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Asymmetric serial interactions between ethanol and cocaine in taste aversion learning

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Abstract

Although the interaction between ethanol and cocaine is well documented, it has generally been limited to situations in which the two drugs are given concurrently. Little exists on the interaction between ethanol and cocaine when one drug is given prior to the other. In Experiment 1, female Long–Evans rats were given five exposures to ethanol (2 g/kg ip) or vehicle prior to taste aversion conditioning with cocaine (32 mg/kg sc) for a total of five conditioning trials. In Experiment 2, rats were given five exposures to cocaine (32 mg/kg sc) or vehicle prior to taste aversion conditioning with ethanol (2 g/kg ip) for a total of five conditioning trials. Ethanol-preexposed, cocaine-conditioned animals (Experiment 1) displayed attenuated aversions to the cocaine-associated solution, drinking significantly greater amounts of saccharin than vehicle-preexposed, conditioned subjects. Conversely, cocaine-preexposed, ethanol-conditioned animals (Experiment 2) displayed robust aversions to the ethanol-associated solution, drinking levels comparable to those consumed by vehicle-preexposed, conditioned subjects and drinking significantly less than controls. Although the basis for these asymmetric effects is not known, they may have implications for abuse vulnerability in that drug history may impact subsequent drug toxicity that, in turn, may alter drug acceptability.

Keywords: Ethanol; Cocaine; Interaction; Conditioned taste aversion; Rats

1. Introduction

The interaction of ethanol and cocaine has been reported for a variety of behavioral and physiological effects, including liver and cardiovascular toxicity, depression of myocardial function, delayed offspring physical maturation, postnatal mortality, disruption of rotarod performance and suppression of schedule-controlled responding (Boyer and Petersen, 1990; Church et al., 1991; Foltin and Fischman, 1989; Henning et al., 1994; Masur et al., 1989; Misra et al., 1989; Perez-Reyes and Jeffcoat, 1992; Rech et al., 1978; Sobel and Riley, 1997; Uszenski et al., 1992). Within the abovementioned physiological and behavioral preparations, the combination of ethanol and cocaine generally produces greater effects than either drug alone.

Although such concurrent interactions have been well documented, the examination of a serial interaction between ethanol and cocaine in which one drug is given prior to administering the other is somewhat limited (Itzhak and Martin, 1999; Peris et al., 1997; York and MacKinnon, 1999). Interest in serial interactions, in general, stems from the fact that drug history has a significant impact on subsequent drug reactivity (both under conditions in which the drugs are similar or different). This has become increasingly important in relation to how drug history might impact the subsequent abuse liability of specific drugs. As noted by others, a drug's acceptability (and likelihood of self-administration) may be a function of the balance of its rewarding and aversive effects, and manipulations that affect either of these two properties may impact the subsequent use and/or abuse of that compound (Cunningham and Henderson, 2000; Gaiardi et al., 1991, 1997; Goudie, 1979; Krank and O'Neill, 2002; Stefurak et al., 1990; Stolerman and D'Mello, 1981). One such factor is drug history. For example, prior exposure to ethanol has been reported to increase its reinforcing effects (as measured in the conditioned place preference preparation; Bienkowski et al., 1996; Gauvin and Holloway, 1991; Gauvin et al., 2000; Holloway et al., 1992; Reid et al., 1985) and decrease its aversive effects (as measured in the conditioned taste aversion (CTA) design; for a review, see Riley and Simpson, 2001). Similar effects of cocaine preexposure have

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been reported (Le Pen et al., 1998; Lett, 1989; Shippenberg and Heidbreder, 1994, 1995a,b; for a review, see Riley and Simpson, 2001). Given that the likelihood of the acceptability (and use of a drug) may depend on the relative strengths of its rewarding and aversive properties, some understanding of changes in the relative reinforcing and aversive effects of that drug with drug history (its own or some other compound) may provide insight into the abuse potential of that drug.

As noted, although the serial interaction between ethanol and cocaine has been investigated, such assessments are limited. In an initial report on this interaction, Peris et al. (1997) reported that cocaine pretreatment had no effect on ethanol-induced motor disruption (for similar results, see Cailhol and Mormede, 2000). On the other hand, Itzhak and Martin (1999) reported that cocaine pretreatment sensitized the motoric effects of ethanol, while York and MacKinnon (1999) reported that cocaine attenuated ethanol-induced changes in body temperature. The effects of ethanol preexposure on cocaine have also been assessed (Itzhak and Martin, 1999; Le Pen et al., 1998; Manley and Little, 1997). In these assessments, ethanol preexposure has been reported to potentiate the effects of cocaine on locomotor activity (Itzhak and Martin, 1999; Manley and Little, 1997) and to attenuate (or have no effect on) cocaine-induced place preferences (Le Pen et al., 1998). Thus, the effects of such preexposure are often parameter-dependent.

