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The effects of alcohol preexposure on cocaine, alcohol and cocaine/alcohol place conditioning

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Abstract

The present experiment examined the effects of alcohol preexposure on place conditioning with cocaine, alcohol or the cocaine/alcohol combination. Specifically, 91 male Sprague–Dawley rats were injected i.p. with 1.5 g/kg alcohol ($n=46$) or vehicle ($n=45$) every fourth day for 17 days prior to conditioning. On day 21, half of the animals from each preexposure condition were injected with 20 mg/kg cocaine, 1.5 g/kg alcohol or the cocaine/alcohol combination before being restricted for 30 min to a distinctive compartment of a place conditioning apparatus. The remaining subjects were injected with vehicle and restricted to the alternative side of the chamber. The following day, subjects previously given drug (or vehicle) were given vehicle (or drug) and placed in the alternative compartment of the chamber. Following four conditioning cycles, subjects were allowed 15-min access to the entire chamber. Both alcohol- and vehicle-preexposed animals conditioned with cocaine displayed a preference for the cocaine-paired compartment. Those conditioned with alcohol had an aversion to the alcohol-paired compartment. Consistent with our previous work, animals given the cocaine/alcohol combination displayed no compartment preference, indicating that concurrent alcohol affected the reinforcing effects of cocaine. Further, the attenuating effect of concurrent alcohol was unaffected by alcohol history. Under the present parameters, alcohol pretreatment has no effect on the rewarding (and possibly aversive) properties of cocaine alone or the cocaine/alcohol combination. Continued investigation of the conditions under which preexposure to alcohol might modulate the aversive/reinforcing properties of a cocaine/alcohol combination may be important for understanding vulnerability to the use and/or abuse of this drug combination.

Keywords: Alcohol; Aversion; Cocaine; Conditioned place preference; Polydrug; Rats; Reward

1. Introduction

Although cocaine and alcohol have been reported to interact within a variety of behavioral and physiological preparations (see Boyer and Petersen, 1990; Foltin and Fischman, 1989; Henning et al., 1994; Perez-Reyes and Jeffcoat, 1992), little is known how such interactions are affected by drug history (Grakalic and Riley, 2002a; Grathwohl et al., 2001; Hedaya and Pan, 1996; Peris et al., 1997). In one of the earlier assessments of the effects of alcohol history on the interaction of cocaine and alcohol, Peris et al. (1997) demonstrated that the disruptive effects of a cocaine/alcohol combination on rotarod performance were weakened in animals preexposed to alcohol. Specifically, rats pretreated with saline and given a cocaine/alcohol combination displayed a disruption in locomotor coordination (as evidenced on a rotorod test). Conversely, alcohol-pretreated rats exhibited little disruption when given the cocaine/alcohol combination. More recently, Grakalic and Riley (2002a) have extended these findings to the conditioned taste aversion (CTA) preparation. Specifically, they reported that, in drug-naïve animals, alcohol given concurrently with cocaine potentiated cocaine-induced taste aversions (see also Etkind et al., 1998). Conversely, concurrently

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administered alcohol did not potentiate cocaine-induced aversions in animals that had been preexposed to alcohol (five exposures every fourth day prior to the initiation of taste aversion conditioning), suggesting that alcohol preexposure attenuated the subsequent interaction of the two drugs.

The fact that the effect of alcohol preexposure on the interaction between cocaine and alcohol was extended to a measure that examines the aversive properties of the cocaine/alcohol combination (i.e., the conditioned taste aversion preparation; see Riley and Freeman, 2004; see also www.CTAlearning.com) may be important for understanding its impact on the vulnerability to use and abuse this particular drug combination. Specifically, given that the acceptability of a drug (or drugs) appears to be a function of the balance between its rewarding and aversive effects (Cunningham and Henderson, 2000; Gaiardi et al., 1991; Gauvin et al., 2000; Grakalic and Riley, 2002a; Hunt and Amit, 1987; Riley and Simpson, 2001; White et al., 1977; Wise et al., 1976), any change in either of these properties with drug pretreatment may affect the subsequent acceptability of the drug (or drug combination). That preexposure to alcohol reduced the aversive effects of the alcohol/cocaine combination suggests that it may impact the subsequent use and abuse of this combination (see Grakalic and Riley, 2002a).

