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Intravenous ethanol/cocaine self-administration initiates high intake of intravenous ethanol alone

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Abstract

Evidence suggests that ethanol (EtOH) preexposure influences the rewarding valence of subsequent EtOH use. This study was conducted to determine if EtOH preexposure through EtOH/cocaine self-administration facilitates the motivational effects of EtOH alone. Rats self-administered intravenous (iv) EtOH/cocaine combinations (EtOH/Cocaine Fading group; EtOH 125.0 mg/kg/inj + Cocaine 0.1–0.75 mg/kg/inj) during a preexposure period. Consequently, these rats self-administered intravenous EtOH alone (62.5, 125.0, 250.0 and 500.0 mg/kg/inj) significantly more than a control group with prior cocaine self-administration experience (0.1–0.75 mg/kg/inj). In addition, at equal EtOH intake levels, locomotor activity was significantly enhanced in the EtOH/Cocaine Fading group but not the Cocaine Control animals (P=.01). The amount of EtOH self-administered in the EtOH/Cocaine Fading group during 1-h sessions ($\approx$0.5–2.0 g/kg) corresponded with blood alcohol levels (BAL) ranging from 44 to 221 mg/dl. The highest BALs reported here have not previously been demonstrated after voluntary EtOH intake through any route of administration. These data suggest that preexposure to EtOH during EtOH/cocaine self-administration sessions modified neural substrates underlying both the reinforcing and locomotor responses to EtOH alone. Further studies utilizing intravenous EtOH self-administration will allow identification of various long-term behavioral and neural consequences of voluntary high EtOH intake.

Keywords: Ethanol preexposure; Intravenous ethanol; Ethanol-induced hyperlocomotion; Ethanol/cocaine combinations; Ethanol self-administration

1. Introduction

A continuum of neurobiological changes, ranging from neuroadaptation to neuropathology and neurodegeneration, has been shown to result from chronic ethanol (EtOH) consumption. It is well documented that neurobiological alterations are induced after high levels of experimenter-administered EtOH (Diana et al., 1992; Gil et al., 1992; Spencer and McEwen, 1997; Fadda and Rossetti, 1998; Gallegos et al., 1999; Mittal et al., 1999). Recently, it has also been shown that neuroadaptations are induced after lower self-administered levels of EtOH. For example, animals given chronic free access to oral EtOH and then deprived of EtOH subsequently displayed long-term increases in dopaminergic and cholinergic neurotransmission in the NAcc and caudate. In addition, the magnitude of these increases corresponded to the amount of daily EtOH consumption before deprivation (Nestby et al., 1999).

There is evidence to support the notion that EtOH preexposure influences EtOH reward valence. While oral EtOH self-administration is widely utilized as an index of rewarding EtOH effects, a routine procedure to establish drinking behavior requires sustained exposure to oral EtOH via EtOH/sucrose combinations (Samson, 1986). This "sucrose fading" technique allows for habituation to the aversive EtOH taste, but preexposure to EtOH during this procedure may also be an important factor contributing to the initiation of EtOH drinking. Indeed, even when taste factors are circumvented (e.g., via parenteral administration of EtOH), prolonged exposure to EtOH may be necessary for the development of EtOH-conditioned reward. For instance, place conditioning procedures inevitably result in place preferences for environments paired with many drugs of abuse, but place aversions result when these same procedures are used in conjunction with EtOH treatment (Holloway et al., 1992; Cunningham et al., 1993; Bormann and

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Cunningham, 1997). However, if rats undergo chronic EtOH exposure prior to place conditioning procedures (Holloway et al., 1992; Bienkowski et al., 1995; Biala and Kotlinska, 1999) or if several conditioning trials and a relatively high EtOH dose are utilized (Bozarth, 1990), EtOH place preference can be established in rats. Also, animals that are chronically exposed to EtOH through their diet subsequently increase their intake of oral EtOH (Schulteis et al., 1996). These findings give strong credence to the possibility that EtOH preexposure is an important prerequisite for EtOH-induced positive reinforcing effects.

