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Interaction of ethanol with excitatory amino acid receptor antagonists in mice

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Abstract

The purpose of the present study was to determine whether the motor impairment (myorelaxation/ataxia) induced by excitatory amino acid receptor antagonists was exaggerated by pretreatment with ethanol. The results were compared with those of γ-aminobutyric acid$_A$ (GABA$_A$) receptor positive modulators alone and in combination with ethanol. The excitatory amino acid receptor antagonists, dizocilpine {(+)-MK-801; (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine}, (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), LY 326325 {(−)-(3*S*,4*aR*,6*R*,8*R*)-6-[2-(1(2)*H*-tetrazol-5-yl)-ethyl]-decahydroisoquinaline-3-carboxylic acid}, LY 300164 [7,8-methylenedioxy-1-(4-aminophenyl)-4-methyl-3-acetyl-4,5-dihydro-2,3-benzodiazepine], and ACEA 1011 (5-chloro-7-trifluoromethyl-1,4-dihydro-2,3-quinoxalinedione) produced dose-dependent myorelaxation/ataxia in mice as determined using the horizontal wire assay. Their behaviorally toxic doses (TD_{50}s) were 0.41, 5.8, 33.0, 5.9, and 31.0 mg/kg, respectively, when administered alone i.p. In the presence of a sub-ataxic dose of ethanol (1.5 g/kg, i.p.), the TD_{50}s of the excitatory amino acid antagonists were 0.13, 1.8, 10.4, 1.3, and 14.0 mg/kg, respectively. Similarly, the GABA$_A$ receptor positive modulators, pregnanolone, chlordiazepoxide, and pentobarbital exhibited TD_{50}s of 20.8, 4.6, and 29.7 mg/kg, respectively, when administered alone and 2.7, 0.3, and 11.4 mg/kg, respectively, when administered in the presence of ethanol. Thus, similar to the GABA$_A$ receptor positive modulators, excitatory amino acid receptor antagonists exhibit the propensity to interact with ethanol and to have their motor side-effects exaggerated.

Keywords: Ethanol; Glutamate; NMDA receptor; AMPA receptor; Kainate; GABA receptor

1. Introduction

Ethanol is known to have a variety of behavioral effects including discriminative stimulus effects, anticonvulsant effects, ataxia, and loss of righting reflex (Kulkarni and Ticku, 1989; Dudek and Phillips, 1990; Grant et al., 1991; Prospero-García et al., 1994). Some of these effects are shared by positive allosteric modulators of γ-aminobutyric acid$_A$ (GABA$_A$) receptors (Saano, 1987; Ator et al., 1993; Wieland et al., 1995). Similarly, the behavioral profiles of excitatory amino acid receptor antagonists share many features with ethanol (Kulkarni and Ticku, 1989; Grant et al., 1991; Prospero-García et al., 1994; Czuczwar et al., 1995). The behavioral effects induced by ethanol are thought to be mediated both by enhancement of GABA$_A$ receptor function (Frye and Breese, 1982; Liljequist and Engel, 1982; Martz et al., 1983; Deitrich et al., 1989) and by inhibition of excitatory amino acid receptor function (Deitrich et al., 1989; Hoffman et al., 1990; Leslie et al., 1990; Wilson et al., 1990).

GABA$_A$ receptor complex positive allosteric modulators have shown a great propensity for interaction with ethanol, producing marked decrements in psychomotor performance (Hu et al., 1986; Wessinger and Balster, 1987; Barnhill et al., 1991; Melchoir and Allen, 1992). Fewer studies, however, have addressed the interaction excitatory amino acid receptor antagonists with ethanol. Of all the excitatory amino acid receptor antagonists, dizocilpine {(+)-MK-801; (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine}, a non-competitive NMDA receptor antagonist, has been characterized the most frequently in combination with ethanol. Consistent with their shared mechanism of action, one study reported dizocilpine to potentiate the anticonvulsant

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effects of ethanol (Kulkarni and Ticku, 1989). However, there have been mixed reports concerning the interaction of dizocilpine and ethanol on locomotor activity, with the effects being described as potentiated (Kuribara, 1994), additive (Robledo et al., 1991), or inhibited (Liljequist, 1991). In yet another study, dizocilpine was found to attenuate ethanol-induced hypothermia, but to prolong ethanol-induced loss of righting reflex (Danysz et al., 1992). Thus, the interaction between dizocilpine and ethanol remains unclear with dose- and behavior-dependency adding to the complexity. Even less is known about the behavioral interaction of ethanol with antagonists at excitatory amino acid receptor subtypes other than NMDA receptors, such as α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, kainate receptors, or glycine sites on NMDA receptors.

