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Metabotropic and ionotropic glutamate receptors as potential targets for the treatment of alcohol use disorder

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Abstract

Emerging evidence indicates that dysfunctional glutamate neurotransmission is critical in the initiation and development of alcohol and drug dependence. Alcohol consumption induced downregulation of glutamate transporter 1 (GLT-1) as reported in previous studies from our laboratory. Glutamate is the major excitatory neurotransmitter in the brain, which acts via interactions with several glutamate receptors. Alcohol consumption interferes with the glutamatergic signal transmission by altering the functions of these receptors. Among the glutamatergic receptors involved in alcohol-drinking behavior are the metabotropic receptors such as mGluR1/5, mGluR2/3, and mGluR7, as well as the ionotropic receptors, NMDA and AMPA. Preclinical studies using agonists and antagonists implicate these glutamatergic receptors in the development of alcohol use disorder (AUD). Therefore, the purpose of this review is to discuss the neurocircuitry involving glutamate transmission in animals exposed to alcohol and further outline the role of metabotropic and ionotropic receptors in the regulation of alcohol-drinking behavior. This review provides ample information about the potential therapeutic role of glutamatergic receptors for the treatment of AUD.

Keywords

mGluR1/5; mGluR2/3; mGluR7; NMDA; AMPA; glutamate; alcohol

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Conflict of Interest

The authors declare no conflict of interest.

1. Introduction

Alcoholism is a progressive and chronic relapsing disorder, consequently leading to detrimental health outcomes. The positive reinforcing effect, known as the rewarding effect, associated with initial alcohol consumption is suggested to be the driving force promoting chronic alcohol consumption, subsequently leading to the development of alcohol use disorder (AUD) [For review see ref. (Gilpin and Koob, 2008)]. This effect is associated with changes in brain neurochemistry, specifically alterations of the neurotransmitters that are sensitive to the acute effects of alcohol (Weiss and Porrino, 2002).

Ample evidence suggests the involvement of the mesocorticolimbic dopaminergic system in the development of drug dependence. In addition, enhanced dopaminergic transmission in the nucleus accumbens (NAc) plays a key role in the initiation of addictive behavior. It is important to note that the reward pathways involve multiple brain regions, including the ventral tegmental area (VTA) and NAc (Russo and Nestler, 2013). Alcohol acts as a positive reinforcer in the mesocorticolimbic reward system by inducing the release of dopamine in the VTA, which stimulates the reinforcing effect of alcohol (Imperato and Di Chiara, 1986). For instance, studies have reported that acute administration of alcohol induced rewarding effects due to an increase in dopaminergic neurotransmission in the VTA and NAc [For review see ref. (Spanagel and Weiss, 1999)]. However, an increase in the number of spontaneously active dopaminergic neurons was found in the posterior VTA after chronic alcohol consumption (Morzorati et al., 2010). Importantly, the primary dopaminergic projections within this system originate in the VTA and innervate several areas, including the NAc and the prefrontal cortex (PFC). However, the circuitry is complex and involves innervation through dopaminergic, glutamatergic and GABAergic projections. Moreover, enhanced responses of postsynaptic glutamate receptors are responsible for the increase in dopaminergic firing (Fitzgerald et al., 2012). This later study suggests that glutamatergic innervation in the VTA plays a crucial role in glutamate-stimulated dopamine release. The dysfunctional connectivity and alteration in glutamatergic transmission are associated with chronic alcohol seeking, relapse, craving, tolerance and withdrawal (Alasmari et al., 2015a; Bäckström and Hyytiä, 2004; Dahchour et al., 1998; Krupitsky et al., 2007a; Nagy, 2008; Rossetti et al., 1999), which provide evidence of the involvement of glutamate transmission in the NAc and VTA in alcohol-seeking behavior. The apparent role of glutamate in the development of AUD suggests glutamatergic system as a potential therapeutic target to block the reinforcing effects of alcohol as well as to attenuate chronic and reinstatement of alcohol-seeking behavior (Alasmari et al., 2016; Bäckström and Hyytiä, 2004; Besheer et al., 2010; Qrunfleh et al., 2013).

2. Neurocircuitry involving glutamate transmission in AUD

Dependence on drugs of abuse involve a number of brain regions, including the NAc, located in the ventral striatum (Sobolevsky et al.), VTA, basal lateral amygdala (BLA), PFC, hippocampus (HPC), dorsal medial thalamus (DMT), ventral palladium (VP), substantial nigra (SNr), motor thalamus (MT), and motor cortex (MC) (Koob and Volkow, 2010) (Fig. 1). Each of these regions has glutamatergic projections and neurons containing glutamate receptors, providing an anatomical basis for glutamatergic transmission in addiction (Gass

and Olive, 2008). Glutamatergic projections from the PFC to the NAc have been implicated in the initiation and learning of addictive behaviors (Moussawi and Kalivas, 2010), which are subsequently regulated by dopaminergic projections from the VTA (Deng et al., 2009). These glutamatergic pathways, between the PFC and NAc, are also thought to play a key role in addictive behaviors and are important for reinstituting drug seeking behavior (Kalivas and Volkow, 2005). Glutamatergic projections from the AMG and HPC to the PFC and NAc establish and provide previously learned information associated with experience, further influencing complex behavioral responses (Kalivas and Volkow, 2005). Interestingly, it is also found that the glutamatergic system plays a critical role in alcohol-associated dependence, including chronic alcohol seeking and relapse (Alasmari et al., 2015a; Bäckström and Hyytiä, 2004; Dahchour et al., 1998; Krupitsky et al., 2007a; Nagy, 2008; Rossetti et al., 1999).

The NAc is a key player in the mesolimbic dopaminergic system, which receives dopaminergic inputs through afferent connections from the VTA [For review see ref. (Alasmari et al., 2015b; Pistillo et al., 2015)]. It is important to note that the NAc shell receives dopaminergic projections from the VTA and is responsible for motivation and reward; however, the NAc core is innervated mainly by glutamatergic projections from the HPC and AMG and is responsible for sensory motor integration, goal-directed behavior, and emotional cues (Guo et al., 2009; Suto et al., 2010). Despite the complexity of the brain regions and signaling pathways, chronic alcohol exposure is characterized by a reduced function of the reward neurocircuitry and an increased glutamatergic system function (Vengeliene et al., 2008).

3. Glutamate homeostasis

Under normal conditions, glutamate is released from the presynaptic neurons and activates post-synaptic ionotropic receptors, which can lead to an increased influx of Na^+ and Ca^{+2} ions (Mark et al., 2001). Glutamate concentrations in the synaptic cleft is stringently regulated by a combination of two processes, glutamate release and glutamate clearance (Kanai and Hediger, 2003). It is noteworthy that the astrocytes play an important role in the process of glutamate clearance (Danbolt, 2001). The excess of synaptic glutamate is taken up by astrocytes and converted to glutamine by glutamine synthetase; glutamine is then released into the extracellular space and further taken up by the presynaptic neurons and reconverted to glutamate (Danbolt, 2001; Newcomb et al., 1997). We suggest here that the glutamine-glutamate cycle is responsible for regulating the extracellular glutamate concentration and maintenance of glutamate homeostasis.

Currently, the literature shows that there are five known astrocytic membrane-bound glutamate transporters, or excitatory amino acid transporters (EAAT1-5). Each of these transporters is expressed in varying proportions within different brain regions. EAAT1 (glutamate aspartate transporter, GLAST) and EAAT2 (glutamate transporter 1, GLT-1) are Na^+ dependent transporters that intake 3 Na^+ and 1 H^+ ions and outputs K^+ ions therefore, generating a concentration gradient leading to an influx of glutamate (Fig. 2). EAAT1 is primarily localized in the cerebellum with moderate expression in the forebrain (Fig. 2) (Furuta et al., 1997). Alternatively, GLT-1 is physiologically predominant in the forebrain,

with minimal expression in the cerebellum (Furuta et al., 1997). Due to its nominal expression in the brain, the role of EAAT3 remains debatable. EAAT4 is mostly expressed in the cerebellum, whereas EAAT5 is predominantly expressed in the retina (Arriza et al., 1997; Furuta et al., 1997). Thus, EAAT1 and EAAT2 are the driving forces in regulating glutamate uptake in the brain (Danbolt, 2001; Duan et al., 1999). In contrast to the aforementioned family, cystine/glutamate exchange transporter (xCT) is predominantly involved in elevating extracellular glutamate concentrations (Fig. 2). It is important to note that glutamate is exchanged for extracellular cystine through xCT. This glutamate interacts with the metabotropic receptors present on the pre- and post-synaptic neurons (Moran et al., 2005). The stimulation of xCT has been found to modulate glutamate release from the presynaptic neurons (Kalivas, 2009; Pomierny-Chamiolo et al., 2014). xCT regulates glutamate homeostasis through the involvement of the presynaptic mGluR2/3. Moreover, a decrease of xCT expression can lead to a reduction in extrasynaptic glutamate level. This effect may cause a loss of glutamatergic tone on presynaptic mGluR2/3, which can lead to a marked increase in glutamate release from presynaptic glutamatergic neurons (Moran et al., 2005).

Importantly, acute alcohol consumption is known to have an inhibitory effect on glutamatergic neurotransmission in the mesocorticolimbic regions. Moreover, studies have shown that acute alcohol intake decreases extracellular glutamate concentrations in the cortical area (Tiwari et al., 2014). Despite its acute inhibitory effects on glutamate activity, chronic alcohol consumption increases extracellular glutamate concentrations in the NAc (Das et al., 2015). Several preclinical studies have shown that alcohol consumption elevates the extracellular glutamate concentrations within several mesocorticolimbic regions (Das et al., 2015; Ding et al., 2012; Ding et al., 2013; Ward et al., 2009). We suggest here that an increase in extracellular glutamate concentrations could be due to an increase in glutamate release or a decrease in glutamate uptake.

Initially, acute ethanol exposure is known to attenuate glutamate release from the presynaptic neuron as well as postsynaptic receptor activity. In addition, the concentration of alcohol is an important determinant of the receptor activity. For instance, exposure to lower concentrations of ethanol primarily affects NMDAR-mediated currents, while AMPAR-mediated currents are exclusively affected by exposure to high concentrations of ethanol (Kalev-Zylinska and During, 2007; Marty and Spigelman, 2012; Santerre et al., 2014). However, as the exposure progresses to a chronic state, studies have found an increase in the expression of the NMDA and AMPA receptor in mesocorticolimbic areas (Chandler et al., 1999). Several preclinical studies have reported that acute and chronic ethanol consumption increase extracellular glutamate concentrations in the NAc (Dahchour et al., 2000; Das et al., 2015; Lallemand et al., 2011; Melendez et al., 2005). This has been substantiated, in animal models, through behavioral responses induced by investigational alterations of extracellular glutamate concentrations. It is noteworthy that an increase in glutamate concentrations actuated alcohol consumption, while depletion in glutamate concentrations attenuated consumption (Das et al., 2015; Kapasova and Szumlinski, 2008; Szumlinski et al., 2008). Moreover, increased extracellular glutamate concentrations, associated with chronic ethanol consumption, have been attributed to diminishglutamate uptake (Melendez et al., 2005). In conjunction, a downregulation of glutamate uptake was observed in the cerebral cortex of

alcohol-preferring cAA rats (Schreiber and Freund, 2000). Our lab has shown that chronic ethanol consumption decreases the expression of GLT-1, GLT-1 isoforms and xCT (Aal-Aaboda et al., 2015; Alhaddad et al., 2014a; Alhaddad et al., 2014b; Hakami et al., 2016; Sari and Sreemantula, 2012). We have also shown that pharmacological upregulation of GLT-1 and xCT attenuated ethanol-drinking behaviors, including continuous and relapse ethanol drinking (Alasmari et al., 2015a; Alhaddad et al., 2014a; Alhaddad et al., 2014b; Goodwani et al., 2015; Rao and Sari, 2014; Rao et al., 2015). Ceftriaxone, a β-lactam antibiotic, was able to decrease ethanol intake, an effect was associated with upregulation of GLT-1 expression in central reward brain regions (Rao and Sari, 2014). However, it is apparent that xCT activation in the NAc stimulates presynaptic metabotropic receptors 2/3 (mGluR2/3), thereby decreasing the synaptic glutamate levels (Moran et al., 2005). Furthermore, stimulation of mGluR2/3 has been found to attenuate ethanol-seeking behavior. In addition, inhibition of mGluR5, mainly localized to post-synaptic neurons, revealed a significant decrease in ethanol-seeking behavior (Adams et al., 2010; Backstrom et al., 2004; Sinclair et al., 2012). Together, acute and chronic alcohol consumption may affect various aspects of glutamatergic system, including glutamate receptors and transporters through distinct target proteins in the synapse.

4. Glutamate receptors in AUD

Two major types of receptors are involved in the development of AUD: metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors (iGluRs). The pharmacological roles of these receptors are summarized in Table 1. Several studies demonstrated the implications of these receptors in AUD (Table 1).

4.1. Metabotropic glutamate receptors

mGluRs belong to the G-protein coupled receptor (GPCR) superfamily (Fig. 3). These receptors mediate synaptic glutamatergic neurotransmission through an intracellular second messenger, making mGluRs slow mediators of glutamate, as compared to iGluRs. These seven-transmembrane spanning receptors consist of a large extracellular N-terminal domain, which encompasses an endogenous ligand binding site for glutamate, and an intracellular C-terminus (Niswender and Conn, 2010). Eight subtypes of mGluRs have been identified and categorized into three distinct groups based on pharmacological selectivity, sequence homology, and signal transduction effector pathway (Kearney et al., 1997; Niswender and Conn, 2010) (Fig. 3). Several studies demonstrated that mGluRs ligands reduced alcohol seeking behaviors (Table 2). The chemical names of mGluRs ligands are listed in Table 3.

4.1.1. Group 1 mGluRs—Group 1 receptors (mGluR1 and mGluR5) are mainly located postsynaptically. These receptors mediate their signaling by coupling to G_q proteins followed by stimulation of phospholipase C (PLC), which further increases the production of inositol (1,4,5)-triphosphate [Ins (1,4,5)P_3] (Kenny and Markou, 2004). This subsequently induces the release of Ca^{2+} from intracellular stores as well as stimulates diacylglycerol that increases phosphokinase C (PKC) activity (Kenny and Markou, 2004).

4.1.1.1. mGluR1: mGluR1 is widely distributed in the central nervous system (CNS) with significant levels of expression localized in the olfactory bulb, superior colliculus, HPC, lateral septum, superior colliculus, thalamus and cerebellum (Ryo et al., 1993; Salt et al., 2014; Shigemoto et al., 1992). Furthermore, mGluR1 is moderately expressed in other areas of the CNS such as the dorsal striatum, hypothalamus, pallidum, ventral midbrain, and cerebral cortex; while considerably low expression is observed in the AMG, medial septum, NAc and brainstem [For review see ref. (Olive, 2009)]. The role of mGluR1 in AUD has not been well-established. Interestingly, JNJ 16259685, a potent mGluR1 antagonist, reduced alcohol self-administration as well as alcohol reinforcement break-points in alcohol-preferring rats. However, another study reported that this compound induced a significant impairment in locomotor behavior and a reduction in sucrose break-points (Besheer et al., 2008a). In addition, EMQMCM, a selective mGluR1 antagonist, attenuated the conditioned place preference (CPP) to alcohol and the seizures associated with alcohol withdrawal (Kotlinska et al., 2011). Moreover, CPCCOEt, another selective mGluR1 antagonist, also reduced the rewarding properties of alcohol, voluntary consumption of alcohol, and alcohol-induced place conditioning (Szumlinski et al., 2006). In contrast, other studies reported a finding where CPCCOEt failed to alter the response to the reinforcing effects of alcohol in mouse models (Hodge et al., 2006). Thus, further studies are warranted to demonstrate the role of mGluR1 in alcohol seeking. However, from the available literature, it appears that antagonizing mGluR1 can be a prolific therapeutic approach in targeting AUD.

4.1.1.2. mGluR5: mGluR5 is expressed mainly in the forebrain and in the limbic structures, specifically in the cerebral cortex, HPC (CA1-CA3 regions and dentate gyrus), basal ganglia, olfactory bulb, striatum and NAc (Pomierny-Chamiolo et al., 2014). A competitive antagonist to mGluR5, MPEP, was able to reduce the expression of alcohol-associated rewarding effects assessed by an alcohol self-administration paradigm (Hodge et al., 2006; Schroeder et al., 2005; Szumlinski et al., 2006). Furthermore, studies reported that mice lacking mGluR5 show a reduced consumption of alcohol, displayed a place preference for alcohol in a CPP paradigm, and exhibited increased sensitivity to the reinforcing effects of alcohol (Bird et al., 2008). mGluR5 blockers, MPEP and acamprosate, have the ability to attenuate alcohol-seeking behavior (Blednov and Harris, 2008). MPEP also attenuated alcohol-seeking and relapse behaviors determined by measuring the alcohol deprivation effect (Yin et al.) (Backstrom et al., 2004). Previous studies were performed to evaluate the functional role of mGluR5 in effects associated with alcohol, these studies revealed that interoceptive effects of alcohol require activation of mGluR5 in the NAc (Besheer et al., 2009). Furthermore, microinjection of MPEP in NAc reduced alcohol self-administration (Besheer et al., 2010). In addition, MPEP attenuated relapse of alcohol seeking behavior associated with increased ERK1/2 phosphorylation (Schroeder et al., 2008).