NAcc dopamine activity, which has been associated with the rewarding effects of natural and drug stimuli (Zito et al., 1985; Hernandez and Hoebel, 1988; Young et al., 1992; Weiss et al., 2000), increases in responsiveness after repetitive EtOH treatment. After repeated EtOH, NAcc dopamine increases in the presence of EtOH context (Katner and Weiss, 1999) and is enhanced after morphine treatment (Nestby et al., 1997). In addition, similar EtOH treatment results in increased basal NAcc dopamine levels in the alcohol-preferring P rats but not in the nonpreferring NP rats (Smith and Weiss, 1999). These data further demonstrate that recurring EtOH exposure produces fundamental changes in neural pathways most associated with positive reinforcement.

Intravenous self-administration methodology has been extremely useful for determining various constituents of positive reinforcement for many abused drugs. The distinct advantage of this procedure is that self-administration behavior provides a direct demonstration of incentive motivational drug properties. The self-administration mode of drug delivery is particularly important because of data showing that drugs taken voluntarily have different effects on the brain than those delivered by the experimenter (Hemby et al., 1997; Galici et al., 2000). Therefore, utilizing self-administration methodology undoubtedly strengthens the predictive validity of experimental outcomes in drug abuse studies. Theoretically then, intravenous self-administration should be an excellent way to investigate the neurobiological basis of EtOH reinforcement without interference from orosensory factors, such as aversive taste or smell. In reality, however, published studies of intravenous EtOH self-administration are extremely sparse and limited in scope. In addition, previous studies used low unit doses of EtOH and report very low levels of cumulative EtOH intake during self-administration sessions (Hyytia et al., 1996; Kuzmin et al., 1999). Indeed, this outcome prompted authors of one study to question the central relevance of the self-administered EtOH (Hyytia et al., 1996). Yet, it should be noted that the data reported in these studies were collected after very limited exposure to EtOH. Since the conditioning studies cited above found repeated or high-dose EtOH treatment increased the positive reinforcing effects of EtOH (Holloway et al., 1992; Bienkowski et al., 1995; Biala and Kotlinska, 1999), it is suggested that extended EtOH self-administration training, higher EtOH unit doses or EtOH preexposure may lead to a more convincing demonstration of EtOH reward through intravenous EtOH self-administration behavior.

Cocaine reinforcement can support high rates of operant responding (Depoortere et al., 1993; Emmett-Oglesby et al., 1993). In addition, a drug such as heroin, which does not elicit vigorous operant behavior alone, is self-administered at a much greater level when combined with cocaine (Duvauchelle et al., 1998). The present study was performed to determine if preexposure to EtOH through EtOH/cocaine self-administration facilitates the motivational effects of EtOH as subsequently assessed by intravenous EtOH self-administration. To achieve EtOH preexposure through self-administration, cocaine in combination with a 10% (w/v) EtOH solution was used to reinforce operant responses. The cocaine component was gradually decreased on a weekly basis until rats were responding for 10% EtOH alone. Infusion times were varied to allow a range of EtOH unit dosages across a higher dose range than previously utilized in intravenous EtOH self-administration studies (e.g., Hyytia et al., 1996; Kuzmin et al., 1999). A control group was also given the opportunity to self-administer intravenous EtOH alone after a preexposure period consisting of cocaine-reinforced self-administration sessions.

2. General methods

The University of Texas Institutional Animal Care and Use Review Committee approved the experimental protocol for this study.

2.1. Animals

Fifteen male Sprague–Dawley rats weighing approximately 200–250 g at the start of the experiment were used. Animals were handled daily for 2 weeks prior to the start of food training sessions.

2.2. Apparatus

Operant sessions were conducted in identical one-lever operant chambers ($28 \times 22 \times 21$ cm). Chambers were located in sound-attenuating chambers. In all self-administration chambers, the ceiling, front and back walls were constructed of Plexiglas. The walls on the right and left of the operant chamber were metal, and a single retractable operant lever was located on the right wall. A stimulus light was located above the retractable lever and a house light was located on the opposite wall. Three sets of photocells were located on the front and back walls of the chamber, in the center and at 5 cm from each metal wall. During drug self-administration sessions, drugs were administered through a single channel swivel mounted on a counterbalanced arm at the top of each chamber. One end of the swivel was connected via polyethylene tubing to a syringe mounted

in a syringe pump (Model A, Razel) that delivered injections of drugs over programmed time periods.

