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Effects of topiramate and other anti-glutamatergic drugs on the acute intoxicating actions of ethanol in mice: modulation by genetic strain and stress

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Abstract

Compounds with anti-glutamatergic properties currently in clinical use for various indications (e.g., Alzheimer's disease, epilepsy, psychosis, mood disorders) have potential utility as novel treatments for alcoholism. Enhanced sensitivity to certain acute intoxicating effects (ataxia, sedative) of alcohol may be one mechanism by which anti-glutamatergic drugs modulate alcohol use. We examined the effects of six compounds (memantine, dextromethorphan, haloperidol, lamotrigine, oxcarbazepine, topiramate) on sensitivity to acute intoxicating effects of ethanol (ataxia, hypothermia, sedation/hypnosis) in C57BL/6J mice. Analysis of topiramate was extended to determine the influence of genetic background (via comparison of the 129S1, BALB/cJ, C57BL/6J, DBA/2J inbred strains) and prior stress history (via chronic exposure of C57BL/6J to swim stress) on topiramate's effects on ethanol-induced sedation/hypnosis. Results showed that one *N*-methyl-D-aspartate receptor (NMDAR) antagonist, memantine, but not another, dextromethorphan, potentiated the ataxic but not hypothermic or sedative/hypnotic effects of ethanol. Haloperidol increased ethanol-induced ataxia and sedation/hypnosis to a similar extent as the prototypical NMDAR antagonist MK-801. Of the anticonvulsants tested, lamotrigine accentuated ethanol-induced sedation/hypnosis, while oxcarbazepine was without effect. Topiramate was without effect *per se* under baseline conditions in C57BL/6J, but had a synergistic effect with MK-801 on ethanol-induced sedation/hypnosis. Comparing inbred strains, topiramate was found to significantly potentiated ethanol's sedative/hypnotic effects in BALB/cJ, but not 129S1, C57BL/6J or DBA/2J strains. Topiramate also increased ethanol-induced sedation/hypnosis in C57BL/6J after exposure to chronic stress exposure. Current data demonstrate that, with the exception of MK-801 and haloperidol, the compounds tested had either no significant or assay-selective effects on sensitivity to acute ethanol under baseline conditions in C57BL/6J. However, significant effects of topiramate were revealed as a function of co-treatment with a

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NMDAR blocker, genetic background or prior stress history. These findings raise the possibility that topiramate and possibly other anti-glutamatergic drugs could promote the acute intoxicating effects of ethanol in specific subpopulations defined by genetics or life history.

Keywords

alcohol; glutamate; NMDA; AMPA; alcoholism; treatment

Introduction

There is growing evidence that the glutamate system plays a major role in the neural and behavioral actions of alcohol and the processes driving the development of alcoholism (Heilig and Egli, 2006; Spanagel and Kiefer, 2008). *In vitro*, ethanol (EtOH) acts an allosteric inhibitor of *N*-methyl-D-aspartate receptors (NMDAR) at behavioral intoxicating doses, likely via direct receptor occupancy and actions on gating, as well as receptor phosphorylation (Lovinger et al., 1989; Woodward, 2000). EtOH also inhibits the function of L-alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid ionotropic glutamate receptors (AMPAR) *in vitro*, perhaps by facilitating receptor desensitization (Costa et al., 2000; Fischer et al., 2003; Frye and Fincher, 2000; Lovinger et al., 1989; Moykkynen et al., 2003). Furthermore, chronic exposure to EtOH produces an upregulation of NMDAR protein levels, synaptic NMDAR clustering and NMDAR-mediated synaptic currents (Carpenter-Hyland et al., 2004; Crabbe et al., 1991; Kumari and Ticku, 2000; Liu and Weiss, 2002; Roberto et al., 2006; Smothers et al., 1997). These adaptive changes are thought to contribute to the behavioral tolerance, acute withdrawal and increased alcohol consumption that occurs with repeated EtOH exposure (Mulholland and Chandler, 2007).

Pharmacological or genetic blockade of glutamate receptors alters the behavioral effects of EtOH. For example, NMDAR antagonists mimic the subjective feelings of intoxication in humans and substitute for the discriminative stimulus effects of EtOH in mice (for comprehensive review, see Gass and Olive, 2008). NMDAR inactivation reduces EtOH self-administration and reward-related responses to EtOH and also attenuates withdrawal from chronic EtOH exposure (Gass and Olive, 2008). On the other hand, when given in combination with EtOH, NMDAR antagonists exacerbate the acute behavioral effects of EtOH (Gass and Olive, 2008). Pharmacological blockade of AMPAR also reduces EtOH consumption in alcohol-deprived mice, possibly via the GluR3 subunit, (Sanchis-Segura et al., 2006), while gene deletion of the GluR1 subunit does not alter most acute responses to EtOH (Cowen et al., 2003; Palachick et al., 2008). Finally, metabotropic glutamate receptor (mGluR)-acting drugs such as MPEP (mGluR5 antagonist) and LY379268 (mGluR2/3 agonist) reduce EtOH self-administration in various assays (e.g., Backstrom et al., 2004; Cowen et al., 2005; Hodge et al., 2006; Zhao et al., 2006).

Against the background of preclinical data, there is growing interest in the potential efficacy of various clinically available drugs with ‘anti-glutamatergic’ properties for the treatment of alcoholism (Krupitsky et al., 2007b). For example, the Alzheimer's disease medication memantine has anti-alcohol craving effects in recovering alcoholics (e.g., Krupitsky et al.,

2007a; Krupitsky et al., 2007b); although a recent large double-blind study found no effect in actively drinking alcoholics (Evans et al., 2007). Like memantine, the antitussive dextromethorphan has NMDAR antagonist activity and appears to mimic the subjective intoxicating effects of alcohol (Soyka et al., 2000). Although primarily known as an antipsychotic and dopamine D2 receptor blocker, haloperidol also has NMDAR antagonist effects and efficacy as a treatment for certain populations of alcoholics (e.g., Coyle, 2006; Lynch and Gallagher, 1996). Lamotrigine, oxcarbazepine and topiramate represent a class of anticonvulsant compounds with glutamate release inhibiting properties that shows encouraging evidence as novel mediations for alcoholism. Lamotrigine attenuates withdrawal (Krupitsky et al., 2007b) and reduces craving in alcoholics comorbid for schizophrenia or bipolar disorder (Kalyoncu et al., 2005; Rubio et al., 2006). Although the efficacy of oxcarbazepine in alcoholism has not yet been well established (Croissant et al., 2006; Koethe et al., 2007; Schik et al., 2005), there is now good evidence that topiramate reduces craving, withdrawal and drinking in recovering alcoholics (Johnson et al., 2004; Johnson et al., 2003; Johnson et al., 2007; Komanduri, 2003; Krupitsky et al., 2007b; Rubio et al., 2004; Rustembegovic et al., 2002).

Current models propose that alcohol abuse and alcoholism results from multiple risk factors, including a drive to alleviate the negative reinforcing effects of alcohol withdrawal (Koob, 2003) and a progressive impairment of executive control over alcohol seeking (Everitt and Robbins, 2005). Predisposition towards alcoholism is also associated with decreased sensitivity/increased acute tolerance to certain intoxicating (e.g., ataxic) effects of EtOH (Newlin and Thomson, 1990; Schuckit, 1994). However, although the aforementioned preclinical literature supports a major interaction between experimental glutamate-acting compounds and EtOH, it is currently unclear whether clinically tolerated ‘anti-glutamatergic’ drugs also modulate (i.e., promote) the acute intoxicating effects of EtOH; an effect that could contribute to their therapeutic profile. Thus, the aim of the present study was to assess six clinically available compounds that have some degree of anti-glutamatergic activity (memantine, dextromethorphan, haloperidol, lamotrigine oxcarbazepine, topiramate) for effects on the acute intoxicating effects of EtOH in mice. To provide a positive control, and to test for potential interactions (e.g., additive effects) with a NMDAR antagonist that robustly potentiates the ataxic and sedative/hypnotic effects of EtOH in mice (e.g., Palachick et al., 2008), each of the compounds was administered alongside, or in combination with MK-801. In addition, because, of these compounds, clinical and pre-clinical studies of topiramate have been the most extensive, we also tested whether topiramate's effects on EtOH-induced sedation/hypnosis varied as a function of two major influences on risk and treatment for alcoholism: genetic background and stress history (Goldman et al., 2005; Grant et al., 2008; Koob, 2003).

