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Ethanol Modulates Cocaine-Induced Behavioral Change in Inbred Mice

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COOK, M. N., D. D. WARE, E. M. BOONE, X. HOU, A. C. MORSE, C. L. REED, V. GENE ERWIN AND BYRON C. JONES. *Ethanol modulates cocaine-induced behavioral change in inbred mice.* PHARMACOL BIOCHEM BEHAV **59**(3) 567–575, 1998.—We recently conducted a study of the behavioral effects of combined cocaine and ethanol in genetically defined mice. Male and female C57BL/6 (B6) and DBA/2 (D2) were tested in an automated activity monitor on 2 consecutive days. On day 1, all animals received an IP injection of sterile saline and were placed into the activity monitor for 30 min. Behaviors measured were total distance traveled, stereotypy, nosepokes, and wall-seeking. On day 2, all animals were tested again for 15 min following injection of one of the following: saline, 10% v/v ethanol at 2.0 g kg^{-1} or 2.0 g kg^{-1} ethanol plus 5, 15, or 30 mg kg^{-1} cocaine. Cocaine alone at the same doses was injected into separate groups of animals. For the B6 strain, the overall effect of ethanol was to reduce cocaine-induced locomotor stimulation; no consistent effect of ethanol on cocaine-induced locomotion was observed in D2 mice. Cocaine-induced inhibition of nosepokes in both strains and sexes was partially reversed by ethanol. Ethanol also partially reversed cocaine-elevated stereotypy in both strains and both sexes. In B6 mice, cocaine-increased wall seeking tended to be reversed by coadministration of ethanol, whereas no consistent pattern was observed in the D2s. Results from this study suggest that the several measures affected by cocaine (locomotor activity, stereotypy, exploration, thigmotaxis) were, in turn, differentially affected by concurrent treatment with ethanol. Furthermore, our results point to genetic-based differences in ethanol's effects on cocaine-related behaviors. We address the implications for combined ethanol and cocaine use in humans. © 1998 Elsevier Science Inc.

Ethanol Cocaine Inbred mice Behavior Pharmacogenetics

COCAINE misuse has become one of the most salient public health problems in North America. This is believed to be due to its euphoric, psychostimulatory, and reinforcing effects. For example in humans, cocaine produces reported subjective effects related to euphoria and well-being (17). Cocaine's stimulatory effects are well known, and people will go to great lengths to procure this drug. Moreover, humans are not alone in their avidity for cocaine. Nonhuman primates will self-administer cocaine intravenously (IV) and maintain rates of operant responding for IV cocaine (3). Cocaine is also self-administered by rodents with routes of administration ranging from intracranial (21) to intravenous (25) to oral (24,39). Locomotor activation by cocaine in rodents is believed to be related to its putative rewarding effects (51) and, depending upon the dose administered, cocaine does produce locomotor stimulation effects in rodents (29,31). At lower doses, however, cocaine may produce locomotor depressant effects (19).

Among humans, multiple drug use may be the rule rather than the exception. For example, it is commonly reported that persons who use cocaine take it in combination with alcohol (22). Moreover, the public health concern of the combined use of cocaine and ethanol is indicated from the pharmacological perspective of cocaine and ethanol when taken together being metabolized to form cocaethylene (8,23,26). Cocaine and its ethanol-derived metabolite, cocaethylene, have been shown to produce qualitatively similar psychomotor stimulant

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effects (31), and the combination of cocaine and ethanol has been shown to increase cocaine-induced euphoria (17,36). It may also be that alcohol is often taken to mask or otherwise offset possible aversive effects of cocaine. Indeed, cocaine has been shown to have anxiogenic effects in mice (6,52). To date, there have been few studies investigating the effects of simultaneously administered ethanol and cocaine. A recent study by Masur and co-workers, however, showed that ethanol and cocaine combined additively to increase locomotor activity in male outbred Swiss mice (35). This finding is among the first to demonstrate a behavioral effect of the combined administration of cocaine and ethanol in animals.

Individual differences, in sensitivity to, and liability for, ethanol misuse among humans have been linked to genetic makeup (5,47). However, genetic correlates of cocaine or other illicit drug misuse are not well known. Animal research using inbred strains and selected lines of mice and rats show that for most phenotypes used to model human alcohol sensitivity and use, the genetic influence is polygenic and not a collection of single gene effects. This has been shown, for example, for hypnotic sensitivity to ethanol (9) locomotor activation by ethanol (14) and ethanol consumption (13). Recent studies have demonstrated genetic-based differential sensitivity to the locomotor activating effects of cocaine (7,27,29,45,49) and cocaine self-selection in mice (27,29). For a review of the genetics of cocaine, see Morse et al. (41). Pharmacogenetic studies examining the separate effects of ethanol and cocaine have characterized differences between the C57BL6(B6) and DBA/2 (D2) inbred mouse strains. For example, D2 mice show greater locomotor activation by 15 mg kg^{-1} cocaine than do the B6s, and the latter consume more of a dilute cocaine solution (29). D2s are also stimulated to greater locomotor activity by low doses of ethanol (e.g., 1–3 g kg^{-1}), whereas B6s are usually not significantly stimulated by these same doses of ethanol (12). By contrast, B6s are well known for their appetite for alcohol and D2s for their near total aversion to ethanol (37,38,44).