2.3. Food training

After the 2-week handling period, animals were food restricted and trained in the operant chambers to lever press for food on a FR-1 schedule of reinforcement. After lever press acquisition, they had daily 30-min food-reinforced operant sessions (FR-1) for 6 days. In these sessions, animals are placed within the operant chamber, the houselights illuminate and the lever extends. After each lever press, the stimulus light switches on and a food pellet (45 mg) is delivered.

2.4. Surgery

After the six food-reinforced operant sessions, animals were anesthetized with sodium pentobarbital (50 mg/kg ip) supplemented with chloral hydrate (80 mg/kg ip). Atropine sulfate (250 μg/rat sc) was administered prophylactically to alleviate potential respiratory congestion. A Silastic catheter (0.625 mm o.d.) was inserted into the right external jugular and its tip advanced into the right atrium. The free end of the catheter fused with a modified cannula termination (C313G, Plastics One) was run subcutaneously along the side of the neck and out an incision in the skin at the top of the skull. Details of surgery have been previously reported (Duvauchelle et al., 1998). Animals were allowed to recover from surgery for 5 days before their participation in self-administration sessions.

2.5. Drugs

During self-administration sessions, animals in this experiment were reinforced with EtOH (10% w/v), cocaine hydrochloride (NIDA, Bethesda, MD) or EtOH/cocaine combinations. The 10% EtOH solution was made by diluting 95% EtOH (AAPER Alcohol & Chemical, Shelbyville, KY) with physiological saline and adding NaCl to the mixture to achieve an isotonic solution. The EtOH concentration was constant at 10%. Therefore, EtOH dosages dictated infusion volume (e.g., for a 400-g rat: 125 mg/kg/inj = 0.5 ml of 10% EtOH). For the EtOH/cocaine combinations, cocaine was added to 10% EtOH at the appropriate concentrations throughout the preexposure period (e.g., 0.75, 0.6, 0.5, 0.4, 0.3, 0.2 and 0.1 mg/kg/inj). Speed of drug infusion was approximately 6 s per 0.1-ml solution. To ensure equivalent drug infusion volumes between groups, the control group's cocaine was dissolved in physiological saline at concentrations matching the EtOH/cocaine combination solution.

2.6. Drug self-administration sessions

After recovery from surgery, animals were allowed daily 1-h drug self-administration sessions. Self-administering animals were on a FR-1 schedule of reinforcement. The stimulus light above the lever remained on for the duration of each drug infusion. After each infusion, there was a 20-s timeout, during which time the stimulus and house lights remained off and the lever was retracted. Animals had drug administration sessions 5 days/week (drug-free weekends).

2.7. Procedure

The first 7 weeks of self-administration sessions were "preexposure" training sessions. During this time, operant responses resulted in either EtOH/cocaine combinations (EtOH/Cocaine Fading) or cocaine alone (Cocaine Control). For the EtOH/Cocaine Fading group, the EtOH component dose during the preexposure period remained at 125.0 mg/kg/inj, while the cocaine component started at a dose of 0.75 mg/kg/inj and decreased (e.g., by 0.1–1.5 mg/kg) on a weekly basis. For the Cocaine Control group, cocaine reinforcement was available at the same dosages and over the same time course as the cocaine components of the EtOH/Cocaine Fading group. After the preexposure period, animals were reinforced for operant responses with intravenous EtOH alone (125.0 mg/kg) for 5 consecutive days. Over the next 5 weeks, for a period of 5 consecutive days each, four EtOH unit dosages (62.5, 125.0, 250.0 and 500 mg/kg) and saline (at an equal volume to the 125.0-mg/kg dose) were presented in random order for each animal. EtOH concentration was consistent at 10% for all dosages. Therefore, changes in EtOH unit dose were adjusted through infusion volume. Out of the 15 animals that started the experiment, 10 rats completed all treatment conditions.