The present experiment extended the analysis of the effects of alcohol preexposure on the cocaine/alcohol combination. Specifically, the effects of preexposure to alcohol on the interaction of cocaine and alcohol in the conditioned place preference procedure were examined. The conditioned place preference procedure entails exposing an animal to one side of a two-chambered place preference apparatus after it has been injected with a drug (or drugs) and the other side of the apparatus following an injection of the drug's vehicle (see Mucha et al., 1982; Tzschentke, 1998). Following this conditioning period, animals are then placed in the apparatus 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 compartment if the drug (or drug combination) is reinforcing (for a bibliography, see Schechter and Calcagnetti, 1993, 1998). We have previously reported that, although cocaine readily produces a place preference for the drug-associated side, this preference is significantly attenuated when alcohol is given concurrent with cocaine (see Busse et al., 2004; Busse and Riley, 2002). That is, concurrently administered alcohol appears to attenuate the rewarding effects of cocaine within the CPP design. Given that alcohol preexposure affects the interaction of alcohol/cocaine within assessments of the aversive properties of drugs (Grakalic and Riley, 2002a), the present study examined the effects of this preexposure on alcohol's ability to attenuate cocaine's rewarding effects within the conditioned place preference design. Determining how these properties are affected by drug preexposure may be important to a more complete understanding of the behavioral vulnerability to drugs of abuse.

2. Methods

2.1. Subjects

Ninety-one drug-naïve, male Sprague–Dawley rats (Harlan Sprague Dawley Laboratories), weighing approximately 250 to 350 g at the start of the experiment, were housed in separate hanging wire cages in a room maintained on a 12 L:12 D light cycle (lights on at 0800 h) and at an ambient temperature of 23 °C. Food and water were available ad-libitum throughout the experiment. Animals were handled daily beginning 2 weeks prior to the start of the experiment in order to limit any effects of handling stress during conditioning and testing. Procedures recommended by the Guide for the Care and Use of Laboratory Animals (1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003) and the Institutional Animal Care and Use Committee at American University were followed at all times.

2.2. Drugs

Cocaine hydrochloride (generously supplied by the National Institute on Drug Abuse) was dissolved in distilled water and was injected intraperitoneally (i.p.) in a concentration of 10 mg/ml (cocaine doses are expressed as the salt). Ethyl alcohol was prepared in a 15% solution with distilled water (v/v) and was also injected i.p. Vehicle injections were distilled water.

2.3. Apparatus

The place conditioning apparatus consisted of six identical shuttle-box chambers ($72.4 \times 30.5 \times 42.9$ cm). Each chamber had three compartments (i.e., two conditioning and one induction compartment) separated by two removable wooden barriers. One conditioning compartment ($30.5 \times 30.5 \times 41.9$ cm) was black in color and had a smooth Plexiglas floor. The other conditioning compartment ($30.5 \times 30.5 \times 41.9$ cm) was white in color and had a textured floor (cracked-ice polypropylene) with black stripes (2.54×30.5 cm) painted horizontally 3.85 cm apart. The induction compartment ($10.16 \times 30.5 \times 41.9$ cm) was gray in color and had a steel grated floor. Preliminary data from our laboratory using this apparatus indicated no systematic compartment bias.

2.4. Procedure

Following adaptation, animals were assigned to be injected i.p. with vehicle (V, $n=45$) or 1.5 g/kg alcohol (A, $n=46$) every fourth day for a total of five vehicle or

drug injections. Three days following the final alcohol injection, place conditioning began using the unbiased (i.e., counterbalanced) procedure (see Bardo et al., 1995; see also Cunningham et al., 2003). Specifically, half of the subjects from each preexposure condition were injected with drug (20 mg/kg cocaine, 1.5 g/kg alcohol or the cocaine/alcohol combination) immediately prior to being restricted for 30 min to one conditioning compartment of the apparatus (drug-paired, DP), while the remainder of the subjects from each preexposure condition were injected with vehicle (matched in volume to the cocaine/alcohol combination injections) and restricted for 30 min to the other conditioning compartment (vehicle-paired, VP). On the following day, those animals that were administered drug(s) on the first conditioning day were given vehicle and placed in the VP compartment, while those initially administered vehicle were given drug(s) and placed in the DP compartment. Such a procedure eliminates the need for a vehicle control group, given that animals are counterbalanced to receive drug in either compartment regardless of their natural compartment preference (see Bardo et al., 1995; Schechter and Calcagnetti, 1993). This procedure yielded the following groups: groups V–C, V–A, V–CA, A–C, A–A and A–CA. The first letter in each group designation refers to the drug given during preexposure; the second letters refers to the drug(s) given during place preference conditioning. All subjects received a total of two injections during conditioning to match the number of injections received by groups V–CA and A–CA. Specifically, groups V–C, V–A, A–C and A–A also received an injection of vehicle along with their drug injection during conditioning. The alternating drug/vehicle (or vehicle/drug) sequence described for days 1 and 2 of place preference conditioning continued for an additional 6 days (totaling four drug cycles).