Material and methods

Subjects

Unless stated otherwise, subjects were male C57BL/6J mice obtained from The Jackson Laboratory (Bar Harbor, ME). This strain was chosen as a reference strain given its common use in models of alcoholism (Crabbe et al., 2006; Lopez and Becker, 2005) and because we

have recently characterized the effects of glutamate receptor manipulations on EtOH behaviors in this strain (Boyce-Rustay and Holmes, 2005; Boyce-Rustay and Holmes, 2006; Palachick et al., 2008). For the strain comparison experiment, subjects were 129S1/SvImJ (hereafter abbreviated 129S1), BALB/cJ, C57BL/6J, and DBA/2J obtained from The Jackson Laboratory. These strains were chosen based on their frequent use in behavioral neuroscience, including studies of EtOH-related behaviors (e.g., Crabbe et al., 2006; Millstein et al., 2006), as genetic backgrounds for mutants and inclusion as 'group A' priority strains in the Mouse Phenome Project, an international effort to provide the biomedical research community with phenotypic data on the most commonly used mouse strains (www.jax.org/phenome). Mice were housed 2/cage in a temperature and humidity controlled vivarium under a 12 h light/dark cycle (lights on 0600 h) with *ad libitum* access to food and water. All experimental procedures were approved by the National Institute on Alcohol Abuse and Alcoholism Animal Care and Use Committee and strictly followed the NIH guidelines 'Using Animals in Intramural Research.'

General procedures

Sensitivity to EtOH's acute intoxicating effects was assessed using a battery of 3 behavioral assays: EtOH-induced ataxia, hypothermia and sedation/hypnosis. Mice were tested on each assay with the assay involving the lowest dose (i.e., ataxia) first, followed by hypothermia and sedation/hypnosis, with an interval of at least 1 week between tests. This regimen is not expected to produce long-term tolerance to EtOH's effects (Crabbe, 2007). To our knowledge, there is also no evidence that infrequent treatment with any of the 'anti-glutamatergic' compounds tested here would produce tolerance or sensitization. Nonetheless, to minimize this possibility and avoid a potential bias introduced by treating the same group of mice with the same treatment, mice were randomly reassigned to drug treatment groups between each of the 3 assays. For each assay, the effects of the 6 'anti-glutamatergic' drugs were tested in 7−10 C57BL/6J mice per drug treatment (i.e., in each of 6 different treatment conditions, see below). Strain differences in responses to topiramate were tested in 6−10 mice per strain, per drug treatment. Stress effects on responses to topiramate were tested in 8 mice per stress condition, per drug treatment.

Rotarod training and EtOH-induced ataxia

EtOH-induced ataxia was assessed using the accelerating rotarod as previously described (Hefner and Holmes, 2007; Rustay et al., 2003). The apparatus was a Med Associates rotarod typically used for testing rats (model ENV-577). The 7-cm-diameter dowel was covered with 320 grit sandpaper to provide a uniform surface that prevented mice gripping the rubberized dowel. Mice were placed onto the rotarod dowel which was then accelerated at a constant rate of 8 rpm/min up to 40 rpm. The latency to fall to the floor 10.5 cm below was automatically recorded by photocell beams, with a maximum cutoff latency of 5 min. Mice first received 10 consecutive training trials separated by a 30-sec inter-trial interval. Change in latency to fall was measured by repeated measures analysis of variance. Results showed that there was a significant increase in latency to fall across rotarod training trials in the experiments assessing the effects of memantine ($F_{9,423}=25.15$, $p<.01$, Supplemental Fig. 1A), dextromethorphan ($F_{9,423}=18.75$, $p<.01$, Supplemental Fig. 1B), haloperidol ($F_{9,459}=28.94$, $p<.01$, Supplemental Fig. 1C), lamotrigine ($F_{9,513}=31.92$, $p<.01$,

Supplemental Fig. 1D), oxcarbazepine (F9,423=13.10, $p<.01$, Supplemental Fig. 1E), and topiramate (F9,423=31.87, $p<.01$, Supplemental Fig. 1F).

Twenty-four hr after training, there was a baseline acclimation trial followed by 2 more baseline trials (average=pre-drug performance). Mice were then injected intraperitoneally (i.p.) with the 'anti-glutamatergic' drug followed, 30 min later, by either saline vehicle or 0.2 mg/kg MK-801 ((+)-5-methyl-10,11-dihydro-S*H*-dibenzo[a,d]cyclohepten-5,10-imine maleate) (dissolved in a 0.9% saline vehicle). Thirty min later, mice were injected with 1.75 g/kg EtOH (for schematic of treatment procedure, see Supplemental Fig. 2). For this (and the 2 assays below) EtOH (200 proof) was prepared in 0.9% saline to produce 20% v/v solutions and injected i.p. with the dose determined by manipulating the volume of injection. Thirty min after EtOH challenge, there was 1 acclimation trial followed by 2 test trials (average=post-drug performance). The dependent measure was the difference in pre- versus post-drug performance (=delta latency). Note, we have previously shown that 0.2 mg/kg MK-801 *per se* does not produce significant rotarod ataxia in C57BL/6J mice (Palachick et al., 2008).

EtOH-induced hypothermia

EtOH-induced hypothermia was tested as previously described (Hefner and Holmes, 2007). Basal core body temperature was first measured by inserting a Thermalert TH-5 thermometer (Physitemp, Clifton, NJ, USA) 2 cm into the rectum until a stable reading was obtained. Mice were then injected with the 'anti-glutamatergic' drug followed, 30 min later, by saline vehicle or 0.2 mg MK-801. Thirty min later, mice were injected with 3.0 g/kg EtOH (for schematic of treatment procedure, see Supplemental Fig. 2). Temperature was measured prior to each drug treatment and 30, 60, 90, and 120 min later to provide an average post-EtOH measure. The difference between pre-EtOH (i.e., post-'anti-glutamatergic drug'/post-MK-801) and post-EtOH temperature was taken as the dependent measure (=delta temperature). Ambient room temperature was 23°C. Note, we have previously reported that 0.2 mg/kg MK-801 *per se* does not produce hypothermia in C57BL/6J mice (Palachick et al., 2008).

EtOH-induced sedation/hypnosis

EtOH-induced sedation/hypnosis was assessed as previously described (Daws et al., 2006). Mice were then injected with the 'anti-glutamatergic' drug followed, 30 min later, by saline vehicle or 0.2 mg/kg MK-801. Thirty min later, mice were injected with 3.0 g/kg EtOH (for schematic of treatment procedure, see Supplemental Fig. 2) and immediately placed into the supine position in a 'V'-shaped chamber. Sleep time was measured as the time from injection to recovery of the righting reflex (turning onto all 4 paws twice in 30 sec after initial self-righting), with a maximum latency of 180 min before the experiment was terminated. To measure blood EtOH concentrations (BECs) at recovery, mice were sacrificed via cervical dislocation and rapid decapitation and trunk blood was taken for analysis using the Analox AM1 Alcohol Analyzer (Analox Instruments USA Inc, Lunenburg, MA). Note, we have previously reported that 0.2 mg/kg MK-801 *per se* does not produce sedation/hypnosis in C57BL/6J mice (Palachick et al., 2008).