Although serial interactions between ethanol and cocaine have been reported, as noted, they have been restricted to assessments of motor activity, body temperature and conditioned place preferences (see above). Given the potential effects of drug history on the aversive effects of drugs and, consequently, on subsequent abuse liability, the present study examined the serial interaction between ethanol and cocaine within the CTA baseline, a procedure sensitive to the aversive or toxic effects of drugs. In addition to being used as a behavioral index of drug toxicity (Riley and Tuck, 1985), the aversion design has often been used to assess serial interactions between drugs (Aragon et al., 1986; Bienkowski et al., 1998a; Cannon et al., 1977; De Beun et al., 1993; Ford and Riley, 1984; Goudie and Thornton, 1975; Kunin et al., 1999a,b; Riley and Simpson, 1999). Specifically, one can assess the effect of exposure to one drug on the ability of a second drug to condition an aversion. In such work, preexposure to one drug has been reported to attenuate or potentiate aversions induced by a second drug. For example, in the initial report by Braveman (1975) on the effects of cross-drug preexposure, preexposure to methylscopolamine attenuated both LiCl- and amphetamine-induced taste aversions. Since that report, similar attenuating effects of cross-drug preexposure have been demonstrated with other drugs (for a review, see Riley and Simpson, 2001). Although preexposure to one drug can attenuate aversions induced by another drug, potentiated effects also have been reported. In one of the initial reports, Miceli et al. (1979) noted that preexposure to naloxone potentiated both ethanol- and LiCl-induced taste aversions. Subsequent to this demonstration, others have reported potentiating effects of cross-drug preexposure with a variety of drugs (Bienkowski et al., 1998b; Heinrichs et al., 1998; Le Magnen et al., 1980; Lipinski et al., 1995; Risinger, 1997). Similar potentiated effects have been reported with footshock and apomorphine (Lasiter and Braun, 1981) and footshock and amphetamine (Bowers et al., 1996).

Given the general utility of cross-drug preexposure within the CTA design to assay serial interactions between drugs, the present study investigated the serial interaction of cocaine and ethanol within this design. Specifically, in Experiment 1, rats were exposed to ethanol prior to taste aversion conditioning with cocaine. In Experiment 2, rats were exposed to cocaine prior to taste aversion conditioning with ethanol.

2. General method

2.1. Subjects

The subjects were 78 experimentally naive, female rats of Long–Evans descent, approximately 120 days of age and between 180 and 250 g in weight at the beginning of the experiment. Guidelines established by the Institutional Animal Care and Use Committee (IACUC) at American University were followed at all times. Each animal's body weight and food and water consumption were monitored daily. Food and water consumption were normal during the course of the study, and the average body weight loss for each group was approximately 6.2%.

2.2. Apparatus

Subjects were individually housed in stainless steel, wire-mesh cages on the front of which graduated Nalgene tubes were placed to provide 20-min access to water or saccharin. Subjects were maintained on a 12:12 LD cycle (lights on at 0800 h) and at an ambient temperature of 23 °C for the duration of the experiment. Food was available ad libitum.

2.3. Drugs and solutions

Cocaine hydrochloride (generously provided by NIDA) was prepared as a 10-mg/ml solution in distilled water. Ethanol (generously provided by the Department of Chemistry, American University) was prepared as a 95% solution in distilled water and was diluted to a 15% injectable solution. Saccharin (0.1% sodium saccharin, Sigma) was prepared as a 1-g/l solution in tap water.

2.4. Procedure

2.4.1. Phase I: habituation

Following 24-h water deprivation, subjects were given 20-min access to water for 10–12 consecutive days until

they approached and drank from the tube within 2 s of its presentation.

2.4.2. Phase II: preexposure

On Day 1 of Phase II, subjects were given 20-min access to water. Following this exposure, subjects were ranked according to their water consumption and were assigned to a preexposure condition. Four to five hours following water consumption, subjects were given an injection of one of two drugs (cocaine or ethanol) or the drug vehicle (equivolume). These preexposure injections were given every fourth day for a total of five drug exposures. Subjects received 20-min access to water on the intervening recovery days. No injections were given following water access on these days.