To test for the presence or absence of a conditioned place preference, on the day following the last injection of the fourth conditioning cycle, all animals were placed in the center, gray induction compartment, the barriers were removed and the animals were allowed free access to the entire chamber for 15 min. Activity was recorded by one 8 mm Canon ES-50 camcorder located approximately 1.83 m directly above the place preference chambers. The animal's location, as noted in previous reports (Gong et al., 1997), was determined by the position of its forepaws. Conditioning and testing were carried out between 0900 h and 1400 h.

2.5. Statistical analysis

Time spent (±S.E.M.) in each conditioning compartment was recorded and scored. The mean time animals spent in the two conditioning compartments was transformed to a percentage and compared with a related samples Student's *t*-test in order to determine if animals in each group spent more time in the DP or VP compartment (Busse et al., 2004; Busse and Riley, 2002). Time spent in the induction compartment was excluded from this analysis given reports that have indicated that this compartment has no impact on the place conditioning effects of a variety of compounds, including cocaine and alcohol (Busse and Riley, 2002; Tzschentke, 1998). Animals were considered to be displaying a CPP if the mean percentage of time spent in the DP compartment was statistically greater ($\alpha = 0.05$) than the mean percentage of time spent in the VP compartment (Shippenberg and Heidbreder, 1995).

A 2×3 ANOVA [preexposure drug (vehicle and alcohol) × conditioning drug (cocaine, alcohol and cocaine/alcohol)] was used to compare the mean difference in percentage of time spent in either the DP or VP compartment among groups. These scores were calculated by subtracting the percentage of time spent in the VP compartment from the percentage of time spent in the DP compartment. Therefore, a positive score would indicate that animals spent more time in the DP compartment, while a negative score would reflect that animals spent more time in the VP compartment. Post-hoc analyses were conducted with the Tukey's HSD test. Alpha was set at 0.05.

3. Results

Fig. 1 illustrates the comparisons of the percentage of time spent (±S.E.M.) in the DP and VP compartments for all groups. Comparisons of the percentage of time spent in the DP and VP compartments using a related sample Student's *t*-test revealed that animals in both groups V–C and A–C (top panel) spent a greater percentage of time in the DP than VP compartment [$t(14) = 3.00$, $p < 0.01$ and $t(15) = 2.62$, $p < 0.05$, respectively]. That is, animals that underwent place conditioning with 20 mg/kg cocaine, regardless of alcohol preexposure, had a significant place preference for the DP compartment. Similar comparisons of the percentage of time spent in the DP and VP compartments for groups V–A and A–A (middle panel) revealed that animals in these groups spent a greater percentage of time in the VP than DP compartment [$t(14) = -3.39$, $p < 0.01$ and $t(14) = -2.23$, $p < 0.05$, respectively]. That is, animals that underwent place conditioning with 1.5 g/kg alcohol, regardless of alcohol preexposure, had a significant place aversion for the DP compartment. Comparisons of the percentage of time spent in the DP and VP compartments for groups V–CA and A–CA (bottom panel) revealed that animals in both of these groups spent neither a greater percentage of time in the VP nor DP compartment on test day [$t(14) = -1.41$, $p = 0.18$ and $t(14) = -0.51$, $p = 0.62$, respectively]. That is, animals that underwent place conditioning with the combination of 20 mg/kg cocaine and 1.5 g/kg alcohol, regardless of alcohol preexposure, had neither a significant place preference nor aversion for the DP compartment.

