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Strain-dependent sex differences in the effects of alcohol on cocaine-induced taste aversions

Jermaine D. Jones [a,*], Gregory D. Busse [a,b], Anthony L. Riley [a]

[a] *Psychopharmacology Laboratory, Department of Psychology, American University, 4400 Massachusetts Ave., NW, Washington, DC 20016, United States*
[b] *Department of Psychology, George Washington University, Washington DC 20052, United States*

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Abstract

Research using the conditioned taste aversion procedure has reported that a cocaine/alcohol combination induces a significantly stronger taste aversion than either cocaine or alcohol alone. These findings suggest that the co-administration of alcohol intensifies the aversive effects of cocaine. Although the behavioral interaction of cocaine and alcohol is well established, little is known about how the effects of this drug combination might be modulated by a variety of subject variables. The current investigation addressed this by assessing if the ability of alcohol to potentiate cocaine-induced taste aversions is dependent upon the strain and/or sex of the subject. In this series of studies, male and female rats of Long–Evans (Experiment 1) and Sprague–Dawley (Experiment 2) descent were given limited access to a novel saccharin solution to drink and were then injected with either vehicle, cocaine (20 mg/kg), alcohol (0.56 g/kg) or the alcohol/cocaine combination. This procedure was repeated every fourth day for a total of four conditioning trials. All subjects were then compared on an Aversion Test that followed the fourth conditioning cycle. In three of the groups tested (male Long–Evans; male and female Sprague–Dawley), cocaine induced a significant taste aversion that was unaffected by the co-administration of alcohol. However, in female Long–Evans subjects, the addition of alcohol significantly strengthened the avoidance of the saccharin solution. Although the effects of alcohol on cocaine-induced taste aversions are dependent upon an interaction of sex and strain, the basis for this Sex × Strain interaction is not known. That such an interaction is evident suggests that attention to such factors in assessing the effects of drug combinations is important to understanding the likelihood of the use and abuse of such drugs.

Keywords: Cocaine; Alcohol; Conditioned taste aversion; Drug interactions; Sex; Strain; Sprague–Dawley; Long–Evans

1. Introduction

Within a variety of behavioral and physiological preparations, alcohol has been reported to potentiate the effects of cocaine. That is, doses of cocaine that alone have little effect produce significant changes in behavior when given in combination with alcohol (Aston-Jones et al., 1984; Boyer and Petersen, 1990; Busse and Riley, 2003; Manley and Little, 1997; Peris et al., 1997; Pecins-Thompson and Peris, 1993). Recently, investigation into this interaction has been extended to the affective (aversive, rewarding, anxiogenic) properties of cocaine (Busse et al., 2004; Busse and Riley, 2002; Knackstedt and Ettenberg, 2005; Kunin et al., 1999; McCance-Katz et al., 2005; Lewis and June, 1994). In the analysis of the effects of alcohol on cocaine-induced taste aversions, Etkind et al. (1998) (see also Grakalic and Riley, 2002) reported that in Long–Evans female rats a dose of cocaine which alone produced a small suppression in saccharin consumption (a weak taste aversion) resulted in significant suppression when given in combination with an ineffective dose of alcohol, i.e., alcohol potentiated the cocaine-induced taste aversion (CTA).

One interesting aspect of the CTA design is that it is affected by a variety of subject parameters. For instance, taste aversion learning is affected by both the sex and strain of the subject used (Klosterhalfen and Klosterhalfen, 1985; Riley and Freeman, 2004). In the context of sex, males generally display greater acquisition (or slower extinction) of conditioned taste aversions than females when LiCl, THC and cocaine are used as the

* Corresponding author. Tel.: +1 202 885 1721.
E-mail address: JermaineDJones@gmail.com (J.D. Jones).

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aversion-inducing agent (Busse et al., in press; Chambers, 1976; Dacanay et al., 1984; Lucas and McMillen, 2002; though see van Haaren and Hughes, 1990; Randall-Thompson and Riley, 2003). As noted, the strain of the subject also affects taste aversion learning. For example, rats of the LEW strain acquire cocaine-induced taste aversions at significantly lower doses than do the histocompatible F344 strain (Glowa et al., 1994; see also Grigson, 1997), while the F344 strain displays greater aversions than the LEW strain when morphine is the aversion-inducing agent (Lancellotti et al., 2001). Further, differences in ethanol-induced CTAs have been observed between rat strains selectively bred for ethanol preference (Brunetti et al., 2002; Kulkosky et al., 1995; Quintanilla et al., 2001).

