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Metabotropic Glutamate Receptors in Alcohol Use Disorder: Physiology, Plasticity, and Promising Pharmacotherapies

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Abstract

Developing efficacious treatments for alcohol use disorder (AUD) has proven difficult. The insidious nature of the disease necessitates a deep understanding of its underlying biology as well as innovative approaches to ameliorate ethanol-related patho-physiology. Excessive ethanol seeking and relapse are generated by long-term changes to membrane properties, synaptic physiology, and plasticity throughout the limbic system and associated brain structures. Each of these factors can be modulated by metabotropic glutamate (mGlu) receptors, a diverse set of G protein-coupled receptors highly expressed throughout the central nervous system. Here, we discuss how different components of the mGlu receptor family modulate neurotransmission in the limbic system and other brain regions involved in AUD etiology. We then describe how these processes are dysregulated following ethanol exposure and speculate about how mGlu receptor modulation might restore such pathophysiological changes. To that end, we detail the current understanding of the behavioral pharmacology of mGlu receptor-directed drug-like molecules in animal models of AUD. Together, this review highlights the prominent position of the mGlu

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receptor system in the pathophysiology of AUD and provides encouragement that several classes of mGlu receptor modulators may be translated as viable treatment options.

Graphical abstract

Keywords

Alcohol use disorder; metabotropic glutamate receptor; synaptic plasticity; prefrontal cortex; nucleus accumbens; bed nucleus of the stria terminalis

BACKGROUND

Alcohol use disorder (AUD) persists as a major societal burden. A recent epidemiological survey reported the United States 12 month and lifetime prevalence as 13.9 and 29.1%,¹ respectively. These staggering statistics suggest that AUD is an insidious disease with poor availability of satisfactory treatment options. Developing an efficacious treatment for AUD is a remarkably complex undertaking, as primary risk factors for relapse—alcohol and related cues—are ubiquitous. In addition, relapse is readily instigated by social, economic, and physical stressors, which cannot be eliminated from a modern lifestyle. To overcome the pervasive nature of these hazards, medication development necessitates a deeper understanding of the underlying biology of AUD.

The acute actions of ethanol are complex and have been the subject of recent extensive reviews.^{2,3} In brief, ethanol acts primarily by modulating a variety of ion channels, including

voltage-gated potassium channels and ionotropic receptors for the major neurotransmitters glutamate and γ -aminobutyric acid (GABA). Collectively, these molecular actions alter the function of meso-corticolimbic neurotransmission, which, over time, can generate a disease state that promotes excessive, persistent, and maladaptive ethanol seeking. AUD is a chronic disorder, characterized by repeated cycles of bingeing, withdrawal, preoccupation, and relapse.⁴ Distinct but overlapping brain circuits are thought to mediate the motivational and affective states across these periods (Box 1 and Figure 1), and we refer the reader to other thorough reviews for additional information.^{2,5}

The persistent ethanol-induced changes to circuit function proceed through a diverse set of pathophysiological adaptations. Ethanol usurps several modes of signaling to alter behavior. Changes in membrane properties, excitatory and inhibitory synaptic strength, and synaptic plasticity are each important to consider, as each of these factors modulates neurotransmission and therefore ethanol seeking, negative affect, and vulnerability to relapse. Collectively, the metabotropic glutamate (mGlu) receptor family modulates each of the physiological parameters mentioned above, suggesting that modulating mGlu receptor signaling may provide mechanisms for ameliorating ethanol-induced physiological and behavioral disruptions. Here, we will extensively describe the physiology and pharmacology of the mGlu receptors, a diverse family of receptors that regulate physiology and plasticity throughout the central nervous system (CNS). Afterward, we will delve into behavioral pharmacology. We discuss what is currently known about how individual mGlu receptor subtypes contribute to ethanol seeking and how these exciting targets might be exploited to develop treatments for AUD.

BASIC MGLU RECEPTOR PHYSIOLOGY

The mGlu receptor family is composed of eight receptor subtypes, which are divided into three groups based on genetics, pharmacology, and function.⁶ The group I subtypes, mGlu₁ and mGlu₅, are generally expressed at postsynaptic sites where canonical downstream signaling proceeds through G_q proteins and related effectors. In contrast, the group II (mGlu₂ and mGlu₃) and group III (mGlu₄ and mGlu₆–mGlu₈) sub-types couple with G_i proteins and are enriched at presynaptic locations in many parts of the CNS. mGlu₆ expression is limited to the retina and is thought not to play a role in the CNS (for a review, see ref 7). All mGlu receptor subtypes are members of the class C family of G protein-coupled receptors (GPCRs) and are characterized by large, extracellular, ligand-binding domains at the N-terminus. Like other class C GPCRs, mGlu receptors assemble as obligate dimers. Both homodimerization and heterodimerization occur, although only a few receptor pairs in groups II and III have been shown to form dimers with receptors outside their own group. We refer the reader elsewhere for more information about mGlu receptor structural characteristics⁸ and expression of mGlu receptors in the periphery.⁹ Here, we will extensively describe mGlu receptor functions and plasticity mechanisms across the limbic system (Figure 2 and Table 1), along with the currently known dysfunctions following ethanol exposure.

Group I mGlu Receptor Physiology.

mGlu₁ and mGlu₅ are perhaps the best-studied mGlu receptor subtypes. The two receptors perform a diverse array of functions involving the regulation of neuronal excitability, excitatory and inhibitory synaptic strength, and synaptic plasticity. In addition to canonical G_q-coupled signaling [i.e., phospholipase C, protein kinase C (PKC), and mobilization of intracellular Ca²⁺ stores¹⁰], activation of the group I mGlu receptor subtypes can promote signaling through phosphoinositide 3-kinase (PI3K),¹¹ casein kinase,¹² Ca²⁺/calmodulin-dependent kinase II (CaMKII),^{13,14} Src-family kinases,^{15,16} the mechanistic target of rapamycin (mTOR),¹⁷ protein kinase A (PKA),¹⁸ phospholipase D,¹⁹ and a variety of voltage-sensitive ion channels.^{10,20} Moreover, mGlu₅ activation modulates the function of NM DA receptors through second-messenger-mediated posttranslational modifications^{10,21,22} and physical interactions with scaffolding proteins like Homer.²³ Activation of these signaling pathways, as well as the endocannabinoid (eCB) system,²⁴ places the group I mGlu receptors in a key position to regulate synaptic plasticity in many different cell types and circuits throughout the CNS.

Group I mGlu Receptors and Synaptic Plasticity.

