, in a drug user who concurrently consumes COC and alcohol, the onset of CE's action would naturally be delayed relative to COC's since it is a metabolite of COC. Thus, the delayed CE-induced euphoria could then mask any dysphoria associated with declining plasma levels of COC, thereby ameliorating the negative affective components of the COC experience. Because of its longer half-life, CE levels remain high even while COC levels drop. When CE levels finally drop, they do not appear to be associated with as negative an experience as that of COC. Thus, the combination of ethanol + COC likely lengthens the duration of the subjective "high" and decreases the severity of the subjective "crash" that follows COC alone—both actions of which can be attributable to the endogenous production of CE.

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