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Alcohol consumption is preferred to water in rats pretreated with intravenous cocaine

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Abstract

Clinical and anecdotal reports suggest a high incidence of alcohol administration during cocaine use, potentially as a means to diminish the aversive effects of cocaine that follow the initial positive drug effects. We have previously shown that in the operant runway, oral ethanol significantly reduces the approach–avoidance retreats that develop in response to IV cocaine. The current study was intended to test whether rats given the same dose of IV cocaine administered in our previous study would *choose* to consume ethanol rather than water in a two bottle choice paradigm. We also examined whether significant serum levels of the psychoactive cocaine metabolite, cocaethylene, were found in our animals that may account for the preference for ethanol. Animals pretreated with cocaine drank significantly more ethanol than did animals pretreated with saline. There were no measurable levels of cocaethylene at 10 or 40 min post-cocaine and extremely low values at the 20-min time point, indicating that cocaethylene formation does not reinforce the co-administration of cocaine and alcohol in rats. These data demonstrate that the presence of cocaine serves as a primary factor in the preference for alcohol in thirsty rats, potentially to reduce the well-documented negative/anxiogenic properties of cocaine.

Keywords: Drug self-administration; Alcohol; Cocaine; Cocaethylene; Drug reward

1. Introduction

Several reports have now formally documented the high prevalence of alcohol–cocaine co-administration in human drug users (Anthony et al., 1994; Carroll et al., 1993; Grant and Harford, 1990; Magura and Rosenblum, 2000). A survey conducted by the National Institute of Drug Abuse in the early 1990s revealed that 4.7% of Americans used cocaine and alcohol simultaneously (Grant and Harford, 1990). The same survey reported that the 1-year prevalence of cocaine use was 6.2%, demonstrating that the majority of cocaine users had a propensity to consume alcohol with their cocaine. Indeed, more recent reports estimated that anywhere from 50% to 90% of cocaine users co-abuse alcohol (Anthony et al., 1994; Brookoff et al., 1996; Rounsaville et al., 1991; Weiss et al., 1988). The lifetime prevalence for comorbid alcohol abuse in cocaine users is 62%, whereas comorbid alcoholism with opiate dependence occurs at the much lower lifetime prevalence of 35% (Rounsaville et al., 1991).

There are several putative explanations for the prevalence of cocaine and alcohol co-administration in human users. Subjects in clinical studies have reported that the use of alcohol reduces the anxiety and other acutely dysphoric psychological side effects that characterize the cocaine "crash" (McCance-Katz et al., 1993; McCance et al., 1995; Perez-Reyes and Jeffcoat, 1992; Higgins et al., 1993). Thus, alcohol may be acting to reduce the negative components of the cocaine experience. A recent experiment conducted in our laboratory provided evidence to support this hypothesis. Animals running an alley for IV cocaine developed an ambivalence about entering the goal-box that is characterized by approach–avoidance behaviors described as "retreats" (e.g., Ettenberg and Geist, 1993; Raven et al., 2000). These retreats are identical in nature to those observed in animals running the alley for food + footshock reinforcement (Geist and Ettenberg, 1997). This approach–avoidance conflict behavior has been shown to result from concurrent positive and negative associations with the goal-box

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and can be reduced by pretreatment with anxiolytic agents (Ettenberg, 2004; Ettenberg and Geist, 1991; Geist and Ettenberg, 1997; see also Miller, 1944). Ethanol, of course, also has been shown to have anxiolytic actions (for review, see Chester and Cunningham, 2002) and we recently reported that an ethanol solution (8% v/v) effectively ameliorated the retreat behavior produced by IV cocaine in the runway (Knackstedt and Ettenberg, 2005).