MTEP, another selective mGluR5 antagonist, has revealed ability to reduce alcohol self-administration as well as reinstatement of alcohol-drinking behavior (Sidhpura et al., 2010). A recent study reported that mGluR5 blockade by MTEP, in the NAc and basolateral AMG, eliminated cue-induced reinstatement to alcohol in rat models (Sinclair et al., 2012), suggesting a significant role of mGluR5 antagonism in attenuating reinstatement of alcohol seeking. Moreover, MTEP has also been shown to attenuate CPP to alcohol and seizures

associated with alcohol withdrawal (Kotlinska et al., 2011) as well as alcohol withdrawal-induced anxiety behavior measured in elevated plus-maze tests in rats (Kotlinska and Bochenski, 2008). The anti-alcohol effect assessed by measuring alcohol consumption of a new compound, GET73, N-[(4-trifluoromethyl) benzyl] 4-methoxybutyramide, has also been attributed to the ability of the compound to interact with mGluR5 (Ferraro et al., 2013). These findings suggest that a pharmacological blockade of mGluR5 may be a feasible therapeutic approach to modulate alcohol-drinking behavior.

4.1.2. Group 2 mGluRs—Group 2 receptors (mGluR2 and mGluR3) are present both pre- and post-synaptically; these receptors are linked to $G_{i/o}$ proteins, negatively controlling the activity of adenylyl cyclase thereby decreasing the intracellular concentrations of cAMP (Kenny and Markou, 2004). In vivo studies have revealed that LY379268, an mGluR2/3 agonist, has shown promising results in reducing alcohol self-administration, cue-induced alcohol seeking (Backstrom and Hyytia, 2005; Sidhpura et al., 2010) as well as foot-shock stress-induced reinstatement to alcohol-seeking (Sidhpura et al., 2010; Zhao et al., 2006). Furthermore, LY404039, an mGluR2/3 agonist, showed a reduction in the response to alcohol in a Pavlovian spontaneous recovery test and expression of an ADE during relapse without any effect on response to alcohol under maintenance conditions (Rodd et al., 2006). Therefore, stimulating mGluR2/3 can lead to attenuation of alcohol-seeking and relapse behavior with no effect on alcohol self-administrative behavior (Rodd et al., 2006). Interestingly, several studies suggested that alterations in mGluR2/3 sensitivity is involved in chronic alcohol exposure or withdrawal-induced neuroadaptive changes assessed by measuring the ability of LY379268 to reduce foot-shock stress-induced alcohol self-administration and reinstatement to alcohol seeking in non-dependent and post-dependent rats (Kufahl et al., 2011; Sidhpura et al., 2010). However, LY379268, at high doses, also was able to interfere with the behavior associated with natural reward, observed with common reinforcers such as sweetened condensed milk (Baptista et al., 2004), or sucrose (Bossert et al., 2006), suggesting that effects of LY379268 on alcohol seeking are not specific to alcohol. Interestingly, this compound also exhibited a significant reduction in the spontaneous locomotor activity at doses reported to attenuate alcohol self-administration and reinstatement (Backstrom and Hyytia, 2005). Moreover, LY379268 exerts neuroprotective effects by inhibiting glutamate release through the stimulatory action on both presynaptic mGluR2/3 as well as glial mGluR3 [For review see ref. (Imre, 2007)]. These data suggest that mGluR2/3 agonists might be promising therapeutic compounds to attenuate alcohol-seeking behavior.

4.1.3. Group 3 mGluRs—Group 3 of mGlu family receptors are comprised of mGluR4, mGluR6, mGluR7 and mGluR8, all of which are mainly localized presynaptically. These receptors are also coupled to $G_{i/o}$ proteins, which negatively regulate adenylyl cyclase activity (Kenny and Markou, 2004). Both mGluR4 and mGluR7 are autoreceptors on presynaptic glutamatergic corticostriatal terminals and/or hetereceptors on GABAergic striatopallidal and striatonigral terminals (Corti et al., 2002), while mGluR8 mRNA is highly expressed in the cortex and striatum (Bragina et al., 2015; Brandstatter et al., 1996; Messenger et al., 2002). mGluR6 mRNA is restrictedly expressed in retina (Laurie et al., 1997), and therefore this receptor is not suggested to play a major role in drug addiction.

Among several group 3 mGluRs, mGluR7 has been investigated extensively for its important functional role in drug addiction. An exciting study performed in mouse models revealed a mutation of a *cis*-regulated gene (*Grm7*), which encodes mGluR7, is involved in the development of AUD. This mutation was found to reduce mGluR7 (*Grm7*) expression and consequently increase alcohol consumption in a preference-drinking behavioral paradigm (Vadasz et al., 2007). Several studies, involving mGluR7 knockdown animal models, have also substantiated the importance of this receptor in modulating alcohol intake. Furthermore, studies revealed that deletion of *Grm7* in mouse models, can lead to an increase in alcohol consumption. Conversely, a *Grm7* variant-possessing subcongenic and congenic mice, characterized by greater Grm7 mRNA, consumed less alcohol (Gyetvai et al., 2011) suggesting that *Grm7* plays a major role in mGluR7-mediated alcohol drinking. Several positive and negative pharmacological modulators of mGluR7 have also been investigated against alcohol seeking to establish the importance of this receptor in alcohol addiction. An mGluR7-specific allosteric agonist, AMN082, has been reported to attenuate alcohol consumption (Salling et al., 2008). However, this compound also has been shown to reduce sucrose intake in the B6 mouse model indicating that the effect of mGluR7-agonist on alcohol intake is not specific (Salling et al., 2008). The plausible mechanism of action underlying the effect of AMN082 could be due to its ability to increase non-vesicular GABA levels and consequently extracellular vesicular glutamate levels in the brain, since group 3 mGluR antagonist abolished AMN082-increased glutamate but not GABA concentrations in the NAc (Li et al., 2008).

Additionally, other group 3 mGluRs have been examined for their efficacy in reducing alcohol-drinking behavior. Mice lacking mGluR4 failed to show alcohol-induced stimulation of motor activity, which was observed in wild type animals (Blednov et al., 2004). However, there was no difference observed in alcohol intake and preference in a two-bottle paradigm, the severity of withdrawal associated with acute alcohol intake, as well as the duration of loss of the righting reflex (Blednov et al., 2004). Thus, these findings implicate that mGluR4 might mediate the motor stimulant effects of alcohol, with no effect on alcohol-consumption. Furthermore, systemic administration of mGluR8 agonist, (*S*)-3,4-DCPG, reduced alcohol self-administration and reinstatement to alcohol seeking in rats, although the effect on alcohol was observed with doses that have been found to decrease spontaneous locomotor activity (Backstrom and Hyytia, 2005). However, a compound with agonistic activity at mGluR8 and less motor-suppressant effects may be helpful in establishing the role of these receptors in alcohol-seeking behavior (Backstrom and Hyytia, 2005).

4.2. Ionotropic glutamate receptors

Ionotropic glutamate receptors (iGluRs) are tetrameric ligand-gated ion channels responsible for mediating the rapid-responses to all major excitatory neurotransmitters of the CNS in mammals (Cognet et al., 2007; Stawski et al., 2010). Importantly, all iGluR subunits encompass three transmembrane domains (M1, M3 and M4); the M2 domain forms a re-entrant loop on the cytoplasmic side that determines the selectivity of the ion channel (Sobolevsky et al., 2009; Traynelis et al., 2010) (Fig. 4). The glutamate recognition site (S1) is located on the extracellular amino-terminal domain, with the M3-M4 loop comprising the second necessary component of the glutamate recognition site (S2) (Bigge, 1999). In

addition, iGluR activity is modulated by the phosphorylation sites present on the intracellular carboxyl terminus, which are also involved in signal transduction (Bigge, 1999). These receptors are further categorized into three subtypes: 1) N-methyl-D-Aspartic acid (NMDA) receptors; 2) α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (Chaudhry et al.) receptors; and 3) Kainic acid (Kainate, KA) receptors. AMPA and KA receptors are often termed as non-NMDA receptors. Studies revealed that NMDA receptor antagonists, AMPA receptor antagonists and KA receptor antagonists were able to attenuate alcohol-drinking behaviors (Table 2). Chemical name of NMDA, AMPA and KA receptors ligands are listed in Table 3.

4.2.1. NMDA receptors—NMDA receptors are nonspecific cation channels that allow calcium and sodium influx as well as potassium efflux from neurons. These heterotetrameric proteins are composed of two main subunits, NR1 and NR2. NMDA receptors are distinct due to the need for co-activation by binding with two ligands. NR1 subunits bind glycine or d-serine, a co-agonist for efficient function, while NR2 contains a glutamate binding domain (Gonda, 2012). NMDA is regulated by several endogenous and exogenous compounds. Glutamate, sodium, calcium, and potassium are responsible for the receptor stimulation and excitatory effects. However, zinc, copper and magnesium have been reported to block the channel and causing antagonistic effects (Eby and Eby, 2006; Gass and Olive, 2008; Huggins and Grant, 2005; Rambo et al., 2012; Trombley et al., 1998). These receptors have been mostly found on presynaptic nerve-terminals and glial cells (Garcia-Junco-Clemente et al., 2005; Paoletti and Neyton, 2007), with an implication in neural plasticity (Coyle and Tsai, 2004; Malenka and Nicoll, 1993; Paoletti et al., 2013).

An increase in glutamatergic transmission has been detected in the striatum of mice undergoing alcohol withdrawal (Chen et al., 2011). This later study demonstrated that alcohol withdrawal increased the activity of NR2B NMDA receptor subunit, which may cause a significant increase in alcohol consumption. Moreover, alterations in NMDA receptor synaptic plasticity in the NAc might be associated with ethanol-induced locomotor sensitization, and this effect was associated with significant increase in alcohol intake (Abrahao et al., 2013). Furthermore, inhibition of the NR2B subunit of NMDA in the dorsal medial striatum has been shown to significantly decrease alcohol consumption in chronically exposed rats, which is indicative of NR2B NMDA receptor subunit playing a crucial role in alcohol consumption (Wang et al., 2010). Additionally, studies have shown that memantine and MK-801, NMDA receptor antagonists, affect several behavioral aspects associated with alcohol consumption such as alcohol sensitization, locomotor activities and sedative properties (Malpass et al., 2010; Meyer and Phillips, 2003; Paoletti et al., 2013; Shen and Phillips, 1998). Memantine also exhibited promising results in attenuating motor impairment as well as preventing cerebellar cell loss, thus indicating its neuroprotective effects (Idrus et al., 2011). However, memantine was not able to improve the learning deficit associated with binge alcohol consumption (Idrus et al., 2011). Interestingly, a study performed on male Myers' high-alcohol-preferring (mHEP) rats reported that memantine dose-dependently decreased alcohol consumption in a 24-hour two-choice volitional consumption paradigm (Malpass et al., 2010). However, a study reported that memantine administration heightened the aggressive behavior associated with alcohol consumption (Newman et al., 2012). It is

noteworthy that memantine treatments exerted the ability to reduce self-administration to alcohol (Jeanblanc et al., 2014).

Interestingly, blocking the NMDA receptor by memantine or MK-801 has been shown to reduce alcohol withdrawal induced-seizures and neurotoxicity (Grant et al., 1990; Stepanyan et al., 2008). In clinical studies, memantine has been found to attenuate cue-induced craving for alcohol (Krupitsky et al., 2007a) and withdrawal associated with alcohol consumption (Krupitsky et al., 2007b). We suggest here that NMDA receptor antagonists might have beneficial effects against alcohol withdrawal-induced seizure.

Several studies found that NMDA receptors have a major role in the intoxicating effects of alcohol. Most studies have focused on finding NMDA receptor antagonists to block the inhibitory effects of alcohol on NMDA receptor. However, the effects of NMDA receptor agonists on alcohol intoxication have not been well studied yet. A study used d-serine as an agonist to overstimulate the NMDA receptors and counteract the alcohol intoxicating effects (Lockridge et al., 2012). This study also showed that administration of d-serine prior to alcohol exposure prolonged the latency of the loss of righting reflex and shortened the duration of the reflex (Lockridge et al., 2012). Interestingly, a significant decrease in alcohol preference has been reported in mice treated with d-serine (Lockridge et al., 2012). Together, targeting NMDA receptor could be a potential therapeutic approach for treatment of AUD.

4.2.2. AMPA and kainic acid receptors—AMPA receptors are heterotetrameric protein complexes composed of four subunits: GluR1, GluR2, GluR3, and GluR4. Each GluR subunit has a glutamate binding site. Agonists can bind to any of the four subunits on the channel. However, the stimulation of this receptor starts after the binding of two ligands, which may cause an increase in the current (Mayer and Armstrong, 2004; Mayer, 2005). It is important to note that channel's permeability to ions is governed by the GluR2 subunit. Studies have shown that AMPA receptors containing GluR2 subunit are impermeable to Ca^{2+}. Additionally, AMPA receptors modulate most of the excitatory neurotransmissions in the brain, which make them potential drug targets for treatment of neurological disorders and alcohol addiction (Chang et al., 2012). AMPA receptors are suggested to be involved in the induction of synaptic plasticity (Cooke and Bliss, 2006; Cull-Candy et al., 2006; Derkach et al., 2007; Santos et al., 2009).

Similar to NMDA and AMPA receptors, KA receptors also are heterotetrameric complexes comprised of several subunits termed as GluR5, GluR6, GluR7, KA1 and KA2 (Darstein et al., 2003). KA receptors have been found permeable to Na^+ and K^+ ions, suggesting that KA receptors participate in excitatory postsynaptic currents. It is important to note that KA receptors have been located in presynaptic neurons modulating glutamate release (Huettner, 2003).

AMPA is a well-known ionotropic glutamatergic receptor that is implicated in the acute and chronic effects of alcohol addiction. Studies revealed that moderate alcohol intake upregulated AMPA receptor expression in the central nucleus of the AMG (Salling et al., 2014). However, certain alcohol concentrations inhibit AMPA receptors by stabilizing the receptor in a desensitized state (Moykkynen et al., 2003). Importantly, alcohol exposure was

able to increase neural activity dependent pentraxin (NARP) in the NAc (Ary et al., 2012). NARP interacts with AMPA receptors, which facilitates excitatory synapse formation through aggregation of AMPA receptors at specific synapses. This interactive mechanism is an important part of regulating neuroplasticity and might be affected by alcohol exposure (Ary et al., 2012). In several preclinical studies performed in rodents, exposure to alcohol induced a significant increase in the expression and synaptic localization as well as modulate the function of AMPA receptor in certain regions of the brain reward circuitry (Chandler et al., 1999; Christian et al., 2012; Wang et al., 2012). Moreover, infusion of an AMPA receptor inhibitor into the dorsomedial striatum exhibited promising results in reducing alcohol consumption in rats (Wang et al., 2012).

Studies indicate that potentiation of AMPA receptors may be able to inhibit alcohol-induced intoxication. LY404187 and LY451395, both selective biarylsulfonaminde AMPA agonists, were found to reverse the acute intoxication induced by alcohol consumption. In addition, both compounds significantly reversed the loss of motor coordination and operant task disruption induced by ethanol (Jones et al., 2008). Thus, AMPA receptor antagonists may have an important role as a possible therapeutic compounds for managing acute ethanol intoxication (Jones et al., 2008).

Additionally, AMPA receptors have shown an extensive role in alcohol craving and relapse-like behavior (Bäckström and Hyytiä, 2004; Sanchis-Segura et al., 2006; Stephens and Brown, 1999). Increased AMPA receptor activity with aniracetam was shown to increase both self-administration and cue-induced reinstatement of alcohol (Cannady et al., 2013). Furthermore, GYKI 52466, a selective AMPA antagonist, reduced the reinstatement of alcohol-seeking behavior and ADE. These data provide ample evidence that AMPA receptors might be used as therapeutic targets for treatment of relapse-like alcohol behavior (Sanchis-Segura et al., 2006). Several *in vivo* studies have revealed that mixed AMPAR/KAR antagonists CNQX or NBQX can attenuate operant alcohol reinforcement (Stephens and Brown, 1999) and cue-induced alcohol-seeking behaviors (Bäckström and Hyytiä, 2004; Czachowski et al., 2012). However, the AMPA/KA receptor blockade also has shown ability to attenuate sucrose or saccharin intake, thus indicating the attenuation as a general appetitive suppressant effect (Stephens and Brown, 1999). A study revealed that injection of DNQX directly into the AMG attenuated withdrawal-related anxiety (Lack et al., 2007). Additionally, administration of the AMPA receptor antagonist, into the dorsomedial striatum, attenuated alcohol self-administration with no effect on sucrose (Wang et al., 2012). These data further support AMPA receptors as a potential therapeutic target for the treatment of AUD. However, studies are warranted to investigate the role of KA receptor in the attenuation of alcohol drinking behavior.

