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Cocaine and Alcohol Synergism in Taste Aversion Learning

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ETKIND, S. A., W. E. FANTEGROSSI AND A. L. RILEY. *Cocaine and alcohol synergism in taste aversion learning.* PHARMACOL BIOCHEM BEHAV **59**(3) 649–655, 1998.—Female Long–Evans rats were given 20-min access to saccharin followed by injections of alcohol and cocaine, alone and in combination. Although there was no significant interaction between alcohol and cocaine when cocaine was given intraperitoneally (IP), aversions induced by the drug combination when cocaine was administered subcutaneously (SC) were significantly greater than those induced by either drug alone. Further, the aversions induced by the combination were significantly greater than the summed effects of the individual drugs administered alone, indicating a synergistic interaction between cocaine and alcohol. It was suggested that this synergism might result from a summation of the effects of alcohol, cocaine, and cocaethylene, a unique and toxic metabolite of cocaine produced when alcohol is coadministered. To assess the role of cocaethylene in the present design, additional taste aversion assessments were performed in which saccharin was paired with either IP or SC injections of cocaethylene. Although cocaethylene was found to induce aversions, the summed changes in consumption from baseline produced by cocaine, alcohol, and cocaethylene were significantly less than the changes produced by cocaine and alcohol in combination. These results indicate that the synergistic interaction between cocaine and alcohol in the present design cannot be attributed solely to summation of the effects of the individual drugs and the metabolite cocaethylene. Additional mechanisms by which cocaethylene might contribute to the synergistic interaction between cocaine and alcohol, as well as the role pharmacokinetic interactions between cocaine and alcohol might have in the interaction, were discussed. © 1998 Elsevier Science Inc.

Cocaine Alcohol Cocaethylene Drug interactions Conditioned taste aversions Rats

ACCORDING to the 1985 National Survey on Drug Abuse, approximately 9 and 12 million people, respectively, co-used cocaine and alcohol either concurrently or simultaneously. Of current cocaine users, nearly all report concurrent (96.5%) and/or simultaneous (98.4%) alcohol use (28). In a recent study by Carroll et al. (7) of treatment-seeking cocaine abusers, alcoholism diagnoses were merited for 29% (current) and 62% (lifetime). Higgins et al. (32) found that of 124 consecutive cocaine-dependent admissions to an outpatient substance abuse clinic, 64% of the patients reported greater than 50% simultaneous alcohol co-use.

Interestingly, despite the frequency with which the substances are combined, cocaine and alcohol co-use has documented cardiovascular (16,18,33,34,44,50,59), hepatotoxic (4, 48), and teratological effects (8). Cocaine and alcohol combinations also increase the likelihood of death compared to administration of either drug alone (56). The combination of cocaine and alcohol has also been reported to affect behavior, for example, increased duration of the loss of the righting reflex (46) and disruption of rotarod performance (52). Consistent with the motoric effects described above, Aston-Jones et al. (1) noted that cocaine in rats enhanced the ataxic effects of alcohol. Recently, Sobel and Riley (58) reported that the combination suppressed scheduled-controlled responding in rats more than either drug alone.

The following studies extended the behavioral assessment of the interaction between alcohol and cocaine by examining the aversive effects of their combination as indexed by conditioned taste aversion learning [for reviews, see (5,23,24,26)]. Such learning is generally rapidly acquired and robust (22), often at doses ineffective in other preparations (53). Thus, conditioned taste aversion learning may be a sensitive behavioral index of the aversive effects of drugs (53). Accordingly, in the present study rats were given access to a saccharin solution and injected with cocaine and alcohol, either alone or in combination (Experiments 1 and 2). The contribution of coca-

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ethylene, the unique metabolite of cocaine produced in the presence of alcohol (10,16,36,44,50,51), to the aversive effects of the combination was assessed in Experiment 3.