The importance of combining genetic differences and multiple measures in animal models of polydrug use is indicated from the public health perspective. Because of the increased awareness of the combined use and effects of cocaine and ethanol in humans, there is a need to develop a suitable animal model to study polydrug misuse. Because the B6 and D2 strains are so well studied in this regard, we believe the use of these strains is an appropriate starting point for investigating possible individual differences in polydrug misuse. Finally, other studies suggest that genetically defined animals may prove useful in identifying the mechanisms of cocaine's behavioral effects (48). This is particularly true for the B6 and D2 strains because, from these progenitors, a panel of 25 recombinant inbred strains have been derived. These strains are the best mapped for chromosomal polymorphisms and are suitable for genetic correlational analysis. Future work in recombinant inbred strains will lead to the identification of candidate genes that influence cocaine–ethanol interactions.

We have started this research building on the methods of Masur et al. (35), by adding genetic definition and multiple measures. Based on Masur's findings of an additive effect of cocaine and ethanol and the observations of others (12) that D2s are stimulated by 2.0 g kg^{-1} ethanol, we expected to find an additive, stimulatory effect of cocaine and ethanol in this strain. Alternatively, B6s are not typically activated at any dose of ethanol; therefore, we did not expect to find an additive effect of ethanol and cocaine in this strain. Locomotor activity, by itself, may provide an incomplete picture of cocaine-ethanol interactions; therefore, because cocaine has effects on exploration and anxiety, we employed a method in which we could investigate these measures simultaneously. If, therefore, cocaine has both attractive and aversive properties, multiple behaviors measured simultaneously can help in teasing these effects apart and provide a more informative base for investigating the influence of ethanol on cocaine behaviors. Recent work in our laboratory (unpublished data) suggest sex-related differences in neurobiological effects of cocaine. We found that cocaine differentially affected dopamine levels and dopamine utilization (HVA/DA) in male and female mice. Because locomotion and other behaviors of interest are mediated through one or several dopamine systems, we were interested in whether the behavioral effects of cocaine also show sex-related differences. We, therefore, included both male and female animals. We report the effects of combined cocaine and ethanol on several behavioral measures in genetically defined animals.

METHOD

Subjects

Male and female mice from two inbred strains, C57BL/6 (B6) and DBA/2 (D2) were used in this study. All animals were reared in our laboratory, weaned between 21 and 23 days of age, and reared in same-sex groups of four to five until the time of testing at 60 to 80 days of age. Ten male and female mice were assigned to each of the treatment conditions, and siblings were assigned to different treatment conditions. Ambient temperature and humidity were maintained at 21 $\pm$ 2°C and 25%, respectively. Mice were maintained on laboratory chow and water ad lib on a 12 L:12 D rotation (0600–1800 h).

Drugs

Absolute ethanol was diluted in sterile saline to make a 10% v/v solution suitable for intraperitoneal (IP) injection. Cocaine as the HCl salt (provided courtesy of NIDA) was prepared also for IP injection using either sterile saline or 10% ethanol–saline solution as solvent for 5, 15, or 30 mg kg^{-1} doses.

Activity Monitor Testing

At 60–80 days of age mice were tested on 2 consecutive days for locomotor activity, stereotypy, nosepokes, and time spent near the margin in an automated activity monitor (Ominitech, Inc., Columbus, OH). The Digiscan® activity monitor is a 40 $\times$ 40 $\times$ 30.5 cm acrylic cage with vertical and horizontal infrared sensors. The flooring is an elevated acrylic platform with 16 equally spaced holes (4 $\times$ 4 approximately 1.4 cm in diameter). Behaviors monitored were total distance traveled (cm), stereotyped movements, nosepokes (a putative measure of exploratory behavior), and margin time (thigmotaxis or wall seeking, a putative measure of fear) recorded in successive 5-min intervals. The Digiscan measure of stereotypy is defined as episodes of breaking the same beam pattern repeatedly. Automated measurement of these behaviors has been validated and shown to be highly correlated with visual observations of stereotypy (46).

Experiment 1: Saline–Ethanol

On day 1, animals were given an intraperitoneal (IP) injection of sterile 0.9% saline and were placed into the activity monitors for 30 min. On day 2, animals were tested again, but for 15 min following an IP injection of 2.0 g kg^{-1} ethanol.

Experiment 2: Saline–Cocaine vs. Saline–Cocaine plus Ethanol

On day 1, animals were given an IP injection of sterile 0.9% saline and were placed into the activity monitors for 30 min. On day 2, animals were tested again, but for 15 min following an IP injection of either 5, 15, or 30 mg kg^{-1} cocaine. A separate group of animals was treated the same; however, on day 2 they were injected IP with a cocktail of EtOH (2.0 g kg^{-1}) and cocaine at one of the three doses of 5, 15, or 30 mg kg^{-1}.