2.4.3. Phase III: conditioning

On Day 1 of this phase, all subjects were given 20-min access to a novel saccharin solution. Immediately following saccharin access, subjects in each preexposure group were ranked according to their saccharin consumption and assigned to a different treatment condition such that mean saccharin consumption was similar among groups. Subjects were then given an injection of one of two drugs (cocaine or ethanol) or the drug vehicle (equivolume). On the following three water-recovery days, 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 five complete cycles. On the day following the final water-recovery session, all subjects were given 20-min access to saccharin in a final one-bottle test of the aversion to saccharin. No injections were given following this test.

3. Experiment 1: ethanol preexposure on cocaine-induced taste aversions

3.1. Specific procedure

During drug preexposure, subjects were given an intraperitoneal injection of 2-g/kg ethanol (Group E) or its distilled water vehicle (Group W) for a total of five preexposures. During taste aversion conditioning, subjects in both preexposure groups were divided into two groups and received a subcutaneous injection of 32-mg/kg cocaine or an equivolume sc injection of distilled water. This resulted in four groups: E/W ($n=9$), E/C ($n=10$), W/W ($n=9$), W/C ($n=10$). The first letter in each group designation refers to the compound given during preexposure, i.e., ethanol (E) or water (W). The second letter refers to the compound given during conditioning, i.e., cocaine (C) or water (W). Given that the purpose of Experiment 1 was to assess the ability of ethanol preexposure to attenuate cocaine-induced taste aversions, a dose of ethanol (2 g/kg) known to affect the acquisition of CTAs was administered during preexposure (June et al., 1992; Risinger and Cunningham, 1995) and a dose of cocaine sufficiently large to induce an aversion was administered during conditioning (Ferrari et al., 1991; Riley and Diamond, 1998; Riley and Simpson, 1999).

4. Experiment 2: cocaine preexposure on ethanol-induced taste aversions

4.1. Specific procedure

During drug preexposure, subjects were given a subcutaneous injection of 32-mg/kg cocaine (Group C) or its distilled water vehicle (Group W) for a total of five preexposures. During taste aversion conditioning, subjects in both preexposure groups were divided into two groups and received an ip injection of 2.0-g/kg ethanol or an equivolume injection of distilled water. This resulted in four groups: C/W ($n=10$), C/E ($n=10$), W/W ($n=10$), W/E ($n=10$). The first letter in each group designation refers to the compound given during preexposure, i.e., cocaine (C) or water (W). The second letter refers to the compound given during conditioning, i.e., water (W) or ethanol (E). Given that the purpose of Experiment 2 was to assess the ability of cocaine preexposure to attenuate ethanol-induced taste aversions, a dose of cocaine known to affect the acquisition of CTAs was administered during preexposure (Riley and Diamond, 1998; Riley and Simpson, 1999) and a dose of ethanol sufficiently large to induce aversions on its own was administered during conditioning (Kulkosky et al., 1980).

4.2. Statistical analysis

Differences in mean water consumption during preexposure were assessed using a 2×5 repeated-measure analysis of variance (ANOVA) with between-subjects variable of Group (Groups E and W in Experiment 1; Groups C and W in Experiment 2) and within-subjects variable of Day (1–5). Post-hoc assessments were conducted using independent sample *t*-tests. Within-subjects differences in consumption from baseline (Preexposure Day 1) were assessed using paired sample *t*-tests (Bonferroni correction). α was set at .05.

Differences in mean saccharin consumption during conditioning for each group were assessed using a $2 \times 2 \times 5$ repeated-measure ANOVA with between-subjects variables of Preexposure Drug (ethanol or vehicle in Experiment 1; cocaine or vehicle in Experiment 2) and Conditioning Drug (cocaine or vehicle in Experiment 1; ethanol or vehicle in Experiment 2) and within-subjects variable of Trial (1–5). Post-hoc assessments were conducted using Tukey HSD pairwise comparisons. Within-subjects differences in consumption from baseline (Trial 1) were assessed using paired sample *t*-tests (Bonferroni correction). α was set at .05.