5. Allosteric modulation of GPCRs: pros and cons

Allosteric modulation of GPCRs provides a plethora of practical advantages over the orthosteric modulation. For example, many orthosteric ligands (proteins and peptides) of GPCRs are limited due to their lack of drug-like properties as well as their ability to cross the blood-brain barrier (Conn et al., 2014). Thus, small-molecule allosteric modulators provide an alternative strategy to target GPCRs in the CNS (Gregory et al., 2011). The

highly conserved orthosteric binding site within the subfamily is a significant hurdle to achieve optimum selectivity to target one particular GPCR (Fig. 5). In contrast, the heterogeneity in the allosteric binding sites across the receptor subtypes presents a valuable approach to obtain receptor selectivity (Fig. 5). Furthermore, some allosteric modulators, with no inherent agonistic activity, are effective only in the presence of the endogenous ligand (Melancon et al., 2012a). This is critical in maintaining the activity dependence of the endogenous ligand without affecting its physiological signaling. The saturation of the allosteric binding sites leading to the "ceiling effect" is especially advantageous with molecules that have smaller therapeutic window. Unlike orthosteric modulation, the ceiling effect associated with the allosteric modulation facilitates higher degree of titration of the pharmacological effect without causing significant target-associated toxicity. This can be particularly useful where higher doses of the drug are required to obtain a pharmacological effect. Allosteric modulation using small molecule modulators also offers improved tractability. Despite having important advantages, allosteric modulation has critical deficiencies associated with the concept. The significant species differences across the allosteric sites, due to their evolutionary divergence, has been a key challenge in preclinical studies and in translation of hits from in vitro screens (employing human GPCR) to in vivo disease models. Often the allosteric agonists show different pharmacological outcome towards different orthosteric ligand for the same receptor – often described as 'probe dependence'. This 'probe dependence' becomes a barrier in determining functional parameters that are transferrable across different assays in the drug screening process. Another important aspect of allosteric modulation is its effect on both the affinity as well as the efficacy of the orthosteric ligand. This often necessitates applying multiple-independent assays to determine each property of the allosteric modulators, thereby increasing the drug-discovery program timelines as well as the resources involved (Conn et al., 2009; Conn et al., 2014; Gregory et al., 2011; Melancon et al., 2012b).

6. Future directions, limitations and concluding remarks

This review provides ample evidence supporting the possibility to develop drugs that target glutamate receptors for the treatment of alcohol use disorders. However, this theoretical notion of pharmacologically targeting glutamate receptors for treating AUD often precludes the complexity associated with this concept. From drug discovery perspective, in spite of overcoming the druggability aspect of the process, few of the key challenges associated with targeting glutamate receptors such as selectivity towards its target, efficacy, safety or combination of the two or more still remain to be addressed. For example, JNJ 16259685, an mGluR1antagonist, induced locomotor impairment and significantly affected sucrose intake (Besheer et al., 2008a), despite its high selectivity towards its target. The limitations also extend as far as contradiction in findings when the same molecule has been used in different studies. For example, there have been inconsistencies in the efficacy of CPCCOEt, an mGluR1 antagonist, in two different studies (Hodge et al., 2006; Szumlinski et al., 2006). This contradiction in the effect of drug may be due to differences in the models involved in the studies. LY379268, an mGluR2/3 agonist, is effective in alcohol intake in different animal models. However, its effect on other natural reinforcers such as sweetened milk

questions the specificity of the effect of this compound on AUD (Backstrom and Hyytia, 2005; Baptista et al., 2004; Sidhpura et al., 2010).

The three drug candidates affecting the glutamate-receptors, which are extensively studied in preclinical as well as clinical settings for AUD, are acamprosate, memantine and toprimate. Acamprosate is known to affect two neurotransmitter systems, including GABA (as an agonist) and glutamate (as a NMDAR as well as mGluR5 antagonist). The drug was effective in increasing the complete abstinence rate as well as cumulative abstinence duration in several long-term placebo-controlled trials in alcohol-dependent patients (Lhuintre et al., 1990; Paille et al., 1995; Sass et al., 1996; Whitworth et al., 1996). However, in a large clinical trial involving 1383 patients in nine possible treatment groups, acamprosate neither alone nor with naltrexone or combined behavioral intervention shows a statistically significant reduction in alcohol consumption over placebo (Anton et al., 2006). Despite the inconsistencies in findings, acamprosate has an overall advantageous pharmacological effect on the alcohol consumption in patients, thereby leading to its approval for treatment of AUD in Europe and USA.

Another drug that surpassed the safety and tolerability hurdle and has an extensive potential for treatment of AUD is memantine. This drug noncompetitively antagonizes the NMDAR in the brain. Clinical studies in alcohol-dependent patients revealed promising results with memantine in different aspects of the disease like craving (Krupitsky et al., 2007a)and withdrawal (Krupitsky et al., 2007b). However, the drug was not very effective in preventing relapse in alcohol-dependent patients (Spanagel and Vengeliene, 2013). This difference in the outcomes could be attributed to the involvement of patients at different stages of the disease in both trials.

Additional important candidate in the clinical pipeline for treatment of AUD is an AMPAR/KAR antagonist, topiramate. Topiramate reduced craving, withdrawal and consumption in patients with AUD in several clinical studies (Baltieri et al., 2008; Florez et al., 2008; Johnson et al., 2006; Johnson et al., 2003; Johnson et al., 2007; Krupitsky et al., 2007a; Miranda Jr et al., 2008; Paparrigopoulos et al., 2011; Rubio et al., 2004; Rustembegovic et al., 2001). An interesting pharmacogenomics study revealed that a SNP in (rs2832407) GRIK1, a gene encoding the kainate GluK1 receptor subunit, moderated the efficacy of topiramate (Kranzler et al., 2014).

Drugs like acamprosate and topiramate provide compelling evidence of the potential of targeting glutamate receptors to treat AUD. Nevertheless, more preclinical development of the molecules to address important questions such as safety, efficacy, potency and specificity are warranted to advance these investigational agents into clinical development. The heterogeneity of the AUD resulted from different genetic and environmental interactions eventually lead to different phenotypes in patients. These phenotypic differences in patients remain a key challenging in designing the clinical trials. Thus, employing pharmacogenomic tools to understand the right patient-subpopulation for the trial might be a good strategy to increase the likelihoods of positive outcome in the clinical trials.

Antagonism of group 1 mGluRs and iGluRs, AMPA and NMDA, and agonism of group 2 mGluRs have been suggested to play a key role in preventing relapse and drug-seeking behaviors, including alcohol, as well as attenuating withdrawal effects. The metabotropic receptors showed fewer negative side effects than their ionotropic counterparts, possibly providing a more effective pharmacotherapeutic target. Despite the complexity of addiction, dependence, and drug abuse, the discovery of glutamate's role expands the knowledge of the neuromechanisms behind substance dependence. Further studies are warranted to determine the mechanisms and pathways involving glutamate receptors in alcohol seeking for more effective pharmacotherapies.

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Abbreviations

AC	Adenylyl Cyclase
ADE	Alcohol Deprivation Effect
AMG	Amygdala
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AUD	Alcohol Use Disorder
BLA	Basolateral Amygdala
CNS	Central Nervous System
CPP	Conditioned Place Preference
DAG	Diacylglycerol
EAAT	Excitatory Amino Acid Transporter
GABA	γ-Aminobutyric acid
GLAST	Glutamate Aspartate Transporter
GLT-1	Glutamate Transporter 1
GPCR	G-protein coupled receptor
HPC	Hippocampus
iGluR	Ionotropic Glutamate Receptor
IP3	Inositol (1,4,5)-Triphosphate
KA	Kainic Acid Receptor

MC	Motor Cortex
mGluR	Metabotropic Glutamate Receptor
MT	Motor Thalamus
NAc	Nucleus Accumbens
NARP	Neural Activity Dependent Pentraxin
NMDA	N-Methyl-D-aspartic acid
PFC	Prefrontal Cortex
PKC	Phosphokinase C
PLC	Phospholipase C
SNr	Substantia Niagra
VGLUT	Vesicular Glutamate Transporter
VP	Ventral Pallidum
VS	Ventral Striatum
VTA	Ventral Tegmental Area
xCT	Cystine/Glutamate Exchange Transporter

References

Aal-Aaboda M, Alhaddad H, Osowik F, Nauli SM, Sari Y. Effects of (R)-(–)-5-methyl-1-nicotinoyl-2-pyrazoline on glutamate transporter 1 and cysteine/glutamate exchanger as well as ethanol drinking behavior in male, alcohol-preferring rats. Journal of neuroscience research. 2015; 93:930–937. [PubMed: 25601490]

Abrahao KP, Ariwodola OJ, Butler TR, Rau AR, Skelly MJ, Carter E, Alexander NP, McCool BA, Souza-Formigoni ML, Weiner JL. Locomotor sensitization to ethanol impairs NMDA receptor-dependent synaptic plasticity in the nucleus accumbens and increases ethanol self-administration. J Neurosci. 2013; 33:4834–42. [PubMed: 23486954]

Adams CL, Cowen MS, Short JL, Lawrence AJ. Combined antagonism of glutamate mGlu5 and adenosine A2A receptors interact to regulate alcohol-seeking in rats. Int J Neuropsychopharmacol. 2008; 11:229–41. [PubMed: 17517168]

Adams CL, Short JL, Lawrence AJ. Cue-conditioned alcohol seeking in rats following abstinence: involvement of metabotropic glutamate 5 receptors. Br J Pharmacol. 2010; 159:534–42. [PubMed: 20067474]

Alasmari F, Abuhamdah S, Sari Y. Effects of ampicillin on cystine/glutamate antiporter and glutamate transporter 1 isoforms as well as ethanol drinking in male P rats. Neurosci Lett. 2015a; 600:148–52. [PubMed: 26071905]

Alasmari F, Al-Rejaie SS, AlSharari SD, Sari Y. Targeting glutamate homeostasis for potential treatment of nicotine dependence. Brain Res Bull. 2015b; 121:1–8. [PubMed: 26589642]

Alasmari F, Rao P, Sari Y. Effects of cefazolin and cefoperazone on glutamate transporter 1 isoforms and cystine/glutamate exchanger as well as alcohol drinking behavior in male alcohol-preferring rats. Brain Research. 2016

Alaux-Cantin S, Buttolo R, Houchi H, Jeanblanc J, Naassila M. Memantine reduces alcohol drinking but not relapse in alcohol-dependent rats. Addict Biol. 2015; 20:890–901. [PubMed: 25138717]

Alhaddad H, Das SC, Sari Y. Effects of ceftriaxone on ethanol intake: a possible role for xCT and GLT-1 isoforms modulation of glutamate levels in P rats. Psychopharmacology (Berl). 2014a; 231:4049–57. [PubMed: 24687412]

Alhaddad H, Kim NT, Aal-Aaboda M, Althobaiti YS, Leighton J, Boddu SH, Wei Y, Sari Y. Effects of MS-153 on chronic ethanol consumption and GLT1 modulation of glutamate levels in male alcohol-preferring rats. Front Behav Neurosci. 2014b; 8:366. [PubMed: 25400560]

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A, Group CSR. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006; 295:2003–17. [PubMed: 16670409]

Arriza JL, Eliasof S, Kavanaugh MP, Amara SG. Excitatory amino acid transporter 5, a retinal glutamate transporter coupled to a chloride conductance. Proc Natl Acad Sci U S A. 1997; 94:4155–60. [PubMed: 9108121]

Ary AW, Cozzoli DK, Finn DA, Crabbe JC, Dehoff MH, Worley PF, Szumlinski KK. Ethanol up-regulates nucleus accumbens neuronal activity dependent pentraxin (Narp): implications for alcohol-induced behavioral plasticity. Alcohol. 2012; 46:377–87. [PubMed: 22444953]

Augier E, Dulman RS, Rauffenbart C, Augier G, Cross AJ, Heilig M. The mGluR2 Positive Allosteric Modulator, AZD8529, and Cue-Induced Relapse to Alcohol Seeking in Rats. Neuropsychopharmacology. 2016; 41:2932–2940. [PubMed: 27339394]

Backstrom P, Bachteler D, Koch S, Hyytia P, Spanagel R. mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior. Neuropsychopharmacology. 2004; 29:921–8. [PubMed: 14735132]

Backstrom P, Hyytia P. Suppression of alcohol self-administration and cue-induced reinstatement of alcohol seeking by the mGlu2/3 receptor agonist LY379268 and the mGlu8 receptor agonist (S)-3,4-DCPG. Eur J Pharmacol. 2005; 528:110–8. [PubMed: 16324694]

Backstrom P, Hyytia P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. Neuropsychopharmacology. 2006; 31:778–86. [PubMed: 16123768]

Backstrom P, Hyytia P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. Psychopharmacology (Berl). 2007; 192:571–80. [PubMed: 17347848]

Bäckström P, Hyytiä P. Ionotropic Glutamate Receptor Antagonists Modulate Cue-Induced Reinstatement of Ethanol-Seeking Behavior. Alcoholism: Clinical and Experimental Research. 2004; 28:558–565.

Bahi A. The selective metabotropic glutamate receptor 7 allosteric agonist AMN082 prevents reinstatement of extinguished ethanol-induced conditioned place preference in mice. Pharmacol Biochem Behav. 2012a; 101:193–200. [PubMed: 22269296]

Bahi A. The selective metabotropic glutamate receptor 7 allosteric agonist AMN082 prevents reinstatement of extinguished ethanol-induced conditioned place preference in mice. Pharmacology Biochemistry and Behavior. 2012b; 101:193–200.

Bahi A, Fizia K, Dietz M, Gasparini F, Flor PJ. Pharmacological modulation of mGluR7 with AMN082 and MMPIP exerts specific influences on alcohol consumption and preference in rats. Addict Biol. 2012; 17:235–47. [PubMed: 21392179]

Baltieri DA, Daro FR, Ribeiro PL, de Andrade AG. Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction. 2008; 103:2035–44. [PubMed: 18855810]

Baptista MA, Martin-Fardon R, Weiss F. Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. The Journal of neuroscience. 2004; 24:4723–4727. [PubMed: 15152032]

Barker JM, Lench DH, Chandler LJ. Reversal of alcohol dependence-induced deficits in cue-guided behavior via mGluR2/3 signaling in mice. Psychopharmacology (Berl). 2016; 233:235–42. [PubMed: 26449720]

Besheer J, Hodge CW. Pharmacological and anatomical evidence for an interaction between mGluR5- and GABA(A) alpha1-containing receptors in the discriminative stimulus effects of ethanol. Neuropsychopharmacology. 2005; 30:747–57. [PubMed: 15549054]

Besheer J, Stevenson RA, Hodge CW. mGlu5 receptors are involved in the discriminative stimulus effects of self-administered ethanol in rats. Eur J Pharmacol. 2006; 551:71–5. [PubMed: 17026991]

Besheer J, Faccidomo S, Grondin JJ, Hodge CW. Effects of mGlu1-receptor blockade on ethanol self-administration in inbred alcohol-preferring rats. Alcohol. 2008a; 42:13–20. [PubMed: 18164577]

Besheer J, Faccidomo S, Grondin JJ, Hodge CW. Regulation of motivation to self-administer ethanol by mGluR5 in alcohol-preferring (P) rats. Alcohol Clin Exp Res. 2008b; 32:209–21. [PubMed: 18162077]

Besheer J, Grondin JJ, Salling MC, Spanos M, Stevenson RA, Hodge CW. Interoceptive effects of alcohol require mGlu5 receptor activity in the nucleus accumbens. J Neurosci. 2009; 29:9582–91. [PubMed: 19641121]

Besheer J, Grondin JJ, Cannady R, Sharko AC, Faccidomo S, Hodge CW. Metabotropic glutamate receptor 5 activity in the nucleus accumbens is required for the maintenance of ethanol self-administration in a rat genetic model of high alcohol intake. Biol Psychiatry. 2010; 67:812–22. [PubMed: 19897175]

Biala G, Kotlinska J. Blockade of the acquisition of ethanol-induced conditioned place preference by N-methyl-D-aspartate receptor antagonists. Alcohol Alcohol. 1999; 34:175–82. [PubMed: 10344778]

Bienkowski P, Krzascik P, Koros E, Kostowski W, Scinska A, Danysz W. Effects of a novel uncompetitive NMDA receptor antagonist, MRZ 2/579 on ethanol self-administration and ethanol withdrawal seizures in the rat. Eur J Pharmacol. 2001; 413:81–9. [PubMed: 11173066]

Bigge CF. Ionotropic glutamate receptors. Current opinion in chemical biology. 1999; 3:441–447. [PubMed: 10419857]

Bird MK, Kirchhoff J, Djouma E, Lawrence AJ. Metabotropic glutamate 5 receptors regulate sensitivity to ethanol in mice. Int J Neuropsychopharmacol. 2008; 11:765–74. [PubMed: 18400131]

Bisaga A, Evans SM. Acute effects of memantine in combination with alcohol in moderate drinkers. Psychopharmacology (Berl). 2004; 172:16–24. [PubMed: 14530901]