Others have shown that exposure to novelty increases locomotor activity (2). We and others have shown differential effects of administering cocaine or ethanol in a novel vs. familiar environment (27,30,34). For example, Jones et al. (27) showed that cocaine administered in a novel environment diminished locomotor activation compared to cocaine administered in a familiar environment. For these reasons, all of our subsequent studies (29) have employed the method of administering saline on day 1 and cocaine on day 2 and in the same environment.

Data Analysis

Experiment 1: saline–ethanol. Statistical analysis of behavioral data was performed using analysis of variance (ANOVA) for a two between-subjects (strain, sex) and one within-subjects variables (day) experiment.

Experiment 2: saline–cocaine vs. saline–cocaine plus ethanol. Statistical analysis of behavioral data was performed using analysis of variance for a four between-subjects (strain, sex, dose, drug combination) and one within-subjects variables (day) experiment.

To bring the cocaine vs. cocaine plus ethanol results into sharper focus and for ease of graphic presentation, means for behavioral effects of cocaine alone and in combination with ethanol were adjusted by analysis of covariance, using saline scores as the covariate. This was done primarily because of the moderate to high correlations between saline and drug values for locomotion, nosepokes, stereotypy, and margin time ($r = 0.84, 0.75, 0.73, 0.28$, respectively, $p < 0.001$ for all). Also, with such correlations between baseline and treatment values, means so adjusted may present a clearer picture than difference or percent change scores.

Post hoc tests, where appropriate, were performed using Dunnett's *t*-test or the Tukey HSD method.

RESULTS

Experiment 1: Saline–Ethanol

Table 1 presents raw means for behaviors in the activity monitor by B6 and D2 mice after saline (day 1) or after ethanol (2.0 g kg^{-1}) injection (day 2).

Locomotion. ANOVA revealed a significant strain by treatment interaction, $F(1, 36) = 21.844.50$, $p < 0.001$. The overall effect of ethanol was to increase locomotor activity in D2 mice.

Nosepokes. Overall, ethanol increased nosepoke activity, $F(1, 36) = 25.15$, $p < 0.0002$. The significant interaction, among strain, sex and treatment $F(1, 36) = 9.83$, $p < .005$ was accounted for by the B6 females, unlike the other groups, not responding to ethanol.

Stereotypy. Analysis of variance revealed a significant strain difference in stereotyped movements. Overall, B6 mice displayed more stereotyped movements than D2 mice, $F(1, 36) = 15.84$, $p < 0.005$. A significant treatment effect was also observed. Ethanol decreased the number of stereotyped movements, $F(1, 36) = 21.65$, $p < 0.0002$. The significant interaction between strain and treatment $F(1, 36) = 11.84$, $p < 0.005$, was accounted for by a greater ethanol effect in the B6 than D2 mice.

TABLE 1

RAW MEANS FOR LOCOMOTOR ACTIVITY, NOSE POKES IN A HOLE BOARD, STEREOTYPY, AND WALL SEEKING IN THE OPEN FIELD IN THE ACTIVITY MONITOR BY B6 AND D2 MICE AFTER SALINE (DAY 1) OR AFTER ETHANOL (2.0 g kg^{-1}) INJECTION (DAY 2)

	Saline	Ethanol (2.0 g/kg)
Mean Total Distance (cm) ± SEM		
C57BL/6		
Male	3852.20 ± 377.15	3990.30 ± 475.31*
Female	3725.20 ± 234.27	2905.00 ± 311.24*
DBA/2		
Male	4391.40 ± 313.85	6276.50 ± 830.59*
Female	3658.80 ± 253.77	5749.80 ± 435.04
Mean Nosepokes ± SEM		
C57BL/6		
Male	28.30 ± 4.72	46.70 ± 6.19*
Female	32.00 ± 5.87	33.70 ± 6.04*
DBA/2		
Male	16.60 ± 2.50	24.30 ± 5.96
Female	18.00 ± 2.91	40.40 ± 5.45*
Mean Stereotypy ± SEM		
C57BL/6		
Male	95.30 ± 13.08	65.50 ± 13.85
Female	85.50 ± 6.77	45.20 ± 7.77*
DBA/2		
Male	47.90 ± 5.90	35.40 ± 6.02
Female	40.50 ± 6.48	42.50 ± 7.85
Mean Margin Time (s) ± SEM		
C57BL/6		
Male	796.80 ± 15.34	812.90 ± 9.81
Female	808.60 ± 9.64	815.20 ± 13.59
DBA/2		
Male	773.70 ± 8.42	803.80 ± 19.36
Female	808.10 ± 8.021	808.20 ± 8.79

*$p < 0.05$.

Margin time. ANOVA revealed no significant effect of strain, sex, or ethanol on this measure.

Experiment 2: Saline–Cocaine vs. Saline–Cocaine Plus Ethanol

Table 2 presents raw means for the behaviors following saline (day one) or each of the three doses of cocaine (day 2). Table 3 presents raw means for the behaviors following saline (day one) or cocaine at the three doses combined with ethanol (day 2).