2.8. Gas chromatography/blood alcohol level (BAL) determination

After intravenous EtOH alone self-administration sessions, blood was drawn from rats in the EtOH/Cocaine Fading group to determine BALs. Testing proceeded as follows: immediately after self-administration sessions were completed, animals were flushed through their central catheters with heparinized saline (fluid equivalent is three times the catheter volume). After discarding the first 0.1 ml of collected blood, a clean 1-ml syringe was used to extract another 0.1 ml of blood for BAL analysis using gas chromatography. Samples were compared to EtOH blood standards ranging from 0 to 40 mM. EtOH analyses using gas chromatography were performed as previously described (Crippens et al., 1999).

2.9. Statistical analyses

Two-way ANOVAs were performed to compare the EtOH/Cocaine Fading ($n = 5$) and Cocaine Control ($n = 5$) groups in weekly EtOH and cocaine drug intake and response rates during the preexposure period and EtOH

intake and locomotor activity data during the EtOH alone sessions. One-way repeated-measures ANOVA was performed on EtOH intake across the preexposure weeks, the number of lever responses elicited at each dose and dose-related response intervals during EtOH-reinforced sessions in the EtOH/Cocaine Fading group. Response rates, intake levels and locomotor activity data were calculated by using the last two sessions at each dose to determine the means. Response intervals were determined by compiling the number of reinforced responses during each 10-min interval across all EtOH doses. To rule out potential extinction responding or conditioned cocaine effects, data collected during the first week of EtOH alone self-administration were not used in the data analyses. Post hoc tests (Fisher's LSD/Protected t tests) were performed to detect significant differences associated with particular dosages within and between the groups. In addition, a Student's t test was performed to compare the total amount of self-administered cocaine between the two groups during the preexposure period, and a simple linear regression analysis was performed on intravenous EtOH intake (g/kg) and the resulting BALs in the EtOH/Cocaine Fading group.

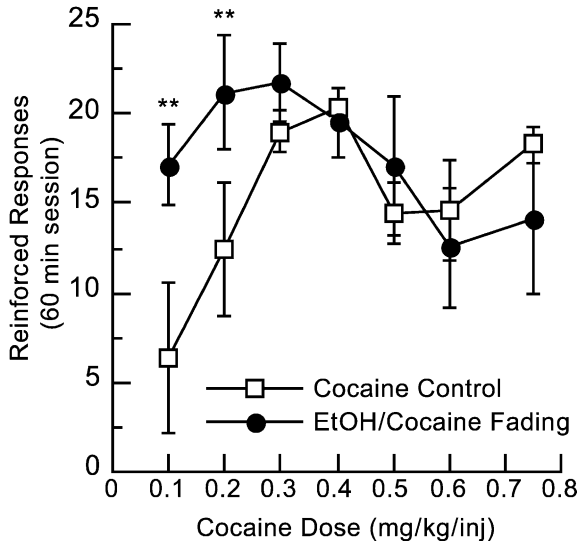

Fig. 1. Number of responses during preexposure sessions. Mean ± S.E.M. (n = 10). EtOH/Cocaine Fading group received 125.0-mg/kg/inj EtOH in addition to cocaine dose indicated. Compared to the Cocaine Control group at the same cocaine component doses, the EtOH/Cocaine Fading group elicited significantly more responses at the 0.1 and 0.2 mg/kg/inj cocaine doses. ** P < .01.

3. Results

3.1. Cocaine/EtOH and cocaine preexposure: self-administration behavior

Table 1 shows the mean self-administered intake levels of cocaine and EtOH during the preexposure period across cocaine doses. A two-way ANOVA performed on the cocaine data revealed no significant difference in cocaine intake between groups, no Interaction effects [$F(1,8) = 1.14$, n.s., and $F(6,48) = 1.2$, n.s., respectively], but a significant effect of Dose on cocaine intake [$F(6,48) = 23.8$, $P < .0001$]. However, a one-way ANOVA performed on EtOH intake levels during different component cocaine doses showed that changes in cocaine dose did not significantly alter EtOH intake [$F(6,24) = 1.52$, n.s.] in the EtOH/Cocaine Fading group.