Blednov YA, Walker D, Osterndorf-Kahanek E, Harris RA. Mice lacking metabotropic glutamate receptor 4 do not show the motor stimulatory effect of ethanol. Alcohol. 2004; 34:251–259. [PubMed: 15902920]

Blednov YA, Harris RA. Metabotropic glutamate receptor 5 (mGluR5) regulation of ethanol sedation, dependence and consumption: relationship to acamprosate actions. Int J Neuropsychopharmacol. 2008; 11:775–93. [PubMed: 18377703]

Bossert JM, Poles GC, Sheffler-Collins SI, Ghitza UE. The mGluR 2/3 agonist LY379268 attenuates context-and discrete cue-induced reinstatement of sucrose seeking but not sucrose self-administration in rats. Behavioural brain research. 2006; 173:148–152. [PubMed: 16834996]

Boyce-Rustay JM, Cunningham CL. The role of NMDA receptor binding sites in ethanol place conditioning. Behav Neurosci. 2004; 118:822–34. [PubMed: 15301608]

Bragina L, Bonifacino T, Bassi S, Milanese M, Bonanno G, Conti F. Differential expression of metabotropic glutamate and GABA receptors at neocortical glutamatergic and GABAergic axon terminals. Front Cell Neurosci. 2015; 9:345. [PubMed: 26388733]

Brandstatter JH, Koulen P, Kuhn R, van der Putten H, Wassle H. Compartmental localization of a metabotropic glutamate receptor (mGluR7): two different active sites at a retinal synapse. J Neurosci. 1996; 16:4749–56. [PubMed: 8764662]

Broadbent J, Kampmueller KM, Koonse SA. Expression of behavioral sensitization to ethanol by DBA/2J mice: the role of NMDA and non-NMDA glutamate receptors. Psychopharmacology (Berl). 2003; 167:225–34. [PubMed: 12669179]

Camp MC, Feyder M, Ihne J, Palachick B, Hurd B, Karlsson RM, Noronha B, Chen YC, Coba MP, Grant SG, Holmes A. A novel role for PSD-95 in mediating ethanol intoxication, drinking and place preference. Addict Biol. 2011; 16:428–39. [PubMed: 21309945]

Cannady R, Grondin JJ, Fisher KR, Hodge CW, Besheer J. Activation of group II metabotropic glutamate receptors inhibits the discriminative stimulus effects of alcohol via selective activity within the amygdala. Neuropsychopharmacology. 2011; 36:2328–38. [PubMed: 21734651]

Cannady R, Fisher KR, Durant B, Besheer J, Hodge CW. Enhanced AMPA receptor activity increases operant alcohol self-administration and cue-induced reinstatement. Addict Biol. 2013; 18:54–65. [PubMed: 23126443]

Chandler LJ, Norwood D, Sutton G. Chronic ethanol upregulates NMDA and AMPA, but not kainate receptor subunit proteins in rat primary cortical cultures. Alcoholism: Clinical and Experimental Research. 1999; 23:363–370.

Chang PKY, Verbich D, McKinney RA. AMPA receptors as drug targets in neurological disease–advantages, caveats, and future outlook. European Journal of Neuroscience. 2012; 35:1908–1916. [PubMed: 22708602]

Chaudhry FA, Lehre KP, van Lookeren Campagne M, Ottersen OP, Danbolt NC, Storm-Mathisen J. Glutamate transporters in glial plasma membranes: highly differentiated localizations revealed by quantitative ultrastructural immunocytochemistry. Neuron. 1995; 15:711–20. [PubMed: 7546749]

Chen G, Cuzon Carlson VC, Wang J, Beck A, Heinz A, Ron D, Lovinger DM, Buck KJ. Striatal involvement in human alcoholism and alcohol consumption, and withdrawal in animal models. Alcohol Clin Exp Res. 2011; 35:1739–48. [PubMed: 21615425]

Christian DT, Alexander NJ, Diaz MR, Robinson S, McCool BA. Chronic intermittent ethanol and withdrawal differentially modulate basolateral amygdala AMPA-type glutamate receptor function and trafficking. Neuropharmacology. 2012; 62:2430–9. [PubMed: 22387532]

Cognet L, Groc L, Lounis B, Choquet D. Multiple routes for glutamate receptor trafficking: surface diffusion and membrane traffic cooperate to bring receptors to synapses. 2007 arXiv preprint arXiv:0704.3854.

Conn PJ, Christopoulos A, Lindsley CW. Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders. Nat Rev Drug Discov. 2009; 8:41–54. [PubMed: 19116626]

Conn PJ, Lindsley CW, Meiler J, Niswender CM. Opportunities and challenges in the discovery of allosteric modulators of GPCRs for treating CNS disorders. Nature reviews Drug discovery. 2014; 13:692–708. [PubMed: 25176435]

Cooke SF, Bliss TV. Plasticity in the human central nervous system. Brain. 2006; 129:1659–73. [PubMed: 16672292]

Corbit LH, Nie H, Janak PH. Habitual responding for alcohol depends upon both AMPA and D2 receptor signaling in the dorsolateral striatum. Front Behav Neurosci. 2014; 8:301. [PubMed: 25228865]

Corti C, Aldegheri L, Somogyi P, Ferraguti F. Distribution and synaptic localisation of the metabotropic glutamate receptor 4 (mGluR4) in the rodent CNS. Neuroscience. 2002; 110:403–20. [PubMed: 11906782]

Cowen MS, Djouma E, Lawrence AJ. The metabotropic glutamate 5 receptor antagonist 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine reduces ethanol self-administration in multiple strains of alcohol-preferring rats and regulates olfactory glutamatergic systems. J Pharmacol Exp Ther. 2005; 315:590–600. [PubMed: 16014750]

Cowen MS, Krstew E, Lawrence AJ. Assessing appetitive and consummatory phases of ethanol self-administration in C57BL/6J mice under operant conditions: regulation by mGlu5 receptor antagonism. Psychopharmacology (Berl). 2007; 190:21–9. [PubMed: 17096086]

Coyle JT, Tsai G. NMDA receptor function, neuroplasticity, and the pathophysiology of schizophrenia. Int Rev Neurobiol. 2004; 59:491–515. [PubMed: 15006500]

Cozzoli DK, Goulding SP, Zhang PW, Xiao B, Hu JH, Ary AW, Obara I, Rahn A, Abou-Ziab H, Tyrrel B, Marini C, Yoneyama N, Metten P, Snelling C, Dehoff MH, Crabbe JC, Finn DA, Klugmann M, Worley PF, Szumlinski KK. Binge drinking upregulates accumbens mGluR5-Homer2-PI3K signaling: functional implications for alcoholism. J Neurosci. 2009; 29:8655–68. [PubMed: 19587272]

Cozzoli DK, Strong-Kaufman MN, Tanchuck MA, Hashimoto JG, Wiren KM, Finn DA. The Effect of mGluR5 Antagonism During Binge Drinkingon Subsequent Ethanol Intake in C57BL/6J Mice:

Sex- and Age-Induced Differences. Alcohol Clin Exp Res. 2014; 38:730–738. [PubMed: 27695144]

Cull-Candy S, Kelly L, Farrant M. Regulation of Ca2+-permeable AMPA receptors: synaptic plasticity and beyond. Curr Opin Neurobiol. 2006; 16:288–97. [PubMed: 16713244]

Czachowski CL, Delory MJ, Pope JD. Behavioral and neurotransmitter specific roles for the ventral tegmental area in reinforcer-seeking and intake. Alcohol Clin Exp Res. 2012; 36:1659–68. [PubMed: 22432593]

Dahchour A, De Witte P, Bolo N, Nedelec JF, Muzet M, Durbin P, Macher JP. Central effects of acamprosate: part 1. Acamprosate blocks the glutamate increase in the nucleus accumbens microdialysate in ethanol withdrawn rats. Psychiatry Res. 1998; 82:107–14. [PubMed: 9754453]

Dahchour A, Hoffman A, Deitrich R, de Witte P. Effects of ethanol on extracellular amino acid levels in high-and low-alcohol sensitive rats: a microdialysis study. Alcohol Alcohol. 2000; 35:548–53. [PubMed: 11093960]

Danbolt NC. Glutamate uptake. Prog Neurobiol. 2001; 65:1–105. [PubMed: 11369436]

Darstein M, Petralia RS, Swanson GT, Wenthold RJ, Heinemann SF. Distribution of kainate receptor subunits at hippocampal mossy fiber synapses. The Journal of neuroscience. 2003; 23:8013–8019. [PubMed: 12954862]

Das SC, Yamamoto BK, Hristov AM, Sari Y. Ceftriaxone attenuates ethanol drinking and restores extracellular glutamate concentration through normalization of GLT-1 in nucleus accumbens of male alcohol-preferring rats. Neuropharmacology. 2015; 97:67–74. [PubMed: 26002627]

Deng C, Li KY, Zhou C, Ye JH. Ethanol enhances glutamate transmission by retrograde dopamine signaling in a postsynaptic neuron/synaptic bouton preparation from the ventral tegmental area. Neuropsychopharmacology. 2009; 34:1233–44. [PubMed: 18784647]

Derkach VA, Oh MC, Guire ES, Soderling TR. Regulatory mechanisms of AMPA receptors in synaptic plasticity. Nat Rev Neurosci. 2007; 8:101–13. [PubMed: 17237803]

Ding ZM, Engleman EA, Rodd ZA, McBride WJ. Ethanol increases glutamate neurotransmission in the posterior ventral tegmental area of female wistar rats. Alcohol Clin Exp Res. 2012; 36:633–40. [PubMed: 22017390]

Ding ZM, Rodd ZA, Engleman EA, Bailey JA, Lahiri DK, McBride WJ. Alcohol drinking and deprivation alter basal extracellular glutamate concentrations and clearance in the mesolimbic system of alcohol-preferring (P) rats. Addict Biol. 2013; 18:297–306. [PubMed: 23240885]

Downing C, Marks MJ, Larson C, Johnson TE. The metabotropic glutamate receptor subtype 5 mediates sensitivity to the sedative properties of ethanol. Pharmacogenet Genomics. 2010; 20:553–64. [PubMed: 20657349]

Duan S, Anderson CM, Stein BA, Swanson RA. Glutamate induces rapid upregulation of astrocyte glutamate transport and cell-surface expression of GLAST. J Neurosci. 1999; 19:10193–200. [PubMed: 10575016]

Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. Medical hypotheses. 2006; 67:362–370. [PubMed: 16542786]

Eisenhardt M, Leixner S, Lujan R, Spanagel R, Bilbao A. Glutamate Receptors within the Mesolimbic Dopamine System Mediate Alcohol Relapse Behavior. J Neurosci. 2015; 35:15523–38. [PubMed: 26609150]

Escher T, Call SB, Blaha CD, Mittleman G. Behavioral effects of aminoadamantane class NMDA receptor antagonists on schedule-induced alcohol and self-administration of water in mice. Psychopharmacology (Berl). 2006; 187:424–34. [PubMed: 16835770]

Evans SM, Levin FR, Brooks DJ, Garawi F. A pilot double-blind treatment trial of memantine for alcohol dependence. Alcohol Clin Exp Res. 2007; 31:775–82. [PubMed: 17378918]

Ferraro L, Loche A, Beggiato S, Tomasini MC, Antonelli T, Colombo G, Lobina C, Carai MA, Porcu A, Castelli MP, Clerici F, Borelli AC, Cacciaglia R, Tanganelli S. The new compound GET73, N-[(4-trifluoromethyl)benzyl]4-methoxybutyramide, Regulates hippocampal Aminoacidergic transmission possibly via an allosteric modulation of mGlu5 receptor. Behavioural evidence of its “anti-alcohol” and anxiolytic properties. Curr Med Chem. 2013; 20:3339–57. [PubMed: 23862615]

Fitzgerald GJ, Liu H, Morzorati SL. Decreased sensitivity of NMDA receptors on dopaminergic neurons from the posterior ventral tegmental area following chronic nondependent alcohol consumption. Alcohol Clin Exp Res. 2012; 36:1710–9. [PubMed: 22433065]

Florez G, Garcia-Portilla P, Alvarez S, Saiz PA, Nogueiras L, Bobes J. Using topiramate or naltrexone for the treatment of alcohol-dependent patients. Alcohol Clin Exp Res. 2008; 32:1251–9. [PubMed: 18482157]

Fu R, Zuo W, Gregor D, Li J, Grech D, Ye JH. Pharmacological Manipulation of the Rostromedial Tegmental Nucleus Changes Voluntary and Operant Ethanol Self-Administration in Rats. Alcohol Clin Exp Res. 2016; 40:572–82. [PubMed: 26876382]

Furuta A, Rothstein JD, Martin LJ. Glutamate transporter protein subtypes are expressed differentially during rat CNS development. J Neurosci. 1997; 17:8363–75. [PubMed: 9334410]

Garcia-Junco-Clemente P, Linares-Clemente P, Fernandez-Chacon R. Active zones for presynaptic plasticity in the brain. Mol Psychiatry. 2005; 10:185–200. image 131. [PubMed: 15630409]

Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol. 2008; 75:218–65. [PubMed: 17706608]

Gass JT, Olive MF. Positive allosteric modulation of mGluR5 receptors facilitates extinction of a cocaine contextual memory. Biol Psychiatry. 2009a; 65:717–20. [PubMed: 19100966]

Gass JT, Olive MF. Role of protein kinase C epsilon (PKCvarepsilon) in the reduction of ethanol reinforcement due to mGluR5 antagonism in the nucleus accumbens shell. Psychopharmacology (Berl). 2009b; 204:587–97. [PubMed: 19225761]

Gass JT, Trantham-Davidson H, Kassab AS, Glen WB Jr, Olive MF, Chandler LJ. Enhancement of extinction learning attenuates ethanol-seeking behavior and alters plasticity in the prefrontal cortex. J Neurosci. 2014; 34:7562–74. [PubMed: 24872560]

Gilpin NW, Koob GF. Neurobiology of alcohol dependence: focus on motivational mechanisms. Alcohol research & health: the journal of the National Institute on Alcohol Abuse and Alcoholism. 2008; 31:185. [PubMed: 19881886]

Gonda X. Basic pharmacology of NMDA receptors. Curr Pharm Des. 2012; 18:1558–67. [PubMed: 22280436]

Goodwani S, Rao PS, Bell RL, Sari Y. Amoxicillin and amoxicillin/clavulanate reduce ethanol intake and increase GLT-1 expression as well as AKT phosphorylation in mesocorticolimbic regions. Brain Res. 2015; 1622:397–408. [PubMed: 26168897]

Grant KA, Valverius P, Hudspith M, Tabakoff B. Ethanol withdrawal seizures and the NMDA receptor complex. Eur J Pharmacol. 1990; 176:289–96. [PubMed: 2158451]

Gregory KJ, Dong EN, Meiler J, Conn PJ. Allosteric modulation of metabotropic glutamate receptors: structural insights and therapeutic potential. Neuropharmacology. 2011; 60:66–81. [PubMed: 20637216]

Griffin WC 3rd, Haun HL, Hazelbaker CL, Ramachandra VS, Becker HC. Increased extracellular glutamate in the nucleus accumbens promotes excessive ethanol drinking in ethanol dependent mice. Neuropsychopharmacology. 2014; 39:707–17. [PubMed: 24067300]

Guo Y, Wang HL, Xiang XH, Zhao Y. The role of glutamate and its receptors in mesocorticolimbic dopaminergic regions in opioid addiction. Neurosci Biobehav Rev. 2009; 33:864–73. [PubMed: 19428497]

Gupta T, Syed YM, Revis AA, Miller SA, Martinez M, Cohn KA, Demeyer MR, Patel KY, Brzezinska WJ, Rhodes JS. Acute effects of acamprosate and MPEP on ethanol Drinking-in-the-Dark in male C57BL/6J mice. Alcohol Clin Exp Res. 2008; 32:1992–8. [PubMed: 18782337]

Gyetvai B, Simonyi A, Oros M, Saito M, Smiley J, Vadasz C. mGluR7 genetics and alcohol: intersection yields clues for addiction. Neurochem Res. 2011; 36:1087–100. [PubMed: 21448595]

Hakami AY, Hammad AM, Sari Y. Effects of Amoxicillin and Augmentin on Cystine-Glutamate Exchanger and Glutamate Transporter 1 Isoforms as well as Ethanol Intake in Alcohol-Preferring Rats. Front Neurosci. 2016; 10:171. [PubMed: 27199635]

Hodge CW, Miles MF, Sharko AC, Stevenson RA, Hillmann JR, Lepoutre V, Besheer J, Schroeder JP. The mGluR5 antagonist MPEP selectively inhibits the onset and maintenance of ethanol self-administration in C57BL/6J mice. Psychopharmacology (Berl). 2006; 183:429–38. [PubMed: 16292590]

Huettner JE. Kainate receptors and synaptic transmission. Prog Neurobiol. 2003; 70:387–407. [PubMed: 14511698]

Huggins DJ, Grant GH. The function of the amino terminal domain in NMDA receptor modulation. J Mol Graph Model. 2005; 23:381–8. [PubMed: 15670959]

Idrus NM, McGough NN, Riley EP, Thomas JD. Administration of memantine during ethanol withdrawal in neonatal rats: effects on long-term ethanol-induced motor incoordination and cerebellar Purkinje cell loss. Alcohol Clin Exp Res. 2011; 35:355–64. [PubMed: 21070252]

Imperato A, Di Chiara G. Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol. J Pharmacol Exp Ther. 1986; 239:219–28. [PubMed: 3761194]

Imre G. The preclinical properties of a novel group II metabotropic glutamate receptor agonist LY379268. CNS Drug Rev. 2007; 13:444–64. [PubMed: 18078428]

Jaramillo AA, Randall PA, Frisbee S, Fisher KR, Besheer J. Activation of mGluR2/3 following stress hormone exposure restores sensitivity to alcohol in rats. Alcohol. 2015; 49:525–32. [PubMed: 26142564]

Jeanblanc J, Coune F, Botia B, Naassila M. Brain-derived neurotrophic factor mediates the suppression of alcohol self-administration by memantine. Addict Biol. 2014; 19:758–69. [PubMed: 23414063]

Johnson B, Ait-daoud N, Akhtar F. Oral Topiramate Reduces the Consequences of Drinking and Improves the Quality of Life of Alcohol-dependent Individuals. Year Book of Psychiatry & Applied Mental Health. 2006; 2006:96–97.