Fig. 2 illustrates the mean difference in percentage of time (±S.E.M.) spent in the DP and VP compartments for

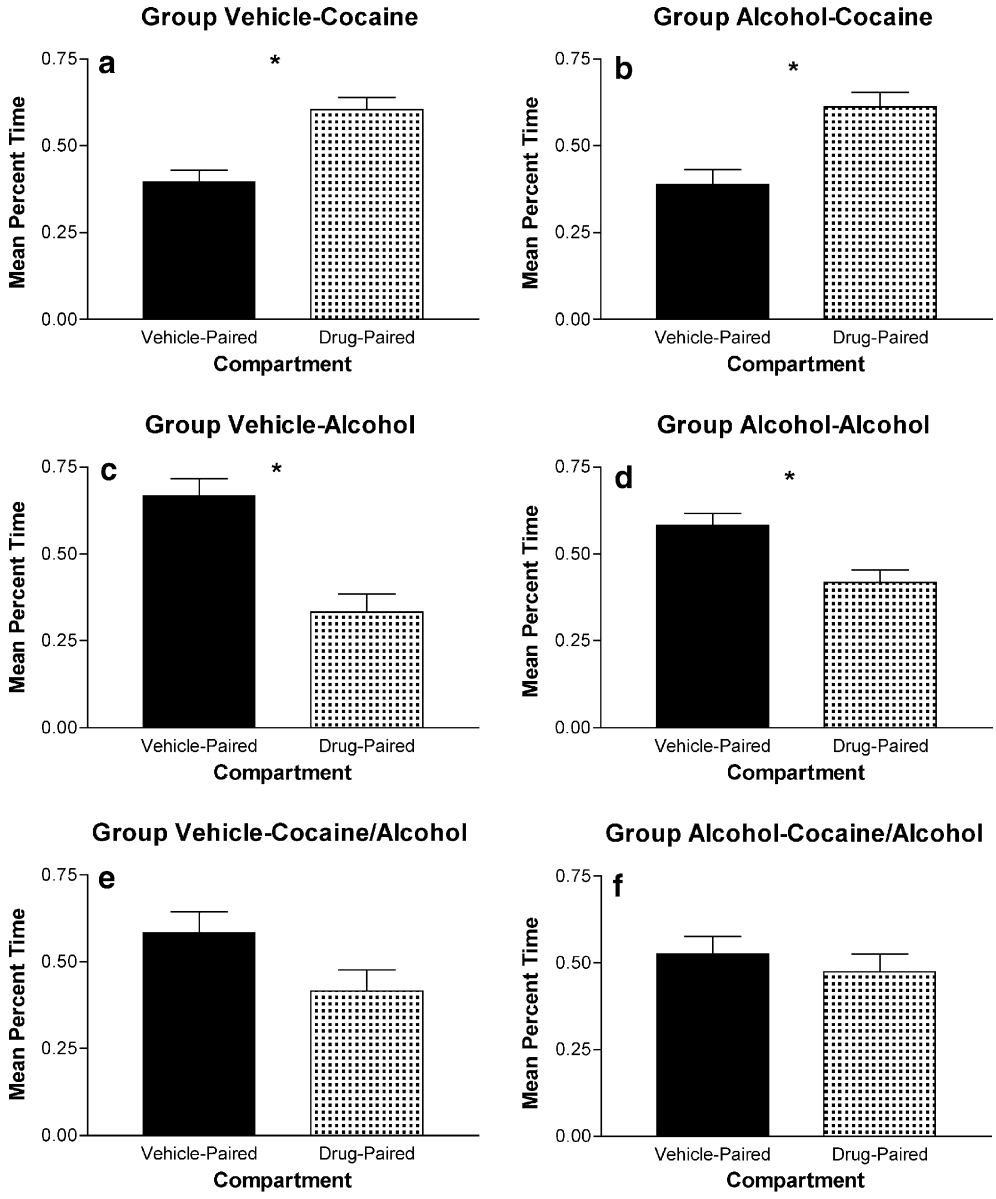

Fig. 1. The effects of vehicle preexposure (a, c and e) versus alcohol (1.5 g/kg) preexposure (b, d and f) on the place conditioning effects of 20 mg/kg cocaine (top panel), 1.5 g/kg alcohol (middle panel) and the cocaine/alcohol combination (bottom panel). *Significant difference between mean percentage of time in the vehicle-paired (VP) and drug-paired (DP) compartments ($p<0.05$).