There are significant sex and strain differences in aversion learning with a variety of drugs of abuse, including cocaine and alcohol (Church et al., 1995; Glowa et al., 1994; Van Haaren and Hughes, 1990). Yet, it is unknown to what extent the potentiation of cocaine-induced taste aversions by alcohol that occur with female Long–Evans rats generalizes to males of the same strain or to either sex of other strains. It is interesting in this context that sex and strain differences have been reported in several assessments of the interaction between cocaine and alcohol. Specifically, the behavioral and physiological effects of cocaine/alcohol combinations and cocaethylene (a neuroactive metabolite of cocaine only produced in the presence of alcohol) have been reported to differ between Long–Evans and Sprague–Dawley strains of both sexes (see Baunmann et al., 1998; Horowitz et al., 1997; Sobel et al., 1998). For instance, Long–Evans rats have been reported to be less sensitive to the stimulatory effects of combined cocaine–alcohol exposure as well as to cocaethylene-induced locomotor and exploratory behavior when compared with rats of Sprague–Dawley descent (Baunmann et al., 1998; Horowitz et al., 1997, 1999). Studies have also found that alcohol's potentiation of cocaine's lethality is more pronounced in female heterogeneous stock mice than in male mice (Schechter and Meehan, 1995).

These reported sex and strain differences to combinations of alcohol and cocaine (or the metabolite cocaethylene) raise the possibility that similar differences might also be seen in alcohol's potentiation of cocaine-induced taste aversions. Accordingly, the present study examined the effects of sex and strain on the interaction of alcohol and cocaine in the conditioned taste aversion preparation. Specifically, female and male rats of Long–Evans (Experiment 1) and Sprague–Dawley (Experiment 2) descent were given access to a novel saccharin solution and injected with cocaine (20 mg/kg), alcohol (0.56 g/kg) or the cocaine/alcohol combination. Given that the use and possible abuse of a drug (or a drug combination) is reported to be a function of the relative balance of the rewarding and aversive effects of the drug (Hunt and Amit, 1987; Riley and Tuck, 1985; Simpson and Riley, 2005), it is important to understand under what conditions the rewarding and/or aversive effects of the drug may vary. The demonstration of a specific strain and/or sex-dependent interaction in the effects of the cocaine–alcohol combination may be useful in identifying the nature of variability in drug sensitivity to this combination.

2. General methods

2.1. Subjects

Subjects were male and female rats of the Long–Evans and Sprague–Dawley strains. All subjects were individually housed and maintained on a 12:12 light–dark cycle and at an ambient temperature of 23 °C. Food was available ad libitum throughout the experiment with water consumption restricted to 20 min daily. Daily handling and weighing of the subjects began three weeks prior to the onset of training. 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. Apparatus

Subjects were individually housed in stainless-steel, wire-mesh hanging cages. Graduated Nalgene 50 ml tubes were used to provide 20-min access to water and saccharin.

2.3. Drugs

Cocaine hydrochloride (generously supplied by the National Institute on Drug Abuse) was dissolved in distilled water and was injected subcutaneously (SC) in a concentration of 10 mg/ml (cocaine doses are expressed as the salt). Alcohol was prepared in a 15% solution with distilled water (v/v) and was injected intraperitoneally (IP). Vehicle injections of saline were matched in number and volume to the injections of cocaine and alcohol. The doses (and route of administration) of alcohol and cocaine were based on Etkind et al. (1998) (see below). Saccharin (0.1% sodium saccharin, Sigma Chemical Co., St. Louis, MO) was prepared as a 1 g/l solution in tap water.

2.4. Procedure

2.4.1. Phase I: habituation

Following 23 h of water deprivation, all subjects were allowed 20-min access to water. This procedure was repeated daily until water consumption was stable for all subjects.