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. The Lancet. 2003; 361:1677–1685.

Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA. Topiramate for treating alcohol dependence: a randomized controlled trial. Jama. 2007; 298:1641–1651. [PubMed: 17925516]

Jones N, Messenger MJ, O'Neill MJ, Oldershaw A, Gilmour G, Simmons RM, Iyengar S, Libri V, Tricklebank M, Williams SC. AMPA receptor potentiation can prevent ethanol-induced intoxication. Neuropsychopharmacology. 2008; 33:1713–1723. [PubMed: 17851540]

Kalev-Zylinska ML, During MJ. Paradoxical facilitatory effect of low-dose alcohol consumption on memory mediated by NMDA receptors. J Neurosci. 2007; 27:10456–67. [PubMed: 17898217]

Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005; 162:1403–13. [PubMed: 16055761]

Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci. 2009; 10:561–72. [PubMed: 19571793]

Kanai Y, Hediger MA. The glutamate and neutral amino acid transporter family: physiological and pharmacological implications. Eur J Pharmacol. 2003; 479:237–47. [PubMed: 14612154]

Kapasova Z, Szumlinski KK. Strain differences in alcohol-induced neurochemical plasticity: a role for accumbens glutamate in alcohol intake. Alcohol Clin Exp Res. 2008; 32:617–31. [PubMed: 18341649]

Karcz-Kubicha M, Liljequist S. Effects of post-ethanol administration of NMDA and non-NMDA receptor antagonists on the development of ethanol tolerance in C57B1 mice. Psychopharmacology (Berl). 1995; 120:49–56. [PubMed: 7480535]

Kearney JA, Frey KA, Albin RL. Metabotropic glutamate agonist-induced rotation: a pharmacological, FOS immunohistochemical, and [14C]-2-deoxyglucose autoradiographic study. J Neurosci. 1997; 17:4415–25. [PubMed: 9151758]

Kenny PJ, Markou A. The ups and downs of addiction: role of metabotropic glutamate receptors. Trends Pharmacol Sci. 2004; 25:265–72. [PubMed: 15120493]

Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010; 35:217–38. [PubMed: 19710631]

Koros E, Kostowski W, Danysz W, Bienkowski P. Ethanol discrimination in the rat: lack of modulation by restraint stress and memantine. Naunyn Schmiedebergs Arch Pharmacol. 1999; 359:117–22. [PubMed: 10048596]

Kotlinska J. NMDA antagonists inhibit the development of ethanol dependence in rats. Pol J Pharmacol. 2001; 53:47–50. [PubMed: 11785910]

Kotlinska J, Bochenski M, Danysz W. N-methyl-D-aspartate and group I metabotropic glutamate receptors are involved in the expression of ethanol-induced sensitization in mice. Behav Pharmacol. 2006; 17:1–8. [PubMed: 16377958]

Kotlinska J, Bochenski M. The influence of various glutamate receptors antagonists on anxiety-like effect of ethanol withdrawal in a plus-maze test in rats. Eur J Pharmacol. 2008; 598:57–63. [PubMed: 18838071]

Kotlinska JH, Bochenski M, Danysz W. The role of group I mGlu receptors in the expression of ethanol-induced conditioned place preference and ethanol withdrawal seizures in rats. Eur J Pharmacol. 2011; 670:154–61. [PubMed: 21946112]

Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM. Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry. 2014; 171:445–52. [PubMed: 24525690]

Krishnan-Sarin S, O'Malley SS, Franco N, Cavallo DA, Morean M, Shi J, Pittman B, Krystal JH. N-methyl-D-aspartate receptor antagonism has differential effects on alcohol craving and drinking in heavy drinkers. Alcohol Clin Exp Res. 2015; 39:300–7. [PubMed: 25664775]

Krupitsky EM, Neznanova O, Masalov D, Burakov AM, Didenko T, Romanova T, Tsoy M, Bespalov A, Slavina TY, Grinenko AA, Petrakis IL, Pittman B, Gueorguieva R, Zvartau EE, Krystal JH. Effect of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients. Am J Psychiatry. 2007a; 164:519–23. [PubMed: 17329479]

Krupitsky EM, Rudenko AA, Burakov AM, Slavina TY, Grinenko AA, Pittman B, Gueorguieva R, Petrakis IL, Zvartau EE, Krystal JH. Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. Alcohol Clin Exp Res. 2007b; 31:604–11. [PubMed: 17374039]

Krystal AD, Weiner RD, Dean MD, Lindahl VH, Tramontozzi LA 3rd, Falcone G, Coffey CE. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. J Neuropsychiatry Clin Neurosci. 2003; 15:27–34. [PubMed: 12556568]

Kufahl PR, Martin-Fardon R, Weiss F. Enhanced sensitivity to attenuation of conditioned reinstatement by the mGluR2/3 agonist LY379268 and increased functional activity of mGluR2/3 in rats with a history of ethanol dependence. Neuropsychopharmacology. 2011; 36:2762–2773. [PubMed: 21881571]

Kumar J, Hapidin H, Bee YT, Ismail Z. Effects of the mGluR5 antagonist MPEP on ethanol withdrawal induced anxiety-like syndrome in rats. Behav Brain Funct. 2013; 9:43. [PubMed: 24279870]

Lack AK, Diaz MR, Chappell A, DuBois DW, McCool BA. Chronic ethanol and withdrawal differentially modulate pre- and postsynaptic function at glutamatergic synapses in rat basolateral amygdala. J Neurophysiol. 2007; 98:3185–96. [PubMed: 17898152]

Lallemand F, Ward RJ, De Witte P, Verbanck P. Binge drinking +/− chronic nicotine administration alters extracellular glutamate and arginine levels in the nucleus accumbens of adult male and female Wistar rats. Alcohol Alcohol. 2011; 46:373–82. [PubMed: 21478495]

Laukkanen V, Karkkainen O, Kupila J, Kautiainen H, Tiihonen J, Storvik M. Increased metabotropic glutamate 2/3 receptor binding in the perigenual anterior cingulate cortex of Cloninger type 2 alcoholics: a whole-hemisphere autoradiography study. Alcohol Alcohol. 2015; 50:62–7. [PubMed: 25425009]

Laurie DJ, Schoeffter P, Wiederhold KH, Sommer B. Cloning, distribution and functional expression of the human mGlu6 metabotropic glutamate receptor. Neuropharmacology. 1997; 36:145–52. [PubMed: 9144651]

Lee JY, Choe ES, Yang CH, Choi KH, Cheong JH, Jang CG, Seo JW, Yoon SS. The mGluR5 antagonist MPEP suppresses the expression and reinstatement, but not the acquisition, of the ethanol-conditioned place preference in mice. Pharmacol Biochem Behav. 2016; 140:33–8. [PubMed: 26521964]

Lhuintre JP, Moore N, Tran G, Steru L, Langrenon S, Daoust M, Parot P, Ladure P, Libert C, Boismare F, et al. Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol Alcohol. 1990; 25:613–22. [PubMed: 2085344]

Li X, Gardner EL, Xi ZX. The metabotropic glutamate receptor 7 (mGluR7) allosteric agonist AMN082 modulates nucleus accumbens GABA and glutamate, but not dopamine, in rats. Neuropharmacology. 2008; 54:542–51. [PubMed: 18155073]

Lockridge A, Romero G, Harrington J, Newland B, Gong Z, Cameron A, Yuan LL. Timing-dependent reduction in ethanol sedation and drinking preference by NMDA receptor co-agonist d-serine. Alcohol. 2012; 46:389–400. [PubMed: 22445805]

Lominac KD, Kapasova Z, Hannun RA, Patterson C, Middaugh LD, Szumlinski KK. Behavioral and neurochemical interactions between Group 1 mGluR antagonists and ethanol: potential insight into their anti-addictive properties. Drug Alcohol Depend. 2006; 85:142–56. [PubMed: 16697125]

Long C, Yang L, Faingold CL, Steven Evans M. Excitatory amino acid receptor-mediated responses in periaqueductal gray neurons are increased during ethanol withdrawal. Neuropharmacology. 2007; 52:802–11. [PubMed: 17123553]

Lukoyanov NV, Paula-Barbosa MM. Memantine, but not dizocilpine, ameliorates cognitive deficits in adult rats withdrawn from chronic ingestion of alcohol. Neurosci Lett. 2001; 309:45–8. [PubMed: 11489543]

Lum EN, Campbell RR, Rostock C, Szumlinski KK. mGluR1 within the nucleus accumbens regulates alcohol intake in mice under limited-access conditions. Neuropharmacology. 2014; 79:679–87. [PubMed: 24467847]

Malenka RC, Nicoll RA. NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. Trends Neurosci. 1993; 16:521–7. [PubMed: 7509523]

Malpass GE, Williams HL, McMillen BA. Effects of the non-competitive NMDA receptor antagonist memantine on the volitional consumption of ethanol by alcohol-preferring rats. Basic Clin Pharmacol Toxicol. 2010; 106:435–44. [PubMed: 20210793]

Manto M, Laute MA, Pandolfo M. Depression of extra-cellular GABA and increase of NMDA-induced nitric oxide following acute intra-nuclear administration of alcohol in the cerebellar nuclei of the rat. Cerebellum. 2005; 4:230–8. [PubMed: 16321878]

Mark LP, Prost RW, Ulmer JL, Smith MM, Daniels DL, Strottmann JM, Brown WD, Hacein-Bey L. Pictorial review of glutamate excitotoxicity: fundamental concepts for neuroimaging. AJNR Am J Neuroradiol. 2001; 22:1813–24. [PubMed: 11733308]

Marty VN, Spigelman I. Long-lasting alterations in membrane properties, k(+) currents, and glutamatergic synaptic currents of nucleus accumbens medium spiny neurons in a rat model of alcohol dependence. Front Neurosci. 2012; 6:86. [PubMed: 22701402]

May LT, Leach K, Sexton PM, Christopoulos A. Allosteric modulation of G protein-coupled receptors. Annu Rev Pharmacol Toxicol. 2007; 47:1–51. [PubMed: 17009927]

Mayer ML, Armstrong N. Structure and function of glutamate receptor ion channels. Annu Rev Physiol. 2004; 66:161–81. [PubMed: 14977400]

Mayer ML. Glutamate receptor ion channels. Curr Opin Neurobiol. 2005; 15:282–8. [PubMed: 15919192]

McGeehan AJ, Olive MF. The mGluR5 antagonist MPEP reduces the conditioned rewarding effects of cocaine but not other drugs of abuse. Synapse. 2003; 47:240–2. [PubMed: 12494407]

Melancon BJ, Hopkins CR, Wood MR, Emmitte KA, Niswender CM, Christopoulos A, Conn PJ, Lindsley CW. Allosteric modulation of seven transmembrane spanning receptors: theory, practice, and opportunities for central nervous system drug discovery. J Med Chem. 2012a; 55:1445–64. [PubMed: 22148748]

Melancon BJ, Hopkins CR, Wood MR, Emmitte KA, Niswender CM, Christopoulos A, Conn PJ, Lindsley CW. Allosteric modulation of seven transmembrane spanning receptors: theory, practice, and opportunities for central nervous system drug discovery. Journal of medicinal chemistry. 2012b; 55:1445–1464. [PubMed: 22148748]

Melendez RI, Hicks MP, Cagle SS, Kalivas PW. Ethanol exposure decreases glutamate uptake in the nucleus accumbens. Alcohol Clin Exp Res. 2005; 29:326–33. [PubMed: 15770106]

Messenger MJ, Dawson LG, Duty S. Changes in metabotropic glutamate receptor 1–8 gene expression in the rodent basal ganglia motor loop following lesion of the nigrostriatal tract. Neuropharmacology. 2002; 43:261–71. [PubMed: 12213280]

Meyer PJ, Phillips TJ. Bivalent effects of MK-801 on ethanol-induced sensitization do not parallel its effects on ethanol-induced tolerance. Behavioral neuroscience. 2003; 117:641. [PubMed: 12802892]

Milton AL, Schramm MJ, Wawrzynski JR, Gore F, Oikonomou-Mpegeti F, Wang NQ, Samuel D, Economidou D, Everitt BJ. Antagonism at NMDA receptors, but not beta-adrenergic receptors, disrupts the reconsolidation of pavlovian conditioned approach and instrumental transfer for ethanol-associated conditioned stimuli. Psychopharmacology (Berl). 2012; 219:751–61. [PubMed: 21766171]

Miranda R Jr, MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, Swift R, Ray L, McGeary J. Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcoholism: Clinical and Experimental Research. 2008; 32:489–497.

Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. J Neurosci. 2005; 25:6389–93. [PubMed: 16000629]

Morzorati SL, Marunde RL, Downey D. Limited access to ethanol increases the number of spontaneously active dopamine neurons in the posterior ventral tegmental area of nondependent P rats. Alcohol. 2010; 44:257–64. [PubMed: 20682193]

Moussawi K, Kalivas PW. Group II metabotropic glutamate receptors (mGlu2/3) in drug addiction. Eur J Pharmacol. 2010; 639:115–22. [PubMed: 20371233]

Moykkynen T, Korpi ER, Lovinger DM. Ethanol inhibits alpha-amino-3-hydyroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function in central nervous system neurons by stabilizing desensitization. J Pharmacol Exp Ther. 2003; 306:546–55. [PubMed: 12734392]

Nagy J. Alcohol related changes in regulation of NMDA receptor functions. Curr Neuropharmacol. 2008; 6:39–54. [PubMed: 19305787]

Narayanan B, Stevens MC, Jiantonio RE, Krystal JH, Pearlson GD. Effects of memantine on event-related potential, oscillations, and complexity in individuals with and without family histories of alcoholism. J Stud Alcohol Drugs. 2013; 74:245–57. [PubMed: 23384372]

Newcomb R, Sun X, Taylor L, Curthoys N, Giffard RG. Increased production of extracellular glutamate by the mitochondrial glutaminase following neuronal death. J Biol Chem. 1997; 272:11276–82. [PubMed: 9111031]

Newman EL, Chu A, Bahamon B, Takahashi A, Debold JF, Miczek KA. NMDA receptor antagonism: escalation of aggressive behavior in alcohol-drinking mice. Psychopharmacology (Berl). 2012; 224:167–77. [PubMed: 22588250]

Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol. 2010; 50:295–322. [PubMed: 20055706]

Oberlin BG, Bristow RE, Heighton ME, Grahame NJ. Pharmacologic dissociation between impulsivity and alcohol drinking in high alcohol preferring mice. Alcohol Clin Exp Res. 2010; 34:1363–75. [PubMed: 20491739]

Olive MF, McGeehan AJ, Kinder JR, McMahon T, Hodge CW, Janak PH, Messing RO. The mGluR5 antagonist 6-methyl-2-(phenylethynyl)pyridine decreases ethanol consumption via a protein kinase C epsilon-dependent mechanism. Mol Pharmacol. 2005; 67:349–55. [PubMed: 15548766]

Olive MF, Becker HC. Effects of the mGluR2/3 agonist LY379268 and the mGluR5 antagonist MPEP on handling-induced convulsions during ethanol withdrawal in mice. Alcohol. 2008; 42:191–7. [PubMed: 18420113]

Olive MF. Metabotropic glutamate receptor ligands as potential therapeutics for addiction. Curr Drug Abuse Rev. 2009; 2:83–98. [PubMed: 19630739]

Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol. 1995; 30:239–47. [PubMed: 7662044]

Paoletti P, Neyton J. NMDA receptor subunits: function and pharmacology. Curr Opin Pharmacol. 2007; 7:39–47. [PubMed: 17088105]

Paoletti P, Bellone C, Zhou Q. NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. Nat Rev Neurosci. 2013; 14:383–400. [PubMed: 23686171]

Paparrigopoulos T, Tzavellas E, Karaiskos D, Kourlaba G, Liappas I. Treatment of alcohol dependence with low-dose topiramate: an open-label controlled study. BMC psychiatry. 2011; 11:41. [PubMed: 21401921]