The group I mGlu receptor subtypes have been intimately linked with several forms of synaptic plasticity, including long-term potentiation (LTP) and its primary counterpart, long-term depression (LTD).^{25,26} mGlu₁ and mGlu₅ have been shown to promote LTP and LTD in different brain regions and even at the same synapse under different circumstances.^{25,27} Mammalian research on synaptic plasticity has its roots in the Schaeffer collateral (SC) CA1 synapses in the hippocampus. Here, mGlu₁ and mGlu₅ both contribute to a postsynaptic form of LTD involving PI3K-Akt signaling and the dephosphorylation and subsequent internalization of AMPA receptors.^{25,26} This LTD can be induced pharmacologically or through low-frequency stimulation of SC inputs. Similar postsynaptic forms of plasticity have been observed in other brain regions, including mGlu₅-mediated LTD in the BNST,^{28–30} as well as mGlu₁-mediated depotentiation in the VTA.^{31,32} In many of these brain regions, mGlu_{1/5} LTD requires mTOR activity, the rapid initiation of protein translation, and the local synthesis of important signaling proteins;^{32–34} however, notable exceptions in specific disease states have been reported.^{35–37} In any case, the rapid translation of cytoskeletal association proteins,^{38,39} tyrosine phosphatases,³⁶ and small-conductance AMPA receptor subunits³² have been shown to occur during mGlu_{1/5} LTD.

Interestingly, the underlying mechanisms of group I mGlu receptor-mediated LTD can vary following *in vivo* experience. For example, the extinction of fear conditioning induces meta-plastic changes such that strong activation of mGlu₅ promotes CA1 LTP instead of LTD.⁴⁰ Accordingly, in preparations from control animals, modest activation of mGlu₅ promotes the induction of NMDA receptor-mediated LTP in animals.^{41,42} This effect, termed “priming”, occurs through eCB production and the inhibition of the release of GABA from nearby interneurons. In addition to its effects on inhibitory transmission, group I mGlu/eCB synaptic plasticity of excitatory transmission has been observed in several components of the limbic system, including the prefrontal cortex (PFC),^{43,44} dorsolateral striatum (DLS),^{45,46} nucleus accumbens (NAC),^{47–51} and lateral habenula.⁵² mGlu₁ has also been extensively linked with the eCB system in the cerebellum.⁵³ Heterogeneous eCB-driven effects occur through

multiple lipid species [e.g., anandamide (AEA) and 2-arachidonoylglycerol (2-AG)] and receptor targets [e.g., CB1, CB2, and transient receptor potential vanilloid 1 (TRPV1) receptors], varying based on the brain region, cell type, and stimulation parameters.²⁴ CB1 and CB2 are generally thought to inhibit neurotransmitter release probability through the translation-dependent^{54,55} modulation of presynaptic Ca^{2+} and K^{+} channels,⁵⁶ whereas TRPV1 has been shown to induce LTD with both presynaptic⁵⁷ and postsynaptic⁴⁷ loci of action. Finally, the eCB system is increasingly being recognized as modulating dopaminergic transmission,^{58,59} and these actions are thought to guide goal-directed behaviors, including ethanol seeking.

As mentioned, mGlu₅ activation can facilitate NM DA receptor-dependent LTP at SC CA1 through GABAergic disinhibition.^{41,42} Similar phenomena have been observed in other brain regions; however, some underlying mechanistic differences can occur. In the PFC, for example, activation of mGlu₅ inhibits the function of small-conductance Ca^{2+} -activated K^{+} (SK) channels.²¹ SK channel inhibition reduces synaptic K^{+} currents and enhances postsynaptic depolarization and NMDA receptor activation. Through this disinhibitory pathway, PFC mGlu₅ activation thereby promotes NMDA receptor-dependent signaling and LTP. Alternatively, activation of group I mGlu receptors has been linked with direct phosphorylation of NMDA receptors by Src-family kinases.^{15,16} These posttranslational modifications, along with physical interactions via Homers and associated scaffolding proteins,^{23,60} contribute to enhanced NMDA receptor-dependent plasticity. Finally, activation of mGlu₁ (but not mGlu₅) has been linked to a unique form of LTD that proceeds through the internalization of Ca^{2+} -permeable, GluA2-lacking AMPA receptors.^{32,61} Each of these molecular cascades is important for modulating synaptic strength and is important to consider in the development and expression of ethanol-related behaviors.

Group I mGlu Receptor Dysfunction following Ethanol Exposure.

Throughout many brain regions, acute ethanol exposure disrupts NM DA receptor-dependent LTP, in a manner consistent with direct antagonism or blockade of the NMDA receptor itself.^{62–67} However, several findings also point toward ethanol disrupting mGlu_{1/5} function and interactions with NMDA receptor signaling. In the NAC, application of acute ethanol (50 mM) disrupts the ability of mGlu_{1/5} activation to potentiate NMDA receptor function⁶⁸ and also disrupts a form of LTP that requires activation of group I mGlu receptors.⁶⁹ Moreover, acute ethanol disrupts mGlu₅-stimulated eCB mobilization in the NAC (40 mM)⁷⁰ as well as mGlu₁- and eCB-dependent LTD in the cerebellum (50 mM).^{71,72} These effects may stem from an induced posttranslational modification, as ethanol has been shown to promote PKC phosphorylation of mGlu₅ at an inhibitory site (30–200 mM).⁷³ In addition to these acute actions, exposure to chronic intermittent ethanol (CIE) dysregulates mGlu_{1/5} LTD in both the DLS^{74,75} and CA1.⁷⁶ Together, these data indicate that acute ethanol generally disrupts mGlu_{1/5} function and/or interactions between group I mGlu receptors and NMDA receptors.

In accordance with the functional effect on SC CA1 LTD, CIE decreases the level of association between NMDA receptors and several proteins that interact with mGlu_{1/5}, such as Homer.⁷⁶ Conversely, changes in the response to ethanol exposure have been observed by

manipulating Homer protein expression and its interactions with mGlu_{1/5}. Through interactions with the mGlu_{1/5} C-terminal EVH1 domain, Homers link group I mGlu receptors to intracellular scaffolding proteins and effector systems.⁶⁰ Three genes encode Homer proteins, and multiple splice variants exist for Homer1 and Homer2. Genetic deletion of Homer2 leads to a behavioral phenotype that avoids high concentrations of ethanol and remains relatively insensitive to its rewarding properties.⁷⁷ This phenotype is reversed by restoration of the Homer2b splice variant in the NAC, suggesting that Homer2b–mGlu_{1/5} interactions are essential for the expression of ethanol-related reward. Conversely, overexpression of Homer2 in the NAC facilitates the rewarding properties of ethanol exposure.⁷⁸ Consistent with these genetic manipulations, repeated periods of binge drinking enhance NAC Homer2 expression, and ethanol intake is inhibited by NAC knockdown of Homer2 or pharmacological inhibition of mGlu₅.^{79–81} Similarly, chronic mild stress has been shown to elevate NAC levels of Homer2 and mGlu₁ and, in turn, enhance the psychomotor and rewarding properties of ethanol.⁸² Homer–mGlu_{1/5} interactions within the central nucleus of the amygdala (CEA) have also been implicated in the behavioral effects of withdrawal,⁸³ demonstrating the diversity of Homer–mGlu_{1/5} involvement in ethanol-related behaviors across multiple brain areas. Clearly, this literature provides strong evidence that dysregulation of group I mGlu receptor function is intimately linked with several behavioral components of ethanol consumption. Modulating these signaling pathways may provide a means to develop novel approaches for treating AUD.

