1521-0081/74/3/630–661$35.00
PHARMACOLOGICAL REVIEWS


dx.doi.org/10.1124/pharmrev.121.000540
Pharmacol Rev 74:630–661, July 2022

ASSOCIATE EDITOR: LYNETTE DAWS

# Allosteric Modulators of Metabotropic Glutamate Receptors as Novel Therapeutics for Neuropsychiatric Disease

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***Abstract*——Metabotropic glutamate (mGlu) receptors, a family of G-protein-coupled receptors, have been identified as novel therapeutic targets based on extensive research supporting their diverse contributions to cell signaling and physiology throughout the nervous system and important roles in regulating complex behaviors, such as cognition, reward,**

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This work was supported by National Institutes of Health National Institute of Mental Health [Grants MH119673 (PJC), MH062646 (PJC), MH073676 (PJC), and MH065215 (DJL)] and National Institutes of Health National Institute of Neurologic Disorders and Stroke [Grant NS031373 (PJC)].

P.J.C. received research support from Boehringer Ingelheim and Acadia Pharmaceuticals. P.J.C. is an inventor on multiple patents for allosteric modulators of metabotropic glutamate receptors. D.J.L. has no actual or perceived conflict of interest with the contents of this article.

dx.doi.org/10.1124/pharmrev.121.000540.

**and movement. Thus, targeting mGlu receptors may be a promising strategy for the treatment of several brain disorders. Ongoing advances in the discovery of subtype-selective allosteric modulators for mGlu receptors has provided an unprecedented opportunity for highly specific modulation of signaling by individual mGlu receptor subtypes in the brain by targeting sites distinct from orthosteric or endogenous ligand binding sites on mGlu receptors. These pharmacological agents provide the unparalleled opportunity to selectively regulate neuronal excitability, synaptic transmission, and subsequent behavioral output pertinent to many brain disorders. Here, we review preclinical and clinical evidence supporting the utility of mGlu receptor allosteric modulators as novel therapeutic approaches to treat neuropsychiatric diseases, such as schizophrenia, substance use disorders, and stress-related disorders.**

***Significance Statement*——Allosteric modulation of metabotropic glutamate (mGlu) receptors represents a promising therapeutic strategy to normalize dysregulated cellular physiology associated with neuropsychiatric disease. This review summarizes preclinical and clinical studies using mGlu receptor allosteric modulators as experimental tools and potential therapeutic approaches for the treatment of neuropsychiatric diseases, including schizophrenia, stress, and substance use disorders.**

## I. Introduction

Glutamate is the primary excitatory neurotransmitter within the central nervous system (CNS). Glutamate modulates cell excitability and synaptic transmission through actions on glutamate receptors, including ionotropic glutamate and metabotropic glutamate (mGlu) receptors. Ionotropic glutamate receptors, which include amino-3-hydroxy-5-methyl-isoxazolepropionic acid, N-methyl-d-aspartate (NMDA), and kainate receptors, are ligand-gated ion channels that mediate fast excitatory synaptic transmission (Traynelis et al., 2010). mGlu receptors are members of the G-protein-coupled receptor superfamily and can be classified into three distinct groups based on their sequence homology, G-protein coupling, and ligand selectivity (Conn and Pin, 1997). The mGlu receptor subtypes are differentially expressed pre- and postsynaptically throughout the CNS and are located on both neurons and glial cells.

### *A. Metabotropic Glutamate Receptors: Structure and Signal Transduction*

*1. Structural Components of Metabotropic Glutamate Receptors.* mGlu receptors feature a large extracellular N-terminal domain, coined the Venus flytrap domain (VFD), which contains the orthosteric glutamate binding site and is critical for homo- and heterodimerization of these receptors (Yin and Niswender, 2014). Extensive evidence shows that VFDs form dimers, which can exist in three main states: open-open, open-closed, and closed-closed. Antagonist binding stabilizes the open-open (inactive) conformation, whereas ligand binding induces open-closed and closed-closed conformations. Distinct residues that are associated with closure of the VFD strongly contribute to functional switching of ligands from antagonists to agonists (Bessis et al., 2002; Jingami et al., 2003; Niswender and Conn, 2010), highlighting the important role of these domains and their respective orientations for receptor activation. Importantly, a number of conserved residues interact directly with glutamate as well as divalent cations, such as calcium or magnesium, which have the ability to activate the receptor (Kubo et al., 1998; Kunishima et al., 2000; Francesconi and Duvoisin, 2004). Ligand binding results in conformational changes, originating from the VFD via cysteine-rich domains (CRDs) to the heptahelical domain (HD)–C-terminal tail. Studies using mutagenesis and crystallization have shown that the CRD, which consists of nine cysteine residues, are critical to ligand-induced signal transduction, in part via a disulfide bridge formed between a cysteine in lobe 2 of the VFD and the ninth CRD cysteine (Rondard et al., 2006; Muto et al., 2007). Additionally, the second intracellular loop of mGlu receptors regulate selectivity of G protein coupling (Pin et al., 1994; Gomeza et al., 1996) and acts as an important regulatory site for kinases, like G-protein-coupled receptor kinase 2 (Dhami et al., 2005). Importantly, allosteric modulators of mGlu receptors that bidirectionally alter glutamate activity largely bind within the HD (Niswender and Conn, 2010). The C-terminus region of mGlu receptors is important for

