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Cocaine, but not alcohol, reinstates cocaine-induced place preferences

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Abstract

Alcohol has been reported to modulate the reinforcing and aversive properties of cocaine. Given these effects, the present study examined whether this interaction could be extended to cocaine seeking using the conditioned place preference (CPP) procedure. Specifically, 31 drug-naive, male Sprague–Dawley rats were injected every other day (for 8 days) with either 20 mg/kg cocaine or vehicle in an alternating sequence prior to being restricted to a drug or vehicle side of a place preference chamber for 30 min. On Day 9, subjects were given 15-min access to the entire chamber to assess compartment preference. Animals then underwent extinction by pairing both compartments with vehicle for an additional 8 days. Extinction was assessed in the same manner as place conditioning. The animals were then given priming injections of vehicle, 15 mg/kg cocaine, 0.5 or 1.0 g/kg alcohol on the day following the extinction test. Pairing 20 mg/kg cocaine with a specific compartment resulted in a significant place preference. Breaking the relation between the compartment and the drug by pairing both compartments with vehicle extinguished this preference. Interestingly, only 15 mg/kg cocaine was able to reinstate the cocaine-induced place preference, suggesting that the ability to reinstate cocaine seeking may be drug specific.

Keywords: Alcohol; Cocaine; Conditioned place preference; Extinction; Polydrug; Reinstatement; Relapse

1. Introduction

Alcohol has been shown to modulate a variety of cocaine's physiological and behavioral effects in humans and animals (Busse and Riley, 2003; Boyer and Petersen, 1990; Henning et al., 1994; Jover et al., 1991; Odeleye et al., 1993; Schechter and Meehan, 1995; Sobel and Riley, 1997). Included in these effects is the ability of alcohol to modulate the affective (i.e., rewarding and aversive) properties of cocaine (Busse et al., 2004; Busse and Riley, 2002; Cook et al., 1998; Farré et al., 1993; Gawin and Kleber, 1986; Grakalic and Riley, 2002a; Lewis and June, 1994; Magura and Rosenblum, 2000; McCance-Katz et al., 1998; Moolten and Kornetsky, 1990; Wiseman and McMillan, 1996). For example, alcohol has been demonstrated to potentiate cocaine's rewarding properties in the conditioned place preference (CPP; Busse et al., 2004) and intracranial self-stimulation (ICS; Lewis and June, 1994) designs, suggesting that combining alcohol with cocaine results in greater cocaine reward. In addition, Grakalic and Riley (2002b) demonstrated that preexposure to alcohol attenuated cocaine-induced taste aversions, indicating a reduction in the aversive properties of cocaine with alcohol exposure. These changes (i.e., increases in reward and decreases in aversion) may mediate, in part, the co-use of recreational compounds (see Hunt and Amit, 1987; Riley and Simpson, 2001; White et al., 1977).

Although the aforementioned evidence demonstrates that alcohol can directly affect the rewarding and aversive properties of cocaine, little research has been done that assesses the effects of alcohol on other properties of cocaine that are related to drug use and abuse (e.g., relapse and craving). Given alcohol's ability to modulate cocaine's affective properties, it is possible that alcohol may also impact the likelihood that animals will seek out cocaine and/or cocaine-related stimuli, an effect that may explain cocaine relapse after exposure to alcohol. Supporting this assumption is the fact that alcohol increases the preference for cocaine over a nonpharmacological reinforcer in current cocaine users who are abstaining from cocaine use, indicating that, even in the absence of cocaine, exposure to alcohol may affect the motivation to seek out this drug (Higgins et al.,

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1996). In addition, McKay et al. (1999) noted that, at a 3- and 6-month posttreatment follow-up, 40% to 61% (respectively) of cocaine users relapsed after exposure to alcohol, suggesting that the likelihood for cocaine relapse increases after exposure to alcohol. Given this evidence, exposure to alcohol after a period of cocaine abstinence may serve as a significant trigger for cocaine seeking.