GENERAL METHOD

Subjects

The subjects were experimentally naive, female rats of Long–Evans descent, approximately 150 days of age at the beginning of the experiment. They were maintained on a 12 L:12 D cycle (lights on at 0800 h) and at an ambient temperature of 23°C. Food was available ad lib. Guidelines established by the Institutional Animal Care and Use Committee at American University were followed at all times.

Apparatus

Subjects were individually housed in stainless steel, wire-mesh cages. Graduated Nalgene 50 ml centrifuge tubes were attached to the front of the cages to provide 20-min access to water or saccharin.

Drugs and Solutions

Cocaine hydrochloride (generously supplied by NIDA) was prepared as a 10 mg/ml solution in distilled water. Ethanol was prepared as a 95% solution in distilled water and was diluted to a 15% injectable solution. Cocaethylene fumarate (also generously supplied by NIDA) was prepared as a 10 mg/ml solution in distilled water. Saccharin (0.1% Sodium Saccharin, Sigma, St. Louis, MO) was prepared as a 1 g/l solution in tap water.

Procedure

Phase I: Habituation. Following 23-h water deprivation, all subjects were given 20-min access to water. This procedure was repeated daily until all subjects were approaching and drinking from the tube within 2 s of its presentation (14 days).

Phase II: Conditioning. On day 1 of this phase, all subjects were presented with a novel saccharin solution during their scheduled 20-min fluid-access period. Following saccharin access, subjects within each experiment were matched on saccharin consumption and assigned to groups and then injected with vehicle, a drug, or a drug combination. On the 3 days following this conditioning trial, all subjects were given 20-min access to water. No injections were given following fluid access on these recovery days. This alternating procedure of conditioning/water recovery was continued until all subjects had received five complete cycles (the specific quadrant in which the subjects were injected rotated on a per trial basis). On the day following the final water-recovery session of the fifth cycle, all subjects were presented with saccharin for 20 min in a final one-bottle test of the aversion. No injections were given following this test.

Statistical Analyses

Between-group differences in consumption on each conditioning trial were assessed using a one-tailed Kruskal–Wallis one-way analysis of variance. Within-group changes in consumption across trials were evaluated by a one-tailed Friedman two-way analysis of variance. When drug combinations were given, additional one-tailed Kruskal–Wallis analyses of variance were performed to assess the nature of the interaction between the two drugs (i.e., cocaine and alcohol). In the assessment of the drug interaction, the percentage changes in saccharin consumption from baseline (trial 1) for subjects given both cocaine and alcohol were calculated for each trial and compared to the summed values of the percent changes for subjects given either cocaine alone or alcohol alone. If changes from baseline for subjects given the combination were equal to the summation of the changes from baseline in subjects given the individual drugs, a summative interaction between cocaine and alcohol would be suggested, whereas if changes from baseline for subjects given the combination were significantly greater than the summed changes from baseline in subjects given the individual drugs, a synergistic interaction between cocaine and alcohol would be indicated [see (43)]. All determinations of statistical significance are based on $p < 0.05$.

EXPERIMENT 1

In Experiment 1, the specific doses of the combination administered (alcohol—0.56 g/kg; cocaine—10 mg/kg) and the route of administration used (IP) were based on the aforementioned report by Sobel and Riley (58), wherein a cumulative dosing procedure was used to assess the separate and combined effects of intraperitoneally administered cocaine and alcohol on schedule-controlled responding. They reported that both cocaine alone and alcohol alone produced dose-related decreases in responding. When ineffective doses of alcohol (0.56 g/kg) and cocaine (up to 10 mg/kg) were combined, dramatic behavioral suppression was observed, i.e., fluid-deprived subjects ceased responding. Given that the combination of alcohol and cocaine at these doses and by this route of administration produced greater behavioral suppression than either drug alone, these parameters were used in the current analysis of the aversive effects of the interaction.