5. Results

5.1. Experiment 1: ethanol preexposure on cocaine-induced taste aversions

5.1.1. Preexposure

Fig. 1 (top panel) illustrates the mean (±S.E.M.) consumption of water for subjects receiving ethanol (Group E) and water (Group W) over repeated preexposures. A 2 × 5 repeated-measure ANOVA revealed a significant Day effect [$F(4,144) = 4.604$, $P < .05$]. There was neither a significant Group effect [$F(1,36) = 0.528$, $P = .472$] nor a Group × Day interaction [$F(4,144) = 0.205$, $P = .935$]. Post-hoc assessments using independent sample t-tests revealed that at no point during preexposure did Groups E and W differ (t's ≥ 0.284, $df = 36$, P's ≥ .469). Within-group paired sample t-tests (Bonferroni corrected $P = .0125$) revealed that relative to the baseline (Preexposure Day 1), water consumption significantly decreased on Trial 5 ($t = 3.794$, $df = 18$, $P < .0125$) for Group E, whereas there was no decrease on any trial for Group W (t's ≥ 0.130, $df = 18$, P's ≥ .017).

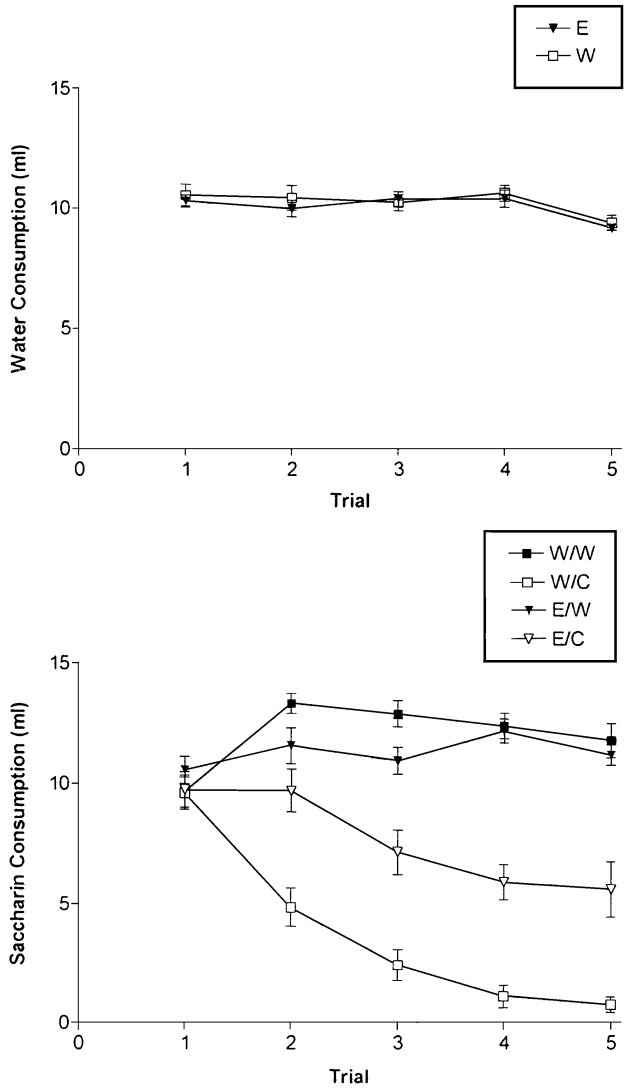

Fig. 1. The mean (±S.E.M.) consumption of water for subjects receiving ethanol (Group E) and water (Group W) over repeated preexposures (top panel). The mean (±S.E.M.) consumption of saccharin for all four groups over repeated conditioning trials (Groups W/W, W/C, E/W and E/C; bottom panel). The first letter in the group designation refers to the drug given during preexposure, i.e., distilled water (W) or ethanol (E); the second letter refers to the drug given during conditioning, i.e., distilled water (W) or cocaine (C).

5.1.2. Conditioning

Fig. 1 (bottom panel) illustrates the mean (±S.E.M.) consumption of saccharin for all four groups over repeated conditioning trials. A 2 × 2 × 5 repeated-measure ANOVA revealed significant effects of Preexposure Drug [$F(1,34) = 9.576$, $P < .05$], Conditioning Drug [$F(1,34) = 137.619$, $P < .05$] and Trial [$F(4,136) = 19.301$, $P < .05$], as well as significant Preexposure Drug × Conditioning Drug [$F(1,34) = 20.583$, $P < .05$], Conditioning Drug × Trial [$F(4,136) = 40.753$, $P < .05$] and Preexposure Drug × Conditioning Drug × Trial interactions [$F(4,136) = 8.410$, $P < .05$]. Post-hoc analyses using Tukey HSD revealed no significant differences among groups on the initial conditioning trial (all P's ≥ .743), with subjects in all groups drinking approximately 10.0 ml of saccharin. Over subsequent conditioning trials, significant differences emerged among groups. Specifically, vehicle-preexposed, conditioned subjects (Group W/C) drank significantly less than their controls (Group W/W) on Trials 2–5 (all P's < .05). Ethanol-preexposed, conditioned subjects (Group E/C) drank significantly less than their controls (Group E/W) on Trials 3–5 (all P's < .05). Further, there were significant differences between the two experimental groups, i.e., Groups E/C and W/C, with subjects in Group W/C drinking significantly less than Group E/C throughout conditioning (all P's < .05). There were no significant differences between the two control groups at any point during conditioning (all P's ≥ .259). All groups drank comparable amounts of water during recovery days, where the average consumption for animals in each group on the recovery day immediately preceding each conditioning trial ranged from 12.44 to 13.8 ml.