One animal model that has been used in the assessment of drug seeking is the CPP design. In this procedure, an animal, after it has been injected with a compound (e.g., cocaine), is exposed to one side of a two-chamber place preference shuttle-box and the other side of the shuttle-box following an injection of the drug's vehicle (see Mucha et al., 1982; Tzschentke, 1998). Following this conditioning procedure, animals are placed in the shuttle box and given unrestricted access to both compartments in a drug-free state. Such a procedure generally results in a relative preference for the drug-associated side if the drug is reinforcing, a preference that is considered reflective of the drug's motivational (i.e., rewarding) properties (Tzschentke, 1998).

Interestingly, following a period of extinction, place preferences can be reinstated (Itzhak and Martin, 2002; Mueller and Stewart, 2000; Parker and Mcdonald, 2000); that is, preferences for the drug-associated compartment are renewed with priming injections of the training drug. Such an effect has been suggested to reflect a renewed interest in the drug or motivation for drug seeking, i.e., relapse. Reinstatement within the place preference design has been demonstrated with both cocaine (Itzhak and Martin, 2002; Mueller and Stewart, 2000) and morphine (Lu et al., 2002; Mueller et al., 2002; Parker and Mcdonald, 2000). In terms of cocaine, Mueller and Stewart (2000) initially conditioned place preferences with 5, 10 and 20 mg/kg cocaine. Following conditioning, they extinguished these preferences by repeatedly pairing both compartments of the place preference apparatus with saline injections and then reinstated them by administering a priming injection of 5 mg/kg cocaine. Thus, exposure to the training drug (even at doses lower than the one with which animals were initially trained) reestablished the preference in animals for the drug-associated chamber. Given these findings and those of others reporting that alcohol directly affects cocaine-induced place preferences (see Busse et al., 2004; Busse and Riley, 2002), it may be possible to assess the ability of alcohol to affect cocaine seeking within the CPP design. The present study examined this possibility by assessing the effects of 0.5 and 1.0 g/kg alcohol on the reinstatement of extinguished cocaine-induced place preferences.

2. Methods

2.1. Subjects

Thirty-one drug naive, male Sprague–Dawley rats, weighing approximately 250 to 400 g at the start of the experiment, were housed in separate hanging wire-mesh cages in a room maintained on a 12:12 L/D cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Food and water were available ad libitum throughout the experiment. The animals were handled daily beginning 2 weeks prior to the start of the experiment to limit any effects of handling stress during conditioning and testing. All conditioning and testing were carried out between the 0900 and 1400 h. The use of live animals in this experiment was approved by the American University's IACUC committee.

2.2. Drugs

Cocaine hydrochloride (generously supplied by the National Institute on Drug Abuse) was dissolved in distilled water and was injected intraperitoneally in a concentration of 10 mg/ml. Alcohol was prepared in a 15% (v/v) solution with distilled water and was also injected intraperitoneally.

2.3. Apparatus

The place conditioning apparatus consisted of four identical shuttle-box chambers (94.5 × 41 × 37.5 cm). Each chamber had three compartments separated by two removable Plexiglas barriers. One compartment (40 × 41 × 37.5 cm) was black in color and had a smooth Plexiglas floor. Another compartment (40 × 41 × 37.5 cm) was white in color and had a natural wood grain (1/4 in. plywood) floor with black sandpaper strips (2.54 × 41 cm) placed horizontally 2.54 cm apart. The third (central) compartment (11 × 41 × 37.5 cm) was gray in color and had a wire-mesh (23 gauge) floor. Each chamber was dimly lit with a 60 W Halogen bulb placed approximately 1.54 m overhead. Preliminary data from our laboratory using this apparatus indicate no systematic compartment bias.