Specific Procedure

Following adaptation, subjects were assigned to four groups ($n = 5$ per group) such that during conditioning they were intraperitoneally injected with either vehicle (V), cocaine (C; 10 mg/kg), ethanol (E; 0.56 g/kg), or both cocaine and ethanol, yielding groups VV, CV, VE, and CE. All subjects in groups VV, CV, and VE received two injections on each conditioning trial to match the number of injections given to the subjects receiving both cocaine and ethanol, i.e., group CE. The second injection was vehicle.

Results

Figure 1 illustrates the mean consumption of saccharin for subjects in all groups over repeated conditioning trials and on the final aversion test. On the first exposure to saccharin, there were no significant differences in consumption between groups, $H(3) = 0.145$, with subjects in all groups drinking approximately 9 ml of saccharin. No significant differences emerged among groups over repeated trials.

Further, there were no significant within-group changes over trials [group CE, $\chi^2(5) = 2.457$, $p = 0.783$; group CV, $\chi^2(5) = 8.086$, $p = 0.152$; group VE, $\chi^2(5) = 2.514$, $p = 0.774$; group VV, $\chi^2(5) = 8.500$, $p = 0.131$]. At no point were changes in consumption from baseline in subjects administered cocaine and alcohol in combination (i.e., group CE) significantly different from the summed differences in consumption from baseline for subjects administered either drug alone (i.e., groups CV and VE) [all $Hs(4) \leqslant 3.184$, for all trials].

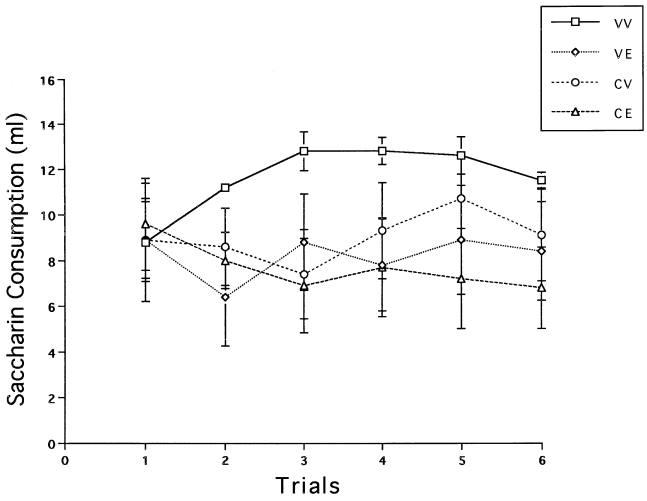

FIG. 1. Mean saccharin consumption for subjects in groups VV, VE, CV, and CE (n = 5 per group) on each of the six conditioning trials in Experiment 1. Bars above and below each point represent SEM. VV = vehicle/vehicle; VE = vehicle/ethanol (0.56 g/kg; IP); CV = cocaine (10 mg/kg; IP)/vehicle; CE = cocaine (10 mg/kg; IP)/ethanol (0.56 g/kg; IP).

EXPERIMENT 2

As described, saccharin consumption of the drug combination group did not differ significantly from that of the groups receiving only a single drug treatment (i.e., cocaine or alcohol alone). Further, the percentage changes in saccharin consumption for group CE did not differ from the summed percent changes in consumption for subjects receiving either cocaine or alcohol alone. Thus, unlike other preparations in which alcohol and cocaine in combination produced greater effects than either drug alone and greater effects than the summation of individual effects of each drug, there did not appear to be a significant interaction between cocaine and alcohol in the conditioned taste aversion design. It is important to note, however, that no aversions were produced to either cocaine or alcohol in Experiment 1. The failure to see a significant interaction between cocaine and alcohol within the aversion design might be attributed to the fact that taste aversions are difficult to establish under the specific parametric conditions used in this experiment. Such a possibility is especially likely with cocaine, given that aversions are generally weakly induced by intraperitoneally administered cocaine even at high doses, for example, up to 50 mg/kg, and with extended training [see (6,17,20,27); for comparisons with emetics, see (40)]. Given the ability of subcutaneously administered cocaine to induce aversions at intermediate doses, i.e., 18–32 mg/kg (17,25), the present study examined the interaction between alcohol and cocaine in taste aversion learning when cocaine was administered by this route and within this dose range.

