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The effects of cocaine, alcohol and cocaine/alcohol combinations in conditioned taste aversion learning

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Abstract

We have recently reported that alcohol attenuates cocaine place preferences. Although the basis for this effect is unknown, alcohol may attenuate cocaine reward by potentiating its aversive effects. To examine this possibility, these experiments assessed the effects of alcohol on cocaine-induced taste aversions under conditions similar to those that resulted in attenuated place preferences. Specifically, Experiments 1 and 2 assessed the effects of alcohol (0.5 g/kg) on taste aversions induced by 20, 30 and 40 mg/kg cocaine. Experiment 3 examined the role of intertrial interval in the effects of alcohol (0.5 g/kg) on cocaine (30 mg/kg) taste aversions. In Experiments 1 and 2, cocaine was effective at conditioning aversions. Alcohol produced no measurable effect. Combining cocaine and alcohol produced no greater aversion than cocaine alone (and, in fact, weakened aversions at the lowest dose of cocaine). In Experiment 3, varying the intertrial interval from 3 days (as in the case of Experiments 1 and 2) to 1 day (a procedure identical to that in which alcohol attenuated cocaine place preferences) resulted in significant alcohol- and cocaine-induced taste aversions. Nonetheless, alcohol remained ineffective in potentiating cocaine aversions. Thus, under these conditions alcohol does not potentiate cocaine's aversiveness. These results were discussed in terms of their implication for the effects of alcohol on cocaine-induced place preferences. Further, the effects of alcohol on place preferences conditioned by cocaine were discussed in relation to other assessments of the effects of alcohol on the affective properties of cocaine and the implications of these interactions for alcohol and cocaine co-use.

Keywords: Alcohol; Aversion; Cocaine; Rats; Sprague–Dawley; Drug interaction

1. Introduction

Alcohol consumption commonly co-occurs with cocaine use (Caetano and Schafer, 1996; Caetano and Weisner, 1995; Carroll et al., 1993; Grant and Harford, 1990; Heil et al., 2001; Higgins et al., 1994). For instance, the prevalence of cocaine and alcohol co-use has been reported to be as high as 85% in the general population (see Grant and Harford, 1990) and 62% in a treatment-seeking population (Caetano and Schafer, 1996; Caetano and Weisner, 1995; Carroll et al., 1993; Heil et al., 2001; Higgins et al., 1994). Although it remains unknown why individuals use this combination at such high rates, many have suggested that alcohol possesses the ability to modulate the affective (e.g., rewarding, aversive, anxiogenic) properties of cocaine in a manner that increases the likelihood of their co-use (see Farré et al., 1993; Knackstedt and Ettenberg, 2005; Lewis and June, 1994; Magura and Rosenblum, 2000; McCance-Katz et al., 1998; see also Moolten and Kornetsky, 1990). Specifically, alcohol may either increase cocaine's rewarding properties (see Farré et al., 1993; Lewis and June, 1994; McCance-Katz et al., 1998; see also Moolten and Kornetsky, 1990) and/or decrease its aversive (including anxiogenic) effects (Knackstedt and Ettenberg, 2005; Magura and Rosenblum, 2000; McCance-Katz et al., 2005).

We have recently reported that alcohol modulates cocaine's rewarding properties within the place conditioning design (see Busse et al., 2004; Busse and Riley, 2002). In particular, cocaine-induced place preferences were significantly *attenuated* when animals were conditioned with a combination of 0.5 g/kg alcohol and 20, 30 or 40 mg/kg cocaine (see Busse et al., 2004; Busse and

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Riley, 2002). Although the bases for the attenuation of cocaine-induced place preferences by alcohol remains unknown, e.g., whether such interactions reflect pharmacokinetic and/or pharmacodynamic changes (see Horowitz et al., 1997; McCance-Katz et al., 2005; Pan and Hedaya, 1999), it is possible that, under some conditions, alcohol may increase both the rewarding (see Farré et al., 1993; Lewis and June, 1994; McCance-Katz et al., 1998; see also Moolten and Kornetsky, 1990) and aversive effects of cocaine (Etkind et al., 1998; Grakalic and Riley, 2002). Under these conditions, e.g., high doses of cocaine, the potentiation of cocaine's aversive effects may mask or outweigh any potentiation that occurs to its rewarding effects. Interestingly, Le Pen et al. (1998) offered a similar interpretation of their findings that place preferences induced by 20 mg/kg cocaine were attenuated by pretreatment with the dopamine uptake inhibitor, GBR12783. Specifically, they attributed the attenuation by GBR12783 to a masking of cocaine rewarding properties by its potentiation of cocaine's aversive effects.