2.4. Procedure

2.4.1. Place conditioning

Using the unbiased design (Bardo et al., 1995), place conditioning occurred immediately following an injection of the drug or its vehicle over the course of 8 days. On Day 1 of the place conditioning, the subjects were injected with cocaine (20 mg/kg) or vehicle immediately prior to placement in either the black or white compartment of the place preference apparatus for 30 min. The placement of subjects in the chamber was counterbalanced such that half the subjects had the drug paired with the black compartment while the remainder had the drug paired with the white compartment. The compartment paired with the drug was designated drug-paired (DP), while the compartment paired with vehicle was designated vehicle-paired (VP). On Day 2, subjects injected with cocaine on Day 1 were injected with vehicle and restricted to the VP compartment, and those injected with vehicle on Day 1 were injected with cocaine and restricted to the DP compartment. Counterbalancing the

placement of subjects into specific conditioning compartments on Days 1 and 2 controls for any natural preferences (or biases) that might exist (for a review, see Schechter and Calcagnetti, 1993). This procedure was repeated for a total of four conditioning cycles. On Day 9, animals were tested for their chamber preference by placing subjects in the center gray (neutral, N) compartment, removing the Plexiglas barriers and allowing them to have free access to the entire chamber for 15 min. Activity was recorded by four 8-mm Canon ES-50 camcorders located approximately 1.93 m directly above the place preference chambers. The animal's location, as noted in previous reports (Busse et al., 2004; Busse and Riley, 2002; Gong et al., 1997), was determined by the position of its forepaws.

2.4.2. Extinction

On the day (Day 11) following the initial preference test (see above), animals that displayed a place preference for the DP compartment ($n=28$) underwent extinction by pairing both compartments in an alternating sequence with a vehicle injection (matched in volume to cocaine) for an additional four cycles (8 days). That is, animals were given an injection of vehicle immediately prior to being placed in either the DP or VP compartments for an additional four cycles (8 days). Such a procedure has previously been found to rapidly extinguish cocaine-induced place preferences (Mueller and Stewart, 2000). On Day 19, extinction was assessed in the same manner as with the cocaine-induced place preferences (see above).

2.4.3. Reinstatement

In the final phase of the experiment (Day 21), animals that underwent extinction received a priming injection of either vehicle (Group V, $n=7$), 15 mg/kg cocaine (Group C, $n=7$), 0.5 g/kg alcohol (Group A5, $n=7$) or 1.0 g/kg alcohol (Group A10, $n=7$). Five minutes following the priming injection, each subject was placed in the place preference chamber for 15 min, and compartment preference was assessed in the manner noted above.

To generate these four priming conditions, subjects were rank ordered on their degree of preference and assigned to groups such that the mean preference for each group was equivalent. The doses of cocaine and alcohol used were chosen to maximize the likelihood of producing reinstatement without the confound of motor debilitation. The dose of cocaine is within the range of doses shown to be effective within the place preference design (Busse et al., 2004). The doses of alcohol are within the range of doses shown to modulate cocaine's effects within this same preparation (Busse and Riley, 2002).

2.5. Statistical analysis

For each test (i.e., initial preference, extinction and reinstatement), the time spent (± S.E.M.) in each compartment was recorded and scored. The time animals spent in the two conditioning compartments was transformed to a percentage (seconds spent in the DP or VP compartment divided by the total time spent in both DP and VP compartments) and compared with a Student's Related Sample t Test to determine if animals in each group spent more time in the DP or in the VP compartment. Animals were considered to be displaying a place preference if the percentage of time spent on the DP side was statistically greater (α=.05) than the percentage of time spent on the VP side (Shippenburg and Heidbreder, 1995). Alternatively, the absence of a compartment preference was indicated by no significant difference in percentage of time animals spent in the DP and VP compartments.

3. Results

3.1. Place conditioning

Fig. 1 illustrates the percentage of time (± S.E.M.) that the animals spent in each compartment on the initial preference test. Comparisons of the relative percentage of time spent in the DP and VP compartments using a paired Student's Related Sample t Test revealed that animals that underwent place conditioning with 20 mg/kg cocaine spent a greater percentage of time in the DP than in the VP compartment [$t(30)=9.988$, $P<.0001$], indicating that animals had a significant place preference for the DP compartment.