Group II and Group III mGlu Receptor Physiology.

mGlu₂–mGlu₄, mGlu₇, and mGlu₈ are enriched at presynaptic sites in many brain regions, where they generally function as autoreceptors or heteroreceptors to reduce neurotransmitter release probability. Group II and group III mGlu receptors signal through G_{i/o}–coupled pathways,⁶ notably including a decreased rate of accumulation of cyclic adenosine monophosphate (cAMP) and subsequent inhibition of PKA, Ca²⁺ channels, and hyperpolarization-activated cyclic nucleotide-gated channels. Liberation of the G_{βγ} subunit can also act on intracellular signaling cascades,⁸⁴ G protein-gated K⁺ channels,⁸⁵ and presynaptic neurotransmitter release machinery.⁸⁶

Unique among the G_{i/o}–coupled mGlu receptors, mGlu₃ is highly expressed at perisynaptic areas,⁸⁷ where its activation can modulate Ca²⁺ mobilization and the function of AMPA and NMDA receptors.^{84,88,89} Interestingly, we have shown that some of these functions occur, at least in part, through a functional interaction between mGlu₃ and the group I subtype, mGlu₅.⁸⁴ mGlu₃ is also the only mGlu receptor subtype expressed on astrocytes in the adult CNS.⁹⁰ While its specific functions remain to be fully characterized, glial mGlu₃ is believed to exert neuroprotective effects and may modulate interactions between glutamate signaling and other neurotransmitter systems. In addition, mGlu₃ and other mGlu receptor subtypes are thought to be expressed on microglia and dendritic cells and are currently being investigated for their involvement in neuro-inflammation.⁹¹

Group II and Group III mGlu Receptors and Synaptic Plasticity.

Consistent with their predominant presynaptic localization, group II mGlu receptor agonists generally depress glutamate release probability. Indeed, mGlu_{2/3} agonists generate

presynaptic LTD in the NAC,⁸⁶ DLS,^{92,93} basolateral amygdala (BLA),⁹⁴ and lateral amygdala⁹⁵ and at the mossy fiber synapse.⁹⁶ In the PFC, autoreceptor function has been linked with mGlu₂ specifically, as selectively inhibiting mGlu₂, but not mGlu₃, increases the rate of basal glutamate release.⁹⁷ Similar to the effects of CB1 cannabinoid receptor activation, the mechanism involved in these presynaptic actions is thought to involve inhibition of P/Q-type Ca²⁺ channels.^{86,98}

In contrast to this presynaptic mechanism, but in accordance with its cellular localization, mGlu₃ induces postsynaptic forms of plasticity in the PFC and area CA1 of the hippocampus. In the PFC, activation of mGlu₃ induces LTD through the internalization of AMPA receptors and reduction of the number of functional synapses.^{84,88,99} Similar to group I LTD at the SC-CA1 synapse, interactions with mGlu₅, Homer proteins, and PI3K/Akt signaling are involved in this form of LTD. However, PFC mGlu₃ LTD does not require activation of mTOR or protein translation.¹⁰⁰ At the SC-CA1 synapse, on the other hand, prolonged activation of mGlu₃ induces NMDA receptor-dependent LTP.⁸⁹ Remarkably, this LTP also requires the activity of mGlu₅ and related downstream effectors, including CaMKII.¹⁴ Together, these recent findings suggest that neuronal mGlu₃ exerts a major impact on synaptic strength and raise the possibility that mGlu₃ may regulate other forms of plasticity and neuromodulation that involve mGlu₅. In addition, astrocytic mGlu₃ is likely involved in several forms of plasticity, including regulation of synaptic plasticity through interactions with the adrenergic system.^{101,102} While research on astrocytic mGlu₃ has historically relied on glial toxins and correlative immunohistochemistry, the development of cell-type-specific mouse models may soon provide conclusive evidence of the separable functions of neuronal and glial mGlu₃ populations.

The group III mGlu receptor subtypes also attenuate pre-synaptic release probability. mGlu₄ transiently depresses synaptic transmission from the thalamus^{103,104} and olfactory tract;¹⁰⁵ however, persistent mGlu₄-mediated LTD has only been shown to occur in the cerebellum.¹⁰⁶ Expression of mGlu₇ has been detected within the hippocampus, cortex, and basal ganglia.¹⁰⁷ mGlu₇ is unique among mGlu receptor subtypes in that its affinity for glutamate is extremely low,¹⁰⁸ such that receptor activation is thought to occur only under conditions of excessive glutamate release.^{109,110} Accordingly, mGlu₇ is involved in short- and long-term plasticity following tetanic stimulation at SC CA1.¹¹⁰ Activation of mGlu₇ on parvalbumin-expressing interneurons decreases GABA release probability, disinhibiting NMDA receptors and thereby promoting LTP. Finally, mGlu₈ exhibits the lowest level of expression of the group III mGlu receptor subtypes and can be detected in the cortex, amygdala, olfactory bulb, and reticular nucleus of the thalamus.¹¹¹ mGlu₈ transiently depresses excitatory synaptic transmission at multiple synapses, including the BNST,^{112,113} lateral amygdala,¹⁰⁹ olfactory tract,¹⁰⁵ and lateral periformant path;¹¹⁴ however, no effects on long-term plasticity have been identified. Ultimately, while relatively little is known about how group III mGlu receptor subtypes modulate synaptic plasticity in the limbic system, their expression patterns suggest that these targets merit further study in the context of AUD.

Group II and Group III mGlu Receptor Dysfunction following Ethanol Exposure.

In addition to changes in post-synaptic mGlu receptor function in the NAC, disruptions in glutamate homeostasis have been observed following chronic ethanol exposure. Both CIE and voluntary access to ethanol increase basal glutamate levels in the NAC core,^{115,116} and such increases can promote excessive ethanol consumption.¹¹⁷ In these studies, the function of presynaptic mGlu_{2/3} autoreceptors was left intact;¹¹⁶ however, others have observed decreased infralimbic (IL) PFC *Grm2* transcript and NAC shell mGlu_{2/3} autoreceptor function in ethanol-dependent rats.¹¹⁸ While at apparent odds with Pati et al., Meinhardt et al. found no change in the *Grm2* transcript in the prelimbic PFC, the subregion from which the NAC core receives its major cortical input. These studies suggest that within the NAC, mGlu_{2/3} function in the shell subregion may be particularly sensitive to the effects of ethanol exposure. In addition, drinking-induced decreases in mGlu_{2/3} autoreceptor function have also been observed in the VTA.¹¹⁹ In contrast to these findings in the mesocorticolimbic system, enhanced sensitivity to mGlu_{2/3} agonists has been observed in the CEA and BNST of ethanol-dependent rats.¹²⁰ Interestingly, these findings were associated with enhanced behavioral sensitivity to mGlu_{2/3} agonists in their ability to reduce ethanol-motivated behavior. Together, the physiological studies of group II mGlu receptor subtypes suggest that potentiating the function of mGlu_{2/3} could attenuate consumption under normal and disease-like conditions of ethanol intake. While group III mGlu receptor modulators do exert behavioral effects in behavioral models of ethanol seeking, little is known about corresponding ethanol-related changes in the physiology or function of mGlu₄, mGlu₇, or mGlu₈.