2.4.2. Phase II: conditioning

On Day 1 of this phase, subjects were allowed 20-min access to a novel saccharin solution during their scheduled fluid-access period. Based on their level of saccharin consumption, subjects within each experiment were assigned to one of four conditions so that saccharin consumption was comparable among groups. Within 10 min following saccharin access, subjects were injected with alcohol (0.56 g/kg), cocaine (20 mg/kg), the alcohol/cocaine combination or vehicle. Cocaine or its vehicle always preceded the administration of alcohol or its vehicle. The different vehicle and drug combinations resulted in the following groups: Saline–Saline (S–S), Saline–Alcohol (S–A),

Cocaine–Saline (C–S) and Cocaine–Alcohol (C–A). On the three days following each conditioning day, all subjects were allowed 20-min access to water with no injections given on these recovery days. This alternating procedure of conditioning/water recovery was repeated for a total of four complete cycles. On the day following the final water-recovery session of the fourth conditioning cycle, all subjects were given 20-min access to saccharin in an Aversion Test. No injections were given following this presentation of saccharin.

2.5. Statistical analysis

For each experiment, saccharin consumption was compared on the Aversion Test using a 2×4 ANOVA with between-group variables of Sex (Male, Female) and Drug Condition (Saline–Saline; Saline–Alcohol; Cocaine–Saline; Cocaine–Alcohol). Tukey's HSD post hoc tests were utilized for all subsequent comparisons.

3. Experiment 1

As noted above, it is unknown to what extent the aforementioned potentiation of cocaine-induced taste aversions by alcohol in female Long–Evans rats as reported by Etkind et al. (1998) generalizes to males of the same strain. As such, Experiment 1 assessed alcohol's effect on cocaine-induced taste aversions in female and male Long–Evans rats. Specifically, in Experiment 1, 68 experimentally naïve female and male rats of the Long–Evans strain were given access to saccharin followed by injections of saline ($n=8$ for each sex), cocaine ($n=9$ for each sex), alcohol ($n=8$ for each sex) or the cocaine/alcohol combination ($n=9$ for each sex).

4. Experiment 1: results

Fig. 1 illustrates absolute saccharin consumption (ml) in Long–Evans rats for each Sex and Drug Condition on the Aversion Test. Although a 2×4 ANOVA indicated no significant main effect of Sex [F (1, 59)=3.434, $p=0.069$], there was a significant main effect for Drug Condition [F (3, 59)=58.47, $p<0.001$]. Tukey's post hoc tests indicated that animals conditioned with alcohol did not differ from saline controls on the Aversion Test. Alternatively, those animals conditioned with cocaine consumed significantly less saccharin on the Aversion Test than those conditioned with either saline or alcohol (p's<0.05). Furthermore, animals conditioned with the cocaine–alcohol combination displayed a greater reduction in saccharin consumption than animals conditioned with saline, alcohol or cocaine (p's<0.05). These effects were independent of sex.

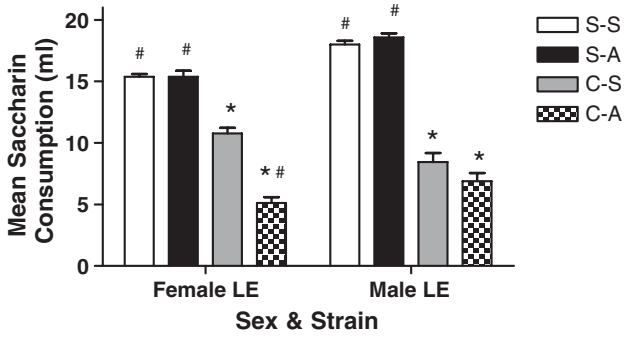

Fig. 1. Mean (± SEM) saccharin consumption (ml) on the Aversion Tests for female (left panel) and male (right panel) Long–Evans rats injected with Saline–Saline (Group S–S), Saline–0.56 g/kg Alcohol (S–A), 20 mg/kg Cocaine–Saline (Group C–S) or the cocaine/alcohol combination (Group C–A). *Indicates a significant difference from Group S–S ($p<.05$). # Indicates a significant difference from Group C–S ($p<.05$).

Interestingly, a significant Sex×Drug Condition interaction [F (3, 59)=3.21, $p<0.05$] was also evident. Although Tukey's post hoc comparisons indicated no difference in saccharin consumption on the Aversion Test between female and male subjects conditioned with either saline, alcohol, cocaine or the cocaine–alcohol combination (p's<0.05), there were differences in saccharin consumption on the Aversion Test within each sex. Specifically, females conditioned with alcohol did not differ in saccharin consumption from females injected with saline ($p>0.05$), but females conditioned with cocaine consumed less saccharin on the Aversion Test than females conditioned with saline or alcohol (p's<0.05), indicative of a cocaine-induced taste aversion. Moreover, females conditioned with the cocaine–alcohol combination consumed significantly less saccharin on the Aversion Test than females conditioned with saline, alcohol or cocaine (p's<0.05). These data suggest that in females, alcohol potentiated the cocaine-induced taste aversion. Furthermore, this potentiation in cocaine aversions occurred despite alcohol's inability to produce a significant aversion on its own.