Specific Procedure

Following adaptation, subjects were assigned to four groups (n = 6 per group) such that during conditioning they were injected with either vehicle (V), cocaine (C; 25 mg/kg), ethanol (E; 0.56 g/kg), or the cocaine/ethanol combination, yielding groups VV, CV, VE, and CE. All ethanol (and its distilled water vehicle) injections were administered intraperitoneally. Cocaine (and its distilled water vehicle) injections were administered subcutaneously.

Results

Figure 2 illustrates the mean consumption of saccharin for subjects in all groups over repeated conditioning trials and on the final aversion test. On the first exposure to saccharin, there were no significant differences in saccharin consumption between groups, $H(3) = 0.927$, with subjects in all groups drinking approximately 11 ml of saccharin. Over repeated conditioning trials, significant differences emerged among groups. Specifically, subjects injected with cocaine alone during conditioning (i.e., group CV) drank significantly less saccharin than vehicle-injected subjects (i.e., group VV) on trials 2–6 [all $Hs(3) \geqslant 8.313$, on all trials]. Subjects in group CV also drank significantly less saccharin than subjects injected with ethanol alone (i.e., group VE) on trials 3, 5, and 6, [all $Hs(3) \geqslant 15.532$, on all trials]. At no point in conditioning did subjects in group VE drink less saccharin than the vehicle-injected controls (group VV). Throughout conditioning, subjects injected with both cocaine and ethanol during conditioning (i.e., group CE) drank significantly less saccharin than subjects in the remaining groups (i.e., groups VV, CV, and VE) [all $Hs(3) \geqslant 8.313$, on all trials; although on trial 2, differences in consumption between subjects in group CE and group CV did not reach significance]. Although there were no significant within-group changes in saccharin intake over conditioning for subjects in groups VV, CV, and VE [all $\chi^2s(5) = 9.265$, on all trials], subjects in group CE significantly decreased saccharin consumption with repeated conditioning, $\chi^2(5) = 23.952$, $p = 0.001$. In relationship to the nature of the drug interaction, differences in consumption from baseline for subjects adminis-

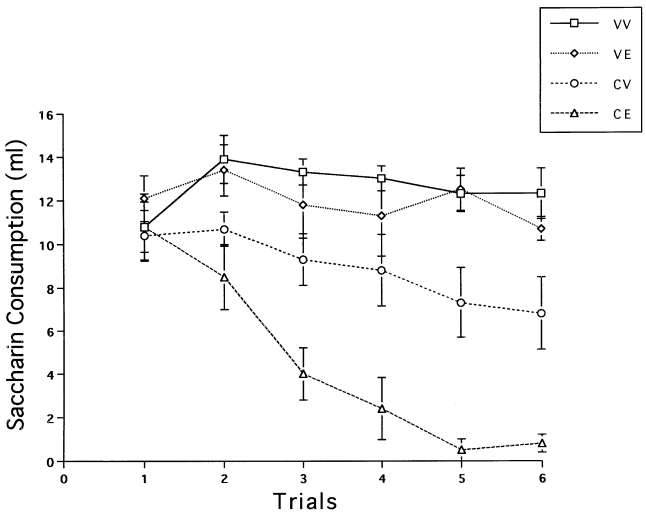

FIG. 2 Mean saccharin consumption for subjects in group VV, VE, CV, and CE (n = 6 per group) on each of the six conditioning trials in Experiment 2. Bars above and below each point represent SEM. VV = vehicle/vehicle; VE = vehicle/ethanol (0.56 g/kg; IP); CV = cocaine (25 mg/kg; SC)/vehicle; CE = cocaine (25 mg/kg; SC)/ethanol (0.56 g/kg; IP).

tered both cocaine and ethanol (i.e., group CE) were significantly greater than the summed changes in consumption from baseline for subjects administered either drug alone (i.e., groups CV and VE) on trials 3–6 [all $Hs(4) \geq 12.082$, for all trials], indicating a synergistic interaction between ethanol and cocaine.