Locomotion. Analysis of variance revealed a significant strain difference in locomotion; D2 mice evinced more locomotor activity than B6 mice, $F(1, 223) = 70.19$, $p < 0.0001$. A significant strain by dose interaction, $F(2, 223) = 6.32$, $p < 0.0021$ was also observed. Locomotor activity peaked at 15 mg kg^{-1} in B6 mice, whereas D2 mice showed an increase in locomotion across all doses. D2 mice, furthermore, showed greater cocaine-induced locomotion than B6 mice at all doses. Overall, locomotor activation by cocaine was reduced by ethanol in B6s; however, inspection of Figure 1 shows that the greatest effect was at 15 mg kg^{-1} ($p < 0.05$). Modest increases

TABLE 2

RAW MEANS FOR LOCOMOTOR ACTIVITY, NOSEPOKES IN A HOLE BOARD, STEREOTYPY, AND WALL SEEKING IN THE OPEN FIELD FOLLOWING SALINE (DAY 1) OR EACH OF THE THREE DOSES OF COCAINE (DAY 2)

	Saline	Cocaine (5 mg/kg)	Cocaine (15 mg/kg)	Cocaine (30 mg/kg)
Mean Total Distance (cm) ± SEM				
C57Bl/6				
Male	3697.53 ± 127.20	4570.10 ± 413.61	9370.20 ± 508.57*	7956.75 ± 759.37*
Female	4110.81 ± 160.57	4791.46 ± 402.33	9109.80 ± 993.93*	8363.36 ± 721.95*
DBA/2				
Male	3488.03 ± 201.32	5671.20 ± 676.05*	11136.90 ± 934.74*	11375.00 ± 647.02*
Female	4250.49 ± 154.82	8644.42 ± 603.41*	9796.20 ± 1151.21*	13539.18 ± 814.83*
Mean Nosepokes ± SEM				
C57Bl/6				
Male	21.34 ± 4.57	24.10 ± 4.36	18.40 ± 5.87	23.08 ± 7.66
Female	27.69 ± 2.54	38.00 ± 5.85	18.90 ± 6.35	19.55 ± 13.40
DBA/2				
Male	14.63 ± 1.75	5.70 ± 1.31	5.40 ± 1.53	4.60 ± 0.85
Female	17.27 ± 2.30	21.92 ± 7.04	8.10 ± 2.68	3.36 ± 0.98
Mean Stereotypy ± SEM				
C57Bl/6				
Male	116.72 ± 4.57	102.40 ± 8.86	163.60 ± 7.19*	165.08 ± 8.43*
Female	116.34 ± 4.71	112.27 ± 7.046	152.60 ± 9.96	133.55 ± 13.40
DBA/2				
Male	65.53 ± 4.24	97.60 ± 10.20	124.00 ± 11.67	136.20 ± 14.90*
Female	73.42 ± 4.62	104.33 ± 11.31	132.20 ± 14.97*	147.91 ± 14.34*
Mean Margin Time (s) ± SEM				
C57Bl/6				
Male	795.94 ± 5.97	852.20 ± 10.98	844.40 ± 9.061	837.58 ± 11.26
Female	802.72 ± 5.47	820.27 ± 8.19	838.10 ± 8.31	828.91 ± 16.95
DBA/2				
Male	788.67 ± 9.33	828.90 ± 14.32	824.30 ± 13.47	798.80 ± 19.79
Female	793.76 ± 6.27	817.50 ± 12.01	814.40 ± 14.64	800.18 ± 27.01

*$p < 0.05$.

($p < 0.05$) by ethanol of cocaine-induced locomotor activation at 5 and 30 mg kg^{-1} were observed in the D2 strain.

Nosepokes. A significant strain difference for this measure was observed. B6 mice displayed more nosepoke activity than D2 mice, $F(1, 223) = 62.56$, $p < 0.0001$. Overall, cocaine tended to decrease nosepokes, $F(2, 223) = 2.59$, $p < 0.07$ and, as illustrated in Figure 2, the addition of ethanol to the cocaine treatment increased nosepokes, compared to cocaine alone $F(1, 223) = 31.07$, $p < 0.0001$.

Stereotypy. Analysis of variance revealed a significant strain difference in the number of stereotyped movements, $F(1, 223) = 78.44$, $p < 0.0001$. B6 mice displayed more stereotypies than D2 mice. A significant effect of dose was also observed, $F(2, 223) = 22.89$, $p < 0.0001$. Cocaine increased stereotyped movements in a dose-dependent fashion. Dunnett's *t*-test revealed that at 15 and 30 mg kg^{-1} cocaine, the increased stereotypy was significant for both strains ($p < 0.05$). We also observed a significant drug by dose interaction, $F(2, 223) = 3.85$, $p < 0.03$. Tukey's HSD revealed that ethanol significantly reduced cocaine-induced stereotypies at 15 mg kg^{-1} in B6 mice and D2 females and at 30 mg kg^{-1} in D2 female mice. This effect is illustrated in Figure 3.