The purpose of the present study was to determine whether the motor impairment (myorelaxation/ataxia) induced by excitatory amino acid receptor antagonists was exaggerated by pretreatment with ethanol. The effects of the excitatory amino acid antagonists were compared to the effects of $GABA_A$ positive allosteric modulators in the absence and presence of ethanol. The excitatory amino acid receptor antagonists included dizocilpine, a noncompetitive NMDA receptor antagonist, (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP), a competitive NMDA receptor antagonist, 5-chloro-7-trifluoromethyl-1,4-dihydro-2,3-quinoxalinedione (ACEA 1011), a competitive antagonist of NMDA receptors at the glycine site, (−)-(3*S*,4*aR*,6*R*,8*R*)-6-[2-(1(2)*H*-tetrazol-5-yl)-ethyl]-decahydroisoquinaline-3-carboxylic acid (LY 326325; LY 293558 monohydrate), a competitive AMPA/kainate receptor antagonist, and 7,8-methylenedioxy-1-(4-aminophenyl)-4-methyl-3-acetyl-4,5-dihydro-2,3-benzodiazepine (LY 300164; GYKI 53773), a noncompetitive AMPA/kainate receptor antagonist. The $GABA_A$ receptor positive allosteric modulators included pregnanolone, a neuroactive steroid, chlordiazepoxide, a benzodiazepine, and pentobarbital, a barbiturate.

2. Materials and methods

2.1. Subjects

Naive male mice (NSA) weighing 20–25 g were obtained from Harlan Sprague–Dawley (San Diego, CA). Animals were housed in polycarbonate cages (four mice per cage) containing sterilized bedding material (Sani-Chips, P.J. Murray; Montville, NJ) and were kept in a room maintained at 23.0°C (±2.5°C) and on a 12:12 h light:dark cycle. Food (LM 485, Harlan Teklad; Orange, CA) and water were freely available. Mice were acclimated to housing conditions for a minimum of 4 days prior to experimentation.

2.2. Apparatus and procedure

The horizontal wire test or traction test for myorelaxation/ataxia consisted of a simple procedure as described previously by Bennett et al. (1989). The test used a custom-built apparatus that consisted of a metal wire (2 mm diameter) suspended horizontally 25 cm above padded bench top. After the appropriate pretreatment interval following drug administration, mice were held using the thumb and forefinger by the base of the tail. The forepaws of the mice were placed in contact with the wire and then the mice were released. Mice were required to bring at least one hindpaw in contact with the wire within 10 s in order to be scored as a pass. Failure to respond within 10 s was considered behavioral toxicity. Normal untreated mice always pass the test.

2.3. Data analysis

Results from the horizontal wire assay were treated quantally. To determine whether ethanol potentiated the myorelaxation/ataxia of a test drug, dose–response functions ($n = 16$/dose) of the test drug were determined alone and in the presence of ethanol (1.5 g/kg). Each dose–response function was based on two separate experiments ($n = 8$/dose), generally conducted on different days, and the results summed. A dose that caused behavioral toxicity in half the animals (toxic dose; TD_{50}) was calculated based on each dose response function by the method of Litchfield and Wilcoxon using PHARM/PCS version 4.2 software (Springer-Verlag, New York). In addition, the 95% confidence intervals were calculated around each TD_{50}. If the 95% confidence intervals of two TD_{50}s did not overlap, they were considered statistically different.