Effects of memantine, dextromethorphan, haloperidol

The effects of pre-treatment with memantine (1-amino-3,5-dimethyl-adamantane), dextromethorphan ((+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan) and haloperidol (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one) were tested as described above. Memantine (7.5 and 15 mg/kg), dextramethorphan (30 and 60 mg/kg) and haloperidol (0.15 and 0.30 mg/kg) were dissolved in a 0.9% saline vehicle, which also served as the 0 mg/kg dose and injected i.p. in a volume of 10 mL/kg body weight. Doses were chosen on the basis of prior behavioral studies in rats and mice: memantine (Holter et al., 1996; Piasecki et al., 1998), dextramethorphan (Erden et al., 1999), haloperidol (Karlsson et al., 2008; Wiedholz et al., 2008), as well as pilot work showing that when injected alone (i.e., without EtOH) these doses did not produce significant rotarod ataxia or sedation/hypnosis (effects on core body temperature are described in the Results below). All 3 drugs were obtained from Sigma (St. Louis, MO).

Effects of lamotrigine, oxcarbazepine, topiramate

The effects of pre-treatment with lamotrigine (6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine), oxcarbazepine (10,11-Dihydro-10-oxo-5 H -dibenz(b,f)azepine-5-carboxamide) and topiramate (2,3:4,5-bis-O-(1 methylethylidene)-[beta]-D-fructopyranose sulfamate) were tested as described above. Lamotrigine (15 and 30 mg/kg) was dissolved in 30% DMSO, which served as the 0 mg/kg dose for this drug. Topiramate (25 and 50 mg/kg) was dissolved in 0.9% physiological saline, which also served as the 0 mg/kg dose. Both drugs were injected i.p. in a volume of 10 mL/kg body weight. Oxcarbazepine (25 and 50 mg/kg) was dissolved in 60% DMSO, which served as the 0 mg/kg dose, and injected i.p. at a (lower) volume of 5 mL/kg body weight. Doses were chosen on the basis of prior behavioral studies in rats and mice: lamotrigine (Brody et al., 2003; Vengeliene et al., 2007), oxcarbazepine (Beijamini et al., 1998), topiramate (Gabriel and Cunningham, 2005; Hargreaves and McGregor, 2007; Knapp et al., 2007a; Nguyen et al., 2007) and pilot work showing that when injected alone (i.e., without EtOH) these doses did not produce significant rotarod ataxia or sedation/hypnosis (effects on core body temperature are described in the Results below). All 3 drugs were obtained from Sigma (St. Louis, MO).

Strain comparison of effects of topiramate on EtOH-induced sedation/hypnosis

The effect of topiramate pre-treatment on EtOH-induced sedation/hypnosis was tested in EtOH-naïve C57BL/6J, DBA/2J, 129S1, and BALB/cJ mice. Mice were injected i.p. with 0 or 50 mg topiramate 60 min (to mimic the time interval between topiramate and EtOH used above) prior to 3.0 g/kg EtOH and tested for sleep time as above.

Effects of topiramate on EtOH-induced sedation/hypnosis following chronic stress

C57BL/6J mice were exposed to a regimen of chronic swim stress previously shown to produce decreases in EtOH self-administration and produce increases in sensitivity to the sedative/hypnotic effects of 4.0 g/kg EtOH in BALB/cByJ, C57BL/6J and DBA/2J (Boyce-Rustay et al., 2008a; Boyce-Rustay et al., 2007; Boyce-Rustay et al., 2008b). Mice were placed in a transparent Plexiglas cylinder (20 cm diameter) filled halfway with water (24±1 °C) for 10 min each day for 14 consecutive days. We have previously shown that this

procedure produces significant elevation of corticosterone levels that persist after 14 days (Boyce-Rustay et al., 2007). Twenty-four hr after the final stress exposure, mice were injected i.p. with 0 or 50 mg topiramate 60 min (to mimic the time interval between topiramate and EtOH used above) prior to 3.0 g/kg EtOH and tested for sleep time as above.

Statistical analysis

Drug ('anti-glutamatergic' drug) x drug (MK-801), strain x topiramate and stress x topiramate effects were analyzed using analysis of variance and Newman Keuls *post hoc* tests. The relationship between sleep time duration and blood EtOH concentrations were analyzed using linear regression. Statistical significance was set at $p<.05$.

Results

Memantine

There was a significant memantine x MK-801 interaction for delta latency to fall from the rotarod ($F2,42=4.15$, $p<.05$). *Post hoc* analysis showed that memantine dose-dependently increased EtOH-induced ataxia relative to vehicle, and that MK-801 pre-treatment augmented EtOH-induced ataxia relative to vehicle pre-treatment, regardless of memantine dose (Fig. 1A). Although there was no indication of an additive effect between these two drug treatments on ataxia, this may have been obscured by a 'floor effect' because MK-801 *per se* impaired rotarod performance to near baseline. This general caveat should be borne in mind for all the drugs tested.

Neither memantine nor MK-801 affected core temperature or EtOH-induced hypothermia (Fig. 1B).

There was a significant effect of MK-801 ($F2,41=119.52$, $p<.01$) but not memantine and no drug x drug interaction for sleep time. MK-801 pre-treatment prolonged EtOH-induced sleep time relative to vehicle pre-treatment (Fig. 1C). Although there was a significant memantine x MK-801 interaction for BECs at recovery ($F2,41=14.52$, $p<.01$), *post hoc* analysis found lower BECs after MK-801 regardless of memantine treatment (Supplemental Table 1). There was a significant negative relationship between sleep time and BECs at recovery ($R^2=.75$, $p<.01$, Supplemental Fig. 3A).

In summary, memantine potentiated the ataxic, but not hypothermic or sedative/hypnotic, effects of EtOH.

Dextromethorphan

There was a significant effect of MK-801 ($F2,42=138.71$, $p<.01$) but not dextromethorphan and no inter-drug interaction for delta latency to fall. MK-801 pre-treatment promoted EtOH-induced ataxia relative to vehicle pre-treatment (Fig. 2A).

Prior to MK-801 and EtOH treatment, the highest dose of dextromethorphan significantly decreased core body temperature relative to vehicle ($F2,45=8.89$, $p<.01$; 0 mg/kg=38.1 ±0.1 °C, 30 mg/kg=37.9 ±0.1, 60 mg/kg=37.0 ±0.3). Neither dextromethorphan nor MK-801 altered the hypothermic effects of EtOH (Fig. 2B).

There was a significant effect of MK-801 (F1,42=330.78, $p<.01$) and dextromethorphan (F2,42=4.50, $p<.05$) but no inter-drug interaction for sleep time. The 60 mg/kg dose of dextromethorphan treatment produced a non-significant trend (as measured by *post hoc* tests) for prolonged EtOH-induced sleep time relative to vehicle (Fig. 2C). MK-801 pre-treatment prolonged EtOH-induced sleep time relative to vehicle pre-treatment. There was a significant dextromethorphan x MK-801 interaction for BECs at recovery (F2,41=14.52, $p<.01$). *Post hoc* tests showed that BECs were significantly lower in MK-801 pre-treated mice than in mice pre-treated with vehicle, irrespective of dextromethorphan treatment (Supplemental Table 1). There was a significant negative correlation between sleep time duration and BECs at recovery ($R^2=.89$, $p<.01$, Supplemental Fig. 3B).

To summarize, dextromethorphan failed to alter the ataxic, hypothermic or sedative/hypnotic effects of EtOH.