Margin time. There was no overall strain effect in this measure (Figure 4), however, there was a trend for a sex effect for this measure, $F(1, 223) = 3.52$, $p < 0.062$. Males tended to spend more time near the margin than females. A significant strain by drug interaction was observed, $F(1, 223) = 3.75$, $p < 0.05$. The effect was for ethanol to reduce wall-seeking, compared to cocaine in B6 mice, with inconsistent effects in D2 mice.

DISCUSSION

Upon review of the effects of ethanol and cocaine given separately on the activity measures in this study, we observed essentially what we expected in terms of differences between the subject strains. In general, B6s were less activated by both ethanol and cocaine than were the D2s. This finding is in agreement with other findings from our laboratory (29,39) as well as with findings by others (12,48).

In contrast with the Masur et al. study (35), ethanol did not produce notable increases in cocaine-induced hyperlocomotion. In fact, at 15 mg kg^{-1}, ethanol decreased locomotor activation by cocaine in B6 males and females while the effect in D2 mice was minimal. Exactly why we failed to replicate Masur's findings is not known; however, the 2-day test regimen may have contributed to this by reducing the effect of administering drugs in a novel environment. Among others, two possibilities for not replicating Masur's findings exist: 1) although we built upon the methods of Masur and co-workers, our study used two inbred strains of mice, whereas the Masur study used genetically heterogeneous Swiss mice. Genetic dif-

TABLE 3

RAW MEANS FOR LOCOMOTOR ACTIVITY, NOSEPOKES IN A HOLE BOARD, STEREOTYPY, AND WALL SEEKING IN THE OPEN FIELD FOLLOWING SALINE (DAY 1) OR COCAINE AT THE THREE DOSES COMBINED WITH ETHANOL (DAY 2)

	Saline	Ethanol plus Cocaine (5 mg/kg)	Ethanol plus Cocaine (15 mg/kg)	Ethanol plus Cocaine (30 mg/kg)
Mean Total Distance (cm) ± SEM				
C57Bl/6				
Male	3650.25 ± 136.18	4998.00 ± 365.47	6186.20 ± 632.08	6967.10 ± 981.67*
Female	3894.25 ± 139.88	5093.60 ± 49.37	5573.60 ± 546.32	8558.50 ± 783.12*
DBA/2				
Male	4118.50 ± 165.81	8701.00 ± 727.85*	10362.60 ± 812.66*	13125.10 ± 1828.45*
Female	3914.85 ± 156.95	7322.00 ± 602.37*	9156.40 ± 1020.85*	15566.10 ± 1968.80*
Mean Nosepokes ± SEM				
C57Bl/6				
Male	29.05 ± 2.42	43.90 ± 7.77	39.70 ± 5.58	48.10 ± 12.52
Female	32.58 ± 2.79	48.00 ± 7.12	49.80 ± 10.39	37.20 ± 5.15
DBA/2				
Male	17.68 ± 1.92	19.10 ± 3.63	17.10 ± 4.11	15.70 ± 3.73
Female	19.45 ± 2.24	31.40 ± 7.21	20.20 ± 3.16	17.50 ± 5.97
Mean Stereotypy ± SEM				
C57Bl/6				
Male	96.63 ± 4.57	107.90 ± 11.48	100.90 ± 11.86	124.90 ± 13.09
Female	93.53 ± 4.30	88.00 ± 14.46	86.40 ± 11.56	108.70 ± 14.67
DBA/2				
Male	51.78 ± 3.98	69.20 ± 11.73	83.20 ± 12.26	88.00 ± 18.07
Female	46.63 ± 4.49	63.50 ± 9.48	73.10 ± 13.09	74.00 ± 16.93
Mean Margin Time (s) ± SEM				
C57Bl/6				
Male	803.05 ± 7.05	816.60 ± 6.59	822.00 ± 23.81	815.60 ± 11.42
Female	804.65 ± 5.76	811.40 ± 11.44	823.00 ± 7.09	830.50 ± 9.92
DBA/2				
Male	788.93 ± 4.88	826.10 ± 11.40	831.60 ± 12.29	830.40 ± 14.45
Female	795.88 ± 5.04	809.60 ± 8.44	822.30 ± 8.44	794.90 ± 17.56

*$p < 0.05$.

ferences, therefore, may account for some of the differences in findings, as genetic makeup has a profound effect on sensitivity and response to drugs of abuse. 2) Prior experience in the testing apparatus and drug experience may also influence locomotor activity. This has been shown previously for ethanol (34) and for low doses of cocaine (40); however, this may not be the case for higher doses of cocaine (27). Furthermore, in humans, the order of drug administration has been shown to influence the interactive effects between ethanol and cocaine (43). Masur and her co-workers (35) administered ethanol followed by cocaine, whereas we administered the two simultaneously. The extent to which this temporal difference in administration may have affected the interactive effects of ethanol and cocaine in mice is unclear at this time.

