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Glutamatergic targets for new alcohol medications

Andrew Holmes,
Laboratory of Behavioral and Genomic Neuroscience, National Institute on Alcohol Abuse and Alcoholism, NIH, Bethesda, MD, USA. 5625 Fishers Lane Room 2N09, Rockville, MD 20852-9411, USA

Rainer Spanagel, and
Institute of Psychopharmacology, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany

John H. Krystal
NIAAA Center for the Translational Neuroscience of Alcoholism, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Andrew Holmes: holmesan@mail.nih.gov

Abstract

Rationale—An increasingly compelling literature points to a major role for the glutamate system in mediating the effects of alcohol on behavior and the pathophysiology of alcoholism. Preclinical studies indicate that glutamate signaling mediates certain aspects of ethanol's intoxicating and rewarding effects, and undergoes adaptations following chronic alcohol exposure that may contribute to the withdrawal, craving and compulsive drug-seeking that drive alcohol abuse and alcoholism.

Objectives—We discuss the potential for targeting the glutamate system as a novel pharmacotherapeutic approach to treating alcohol use disorders, focusing on five major components of the glutamate system: the *N*-methyl-D-aspartate (NMDA) receptor and specific NMDA subunits, the glycine$_B$ site on the NMDA receptors (NMDAR), L-alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ionotropic (AMPA) and kainate (KAR) receptors, metabotropic receptors (mGluR), and glutamate transporters.

Results—Chronic alcohol abuse produces a hyperglutamatergic state, characterized by elevated extracellular glutamate and altered glutamate receptors and transporters. Pharmacologically manipulating glutamatergic neurotransmission alters alcohol-related behaviors including intoxication, withdrawal, and alcohol-seeking, in rodents and human subjects. Blocking NMDA and AMPA receptors reduces alcohol consumption in rodents, but side-effects may limit this as a therapeutic approach. Selectively targeting NMDA and AMPA receptor subunits (e.g., GluN2B, GluA3), or the NMDAR glycine$_B$ site offers an alternative approach. Blocking mGluR5 potently affects various alcohol-related behaviors in rodents, and mGluR2/3 agonism also suppresses alcohol consumption. Finally, glutamate transporter upregulation may mitigate behavioral and neurotoxic sequelae of excess glutamate caused by alcohol.

Conclusions—Despite the many challenges that remain, targeting the glutamate system offers genuine promise for developing new treatments for alcoholism.

Correspondence to: Andrew Holmes, holmesan@mail.nih.gov.

Keywords

Ethanol; Craving; NMDA; GluN2A; GluN2B; mGluR2/3; mGluR5; Memantine; Addiction; Glycine

The burden and costs of alcohol abuse

Problems that arise from excessive drinking, bingeing and the long-term chronic abuse of alcohol represent a major public health issue. In the USA, it is estimated that more than 10 % of the population have an alcohol use disorder (NIAAA 2000) while, worldwide, more than 2 billion people consume alcohol and around 6 % of adults have an alcohol use disorder (Rehm et al. 2009). Almost 4 % of deaths worldwide are attributed to alcohol; accounting for one in every ten European male deaths (Rehm et al. 2009). Alcohol abuse accounts for nearly 5 % of premature death and disability caused by disease and injury, and 30–40 % of the death and disability that is specifically attributable to neuropsychiatric disease (Rehm et al. 2009). Of the risk factors for global death and disability, alcohol use was found to rank third, behind only hypertension and tobacco smoking (Lim et al. 2012) (Fig. 1). Correspondingly, health care costs associated with alcohol abuse are on the order of $30 billion per year in the USA alone (Rehm et al. 2009). Adding in other factors indirectly linked to alcohol abuse, such as loss of economic productivity due to days off work, the annual cost to the United States economy was estimated to be $185 billion in the year 2000 and has likely grown further since then (NIAAA 2000).

Glutamate signaling as a target for new alcoholism treatments

While the problem of alcohol abuse continues to grow, the options currently available to treat these conditions remain inadequate and are prescribed at low rates (Iheanacho et al. 2013). Recent meta-analyses have concluded that both the opioid receptor blocker naltrexone (Revia, Vivitrol) and the mixed-pharmacology compound acamprosate (Campral) can significantly reduce heavy drinking and promote abstinence relative to placebo, with better outcomes typically seen for acamprosate (Maisel et al. 2013). However, despite the promise of early clinical data (Garbutt et al. 1999), the long-term efficacy of naltrexone has proven modest (Fuller et al. 1986; Krystal et al. 2001). In large-scale clinical trials and multicenter studies including Project COMBINE, the largest alcoholism pharmacotherapy trial conducted to date, naltrexone was ineffective when combined with cognitive–behavioral therapy and only had a small effect size (0.2) when combined with medication management therapy, while acamprosate was completely ineffective (Anton et al. 2006). Acamprosate also failed to meet its primary efficacy endpoint in its initial large multicenter trial in the United States (Mason et al. 2006a). The effect size for long-acting injectable naltrexone was marginally higher (Garbutt et al. 2005), but it is not clear whether this reflects greater medication efficacy or the selection of patients willing to accept injectable medications.

In the face of compelling need, the field of alcohol research must explore new directions to identify novel therapeutics. There are a variety of putatively therapeutic targets in several neurotransmitter and neuropeptide systems (Vengeliene et al. 2008a). Of these, there has been growing interest in developing pharmacotherapies for alcoholism around the glutamate system (Spanagel and Vengeliene 2013), as there has been for anxiety disorders (Conn and Jones 2009), depression (Skolnick et al. 2009) and schizophrenia (Coyle 2006).