Although it is possible that alcohol's attenuation of cocaine-induced place preferences is a function of an increase in cocaine's aversive effects, there are several difficulties with this interpretation. For example, the attenuation of cocaine-induced place preferences by alcohol (as well as by other drugs, see above) may actually reflect a decrease in cocaine reward rather than a potentiation of its aversive effects (see Gaiardi et al., 1998). Such an effect would also be reflected in a change in the ability of cocaine to induce a place preference. Further, much of the evidence suggesting that alcohol potentiates the aversive effects of cocaine (Etkind et al., 1998; Grakalic and Riley, 2002) do so under different parametric conditions (e.g., route of administration, sex and strain of subject, intertrial interval) than those assessing the effects of alcohol on cocaine-induced place preferences (Busse et al., 2004; Busse and Riley, 2002). These parametric variables have all been shown to be significant factors in aversion learning with cocaine (Elkins et al., 2003; Ferrari et al., 1991; Glowa et al., 1994; Grabus et al., 2004; Grigson and Freet, 2000; van Haaren and Hughes, 1990; see Riley and Freeman, 2004). As such, it remains unknown whether the conditions under which alcohol attenuates cocaine-induced conditioned place preferences also potentiate cocaine's aversiveness. The present series of experiments tested this more directly by examining the ability of alcohol to potentiate cocaine-induced taste aversions under conditions similar to those in which alcohol attenuates cocaine-induced place preferences. Specifically, Experiments 1 and 2 examined the effects of alcohol on conditioned taste aversions induced by a variety of doses of cocaine in male Sprague–Dawley rats injected with cocaine intraperitoneally. Experiment 3 examined the contribution of intertrial interval in mediating the effects of alcohol on cocaine-induced taste aversions.

2. General methods

2.1. Subjects

Male Sprague–Dawley rats (Harlan Sprague Dawley Laboratories), weighing approximately 250 to 350 g at the start of each experiment, were housed in separate hanging wire cages in a room maintained on a 12 L : 12 D light cycle (lights on at 0800 hours) and at an ambient temperature of 23 °C. Food and water were available ad libitum except where noted. Animals were handled daily beginning 2 weeks prior to the start of each 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 (National Research Council, 1996), the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council, 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 (IP) 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 IP. Cocaine and alcohol were administered as separate injections. Vehicle injections were distilled water and were matched in number and volume to the injections of cocaine and alcohol. Saccharin (0.1% sodium saccharin, Sigma Chemical Co., St. Louis, MO) was prepared as a 1 g/l solution in tap water.

2.3. Procedure

Phase I: Habituation. Following 23-h water deprivation, subjects were given 20-min access to water (presented in graduated 50-ml Nalgene tubes). This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 s of its presentation.

Phase II: Conditioning. On Day 1 of this phase, all subjects were given 20-min access to a novel saccharin solution. Immediately following saccharin access, subjects were rank ordered on saccharin consumption and assigned to their respective groups (i.e., either a vehicle, cocaine-only, alcohol-only or cocaine/alcohol treatment group; group designation differs for each experiment). All injections were given within 10 min of removal of the saccharin bottles.

The following 3 days (or 1 day, as in the case of Experiment 3) were water-recovery sessions wherein all subjects were given 20-min access to water. No injections were given following water access on these days. This alternating procedure of conditioning/water recovery was repeated until all subjects received four complete cycles. On the day following the last cycle, all subjects were given 20-min access to saccharin in a Final Aversion Test. No injections followed this access.

2.4. Statistical analysis

Differences in absolute saccharin consumption were assessed using a repeated measures ANOVA with the between-group factor of Group and the within-subjects factor