Pati D, Kelly K, Stennett B, Frazier CJ, Knackstedt LA. Alcohol consumption increases basal extracellular glutamate in the nucleus accumbens core of Sprague-Dawley rats without increasing spontaneous glutamate release. Eur J Neurosci. 2016; 44:1896–905. [PubMed: 27207718]

Piasecki J, Koros E, Dyr W, Kostowski W, Danysz W, Bienkowski P. Ethanol-reinforced behaviour in the rat: effects of uncompetitive NMDA receptor antagonist, memantine. Eur J Pharmacol. 1998; 354:135–43. [PubMed: 9754913]

Pistillo F, Clementi F, Zoli M, Gotti C. Nicotinic, glutamatergic and dopaminergic synaptic transmission and plasticity in the mesocorticolimbic system: focus on nicotine effects. Progress in neurobiology. 2015; 124:1–27. [PubMed: 25447802]

Pomierny-Chamiolo L, Rup K, Pomierny B, Niedzielska E, Kalivas PW, Filip M. Metabotropic glutamatergic receptors and their ligands in drug addiction. Pharmacol Ther. 2014; 142:281–305. [PubMed: 24362085]

Qrunfleh AM, Alazizi A, Sari Y. Ceftriaxone, a beta-lactam antibiotic, attenuates relapse-like ethanol-drinking behavior in alcohol-preferring rats. J Psychopharmacol. 2013; 27:541–9. [PubMed: 23518814]

Rambo LM, Ribeiro LR, Schramm VG, Berch AM, Stamm DN, Della-Pace ID, Silva LF, Furian AF, Oliveira MS, Fighera MR, Royes LF. Creatine increases hippocampal Na(+),K(+)-ATPase activity via NMDA-calcineurin pathway. Brain Res Bull. 2012; 88:553–9. [PubMed: 22742935]

Rao PS, Sari Y. Effects of ceftriaxone on chronic ethanol consumption: a potential role for xCT and GLT1 modulation of glutamate levels in male P rats. J Mol Neurosci. 2014; 54:71–7. [PubMed: 24535561]

Rao PS, Goodwani S, Bell RL, Wei Y, Boddu SH, Sari Y. Effects of ampicillin, cefazolin and cefoperazone treatments on GLT-1 expressions in the mesocorticolimbic system and ethanol intake in alcohol-preferring rats. Neuroscience. 2015; 295:164–74. [PubMed: 25813713]

Reynolds AR, Williams LA, Saunders MA, Prendergast MA. Group 1 mGlu-family proteins promote neuroadaptation to ethanol and withdrawal-associated hippocampal damage. Drug Alcohol Depend. 2015; 156:213–20. [PubMed: 26442908]

Rial D, Takahashi RN, Morato GS. Aniracetam and DNQX affect the acquisition of rapid tolerance to ethanol in mice. Pharmacol Biochem Behav. 2009; 92:32–8. [PubMed: 18992274]

Rodd ZA, McKinzie DL, Bell RL, McQueen VK, Murphy JM, Schoepp DD, McBride WJ. The metabotropic glutamate 2/3 receptor agonist LY404039 reduces alcohol-seeking but not alcohol self-administration in alcohol-preferring (P) rats. Behavioural brain research. 2006; 171:207–215. [PubMed: 16678921]

Rossetti Z, Carboni S, Fadda F. Glutamate-induced increase of extracellular glutamate through N-methyl-D-aspartate receptors in ethanol withdrawal. Neuroscience. 1999; 93:1135–1140. [PubMed: 10473277]

Rubio G, Ponce G, Jimenez-Arriero M, Palomo T, Manzanares J, Ferre F. Effects of topiramate in the treatment of alcohol dependence. Pharmacopsychiatry. 2004; 38:37–40.

Russo SJ, Nestler EJ. The brain reward circuitry in mood disorders. Nat Rev Neurosci. 2013; 14:609–25. [PubMed: 23942470]

Rustembegovic A, Sofic E, Kroyer G. A pilot study of Topiramate (Topamax) in the treatment of tonic-clonic seizures of alcohol withdrawal syndromes. Medicinski arhiv. 2001; 56:211–212.

Ryo Y, Miyawaki A, Furuichi T, Mikoshiba K. Expression of the metabotropic glutamate receptor mGluR1 alpha and the ionotropic glutamate receptor GluR1 in the brain during the postnatal development of normal mouse and in the cerebellum from mutant mice. J Neurosci Res. 1993; 36:19–32. [PubMed: 8230318]

Salling MC, Faccidomo S, Hodge CW. Nonselective suppression of operant ethanol and sucrose self-administration by the mGluR7 positive allosteric modulator AMN082. Pharmacol Biochem Behav. 2008; 91:14–20. [PubMed: 18593591]

Salling MC, Faccidomo SP, Li C, Psilos K, Galunas C, Spanos M, Agoglia AE, Kash TL, Hodge CW. Moderate Alcohol Drinking and the Amygdala Proteome: Identification and Validation of Calcium/Calmodulin Dependent Kinase II and AMPA Receptor Activity as Novel Molecular Mechanisms of the Positive Reinforcing Effects of Alcohol. Biol Psychiatry. 2014

Salt TE, Jones HE, Copeland CS, Sillito AM. Function of mGlu1 receptors in the modulation of nociceptive processing in the thalamus. Neuropharmacology. 2014; 79:405–11. [PubMed: 24373900]

Sanchis-Segura C, Borchardt T, Vengeliene V, Zghoul T, Bachteler D, Gass P, Sprengel R, Spanagel R. Involvement of the AMPA receptor GluR-C subunit in alcohol-seeking behavior and relapse. J Neurosci. 2006; 26:1231–8. [PubMed: 16436610]

Santerre JL, Rogow JA, Kolitz EB, Pal R, Landin JD, Gigante E, Werner DF. Ethanol dose-dependently elicits opposing regulatory effects on hippocampal AMPA receptor GluA2 subunits through a zeta inhibitory peptide-sensitive kinase in adolescent and adult Sprague–Dawley rats. Neuroscience. 2014; 280:50–59. [PubMed: 25218807]

Santos SD, Carvalho AL, Caldeira MV, Duarte CB. Regulation of AMPA receptors and synaptic plasticity. Neuroscience. 2009; 158:105–25. [PubMed: 18424006]

Sari Y, Sreemantula SN. Neuroimmunophilin GPI-1046 reduces ethanol consumption in part through activation of GLT1 in alcohol-preferring rats. Neuroscience. 2012; 227:327–35. [PubMed: 23059796]

Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry. 1996; 53:673–80. [PubMed: 8694680]

Schreiber R, Freund WD. Glutamate transport is downregulated in the cerebral cortex of alcohol-preferring rats. Med Sci Monit. 2000; 6:649–52. [PubMed: 11208385]

Schroeder JP, Overstreet DH, Hodge CW. The mGluR5 antagonist MPEP decreases operant ethanol self-administration during maintenance and after repeated alcohol deprivations in alcohol-preferring (P) rats. Psychopharmacology (Berl). 2005; 179:262–70. [PubMed: 15717208]

Schroeder JP, Spanos M, Stevenson JR, Besheer J, Salling M, Hodge CW. Cue-induced reinstatement of alcohol-seeking behavior is associated with increased ERK1/2 phosphorylation in specific limbic brain regions: blockade by the mGluR5 antagonist MPEP. Neuropharmacology. 2008; 55:546–54. [PubMed: 18619984]

Sciascia JM, Reese RM, Janak PH, Chaudhri N. Alcohol-Seeking Triggered by Discrete Pavlovian Cues is Invigorated by Alcohol Contexts and Mediated by Glutamate Signaling in the Basolateral Amygdala. Neuropsychopharmacology. 2015; 40:2801–12. [PubMed: 25953360]

Sharko AC, Hodge CW. Differential modulation of ethanol-induced sedation and hypnosis by metabotropic glutamate receptor antagonists in C57BL/6J mice. Alcohol Clin Exp Res. 2008; 32:67–76. [PubMed: 18070246]

Shelton KL, Balster RL. Effects of gamma-aminobutyric acid agonists and N-methyl-D-aspartate antagonists on a multiple schedule of ethanol and saccharin self-administration in rats. J Pharmacol Exp Ther. 1997; 280:1250–60. [PubMed: 9067311]

Shen EH, Phillips TJ. MK-801 potentiates ethanol's effects on locomotor activity in mice. Pharmacol Biochem Behav. 1998; 59:135–43. [PubMed: 9443548]

Shigemoto R, Nakanishi S, Mizuno N. Distribution of the mRNA for a metabotropic glutamate receptor (mGluR1) in the central nervous system: an in situ hybridization study in adult and developing rat. J Comp Neurol. 1992; 322:121–35. [PubMed: 1430307]

Sidhpura N, Weiss F, Martin-Fardon R. Effects of the mGlu2/3 agonist LY379268 and the mGlu5 antagonist MTEP on ethanol seeking and reinforcement are differentially altered in rats with a history of ethanol dependence. Biol Psychiatry. 2010; 67:804–11. [PubMed: 20189165]

Sinclair CM, Cleva RM, Hood LE, Olive MF, Gass JT. mGluR5 receptors in the basolateral amygdala and nucleus accumbens regulate cue-induced reinstatement of ethanol-seeking behavior. Pharmacol Biochem Behav. 2012; 101:329–35. [PubMed: 22296815]

Sobolevsky AI, Rosconi MP, Gouaux E. X-ray structure, symmetry and mechanism of an AMPA-subtype glutamate receptor. Nature. 2009; 462:745–56. [PubMed: 19946266]

Spanagel R, Weiss F. The dopamine hypothesis of reward: past and current status. Trends Neurosci. 1999; 22:521–7. [PubMed: 10529820]

Spanagel R, Vengeliene V. New pharmacological treatment strategies for relapse prevention. Curr Top Behav Neurosci. 2013; 13:583–609. [PubMed: 22389180]

Stawski P, Janovjak H, Trauner D. Pharmacology of ionotropic glutamate receptors: A structural perspective. Bioorg Med Chem. 2010; 18:7759–72. [PubMed: 20947363]

Stepanyan TD, Farook JM, Kowalski A, Kaplan E, Barron S, Littleton JM. Alcohol Withdrawal-Induced Hippocampal Neurotoxicity In Vitro and Seizures In Vivo are Both Reduced by Memantine. Alcoholism: Clinical and Experimental Research. 2008; 32:2128–2135.

Stephens DN, Brown G. Disruption of operant oral self-administration of ethanol, sucrose, and saccharin by the AMPA/kainate antagonist, NBQX, but not the AMPA antagonist, GYKI 52466. Alcohol Clin Exp Res. 1999; 23:1914–20. [PubMed: 10630610]

Suto N, Ecke LE, You ZB, Wise RA. Extracellular fluctuations of dopamine and glutamate in the nucleus accumbens core and shell associated with lever-pressing during cocaine self-administration, extinction, and yoked cocaine administration. Psychopharmacology (Berl). 2010; 211:267–75. [PubMed: 20544343]

Szumlinski KK, Abernathy KE, Oleson EB, Klugmann M, Lominac KD, He DY, Ron D, During M, Kalivas PW. Homer isoforms differentially regulate cocaine-induced neuroplasticity. Neuropsychopharmacology. 2006; 31:768–77. [PubMed: 16160706]

Szumlinski KK, Ary AW, Lominac KD, Klugmann M, Kippin TE. Accumbens Homer2 overexpression facilitates alcohol-induced neuroplasticity in C57BL/6J mice. Neuropsychopharmacology. 2008; 33:1365–78. [PubMed: 17568396]

Tiwari V, Veeraiah P, Subramaniam V, Patel AB. Differential effects of ethanol on regional glutamatergic and GABAergic neurotransmitter pathways in mouse brain. Journal of neurochemistry. 2014; 128:628–640. [PubMed: 24164397]

Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, Hansen KB, Yuan H, Myers SJ, Dingledine R. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev. 2010; 62:405–96. [PubMed: 20716669]

Trombley PQ, Horning MS, Blakemore LJ. Carnosine modulates zinc and copper effects on amino acid receptors and synaptic transmission. Neuroreport. 1998; 9:3503–7. [PubMed: 9855307]

Vadasz C, Saito M, Gyetvai BM, Oros M, Szakall I, Kovacs KM, Prasad VV, Toth R. Glutamate receptor metabotropic 7 is cis-regulated in the mouse brain and modulates alcohol drinking. Genomics. 2007; 90:690–702. [PubMed: 17936574]

Vaglenova J, Pandiella N, Wijayawardhane N, Vaithianathan T, Birru S, Breese C, Suppiramaniam V, Randal C. Aniracetam reversed learning and memory deficits following prenatal ethanol exposure by modulating functions of synaptic AMPA receptors. Neuropsychopharmacology. 2008; 33:1071–83. [PubMed: 17609677]

Van Nest D, Hernandez NS, Kranzler HR, Pierce RC, Schmidt HD. Effects of LY466195, a selective kainate receptor antagonist, on ethanol preference and drinking in rats. Neurosci Lett. 2017; 639:8–12. [PubMed: 28013091]

Vengeliene V, Bilbao A, Molander A, Spanagel R. Neuropharmacology of alcohol addiction. Br J Pharmacol. 2008; 154:299–315. [PubMed: 18311194]

Wang J, Lanfranco MF, Gibb SL, Yowell QV, Carnicella S, Ron D. Long-lasting adaptations of the NR2B-containing NMDA receptors in the dorsomedial striatum play a crucial role in alcohol consumption and relapse. J Neurosci. 2010; 30:10187–98. [PubMed: 20668202]

Wang J, Ben Hamida S, Darcq E, Zhu W, Gibb SL, Lanfranco MF, Carnicella S, Ron D. Ethanol-mediated facilitation of AMPA receptor function in the dorsomedial striatum: implications for alcohol drinking behavior. J Neurosci. 2012; 32:15124–32. [PubMed: 23100433]

Ward RJ, Colivicchi MA, Allen R, Schol F, Lallemand F, de Witte P, Ballini C, Corte LD, Dexter D. Neuro-inflammation induced in the hippocampus of ‘binge drinking’ rats may be mediated by elevated extracellular glutamate content. J Neurochem. 2009; 111:1119–28. [PubMed: 19765190]

Weiss F, Porrino LJ. Behavioral neurobiology of alcohol addiction: recent advances and challenges. J Neurosci. 2002; 22:3332–7. [PubMed: 11978808]

Whitworth AB, Fischer F, Lesch OM, Nimmerrichter A, Oberbauer H, Platz T, Potgieter A, Walter H, Fleischhacker WW. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet. 1996; 347:1438–42. [PubMed: 8676626]

Wijayawardhane N, Shonesy BC, Vaglenova J, Vaithianathan T, Carpenter M, Breese CR, Dityatev A, Suppiramaniam V. Postnatal aniracetam treatment improves prenatal ethanol induced attenuation of AMPA receptor-mediated synaptic transmission. Neurobiol Dis. 2007; 26:696–706. [PubMed: 17493826]

Wijayawardhane N, Shonesy BC, Vaithianathan T, Pandiella N, Vaglenova J, Breese CR, Dityatev A, Suppiramaniam V. Ameliorating effects of preadolescent aniracetam treatment on prenatal ethanol-induced impairment in AMPA receptor activity. Neurobiol Dis. 2008; 29:81–91. [PubMed: 17916430]

Yin HH, Park BS, Adermark L, Lovinger DM. Ethanol reverses the direction of long-term synaptic plasticity in the dorsomedial striatum. Eur J Neurosci. 2007; 25:3226–32. [PubMed: 17552991]

Zhao Y, Dayas CV, Aujla H, Baptista MA, Martin-Fardon R, Weiss F. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-fos expression in the hippocampus and amygdala. The Journal of neuroscience. 2006; 26:9967–9974. [PubMed: 17005860]

Zhou Z, Karlsson C, Liang T, Xiong W, Kimura M, Tapocik JD, Yuan Q, Barbier E, Feng A, Flanigan M, Augier E, Enoch MA, Hodgkinson CA, Shen PH, Lovinger DM, Edenberg HJ, Heilig M, Goldman D. Loss of metabotropic glutamate receptor 2 escalates alcohol consumption. Proc Natl Acad Sci U S A. 2013; 110:16963–8. [PubMed: 24082084]

Highlights

- Role of metabotropic receptors mGluR1/5, mGluR2/3, and mGluR7 on alcohol intake.
- Role of ionotropic receptors, NMDA and AMPA on alcohol intake.
- Implication of glutamatergic receptors in development of alcohol dependence.