Currently, two medications that have been studied extensively as alcoholism pharmacotherapies, acamprosate and the anticonvulsant topiramate, appear to have direct effects on glutamatergic neurotransmission. However, although acamprosate was initially

thought to act in part by inhibiting *N*-methyl-D-aspartate receptors (NMDAR) and metabotropic glutamate (mGluR5) receptors (Dahchour and De Witte 2003; Popp and Lovinger 2000), actions on these receptors remain unclear (Brasser et al. 2004; Spanagel et al. 1996), especially at the plasma levels typically achieved in humans with oral administration (Johnson et al. 2003b) (c.f. Burattini et al. 2008). Topiramate is often used, off-label, as a treatment for alcoholism, and inhibits glutamate release and blocks L-alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid ionotropic (AMPAR)/ kainate receptors (KAR) as part of a complex pharmacological profile. In rodents, topiramate promotes alcohol intoxication and reduces alcohol drinking and withdrawal, but does not disrupt alcohol place preference (Breslin et al. 2010; Cagetti et al. 2004; Chen and Holmes 2009; Farook et al. 2007; Gremel et al. 2006; Hargreaves and McGregor 2007; Knapp et al. 2007; Lynch et al. 2011; Nguyen et al. 2007; Zalewska-Kaszubska et al. 2013). Topiramate also reduces craving, withdrawal and drinking in alcoholics (Baltieri et al. 2008; Florez et al. 2008; Johnson et al. 2004; Johnson et al. 2003a; Johnson et al. 2007; Komanduri 2003; Krupitsky et al. 2007b; Miranda et al. 2008; Paparrigopoulos et al. 2011; Rubio et al. 2004; Rustembegovic et al. 2002).

The example of topiramate supports the potential of developing other glutamate-targeting drugs for alcoholism. However, the complexity of glutamate neurotransmission makes designing safe, selective and efficacious drugs that target the system a very difficult task. On the other hand, because there are numerous ways to modulate this system, it affords many potential targets. In addition, the glutamatergic system might be a particularly attractive target for anti-alcohol medications due to its involvement in various aspects not only of alcohol's behavioral effects, but also in the profound neuroadaptations occurring with chronic alcohol exposure (Tsai and Coyle 1998).

Here, we synthesize the preclinical evidence, along with any salient clinical data, addressing the potential of targeting glutamate neurotransmission for the treatment of alcohol use disorders. We first summarize the major effects of alcohol on glutamate neurotransmission, and then focus on preclinical and clinical studies that have investigated five major components of the glutamate system: NMDAR, the glycine$_B$ site on the NMDAR, AMPAR and KAR, metabotropic receptors (mGluR), and glutamate transporters (Table 1).

Alcohol-induced glutamatergic neuroadaptations

As with other drug addictions, alcohol use disorders progress from initial alcohol sampling to social drinking to habitual or compulsive use (Kalivas and O'Brien 2008). For some, alcohol use disorders are chronic relapsing syndromes. In these cases, alcohol use disorders may be associated with progressive functional impairment, medical and neuropsychiatric complications, and accrual of negative social consequences including divorce, unemployment, and legal problems. The progressive nature of alcoholism implies that brain mechanisms of plasticity are recruited and impaired over the course of the disease.

Glutamate-related neuroplasticity has been implicated in many steps of the progression from social drinking to chronic compulsive alcohol use, including Pavlovian conditioning, the development of alcohol-related habits, sensitization to the effects of alcohol, and "kindling" of alcohol withdrawal symptoms (Krystal et al. 2003). Glutamatergic agents might play several roles in the treatment of alcoholism including reducing alcohol consumption, suppressing alcohol withdrawal, and reducing neuroplasticity associated with intoxication and withdrawal (Krystal et al. 2003). Thus, these drugs might attenuate the progression of alcohol use disorders in addition to treating symptoms associated with particular states or phases of these disorders.

There is evidence that the neuroadaptations resulting from chronic alcohol abuse aggregate into a hyperglutamatergic state, typified by elevated extracellular glutamate levels and alterations in glutamate receptors and transporters (Krystal et al. 2003; Tsai and Coyle 1998) (summarized in Fig. 2). Elevated levels of excitatory amino acids are reported in the cerebrospinal fluid (CSF) of alcohol-dependent patients (Tsai et al. 1998) and severity of alcohol dependence, as measured by the Alcohol Dependence Severity Scale, positively correlates with CSF glutamate (Umhau et al. 2010). Magnetic resonance imaging studies have found that glutamate levels in the hippocampus and anterior cingulate cortex are increased during early withdrawal, but return to normal within 3 days post-withdrawal (Hermann et al. 2012; Mason et al. 2006b; Mon et al. 2012). This suggests that enhanced glutamate levels might occur during early conditioned withdrawal in abstinent alcohol-dependent patients—a hypothesis supported by evidence in animals showing increases in extracellular glutamate in rodent forebrain regions during acute alcohol withdrawal (Rossetti and Carboni 1995). A recent meta-analysis of rodent microdialysis studies confirmed elevated extracellular concentrations of glutamate in several brain regions and found that these increases, particularly within the nucleus accumbens, strongly correlated with the severity of alcohol withdrawal (Fliegel et al. 2013). Collectively, these findings illustrate a central role for glutamate in inducing and maintaining some of the adverse long-term behavioral effects of alcohol abuse. By extension, this predicts that drugs modulating glutamate activity may be useful as treatments for alcoholism. Here, we review the available evidence on the potential for developing drugs that target specific glutamate receptors, subunits, and transporters as novel medications for alcoholism.

Glutamatergic targets

NMDA receptors

Acute administration of alcohol inhibits NMDAR function. The manner in which alcohol antagonizes NMDARs is not fully understood, but may be due to direct occupancy, actions on gating and phosphorylation (Lovinger et al. 1989; Woodward 2000). Notwithstanding, the importance of NMDARs to alcohol's pharmacodynamic actions are evidenced by the effect of NMDAR antagonists to mimic the subjective feelings of intoxication in humans (Krupitsky et al. 2007b) and substitute for the discriminative stimulus effects of alcohol in rodents (Gass and Olive 2008; Hundt et al. 1998).

NMDAR ligand binding in human post-mortem brains is increased in cortical and limbic areas of alcoholics in some (Freund and Anderson 1999), but not other studies (Villegas et al. 2011)—perhaps reflecting differences in the extent of alcohol exposure, ante-mortem duration of abstinence, and cumulative effects of alcohol-related neurotoxicity. Abstinent alcoholics have also been shown to have an attenuated response to the perceptual and cognitive effects of the NMDAR antagonist ketamine (Krystal et al. 2003). Studies using distinct pharmacologic probes of NMDAR function have yielded evidence that alcohol dependence and the familial risk for alcoholism are associated with tolerance to the effects of NMDAR antagonists (Petrakis et al. 2004), suggestive of persisting upregulation of NMDAR function.