2.4. Drugs

Dizocilpine maleate and (±)-CPP were purchased from Research Biochemicals International (RBI; Natick, MA)

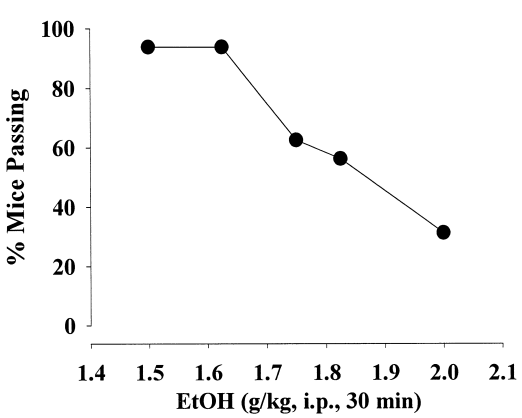

Fig. 1. Dose–response function of ethanol (EtOH). Percent mice passing the horizontal wire assay is shown as a function of dose. Each point represents 16 mice.

and dissolved in 0.9% saline. ACEA 1011 was synthesized at CoCensys and dissolved in 0.1 M L-arginine. LY 326325 (LY 293558 monohydrate), and LY 300164 (GYKI 53773) were generously supplied by Eli Lilly (Indianapolis, IN). LY 326325 was dissolved in 0.05 M Tris base and LY 300164 was dissolved in 10:90 Tween 80:deionized water. A vehicle of 50:50 hydroxypropyl-β-cyclodextrin:0.9% saline was used to dissolve pregnanolone, synthesized by AKZO-Diosynth (Oss, The Netherlands), and chlordiazepoxide (Sigma, St. Louis, MO). Pentobarbital (Sigma) was dissolved in deionized water. Ethanol was purchased from Spectrum Chemical (Gardena, CA) and diluted with deionized water. Drugs were administered i.p. in a volume of 0.1 ml/10 g body weight. Concentrations of drugs varied with dose. Where applicable, doses referred to the salt form.

3. Results

Ethanol (1.5–2.0 g/kg) caused a dose-related decrease in the percent of mice passing the horizontal wire assay (Fig. 1). A low dose of ethanol (1.5 g/kg) that had little effect in the horizontal wire assay was chosen for further interaction studies.

All of the excitatory amino acid antagonists tested exhibited myorelaxation/ataxia (Fig. 2). The potency for myorelaxation/ataxia was dizocilpine > CPP ~ LY 300164 > ACEA 1011 ~ LY 326325 (Table 1). In addition, the myorelaxation/ataxia induced by each excitatory amino acid antagonist was significantly increased by the presence of ethanol (Fig. 2). Mice treated with dizocilpine alone exhibited myorelaxation/ataxia in the horizontal wire assay with a TD_{50} of 0.41 mg/kg (95% CI: 0.31–