MGLU RECEPTOR BEHAVIORAL PHARMACOLOGY

The development of selective ligands was instrumental to the field of mGlu receptor research: this innovation provides a means to isolate the function of distinct mGlu receptor subtypes. These initial selective compounds, many of which are still widely used today, were designed as rotationally constrained glutamate analogues and therefore act at the orthosteric (i.e., glutamate-binding) site.¹²¹ With few exceptions, orthosteric agonists and antagonists display similar potencies at all subtypes across a given mGlu receptor group;¹⁰⁸ however, their high affinities, aqueous solubility, and occasional bioavailability make them invaluable tools in modern preclinical mGlu receptor research.

The highly conserved nature of the orthosteric binding site led to a steep structure—activity relationship and the inability to widely develop ligands selective for a single mGlu receptor subtype.⁶ An alternative approach, targeting allosteric (“other”) sites on the receptors, has been fruitful; positive allosteric modulators (PAMs) and negative allosteric modulators (NAMs) have been developed for most mGlu receptor subtypes. Moreover, many allosteric modulators are systemically active and “drug-like”, enabling researchers to probe how individual mGlu receptor subtypes modulate ethanol seeking behavior. Several common and/or essential orthosteric and allosteric ligands are listed in Table 2 (and reviewed in refs 7 and 108). In tandem with genetically modified mouse lines, these tools provided the ability to discover how specific mGlu receptor subtypes modify synaptic plasticity and behaviors related to ethanol intoxication and drug seeking.

As mentioned in the introductory sections, AUD is composed of several symptom clusters, related to bingeing and intoxication, depressive symptoms and withdrawal, and excessive preoccupation with future alcohol use. As such, alcohol seeking, inebriation, and dependence are modeled by a diverse set of preclinical exposure paradigms and behaviors.¹²² Each model is intended to recapitulate only a specific facet of the disorder. By and large, these preclinical models are widely applied to investigate the motivational properties of most drugs of abuse and natural rewards. In this review, however, we will limit our discussion to alcohol research.

Reward and Reinforcement.

A reward is a stimulus that possesses innate positive value. These stimuli, including ethanol, often serve as reinforcers, items that promote learned behavior with an action—outcome contingency. Models of reward are designed to yield information about the hedonic valence of the stimulus, whether positive or negative. In contrast, models of reinforcement are used to assess how the stimulus engenders future behavior, typically by examining the rate, duration, magnitude, or latency of the appetitive and consummatory responses.

The most common model for assessing conditioned reward is place conditioning, commonly termed conditioned place preference (CPP). In the CPP assay, rodents are conditioned in an apparatus with at least two contextually distinct chambers. Ethanol is repeatedly administered to an animal while it is confined in one component of the chamber and vehicle treatments are administered in the other. Over time, a learned association is formed between the unconditioned stimulus (i.e., ethanol) and the conditioned stimulus (i.e., chamber). The propensity to spend more time in the ethanol-paired side is then taken as a measure of reward. Importantly, this assay can readily detect aversive properties of ethanol or withdrawal, in which case it is commonly termed conditioned place aversion.

Reinforcement, by contrast, is generally assessed through self-administration. These assays are run as a two-bottle choice procedure in the home cage or as an operant task in a separate chamber. Unlike CPP and classical models of reward, which involve experimenter-delivered ethanol, self-administration requires that the animal learn to generate an instrumental response that will result in ethanol delivery (e.g., drinking from the ethanol bottle or pressing a lever). A major advantage of the operant paradigm is that a variety of reinforcement schedules and technical parameters can be adjusted to model compulsive-or addiction-like ethanol seeking.^{123–125} Ethanol self-administration models, in either the home cage or an operant box, can be readily used to examine intake in both dependent and nondependent subjects.

Repeatedly and consistently, genetic or pharmacologic mGlu₅ inhibition decreases ethanol seeking behavior in a wide variety of rodent models.^{126–140} These actions occur at least in part within the NAC, as local mGlu₅ inhibition is sufficient to attenuate ethanol self-administration.^{128,140} Moreover, interactions among mGlu₅, Homer2, and related downstream signaling pathways in the NAC appear to be particularly important for the efficacy of mGlu₅ NAMs.^{79,141,142} Interestingly, mGlu₅ antagonism may not be related to an attenuation of ethanol's rewarding properties per se, as inhibiting mGlu₅ has mixed effects on ethanol CPP.^{129,133,143–145} However, mGlu₅ NAMs do disrupt the interoceptive cue

following ethanol exposure (see below). While less is known about mGlu₁ function in this context, mGlu₁ inhibition appears to reduce ethanol intake^{133,139,146,147} and CPP,¹⁴⁵ but these effects may be somewhat confounded by concomitant reductions in locomotion.

Group II receptor activation reduces ethanol seeking in several animal models.^{117,120,128,137,148,149} Activation of mGlu_{2/3} in the NAC recapitulates these effects,^{117,128} but other brain regions may also be involved in the effects observed following systemic agonist administration. Indeed, data obtained in other behavioral assays suggest that amygdalar regions may also be involved in the attenuation of ethanol's behavioral effects by mGlu_{2/3} activation¹⁵⁰ (see Interoception). Relatively little is known with regard to the role of each mGlu receptor subtype involved in the effects of group II agonists. Recent studies using an mGlu₂-specific PAM have shown mixed effects on alcohol self-administration.^{151,152} Furthermore, genetic deletion of *Grm2* leads to increased ethanol preference and intake in rodent models,^{153,154} consistent with the decreased IL PFC *Grm2* transcript observed in ethanol-dependent rats.¹¹⁸ While specifically potentiating the function of mGlu₂ appears to be a promising means to attenuate ethanol reinforcement, the effects of *Grm3* ablation or pharmacological modulators specific for mGlu₃ have not been reported. As the selective pharmacological and genetic tools continue to develop, teasing apart the mechanisms and circuits underlying group II efficacy in reducing ethanol seeking will be a crucial area of future research.

mGlu₇ has been the best-studied group III subtype in animal models of AUD. Global deletion of *Grm7* has been shown to enhance voluntary ethanol intake in mice, suggesting that mGlu₇ may typically gate this process.¹⁵⁵ Furthermore, regionally specific viral-mediated knockdown of NAC mGlu₇ enhanced ethanol consumption in a two-bottle choice paradigm, without affecting alternative liquid intake.¹⁵⁶ Consistent with an effect on ethanol reward, mGlu₇ knockdown also increased rats' ethanol sensitivity in CPP. Conversely, activation of mGlu₇ with systemic delivery of AMN082 reduces ethanol consumption¹⁵⁷ and preference.¹⁵⁸ Additionally, a recently discovered mGlu_{4/7} orthosteric agonist, LSP2-9166, significantly reduced ethanol self-administration in the reacquisition phase of a rodent relapse model.¹⁵⁹ Future studies using improved pharmacological tools and examining other neurocircuits and behaviors are warranted in efforts to translate mGlu₇ as a potential treatment approach.

Very few studies have examined the other group III mGlu receptors in ethanol seeking contexts. One study reported that mGlu₄ knockout mice exhibited an impairment of locomotor hyperactivity following ethanol administration.¹⁶⁰ Further examination of the mGlu₄ knockouts revealed no differences in models of consumption, withdrawal, and hypnosis, suggesting that mGlu₄ may modulate some of ethanol's stimulatory effects but likely does not substantially impact its addictive properties. In contrast, recent findings posit that activation of mGlu₈ may exert therapeutic-like benefits in models of ethanol reward and reinforcement. Delivery of the agonist DCPG decreased ethanol intake, preference, and the acquisition of CPP.¹⁶¹ Studies using genetic manipulations are warranted as there are few pharmacological tools available to specifically modulate mGlu₈ function.