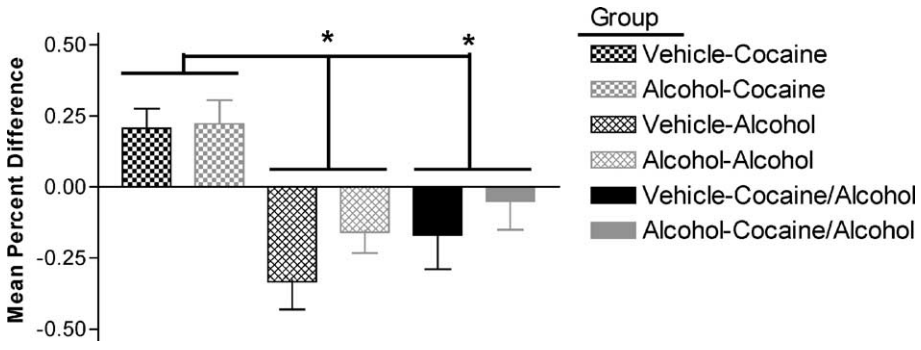

Fig. 2. Mean difference in percent time spent in the drug-paired (DP) versus vehicle-paired (VP) compartments by group. *Significant difference between mean percentage of time in the DP and VP compartments between subjects conditioned with cocaine, alcohol or the cocaine/alcohol combination ($p<0.05$).

each group. The 2 × 3 ANOVA indicated that there was a significant main effect for the mean difference in percentage of time spent in the DP and VP compartments for conditioning drug [$F(2,85)=13.23$, $p<0.01$]. There was no main effect, however, for preexposure drug [$F(1,85)=1.83$, $p=0.18$), nor was there a significant interaction between conditioning drug and preexposure drug ($p=0.69$). Post-hoc analyses (Tukey's HSD) on the conditioning drug differences indicated that animals conditioned with 1.5 g/kg alcohol spent significantly less percentage of time in the DP compartment than animals that underwent place conditioning with 20 mg/kg cocaine ($p<0.05$). Further, animals conditioned with the combination of 1.5 g/kg alcohol and 20 mg/kg cocaine spent significantly less percentage of time in the DP compartment than those animals conditioned with 20 mg/kg cocaine ($p<0.05$).

4. Discussion

Exposing animals to alcohol prior to administering a cocaine/alcohol combination has been shown to alter the behavioral and physiological effects produced by the combination (Grakalic and Riley, 2002a; Hedaya and Pan, 1996; Peris et al., 1997; though see Grathwohl et al., 2001). In particular, Grakalic and Riley (2002a) demonstrated that taste aversions conditioned by a cocaine/alcohol combination were weakened in animals preexposed to alcohol. The fact that alcohol history modulated the effects of a cocaine/alcohol combination in a measure of the aversive properties of drugs (i.e., the CTA design) may be important for understanding the impact of alcohol history on the vulnerability to use and abuse this particular drug combination (see above). As such, the present study extended these earlier assessments in a measure of the rewarding properties of drugs, i.e., the CPP design. Specifically, it has previously been reported that alcohol attenuates cocaine-induced place preferences when these two compounds are co-administered (Busse et al., 2004; Busse and Riley, 2002). The present study assessed if the attenuation of cocaine's rewarding effects by concurrently administered alcohol within the CPP design is modulated by alcohol preexposure.

Conditioning animals with 20 mg/kg cocaine (groups V–C and groups A–C) produced a significant preference for the DP compartment. These findings are consistent with others reporting on the effects of cocaine within this design (Le Pen et al., 1996, 1998; Mayer and Parker, 1993; O'Dell et al., 1996). Conversely, conditioning animals with 1.5 g/kg alcohol (groups V–A and A–A) resulted in a significant place aversion to the DP compartment, an effect also consistent with others reporting on the effects of alcohol within the CPP design (Bormann and Cunningham, 1997, 1998; van der Kooy et al., 1983). Similar to Busse and Riley (2002), 1.5 g/kg alcohol administered concurrently attenuated the place preferences induced by 20 mg/kg cocaine. That is, animals that underwent place conditioning with a combination of cocaine and alcohol displayed an attenuated place preference for the DP compartment (an alternative interpretation is that cocaine weakened alcohol's ability to condition a place aversion, though these effects are usually discussed in terms of cocaine reward; see Busse et al., 2004; Busse and Riley, 2002).