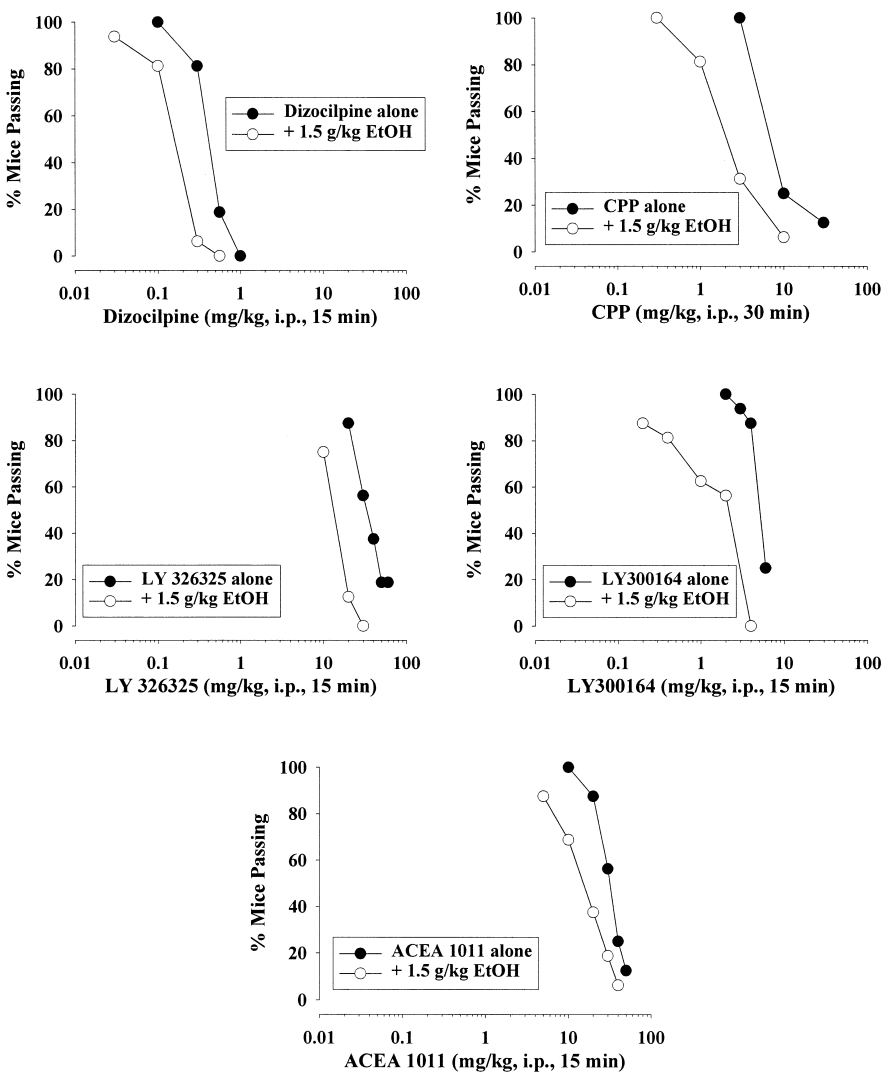

Fig. 2. Dose–response functions of excitatory amino acid antagonists alone (filled circles), in combination with 1.5 g/kg ethanol (EtOH; open circles). Percent mice passing the horizontal wire assay is shown as a function of dose. Each point represents 16 mice.

Table 1
Effects of test drugs alone and in combination with ethanol (EtOH) in the horizontal wire assay in mice

Drug	TD_{50}[a] alone	TD_{50}[a] + 1.5 g/kg EtOH	Ratio EtOH[b]
Dizocilpine	0.41 (0.31–0.54)	0.13 (0.06–0.24)	3.2
CPP	5.8 (3.7–9.0)	1.8 (1.1–3.1)	3.2
ACEA 1011	31.0 (25.5–37.7)	14.0 (10.2–19.3)	2.2
LY 326325	33.0 (27.0–40.3)	10.4 (7.6–14.2)	3.2
LY 300164	5.9 (4.5–7.8)	1.3 (0.8–2.1)	4.5
Pregnanolone	20.8 (13.5–32.0)	2.7 (1.3–5.7)	7.7
Chlordiazepoxide	4.6 (1.2–17.6)	0.3 (0.2–0.7)	15.3
Pentobarbital	29.7 (24.2–36.5)	11.4 (9.1–14.4)	2.6

[a] TD_{50} expressed as mg/kg (95% CI).
[b] (TD_{50} alone)/(TD_{50} + 1.5 g/kg EtOH).

0.54). In combination with 1.5 g/kg ethanol, dizocilpine showed more potent motor incoordination with a TD_{50} of 0.13 mg/kg (0.06–0.24). The motor effects of CPP also were potentiated by ethanol with CPP exhibiting a TD_{50} of 5.8 mg/kg (3.7–9.0) alone and a TD_{50} of 1.8 mg/kg (1.1–3.1) in combination with ethanol. LY 326325 showed similar motor enhancement in the presence of ethanol with a TD_{50} of 33.0 mg/kg (27.0–40.3) alone and a TD_{50} of 10.4 mg/kg (7.6–14.2) in combination with ethanol. The potentiation by ethanol of each of these compounds, dizocilpine, CPP, and LY 326324, resulted in an approximate 3-fold shift in their dose–effect functions. ACEA 1011 exhibited a 2-fold potentiation by ethanol with a TD_{50} of 31.0 mg/kg (25.5–37.7) alone and a TD_{50} of 14.0 mg/kg (10.2–19.3) with ethanol, whereas LY 300164 exhibited a 4.5-fold potentiation by ethanol with a TD_{50} of 5.9 mg/kg (4.5–7.8) alone and a TD_{50} of 1.3 mg/kg (0.8–2.1) with ethanol.