EXPERIMENT 3

As reported in Experiment 1, there was no significant interaction between cocaine and alcohol when both drugs were administered IP. Given that intraperitoneally administered cocaine is only weakly effective in producing aversions (even at doses up to 50 mg/kg), a more effective route of administration (SC) and dose (25 mg/kg) of cocaine was used in Experiment 2 (17,25). Under these conditions, alcohol and cocaine in combination produced stronger aversions than either drug alone, indicating a significant interaction between the two drugs. Further, alcohol and cocaine in combination produced stronger aversions than would be expected from the summation of the effects of cocaine and alcohol alone, indicating a synergistic interaction between the two drugs.

Although there appears to be a synergistic interaction between cocaine and alcohol in conditioning aversions, the mechanism underlying this synergism remains unknown. It has recently been suggested that the greater effects produced by the combination of alcohol and cocaine within other designs may be a function of cocaethylene, the unique metabolite of cocaine formed when cocaine and alcohol are coadministered (10,16,36,44,49,50). Produced in the liver via transesterification of cocaine only in the presence of alcohol (2,3,9,10,29, 37,44), cocaethylene acts comparably to cocaine subjectively (37), cardiovascularly (15), biochemically (3,27,36) and behaviorally (36,57). Like cocaine, cocaethylene has also been reported to be toxic in several preparations, including the induction of convulsions (30,39), respiratory arrest (14) and lethality (14) [see also (3,31,54,57)].

Because cocaethylene is formed when cocaine and alcohol are coadministered and has toxic properties (see above), it is possible that cocaethylene's effects might summate with those of both cocaine and alcohol to produce the synergism seen when cocaine and alcohol were combined in Experiment 2. If cocaethylene contributed to the increased toxicity of the combination of cocaine and alcohol by this mechanism, it would be expected that cocaethylene would be effective in inducing aversions when administered alone. Further, it would be predicted that the reductions in saccharin consumption in subjects administered cocaethylene added to the decreases in saccharin consumption in subjects administered cocaine and alcohol separately (in Experiment 2) would equal the reduction of saccharin consumption in subjects administered cocaine and alcohol in combination (also in Experiment 2). To test these predictions, the toxicity of cocaethylene in the taste aversion design was assessed in Experiment 3. Given that aversions to cocaine are dependent upon route of administration, cocaethylene was administered both intraperitoneally and subcutaneously.

Specific Procedure

Following adaptation, subjects were assigned to four groups ($n = 12$ per group) such that during conditioning they were injected with either vehicle (0), 18, 32, or 50 mg/kg cocaethylene, yielding groups 0, 18, 32, and 50. Cocaethylene (and its distilled water vehicle) injections were administered either intraperitoneally or subcutaneously.

RESULTS

Figure 3 (top panel) illustrates the mean consumption of saccharin for subjects in all groups over repeated conditioning trials and on the final aversion test following conditioning with intraperitoneally administered cocaethylene. On the first exposure to saccharin, there were no significant differences in consumption between groups, $H(3) = 0.022$, with subjects in all groups drinking approximately 9 ml of saccharin. Over repeated conditioning trials, significant differences emerged among groups. Specifically, subjects injected with 32 mg/kg of cocaethylene during conditioning (i.e., group 32) consumed significantly less saccharin than both vehicle-treated subjects and subjects injected with 18 mg/kg cocaethylene on trials 3 and 4, $H(3) = 11.730$ and 12.541, respectively, for both trials. Further, subjects injected with 50 mg/kg of cocaethylene (i.e., group 50) consumed significantly less saccharin than both vehicle-treated subjects and subjects injected with 18 mg/kg cocaethylene on trials 3, 4, and 6 [all $Hs(3) \geq 8.440$, for all trials]. Although there were no significant within-group changes in saccharin consumption over conditioning trials for subjects in groups 0, 18, and 50 [all $\chi^2s(5) = 8.833$, on all trials], subjects in group 32 significantly increased saccharin consumption relative to baseline with repeated conditioning, $\chi^2(5) = 12.643$, $p = 0.027$.