3.2. Extinction

Of the original 31 animals that underwent place conditioning with cocaine, 28 spent a majority of time during the preference test in the DP compartment (i.e., preferred the DP compartment) and underwent extinction trials. A Student's Related Sample t Test indicated that extinction of the previously conditioned preferences was induced in animals after they repeatedly received pairings of the DP and VP compartments with vehicle injections for an additional four

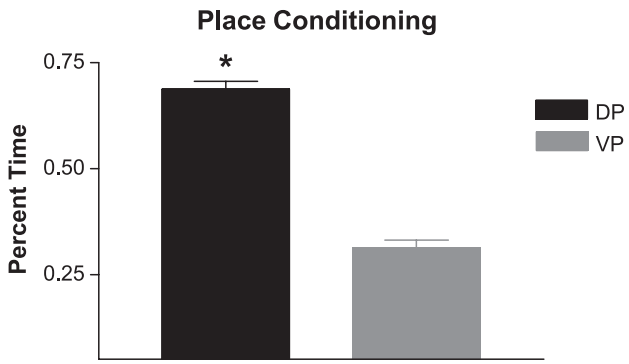

Fig. 1. Percent of time (± S.E.M.) spent by animals in the DP and VP compartments on the test day following place conditioning with 20 mg/kg cocaine ($n=31$). * Significant difference between the percentage of time in the DP and VP compartments ($P<.0001$).

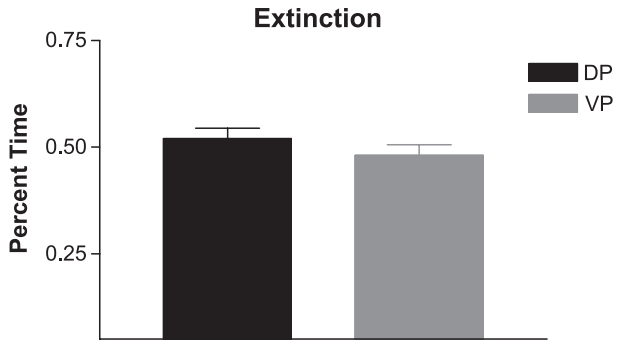

Fig. 2. Percent of time (± S.E.M.) spent by animals in the DP and VP compartments on the test day following extinction ($n=28$). No significant differences were evident between the percentage of time spent in the DP and VP compartments ($P=.4399$).

cycles [$t(27)=0.784$, $P=.4399$; see Fig. 2]. That is, the percentage of time that animals spent in the DP compartment was no longer significantly greater than the percentage of time spent in the VP compartment.

3.3. Reinstatement

The effects of the priming injections are shown in Fig. 3a–d. Specifically, while animals given vehicle immediately prior to the reinstatement test (Group V) failed to show a significant preference for the compartment previously paired with cocaine [$t(6)=-0.189$, $P=.8561$; see Fig. 3a], those animals administered the 15 mg/kg cocaine priming injection (Group C) displayed a reinstated preference for the DP compartment [$t(6)=6.641$, $P=.0450$; see Fig. 3b]. That is, these subjects now spent a significantly greater time on the DP side. Neither the injection of 0.5 nor 1.0 g/kg alcohol (Groups A5 and A10, respectively) was able to reinstate the cocaine preference [$t(6)=-0.067$, $P=.7630$ and $t(6)=0.632$, $P=.5505$, respectively; see Fig. 3c and d], although the data do suggest a trend in that general direction.