Rodents chronically exposed to alcohol also exhibit alterations in the expression of NMDARs in various brain regions. Typically, there is an upregulation of NMDARs early in alcohol abstinence that often rapidly normalizes, within days of the last alcohol exposure (for reviews see, Gass and Olive 2008; Kroener et al. 2012; Kumari and Ticku 2000; Ron 2004). However, decreased NMDAR expression and synaptic function, with associated behavioral alterations has also been found after chronic alcohol exposure (Abrahao et al. 2013; Holmes et al. 2012; Meinhardt et al. 2013). Indeed, the net effect of ethanol–NMDAR

inhibition on neural excitability is complex and likely differs across doses, brain regions, and circuits.

In some circuits, inhibition of NMDARs depresses cortical excitability (Thomson et al. 1985), but in others NMDAR inhibition impairs the recruitment of GABA neurons, resulting in glutamatergic disinhibition and enhanced stimulation of non-NMDA glutamate receptors (Grunze et al. 1996; Moghaddam et al. 1997). Alcohol shows this pattern of effect, disinhibiting glutamate release in some circuits at doses associated with human alcohol intoxication, but more uniformly suppressing cortical excitability at higher doses (Moghaddam and Bolinao 1994). However, the facilitatory effects of ethanol on inhibitory neurotransmission may suppress some behavioral effects of potent NMDAR antagonists, such as their psychotomimetic effects (Krystal et al. 2003). Thus, while the effects of potent NMDAR antagonists fully generalize to those of ethanol, ethanol effects only partially generalize to those of NMDAR antagonists (Grant and Colombo 1993). Further, in animals and humans, NMDAR antagonists are more similar to the effects of “heavy” drinking (five or more drinks in men, four or more drinks in women) than lighter forms of drinking (Krystal et al. 1998).

A large body of data demonstrates profound effects of NMDAR blockers on a variety of alcohol behaviors in rodents. For example, treatment with NMDAR channel blockers, such as MK-801 and memantine, potentiate the acute locomotor and sedative effects of alcohol administration (Boyce-Rustay and Cunningham 2004; Chen and Holmes 2009; Kuribara 1994; Meyer and Phillips 2003; Palachick et al. 2008; Shen and Phillips 1998; Vanover 1999; Wilson et al. 1990) (Fig. 3). These drugs can also reduce alcohol self-administration and cue-induced alcohol-seeking (Backstrom and Hyytia 2006; 2007; Rassnick et al. 1992), disrupt reconsolidation of alcohol-related memories (von der Goltz et al. 2009), dampen elevations in drinking produced by periods of forced abstinence (e.g., Vengeliene et al. 2005), and alleviate behavioral and neurotoxic effects of alcohol withdrawal (e.g., Grant et al. 1990; Stepanyan et al. 2008). These findings suggest that NMDAR antagonism could exert a multi-pronged therapeutic profile; partially substituting alcohol to lessen withdrawal and craving, while simultaneously suppressing withdrawal severity and discouraging drinking by reversing tolerance and increasing negative subjective effects of intoxication (Krystal et al. 2003). Neuroprotective effects of blocking NMDARs could also potentially mitigate neurotoxic the effects of alcohol abuse caused by hyperglutamatergia (Crews and Nixon 2009; Sullivan and Pfefferbaum 2005).

The predicted effects of NMDAR antagonists from preclinical studies have been explored to some extent in the clinic with memantine. Memantine has rapid on/off kinetics at the NMDAR, which may account for the drug being safe and well-tolerated with relatively minor abuse and psychotomimetic potential. In alcohol-dependent patients, memantine has been found to reduce withdrawal (Krupitsky et al. 2007b) and cue-induced alcohol craving (Krupitsky et al. 2007a), and to reduce alcohol consumption in moderate drinkers (Bisaga and Evans 2004). Disappointingly, however, neither memantine (in a double-blind study) (Evans et al. 2007) nor the chemically similar compound, neramexane, reduced drinking in rats or prevented relapse in alcohol-dependent patients (Spanagel and Vengeliene 2013). One interpretation of these various negative findings is that NMDAR antagonism may only be sufficient to reduce alcohol abuse in moderate cases, but may be of limited efficacy in preventing drinking in chronic alcoholism. Higher doses of memantine may be needed are needed to produce NMDAR-like substitution effects and thereby reduce craving, drinking, and relapse in such patients. Alternatively, the alcohol-like subjective effects and executive dysfunction produced by these drugs may have obscured their therapeutic effects (Krupitsky et al. 2007a). More clinical work will be needed to clarify these issues.

NMDA receptor subunits—A caveat to developing drugs for alcoholism that target NMDAR is the potential for poor tolerability due to the likelihood of cognitive and perceptual side-effects. Some of these unwanted effects might be avoided by targeting modulatory sites on the NMDAR. NMDARs are heteromeric complexes consisting of two obligatory GluN1 subunits and various combinations of GluN2 (A-D) (and sometimes GluN3) subunits. Subunit composition determines the pharmacological, biophysical and behavioral properties of the receptor (Brigman et al. 2013; Brigman et al. 2010; Woodward 2000). While the direct site of alcohol binding is probably on GluN1 (Ronald et al. 2001), the presence of the GluN2A and GluN2B subunits, in particular, have been shown to determine NMDAR sensitivity to alcohol (Woodward 2000). GluN2A and GluN2B also have intracellular tails with binding sites modulating NMDAR function (e.g., via phosphorylation state) and downstream signaling pathways implicated in alcohol behaviors (reviewed in Chandler 2003; Newton and Messing 2006).