Myorelaxation/ataxia was induced by all of the $GABA_A$ positive modulators as well (Fig. 3). Administered alone, the TD_{50} values for pregnanolone, chlordiazepoxide, and pentobarbital alone were 20.8 mg/kg (13.5–32.0), 4.6 mg/kg (1.2–17.6), and 29.7 mg/kg (24.2–36.5), respectively (Table 1). The myorelaxation/ataxia induced by each $GABA_A$ positive modulator was significantly increased when administered in combination with ethanol (Fig. 3). The effect of pentobarbital was potentiated to a degree comparable to that observed with the excitatory amino acid antagonists (2.6-fold), with a TD_{50} in the presence of ethanol of 11.4 mg/kg (9.1–14.4). The ataxic effects induced by pregnanolone and chlordiazepoxide were potentiated to a greater degree than the other test compounds. The TD_{50} of pregnanolone in the presence of ethanol was 2.7 mg/kg (1.3–5.7), representing nearly an 8-fold shift in the dose–effect function. Chlordiazepoxide, in the presence of ethanol, exhibited a TD_{50} of 0.3 mg/kg (0.2–0.7), a robust 15-fold shift in its dose–effect function.

4. Discussion

Consistent with their ataxic effects in a variety of animal paradigms (Kulkarni and Ticku, 1989; Dudek and

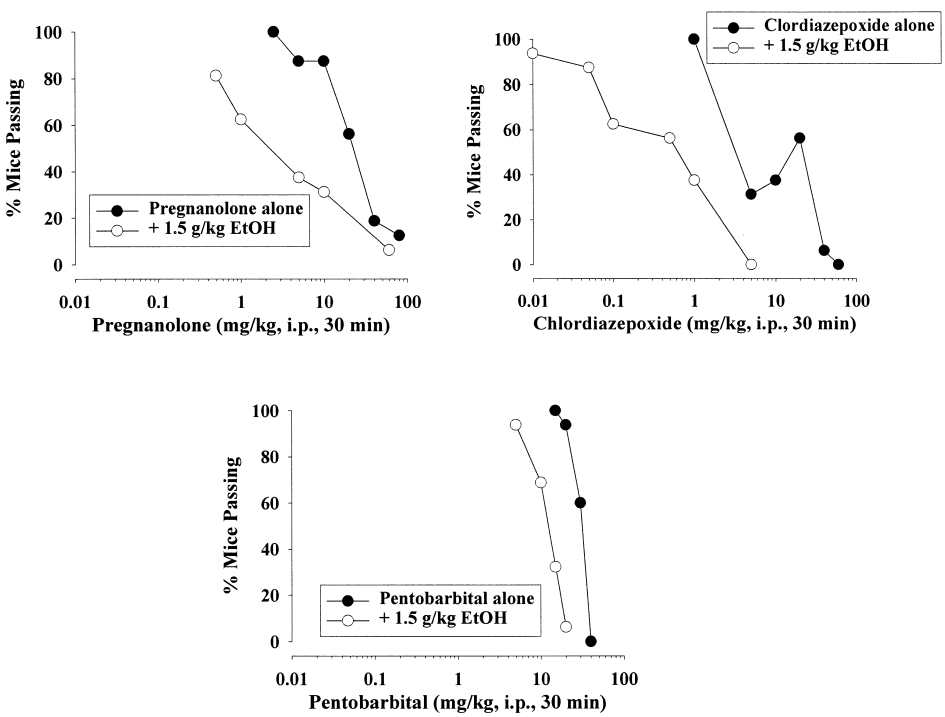

Fig. 3. Dose–response functions of $GABA_A$ positive allosteric modulators alone (filled circles), in combination with 1.5 g/kg ethanol (EtOH; open circles). Percent mice passing the horizontal wire assay is shown as a function of dose. Each point represents 16 mice.