As described, alcohol preexposure had no effect on place conditioning with cocaine, alcohol or the cocaine/alcohol combination. That is, relative to vehicle pretreatment, alcohol preexposure did not significantly alter the place conditioning effects of either drug or the drug combination. Although it is unknown why alcohol preexposure had no effect on cocaine/alcohol place conditioning, several possibilities exist. For example, the particular dose of alcohol used in the present assessment (1.5 g/kg) may not have been optimal to produce large alterations in the place conditioning effects of the cocaine/alcohol combination. In fact, in the sole report demonstrating an effect of alcohol preexposure on the aversive properties of a cocaine/alcohol combination, Grakalic and Riley (2002a) exposed animals to a much higher dose of alcohol (i.e., 3.5 g/kg) prior to the onset of taste aversion learning with the combination. In their report, the taste aversion induced by the cocaine/alcohol combination was attenuated following alcohol pretreatment. The specific dose of alcohol (i.e., 1.5 g/kg) to which animals were preexposed in the present study was chosen for several reasons. Specifically, in addition to being behaviorally active within the CPP design without the accompanying severe behavioral depression and lethality in rodents (Cunningham et al., 1993; Holloway et al., 1992; Lee et al., 1999), 1.5 g/kg alcohol produces reliable (and robust) alterations in place preferences when given in combination with cocaine (see Busse and Riley, 2002). Given that when administered concurrently this dose modulates cocaine's effects, there was interest in other effects this 1.5 g/kg alcohol might have on cocaine and the cocaine/alcohol combination. Further, others have reported that the rewarding (and aversive) properties of many abused drugs (e.g., cocaine and nicotine) are modulated following preexposure with similar doses of alcohol (Grakalic and Riley, 2002b; Kunin et al., 1999; Le Pen et al., 1998; Mierzejewski et al., 2003; Popke et al., 2000). Although preexposure to 1.5 g/kg alcohol did not affect the alcohol/cocaine interaction, it remains unknown how effective other doses might be in this preparation. In this context, it should be noted that lower doses of alcohol (e.g., 0.5 g/kg) produce only marginal and inconsistent changes in place conditioning with 20 mg/kg cocaine (see Busse et al., 2004; Busse and Riley, 2002) when given concurrently with cocaine, suggesting that it would not likely be effective when given under the preexposure conditions. Given that alcohol has been reported to sensitize the effects of cocaine (see Manley and Little, 1997) and that

alcohol can potentiate cocaine seizures and lethality when co-administered with 30 and 40 mg/kg cocaine (see Busse and Riley, 2003), it is possible that preexposure to higher doses (e.g., 3 g/kg) would produce side effects that would nonspecifically impact conditioning.

A second possibility that may account for the fact that preexposure to alcohol did not impact cocaine/alcohol place conditioning is related to the frequency and/or duration of alcohol preexposure. That is, it is possible that alcohol injections may have to be administered with greater frequency and/or for a longer duration than administered in the present study (i.e., one injection every 4 days for 17 days prior to the initiation of place conditioning). In some reports demonstrating an effect of alcohol preexposure on the behavioral (and aversive/reinforcing) properties of recreational drugs (including cocaine, alcohol and a cocaine/alcohol combination), alcohol was administered daily and with multiple exposures prior to their assessment (Bienkowski et al., 1996; Le Pen et al., 1998; Mierzejewski et al., 2003; Peris et al., 1997). In particular, Peris et al. (1997) exposed animals to alcohol for 13 consecutive days prior to demonstrating a weakening in the disruptive effects of a cocaine/alcohol combination on rotorod performance. As such, a greater frequency/duration of alcohol injections may be necessary in order for alcohol to modulate the affective properties of a cocaine/alcohol combination. Although possible, it should be noted that others have shown that preexposing animals to alcohol under conditions similar to that of the present study results in a modulation in the aversive properties of cocaine and a cocaine/alcohol combination (Grakalic and Riley, 2002a,b). Specifically, as noted earlier, Grakalic and Riley (2002a) demonstrated that animals given alcohol once every fourth days for a total of five alcohol exposures displayed weaker aversions to a saccharin solution paired with the cocaine/alcohol combination than animals with no drug history. To what extent the frequency and/or duration of alcohol preexposure accounts for the results of the present assessment remains undetermined.

The present study indicates that at least under the specific parameters examined here alcohol preexposure has no impact on the rewarding effects of cocaine alone or when given in combination with alcohol. Continued investigation is needed to understand if and under what conditions preexposure to alcohol might modulate the aversive/reinforcing properties of a cocaine/alcohol combination. Determining these conditions may be important for understanding why some individuals find combinations of cocaine and alcohol more or less rewarding than either drug alone.

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