Haloperidol

There was a significant interaction between haloperidol and MK-801 (F2,46=4.51, $p<.05$) for delta latency to fall. *Post hoc* analysis showed that 0.3 mg/kg haloperidol significantly promoted EtOH-induced ataxia relative to vehicle, while MK-801 pre-treatment increased EtOH-induced ataxia in mice that also received vehicle or 0.15 mg/kg, but not 0.3 mg/kg, haloperidol (Fig. 3A).

Neither baseline nor EtOH-induced hypothermia was affected by haloperidol or MK-801 (Fig. 3B).

There was a significant MK-801 x haloperidol interaction for sleep time (F2,43=14.13, $p<.01$). *Post hoc* analysis showed that showed that 0.3 mg/kg haloperidol increased EtOH-induced sleep time relative to vehicle, to a level equivalent to that produced by MK-801 pre-treatment (Fig. 3C). There was a significant haloperidol x MK-801 interaction for BECs at recovery (F2,41=14.52, $p<.01$). *Post hoc* analysis revealed that BECs were lower at recovery in haloperidol treated mice regardless of topiramate treatment (Supplemental Table 1). There was a significant negative correlation between sleep time duration and BECs at recovery ($R^2=.67$, $p<.01$, Supplemental Fig. 3C).

In summary, haloperidol potentiated the ataxic and sedative/hypnotic, but not hypothermic, effects of EtOH.

Lamotrigine

There was a significant effect of lamotrigine (F2,51=4.29, $p<.05$) and MK-801 (F1,51=83.40, $p<.01$) but no inter-drug interaction for delta latency to fall. The 30 mg/kg dose of lamotrigine treatment produced a non-significant trend (as determined by *post hoc* tests) for potentiated EtOH-induced ataxia relative to vehicle (Fig. 2A). MK-801 pre-treatment promoted EtOH-induced ataxia relative to vehicle pre-treatment (Fig. 4A).

Prior to MK-801 or EtOH treatment, lamotrigine dose-dependently decreased core temperature relative to vehicle (F2,53=16.99, $p<.01$; 0 mg/kg=37.9 ±0.1°C change, 15 mg/

kg=35.9 ±0.4, 30 mg/kg=34.3 ±0.5). However, neither lamotrigine nor MK-801 affected EtOH-induced hypothermia (Fig. 4B).

There was a significant MK-801 x lamotrigine interaction for sleep time ($F_{2,44}=4.42$, $p<.01$). *Post hoc* analysis showed that 30 mg/kg lamotrigine increased EtOH-induced sleep time relative to vehicle. MK-801 pre-treatment increased EtOH-induced sleep time in mice that also received vehicle or 15 mg/kg, but not 30 mg/kg, lamotrigine — however, the lack of MK-801 effect at the highest lamotrigine dose could be due to a 'ceiling effect' given the 180 min sleep time cutoff at which point we ended experiments (Fig. 4C). There was a significant lamotrigine x MK-801 interaction for BECs at recovery ($F_{2,41}=14.52$, $p<.01$). *Post hoc* analysis revealed lower BECs after MK-801 pre-treatment regardless of lamotrigine treatment (Supplemental Table 1). There was a significant negative relationship between sleep time duration and recovery BECs ($R^2=.26$, $p<.01$, Supplemental Fig. 3D).

To summarize, lamotrigine potentiated the sedative/hypnotic, but not ataxic or hypothermic, effects of EtOH.

Oxcarbazepine

There was a significant effect of MK-801 ($F_{2,42}=72.75$, $p<.01$) but not oxcarbazepine and no drug interaction for delta latency to fall. MK-801 pre-treatment promoted EtOH-induced ataxia relative to vehicle pre-treatment (Fig. 5A).

Prior to MK-801 or EtOH treatment, the highest dose of oxcarbazepine *per se* produced a significant decrease in body temperature relative to vehicle ($F_{2,45}=6.34$, $p<.01$; 0 mg/kg=37.1 ±0.2°C, 25 mg/kg=35.7 ±0.3, 50 mg/kg=34.2 ±0.8). However, neither oxcarbazepine nor MK-801 altered the EtOH-induced hypothermia (Fig. 5B).

There was a significant effect of MK-801 ($F_{1,41}=168.19$, $p<.01$) and oxcarbazepine ($F_{2,41}=8.77$, $p<.01$) but no interaction for sleep time. *Post hoc* analysis showed that 50 mg/kg oxcarbazepine dose produced a non-significant trend for prolonged EtOH-induced sleep time relative to vehicle (Fig. 5C). MK-801 pre-treatment prolonged EtOH-induced sleep time relative to vehicle pre-treatment. Mice pre-treated with MK-801 also showed lower BECs at recovery than vehicle pre-treated mice ($F_{2,41}=103.33$, $p<.01$) (Supplemental Table 1). There was a significant negative correlation between sleep time and recovery BECs ($R^2=.66$, $p<.01$, Supplemental Fig. 3E).

In summary, oxcarbazepine did not reliably potentiate either the ataxic, hypothermia or sedative/hypnotic effects of EtOH.

Topiramate

There was a significant effect of topiramate ($F_{2,42}=3.26$, $p<.05$) and MK-801 ($F_{1,42}=66.58$, $p<.01$) but no inter-drug interaction for delta latency to fall. There was a non-significant (as determined by *post hoc* tests) trend for both topiramate doses to potentiate EtOH-induced ataxia relative to vehicle (Fig. 6A). MK-801 pre-treatment significantly potentiated EtOH-induced ataxia relative to vehicle pre-treatment, irrespective of topiramate treatment.

Neither baseline nor EtOH-induced hypothermia was affected by topiramate or MK-801 (Fig. 6B).

There was a significant topiramate x MK-801 interaction for sleep time ($F_{2,41}=13.59$, $p<.01$). *Post hoc* analysis showed that while topiramate *per se* had no effect on EtOH-induced sleep time, the drug dose-dependently enhanced MK-801-potentiation of EtOH-induced sleep time (Fig. 6C). There was also a significant topiramate x MK-801 interaction for BECs at recovery ($F_{2,41}=14.52$, $p<.01$). *Post hoc* showed that BECs were lower after MK-801 pre-treatment relative to vehicle pre-treatment regardless of topiramate dose (Supplemental Table 1). There was a significant negative correlation between sleep time duration and BECs at recovery ($R^2=.78$, $p<.01$, Supplemental Fig. 3F).

In summary, topiramate *per se* did not affect the ataxic, hypothermic or sedative/hypnotic effects of EtOH in C57BL/6J mice, but augmented the pro-sedative/hypnotic effects of MK-801.

Topiramate across strains

There was a significant strain x topiramate interaction ($F_{2,50}=4.14$, $p<.05$). *Post hoc* showed that topiramate increased EtOH-induced sleep time relative to vehicle in BALB/cJ, but not C57BL/6J, 129S1 or DBA/2J (Fig. 7). In vehicle-treated mice, sleep time was higher in 129S1 than BALB/cJ, C57BL/6J and DBA/2J, and higher in DBA/2J than C57BL/6J. There was a significant strain x topiramate interaction for BECs at recovery ($F_{3,49}=3.73$, $p<.05$). *Post hoc* analysis found lower BECs in 129S1 than the other 3 strains, regardless of treatment (Supplemental Table 2). There was a borderline significant trend ($p=.0782$) for lower BECs in topiramate-treated BALB/cJ relative to vehicle-treated BALB/cJ counterparts.