A second explanation for the co-administration of alcohol and cocaine is that this combination results in a novel metabolite (cocaethylene, CE) whose own psychopharmacological actions may be positively or negatively reinforcing in their own right. CE is formed via the ethyl transesterification of cocaine, a reaction that is thought to be catalyzed by the same nonspecific hepatic carboxylesterases that are responsible for cocaine metabolism (Dean et al., 1991; Sukbuntherng et al., 1996). CE is not a natural metabolite of cocaine; it is only formed when alcohol is simultaneously consumed with cocaine (Farre et al., 1993; McCance-Katz et al., 1993). Unlike the other cocaine metabolites, CE is pharmacologically active (Pan and Hedaya, 1999). Behavioral studies in animals have shown that 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 conditioned place preferences (Schechter, 1995) in a manner comparable to that produced by cocaine. When administered intravenously to humans in clinical studies, CE has been reported to possess the same euphoric and stimulant effects as cocaine (Hart et al., 2000; McCance et al., 1995; Perez-Reyes, 1993; Perez-Reyes et al., 1994). In one study these effects could not be reliably distinguished from cocaine (McCance et al., 1995), while in others, the subjective effects of CE were described as being significantly weaker than those of cocaine (Hart et al., 2000; Perez-Reyes, 1993; Perez-Reyes et al., 1994). CE also has a longer half-life than cocaine in both humans (Farre et al., 1993) and rats (Pan and Hedaya, 1999).

Because CE appears to be eliminated more slowly than cocaine, it may be expected to accumulate during a cocaine and alcohol binge, a prediction that is verified by clinical samples (McCance-Katz et al., 1998). Thus, when humans consume cocaine and alcohol (and thereby induce the formation of endogenous CE), the delayed production and longer duration of action of CE could serve to mask the onset of the anxiogenic effects of cocaine and thereby produce a more desirable outcome for the user.

Our previous work suggested that the negative side effects (e.g., approach–avoidance retreats) of cocaine delivery could be diminished in thirsty animals provided post-cocaine access (forced choice) to alcohol. The current experiment was conducted in order to assess whether rats pretreated with the same dose of intravenous cocaine would *choose* to orally consume more ethanol than non-cocaine treated rats and whether such behavioral preferences were related to serum levels of cocaethylene. If ethanol administration was acting to enhance the positive reinforcing properties or alleviate the negative side effects of cocaine, then one would predict that cocaine-treated subjects would drink more ethanol than saline-treated animals in a two-bottle (water vs. ethanol) free-choice test. Additionally, if any observed elevated ethanol consumption in cocaine-treated rats is attributable to the novel metabolite CE, then serum levels of CE ought to parallel the subjects' drinking preferences.

2. Methods

2.1. Subjects

Forty male albino Sprague–Dawley rats (weighing 300–375 g at the time of surgery) were obtained from Charles River Laboratories (Wilmington, MA). Subjects were individually housed in hanging wire cages within a temperature-controlled vivarium (23 °C) on a 12/12-h light/dark cycle (lights on at 0700 h). Rats were provided *ad libitum* access to food and water in their home cages. Each animal was gentled via individual handling daily for one week prior to surgery. The animals' care and all experimental procedures were conducted in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were reviewed and approved by the University of California at Santa Barbara's Institutional Animal Care and Use Committee.

2.2. Surgery

Each rat was implanted with an indwelling chronic silastic jugular catheter under deep anesthesia induced by inhalation of 4.0% and maintained by constant 2.5% isoflurane gas (VetEquip Inc., Pleasanton, CA). All rats were administered atropine (0.04 mg/kg IM) to reduce respiratory congestion and, prior to the completion of surgery, the non-opiate analgesic, flunixin meglumine (Banamine, 2.0 mg/kg SC), to reduce discomfort upon emerging from anesthesia. During surgery, one end of the catheter was inserted and secured by suture into the jugular vein. The other end was passed subdermally to the animal's back where it protruded through a small incision and was affixed to a stainless steel guide cannula (Item C313G, Plastics One, Inc., Roanoke, VA). In turn, the guide cannula was attached to a 3-cm square of Mersilene Mesh (Ethicon, Somerville, NJ) by means of dental acrylic. The small square of mesh was placed flat and subcutaneously on the rats' back so that tissue could grow through the mesh and secure the cannula in place. Administration of heparin and drug was accomplished by PE 20 tubing attached to a fluid-filled syringe. When injections were not being given, the guide cannula on the animal's back was capped to protect the IV system from contamination. After surgery, catheter patency was maintained by daily injections of 0.05 ml heparin (100 IU/ml) prepared in 0.9% physiological saline. Rats were allowed to recover 6–10 days after surgery prior to the start of the experimental protocol.