The expression GluN2A and/or GluN2B subunits is altered in the brain after chronic alcohol (Carpenter-Hyland et al. 2004; Kroener et al. 2012; Qiang et al. 2007; Roberto et al. 2004), with some exceptions. For example, prolonged ethanol exposure increased GluN2B gene expression but reduced GluN2A mRNA in rat prefrontal cortex (Meinhardt et al. 2013), and did not alter mRNA for either subunit in postmortem brain or neuronal cultures from alcohol-dependent patients (Lieberman et al. 2012; Ridge et al. 2008). Varying changes in both mRNA and protein levels of these subunits have also been observed in striatal and amygdala subregions following chronic alcohol exposure in rodents (e.g., Falco et al. 2009; Floyd et al. 2003; Lack et al. 2005; Obara et al. 2009) and it remains unclear whether GluN2A and GluN2B expression may be differentially affected by chronic alcohol in vivo.

Parsing the role of GluN2A is hampered by the absence of pharmacological probes selective for this subunit (Kash and Winder 2007; Neyton and Paoletti 2006). However, independent genetic association studies have found a significant relationship between human GluN2A gene variation and alcoholism, an association that appeared to be especially strong in individuals scoring high on stress traits (Domart et al. 2012; Schumann et al. 2008). In an interesting parallel, mouse GluN2A gene deletion increases alcohol-induced ataxia and impairs alcohol conditioned place preference, and also attenuates stress- and anxiety-related behaviors (Boyce-Rustay and Holmes 2006a, b).

Regarding GluN2B, this subunit regulates alcohol-induced synaptic plasticity in the bed nucleus of the stria terminalis (Kash et al. 2008; Wills et al. 2012). Moreover, treatment with the selective GluN2B antagonists ifenprodil and Ro 25-6981 lessens deprivation-induced alcohol drinking (Vengeliene et al. 2005). In contrast to NMDAR channel blockers, however, GluN2B antagonists have minimal effects on acute alcohol intoxication or alcohol conditioned place preference (Boyce-Rustay and Cunningham 2004; Boyce-Rustay and Holmes 2005; Palachick et al. 2008). Interestingly, more selective GluN2B deletion on forebrain pyramidal neurons potentiates some measures of alcohol intoxication (stimulant) while attenuating others (depressant) (Badanich et al. 2011). These preliminary findings warrant follow-up, which will be facilitated by access to brain-penetrant bioavailable GluN2B antagonists, such as AZD 6765, that are currently being investigated for neuropsychiatric conditions such as major depression (Zarate et al. 2012).

Finally, the potential for targeting NMDAR interacting molecules should not be discounted. Examples include mammalian target of rapamycin complex 1 which mediates the NMDAR mRNA translation and encodes alcohol-related memories (Barak et al. 2013), and GluN2A/GluN2B trafficking regulator Homer2, which is upregulated by chronic alcohol (Cozzoli et al. 2009; Obara et al. 2009) and is associated with genetic liability to consume alcohol in mice (Goulding et al. 2011). Another example is the NMDAR anchoring protein, PSD-95,

which increasingly clusters with NMDARs after chronic alcohol and, when deleted, significantly markedly potentiates alcohol intoxication and attenuates alcohol drinking (Camp et al. 2011; Mulholland and Chandler 2007) (Fig. 3).

NMDAR glycine$_B$ binding site

Another regulatory site that might be targeted in the treatment of alcohol abuse is the strychnine-insensitive (glycine$_B$) co-agonist site (Clements and Westbrook 1991). Glycine$_B$ binding allosterically modulates the NMDAR, for example by enhancing the receptor's affinity for glutamate and retarding receptor desensitization (Fadda et al. 1988; Parsons et al. 1998; Vyklicky et al. 1990). By altering NMDAR function, pharmacologically manipulating the glycine$_B$ site could modify NMDAR-mediated effects of alcohol in various ways. Blocking the site would remove a positive allosteric action on the NMDAR and thereby exert NMDAR antagonist-like effects with attendant changes in alcohol's effects on intoxication (increased), withdrawal (decreased), and alcohol-seeking and consumption (decreased). On the other hand, stimulating the glycine$_B$ site would augment NMDAR function and potentially have the opposite effects on alcohol behaviors. The modulatory nature of the glycine$_B$ site also raises the possibility that targeting the site for its anti-alcohol actions may produce fewer side-effects (e.g., cognitive, psychotomimetic) than, for example, NMDAR antagonists (Parsons et al. 1998).

A role for the glycine$_B$ site in alcohol behaviors is supported by preclinical findings. One approach has been to pharmacologically raise endogenous glycine levels by blocking the glycine reuptake. In rats, treatment with the GlyT1 transporter blocker, Org25935, decreased alcohol drinking under non-dependent conditions (Lido et al. 2012; Molander et al. 2007) and produced a long-lasting reduction in "compulsive-like" alcohol consumption after a history of chronic alcohol treatment/deprivation (Vengeliene et al. 2010) (Fig. 3). The GlyT1 inhibitors ALX-5407 and NFPS have been shown to significantly potentiate acute intoxication (Debrouse et al. 2013) but these effects are likely due to actions at strychnine-sensitive glycine receptors (Adermark et al. 2011; Molander and Soderpalm 2005).

A more direct approach to targeting the glycine$_B$ site has been to directly activate or antagonize the site. The glycine$_B$ agonist, D-serine, or the partial agonist D-cycloserine, has been found to block the anxiolytic-like effects of alcohol (Moraes Ferreira and Morato 1997), promote tolerance to alcohol-induced ataxia (Khanna et al. 1993; Khanna et al. 1995), facilitate extinction of conditioned reward-related effects of alcohol (Vengeliene et al. 2008b) (but see Groblewski et al. 2009), reduce alcohol drinking (Lockridge et al. 2012), and attenuate acute intoxication in some but not all studies (Debrouse et al. 2013; Lockridge et al. 2012). On the other hand, the glycine$_B$ partial antagonist, L-701,324, substitutes for alcohol (Kotlinska and Liljequist 1997) (but see Bienkowski et al. 1997), potentiates acute intoxication (Debrouse et al. 2013), blocks alcohol conditioned place preference (Biala and Kotlinska 1999) and reduces both cue-induced reinstatement (Backstrom and Hyytia 2004; 2006) and deprivation-induced alcohol drinking (Alen et al. 2009; Vengeliene et al. 2005)—all effects predicted from an NMDAR antagonist-like action of the drug.