In male Long–Evans rats, those subjects conditioned with alcohol did not differ from those conditioned with saline on the Aversion Test ($p>0.05$). Those males, however, conditioned with cocaine consumed significantly less saccharin on the Aversion Test than those conditioned with either saline or alcohol (p's<0.05). Interestingly, although those males conditioned with the cocaine–alcohol combination consumed less saccharin on the Aversion Test than those animals conditioned with either saline or alcohol alone (p's<0.05), they did not differ from those conditioned with cocaine alone ($p>0.05$). Thus, in male Long–Evans rats, there was no evidence of a potentiated cocaine-induced taste aversion by alcohol.

5. Experiment 2

Cocaine was effective in inducing aversions in both male and female LE rats (see Groups C–E and C–S). A potentiation of cocaine-induced aversions by alcohol, however, was only evident in female LE subjects. There was no evidence of potentiation in male LE subjects. That is, in male LE subjects, Groups C–A and C–S did not differ on the Aversion Test. Although the potentiation in female LE subjects is clear and replicates earlier work assessing this specific drug interaction under similar conditions (see above), its basis remains unknown and could be a function of a variety of factors, e.g., changes in the pharmacokinetics of cocaine and alcohol and/or the differential formation of cocaethylene (see Pan and Hedaya, 1999a,b). In this context, it is interesting to note that the simultaneous

administration of alcohol and cocaine has been reported to result in higher and prolonged cocaine plasma concentrations (Farre et al., 1993; Hedaya and Pan, 1996; Pan and Hedaya, 1999a,b; Perez-Reyes and Jeffcoat, 1992; Vadlamani et al., 1984; but see Fowler et al., 1992) as well as the formation of cocaethylene (Boyer and Petersen, 1990; Dean et al., 1992; Rafla and Epstein, 1979; Smith, 1984) which itself causes a reduction in the elimination of cocaine when simultaneously present. Interestingly, changes in the affective properties of cocaine have been reported by extending cocaine's duration of action (Ferrari et al., 1991; Mayer and Parker, 1993; Nomikos and Spyraki, 1988). Although changes in the pharmacokinetics of cocaine (when given with alcohol) may account for the differences reported in the present comparison between male and female LE rats, such pharmacokinetic assessments have not been examined in relation to sex differences. In the absence of independent determinations of cocaine blood levels in males and female LE rats following the administration of cocaine, alcohol and the cocaine/alcohol combination, the role of pharmacokinetic differences to the present results remains unknown.

Independent of the basis for the interaction between alcohol and cocaine or its dependency upon the sex of the subject, it is clear that subject factors are important for its demonstration. Experiment 2 extended this assessment of subject factors by examining the interaction of alcohol and cocaine in a second strain of rats, i.e., Sprague–Dawley rats. Given the sex difference reported for the LE strain, both female and male Sprague–Dawley rats were examined. Specifically, 59 rats of the Sprague–Dawley strain were given access to saccharin followed by injections of saline ($n=8$ for females; $n=6$ for males), cocaine ($n=9$ for females; $n=7$ for males), alcohol ($n=8$ for females; $n=6$ for males) or the alcohol/cocaine combination ($n=9$ for females; $n=6$ for males).

6. Experiment 2: results

Fig. 2 illustrates absolute saccharin consumption (ml) in Sprague–Dawley rats for each Sex and Drug Condition on the Aversion Test. A 2×4 ANOVA indicated no significant main effect of Sex [F (1, 59)=1.879, $p=.176$]. There was, however, a significant main effect for Drug Condition [F (3, 59)=47.231, $p<.001$]. Tukey's post hoc tests indicated that animals conditioned with alcohol did not differ from saline controls on the Aversion Test. Alternatively, those animals conditioned with cocaine consumed significantly less saccharin on the Aversion Test than animals conditioned with either saline or alcohol (p's<0.05). Animals conditioned with the cocaine–alcohol combination displayed a greater reduction in saccharin consumption than animals conditioned with saline or alcohol (p's<0.05). They did not, however, differ in saccharin consumption on the Aversion Test from animals conditioned with cocaine alone ($p>0.05$). The 2×4 ANOVA indicated no Sex×Drug Condition interaction [F (3, 59)=1.57, $p=0.208$]. As such, there was no evidence of a potentiation of cocaine aversions by alcohol in either male or female SD rats.