2.3. Ethanol Pretraining

Subjects were water-deprived and permitted to drink an ethanol/sucrose solution in their home cage for 30 min daily over 10 consecutive days to familiarize the subjects with the

novel tastes. The sucrose was not intended to produce a hedonically pleasant taste, but rather to counteract the bitter taste of the oral ethanol. The drinking solution was initially a 2% (v/v) ethanol solution (prepared from 95% ethanol and water) sweetened with 100 g sucrose per liter of solution. After 3 days, the concentration of ethanol was increased to 4% (v/v). On the seventh day of training, the concentration of ethanol was increased to 8% (v/v). Following the daily 30-min drinking sessions, animals were permitted to drink plain tap water for an additional 30 min. Animals were maintained on a 1-h/day drinking regimen throughout the duration of the experiment in order to ensure reliable levels of fluid consumption on test days.

2.4. Procedure

An initial group of subjects was randomly assigned to one of two groups. The rats were removed from their home cages and each given a single intravenous injection of either 1.0 mg/kg cocaine ($n=11$) or 0.9% physiological saline ($n=9$) in a volume of 0.1 mL delivered over 4.6 s duration. Drug delivery was accomplished via PE tubing that was attached to a fluid-filled syringe (containing either drug or saline) set into a Razel (Stamford, CT) Model A syringe pump. Subjects were then immediately placed into a plastic holding cage with a wire top and moved to a sound attenuated test room. Five minutes after receiving their IV injection, subjects were presented with two identical drinking bottles: one containing an 8% (v/v) EtOH solution sweetened with sucrose and a second bottle containing plain tap water. Each day, the bottles were presented individually for a few seconds (to permit the subject to sample the fluid in each bottle) and then both were set in place side-by-side offering the subject a free choice. The order of presentation (sweetened ethanol or water) was counterbalanced across subjects and alternated daily. Similarly, the location (left side or right side) of the fluids was also counterbalanced and alternated each day to control for inherent or learned side/location preferences. Animals were permitted to drink for 30 min. They were then removed from the test/drinking cages and placed back in their home cages where they were given access to plain tap water for an additional 30 min. The amount of each type of fluid consumed was recorded each day, 5 days per week, over 4 weeks (i.e., 20 trials).

The doses of cocaine and ethanol employed in this study were selected on the basis of our prior work with these two compounds. The 1.0 mg/kg dose of IV cocaine has been shown to produce the fastest run times in the operant runway (e.g., Raven et al., 2000) and to have significant aversive properties 15-min post-injection (Ettenberg et al., 1999; Knackstedt et al., 2002). This dose of cocaine was therefore used to assess the putative anxiolytic action of oral ethanol. Knackstedt and Ettenberg (2005) subsequently demonstrated that the negative consequences of this dose of cocaine could be reversed by post-runway consumption of an 8% (but not lower) v/v solution of ethanol. In that experiment, ethanol blunted the development of approach–avoidance retreat behavior in the runway. The current experiment represents a logical extension of our previous work and therefore employed the same doses of ethanol (8% v/v) and cocaine (1.0 mg/kg). If oral ethanol acts to attenuate cocaine's negative consequences, as we have hypothesized from our previous studies, then one might expect animals to freely choose to consume ethanol at a point in time when the negative effects of IV cocaine are being unmasked. The current study was therefore devised to test this putative negative reinforcement action of ethanol.

On the day following the last trial, blood samples were taken from a subset ($n=6$) of rats that had undergone the 20 day free-choice experiment, and sent to National Medical Services (NMS; Alameda, CA) for "blind" measurements of CE and COC serum levels via gas chromatography/mass spectrometry (GC/MS). Animals drank the 8% ethanol solution for 20 min and were then given an injection of COC (1 mg/kg IV) followed by 2 ml heparin (100 U/ml) to ensure that no cocaine remained in the catheter. These subjects were permitted access to the ethanol solution for the duration of the blood sampling period. Six additional subjects received *only* an injection of an equimolar dose of CE (1.44 mg/kg IV). It should be noted that the order of administration of cocaine and alcohol is the opposite of that used in the behavioral portion of this study. This reversal was implemented in order to maximize the amount of cocaethylene formed in these subjects as it takes some time for significant levels of alcohol to accumulate in the rat after oral consumption of alcohol. Blood samples from both groups were taken at 10-, 20- and 40-min post-injection from either the jugular catheter or (in the case of failure to remove blood from the catheter) the saphenous vein. The samples were collected into ice-cold heparin-coated syringes and then centrifuged at 6000 rpm for 15 min. The serum was collected into vacutainer tubes coated with sodium fluoride potassium oxalate to prevent degradation by cholinesterases, packed in dry ice and mailed to NMS for GC/MS analysis of CE and cocaine levels.