Topiramate after chronic stress

There was a significant effect of stress ($F_{1,28}=6.17$, $p<.05$) and topiramate ($F_{1,28}=7.63$, $p<.05$) and a non-significant stress x topiramate interaction. Planned *post hoc* comparisons showed topiramate increased EtOH-induced sleep time in stressed mice but not non-stressed controls (Fig. 8). In vehicle-treated mice, sleep time did not differ between stressed and non-stressed groups. BECs were not analyzed in this experiment as we have previously found no effect of stress on BECs in C57BL/6J (Boyce-Rustay et al., 2007).

Discussion

The current study assessed the effects of various ‘anti-glutamatergic’ drugs with clinical promise as novel alcoholism treatments for effects on the acute intoxicating actions of EtOH. Results are summarized in Supplemental Table 3.

The first finding was that the uncompetitive NMDAR antagonist, MK-801, reliably potentiated the ataxic and sedative/hypnotic effects of acute EtOH, consistent with previous studies (e.g., Boyce-Rustay and Holmes, 2005; Kuribara, 1994; Meyer and Phillips, 2003; Palachick et al., 2008; Shen and Phillips, 1998; Vanover, 1999; Wilson et al., 1990). By contrast, MK-801 did not affect EtOH-induced hypothermia, and did not appear to impair

EtOH metabolism, at least as evidenced by a negative relationship between sleep time duration and lesser BECs. The same was true for the other six compounds tested. This pattern of findings argues against the possibility that any of these drugs affected sensitivity to EtOH's behavioral actions by disrupting EtOH's pharmacokinetic effects.

While MK-801 effects targets other than the NMDAR, including dopamine (Seeman et al., 2005), norepinephrine (Snell et al., 1988) and acetylcholine (Ramoa et al., 1990), it is likely that the drug's EtOH-potentiating effects are due in large part to antagonism of NMDARs. As such, because memantine and dextromethorphan also act as uncompetitive NMDAR antagonists, they might be expected to mimic the EtOH-potentiating effects of MK-801. Indeed, akin to the ability of the NMDAR antagonist ketamine to mimic subjective intoxicating effects of EtOH (Krystal et al., 2003), memantine potentiated the dissociative effects of EtOH in human volunteers (Bisaga and Evans, 2004), although the same study did not observe an effect on EtOH-induced stimulation or sedation. Dextromethorphan has also been found to mimic the intoxicating effects of EtOH in healthy volunteers and detoxified alcoholics and produce mild craving in the latter (Soyka et al., 2000). In rodents, previous studies found that dextromethorphan attenuates EtOH-withdrawal (Erden et al., 1999) and memantine reduces EtOH self-administration, particularly under conditions such as deprivation or limited access (Holter et al., 1996; Piasecki et al., 1998). Current data showed that memantine significantly potentiated EtOH-induced ataxia on the rotarod test, but did not affect EtOH-induced sedation/hypnosis. On the other hand, dextromethorphan had no effects on either measure at the doses tested. The reason why these drugs did not fully recapitulate the effects of MK-801 is not fully clear. The most parsimonious explanation is that they have lesser affinity for NMDARs than MK-801 (see Parsons et al., 1999), although their actions at other targets such as 5-HT3, dopamine D2 and nicotinic receptors may also have contributed to their pharmacodynamic profile (Aracava et al., 2005; Nankai et al., 1995; Rammes et al., 2001; Seeman et al., 2008).

Though haloperidol is a potent dopamine D2 receptor antagonist, this drug also blocks NMDAR (*in vitro*) amongst its various other actions (Lynch and Gallagher, 1996). Interestingly, haloperidol exerted effects on EtOH sensitivity that were stronger than either memantine or dextromethorphan and, at the higher dose (0.3 mg/kg), actually of a similar magnitude to those produced by MK-801. These data are in agreement with previous studies demonstrating that haloperidol produced effects on EtOH-induced sedation/hypnosis as well as other EtOH-related behaviors that are similar to those produced by NMDAR antagonists, including suppression of EtOH self-administration and attenuation of EtOH-withdrawal (Broadbent et al., 1995; Cohen et al., 1997; Cunningham et al., 1992; Files et al., 1998; Overstreet et al., 2007; Risinger et al., 1992; Uzbay et al., 1994). On the other hand, in contrast to NMDAR inactivation (Boyce-Rustay and Cunningham, 2004; Boyce-Rustay and Holmes, 2006) haloperidol does not block EtOH conditioned place preference (Cunningham et al., 1992; Risinger et al., 1992). Thus, while these data and current findings suggest that anti-glutamatergic activity could contribute to haloperidol's effects on EtOH-related behaviors, the available evidence is not fully consistent and remains indirect. Nonetheless, these data speak to the clinical utility of this antipsychotic drug for treating alcoholism co-morbid with psychosis (Coyle, 2006).

There is growing interest in the therapeutic potential of anticonvulsants for alcoholism. Topiramate, lamotrigine and oxcarbazepine inhibit glutamate release, probably via blockade of voltage-gated sodium and calcium channels (Ahmad et al., 2004b; Cunningham and Jones, 2000; Lees and Leach, 1993; Sitges et al., 2007; Waldmeier et al., 1995; Wang et al., 1996; Wang et al., 2001). However, as with memantine, dextromethorphan and haloperidol, it is important to note that the pharmacological actions of these drugs are not restricted to anti-glutamatergic effects. For example, topiramate activates gamma-aminobutyric acid (GABA) receptors (Gordey et al., 2000; Sitges et al., 2007; White et al., 2007), and lamotrigine increases GABA release and inhibits extracellular levels of serotonin and dopamine (Ahmad et al., 2004a; Cunningham and Jones, 2000; Lees and Leach, 1993; Waldmeier et al., 1995). One or more of these actions could potentially contribute to the *in vivo* effects of these drugs on EtOH-related behaviors along with their anti-glutamatergic properties. In this context, lamotrigine has been found to attenuate cue-induced alcohol-seeking in rats (Vengeliene et al., 2007) but has no effect on EtOH-withdrawal anxiety-like behavior (Knapp et al., 2007b). Moreover, while there are to our knowledge no published reports of oxcarbazepine effects on rodent EtOH-related behaviors, topiramate has no effect on EtOH conditioned place preference but does attenuate EtOH withdrawal and drinking, perhaps most robustly after EtOH deprivation (Cagetti et al., 2004; Farook et al., 2007; Gabriel and Cunningham, 2005; Gremel et al., 2006; Hargreaves and McGregor, 2007; Knapp et al., 2007a; Nguyen et al., 2007).

The current experiments found that these compounds were largely devoid of effects on acute sensitivity to EtOH in the reference mouse strain C57BL/6J. Although the highest dose of lamotrigine tested promoted EtOH's sedative/hypnotic effects, this was associated with a hypothermic effect of lamotrigine treatment *per se* and it is unclear whether prolonged sleep time in response to EtOH was caused by loss of core body temperature. Therefore, one interpretation of these negative data is the increased sensitivity to the intoxicating effects of EtOH is not a major mechanism of action driving the anti-alcohol efficacy of these compounds. However, a number of additional findings point to a more nuanced conclusion. First, topiramate produced a significant increase (and lamotrigine a non-significant trend) in sleep time when mice were co-treated with MK-801. This synergistic-like effect could reflect the combined effects of glutamate release inhibition and NMDAR blockade, which would in turn demonstrate that topiramate effects can be unmasked under conditions of reduced NMDAR function. Second, despite showing no differences in baseline sleep responses to EtOH as compared to C57BL/6J, the BALB/cJ strain exhibited a clear EtOH-potentiating response to topiramate. Interestingly, the BALB/cJ strain is characterized as a relatively stress-reactive, ‘anxious’ strain of mouse (e.g., Belzung, 2001; Norcross et al., 2008). This is noteworthy in the context of the third finding that the normally topiramate-unresponsive C57BL/6J strain could also be rendered sensitive to the drugs pro-EtOH-sedating effects following chronic stress exposure. Stress *per se* had minimal effects on EtOH-induced sleep, consistent with previous reports at this dose (Boyce-Rustay et al., 2007; Boyce-Rustay et al., 2008b). Thus, taken together our data show that topiramate did promote the intoxicating effects of EtOH, but did so in a manner dependent upon NMDAR availability, genetic background and stress exposure.