There has only been limited clinical investigation of glycine$_B$-acting compounds to date. Administration of high dose D-cycloserine, or co-administration of D-cycloserine and alcohol, mimics/augments the subjective feelings of alcohol intoxication in healthy subjects, but does so in a blunted manner in alcohol-dependent individuals (Krystal et al. 2011; Trevisan et al. 2008). That D-cycloserine produced mild effects similar to NMDAR antagonism in these studies could be due to the known NMDAR antagonist activity of the drug at higher doses or high endogenous glycine levels (Emmett et al. 1991). In this context, raising glycine levels via glycine administration increased the alcohol-related effects of D-cycloserine in controls, but again less so in those with alcohol dependence (Krystal et al.

2011). The insensitivity of alcohol-dependent patients to D-cycloserine under these conditions may be explained by a relative failure to oppose a state of hyperglutamatergia and NMDAR upregulation in these patients. In turn, this suggests that more potent glycine$_B$ blockade may be necessary to produce therapeutic effects in patients suffering from an alcohol use disorder.

AMPA and kainate receptors

Ionotropic AMPAR and KAR function is sensitive to alcohol, but to a lesser and less direct extent than is NMDAR function (Costa et al. 2000; Dildy-Mayfield and Harris 1992; Lovinger et al. 1989; Moykkynen et al. 2003). In rodents, chronic alcohol enhances AMPAR-mediated currents in the basolateral amygdala and ventral tegmental area, and increases expression and synaptic localization of the GluA1 and GluA2 subunits in cortical, nucleus accumbens and dorsal striatal tissue or cultures (Ary et al. 2012; Chandler et al. 1999; Chen et al. 1999; Christian et al. 2012; Heikkinen et al. 2009; Lack et al. 2007; Neasta et al. 2010; Stuber et al. 2008; Wang et al. 2012). Also of note, GluA1 and GluA3 immunoreactivity is increased in the post-mortem alcohol brain (Breese et al. 1995), and variation in coding for the multi-PDZ gene, which is involved in NMDAR-mediated AMPAR trafficking, has been associated with risk for alcohol dependence (Czachowski et al. 2012). These adaptive alterations are intriguing in the context of evidence that other drugs of abuse, such as cocaine, produce profound changes in AMPAR-mediated plasticity in some of these same brain regions (Bellone and Luscher 2012; Wolf and Tseng 2012).

Although AMPARs are unlikely to directly mediate alcohol's effects at self-administered doses, the receptors are well placed to modulate the function of alcohol-mediating brain circuits. Indeed, the importance of AMPARs to alcohol-related behaviors has been borne out by a number of published reports. Preclinical studies have found reduced alcohol-seeking behaviors after injection of the mixed AMPAR/ KAR antagonists CNQX and NBQX, either systemically or directly into the nucleus accumbens or ventral tegmental area, while the more specific AMPAR blocker, GYKI 52466, did so in some but not all studies (Backstrom and Hyytia 2004; 2006; 2007; Czachowski et al. 2012; Sanchis-Segura et al. 2006; Stephens and Brown 1999). GYKI 52466 has also been shown to reduce locomotor stimulant effects and the expression of sensitized locomotor responses to alcohol (Broadbent et al. 2003). In addition, DNQX injected directly into amygdala attenuates alcohol withdrawal (Lack et al. 2007) (Fig. 3), while NBQX into the dorsal striatum reduces alcohol consumption (Wang et al. 2012). With regards to the specific AMPAR subunits that may mediate these drug effects, gene deletion of the GluA1 or GluA3 subunits has minimal effects on alcohol intoxication, tolerance, or drinking (Cowen et al. 2003; Palachick et al. 2008), whereas GluA3 deletion attenuates cue-driven alcohol-seeking and deprivation-induced drinking (Sanchis-Segura et al. 2006). Thus, although AMPAR subunit contributions remain to be fully clarified, GluA3 in particular appears to play a prominent role.

Pharmacologically enhancing AMPAR function produces some effects opposite to antagonism. Treatment with the positive allosteric AMPAR modulator, aniracetam, promotes alcohol-seeking behaviors in a DNQX-dependent manner (Cannady et al. 2013). Additionally, the "AMPAkines," LY404187 and LY451395, were found to reverse some of the disruptions in locomotor function caused by alcohol, possibly by exerting opposite (i.e., facilitating) effects on these behaviors (Jones et al. 2008). These data suggest that pharmacologically manipulating AMPARs can bidirectionally modulate alcohol behaviors, with AMPAR inhibition predicted to be of therapeutic benefit for alcoholism. However, with the exception of the aforementioned example of topiramate, which has AMPAR/KAR inhibiting properties and off-label efficacy for alcoholism, this hypothesis remains to be investigated clinically.

Also of uncertain clinical relevance are the alcohol-related effects of manipulating KAR. This is in part due to a relative paucity of pharmacological tools with selectivity for KAR over AMPAR. However, it has been shown that acute alcohol potently inhibits KAR in the amygdala and hippocampus and that there is an upregulation of amygdala KAR function associated with increased anxiety during withdrawal from chronic alcohol (Carta et al. 2003; Lack et al. 2008; Weiner et al. 1999) (but see Chandler et al. 1999; Ferreira et al. 2001). Taken together with evidence that amygdala KAR modulate anxiety-related behaviors in alcohol-naïve subjects (Lack et al. 2007; Mozhui et al. 2010), these initial data raise the possibility that inhibiting KAR could be a strategy for alleviating alcohol withdrawal.