Within-group paired sample t-tests (Bonferroni corrected $P = .0125$) yielded the following results. Relative to the baseline (Conditioning Trial 1), subjects in Group W/W significantly increased saccharin consumption over trials (t's ≥ 3.744, $df = 8$, all P's < .0125). There was no significant change in saccharin consumption from baseline for subjects in Group E/W (t's ≥ 0.441, $df = 8$, all P's ≥ .073). Vehicle-preexposed subjects, conditioned with cocaine (Group W/C) significantly decreased saccharin consumption over conditioning, drinking significantly less saccharin on Trials 2–5 than on Trial 1 (t's ≥ 4.670, $df = 9$, all P's < .0125). Subjects preexposed to ethanol and conditioned with cocaine (Group E/C) displayed a significant decrease on Trials 4 and 5 relative to their baseline (t's ≥ 3.736, $df = 9$, all P's < .0125).

5.2. Experiment 2: cocaine preexposure on ethanol-induced taste aversions

5.2.1. Preexposure

Fig. 2 (top panel) illustrates the mean (±S.E.M.) consumption of water for subjects receiving cocaine (Group C) and water (Group W) over repeated preexposures. A 2 × 5 repeated-measure ANOVA revealed a significant Day effect [$F(4,156) = 22.375$, $P < .05$]. There was neither a significant Group effect [$F(1,39) = 0.106$, $P = .747$] nor a Group × Day interaction [$F(4,156) = 1.067$, $P = .375$]. Post-hoc assessments using independent sample *t*-tests revealed that at no point during preexposure did Groups C and W differ (t's ≥ 0.073, $df = 39$, all P's > .05). Within-group paired sample *t*-tests (Bonferroni corrected $P = .0125$) revealed that relative to the baseline (Preexposure Day 1), water consumption significantly increased on Trials 2–4 for Group C (t's ≥ 4.529, $df = 20$, all P's < .0125) and on Trials 3 and 4 for Group W (t's ≥ 3.744, $df = 19$, all P's < .0125).