Extinction and Reinstatement.

Increasingly, extinction and reinstatement paradigms have been used to model facets of ethanol seeking pertinent for the treatment of recovering patients. Extinction is often considered to be analogous to rehabilitation therapy. Ethanol is replaced with a neutral stimulus, usually water, and the animals learn to cease approach or instrumental behavior. Manipulations that enhance extinction learning are expected to benefit patients in active recovery. Reinstatement then occurs when a stimulus is applied to renew ethanol seeking. Like relapse, reinstatement can occur following a brief exposure to stress, a drinking-related cue, or ethanol itself.

As with reward and reinforcement, mGlu₅ is perhaps the best-studied mGlu receptor subtype in extinction and reinstatement models. Recent research has shown that mGlu₅ potentiation can accelerate the extinction of ethanol seeking. Administration of an mGlu₅ PAM, either systemically or localized to the IL PFC, facilitates the extinction of ethanol seeking.²¹ These effects are dependent on the inhibition of SK channels and persist in a model of ethanol dependence.¹⁶² On the other hand, systemic administration of an mGlu₅ NAM reduces ethanol-induced,¹⁴⁴ cue-induced,^{148,163} and stress-induced¹³⁷ reinstatement, and receptors located in the BLA and NAC appear to be particularly important for these effects. An agonist of mGlu_{2/3} receptors blocked both stress- and cue-induced reinstatement of ethanol seeking, and actions within the extended amygdala may be particularly relevant for these effects.¹⁶⁴ Moreover, activation of group II mGlu receptors reduces stress-induced reinstatement in a manner that is more potent in dependent subjects.^{120,137} No studies have specifically addressed which specific mGlu receptor subtype mediates the effects of group II agonists on reinstatement, but some findings point toward mGlu₂ enhancement as being sufficient. An mGlu₂-specific PAM has been shown to inhibit stress- and cue-induced reinstatement,¹⁵¹ and lentiviral overexpression of mGlu₂ in the IL PFC attenuated cue-induced reinstatement.¹¹⁸ To the best of our knowledge, no studies have directly assessed the involvement of mGlu₁, mGlu₃, or any group III mGlu receptor subtype in the extinction or reinstatement of ethanol seeking.

Interoception.

The interoceptive (i.e., subjective) effects produced by drugs regulate, in part, drug use and drug seeking.¹⁶⁵ Drug discrimination techniques that utilize operant or Pavlovian procedures are useful in investigating ethanol's discriminative stimulus/interoceptive effects. In drug discrimination procedures, the experimenter administers the ethanol training dose (e.g., intraperitoneal injection or intragastric gavage) and the presence or absence of interoceptive ethanol cues guides the behavior (i.e., lever press or head poke).¹⁶⁶ Extensive research has demonstrated that the interoceptive effects of ethanol are mediated systemically and at specific central sites by ligands that reduce excitatory transmission.^{167–171} Preclinical studies utilizing mGlu receptor ligands have demonstrated a role for groups I and II in modulating the discriminative stimulus effects of ethanol. Specifically, the interoceptive effects of a moderate ethanol dose (1.0 g/kg, intragastric) require activation of mGlu₅, as systemic administration of MPEP decreased the sensitivity to the discriminative stimulus effects.¹⁷² Furthermore, NAC-specific infusion of the mGlu₅-preferring agonist, CHPG, enhanced the discriminative stimulus effects of ethanol in a manner that was blocked by

MPEP.¹⁷³ Additionally, systemic administration of the mGlu1 NAM JNJ16259685 had no effect on the ethanol discriminative stimulus, consistent with the specific involvement of mGlu₅.

Albeit less clear, the group II mGlu receptor subtypes also appear to be involved in ethanol interoception. Systemic activation with LY379268 or inhibition with LY341495 decreased the sensitivity to the discriminative stimulus effects of ethanol.^{150,174} Moreover, these effects may occur at specific central sites, as infusion of LY379268 in the amygdala, but not NAC, recapitulated the decreased sensitivity to ethanol's interoceptive cue.¹⁵⁰ Given that mGlu_{2/3} modulation also alters the discriminative stimulus effects of hallucinogens,^{175,176} these findings raise the possibility that mGlu_{2/3} ligands may induce interoceptive effects of their own.¹⁷⁴ To the best of our knowledge, this hypothesis has not yet been tested and studies have not been designed to tease apart the relative contribution of mGlu₂ versus mGlu₃ in modulating ethanol's discriminative stimulus effects.

Taken together, these studies suggest that mGlu receptor signaling can modulate (but not mediate) the interoceptive effects of ethanol, as ligands for these receptors neither substitute nor abolish ethanol's discriminative stimulus.¹⁷⁷ In contrast, NMDA receptor antagonists and GABA_A receptor agonists can completely substitute for the discriminative stimulus effects of ethanol.¹⁷⁸ Interestingly, mGlu₅ may modulate the discriminative stimulus effects of ethanol through downstream interactions with the GABA_A receptor.¹⁷² The more modest effects of mGlu receptor ligands might therefore be attributable to the slower kinetics of GPCR signaling relative to ligand-gated ion channels. Finally, activation of mGlu_{2/3} or mGlu₅ in the NAC core restores the discriminative stimulus effects of ethanol following stress hormone exposure,¹⁷⁹ suggesting these targets merit further study in preclinical models of stress-induced changes in ethanol seeking.¹⁸⁰

Binge/Intoxication.

Episodic heavy drinking (blood alcohol content of >80 mg/dL) occurring in a short time span (2 h) can be hazardous and lead to increased susceptibility to developing an AUD.¹⁸¹ Thus, animal models have been developed to mimic this behavior. In the limited-access drinking-in-the-dark (DID) procedure, ethanol replaces water for a limited time (2–4 h) during the dark photoperiod,¹⁸² while in the scheduled high-alcohol consumption (SHAC) procedure, mice have daily limited access to water that is replaced by ethanol every fourth day.¹⁸³ Utilizing these procedures, group I mGlu receptors and their scaffolding signaling proteins (Homer2, PI3K, and PLC), particularly within the NAC, have been implicated in modulating binge drinking.^{79,141} Furthermore, mGlu₅/Homer2/PI3K/PKC ϵ signaling in the NAC shell is functionally important in maintaining binge-like ethanol intake, as transgenic or pharmacological interruptions reduce ethanol intake in both DID and SHAC procedures.^{79,141,142} Additionally, basal mGlu₁ and Homer2 expression in the NAC shell correlates with high binge drinking in a selectively bred high-DID mouse line.^{79,141} Group I mGlu receptor activity has also been implicated in the CEA. Expression of mGlu₁, Homer2a/b, and PLC is enhanced in the CEA following DID, and infusions of mGlu₁, mGlu₅, or PLC inhibitors were found to decrease binge ethanol intake.¹³⁹ Concurrent inhibition of mGlu₁ and PLC produced additive effects, whereas mGlu₅ and PLC inhibition did not, suggesting that mGlu₅

may be the more relevant group I subtype in the CEA. Thus, on the basis of these reports, group I mGlu receptors in the NAC shell and CEA are recruited following binge-drinking paradigms, through distinct site-dependent alterations in mGlu receptor scaffolding and signaling proteins.