Metabotropic glutamate receptors

mGluRs are G-protein-coupled receptors localized both pre-and post-synaptically throughout brain regions important for alcohol-related behaviors. Postsynaptic Group I mGluRs (mGluR1, mGluR5) have been intensively studied for their effect on rodent alcohol behaviors. Interestingly, gene variation in mGluR5 shows an association with risk for alcoholism (Schumann et al. 2008). In rodent studies, gene deletion or pharmacological blockade (via MPEP) of mGluR5 increases sensitivity to acute alcohol administration (Bird et al. 2008; Blednov and Harris 2008; Downing et al. 2010; Sharko and Hodge 2008). In addition, multiple studies have now shown that the mGluR5 deletion or antagonist treatment with MPEP and MTEP attenuates alcohol drinking, withdrawal, place preference and cue-induced alcohol-seeking (Adams et al. 2008; Backstrom et al. 2004; Backstrom and Hyytia 2006; 2007; Besheer et al. 2008; Besheer et al. 2010; Bird et al. 2008; Blednov and Harris 2008; Cowen et al. 2005; Cowen et al. 2007; Gupta et al. 2008; Hodge et al. 2006; Kotlinska et al. 2011; Lominac et al. 2006; Olive et al. 2005; Schroeder et al. 2005; Schroeder et al. 2008; Sidhpura et al. 2010) (but see Olive and Becker 2008) (Fig. 3).

The effects of mGluR5 inhibition on consumption and ethanol-seeking have been linked to mGluR5 activation specifically within the nucleus accumbens and basolateral amygdala (Besheer et al. 2010; Cozzoli et al. 2012; Cozzoli et al. 2009; Gass and Olive 2009; Sinclair et al. 2012). Recent work has also attributed deprivation-induced alcohol drinking to a population of mGluR5 receptors expressed on dopamine D1 receptor neurons (Parkitna et al. 2013). These findings support the clinical potential of mGluR5 antagonists as treatments for alcoholism. There do, however, remain issues with regards to potential unwanted effects of these drugs on other certain behaviors, including cognitive impairment (Simonyi et al. 2010), appetite suppression (Watterson et al. 2013), and even abuse liability (van der Kam et al. 2009) (c.f., Herzig et al. 2005), that remain to be fully clarified.

Of the other mGluRs, the presynaptic, glutamate inhibiting properties of the mGluR Group II family (mGluR2, mGluR3) are of significant interest to various neuropsychiatric disorders characterized by glutamatergic disturbances (Schoepp 2001). A new generation of mGluR2/3 selective agonists has attracted significant interest for their potential utility in schizophrenia (Karlsson et al. 2008; Patil et al. 2007) and has been studied in preclinical models of alcohol abuse. Treatment with mGluR2/3 agonists (LY379268, LY404039) reduces cue- and stress-induced alcohol-seeking in rats, and appears to do so most robustly in alcohol-preferring and alcohol-dependent subjects (Backstrom and Hyytia 2005; Kufahl et al. 2011; Rodd et al. 2006; Sidhpura et al. 2010; Zhao et al. 2006).

Extending these data, prolonged chronic ethanol exposure has been found to increase nucleus accumbens and central amygdala mGluR1 protein (Obara et al. 2009), reduce prefrontal cortical gene expression of mGluR2, but not mGluR3, and attenuate mGluR2 agonist inhibition of glutamate release in the nucleus accumbens (Meinhardt et al. 2013) (but see Kufahl et al. 2011). Post-mortem analysis revealed a similar decrease in mGluR2 gene expression in the frontal cortex of human alcohol-dependent patients (Meinhardt et al.

2013). Virally re-expressing mGluR2 in the infralimbic cortex of alcohol-exposed rats was sufficient to reduce cue-induced reinstatement (Meinhardt et al. 2013). These effects could conceivably reflect presynaptic inhibition of glutamate release and the attenuation of a hyperglutamatergic state. A similar mechanism might also account for the effect of LY379268 treatment to prevent alcohol-induced neurodegeneration in the entorhinal cortex (Cippitelli et al. 2010) (Fig. 3). Thus, mGluR2/3 agonists could serve a dual role—suppressing alcohol drinking while at the same time protect against the neural damage cause by chronic abuse. Studies in human subjects are awaited to test these hypotheses.

Glutamate transporters

Various approaches to reducing excess extracellular glutamate induced by chronic alcohol have been explored (e.g., via treatment with the cysteine pro-drug, *N*-acetylcysteine, Ferreira Seiva et al. 2009). Glutamate transporters remove glutamate from the synaptic and greater extracellular space. Expression of the glutamate transporters, GLAST and GLT-1, is reduced in post-mortem brains of those with alcohol dependence (Kryger and Wilce 2010). While this reduction likely reflects broader neurodegenerative changes, loss of transporter-mediated glutamate reuptake could augment the already elevated extracellular levels of glutamate resulting from chronic alcohol exposure. An animal model of deficient glutamate transport would therefore be predicted to produce a hyperglutamatergic state analogous with alcohol withdrawal, and thereby promote excessive alcohol drinking.

Two mutant mouse models have been generated that allow for the testing of this hypothesis. The first is a constitutive gene deletion of GLAST. These GLAST-deficient mutants exhibit reduced alcohol consumption and a loss of alcohol conditioned place preference, a seemingly paradoxical phenotype that may be due to the compensatory downregulation of ("pro-alcohol") striatal endocannabinoid signaling observed in these mice (Karlsson et al. 2012). The second model involves gene deletion of the circadian clock gene, *Per2*. Per 2 knockout mice were found to have reduced GLAST expression and a concomitant increase in striatal extracellular glutamate (Spanagel et al. 2005). These mutants showed excessive alcohol drinking, which was reversed by acamprosate treatment (Brager et al. 2011; Spanagel et al. 2005). These data have been extended to humans by the finding that genetic variation in the human *PER2* gene is associated with relative risk for alcoholism (Lee et al. 2011; Spanagel et al. 2005).

What do these findings mean for designing medications for alcoholism that target glutamate transport? One scheme posits that drugs that boost transport could "mop up" excessive glutamate in the alcohol brain and not only work to alleviate withdrawal and craving, but also possibly lessen some of the neuroadaptive and neurotoxic effects caused by a hyperglutamatergic state. Interestingly, recent studies have shown that ceftriaxone and GPI-1046 (another drug known to upregulate GLT-1) can reduce alcohol drinking in alcohol-preferring rats, in addition to blocking psychostimulant reinstatement (Abulseoud et al. 2012; Sari et al. 2011; Sari and Sreemantula 2012). These encouraging preliminary findings warrant further study.