In order to ensure that any observed ethanol consumption was not simply a function of the sucrose sweetener, an additional set of animals was tested. Subjects were assigned to either a cocaine group ($n=10$) or a saline group ($n=10$) and the procedures described above were repeated with one important deviation. The sweetened ethanol solution was replaced with sweetened tap water, leaving subjects with a choice between sweetened water (100 g/l) and plain tap water. Again, subjects underwent one trial/day for 20 days. This group therefore provided a means of assessing whether IV cocaine might induce an enhanced preference for "sweetness" independent of ethanol.

3. Results

Fig. 1 illustrates the mean ethanol consumption (averaged across 5 trials per week) for the cocaine-treated and saline-treated subjects over the course of 4 weeks of testing. A mixed two-factor Group × Trial ANOVA (with repeated measures on one factor) conducted on these data confirmed that cocaine-treated animals consumed significantly more ethanol than saline-treated animals ($F(1,18)=14.616$, $p<0.002$). There was also a significant main effect for week ($F(3,54)=7.950$, $p<.001$) reflecting the increased consumption of ethanol in both groups over the course of trials. However, there was not a

significant Group × Trial interaction ($F(1,18)=.005$, n.s.) indicating that the difference in ethanol consumption between the two groups was maintained over trials (see Fig. 1). The amount of ethanol consumed was expressed as a percentage of total fluid consumed because differences in consumption over time could be seen best by using this larger scale. It should be noted that the absolute amount of alcohol consumed also increased over the course of weeks (a decrease in the amount of water consumed over weeks did not completely account for the differences) for both groups and ranged from 2.34 g/kg to 3.23 g/kg. The Geller–Seifter paradigm has shown that ethanol's anxiolytic effects can be seen when animals are treated with 1 g/kg ethanol (Aston-Jones et al., 1984). Thus, the levels of ethanol consumed by both groups were sufficient to achieve a behavioral effect.

Another mixed two-factor Group × Trial ANOVA (with repeated measures on one factor) was conducted on the total amount of fluid consumed per week to ensure that group differences in ethanol consumption were not an artifact of differing levels of overall fluid intake. The ANOVA produced no main effect for Group ($F(1,18)=0.627$, n.s.), or Trial ($F(3,54)=2.441$, n.s.) nor a Group × Week interaction ($F(1,18)=0.135$, n.s.).

As described in Methods, following the final day of testing, blood and serum cocaine and CE levels were measured via GC/MS. The mean serum levels (in ng/mL) are presented in Table 1 which provides the values of cocaine and CE found in blood at 10, 20 and 40 min post-cocaine + ethanol administration. One-tailed *t*-tests were computed on these data to examine whether serum levels at each time point (10-, 20-, and 40-min post-drug) were significantly above zero. While no CE was found in the serum at either the 10- or 40-min time points, mean CE levels, although low, were significantly greater than zero at the 20-min time point ($t(5)=2.846$, $p<.002$). Cocaine levels were significantly greater than zero at both the 10-min ($t(5)=4.411$, $p<.004$) and 20-min time points ($t(5)=1.795$, $p<.07$), but not at the 40-min point when levels had decreased significantly. The extremely high levels of cocaine measured at the 10 min time point may be due to residual cocaine from the intravenous administration into the catheter contaminating the blood samples. In order to verify that GC/MS was sensitive to the presence of CE levels, serum was drawn from animals who were administered IV CE (1.44 mg/kg). One-tailed *t*-tests revealed that levels were significantly above zero at 10-min post-injection ($t(5)=2.232$, $p<.05$), 20 min post-injection ($t(4)=6.957$, $p<.01$), and 40-min post-injection ($t(4)=13.054$, $p<.001$).