Given the functional role of mGlu₅ in modulating ethanol consumption and interoception, it is no surprise that mGlu₅ has been shown to modulate ethanol intoxication, as well. Antagonism of mGlu₅ with the NAM MPEP enhanced the sedative and hypnotic effects of acute ethanol, as measured with spontaneous locomotor activity and ethanol-induced loss of righting reflex, respectively.¹⁸⁴ In contrast, the mGlu₁ antagonist CPCCOEt had no effects. The mGlu_{2/3} antagonist LY341495 attenuated ethanol's sedative—hypnotic effects; however, the effects of mGlu_{2/3} agonists have not been reported. These findings indicate that while some classes of mGlu receptor modulators attenuate ethanol seeking, these mechanisms may have the potential to exacerbate intoxication while the targets are engaged.

Binge drinking and intoxication have the potential to disrupt cognition, potentially through inflammation signaling processes. Relatively few studies have examined whether mGlu receptor signaling may modulate this phenomenon, but both have focused on the group II mGlu receptor subtypes. Activation of mGlu_{2/3} was shown to be neuroprotective in a rat model of binge-like exposure (experim enter-adm inistered), and the treatment also rescued a deficit in spatial reversal learning.¹⁸⁵ Additionally, activation of group II mGlu receptors rescued an acute ethanol-induced deficit in novel object recognition memory,¹⁸⁶ an effect that was recapitulated by enhancing extracellular levels of *N*-acetylaspartylglutamate, a putative endogenous agonist for mGlu₃. Studies using knockout mice confirmed that these pro-cognitive effects were mediated by activation of mGlu₃ and not mGlu₂. These studies are consistent with the breadth of literature demonstrating that mGlu₃ potentiation exerts pro-cognitive effects in a variety of animal models.¹⁸⁷ Thus, mGlu₃ PAMs may provide a means to attenuate ethanol seeking and ameliorate co-occurring cognitive disturbances in AUD patient populations.

Withdrawal and Negative Affect.

AUD and negative affective symptoms are highly comorbid, particularly during periods of withdrawal and extended abstinence. Withdrawn alcoholics commonly list stress and negative affective states as potent triggers of cravings and relapse. The severity of negative affect is strongly correlated with relapse susceptibility, thus implicating negative affective behaviors in both the initiation and abstinence phases of AUDs. Most rodent species do not voluntarily drink enough ethanol to develop dependence; therefore, modeling withdrawal symptoms often necessitates noncontingent ethanol delivery through forced liquid diets or CIE vapor inhalation.^{188,189} Depressive symptoms, on the other hand, can be readily modeled in rodents following abstinence from voluntary ethanol drinking.¹⁹⁰ The diverse mechanisms through which mGlu receptors modulate neurotransmission provide opportunities for mitigating hyperactive brain circuits associated with ethanol abstinence and many affective disorders. Indeed, group I NAMs and group II and III agonists have been shown to effectively reduce anxiety and depression in a variety of preclinical models (for a

review, see ref 191). However, the effectiveness of targeting the mGlu receptor system for treating withdrawal-induced negative affective symptoms remains unclear.

Despite their convincing efficacy in attenuating ethanol self-administration and reinstatement, group I NAMs produced somewhat conflicting results in treating withdrawal-induced seizures. Blocking mGlu₅ receptors successfully reduced audio-genic seizures in early withdrawal.¹⁴⁵ In contrast, others have shown that MPEP had minimal effects on handling-induced convulsions following repeated cycles of withdrawal.¹⁹² These discrepancies can likely be attributed to variations in ethanol exposure procedures as well as the complex circuitry beyond mGlu receptors involved in producing withdrawal-induced seizures in rodents. A more recent study demonstrated that an mGlu₅ NAM was effective in reducing the overall number of withdrawal-induced affective behaviors.¹⁹³ While induced seizures have long been considered the gold standard for testing early withdrawal, implementing a battery of tests to assess withdrawal-induced affective behaviors may prove to be a more effective strategy for testing mGlu receptor NAMs and antagonists in future ethanol withdrawal studies. Indeed, ethanol-induced increases in mGlu₁ receptor expression in the CEA,^{81,139} a region classically associated with affective disturbances, suggest a group I NAM may display efficacy in models of AUD-induced negative affect. While group I mGlu receptors appear to be involved in ethanol withdrawal, future studies are necessary to fully elucidate their therapeutic potential. Unfortunately, little is known about whether modulating group II or group III mGlu receptors may confer therapeutic benefits for treating withdrawal-induced negative affect. Given their involvement in depressive-like behavior and ethanol reward and reinforcement, these mGlu receptor subtypes certainly merit further investigation in animal models during withdrawal.

CLINICAL FINDINGS AND LOOKING TO THE FUTURE

Here, we have provided an overview of the neurocircuitry underlying AUD and a thorough description of how the mGlu receptor system modulates normal physiology and plasticity. In addition, we described how ethanol exposure dysregulates mGlu receptor function and the corresponding understanding of how modulating various mGlu receptor subtypes affects ethanol-related behaviors. While this burgeoning area of preclinical research provides excitement about the translation of novel therapeutics, very little is known about how mGlu receptor modulators might act in clinical AUD populations. Notwithstanding, some important genetic studies do corroborate these preclinical findings and support further efforts toward the translation of mGlu receptor modulators for AUD.

Single-nucleotide polymorphisms (SNPs) within the genes encoding both group I mGlu receptor subtypes (*Grm1* and *Grm5*) have been associated with the frequency of alcohol consumption and alcohol-related problems.^{194,195} Moreover, an association with a network of genes involved in downstream, postsynaptic plasticity was also discovered. In addition to these genetic studies, enhanced expression of mGlu₅ in the amygdala has been observed in recovering AUD patients relative to controls,¹⁹⁶ and changes in mGlu₅ expression have been previously reported in smokers¹⁹⁷ and in major depressive disorder.¹⁹⁸ Consistent with the rich preclinical literature relating group II mGlu receptor function to ethanol seeking in rodent models, SNPs for *Grm3* have also been related to alcohol dependence¹⁹⁹ as well as

substance use disorder. Finally, a genome-wide association study revealed that variations in *Grm7* and *Grm8* are linked to alcohol response phenotype,²⁰⁰ corroborating findings that enhancing mGlu₇ function may attenuate alcohol seeking behaviors and providing a rationale for continuing to investigate mGlu₈ in preclinical models.