The other measures also showed influences of ethanol on cocaine-related behaviors. Ethanol coadministration partially reversed both the cocaine-induced decreases in nosepokes and increases in stereotyped movements. Consistent with our earlier findings (29), cocaine increased thigmotaxis in B6 and in the present study, ethanol tended to reverse this effect in B6 mice.

Based on this study and those of others, cocaine appears to have a multiplicity of behavioral effects, including those that may be judged to be attractive, for example, self-administration, locomotor activating, and those that may be judged to be aversive, for example, increased thigmotaxis, stereotypy, reduction in exploration. Whether humans or animals are attracted to or repulsed by cocaine is likely determined by the sum of these properties, and based upon the extent to which sensitivity to these attractive/aversive properties is influenced by genetic background. In this study, ethanol appeared to have minimal effects on locomotor activating effects of cocaine, but somewhat more prominent influence on coaine's effects on exploration and stereotypy. An earlier study showed cocaine to reduce the anxiolytic effects of ethanol in rats (1), a finding that complements the present results.

The strain differences in behavioral response to combined cocaine and ethanol may have important implications for individual differences in response to the separate and combined effects of these drugs in humans. For example, genetic makeup has been shown to contribute to differential sensitivity to cocaine (19,20,28,29,39,45). Cocaine is known to inhibit monoamine neurotransmitter reuptake, particularly dopamine (11,32). Furthermore, genetic differences in the activity of dopamine systems, i.e., target tissue sensitivity have been reported (29). Among them, differences in dopamine receptor densities (4) and binding affinities (15,27). Other researchers have reported genetic differences in dopamine neuron sensitivity to the stimulant effect of ethanol (16,50). Furthermore, it has been suggested that inherited or acquired factors,

through their effects on dopamine networks, may predispose individuals to drug abuse (10). Like many psychostimulant drugs, cocaine has sympathomimetic properties that can influence affective responses to situations. If, for example, one

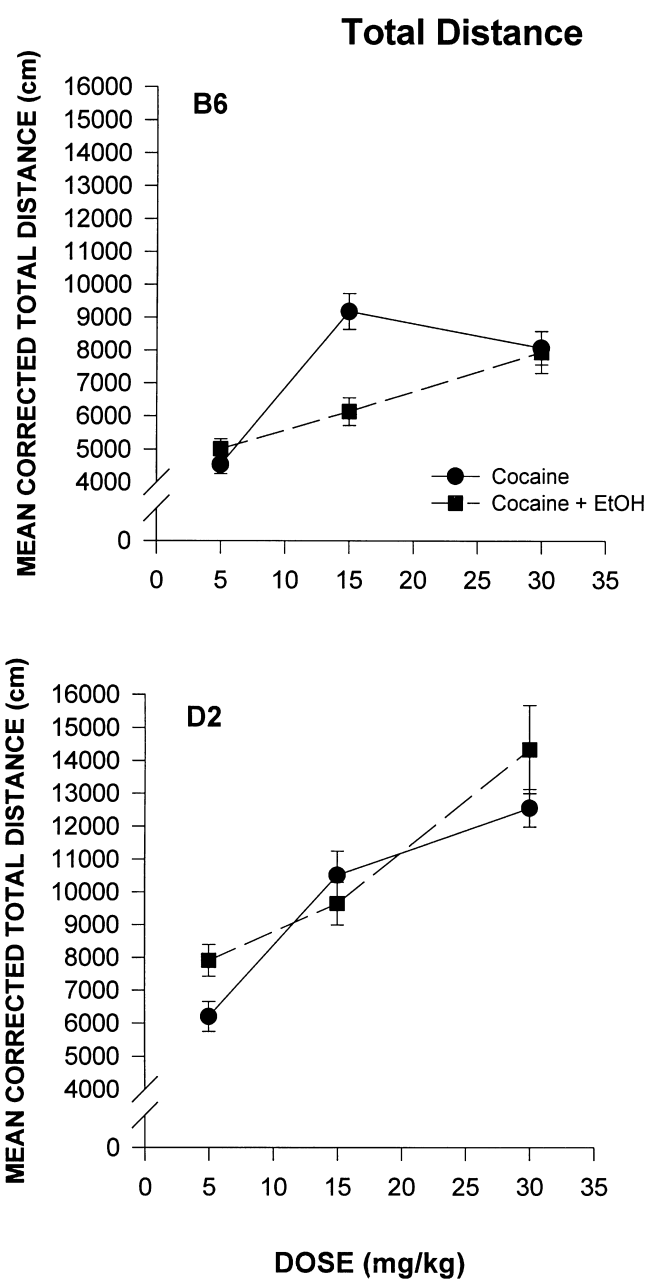

FIG. 1. Dose–response effects of cocaine and cocaine in combination with ethanol on locomotor activity. Animals tested were male and female C57BL/6 and DBA/2 mice at 5, 15, 30 mg kg^{-1} cocaine or these same doses of cocaine in combination with ethanol. All animals were tested on 2 consecutive days with saline treatment on day 1 and drug treatment on day 2. The numbers of animals tested were 10 for each sex and strain in each dose condition. Scores are presented as mean scores ± SEM, adjusted for saline by analysis of covariance.