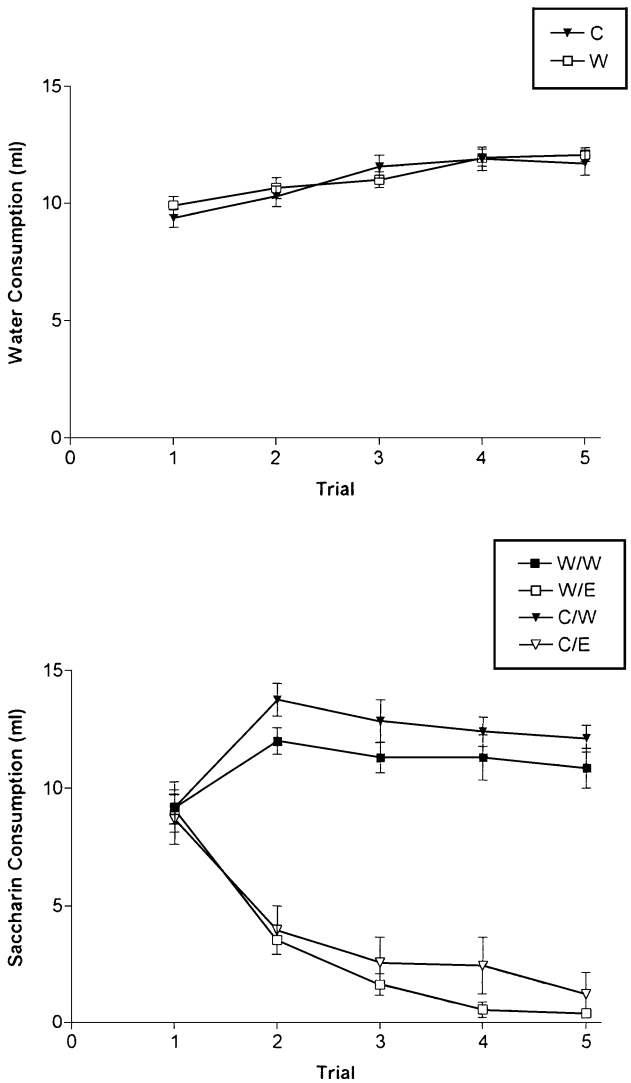

Fig. 2. The mean (±S.E.M.) consumption of water for subjects receiving cocaine (Group C) and water (Group W) over repeated preexposures (top panel). The mean (±S.E.M.) consumption of saccharin for all four groups over repeated conditioning trials (Groups W/W, W/E, C/W and C/E; bottom panel). The first letter in the group designation refers to the drug given during preexposure, i.e., distilled water (W) or cocaine (C); the second letter refers to the drug given during conditioning, i.e., distilled water (W) or ethanol (E).

5.2.2. Conditioning

Fig. 2 (bottom panel) illustrates the mean (±S.E.M.) consumption of saccharin for all four groups over repeated conditioning trials. A 2 × 2 × 5 repeated-measure ANOVA revealed significant effects of Conditioning Drug [$F(1,36) = 171.482$, $P < .05$] and Trial [$F(4,144) = 13.234$, $P < .05$], as well as a significant Conditioning Drug × Trial interaction [$F(4,144) = 50.431$, $P < .05$]. Post-hoc analyses using Tukey HSD revealed no significant differences among groups on the initial conditioning trial (all P's ≥ .959), with subjects in all groups drinking approximately 9.0 ml of saccharin. Over subsequent conditioning trials, significant differences emerged among groups. Specifically, vehicle-preexposed, conditioned subjects (Group W/E) drank significantly less than their controls (Group W/W) on Trials 2–5 (all P's < .05). Cocaine-preexposed, conditioned subjects (Group C/E) drank significantly less than their controls (Group C/W) on Trials 2–5 (all P's < .05). Further, there were no significant differences between the two experimental groups, i.e., Groups C/E and W/E, at any point during conditioning (all P's ≥ 0.221). Similarly, there were no significant differences between the two control groups at any point during conditioning (all P's ≥ .394). All groups drank comparable amounts of water during recovery days, where the average consumption for animals in each group on the recovery day immediately preceding each conditioning trial ranged from 9.75 to 13.05 ml.

Within-group paired sample *t*-tests (Bonferroni corrected $P = .0125$) yielded the following results. Relative to the baseline (Conditioning Trial 1), subjects in Group W/W significantly increased saccharin consumption on Trial 2 ($t \geq 4.023$, $df = 9$, $P < .0125$). Subjects in Group C/W increased their saccharin consumption on Trials 2–4 (t's ≥ 2.960, $df = 9$, P's < .0125). Vehicle-preexposed subjects conditioned with ethanol (Group W/E) significantly decreased saccharin consumption over conditioning, drinking significantly less saccharin on Trials 2–5 than on Trial 1 (t's ≥ 6.960, $df = 9$, P's < .0125). Similarly, subjects preexposed to cocaine and conditioned with ethanol (Group C/E) displayed a significant decrease on Trials 2–5 relative to their baseline (t's ≥ 3.820, $df = 9$, P's < .0125).

6. Discussion

Although the concurrent interaction of ethanol and cocaine has been widely reported, investigations into their serial interaction are limited. In order to extend the scope of research on such interactions, the present studies examined

the cross-drug preexposure effect within CTA learning. As noted, in Experiment 1, animals preexposed to ethanol and conditioned with cocaine displayed attenuated aversions to the cocaine-associated solution, drinking significantly greater amounts of saccharin than vehicle-preexposed, conditioned subjects. Conversely, in Experiment 2, animals preexposed to cocaine and conditioned with ethanol displayed robust aversions to the ethanol-associated solution, drinking at levels comparable to those consumed by vehicle-preexposed, conditioned subjects and drinking significantly less than controls. Thus, the present experiments demonstrated an asymmetric serial interaction between ethanol and cocaine.