Phillips, 1990; Czuczwar et al., 1995; Wieland et al., 1995), ethanol, excitatory amino acid receptor antagonists and $GABA_A$ receptor positive modulators exhibited dose-related impairment in the horizontal wire assay in mice. The ataxic effects of dizocilpine were potentiated by co-administration of a sub-effective dose of ethanol. This is consistent with previous reports that dizocilpine enhances some of the behavioral effects of ethanol (Kulkarni and Ticku, 1989; Robledo et al., 1991; Danysz et al., 1992; Kuribara, 1994). However, other studies have shown dizocilpine blocking behavioral effects of ethanol (Liljequist, 1991; Danysz et al., 1992). Although the interaction between dizocilpine and ethanol appears complex and behavior dependent, the sedative effects of ethanol and dizocilpine, such as myorelaxation/ataxia (present results) and loss-of-righting reflex (Danysz et al., 1992), appear to be enhanced by co-administration of the two drugs.

Similar to the effects of dizocilpine with ethanol, the myorelaxation/ataxia induced by other excitatory amino acid receptor antagonists were potentiated by a low dose of ethanol. The dose–effect functions of the competitive NMDA receptor antagonist, CPP, and the competitive AMPA/kainate receptor antagonist, LY 326325, were shifted approximately 3-fold to the left in the presence of ethanol, a degree of enhancement similar to that observed with dizocilpine. Of all the excitatory amino acid receptor antagonists tested, the noncompetitive AMPA/kainate receptor antagonist, LY 300164, exhibited the most robust interaction with ethanol. The ataxic effects of LY 300164 were potentiated 4.5-fold. In contrast, ACEA 1011, an antagonist for the glycine site on NMDA receptors, exhibited the least interaction with ethanol, with only a 2-fold potentiation.

The effects of the excitatory amino acid receptor antagonists with ethanol were similar to those observed with the $GABA_A$ receptor positive modulators. The dose–effect function of pentobarbital was shifted approximately 2.5-fold to the left in the presence of ethanol. This potentiation was similar in degree to the potentiation reported with the excitatory amino acid receptor antagonists with ethanol. The other two $GABA_A$ receptor modulators, however, showed more robust ethanol interactions. The enhancement of pregnanolone-induced myorelaxation/ataxia in the present study was more robust than that previously reported (Vanover et al., 1998). However, that chlordiazepoxide had a more robust interaction with ethanol than did pregnanolone in the present experiment was consistent with the previous report of a greater propensity for the benzodiazepines to interact with ethanol compared to the neuroactive steroids (Vanover et al., 1998). Further, pregnanolone appears to be potentiated to a greater degree than other, synthetic neuroactive steroids, such as Co 3-0593 (Wieland et al., 1997) and CCD 3693 (Edgar et al., 1997). Of all the test drugs in the present experiment, the dose–response function of chlordiazepoxide was shifted by ethanol to the greatest degree (15-fold).

The current data are consistent with previous reports that ethanol shares some behavioral effects with positive allosteric modulators of $GABA_A$ receptors (Saano, 1987; Ator et al., 1993; Wieland et al., 1995) and with excitatory amino acid receptor antagonists (Kulkarni and Ticku, 1989; Grant et al., 1991; Prospero-García et al., 1994; Czuczwar et al., 1995). Further, the present study demonstrates exaggeration of myorelaxation/ataxia by co-administration of ethanol with either $GABA_A$ receptor positive modulators or excitatory amino acid receptor antagonists. These results are consistent with a neurobiological mechanism of action including both potentiation of $GABA_A$ receptors and inhibition of excitatory amino acid receptors. Finally, it has been suggested that excitatory amino acid receptor antagonists may have clinical utility in the treatment of a variety of disorders, including epilepsy, ischemic stroke, neurodegenerative disorders, and chronic pain (Dingledine et al., 1990; Meldrum and Garthwaite, 1990; Leeson, 1993; Bettler and Mulle, 1995; Thomas, 1995). To the extent that ethanol interaction is an important adverse side-effect of some $GABA_A$ receptor positive modulators (Chan, 1984; Harvey, 1985), the exaggeration of the side-effects of excitatory amino acid receptor antagonists by ethanol should be explored further.

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