4. Discussion

Although alcohol has been shown to modulate cocaine's affective (i.e., rewarding and aversive) properties in a variety of preparations (Busse et al., 2004; Busse and Riley, 2002; Cook et al., 1998; Farré et al., 1993; Gawin and Kleber, 1986; Grakalic and Riley, 2002a; Lewis and June, 1994; Magura and Rosenblum, 2000; McCance-Katz et al., 1998; Moolten and Kornetsky, 1990; Wiseman and McMillan, 1996), it is unclear if alcohol has the ability to affect cocaine seeking. Evidence that such an effect may occur comes from reports that individuals who abstain from cocaine use have an increased preference for this drug over a nonpharmacological reinforcer after exposure to alcohol (Higgins et al., 1996). Furthermore, it has been reported that the likelihood of cocaine relapse increases after alcohol exposure (McKay et al., 1999). As such, it is possible that alcohol affects the motivation to seek out cocaine in individuals with prior cocaine experience. This was assessed in the present experiment by examining the effects of alcohol on the reinstatement of extinguished cocaine place preferences, a suggested model of cocaine relapse (Itzhak and Martin, 2002; Mueller and Stewart, 2000).

In the initial preference test, animals that underwent place conditioning with 20 mg/kg cocaine displayed a

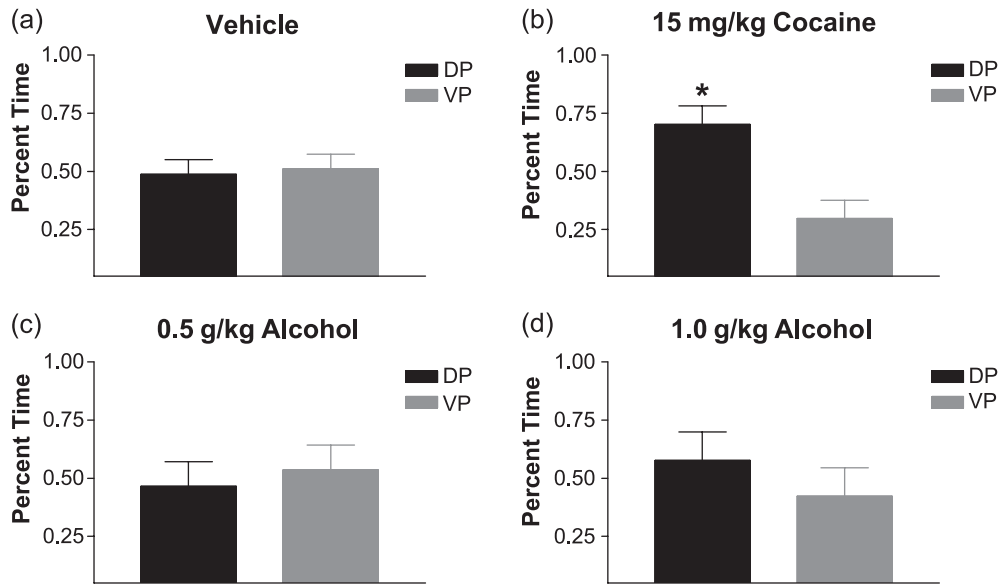

Fig. 3. Percent of time (± S.E.M.) spent by animals in the DP and VP compartments on the test day following priming injections of (a) 15 mg/kg cocaine (Group C, $n=7$), (b) vehicle (Group V, $n=7$), (c) 0.5 g/kg alcohol (Group A5, $n=7$) or (d) 1.5 g/kg alcohol (Group, A10, $n=7$). * Significant difference between the percentage of time in the DP and VP compartments ($P<.05$).

significant preference for the DP compartment, a finding consistent with other reports of cocaine-induced CPP (Busse and Riley, 2002; Busse et al., 2004; Le Pen et al., 1996; Mayer and Parker, 1993; O'Dell et al., 1996). Interestingly, following this preference test, repeatedly pairing both compartments with vehicle subsequently extinguished the cocaine-induced place preference for the DP compartment (Mueller and Stewart, 2000). During the reinstatement test, 15 mg/kg cocaine, but not vehicle, 0.5 or 1.0 g/kg alcohol, reinstated the cocaine place preference. Together, the data from this experiment suggest that only cocaine, and not alcohol, was able to increase the motivation in animals to seek out cues previously associated with cocaine reward.