Figure 3 (bottom panel) illustrates the mean consumption of saccharin for subjects in all groups over repeated condition-

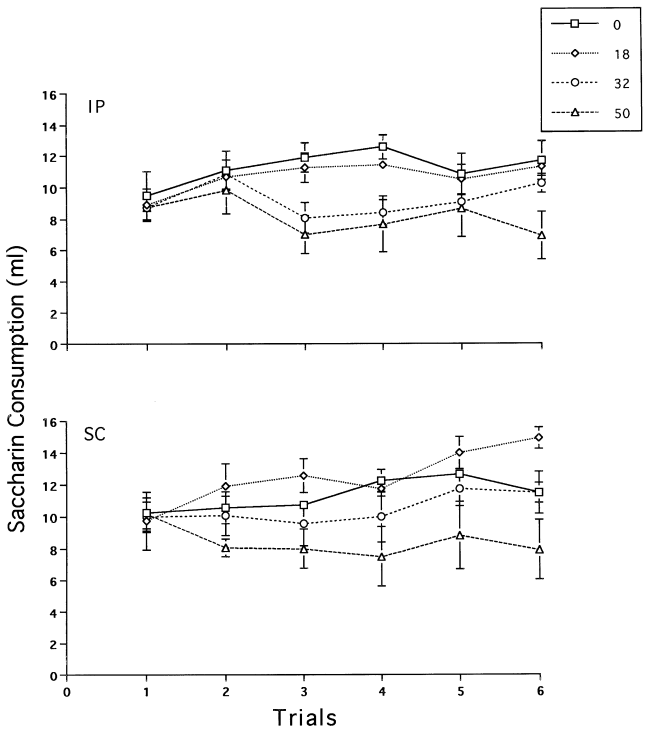

FIG. 3. Mean saccharin consumption for subjects in groups 0, 18, 32, and 50 ($n = 6$ per group) on each of the six conditioning trials in Experiment 3 when cocaethylene was administered intraperitoneally (top panel) and subcutaneously (bottom panel). Bars above and below each point represent SEM. 0 = 0 mg/kg cocaethylene; 18 = 18 mg/kg cocaethylene; 32 = 32 mg/kg cocaethylene; 50 = 50 mg/kg cocaethylene.

ing trials and on the final aversion test following conditioning with subcutaneously administered cocaethylene. On the first exposure to saccharin, there were no significant differences in consumption between groups, $H(3) = 0.012$, with subjects in all groups drinking approximately 10 ml of saccharin. Over repeated conditioning trials, significant differences emerged among groups. Specifically, subjects injected with 18 mg/kg of cocaethylene during conditioning (i.e., group 18) consumed significantly more saccharin than vehicle-treated subjects and subjects injected with 32 and 50 mg/kg cocaethylene on trial 6, $H(3) = 13.596$. Subjects injected with 50 mg/kg of cocaethylene (i.e., group 50) consumed significantly less saccharin than subjects injected with 32 mg/kg cocaethylene, also on trial 6, $H(3) = 13.596$. Although there were no significant within-group changes in saccharin consumption over conditioning trials for subjects in groups 0, 32, and 50 [all χ^2s(5) = 9.714, on all trials], subjects in group 18 significantly increased saccharin consumption with repeated conditioning, $\chi^2(5) = 21.857$, $p < 0.001$.