A two-way ANOVA performed on the number of reinforced responses elicited across the preexposure period also indicated no significant Group differences [$F(1,8) = 1.29$, n.s.]. Yet, significant Dose [$F(6,48) = 3.7$, $P = .004$] and Interaction effects [$F(6,48) = 2.9$, $P = .017$] were observed. Post hoc tests revealed that when the EtOH/Cocaine Fading group received cocaine doses of 0.1 and 0.2 mg/kg/inj in combination with EtOH (125.0 mg/kg/inj), they elicited significantly more responses than animals receiving the same cocaine doses without the EtOH component (e.g., the Cocaine Control group; see Fig. 1).

Table 1
Weekly cocaine and EtOH intake during preexposure

Preexposure period: weekly drug intake			
Cocaine component dose (mg/kg/inj)	Cocaine Control (n = 5)	EtOH/Cocaine Fading (n = 5)	
	Cocaine intake (mg/kg)	Cocaine intake (mg/kg)	EtOH intake (g/kg)
0.75	61.9 (3.6)	51.5 (3.6)	6.9 (1.4)
0.6	40.2 (8.9)	37.8 (10.6)	6.7 (0.7)
0.5	33.3 (4.7)	47.0 (6.9)	8.9 (2.0)
0.4	38.2 (0.7)	40.2 (3.8)	10.8 (1.2)
0.3	28.7 (0.8)	32.7 (4.5)	11.1 (1.5)
0.2	14.2 (3.0)	20.1 (2.3)	9.5 (0.7)
0.1	4.1 (1.0)	8.6 (1.0)	10.0 (1.9)

Mean (S.E.M.). Cocaine dose had significant effects on cocaine intake for both groups ($P < .0001$) but not on EtOH intake in the EtOH/Cocaine Fading group.

3.2. Intravenous EtOH self-administration sessions: intake and activity levels

3.2.1. EtOH intake levels

A two-way ANOVA comparing daily EtOH alone intake after the preexposure period showed significant differences in Group [$F(1,8) = 13.8$, $P = .005$] and Dose factors [$F(3,24) = 10.67$, $P = .0001$] and a significant Group × Dose Dose interaction effect [$F(3,24) = 5.21$, $P = .0065$]. Post hoc tests revealed that animals in the EtOH/Cocaine Fading group had significantly higher intake levels of self-administered EtOH alone in all but one (62.5 mg/kg) of the tested EtOH dosages ($P = .01$ at 125.0 and 250.0 mg/kg, $P = .05$ at 500 mg/kg; see Fig. 2).

3.2.2. EtOH-induced locomotor activity levels

A two-way ANOVA performed on self-administered EtOH-induced locomotor activity levels of the EtOH/

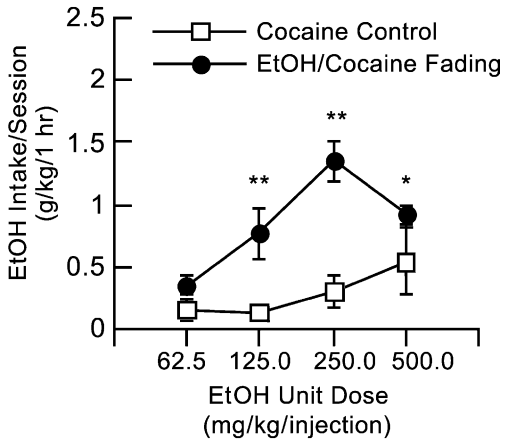

Fig. 2. Intravenous EtOH intake comparisons. Mean ± S.E.M ($n = 10$). Rats preexposed to EtOH/cocaine combinations (EtOH/Cocaine Fading, $n = 5$) self-administered significantly more intravenous EtOH than rats that had self-administered cocaine alone (Cocaine Control, $n = 5$). Group comparisons at each unit dose, * $P < .05$, ** $P < .01$.

Cocaine Fading and the Cocaine Control groups showed significant Group effects [$F(1,8) = 12.12$, $P = .008$], Dose effects approaching significance [$F(4,32) = 2.53$, $P = .059$] and no significant Interaction effects [$F(4,32) = 1.48$, n.s.]. However, since EtOH intake levels were approximately equal during the 62.5-mg/kg dose sessions, post hoc tests were performed to specifically compare the locomotor activity levels between the groups at that particular dose. These tests revealed that locomotor activity in the EtOH/Cocaine Fading group was significantly greater than the Cocaine Control group during the 62.5- and 250.0-mg/kg unit dose sessions ($P = .01$ and .05, respectively).