The fact that alcohol did not reinstate the cocaine-induced place preference is surprising, given the aforementioned ability of alcohol to modulate a variety of behavioral and physiological responses to cocaine (Busse and Riley, 2003; Boyer and Petersen, 1990; Henning et al., 1994; Jover et al., 1991; Odeleye et al., 1993; Schechter and Meehan, 1995; Sobel and Riley, 1997), including those related to cocaine use and abuse (Busse et al., 2004; Busse and Riley, 2002; Cook et al., 1998; Farré et al., 1993; Gawin and Kleber, 1986; Grakalic and Riley, 2002a; Lewis and June, 1994; Magura and Rosenblum, 2000; McCance-Katz et al., 1998; Moolten and Kornetsky, 1990; Wiseman and McMillan, 1996). In fact, not only has alcohol been shown to potentiate cocaine reward (see above) in certain preparations [i.e., CPP (Busse et al., 2004) and ICS (Lewis and June, 1994)], but has also been reported to cross sensitize with some of the behavioral effects of cocaine (Itzhak and Martin, 1999; Lessov and Phillips, 2003; Manley and Little, 1997). For example, Manley and Little (1997) reported that chronic exposure to alcohol resulted in sensitization to cocaine's locomotor effects (see also Itzhak and Martin, 1999). Interestingly, such a cross sensitization has been suggested to parallel other aspects of drug abuse, including the effect of one drug on the incentive properties of another drug (for a discussion on the relation between cross sensitization among drugs and the incentive properties of drugs, see Robinson and Berridge, 2001). As such, this literature suggests that cocaine and alcohol may act on a common neural circuit to mediate the behavioral effects of cocaine. However, based on findings of the present experiment, to what extent this cross-sensitization affects drug-seeking behavior remains unknown.

One possible explanation for alcohol's inability to reinstate the cocaine-induced place preference is that the stimulus properties of alcohol may not have been similar enough to those of cocaine. That is, a priming drug (other than the training drug) may have to possess some overlapping stimulus property (e.g., behavioral or physiological property) to reinstate (or increase the likelihood of) drug seeking. Interestingly, it has recently been demonstrated that the stimulus effects of alcohol do *not* substitute for (and, in fact, block) the stimulus properties of cocaine in the drug discrimination procedure (Gatch et al., 2003; see also Schechter, 1994). Together, this evidence suggests that these two compounds have nonoverlapping properties, an effect that may account for why alcohol did not reinstate cocaine place preferences.

Another possibility for alcohol's failure to reinstate cocaine-induced place preferences is that alcohol may have increased the motivation to avoid the cocaine-related stimuli, an effect which may have offset (or interacted with) any effect that alcohol may have had on the incentive properties of the cocaine-related stimuli. In support of this position are reports demonstrating that alcohol has the ability to modulate both cocaine's rewarding and aversive effects. For example, doses of cocaine shown to be rewarding in other preparations (see Busse et al., 2004) can condition taste aversions (Ferrari et al., 1991). Furthermore, cocaine-induced taste aversions can be potentiated by the coadministration of alcohol (Etkind et al., 1998; Grakalic and Riley, 2002a), suggesting that cocaine's aversive effects can be increased in the presence of alcohol. In addition to this evidence, Busse and Riley (2002) and Busse et al. (2004) have demonstrated that alcohol can attenuate cocaine-induced place preferences. They suggested that alcohol's ability to reduce cocaine-induced place preferences may be a function of the interaction between cocaine reward and an alcohol-induced potentiation of cocaine's aversive effects (for a discussion on the rewarding and aversive properties of recreational drugs, see Hunt and Amit, 1987). Thus, alcohol may have affected cocaine seeking, but this may have been masked by alcohol's co-modulation of cocaine's aversive effects. Without a direct effect of alcohol on cocaine's ability to reinstate place preferences, however, to what extent these changes contribute to the results of the present experiment remains unknown.