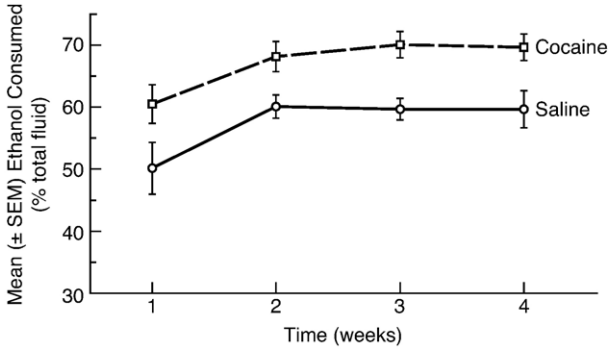

Fig. 1. Mean percentage of total fluid consumed that is ethanol across the 4 weeks (5 trials/week) of *Experiment 1*. Subjects treated with IV cocaine displayed a significantly higher percentage of total fluid intake that was ethanol than did subjects treated with saline across all 4 weeks of the experiment.

Table 1
Mean (±S.E.M.) serum levels of cocaine and cocaethylene (ng/mL) in six subjects having ingested ethanol (mean consumption 1.2 g/kg) for 30 min followed by an IV injection of cocaine (1 mg/kg)

Drug	10 min	20 min	40 min
Cocaine	3206*±727	791*±441	341±331
Cocaethylene	0.0	96*±34	0.0
Cocaethylene (after 1.44 mg/kg CE IV)	2000*±0	220*±31.62	162*±12.41

A separate group of animals ($n=6$) were administered only IV CE (1.44 mg/kg); their data are presented in the last row of the table. Times represent minutes post-cocaine (*$p<.05$).

Control saline and cocaine groups were offered a choice between a sweetened water solution and plain tap water during 20 trials. At the end of those 20 trials, the mean percentage of total fluid consumed that was sweetened water was calculated (mean±S.E.M.; cocaine group: 69%±4.68; saline group: 67.9%±2.34). A one-way ANOVA conducted on the last week of testing revealed no significant differences in the consumption of sweetened water between IV cocaine and IV saline groups ($F(1,18)=.028$, n.s.)—thus, cocaine did not in and of itself enhance a preference for sweet tastes.

4. Discussion

Human clinical data indicate that a large majority of cocaine users choose to co-administer alcohol (Anthony et al., 1994; Brookoff et al., 1996; Rounsaville et al., 1991; Weiss et al., 1988). The current experiment provides animal data that are consistent with the human epidemiological results. Rats freely chose to consume more ethanol when pretreated with IV cocaine than when pretreated with IV saline. As seen in Fig. 1, cocaine-treated animals established this preference for ethanol by week 1 and subsequently increased their consumption until they stabilized in weeks 3 and 4. The saline-treated subjects also increased their preference for the ethanol solution between weeks 1 and 2 but then remained stable for the remainder of the experiment. However, even at their highest consumption rate, saline-treated rats never attained the level of preference demonstrated by the cocaine-treated subjects. These results suggest that the presence of cocaine somehow increases the motivation to consume ethanol.

Alternatively, one might suggest that the observed enhanced consumption of alcohol in cocaine-treated animals is due to the fact that cocaine "simply" enhances the preference for sweetness after cocaine administration independent of the ethanol content of the solution. Hence the data might reflect an increased motivation for, and consumption of, "sucrose" and not ethanol. This seems unlikely, however, since our control subjects, whether cocaine- or saline-treated, when given the choice

between sweet water and plain water, consumed comparable levels of the sweetened solution. Thus, the preferential consumption of ethanol in the experimental cocaine-treated animals was due to the combination of ethanol and cocaine, and not sucrose and cocaine.

It is highly probable that ethanol is preferred by cocaine-treated subjects because ethanol reduces the anxiety that accompanies acute cocaine withdrawal. Humans report that alcohol can lessen the discomfort that accompanies the "crash" that occurs as serum levels of cocaine drop (Margolin et al., 1996). In this scenario, ethanol may reduce the anxiogenic or aversive effects of cocaine. This hypothesis is strengthened by our finding that the frequency of approach–avoidance conflict behavior in rats approaching a runway goal box associated with IV cocaine delivery was dose-dependently reduced in animals who drank ethanol (but not water or sweetened water) following each cocaine experience (Knackstedt and Ettenberg, 2005). In the current context, this same concentration of ethanol was consumed in greater quantity among cocaine-treated rats than saline-treated rats. Since cocaine (and not saline) produces anxiogenic side effects, the present data are consistent with a putative anxiolytic action for oral ethanol. In this view, alcohol may be consumed to offset the negative properties that occur during the cocaine crash which we know to exist 15 min post-IV injection in laboratory animals (Ettenberg et al., 1999; Knackstedt et al., 2002).