These findings raise a number of important issues for future research. One obvious question is whether the other anti-glutamatergic compounds tested herein also show interactions with stress and genetic background. A second key issue is how the profile of these drugs might differ in C57BL/6J mice rendered EtOH-dependent (e.g., Becker and Lopez, 2004). EtOH-dependence not only better models the clinical state, but current theories posit that the development of dependence is associated with increased glutamatergic signaling (Heilig and Egli, 2006; Koob, 2003; Spanagel and Kiefer, 2008). As such, it will be interesting to assess whether topiramate and other anti-glutamatergic drugs promote EtOH intoxication in post-dependent mice, such as C57BL/6J, that are insensitive under baseline conditions.

In summary, the current study found that memantine significantly potentiated the ataxic effects of EtOH, while another compound that also has NMDAR antagonist properties, dextromethorphan, failed to affect three measures of EtOH sensitivity. The antipsychotic haloperidol strongly promoted both the ataxic and sedative/hypnotic effects of EtOH to a similar degree as the prototypical NMDAR antagonist MK-801, but it is unclear to what extent, if any, these effects were due to haloperidol's actions at NMDARs. The anticonvulsants lamotrigine, oxcarbazepine and topiramate largely failed to alter the acute intoxicating effects of EtOH in C57BL/6J under baseline conditions. Importantly however, topiramate significantly potentiated EtOH-induced sedation/hypnosis in the BALB/cJ strain, and in C57BL/6J either co-treated with MK-801 or exposed to chronic swim stress. Although future studies are needed in rodent models and human subjects, these data lend tentative support for the hypothesis that topiramate, and possibly other clinically tolerated anti-glutamatergic drugs, promote the intoxicating effects of alcohol in genetically- or life history-defined sub-populations, and that these actions may contribute to the drugs' profile as treatments for alcoholism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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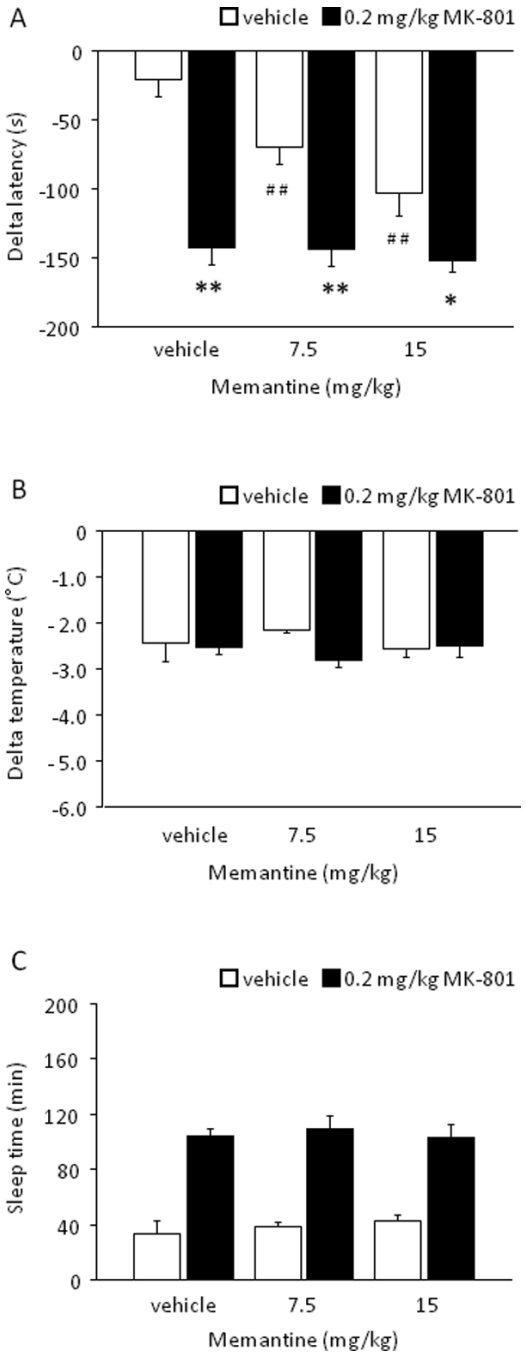

Fig. 1.

Effects of memantine and MK-801. (A) Both memantine and MK-801 potentiated 1.75 g/kg EtOH-induced ataxia (n=8/dose). (B) Neither memantine nor MK-801 affected 3.0 g/kg EtOH-induced hypothermia (n=8/dose). (D) MK-801 but not memantine potentiated 3.0 g/kg EtOH-induced sedation/hypnosis (n=7−8/dose). ***p*<.01, **p*<.05 vs. vehicle (open bars) at the same memantine dose; ##*p*<.01 vs. vehicle/vehicle. Data in Figs 1-8 are Means ±SEM.

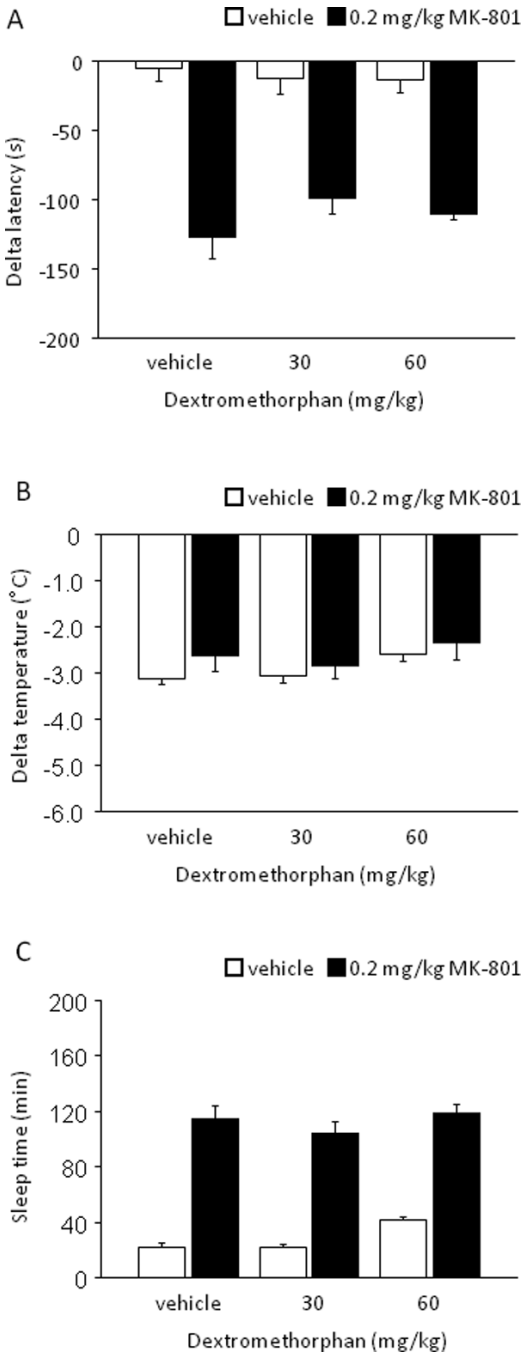

Fig. 2.