That ethanol preexposure attenuated cocaine-induced taste aversions is consistent with Le Pen et al. (1998) who demonstrated that ethanol pretreatment (via consumption) reduced the ability of cocaine to induce a place preference. On the other hand, the present findings are not consistent with the reports that cocaine-induced changes in locomotion are potentiated by ethanol pretreatment (see Itzhak and Martin, 1999; Manley and Little, 1997). That cocaine preexposure did not affect ethanol-induced taste aversions is consistent with Peris et al. (1997) (see also Cailhol and Mormede, 2000) who reported that cocaine had no effect on ethanol-induced changes in locomotion. Again, however, others have noted both potentiation and attenuation of ethanol-induced effects by cocaine pretreatment (see Itzhak and Martin, 1999; York and MacKinnon, 1999). Given the myriad of effects reported in such serial interactions between ethanol and cocaine, the effects of such interactions are likely highly dependent upon the specific conditions under which the interaction is assessed.

To understand the basis for the current asymmetric interaction between ethanol and cocaine, an explanation of the basis for UCS preexposure needs to be addressed. Although a variety of explanations have been suggested for the UCS preexposure effect (Batson and Best, 1979; Gaiardi et al., 1991; Gamzu, 1977; Mikulka et al., 1977; Parker et al., 1973; Randich and LoLordo, 1979), the two that have received the most attention are drug tolerance and habituation to illness (Elkins, 1974; LeBlanc and Cappell, 1974; Riley and Simpson, 1999; Riley et al., 1976). According to these accounts, during drug preexposure animals become tolerant (or habituate) to the aversive effects of the drug such that during subsequent conditioning these effects are reduced below the level sufficient to induce an aversion (Cannon et al., 1977; Cappell et al., 1975; Dacanay and Riley, 1982; Goudie and Thornton, 1975; Goudie et al., 1975, 1976; Hunt et al., 1985; LeBlanc and Cappell, 1974; Riley et al., 1976). These accounts have also been applied to results from cross-drug preexposure studies. Specifically, animals preexposed to one drug develop tolerance (or habituate) to the aversive effects of both the preexposure and conditioning drug. Consequently, during conditioning, the drug does not produce an aversive effect sufficient to condition an aversion (Aragon et al., 1986; Cannon et al., 1977; Cappell et al., 1975; De Beun et al., 1996; Goudie and Thornton, 1975; Hunt and Rabin, 1988; Ng Cheong Ton and Amit, 1985; Vogel and Nathan, 1976).

To account for the present data based on this possibility, it would have to be argued that animals preexposed to ethanol developed cross tolerance to cocaine's aversive effects, but that, during repeated cocaine preexposures, they did not develop cross tolerance to the aversive effects of ethanol. This account assumes that cross-tolerance (or habituation) is not bidirectional. The basis for this asymmetric tolerance may be due to the fact that the aversive properties of ethanol and cocaine, while similar are not identical. Specifically, cocaine's aversive effects may be a subset of ethanol's aversive properties such that tolerance (or habituation) to ethanol may have generalized to cocaine, whereas tolerance (or habituation) to cocaine did not affect the capacity of ethanol to produce aversions (for similar analyses with ethanol and nicotine, see McMillan et al., 1999; with amphetamine and *N-tert*-butyl-α-phenyl nitrone, see Rabin, 1996; with ethanol and LiCl, see Rabin et al., 1988; for other reports on asymmetric interactions in the cross-drug preexposure preparation, see Aragon et al., 1986; Braveman, 1975; Brown et al., 1979; Cappell et al., 1975; Goudie and Thornton, 1975; Switzman et al., 1981; Vogel and Nathan, 1976; for asymmetric interactions between radiation and LiCl, see Rabin et al., 1988; for a review, see Riley and Simpson, 2001).

Although the bases for the aversions induced by cocaine and ethanol remain to be determined, Hunt and Amit (1987) have suggested that these two compounds do work by different mechanisms. Specifically, they have argued that CTAs induced by higher doses of ethanol, unlike other drugs, e.g., cocaine, are a function of both centrally and peripherally mediated toxic effects. In relation to the present results, it is possible that the ability of ethanol to attenuate cocaine-induced aversions is a function of the complete overlap of ethanol's aversive effects (central and peripheral) with those of cocaine (primarily peripheral). The failure of cocaine to attenuate ethanol-induced aversions may be a function of the partial overlap of cocaine's peripheral effects with the central and peripheral effects of ethanol. Although consistent with Hunt and Amit's suggestion, until the specific peripheral and central effects of ethanol and cocaine that mediate aversion learning are clearly assessed, this interpretation of the present asymmetric serial interaction must be cautiously made.