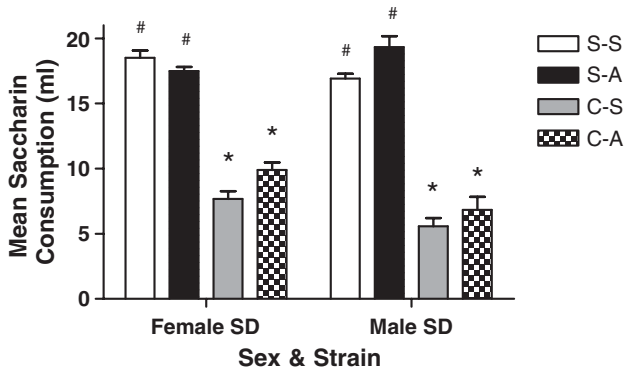

Fig. 2. Mean (± SEM) saccharin consumption (ml) on the Aversion Tests for female (left panel) and male (right panel) Sprague–Dawley rats injected with Saline–Saline (Group S–S), Saline–0.56 g/kg Alcohol (S–A), 20 mg/kg Cocaine–Saline (Group C–S) or the cocaine/alcohol combination (Group C–A). * Indicates a significant difference from Group S–S ($p<.05$). # Indicates a significant difference from Group C–S ($p<.05$).

7. General discussion

It has been previously reported that a dose of alcohol ineffective at conditioning taste aversions potentiated aversions induced by cocaine (Etkind et al., 1998; Grakalic and Riley, 2002). Given that drug effects have been shown to vary as a function of a number of subject parameters (see Cailhol and Mormede, 2000; Lynch and Carroll, 1999; Roth et al., 2004; Sircar and Kim, 1999), the present study assessed whether the effects of alcohol on cocaine-induced taste aversions are dependent on the sex and/or strain of the animal. The testing parameters (e.g., conditioning procedure, dose and route of administration for both cocaine and alcohol) used in the current investigation were comparable to previous studies in which alcohol potentiated cocaine-induced taste aversions (see Etkind et al., 1998; Grakalic and Riley, 2002). As described, alcohol administered at a dose that was ineffective in producing a taste aversion on its own (0.56 g/kg) potentiated a taste aversion conditioned by 20 mg/kg cocaine in female Long–Evans rats (Experiment 1; an alternative explanation is that cocaine potentiated the aversiveness of alcohol, although as described alcohol failed to condition an aversion; as such, the focus of the current discussion is on the impact of alcohol on aversions conditioned by cocaine). Interestingly, this potentiation was not seen in male rats of the same strain (Experiment 1) or male and female rats of Sprague–Dawley descent (Experiments 2; for related findings in male Sprague–Dawley rats, see Busse et al., 2005). The effects of alcohol on cocaine-induced taste aversions clearly appear to be an interaction of sex and strain.

There are several possible explanations for this specificity of the modulation by alcohol of cocaine's aversive effects. For instance, it is possible that the various groups of animals tested in the present studies differ in their sensitivities to the aversive (and/or toxic) effects of alcohol or cocaine and that these differences impacted the ability of alcohol to potentiate cocaine's aversive effects. For example, if aversions induced by cocaine were significantly greater in one sex than the other, it might be more difficult to potentiate the stronger aversions by alcohol (due to floor effects). Conversely, if alcohol-induced

aversions were greater in one sex than the other, it might be more likely that alcohol could affect cocaine-induced aversions (given its relative intensity). Several issues argue against these possibilities. First, there were no sex differences in cocaine-induced aversions for either strain. Further, alcohol was ineffective as an aversion-inducing agent for any sex or strain. Thus, it is unlikely that sex differences in the sensitivity to the aversive effects of either cocaine or alcohol impacted the ability of alcohol to potentiate cocaine-induced aversions. It is certainly possible that had other dose combinations been used, potentiation may have been evident, e.g., Busse et al. (2005) has reported that under different parametric conditions male Sprague–Dawley rats display greater cocaine-induced taste aversions than do female Sprague–Dawley rats. However, under the present conditions, such differences were not evident.