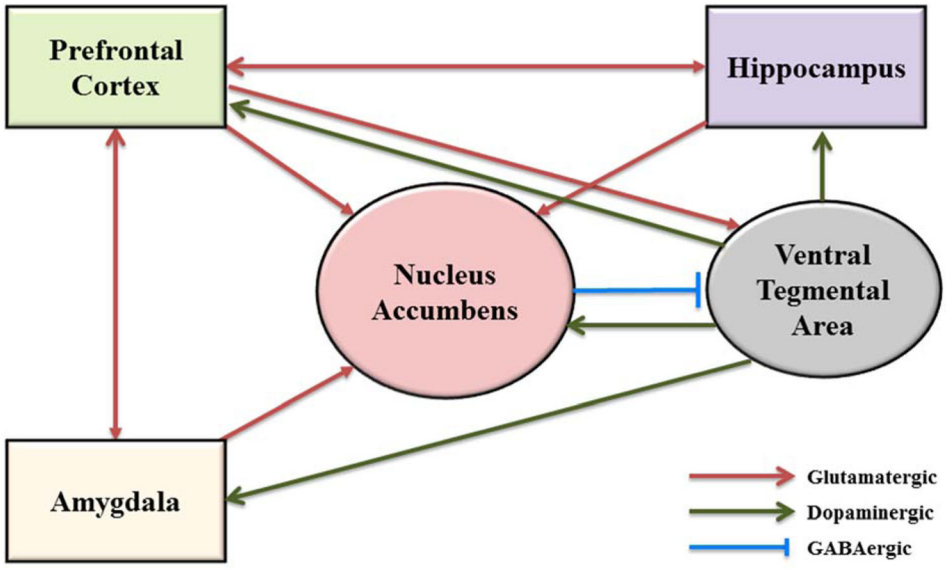

Figure 1. Neurocircuitry involved in AUD

The brain reward circuitry is comprised of five major brain regions – nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala (AMG), hippocampus (HPC) and ventral tegmental area (VTA) – which are interconnected by the glutamatergic and dopaminergic excitatory pathways as well as the inhibitory GABAergic pathway. (A) Glutamatergic System – NAc receives glutamatergic inputs from PFC, AMG and HPC, while all three latter regions are interconnected by reciprocating glutamatergic projections. (B) Dopaminergic System – VTA relays dopaminergic projections to NAc, PFC, AMG and HPC. (C) GABAergic System – NAc sends GABAergic inputs to VTA.

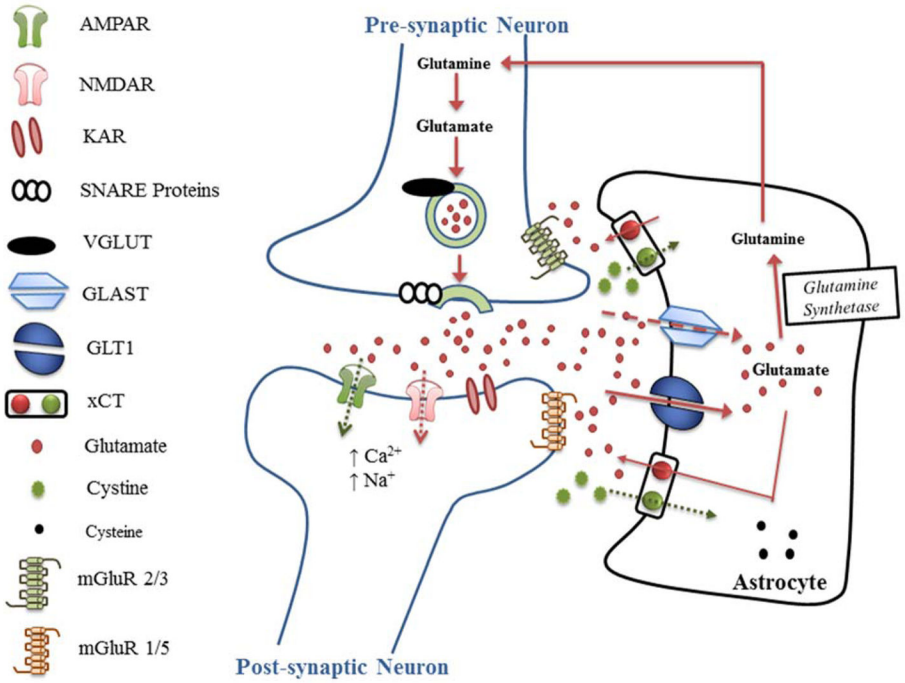

Figure 2. Glutamatergic Neurotransmission

In the presynaptic neuron, glutaminase catalyzes the conversion of glutamine to glutamate, which is further loaded into the vesicles by vesicular glutamate transporters (VGLUTs). Following depolarization of the presynaptic terminal, the vesicle interacts with SNARE proteins on the synaptic membrane, consequently leading to the release of glutamate into the synapse. After being released from the presynaptic terminal, the glutamate in the synapse interacts with the post-synaptic mGluRs and iGluRs, initiating further cell signaling. Group 2 and Group 3 mGlu receptors on the presynaptic terminal inhibit the adenylyl cyclase activity and negatively regulate the glutamate release from the presynaptic terminal. The excess extracellular glutamate is taken up by several glial glutamate transporters such as GLT-1 (also known as excitatory amino acid transporter 2, EAAT2) and GLAST (also known as excitatory amino acid transporter 1, EAAT1). Inside the glial cell, the glutamine synthetase enzyme catalyzes the conversion of glutamate to glutamine, which is further transported to the presynaptic neuronal terminal and can be further used in the glutamate-glutamine cycle. Cystine-glutamate exchanger, (xCT) located on the glial cell, also plays a vital role in elevating the synaptic glutamate concentrations, using l-cystine for exchange.

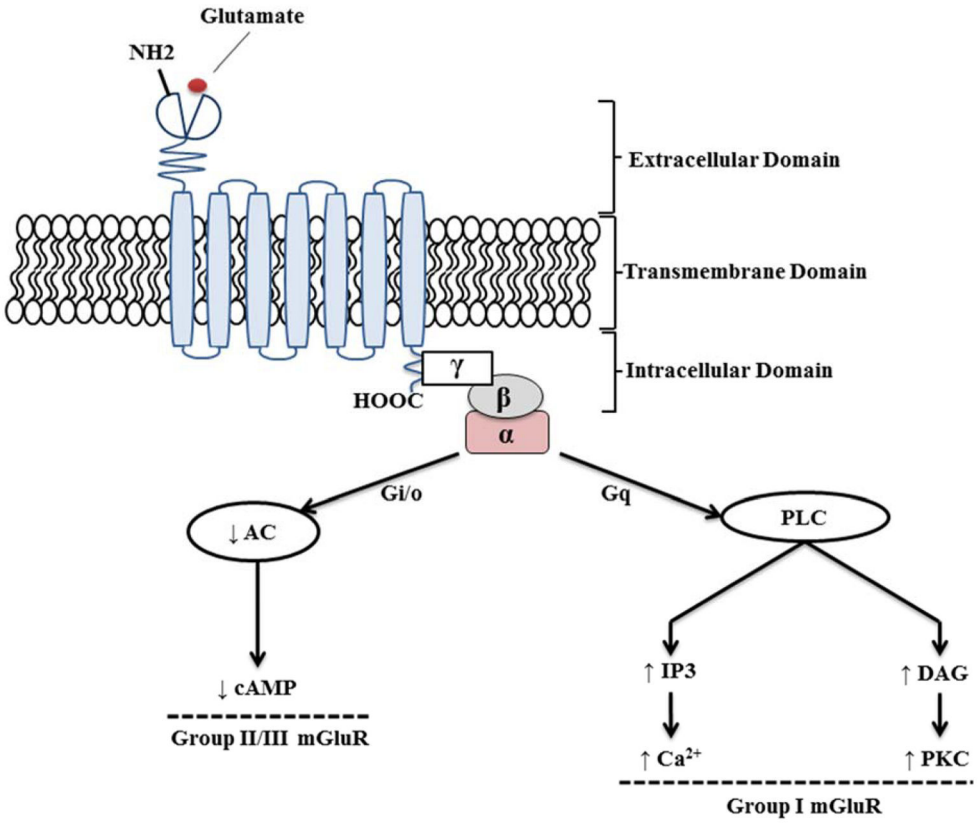

Figure 3. Schematic representation of metabotropic glutamate receptors (mGluRs)

Glutamate activates the receptor by binding to the extracellular N-terminal domain. (A) Upon activation of group 1 mGluR, Gq proteins are stimulated, which further activates phospholipase C (PLC). The activation of PLC subsequently catalyzes the production of diacylglycerol (DAG) and inositol (1,4,5)-triphosphate (IP3). DAG activates protein kinase C (PKC), while IP3 increases the release of Ca^{2+} from intracellular stores. (B) Activation of group 2 mGluRs and group 3 mGluRs leads to stimulation of Gi/o proteins, which further inhibits adenylyl cyclase (AC) activity, eventually reducing the intracellular concentrations of cAMP.

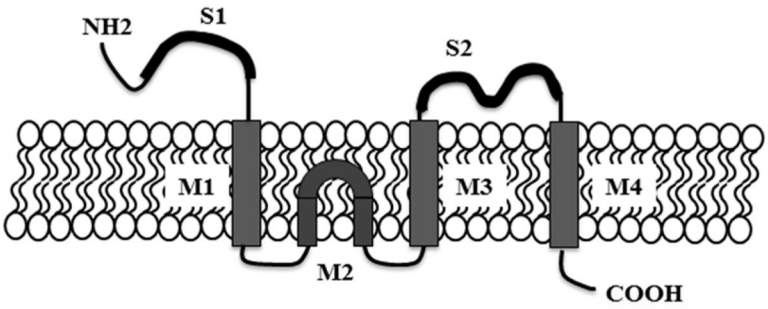

Figure 4. Schematic diagram of ionotropic glutamate receptors (iGluRs) subunits

iGluRs contain a large extracellular amino-terminal (N) domain and an intracellular carboxy-terminal (C) domain. These receptors constitute four transmembrane domains (M1-M4), wherein the M2 domain forms a re-enterant loop. Two distinct extracellular loops containing S1 and S2 form the ligand-binding region in the receptor.

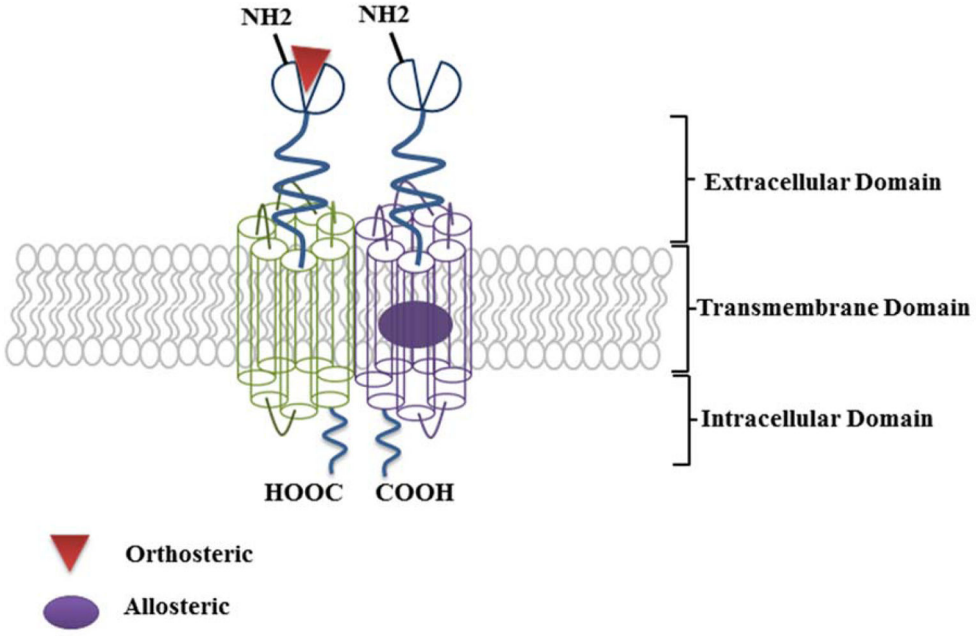

Figure 5.

Schematic representation of orthosteric and allosteric binding sites of metabotropic glutamate receptors (mGluRs). mGluRs belong to Class C subtype of G-protein-coupled receptors (GPCRs). These receptors are characterized by a large extracellular N-terminal domain, termed as the Venus flytrap domain (VFD), which is exclusively used to bind orthosteric ligands (e.g. glutamate) (Conn et al., 2009; Gregory et al., 2011; May et al., 2007). These VFDs are involved in the dimerization of the mGluRs. The transmembrane region of mGluRs forms a pocket where the small-molecule modulators bind allosterically, with the potential to have more than one binding site. Thus, the allosteric modulators bind to a site, which is topographically different from the orthosteric ligand binding site, causing a change in receptor conformation further modifying the receptor activity in a positive or negative modulation of neutral direction. This modulation in receptor activity can be either affected by binding efficacy, binding affinity or varying degrees of both (Melancon et al., 2012a).

Table 1

shows the pharmacological classes of glutamate receptors/subtypes and their corresponding ligands/modulators studied in AUD.

Glutamate receptor	Ligands	Pharmacological class	References
A. Metabotropic glutamate receptors (mGluRs)			
1. Group 1 mGluRs			
mGluR1	JNJ16259685	Antagonist	(Besheer et al., 2008a) (Lum et al., 2014) (Besheer et al., 2009)
	EMQMCM	Antagonist	(Kotlinska et al., 2011)
	CPCCOEt	Antagonist	(Szumlinski et al., 2008) (Hodge et al., 2006) (Reynolds et al., 2015) (Sharko and Hodge, 2008) (Besheer et al., 2008a)
mGluR5	MPEP	Negative allosteric modulator	(Hodge et al., 2006) (Schroeder et al., 2005) (Szumlinski et al., 2008) (Blednov and Harris, 2008) (Backstrom et al., 2004) (Besheer et al., 2010) (Schroeder et al., 2008) (Lee et al., 2016) (Reynolds et al., 2015) (Kumar et al., 2013) (Downing et al., 2010) (Cozzoli et al., 2009) (Besheer et al., 2009) (Gupta et al., 2008) (Olive and Becker, 2008) (Besheer et al., 2008b) (Sharko and Hodge, 2008) (Besheer et al., 2006) (Lominac et al., 2006) (Cowen et al., 2005) (Besheer and Hodge, 2005) (Olive et al., 2005) (McGeehan and Olive, 2003)
	MTEP	Negative allosteric modulator	(Sidhpura et al., 2010) (Sinclair et al., 2012) (Kotlinska et al., 2011) (Kotlinska and Bochenski, 2008) (Cozzoli et al., 2014) (Adams et al., 2010) (Gass and Olive, 2009a) (Adams et al., 2008) (Cowen et al., 2007)
	GET73 N-[(4-trifluoromethyl)benzyl] 4-methoxybutyramide	Unknown	Ferraro, 2013
	SIB-1893	Antagonist	(Reynolds et al., 2015)
	CDPPB	Positive Allosteric Modulator	(Gass et al., 2014)
2. Group 2 mGluRs			
mGluR2/3	LY379268	Agonist	(Backstrom and Hyytia, 2005) (Sidhpura et al., 2010) (Zhao et al., 2006) (Kufahl et al., 2011) (Baptista et al., 2004) (Bossert et al., 2006) (Besheer et al., 2010) (Jaramillo et al., 2015)

Glutamate receptor	Ligands	Pharmacological class	References
			(Cannady et al., 2011) (Olive and Becker, 2008) (Pati et al., 2016) (Barker et al., 2016) (Zhou et al., 2013) (Griffin et al., 2014)
	LY404039	Agonist	(Rodd et al., 2006)
	LY341495	Antagonist	(Barker et al., 2016) (Zhou et al., 2013) (Sharko and Hodge, 2008) (Hodge et al., 2006) (Jaramillo et al., 2015) (Laukkanen et al., 2015)
	AZD8529	Positive Allosteri Modulator	(Augier et al., 2016)
3. Group 3 mGluRs			
mGluR7	AMN-082	Positive Allosteric Modulator	(Salling et al., 2008) (Li et al., 2008) (Bahi, 2012a) (Bahi et al., 2012)
	MMPIP	Negative Allosteric Modulator	(Bahi, 2012a) (Bahi et al., 2012)
mGluR8	(S)-3,4-DCPG	Agonist	(Backstrom and Hyytia, 2005)
B. Ionotropic glutamate receptors (iGluRs)			
NMDAR	MK-801	Antagonist	(Meyer and Phillips, 2003) (Grant et al., 1990) (Stepanyan et al., 2008) (Shen and Phillips, 1998) (Milton et al., 2012) (Camp et al., 2011) (Biala and Kotlinska, 1999) (Boyce-Rustay and Cunningham, 2004)
	Memantine	Antagonist	(Idrus et al., 2011) (Malpass et al., 2010) (Newman et al., 2012) (Jeanblanc et al., 2014) (Krupitsky et al., 2007a; Krupitsky et al., 2007b) (Krishnan-Sarin et al., 2015) (Alaux-Cantin et al., 2015) (Narayanan et al., 2013) (Oberlin et al., 2010) (Evans et al., 2007) (Escher et al., 2006) (Bisaga and Evans, 2004) (Kotlinska, 2001) Lukoyanov, 2001 (Koros et al., 1999) (Piasecki et al., 1998)
	d-serine	Agonist	(Lockridge et al., 2012)
	CPPene	Antagonist	(Shelton and Balster, 1997)
	CGP-3789	Antagonist	(Boyce-Rustay and Cunningham, 2004)
	Ketamine	Antagonist	(Boyce-Rustay and Cunningham, 2004) (Krystal et al., 2003)
	Ifenprodil	Antagonist	(Boyce-Rustay and Cunningham, 2004)
	CP-101,606	Antagonist	(Boyce-Rustay and Cunningham, 2004)
	(+)-HA-966	Partial Agonist	(Boyce-Rustay and Cunningham, 2004)
	MRZ 2/579	Antagonist	(Bienkowski et al., 2001)
AMPAR	AMPA	Agonist	Fu, 2016

Glutamate receptor	Ligands	Pharmacological class	References
	LY404187	Agonist	(Jones et al., 2008)
	LY451395	Agonist	(Jones et al., 2008)
	Aniracetam	Agonist	(Cannady et al., 2013) (Rial et al., 2009) (Vaglenova et al., 2008) (Wijayawardhane et al., 2007) (Wijayawardhane et al., 2008) (Eisenhardt et al., 2015)
	GYKI 52466	Antogonist	(Sanchis-Segura et al., 2006) (Broadbent et al., 2003) (Stephens and Brown, 1999)
AMPAR/KAR	CNQX	Antagonist	(Stephens and Brown, 1999) (Backstrom and Hyytia, 2006) (Backstrom and Hyytia, 2007) (Bäckström and Hyytiä, 2004) (Czachowski et al., 2012) (Cannady et al., 2013)
	NBQX	Antagonist	(Stephens and Brown, 1999) (Bäckström and Hyytiä, 2004) (Czachowski et al., 2012) (Wang et al., 2012) (Sciascia et al., 2015) (Corbit et al., 2014) (Karcz-Kubicha and Liljequist, 1995)
	DNQX	Antagonist	(Lack et al., 2007) (Rial et al., 2009) (Long et al., 2007) (Manto et al., 2005) (Broadbent et al., 2003)
	LY326325	Antagonist	(Karcz-Kubicha and Liljequist, 1995)
KAR	LY466195	Antagonist	(Van Nest et al., 2017)

Table 2

List of ligands/investigational agents studied with the alcohol drinking paradigm employed in each study.