3.3. Intravenous EtOH self-administration: dose-related response patterns

Rats that had self-administered EtOH/cocaine combinations during preexposure sessions subsequently responded at higher operant levels for intravenous EtOH alone than for saline. A one-way ANOVA with repeated measures on EtOH Dose revealed significant effects on response rates [$F(4,16) = 5.29$, $P = .006$]. Post hoc tests revealed that rats responded significantly more times for EtOH reinforcement than for saline infusions at all but the highest EtOH unit dose (500.0 mg/kg; see Fig. 3A).

A two-way ANOVA performed on the number of responses elicited in 10-min intervals across the different EtOH unit doses showed significant Dose [$F(4,20) = 11.06$, $P < .0001$] and Interval effects [$F(5,100) = 2.97$, $P = .015$] but no significant Interaction effects [$F(20,100) = 0.97$, n.s.; see Fig. 3B].

3.4. Intravenous EtOH self-administration: BALs

A simple linear regression analysis performed on the concentration (g/kg) of self-administered intravenous EtOH

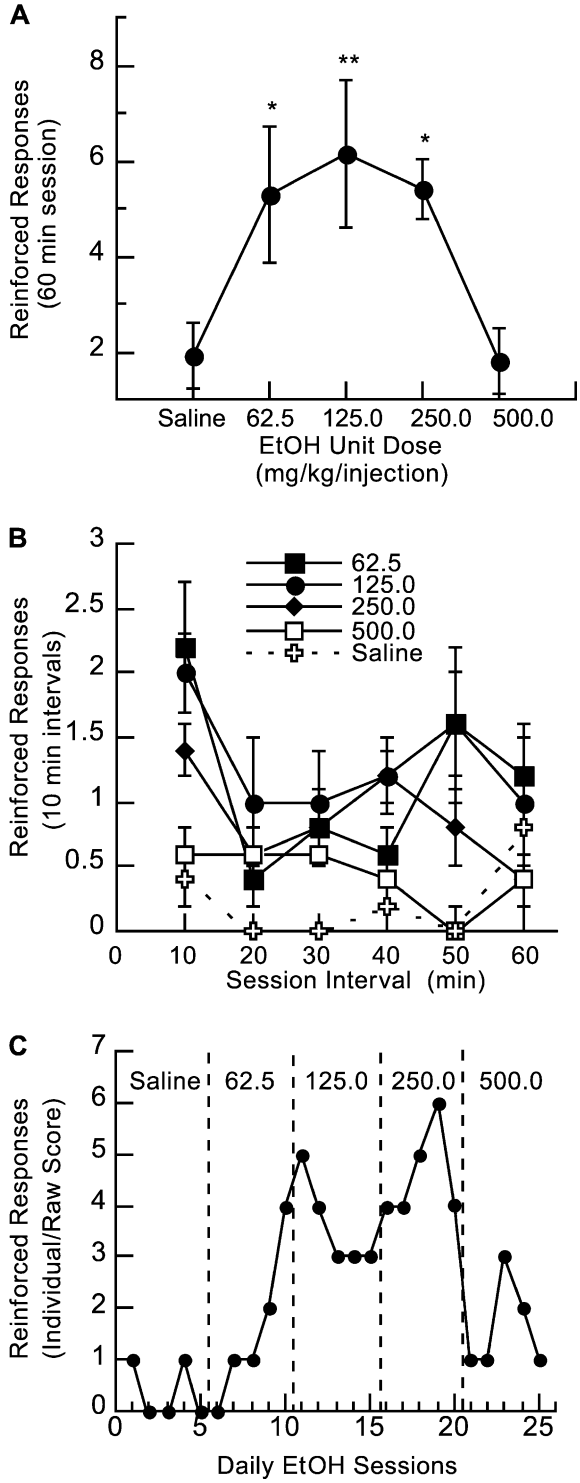

Fig. 3. EtOH dose–response patterns. Mean ± S.E.M. ($n = 5$). All EtOH dosages are expressed as mg/kg/inj. (A) Significant effects of EtOH unit dose on number of responses were observed after EtOH/cocaine self-administration experience. * $P < .05$, ** $P < .01$ compared to saline. (B) Significant effects of Dose and Interval factors reveal dose-related response patterns across EtOH self-administration sessions. (C) Individual self-administration behavior across saline- and EtOH-reinforced sessions in a representative rat.