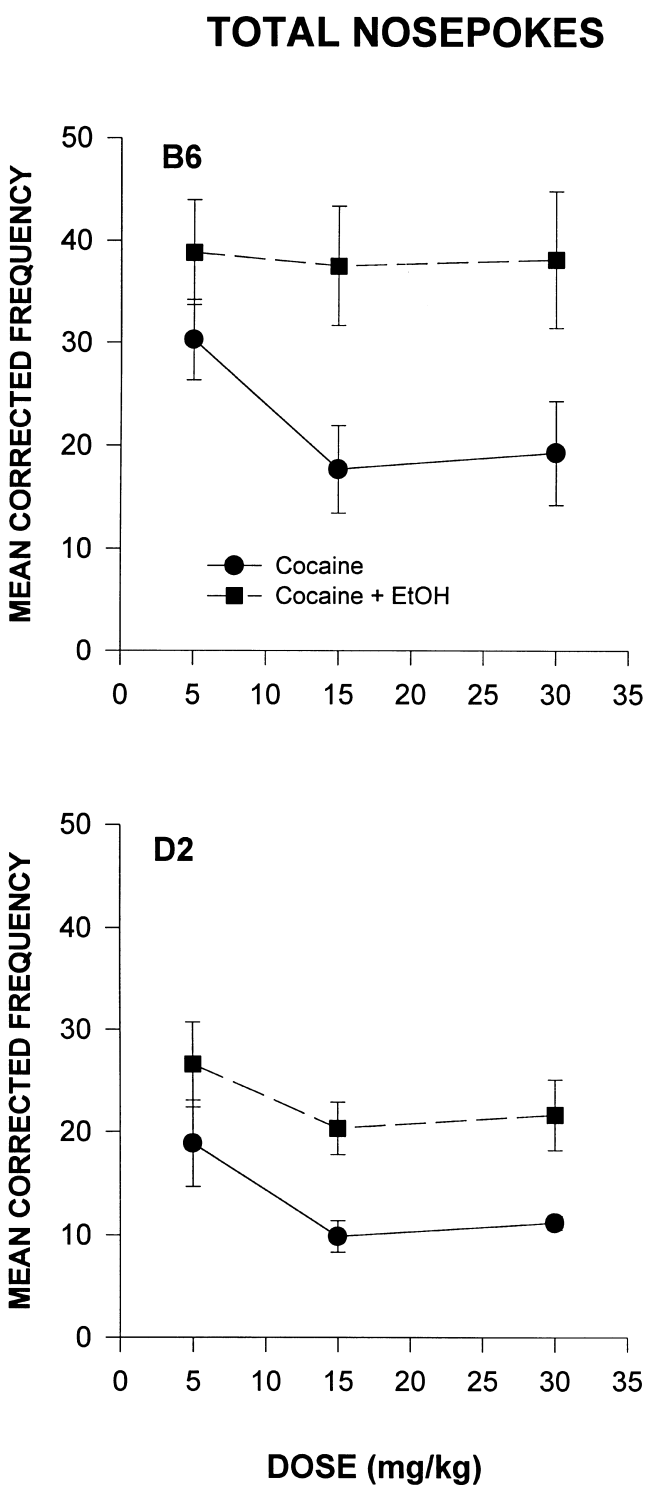

FIG. 2. Dose–response effects of cocaine and cocaine in combination with ethanol on nosepokes. Animals tested were male and female C57BL/6 and DBA/2 mice at 5, 15, 30 mg kg^{-1} cocaine or these same doses of cocaine in combination with ethanol. All animals were tested on 2 consecutive days with saline treatment on day 1 and drug treatment on day 2. The number of animals tested were 10 for each sex and strain in each dose condition. Scores are presented as mean scores ± SEM, adjusted for saline by analysis of covariance.

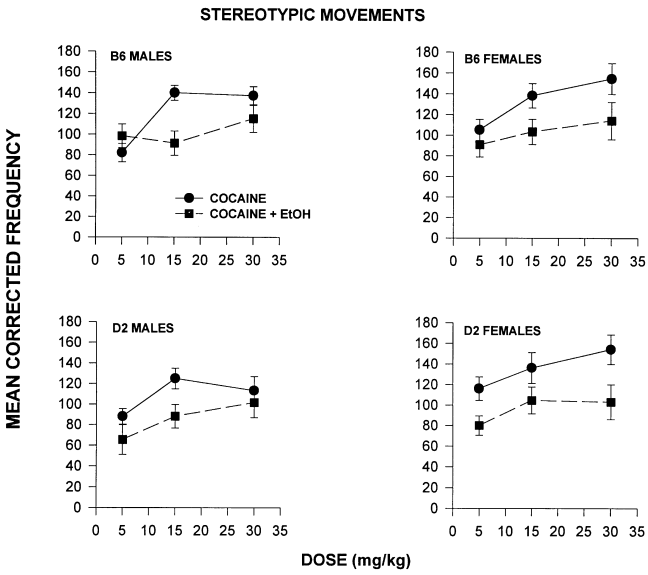

FIG. 3. Dose–response effects of cocaine and cocaine in combination with ethanol on stereotypy. Animals tested were male and female C57BL/6 and DBA/2 mice at 5, 15, 30 mg kg^{-1} cocaine or these same doses of cocaine in combination with ethanol. All animals were tested on 2 consecutive days with saline treatment on day 1 and drug treatment on day 2. The number of animals tested were 10 for each sex and strain in each dose condition. Scores are presented as mean scores ± SEM, adjusted for saline by analysis of covariance.