GENERAL DISCUSSION

To test whether cocaethylene was aversive, Experiment 3 assessed the ability of cocaethylene alone to induce taste aversions. As described, at a low dose (18 mg/kg) cocaethylene failed to induce aversions over repeated trials. In fact, this dose (when administered subcutaneously) appeared to induce a taste preference on the final aversion test, i.e., animals treated with this dose drank significantly more saccharin than vehicle-injected subjects on this test. Interestingly, similar taste preferences have been reported with subcutaneously administered morphine at low doses, while higher doses produce taste aversions (47). Such taste preferences, however, have not been reported with cocaine (17,25). Given that this effect of cocaethylene was significant on only a single trial and only following SC administration, it is not clear to what extent (if any) low doses of cocaethylene are rewarding. An intermediate dose of cocaethylene (32 mg/kg) induced aversions over repeated trials when administered intraperitoneally, but not when administered subcutaneously. At the highest dose tested (50 mg/kg), cocaethylene produced significant decreases in saccharin consumption relative to controls and/or groups 18 and 32 by both routes of administration; decreases of 22% (IP) and 23% (SC) relative to their own baseline were seen after five trials. Thus, cocaethylene was effective in producing taste aversions, although the aversions were weak and evident only at the highest doses tested.

If cocaethylene contributed to the greater aversions produced by the combination of cocaine and alcohol, it was predicted that the individual decreases in drinking seen when cocaine, alcohol, and cocaethylene were each administered alone would summate to equal the decrease in drinking observed when cocaine and alcohol were coadministered. Table 1 provides a summary of the changes in saccharin consumption from baseline for subjects injected with cocaine, alcohol, cocaethylene and the cocaine/alcohol combination during conditioning. As noted, in Experiment 2 when cocaine and alcohol were administered concurrently, a 92.6% decrease in saccharin consumption was seen on the final aversion test (i.e., after five conditioning trials). Cocaine alone produced a 34.6% decrease, and alcohol alone produced an 11.6% decrease in saccharin consumption at this point in conditioning. Cocaethylene (50 mg/kg; IP and SC) alone produced 21.6 and 22.5% decreases in saccharin consumption, respectively, after five conditioning trials. Were the enhanced aversions produced by cocaine and alcohol in combination due to the summed effects of cocaine, alcohol and cocaethylene, one might expect approximately a 93% decrease in saccharin consumption, the percent decrease in consumption seen when cocaine and alcohol were coadministered. However, summating the effects of cocaine, alcohol and cocaethylene produced only approximately a 69% decrease in saccharin consumption, leaving at least 24% of the decreased fluid intake unaccounted for (see Table 1).

It is likely that the decreased intake attributed to cocaethylene in the above equation is an overestimation. Several studies measuring blood levels of cocaethylene following coadministration of cocaine and alcohol have revealed that cocaethylene, when formed, appears in small amounts relative to levels of cocaine (10,16,42,44,50). It is unlikely that an amount as large as 50 mg/kg of cocaethylene (the highest dose tested in Experiment 3) was produced following administra-

TABLE 1

MEAN SACCHARIN CONSUMPTION AND PERCENTAGE CHANGE FROM BASELINE OVER REPEATED TRIALS

	Group										
	CV		VE		Cocaethylene (IP)		Cocaethylene (SC)		CE		CV + VE + Cocaethylene*
Trial	Mean	%△	Mean	%△	Mean	%△	Mean	%△	Mean	%△	%△
1	10.4		12.1		8.8		10.2		10.8		
2	10.7	2.9	13.4	10.7	9.8	11.4	8.1	−20.6	8.5	−21.3	9.0
3	9.3	−10.6	11.8	−2.5	7.0	−20.5	8.0	−21.6	4.0	−63.0	−34.2
4	8.8	−15.4	11.3	−6.6	7.7	−12.5	7.5	−26.5	2.4	−77.8	−41.5
5	7.3	−29.8	12.5	3.3	8.7	−1.1	8.8	−13.7	0.5	−95.4	−33.9
6	6.8	−34.6	10.7	−11.6	6.9	−21.6	7.9	−22.5	0.8	−92.6	−68.3

Mean saccharin consumption (ml) and percentage change from baseline over repeated trials for rats given cocaine (CV; 25 mg/kg, SC), ethanol (VE; 0.56 g/kg, IP), cocaethylene (50 mg/kg, IP or SC), or cocaine (25 mg/kg, SC) and ethanol (0.56 g/kg, IP) in combination (CE).