In addition to these findings in AUD, SNPs for *Grm3* and *Grm1* have been linked with schizophrenia, a disease that carries a high risk for a comorbid AUD diagnosis. Modulators for mGlu₃ and mGlu₁ are being developed and evaluated as potential treatments for schizophrenia,²⁰¹ and the clinical genetic findings are intriguing for the potential treatment of patients with co-occurring AUDs. Along these lines, modulators of mGlu₅ and mGlu₈ have been examined in models of anxiety, and mGlu₅ and mGlu₇ PAMs are being considered for the treatment of autism spectrum disorders.^{7,26} These mechanisms provide the potential to rescue two related sets of symptoms with a single molecular approach, and this opportunity warrants further preclinical research into the etiology of comorbid AUD diagnoses. While the results have been mixed, several mGlu-directed compounds (i.e., mGlu_{2/3} agonists, mGlu_{2/3} NAMs, and mGlu₅ NAMs) have undergone clinical trials for the treatment of schizophrenia, major depressive disorder, Fragile × syndrome, and other psychiatric diseases.^{201–204} Despite some initial successes in small-scale early phase trials, these mechanisms ultimately failed because of a lack of efficacy in expanded patient populations. Concerns with prior medication treatment histories and strong placebo effects have obfuscated potentially beneficial results; however, minimal adverse effect liability was observed throughout these trials. Because all mGlu modulators tested have been well-tolerated overall, their future use in the treatment of AUD still holds promise.

In summary, modulating a variety of components within the mGlu receptor system holds promise for the treatment of AUD. In particular, extensive preclinical evidence supports the development of molecules that inhibit mGlu₁ and mGlu₅ signaling as agents to attenuate alcohol seeking, consumption, and relapse. Additionally, positive modulators for mGlu₂, mGlu₃, or both may be effective in reducing alcohol seeking as well as stress-induced relapse. Finally, while the least is known about mGlu₇ and mGlu₈, the available preclinical literature suggests that PAMs of those receptors may be viable mechanisms for the development of novel AUD treatments. Continued mechanistic and translational research, in tandem, will be vital for the development of novel medications for AUD. The mGlu receptor system contains several exciting targets that may one day be applied as effective pharmacotherapies.

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ABBREVIATIONS

AUD	alcohol use disorder
CIE	chronic intermittent ethanol
CNS	central nervous system
CPP	conditioned place preference
GPCR	G protein-coupled receptor
LTD	long-term depression
LTP	long-term potentiation
NAM	negative allosteric modulator
PAM	positive allosteric modulator
SNP	single-nucleotide polymorphism
2-AG	2-arachidonoylglycerol
AEA	anandamide
Akt	protein kinase B
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase II
cAMP	cyclic adenosine monophosphate
CB1/2	cannabinoid receptor subtype 1/2
eCB	endocannabinoid
GABA	γ -aminobutyric acid
Grm	glutamate receptor, metab-otropic (gene/transcript)
mGlu	metabotropic glutamate receptor (protein)
mTOR	mechanistic target of rapamycin
NMDA	<i>N</i> -methyl-D-aspartate
PI3K	phosphatidylinositide 3-kinase
PLC	phospholipase C
PKA	protein kinase A
PKC	protein kinase C
SK	small-conductance Ca ²⁺ -activated K ⁺ channels

TRPV1	transient receptor potential vanilloid 1
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
CEA	central nucleus of the amygdala
DLS	dorsolateral striatum
DMS	dorsomedial striatum
GP	globus pallidus
IC	insular cortex
IL	infralimbic PFC
MC	motor cortex
MSN	medium spiny neuron
NAC	nucleus accumbens
PFC	prefrontal cortex
PL	prelimbic PFC
SC CA1	Schaeffer collateral <i>Cornu Ammonis</i> 1 synapse
SNC	substantia nigra pars compacta
SNR	substantia nigra pars reticulate
VH	ventral hippocampus
VP	ventral pallidum
VTa	ventral tegmental area

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Box 1.**Neurocircuitry Underlying AUD**

The mesocorticolimbic system lies at the heart of AUD. Dopamine neurons from the ventral tegmental area (VTA) send extensive projections to the nucleus accumbens (NAC) shell and core in the ventral striatum. In a simplified sense, dopamine is released during rewarding experiences and assists in the integration of excitatory transmission from a variety of brain areas. Like other reinforcing experiences, ethanol exposure increases the rate of extracellular NAC dopamine release, generally enhancing glutamatergic drive and modulating excitability of NAC projection neurons. Through direct and indirect projections, these actions lead to a disinhibition of dopamine neurons in the VTA and substantia nigra pars compacta (SNc). This feedforward circuit promotes ethanol seeking, and its dysregulation is often described as the final common pathway of relapse. Over time, ethanol seeking behaviors are thought to be mediated by more dorsal and lateral structures within mesostriatal pathways; analogous loops among the NAC core, SNc, and dorsomedial and dorsolateral striatum (DMS and DLS, respectively) underlie the development of habitual, compulsive-like behaviors.²⁰⁵ Throughout the ventral and dorsal striatum, projection neurons rest at hyperpolarized membrane potentials; therefore, glutamatergic input from cortical and limbic brain areas is essential to activate the striatum and promote subsequent ethanol-driven behaviors. These glutamatergic inputs to the striatum arise from a diverse set of structures. The cortices, notably including the prefrontal cortex (PFC), are thought to exert top-down control onto the striatum. Dysregulation of the PFC, as well as the orbitofrontal and cingulate cortices, is believed to underlie excessive preoccupation and out-of-control ethanol seeking. As mentioned, stressors and ethanol-related cues are the primary events that instigate relapse. These emotional triggers enhance the activity of the basolateral amygdala (BLA), which sends relapse-promoting excitatory projections to the NAC and DMS. In addition, nuclei within the extended amygdala modulate the BLA, mid-brain nuclei, and other stress-related circuits. Notably, the bed nucleus of the stria terminalis (BNST) interfaces with the stress and reward systems and contributes to stress-induced reinstatement as well as negative symptomatology during ethanol withdrawal. In summary, animal models of AUD and patients alike display alterations to the striatal dopamine system, impaired cortical top-down control over that system, and heightened stress-related reactivity of the extended amygdala neurocircuitry.

Figure 1.

Simplified neurocircuitry underlying normal and pathophysiological ethanol seeking. (A) Basic motor circuit supporting initiation of ethanol seeking. Dopaminergic midbrain areas project to the dorsal and ventral striatum to promote motivated behaviors. Dopamine promotes the activation of dopamine receptor subtype 1 (D1)-expressing “direct pathway” medium spiny neurons (MSNs). D1 MSNs send inhibitory afferents back to the VTA and SNC, where they inhibit local GABAergic neurons and disinhibit dopamine neurons. In contrast, striatal dopamine release inhibits D2-MSNs, thereby relieving inhibition on the pallidum. Decreased output from the pallidum disinhibits the thalamus, the striatum, and the MC. The MC and pallidum provide the major outputs of this circuit to the brainstem to promote the initiation of ethanol seeking. (B) Impaired top-down control and excessive compulsive ethanol seeking. Dysregulation of the cortical inputs onto the striatum is believed to underlie the loss of control observed in AUD. Decreased function of the IL PFC

inputs to the NAC shell and enhanced activity of the VH and PL PFC inputs are thought to mediate excessive motivation to seek ethanol as well as reinstatement. Alterations in the OFC projections to the dorsal striatum are also believed to play a part in habitual, compulsive-like ethanol seeking. (C) Enhanced bottom-up stress reactivity in AUD. The extended amygdala plays a key role in the regulation of emotions and stress response, particularly in the context of ethanol seeking. Excitatory projections from the BLA to the PFC, NAC, and BNST may each be important in promoting stress-induced reinstatement. The BNST is composed of both excitatory and inhibitory projection neurons that modulate the function of the NAC and also the dopaminergic midbrain areas. Finally, the enhanced activity of the IC is thought to be involved in stress-related ethanol seeking, and its projections to the NAC and BNST may be particularly important for these effects.