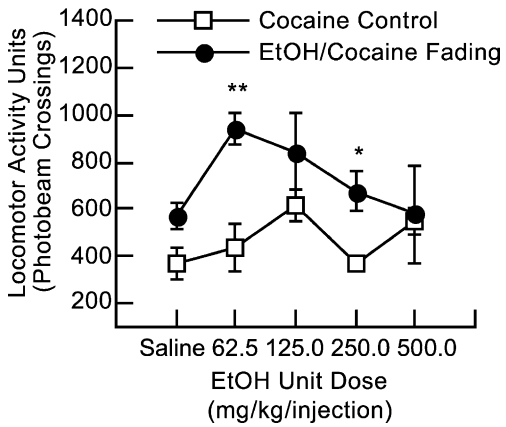

Fig. 4. EtOH-induced locomotor activity. Mean ± S.E.M. ($n = 10$). Compared to the cocaine control rats, the EtOH/Cocaine Fading group showed significant enhancement of locomotor activity at two of the four EtOH unit dosages, * $P < .05$, ** $P < .01$.

(0.5–2.0 g/kg; EtOH/Cocaine Fading group) and the resulting BALs was significant [$r = .93$; $F(1,9) = 64.85$, $P < .0001$; see Fig. 5].

4. Discussion

Prior to intravenous EtOH self-administration sessions, two groups of rats self-administered either EtOH/cocaine combinations (EtOH/Cocaine Fading) or cocaine alone (Cocaine Control). Over the course of the 7-week drug preexposure period, the total amount of self-administered cocaine did not significantly differ between the groups. Rats in the Cocaine Control group did not reliably self-administer EtOH after the preexposure sessions, but those in the EtOH/Cocaine Fading group showed consistent responding for EtOH alone, self-administering intravenous EtOH over an approximate range of 0.50–2.0 g/kg per 1-h session. This level of EtOH intake is extraordinarily greater, over a much shorter session than recently reported in other intravenous EtOH self-administration studies (e.g., AA rats: 0.0275–0.083 g/kg in 3 h, see Hyytia et al., 1996, and roughly 0.044 g/kg in 2 h, see Kuzmin et al., 1999). The present findings strongly suggest that preexposure to EtOH, but not cocaine, was the factor that determined the subsequent high EtOH intake levels.

As can be seen in Fig. 2, at the lowest EtOH dose (62.5 mg/kg/inj), the EtOH/Cocaine Fading and the Cocaine Control groups self-administered approximately the same amount of EtOH. However, even with the same level of EtOH intake, locomotor activity was significantly enhanced in the EtOH/Cocaine Fading animals but not in the Cocaine Control group (see Fig. 4). These findings indicate that prolonged self-administration of EtOH/cocaine, but not cocaine alone, sensitized rats to the locomotor-activating effects of low doses of intravenous EtOH. Another study found that chronic EtOH treatment enhanced hyperlocomotor activity induced by cocaine and amphetamine treatment (Manley and Little, 1997). Therefore, it is also reasonable to suggest that the modification of EtOH-induced effects on locomotor activity seen in the present study was due to lengthy EtOH experience during preexposure self-administration sessions.

Yet, it is also possible that cocaethylene, a unique metabolite formed when EtOH and cocaine are concurrently administered (Dean et al., 1992), contributed to the development of the reinforcing and/or locomotor-sensitizing effects of EtOH. While the present study did not assess cocaethylene levels, the possibility that the presence of cocaethylene influenced the experimental outcome cannot be completely ruled out. Cocaethylene is known to increase motor activity, support self-administration behavior and produce conditioned place preferences in a manner similar to cocaine (Woodward et al., 1991; Schechter, 1995). However, at this time, we are unaware of supporting evidence for a facilitating role of cocaethylene on EtOH-mediated positive reinforcement or hyperlocomotion induced by EtOH.