Ligand	Receptor	Species/Strain	Behavioral paradigm/Model	References
JNJ16259685	mGluR1	Rats/Alcohol preferring (P)	Self-administration	(Besheer et al., 2008a)
		Rats/Long Evans	Drug discrimination	(Besheer et al., 2009)
		Mice/C57BL/6	Drinking-in-the-Dark (Krupitsky et al.)	(Lum et al., 2014)
EMQMCM	mGluR1	Mice/Swiss Albino	Sensitization	(Kotlinska et al., 2006)
		Rats/Wistar	Withdrawal	(Kotlinska and Bochenski, 2008)
		Rats/Wistar	Conditioned place preference (CPP) Withdrawal	(Kotlinska et al., 2011)
CPCCOEt	mGluR1	Mice/C57BL/6	Self-administration	(Szumlinski et al., 2008)
		Mice/C57BL/6	Self-administration	(Hodge et al., 2006)
		Rats/Alcohol preferring (P)	Self-administration	(Besheer et al., 2008a)
		Mice/C57BL/6	Alcohol-induced sedation and hypnosis	(Sharko and Hodge, 2008)
		Mice/C57BL/6	Self-administration Conditioned place preference (CPP)	(Lominac et al., 2006)
MPEP	mGluR5	Mice/C57BL/6	Self-administration	(Hodge et al., 2006)
		Rats/Alcohol preferring (P)	Self-administration	(Schroeder et al., 2005)
		Mice/C57BL/6	Self-administration	(Szumlinski et al., 2008)
		Mice/C57BL/6	2-bottle and 4-bottle free-choice Limited-access test Withdrawal	(Blednov and Harris, 2008)
		Rats/Long Evans and Wistar	Reinstatement to ethanol-seeking Alcohol deprivation effect (ADE)	(Backstrom et al., 2004)
		Rats/Alcohol preferring (P)	Self-administration	(Besheer et al., 2010)
		Rats/Alcohol preferring (P)	Self-administration Reinstatement to ethanol-seeking	(Schroeder et al., 2008)
		Mice/C57BL/6	Conditioned place preference (CPP)	(Lee et al., 2016)
		Rats/Sprague-Dawley	Chronic intermittent ethanol (CIE) Withdrawal	(Reynolds et al., 2015)
		Rats/Wistar	Withdrawal	(Kumar et al., 2013)
		Mice/C57BL/6	Binge-alcohol drinking	(Cozzoli et al., 2009)
		Rats/Long Evans	Drug discrimination	(Besheer et al., 2009)

Ligand	Receptor	Species/Strain	Behavioral paradigm/Model	References
		Mice/C57BL/6	Drinking-in-the-Dark (Krupitsky et al.)	(Gupta et al., 2008)
		Mice/C3H/He	Withdrawal	(Olive and Becker, 2008)
		Rats/Alcohol preferring (P)	Self-administration	(Besheer et al., 2008a)
		Mice/C57BL/6	Alcohol-induced sedation and hypnosis	(Sharko and Hodge, 2008)
		Rats/Long Evans	Self-administration	(Besheer et al., 2006)
		Mice/C57BL/6	Self-administration Conditioned place preference (CPP)	(Lominac et al., 2006)
		Rats/Long Evans	Self-administration Ethanol discrimination	(Besheer and Hodge, 2005)
		Mice/C57BL/6J × 129SvJae	Limited-access two-bottle free-choice	(Olive et al., 2005)
		Mice/C57BL/6	Conditioned place preference (CPP)	(McGeehan and Olive, 2003)
MTEP	mGluR5	Rats/Wistar	Self-administration Reinstatement to ethanol-seeking Withdrawal	(Sidhpura et al., 2010)
		Rats/Wistar	Self-administration Reinstatement to ethanol-seeking	(Sinclair et al., 2012)
		Rats/Wistar	Conditioned place preference (CPP) Withdrawal	(Kotlinska et al., 2011)
		Rats/Wistar	Withdrawal	(Kotlinska and Bochenski, 2008)
		Mice/C57BL/6	Binge-alcohol drinking	(Cozzoli et al., 2014)
		Rats/Alcohol preferring (P)	Self-administration Reinstatement of ethanol-seeking	(Adams et al., 2008)
		Rats/Wistar	Self-administration	(Gass and Olive, 2009b)
		Rats/Alcohol preferring (P)	Self-administration Cue-induced reinstatement of ethanol-seeking	(Adams et al., 2010)
		Mice/C57BL/6	Self-administration	(Cowen et al., 2007)
		Rats/Fawn-Hooded (FH) and Alcohol preferring (P)	Self-administration	(Cowen et al., 2005)
CDPPB	mGluR5	Rats/Wistar	Self-administration, Cue-induced reinstatement to ethanol-seeking	(Gass et al., 2014)
LY379268	mGluR2/3	Rats/Long Evans	Self-administration Reinstatement to ethanol-seeking	(Backstrom and Hyytia, 2005)
		Rats/Wistar	Self-administration Reinstatement to ethanol-seeking Withdrawal	(Sidhpura et al., 2010)
		Rats/Wistar	Self-administration Conditioned reinstatement to ethanol-seeking	(Zhao et al., 2006)

Ligand	Receptor	Species/Strain	Behavioral paradigm/Model	References
		Rats/Wistar	Self-administration Conditioned reinstatement to ethanol-seeking	(Kufahl et al., 2011)
		Rats/Alcohol preferring (P)	Self-administration	(Besheer et al., 2010)
		Rats/Long Evans	Ethanol discrimination	(Jaramillo et al., 2015)
		Rats/Long Evans	Ethanol discrimination	(Cannady et al., 2011)
		Mice/C3H/He	Withdrawal	(Olive and Becker, 2008)
		Rats/Sprague-Dawley	Self-administration, Intermittent access to alcohol	(Pati et al., 2016)
		Mice/C57BL/6	Self-administration Chronic intermittent ethanol (CIE)	(Barker et al., 2016)
		Mice/C57BL/6	Self-administration Chronic intermittent ethanol (CIE)	(Griffin et al., 2014)
LY404039	mGluR2/3	Rats/Alcohol preferring (P)	Self-administration Reinstatement of ethanol-seeking	(Rodd et al., 2006)
LY341495	mGluR2/3	Mice/C57BL/6	Self-administration Chronic intermittent ethanol (CIE)	(Barker et al., 2016)
		Rats/Wistar	Self-administration	(Zhou et al., 2013)
		Mice/C57BL/6	Alcohol-induced sedation and hypnosis	(Sharko and Hodge, 2008)
		Mice/C57BL/6	Self-administration	(Hodge et al., 2006)
		Rats/Long Evans	Ethanol discrimination	(Jaramillo et al., 2015)
AZD8529	mGluR2/3	Rats/Wistar	Self-administration Cue-induced reintstatment to ethanol-seeking	(Augier et al., 2016)
AMN-082	mGluR7	Mice/C57BL/6	Self-administration	(Salling et al., 2008)
		Mice/C57BL/6	Conditioned place preference	(Bahi, 2012b)
		Rats/Wistar	Two-bottle free choice drinking	(Bahi et al., 2012)
MMPIP	mGluR7	Mice/C57BL/6	Conditioned place preference	(Bahi, 2012b)
		Rats/Wistar	Two-bottle free choice drinking	(Bahi et al., 2012)
(S)-3,4-DCPG	mGluR8	Rats/Long Evans	Self-administration Reinstatement to ethanol-seeking	(Backstrom and Hyytia, 2005)
MK-801	NMDAR	Mice/DBA/2J	Sensitization	(Meyer and Phillips, 2003)
		Mice/C57BL/6	Withdrawal	(Grant et al., 1990)
		Rats/Lister-Hooded	Self-administration Pavlovian conditioning	(Milton et al., 2012)
		Mice/PSD-95 KO	Two-bottle free-choice Conditioned place preference Alcohol deprivation effect	(Camp et al., 2011)

Ligand	Receptor	Species/Strain	Behavioral paradigm/Model	References
		Rats/Wistar	Conditioned place preference	(Biala and Kotlinska, 1999)
		Mice/DBA/2J	Conditioned place preference	(Boyce-Rustay and Cunningham, 2004)
		Rats/Long Evans	Self-administration Cue-induced reinstatment to ethano-seeking	(Backstrom et al., 2004)
Memantine	NMDAR	Rats/Sprague-Dawley	Binge-alcohol drinking	(Idrus et al., 2011)
		Rats/Myers' high-ethanol-preferring (mHEP)	Two-bottle free choice	(Malpass et al., 2010)
		Swiss Webster mice	Self-administration	(Newman et al., 2012)
		Rats/Long Evans	Self-administration	(Jeanblanc et al., 2014)
		Rats/Long Evans	Self-administration Withdrawal	(Alaux-Cantin et al., 2015)
		Mice/High Alcohol Preferring (HAP)	Delay Discounting Home-cage drinking	(Oberlin et al., 2010)
		Mice/C57BL/6	Schedule-induced polydipsia (SIP)	(Escher et al., 2006)
		Rats/Wistar	Withdrawal	(Lukoyanov and Paula-Barbosa, 2001)
		Rats/Wistar	Ethanol-discrimination	(Koros et al., 1999)
d-serine	NMDAR	Mice/C57BL/6	Ethanol-discrimination	(Lockridge et al., 2012)
CGP-3789	NMDAR	Mice/DBA/2J	Conditioned place preference	(Boyce-Rustay and Cunningham, 2004)
Ketamine	NMDAR	Mice/DBA/2J	Conditioned place preference	(Boyce-Rustay and Cunningham, 2004)
Ifenprodil	NMDAR	Mice/DBA/2J	Conditioned place preference	(Boyce-Rustay and Cunningham, 2004)
CP-101,606	NMDAR	Mice/DBA/2J	Conditioned place preference	(Boyce-Rustay and Cunningham, 2004)
(+)-HA-966	NMDAR	Mice/DBA/2J	Conditioned place preference (CPP)	(Boyce-Rustay and Cunningham, 2004)
MRZ 2/579	NMDAR	Rats/Wistar	Withdrawal	(Bienkowski et al., 2001)
CGP39551	NMDAR	Rats/Long Evans	Self-administration Cue-induced Reinstatment to ethano-seeking	(Backstrom et al., 2004)

Ligand	Receptor	Species/Strain	Behavioral paradigm/Model	References
AMPA	AMPAR	Rats/Long Evans	Self-administration Intermittent 2-bottle free-choice	(Fu et al., 2016)
Aniracetam	AMPAR	Rats/Alcohol preferring (P)	Self-administration Cue-induced reinstatement	(Cannady et al., 2013)
		Mice/Transgenic	Self-administration Cue-induced reinstatement to ethanol seeking Alcohol deprivation effect (ADE)	(Eisenhardt et al., 2015)
GYKI 52466	AMPAR	Rats/Wistar and Mice/Transgenic	Cue-induced reinstatement to ethanol seeking Alcohol deprivation effect (ADE)	(Sanchis-Segura et al., 2006)
		Mice/DBA/2J	Sensitization	(Broadbent et al., 2003)
		Rats/Lister-Hooded	Self-administration	(Stephens and Brown, 1999)
CNQX	AMPAR/KAR	Rats/Long Evans	Self-administration Cue-induced reinstatment to ethanol-seeking	(Backstrom et al., 2004)
		Rats/Long Evans	Self-administration	(Czachowski et al., 2012)
NBQX	AMPAR/KAR	Hooded Lister rats	Self-administration	(Stephens and Brown, 1999)
		Rats/Long Evans	Self-administration Cue-induced reinstatment to ethanol-seeking	(Sciascia et al., 2015)
		Rats/Long Evans	Self-administration	(Corbit et al., 2014)
DNQX	AMPAR/KAR	Rats/Sprague-Dawley	Chronic intermittent ethanol (CIE) Withdrawal	(Lack et al., 2007)
		Mice/DBA/2J	Sensitization	(Broadbent et al., 2003)
		Rats/Alcohol preferring (P)	Self-administration Cue-induced reinstatement to ethanol	(Cannady et al., 2013)
LY466195	KAR	Rats/Sprague-Dawley and Long Evans	Intermittent two-bottle free-choice	(Van Nest et al., 2017)

Table 3

Glutamate receptors, ligands and their chemical names

Receptor subtype	Ligand	Chemical name
mGluR1	JNJ16259685	(3,4-Dihydro-2*H*-pyranol[2,3-*b*]quinolin-7-yl)-(cis-4-methoxycyclohexyl)-methanone
	EMQMCM	(3-Ethyl-2-methylquinolin-6-yl)-(4-methoxycyclohexyl)-methanone
	CPCCOEt	7-Hydroxyiminocyclopropan[b]chromen-1a-carboxylic acid ethyl ester
mGluR5	MPEP	2-Methyl-6-(phenylethynyl)pyridine
	MTEP	3-[2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine
	GET73	N-[(4-trifluoromethyl)benzyl] 4-methoxybutyramide
	SIB-1893	(E)-2-methyl-6-(2-phenylethenyl)pyridine
	CDPPB	3-Cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide
mGluR2/3	LY379268	(1R,4R,5S,6R)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid
	LY404039	(-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid
	LY341495	(2S)-2-amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl)propanoic acid
	AZD8529	(7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one)
mGluR7	AMN-082	*N,N'-bis*(diphenylmethyl)-1,2-ethanediamine dihydrochloride
	MMPIP	6-(4-Methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-*c*]pyridin-4(*5H*)-one hydrochloride
mGluR8	(S)-3,4-DCPG	(S)-3,4-dicarboxyphenylglycine
NMDAR	MK-801	(5S,10R)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine
	Memantine	3,5-dimethyladamantan-1-amine
	d-serine	(R)-2-amino-3-hydroxypropanoic acid
	CPPene	(R)-4-[(2E)-3-Phosphono-2-propenyl]-2-piperazinecarboxylic acid
	CGP-3789	(DL-(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid; 4-methyl-APPA)
	Ketamine	2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone
	Ifenprodil	2-(4-benzylpiperidino)-1-(4-hydroxyphenyl)-2-methyl-1-ethanol
	CP-101,606	1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol
	(+)-HA-966	(+)-3-Amino-1-hydroxy-2-pyrrolidone
	MRZ 2/579	1-amino-1,3,3,5,5-pentamethylcyclohexane hydrochloride
AMPAR	AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
	LY404187	N-[(2S)-2-(4'-cyanobiphenyl-4-yl)propyl]propane-2-sulfonamide
	LY451395	N-[(2R)-2-[4-[4-[2-(methanesulfonamido)ethyl]phenyl]phenyl]propyl]propane-2-sulfonamide
	Aniracetam	1-(4-methoxybenzoyl)-2-pyrrolidinone
	GYKI 52466	1-(4-aminophenyl)-4-methyl-7, 8-methylenedioxy-5H-2,3-benzodiazepine
AMPAR/KAR	CNQX	7-nitro-2,3-dioxo-2,3-dihydroquinoxaline-6-carbonitrile
	NBQX	2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione
	DNQX	6,7-dinitroquinoxaline-2,3-dione
	LY326325	3-Isoquinolinecarboxylic acid
KAR	LY466195	6-[(2-carboxy-4,4-difluoropyrrolidin-1-yl)methyl]-decahydroisoquinoline-3-carboxylic acid