Summary and conclusions

There is an ever growing understanding of how pharmacologically manipulating glutamatergic neurotransmission can alter alcohol behaviors, including intoxication, withdrawal, craving and alcohol-seeking, in both rodent and human subjects. Of the five major components (NMDAR, the NMDAR glycine$_B$ site, AMPAR, mGluR, and glutamate transporters) of the glutamate system considered here, all have promise as targets to alleviate symptoms of alcohol use disorders.

Both the NMDAR and AMPAR clearly have an important role in mediating alcohol consumption in rodents, but blocking these receptors might be therapeutically difficult due to associated side-effects. Selectively targeting individual subunits, for example GluN2B or GluA3, may be one way to circumvent this problem. Another approach is to target the $glycine_B$ site on the NMDAR. A consistent literature has emerged in support of the ability of mGluR5 antagonists to reduce a range of alcohol-related behaviors in rodents, but the issue of possible side-effects remains to be addressed. Alternatively, drugs that stimulate mGluR2/3 have potential to suppress alcohol drinking and even mitigate neurotoxic effects associated with elevations in glutamate by presynaptically inhibiting neurotransmitter release. Similar effects could be achieved by increasing glutamate transporter function to actively remove glutamate from the synaptic space.

To build upon this foundation and develop safe, well-tolerated pharmacotherapeutics that target a transmitter system as ubiquitous as glutamate is still a major challenge for drug development. However, we believe that by combining basic mechanistic discoveries with well-designed clinical investigations real progress can be made in the coming years to provide new, effective treatments for alcoholism.

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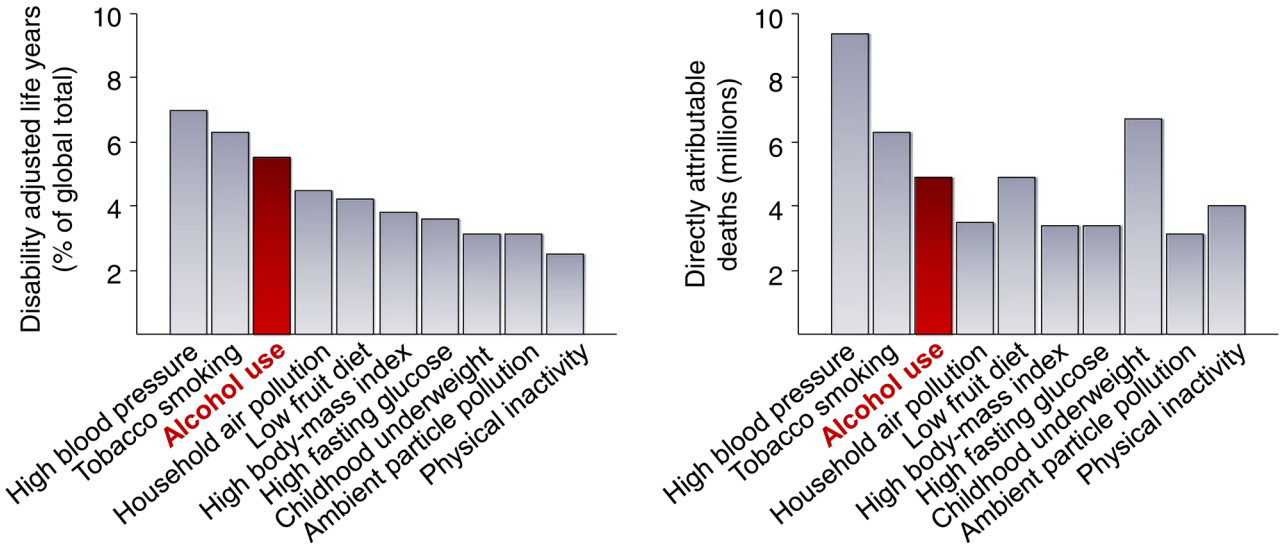

Fig. 1.

The global burden of alcohol use. Alcohol use ranked third in 2010 risk factors for global disease burden, as measured by disability adjusted life years (DALYs) (*left panel*), and accounted for 5.5 million deaths worldwide (right panel). Adapted from Lim et al. 2012

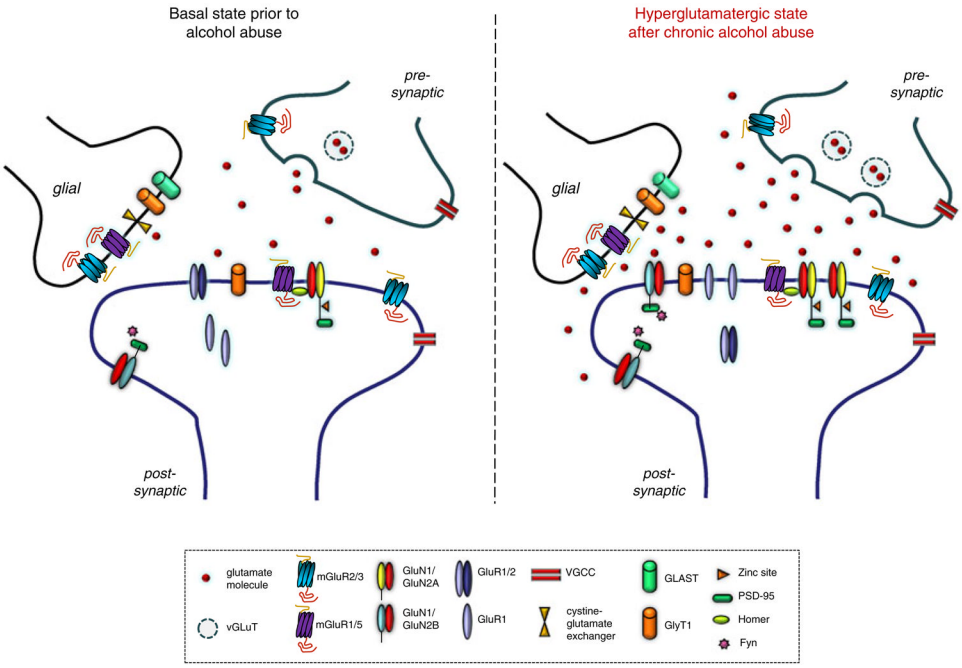

Fig. 2.