Effects of dextromethorphan and MK-801. (A) MK-801 but not dextromethorphan potentiated 1.75 g/kg EtOH-induced ataxia (n=8/dose). (B) Neither dextromethorphan nor MK-801 affected 3.0 g/kg EtOH-induced hypothermia (n=8/dose). (C) MK-801 but not dextromethorphan potentiated EtOH-induced 3.0 g/kg sedation/hypnosis (n=8/dose).

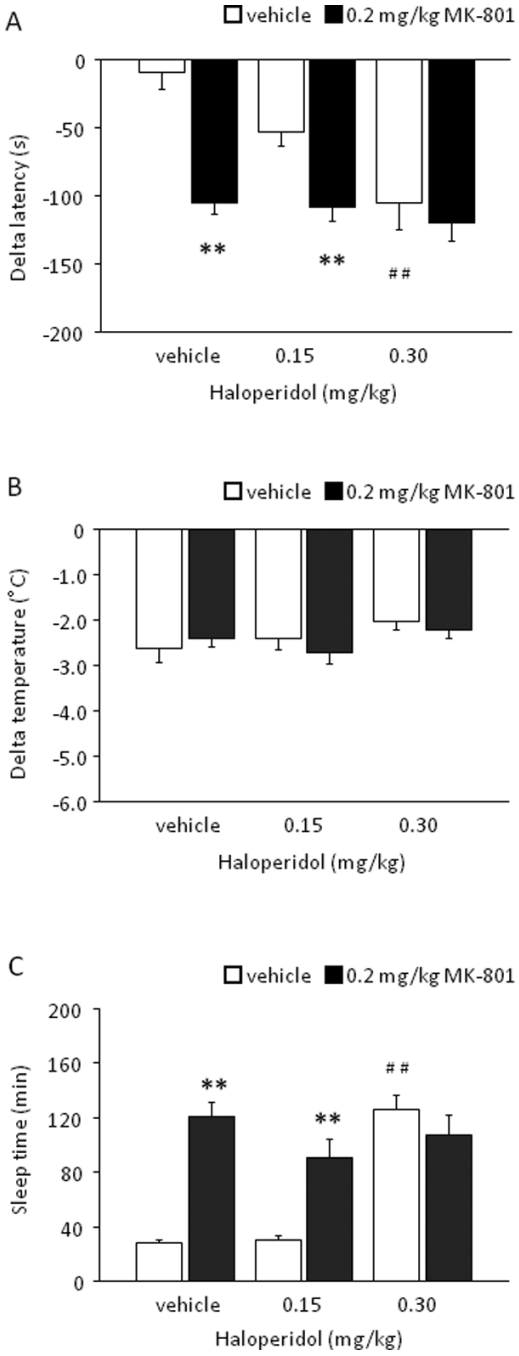

Fig. 3.

Effects of haloperidol and MK-801. (A) Both haloperidol and MK-801 potentiated 1.75 g/kg EtOH-induced ataxia (n=7−10/dose). (B) Neither MK-801 nor haloperidol affected 3.0 g/kg EtOH-induced hypothermia (n=7−10/dose). (C) Both haloperidol and MK-801 potentiated 3.0 g/kg EtOH-induced sedation/hypnosis (n=7−10/dose). ***p*<.01 vs. vehicle (open bars) at the same haloperidol dose; ##*p*<.01 vs. vehicle/vehicle.

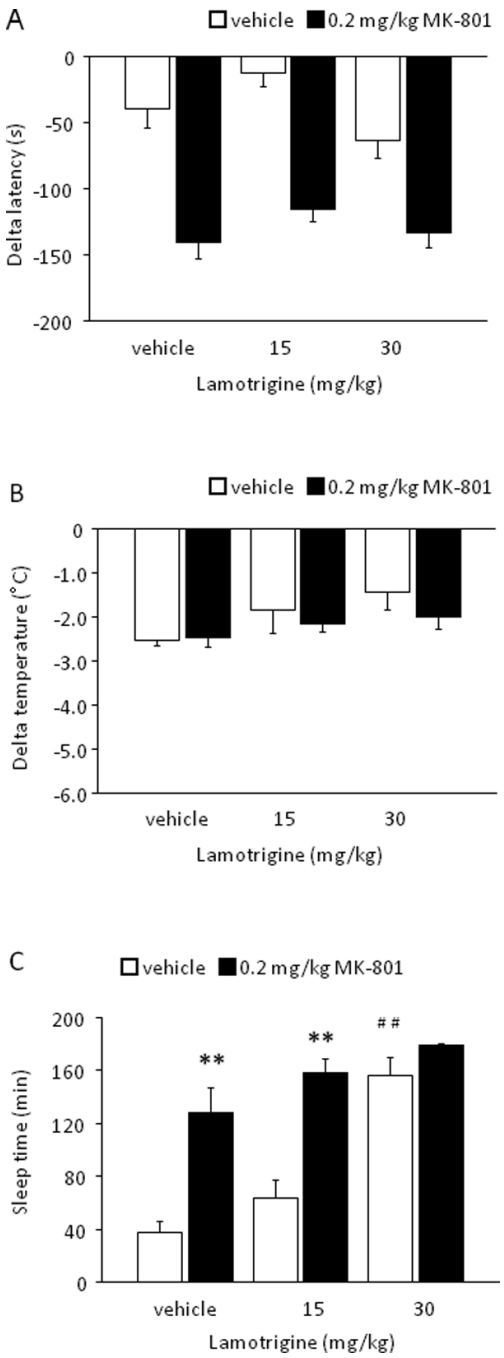

Fig. 4.

Effects of lamotrigine and MK-801. (A) MK-801 but not lamotrigine potentiated 1.75 g/kg EtOH-induced ataxia (n=9−11/dose). (B) Neither lamotrigine nor MK-801 affected 3.0 g/kg EtOH-induced hypothermia (n=8−12/dose). (C) Both lamotrigine and MK-801 potentiated 3.0 g/kg EtOH-induced sedation/hypnosis (n=7−10/dose). ***p*<.01 vs. vehicle (open bars) at the same lamotrigine dose; ##*p*<.01 vs. vehicle/vehicle.

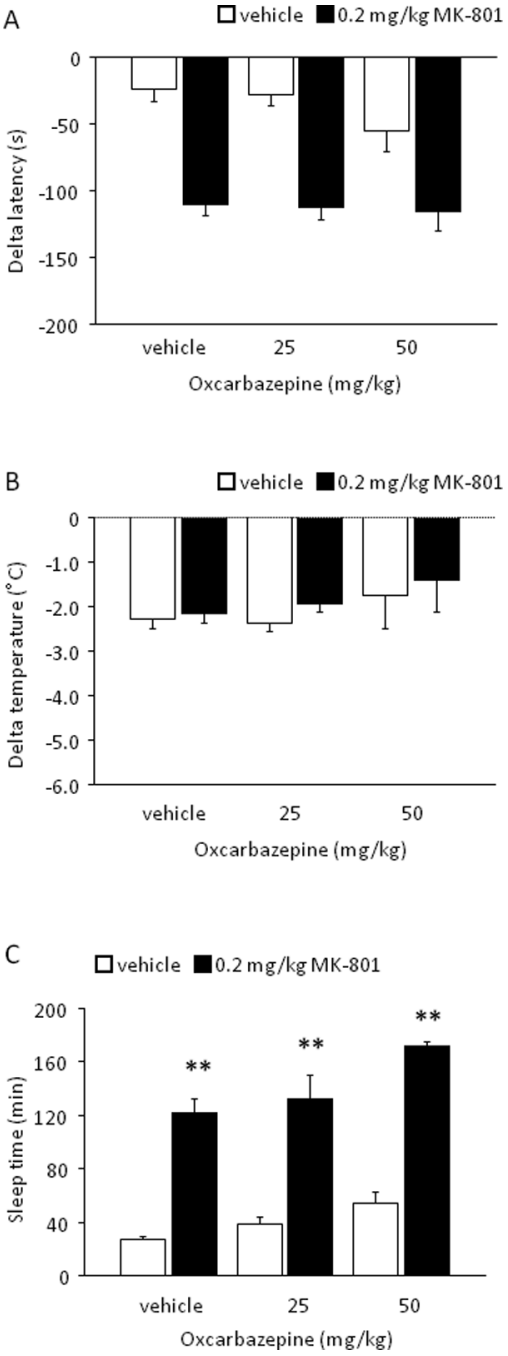

Fig. 5.