were to have a low to moderately stimulated sympathetic nervous system (SNS), subjective reports may include terms indicative of euphoria. If, on the other hand, the SNS were to be highly activated, the subjective reports may now include terms indicative of dysphoria. It may be that people use alcohol to moderate self-perceived anxiety following cocaine-induced SNS activation and thus shift the balance from more aversive, anxiogenic properties to enhance the more attractive properties of cocaine. Others have suggested that combined effects of ethanol and cocaine may be the result of the actions of both drugs on common neuronal substrates (33,42). Finally, it has been suggested that the interactive effects of cocaine and ethanol are subtle and require further study (18). We are currently examining the neurobiological effects of combined cocaine and ethanol in the B6 and D2 mouse strains. The present study, in addition to ones in progress, may aid in our understanding the etiology and consequences of combined cocaine and ethanol use.

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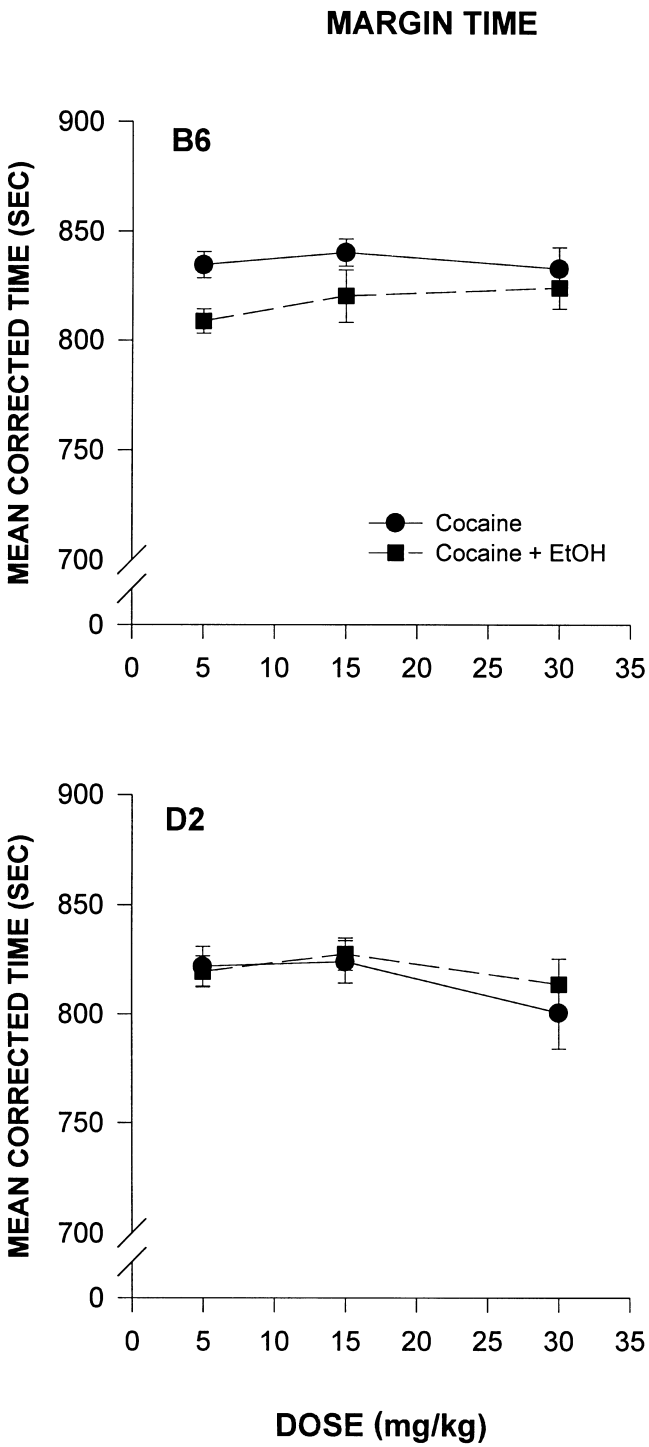

FIG. 4. Dose–response effects of cocaine and cocaine in combination with ethanol on wall seeking. Animals tested were male and female C57BL/6 and DBA/2 mice at 5, 15, 30 mg kg^{-1} cocaine or these same doses of cocaine in combination with ethanol. All animals were tested on 2 consecutive days with saline treatment on day 1 and drug treatment on day 2. The number of animals tested were 10 for each sex and strain in each dose condition. Scores are presented as mean scores ± SEM, adjusted for saline by analysis of covariance.

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