* Summation of percentage change from baseline for subjects receiving either cocaine, ethanol, or cocaethylene (mean of IP and SC routes) over repeated trials.

tion of 10 mg/kg of cocaine combined with 0.56 g/kg ethanol, the doses used in Experiment 2. Thus, the enhanced aversiveness of cocaine and alcohol in combination as indexed by the taste aversion design is not likely caused by the simple summation of the individual effects of cocaine, alcohol, and cocaethylene.

This caveat does not rule out the possibility that cocaethylene might contribute to the enhanced toxicity of cocaine and alcohol used in combination in a manner other than simple summation. For example, several studies have shown cocaethylene to have a longer half-life than cocaine (16,31,35,41,44, 50,51,55), although it is unknown how the extended duration of action of cocaethylene might contribute to the shorter acting aversive effects of cocaine when both drugs are present. Goudie (26) has proposed that prolonging the duration of action of drugs in aversion conditioning enhances the aversive effects of drugs, presumably by increasing the amount of time during which the drugs will exert an aversive influence [see also (11,13,17,19); although see (12)]. Given cocaethylene's longer half-life, it is possible that the formation of cocaethylene following cocaine and alcohol coadministration would extend the duration of toxicity of the drug combination. Alternatively, Bailey (2) found that the incubation of human liver homogenates with cocaethylene and alcohol produced cocaine, suggesting that cocaethylene might extend the duration of action of cocaine through a reverse metabolic pathway. Cross-sensitization among cocaethylene, cocaine, and alcohol (35), as well as specific interactions between cocaethylene and alcohol and cocaethylene and cocaine (45), have also been suggested as possible mechanisms accounting for the synergistic interactions between cocaine and alcohol. Any of these mechanisms (alone or together) might explain how cocaethylene factors into the enhanced aversiveness of the combination of cocaine and alcohol seen in the present study.

Cocaethylene (and/or its interactions with alcohol and cocaine) may not be the only contributing factors to the increased aversiveness. For example, it is possible that the increased aversive effects of cocaine and alcohol are related to changes in the pharmacokinetics of cocaine when alcohol is coadministered. In humans, cocaine and alcohol in combination increase plasma levels (16) and the bioavailability (50) of cocaine. The combination increases cocaine concentrations in the liver of rats (10) and increases the volume of distribution of cocaine in pigs (38) [see also (9,51); although see (50)]. Additionally, the drug combination increases levels of the active compounds benzoylecgonine (10,16,38) and norcocaine (16). Although some studies have noted changes in the pharmacokinetics of cocaine when cocaine and alcohol are coadministered, Fowler et al. (21) reported that in humans the drug combination did not change the uptake, clearance, or steady-state distribution volume of cocaine in either the brain or the heart [see also (38)]. Thus, the role of pharmacokinetic changes to the interaction between alcohol and cocaine remains unclear.

Within the present study, cocaine (SC) and alcohol in combination not only produced greater aversions than either drug alone, but also produced greater aversions than would be expected were individual drug effects summated. These results are indicative of a synergistic interaction between cocaine and alcohol. Given the relatively weak effects of cocaethylene alone in this design, it is unlikely that the summed aversive effects of cocaine, alcohol, and cocaethylene accounted for the whole of the increased aversive effects seen when cocaine and alcohol were coadministered. Although cocaine and alcohol in combination demonstrate toxicological synergism within taste aversion learning, the mechanism for this synergism remains unknown.

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