In the context of the cocaine/alcohol combination, it may be possible that female Long–Evans rats are more sensitive to the aversive effects of the combination than the other sex and strains. Although possible, again there is little experimental evidence to support such an assumption. Most research examining the overall aversiveness (and toxicity) of cocaine/alcohol combinations do so in male and female mice of a single strain (Hearn et al., 1991; Meehan and Schechter, 1995; Schechter and Meehan, 1995) and generally report greater toxicity in males than females (though see Boyer and Petersen, 1990). In addition to these findings, lethality to cocaethylene has been reported to be greater in male Long–Evans (compared to females of the same strain; see Sobel et al., 1998). Thus, it remains unknown whether the potentiating effects of alcohol on cocaine-induced taste aversions in female Long–Evans are a product of a greater sensitivity to the aversiveness of the combination in this specific sex and strain.

Another possibility that may explain the specificity of the cocaine/alcohol effect in female Long–Evans is that estrogen levels may have altered the sensitivity to the aversive effects of this drug combination in these rats. In fact, sensitivity to cocaine has been shown to vary throughout the rat estrous cycle (Haney et al., 1994; Roberts et al., 1989; Sircar and Kim, 1999). Although, the current study did not control for the female estrous cycle, the failure to find a potentiation of cocaine aversions in the female Sprague–Dawley rats makes this an unlikely explanation.

Interestingly, it has also been reported that under some conditions, cocaine/alcohol combinations are more rewarding (and/or less aversive) than either drug alone (see Cook et al., 1998; Grant and Harford, 1990; Knackstedt and Ettenberg, 2005; Magura and Rosenblum, 2000; McCance-Katz et al., 1998; Wiseman and McMillan, 1996). For instance, Lewis and June (1994) reported that within the intracranial self-stimulation (ICSS) design alcohol potentiated cocaine's ability to lower the threshold for brain stimulation in male albino rats, indicative of an increase in cocaine reward (see also Moolten and Kornetsky, 1990). Further, in a recent report by Knackstedt and Ettenberg (2005), rats (male, Sprague–Dawley) were trained with intravenous (IV) cocaine to run to a goal box at the end of a runway apparatus. Animals displayed approach–avoidance behaviors (a suggested index of anxiety) before entering the goal box. The administration of alcohol after training sessions reduced the number of retreats animals displayed on these tests. Such an effect was interpreted as a weakening of the anxiogenic effects of cocaine by alcohol (see also McCance-Katz et al., 2005). Thus, in the sex and strains that failed to show the potentiated aversion, alcohol may actually be potentiating cocaine reward and/or lessening its anxiogenic effects. If this occurred in male Long–Evans or male and female Sprague–Dawley rats, the increase in cocaine's rewarding effects by alcohol may have offset (or masked) any effect that alcohol had on cocaine-induced taste aversions. Although this may account for why male Long–Evans rats and both male and female Sprague–Dawley rats failed to display potentiated taste aversions, it would provide no basis for the potentiation in females. Further, the lack of specific sex and strain comparisons in the increase in the rewarding effects of cocaine with concurrent alcohol administration precludes a critical evaluation of this possibility. It is important to note that when males and females have been compared for their relative sensitivities to the reinforcing effects of cocaine alone (as measured by self-administration), females appear to find cocaine more reinforcing than do males, a finding inconsistent with the above-mentioned position (Lynch and Carroll, 1999; Roth and Carroll, 2004).

Sex and strain interactions have been reported with cocaine (Boyer et al., 1988; Cailhol and Mormede, 1999; Hain et al., 2000; Matulka et al., 1996; Morse et al., 1995; Watanabe et al., 1988), alcohol (Cailhol and Mormede, 2001; Cannon and Carrell, 1987; Finn et al., 2004; Sarviharju et al., 2001) and combinations of alcohol and cocaine (Cook et al., 1998). The present data indicate that these effects extend to measures sensitive to the affective properties of cocaine/alcohol combinations. Given the prevalence of cocaine/alcohol co-use in the general public (see Grant and Harford, 1990), continued investigation into these specific interactions of sex and strain may provide important information about genotype-based differences in drug abuse susceptibility.

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