Oral EtOH self-administration is the most utilized and accepted behavioral model of voluntary EtOH intake (Samson, 1986; Weiss et al., 1993; Files et al., 1997). Since human alcohol abusers are "drinkers," the face validity of voluntary oral alcohol delivery is a definite advantage behind its use in research. Alcohol-preferring rats can average approximately 1.0 g/kg of oral EtOH in 30 min to 1 h of access (Katner et al., 1997; Samson et al., 1998). Under certain training and withdrawal procedures (Heyser et al., 1997), this level of intake can be achieved in nonselected Wistar rats. In the latter case, however, high alcohol intake is only observed for 1 day (e.g.,

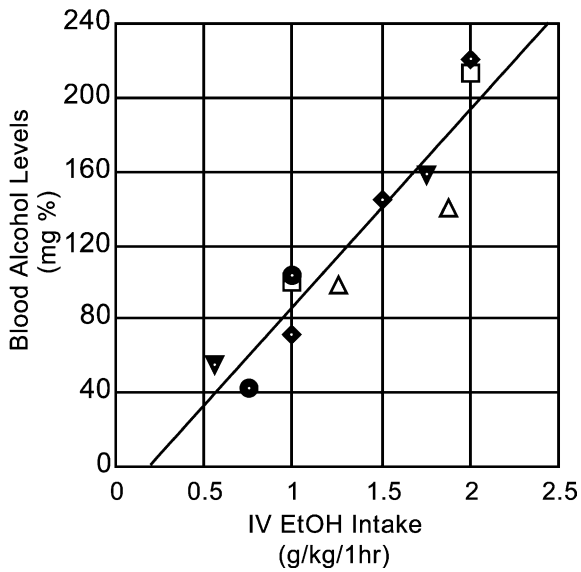

Fig. 5. BAL determination using gas chromatography. Values ranged from approximately 10 to 48 mM of EtOH (≈ 44–221 mg/dl). Blood sampled immediately after intravenous EtOH alone sessions (EtOH/Cocaine Fading group only). Data represent five rats tested on two ($n = 4$) or three ($n = 1$) separate occasions at varied unit dosages. Individual rats are represented by different symbols.

the Alcohol Deprivation Effect), making it difficult for this model to represent long-term voluntary EtOH abuse in heterogeneous rat species. During limited access, a more commonly reported range of EtOH intake in nondependent rats falls between 0.36 and 0.8 g/kg after sucrose training procedures (Hodge et al., 1996; Weiss et al., 1996; Roberts et al., 2000). Consequently, animal studies of EtOH abuse-related processes, such as EtOH dependence and withdrawal, are commonly studied through experimenter-administered EtOH exposure (Hardy et al., 1999; Mittal et al., 1999; Darstein et al., 2000; Roberts et al., 2000), while neural changes resulting from voluntary intake of EtOH are not well represented in the literature. A significant aspect of the study reported here is that high EtOH intake was observed on a consistent, daily basis. EtOH alone self-administration was maintained over a 5-week period, indicating long-term positive reinforcing effects at this level of EtOH consumption. Perhaps equally important is that reliable intravenous EtOH self-administration behavior was induced in Sprague–Dawley rats, a strain more likely to show reduced EtOH intake (Sprague et al., 1994) than substantial self-administration.

As shown by the data presented here, intravenous EtOH self-administration initiated by EtOH/cocaine preexposure results in EtOH intake at levels relevant to EtOH abuse. Though it is yet to be determined if EtOH preexposure through experimenter-administered injections would similarly influence intravenous EtOH self-administration, predictions based on findings from EtOH conditioning studies (Holloway et al., 1992; Bienkowski et al., 1995; Biala and Kotlinska, 1999) would indicate as much. In any event, this procedure of intravenous EtOH self-administration paves the way for future studies to investigate neural adaptations underlying reinforcement processes associated with excessive voluntary EtOH intake.

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