Independent of the basis for the failure of alcohol to reinstate cocaine-induced place preferences, it should be noted that the results of this experiment are consistent with those reporting on the reinstatement of drug seeking in other preparations. In fact, it has been reported that alcohol failed to reinstate lever pressing for cocaine in animals trained to self-administer cocaine (de Wit and Stewart, 1981; Wise et al., 1990). For example, de Wit and Stewart (1981) initially trained animals to lever press for infusions of cocaine. Following this training, animals underwent extinction, with a subsequent attempt to reinstate lever pressing with priming injections of 1, 3 and 10 mg/kg alcohol. Interestingly, none of the doses employed was effective in reinstating the cocaine-trained response. Similar results were reported by Wise et al. (1990), wherein 2 g/kg alcohol failed to reinstate the self-administration of cocaine. Although these results and those of the present experiment are suggestive that, within the context of reinstatement, alcohol does not affect cocaine seeking, it is important to note that other literature indicates that such a relationship exists (see Higgins et al., 1996; McKay et al., 1999). Therefore, if alcohol affects the motivation to seek out

cocaine, it may be possible to see an effect using the reinstatement design, but with different parameters than the ones employed here. For example, given that the subjects used in both the Higgins et al. (1996) and McKay et al. (1999) reports had a history with alcohol, such a history may be an important factor for the effects of alcohol on cocaine seeking. In fact, McKay et al. (1999) indicated that alcohol was more likely to serve as a trigger for cocaine relapse in individuals who met criteria for a past or current diagnosis of alcohol dependence than in individuals without such a history. Furthermore, it has been reported that preexposure to alcohol increases the rewarding properties of cocaine (Horger et al., 1990) and decreases its aversive effects (Grakalic and Riley, 2002b). Although it is unknown to what extent these changes are related to drug seeking, it has been suggested that increasing cocaine reward and/or decreasing cocaine aversion are compatible with, not exclusive from, changes that may occur in the motivation to seek out cocaine (for a discussion on the tolerance to the aversive effects of drugs and drug "wanting", see Robinson and Berridge, 2004). Thus, it may be possible to see an effect of alcohol on the motivation to seek out cocaine in animals with a history of alcohol exposure.

In addition to the possibility that drug history may be an important variable, a majority of the research that report an effect of alcohol on cocaine's rewarding properties administer cocaine and alcohol concurrently (see Busse et al., 2004; Busse and Riley, 2002; Farré et al., 1993; Lewis and June, 1994; McCance-Katz et al., 1998; Moolten and Kornetsky, 1990). For example, Busse et al. (2004) and Lewis and June (1994) report that the combination of cocaine and alcohol produces greater rewarding effects than either drug alone in the CPP and ICS designs, respectively. As such, training animals with the combination of cocaine and alcohol may increase the incentive properties of the cocaine-related stimuli and thus increase the likelihood that alcohol affects motivation to seek out cocaine. However, it should be noted that the temporal sequence in which alcohol and cocaine are administered also plays a significant role in determining the effects of alcohol on the physiological and behavioral (including incentive) properties of cocaine (Higgins et al., 1996; McKay et al., 1999; for a review, see Pennings et al., 2002). In fact, in the Higgins et al. (1996) study, alcohol was administered 30 min prior to a cocaine versus monetary preference test, wherein subjects chose cocaine over money. Furthermore, McKay et al. (1999) indicated that alcohol served as a significant trigger for cocaine relapse, even if exposure occurred a week prior to the onset of cocaine use. As such, while alcohol was administered 5 min prior to the reinstatement test in the present experiment, a longer interval between the alcohol priming injection and the onset of the reinstatement test may prove more effective in reinstating cocaine place preferences. Given these possibilities, continued investigation is needed to understand if and under what circumstances alcohol may lead to cocaine relapse.

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