Figure 2.

Contrasting mechanisms of mGlu receptor plasticity across excitatory synapses in the limbic system. (A) Plasticity mechanisms in the PFC. mGlu₂ and mGlu₄ each inhibit glutamate release in the PFC. Whether mGlu₇ and mGlu₈ function similarly at these synapses has not been determined. On the postsynaptic side, activation of mGlu₃ initiates a cascade of signaling events that culminates with AMPA receptor internalization. This process depends on the activation of mGlu₅ and PI3K. mGlu₅ activation here has also been shown to promote the production of 2-AG, retrograde activation of CB1, and inhibition of glutamate release probability. Furthermore, mGlu₅ inhibits SK channels, relieving an inhibitory constraint on NMDA receptors and promoting additional mechanisms of plasticity not depicted here. (B) Plasticity mechanisms in the NAC. Activation of mGlu_{2/3} decreases glutamate release probability, but the subtype(s) involved has not been determined conclusively. In normal animals, activation of mGlu leads to a presynaptic LTD through the activation of CB1. In the core subregion, this phenomenon is specific to D2 MSNs and coincides with an AEA- and TRPV1-dependent internalization of AMPA receptors. However, in animals conditioned with chronic cocaine self-administration, postsynaptic LTD mediated by mGlu₁ can emerge.

This depotentiation requires the activation of PKC and internalization of GluA2-lacking AMPA receptors, and it is unknown whether similar alterations to plasticity may emerge following ethanol exposure. (C) Plasticity mechanisms in the BNST. Activation of presynaptic group II or group III mGlu receptors transiently inhibits glutamate release probability. mGlu₈ activation is sufficient for this effect, but the contribution of the other subtypes is not well understood. Postsynaptic mGlu₈ induces ERK1-dependent AMPA receptor internalization. Activation of group I mGlu receptors also induces CB1-dependent LTD; however, the subtype and specific endocannabinoid species involved have not been determined.

Table 1

region	no.	first author (ref)	summary
PFC	1	Joffe (88)	Activation of mGlu3 promotes AMPA receptor internalization on pyramidal cells. LTD occurs at long-range inputs from BLA, but not VH, and does not occur on fast-spiking interneurons.
	2	Di Menna/Joffe (84)	mGlu3 enhances mGlu5-mediated signaling, including phosphoinositide production and Ca^{2+} mobilization. mGlu5 activity is also required for the induction of mGlu LTD.
	3	Walker (99)	Genetic deletion of mGlu3, but not mGlu2, blocks LTD induced by group II agonists. Inhibition of mGlu3 disrupts extinction of cued fear.
	4	Joffe (100)	mGlu3 LTD does not require the mobilization of intracellular Ca^{2+} stores. Instead, mGlu3 LTD proceeds through activation of PI3K and Akt. mGlu3 LTD is impaired by acute restraint stress.
	5	Joffe (97)	Glutamate release is enhanced by acute application of a group II mGlu receptor antagonist or mGlu2 NAM. Acute application of an mGlu3 NAM does not affect basal release probability.
	6	Zhang (104)	Application of a group III mGlu receptor agonist reduces glutamate released by serotonin. The specific mGlu receptor subtype mediating this effect is not known.
	7	Lafourcade (44)	Synaptic or pharmacologic stimulation of mGlu5 induces the production of 2-AG. 2-AG activates presynaptic CB1 receptors to induce LTD.
	8	Cannady (21)	mGlu5 activation inhibits SK channels, which normally act to inhibit NMDA receptor function. This mechanism promotes the induction of NMDA receptor LTP and extinction of alcohol seeking.
NAC	9	McCutcheon (50)	mGlu5 induces eCB LTD. Following extended cocaine exposure, mGlu5 function is impaired, and mGlu1 induces postsynaptic PKC-dependent LTD instead.
	10	Loweth (61)	Abstinence from cocaine exposure upregulates GluA2-lacking AMPA receptors. Activating mGlu1 depotentiates these synapses and reduces incubation of cocaine craving.
	11	Turner (51)	In the NAC shell, mGlu5 induces LTD at MDT inputs onto D1-expressing neurons. In contrast, mGlu1 activation generates LTD at PFC inputs onto both D1(+) and D1(-) MSNs.
	12	Robbe (86)	Group II mGlu receptor agonists induce presynaptic LTD. The mechanism involves cAMP, PKA, and the inhibition of P/Q type Ca^{2+} channels.
	13	Robbe (48)	mGlu5 induces canonical eCB LTD through intracellular Ca^{2+} mobilization and activation of presynaptic CB1 receptors.
	14	Fourageaud (98)	A single administration of cocaine impairs mGlu5 LTD. This impairment requires in vivo activation of D1 and is associated with enhanced Homer expression and mGlu5 internalization.
	15	Grueter (47)	In the NAC core, mGlu5 LTD occurs specifically on D2-expressing neurons. AEA is released to activate CB1 as well as postsynaptic TRPV1, which promotes AMPA receptor internalization.
BNST	16	Grueter (28, 29)	Activation of mGlu5 promotes the internalization of AMPA receptors. The mechanism requires the activation of ERK1 and is disrupted by repeated cocaine administration.
	17	McElligott (30)	mGlu5 LTD is distinct from LTD induced by α -adrenergic receptor activation. mGlu5 LTD does not involve GluA2-lacking AMPA receptors and is not impaired by stress.
	18	Grueter (113)	Group II and group III mGlu receptor agonists depress excitatory transmission. Prolonged activation of group II mGlu receptors induces LTD.
	19	Gosnell (112)	An mGlu ₈ -specific agonist induces a transient depression of excitatory transmission, and mGlu4 does not appear to modulate presynaptic release probability.

Table 2

group	effector	agonist	antagonist	subtype	PAMs	NAMs
group I	G _q , PLC/PKC, PI3K/Akt, mTOR ERK, PLD, PKA, NMDAR, eCB	DHPG, CHPG, quisqualate	MCPG, AIDA	mGlu ₁	Ro 67-7476	JNJ16259685
				mGlu ₅	CDPPB, VU29, VU0409551	MPEP, MTEP, fenobam
group II	G _{i/o} , inhibition of adenylyl cyclase, modulation of K ⁺ and Ca ²⁺ channels	DCG-IV, LY354740, LY379268	LY341495	mGlu ₂	BINA, LY487379	
				mGlu ₃		ML337
group III	G _{i/o} , inhibition of adenylyl cyclase, modulation of K ⁺ and Ca ²⁺ channels	L-AP4, LSP4-2022	CPPG	mGlu ₄	PHCCC	
				mGlu ₇	AMN082 (allosteric agonist)	ADX71743
				mGlu ₈	DCPG (orthosteric agonist)	