Adaptations of the glutamate system as a result of chronic alcohol abuse. Chronic alcohol abuse produces a “hyperglutamatergic” state during abstinence. This state is characterized by elevated levels of extracellular glutamate and alterations in the expression and localization of various glutamate receptors, including upregulation of NMDARs, and possibly a decrease in calcium-restricting GluA1/2 heteromers in favor of calcium-permeable GluA1 homomers. Key to acronyms/abbreviations: *vGLUT* vesicular glutamate transporter; *mGluR* metabotropic glutamate receptor; *GluN1*, *GluN2A*, *GluN2B* NMDAR subunits; *GluA1/2*, *GluA1* AMPAR subunits; *VGCC* voltage-gated calcium channel; *GLAST* glutamate transporter subtype (EAAT1); *GlyT1* glutamate transporter 1, *PSD-95* postsynaptic density 95

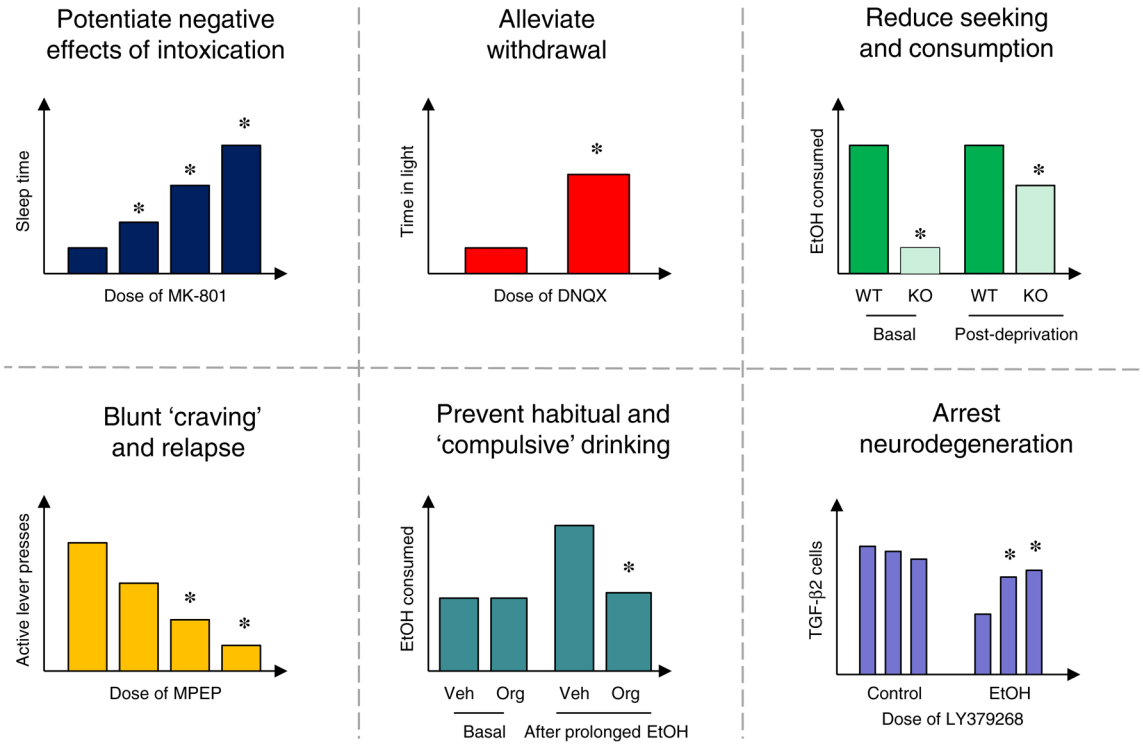

Fig. 3.

Preclinical examples of glutamate-based approaches to therapeutically targeting various elements of alcoholism. Potentiating alcohol intoxication: mice administered the NMDAR antagonist, MK-801, show markedly prolonged sedative/hypnotic responses to ethanol (Palachick et al. 2008). Alleviating alcohol withdrawal: rats infused with the AMPAR antagonist DNQX directly into amygdala exhibited less ethanol-induced withdrawal anxiety (Lack et al. 2007). Blunting alcohol craving: mice with deletion of the NMDAR anchoring protein PSD-95 consumed less ethanol at baseline and after deprivation (Camp et al. 2011). Reducing alcohol-seeking and consumption: mice with deletion of the NMDAR anchoring protein PSD-95 consumed less ethanol at baseline and after deprivation (Camp et al. 2011). Blunting alcohol craving: rats administered the mGluR5 antagonist, MPEP, reduced ethanol-seeking (*black bars* active lever presses) during cue-induced reinstatement (Cowen et al. 2003). Preventing habitual and compulsive alcohol consumption: rats administered the GlyT1 transporter blocker, Org25935, decreased "compulsive-like" alcohol consumption after a history of chronic ethanol treatment/deprivation (Vengeliene et al. 2010). Arresting alcohol-induced neurodegeneration: rats treated with the mGluR2/3 agonist, LY379268, were protected against binge ethanol-induced increased in TGF-β2-immunoreactivity, a measure of neurodegeneration. Adapted from Cippitelli et al. 2010

Table 1

Effects of glutamatergic drugs on alcohol-related behaviors in rodents and clinical populations

Target mechanism	Example compounds	Intoxication	Withdrawal	Consumption	Reinstatement
Blocking NMDAR	MK-801, memantine	↑ [↑*]	↓ [↓]	↓ [↓]	↓
Activating glycine$_B$ site	Org25935, D-cycloserine	↓ [↑*]	–	↓	–
Blocking glycine$_B$ site	L-701,324	↑	–	↓	↓
Activating AMPAR	LY404187, LY451395	–	–	↑	–
Blocking AMPAR	CNQX, GYKI 52466	–	↓	↓	–
Blocking mGluR5	MPEP, MTEP	↑	↓	↓	↓
Activating mGluR2/3	LY379268, LY404039	–	–	–	↓
GLT-1 upregulation	GPI-1046	–	–	↓	–

↑ increase in ethanol-related effect, ↓ decrease in ethanol-related effect, – unclear or not extensively studied, [] clinical data, ↑* mimics subjective feeling of alcohol intoxication