Effects of oxcarbazepine and MK-801. (A) MK-801 but not oxcarbazepine potentiated 1.75 g/kg EtOH-induced ataxia (n=8/dose). (B) Neither MK-801 nor oxcarbazepine affected 3.0 g/kg EtOH-induced hypothermia (n=7−8/dose). (C) MK-801 but not oxcarbazepine potentiated 3.0 g/kg EtOH-induced sedation/hypnosis (n=7−8/dose). ***p*<.01 vs. vehicle (open bars) at the same oxcarbazepine dose.

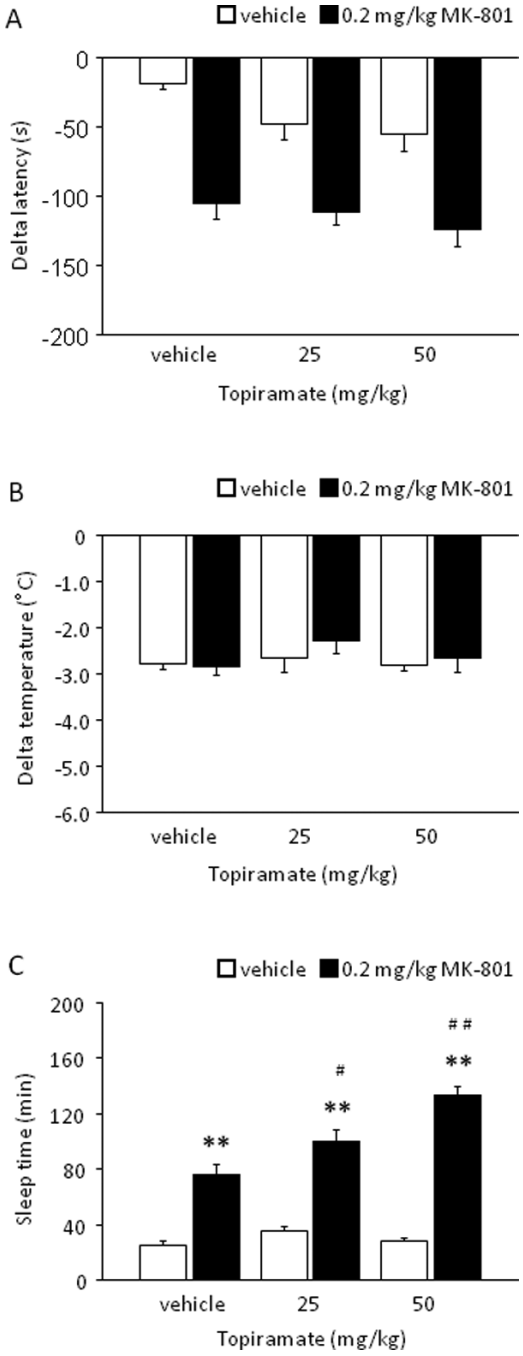

Fig. 6.

Effects of topiramate and MK-801. (A) MK-801 but not topiramate potentiated 1.75 g/kg EtOH-induced ataxia (n=8/dose). (B) Neither MK-801 nor topiramate affected 3.0 g/kg EtOH-induced hypothermia (n=8−9/dose). (C) MK-801 but not topiramate potentiated 3.0 g/kg EtOH-induced sedation/hypnosis, while topiramate augmented MK-801's EtOH-potentiating effects (n=7−8/dose). ***p*<.01 vs. vehicle (open bars) at the same topiramate dose; ##*p*<.01, #*p*<.05 vs. vehicle/vehicle.

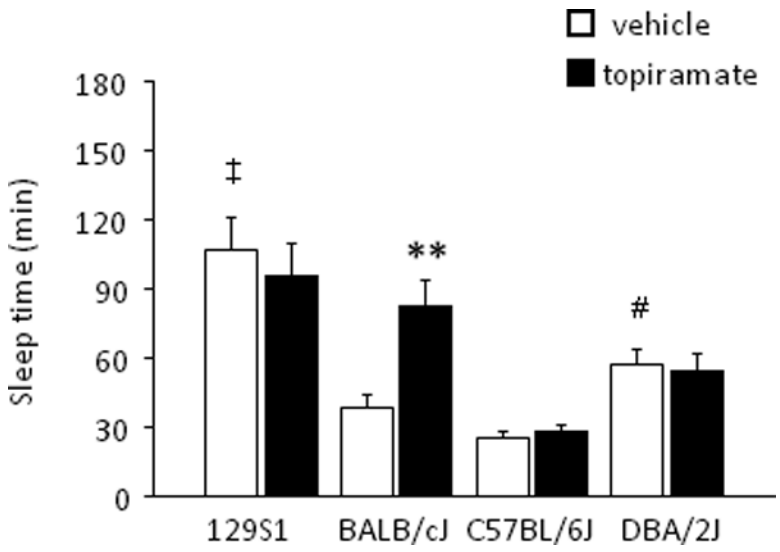

Fig. 7.

Effects of topiramate across inbred strains. Topiramate potentiated 3.0 g/kg EtOH-induced sedation/hypnosis in BALB/cJ but not 129S1, C57BL/6J or DBA/2J. n=6-8/dose/strain. ‡ $p<.01$ vs. all other vehicle-treated strains; ** $p<.01$ vs. vehicle-treated BALB/cJ; # $p<.05$ vs. C57BL/6J.

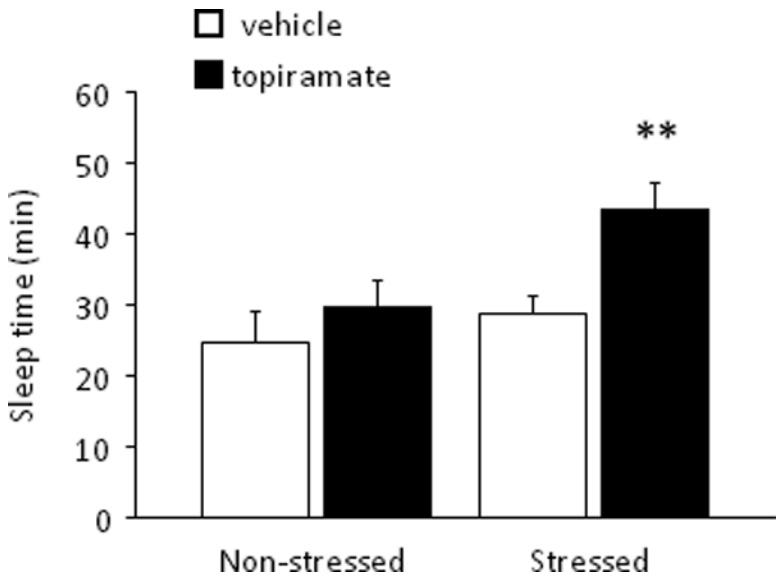

Fig. 8.

Effects of topiramate following exposure to chronic stress. Topiramate potentiated 3.0 g/kg EtOH-induced sedation/hypnosis in C57BL/6J mice exposed to chronic swim stress, but not non-stressed controls. n=8/dose/stress condition. ***p*<.01 vs. vehicle-treated stressed.