Since the combination of cocaine and ethanol results in the production of the novel metabolite, CE, it may be that the consumption of ethanol was motivated by the positive and negative reinforcing actions of CE. In this view, cocaine-treated rats ingested more ethanol than saline-treated rats because of the resultant production of a third psychoactive compound (CE) that serves to sustain the "high" and reduce the "crash" attributable to cocaine alone. However, in the current study, CE serum levels produced by the doses of cocaine and ethanol that occurred in the experimental group were extremely low. At 10 and 40 min post-cocaine+ethanol, no CE was measured in serum; a statistically significant (albeit low) amount of CE was formed 20-min post-administration; however, even at its maximum, CE concentrations were only 12% of cocaine levels (see Table 1). The methods used in the current experiment are similar to those of Levine and Tebbett (1994), who administered 1 g/kg oral ethanol (via gavage) followed by 2 mg/kg IV cocaine. However, these authors found a maximum CE concentration that was approximately 30% of the maximum cocaine serum levels; this occurred 2 min post-cocaine injection. While the levels of CE declined steadily after this point, they were still higher than those observed in the current experiment until 15 min post-injection. The higher levels obtained by Levine and Tebbet may have occurred due to a higher dose of administered cocaine (2 mg/kg vs. 1 mg/kg used in the current study).

The maximum endogenous serum CE levels achieved here when subjects were given cocaine+ethanol was only a fraction of the levels seen after a behaviorally activating dose of IV CE was administered. The dose of CE (1.44 mg/kg) was chosen because it has been shown to be reinforcing in the operant runway and produce retreats in this paradigm (Raven et al., 2000). Although we have found CE to be more positive and less negative than cocaine (Raven et al., 2000) these comparisons were made with behaviorally active equimolar doses of the two compounds. When in the current study, a behaviorally active dose of CE was administered IV, serum levels were reliably different at 10, 20 and 40 min post-injection and at maximum levels (10 min post-CE injection) were 100% greater than the levels observed in the cocaine+ethanol rats. Additionally, IV CE (1.44 mg/kg) has been shown to produce a place preference for an environment paired with the immediate effects of the drug (Knackstedt et al., 2002). However, 30 min after this dose is administered, a place aversion is produced for an environment paired with these delayed drug effects. While we did not measure serum CE levels 30 min post-CE injection, the levels at 20 and 40 min post-injection were still higher than the maximum serum CE levels detected after cocaine+ethanol administration. It therefore seems unlikely that the trace levels of endogenous CE produced in the current subjects could serve as the motivating factor for the alcohol consumption of cocaine-treated animals, especially since levels formed during the free-choice portion of the experiment would be predicted to be lower than those formed when alcohol was administered prior to cocaine as it was on the day of CE measurement. However, it should be noted that serum drug levels are not always reflective of brain drug levels. It is possible that a lipophilic psychoactive drug such as CE could easily cross the blood–brain barrier and be present at a higher distribution there than in the serum.

In conclusion, the current study has determined that animals pretreated with IV cocaine choose to consume ethanol over plain tap water and drink significantly more ethanol than did animals pretreated with IV saline. Animals in this study consumed more ethanol at precisely the same time that place-preference data suggest that the cocaine experience is becoming aversive (Ettenberg et al., 1999; Knackstedt et al., 2002). The current results extend our previous findings that sweetened oral ethanol effectively reduced retreat behavior (approach–avoidance conflict) in rats running an alley for IV cocaine (Knackstedt and Ettenberg, 2005). In that study, post-cocaine consumption of sweetened water alone (a strong reinforcing event) did not serve to reduce "retreat" behaviors of thirsty animals approaching a goal box associated with IV-cocaine administration. The current study also shows that the increased consumption of alcohol cannot be explained by the formation of CE. When taken together, the current and previous results suggest that cocaine subjects are most likely motivated to ingest ethanol because of its negative reinforcing effects that reduce cocaine's delayed aversive, anxiogenic consequences.

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