An alternative interpretation of the asymmetric effects reported here concerns the specific choice of doses used for the preexposure and conditioning drugs. Specifically, in the present experiment, preexposure to ethanol (2 g/kg) attenuated aversions induced by cocaine (32 mg/kg). On the other hand, the same dose of cocaine (i.e., 32 mg/kg) had no effect on aversions induced by 2-g/kg ethanol. It is possible that the asymmetry reported was a function of the specific choice of doses (i.e., a high dose of the preexposure drug attenuates an aversion induced at low doses, but not vice

versa), and had more comparable doses been chosen, different results would have been obtained. Although possible, it should be noted that the choice of doses was based on the degree of aversions produced at these doses and not on their absolute value. That is, ethanol and cocaine (at these doses) induced comparable aversions. Interestingly, the attenuating effects of drug preexposure generally are more a function of the drug's aversion-inducing effect than the specific dose itself (for a review, see Riley and Simpson, 2001; though see Hunt et al., 1985). It is certainly possible, however, that other drug choices may have resulted in different degrees of attenuation.

Interestingly, during the conduct of the present experiments a study by Kunin et al. (1999b) was published demonstrating *symmetrical* interactions between ethanol and cocaine in the CTA design. Specifically, Kunin et al. reported that rats preexposed to ethanol (1.2 g/kg ip for 3 consecutive days) and subsequently injected with cocaine (18 mg/kg ip every third day for a total of three conditioning trials) displayed attenuated aversion learning with cocaine. Similarly, animals preexposed to cocaine (36 mg/kg ip for 3 consecutive days) and subsequently conditioned with ethanol (1.2 g/kg ip) demonstrated attenuated aversions with ethanol. Although the bases for the differences in results of the present study and those of Kunin et al. (1999b) are not known, it is important to note that the studies varied on a number of parameters, including time between preexposure and conditioning (3 vs. 0 days), frequency of drug preexposure (spaced vs. massed), number of drug preexposures (five vs. three), dose of the preexposure drug (36 vs. 32 mg/kg) and route of administration (sc vs. ip). Interestingly, each of these parameters has been reported to influence the UCS preexposure effect in CTA learning (Aguado et al., 1997; Cappel and LeBlanc, 1975; De Beun et al., 1996; Domjan and Siegel, 1983; Goldstein et al., 1974; Hunt et al., 1985; Kalant et al., 1971; Klein et al., 1986; Riley and Diamond, 1998; for a review, see Riley and Simpson, 2001). From work on CTA learning and other response preparations (see Section 1), it is clear that the effects of drug history on subsequent drug responsivity are parameter-dependent.

As noted above, the interest in the effects of drug history and the conditions under which these effects occur may have importance for drug use and abuse. Specifically, exposure to a variety of drugs has been reported to affect their own (and other's) aversive and reinforcing properties (Bienkowski et al., 1998b; Heinrichs et al., 1998; Lipinski et al., 1995; Riley and Simpson, 2001). These properties are important in that their balance has been suggested to determine in part the acceptability of the drug and its likelihood of self-administration. That is, the perceived rewarding effects of a drug (in terms of its self-administration) may be a function of the balance of these two affective properties. If the drug's aversive effects are dominant over its reinforcing effects, the likelihood of its subsequent use may be reduced (Cunningham and Henderson, 2000; Gaiardi et al., 1991, 1997; Goudie, 1979; Stefurak et al., 1990; Stolerman and D'Mello, 1981). Conversely, if the aversive effects are weak relative to its reinforcing effects, the likelihood of its use may increase (Ettenberg et al., 1982; Lynch and Carroll, 2001; Pizzi and Cook, 1996; Siegel et al., 1995). The fact that drug history affects the aversive and reinforcing effects of a drug suggests that it may also affect the drug's subsequent use (for an analysis of changes in the aversive and reinforcing properties of ethanol with repeated exposure and the impact of these change on subsequent ethanol intake, see Badia-Elder and Kiefer, 1999; Kiefer et al., 1994; Stewart et al., 1991). As described, ethanol preexposure reduced the ability of cocaine to induce a taste aversion, an index of cocaine's aversiveness. Given the abovementioned association between changes in such effects and drug self-administration, it is possible that ethanol exposure may also impact the subsequent self-administration of cocaine. Conversely, given that there was no effect of cocaine exposure on ethanol-induced taste aversions suggests that such a history may have little impact on ethanol's subsequent intake. However, given that the effects of drug history are parameter-dependent (see above) and the effects of cocaine history on ethanol intake have not been investigated, this issue remains unknown.

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