**ABBREVIATIONS**: AMN082, N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride; BINA, potassium 3′-([(2-cyclopentyl-6-7-dimethyl-1-o xo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl l-4-carboxylate; CA1, cornu ammonis; $Ca^{2+}$, calcium; CNS, central nervous system; CRD, cysteine-rich domain; CPCCOEt, (–)-ethyl (7E)-7-hydroxyimino-1,7a-dihydrocyclopropa[b]chromene-1a-carboxylate; DHPG, (S)-3,5-dihydroxyphenylglycine; DOI, 2,5-dimethoxy-4-iodoamphetamine; EPM, elevated plus maze; EPS, extrapyramidal side effects; EPSC, excitatory postsynaptic current; FST, forced swim test; Gαi/o, Gi/o alpha subunit; Gβγ, protein beta/gamma; GRM, Glutamate Metabotropic Receptor gene; HD, hepatahelical domain; KO, knockout; L-AP4, L-2-amino-4-phosphonobutyric acid; LTD, long-term depression; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; mGlu, metabotropic glutamate; MK-801, dizocilpine; MPEP, 2-methyl-6-(phenylethynyl)pyridine; mPFC, medial prefrontal cortex; MTEP, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; NAc, nucleus accumbens; NAM, negative allosteric modulator; NMDA, N-methyl-d-aspartate; NMDAR, N-methyl-D-aspartate; PAM, positive allosteric modulator; PCP, phencyclidine; PFC, prefrontal cortex; PHCCC, 7-hydroxyimino-N-phenyl-1,7 adihydrocyclopropa[b]chromene-1a-carboxamide; PPI, prepulse inhibition; PR, progressive ratio; (S)-3, 4-DCPG, (S)-3,4-dichlorophenyl glycine; SC, Shaffer collateral; SIH, stress-induced hypothermia; SST-IN, somatostatin-expressing interneurons; SUD, substance use disorder; VFD, Venus flytrap domain; VTA, ventral tegmental area.

modulating G protein coupling and undergo alternative splicing, modulatory protein-protein interactions, and regulation by phosphorylation (Niswender and Conn, 2010; Enz, 2012). In addition to interacting with G-proteins, the C-terminal domains of mGlu receptor subtypes directly interact with many proteins, including enzymes, ion channels, receptors, scaffolds, and cytoskeletal proteins (Enz, 2012).

*2. Metabotropic Glutamate Receptor Signal Transduction.* As detailed in Table 1, group I mGlu receptor subtypes ($mGlu_{1/5}$) are widely expressed in CNS neurons (Maksymetz et al., 2017). $mGlu_1$ and $mGlu_5$ are primarily expressed postsynaptically but are also located at presynaptic terminals of GABA and glutamate neurons (Higley, 2014). Group I mGlu receptor subtypes canonically couple to the G protein $G_{q/11}$ alpha subunit ($G\alpha_{q/11}$) and activate phospholipase C beta ($\beta$), which in turn results in the hydrolysis of phosphotinositides and generation of inositol 1,4,5-trisphosphate and diacyl-glycerol. This signaling pathway promotes calcium mobilization and downstream activation of protein kinase C. Additionally, group I mGlu receptor subtypes can also signal through alternative pathways including the G protein $G_{i/o}$ alpha subunit ($G\alpha_{i/o}$), $G_s$ alpha subunit ($G\alpha s$), and other molecules independent of G proteins (Hermans and Challiss, 2001). Group I mGlu receptors activate many downstream signaling effectors, including phospholipase D, protein kinase cascades like kinase 1, cyclin-dependent protein kinase 5, mitogen-activated protein kinase (MAPK)/extracellular receptor kinase, Jun kinase, and the mammalian target of rapamycin/P70 S6 kinase (p70-S6) kinase pathways (Page et al., 2006; Li et al., 2007). These signaling cascades, such as mammalian target of rapamycin/p70 S6 kinase and MAPK/extracellular receptor kinase, are critical to synaptic plasticity mediated by group I mGlu receptors. Additionally, group I mGlu receptors represent promising therapeutic targets, based on their ability to directly couple to NMDA receptors via intracellular signaling pathways and scaffolding proteins, such as SRC Homology 3 Domain (SH3), Homer, and multiple ankyrin repeat domains protein, and guanylate kinase-associated protein–postsynaptic density-95 (Aniksztejn et al., 1991; Harvey and Collingridge, 1993; Yu et al., 1997) and their subsequent capacity to activate NMDA receptors in acute brain slices (Fitzjohn et al., 1996).

The group II mGlu receptors, $mGlu_2$ and $mGlu_3$, are expressed presynaptically (Niswender and Conn, 2010) on axonal preterminal regions where they can be activated by excessive synaptic or astrocytic glutamate release (Nicoletti et al., 2011; Maksymetz et al., 2017). $mGlu_3$ is located postsynaptically as well as on astrocytes where it promotes neuroprotective effects (Nicoletti et al., 2011) and facilitates astrocytic-neuronal communication (Winder and Conn, 1996; Winder et al., 1996). Group II mGlu receptor

TABLE 1
Summary of mGlu receptor subtype expression, signaling, and interacting partners

| Group | Receptor | CNS Expression | Synaptic Localization | G protein Coupling | Primary Signaling Pathways | Interacting Partners |
|---|---|---|---|---|---|---|
| Group I | $mGlu_1$ | Widespread in neurons | Predominantly postsynaptic | Primarily $G\alpha_{q/11}$ noncanocial $G\alpha_{i/0}$, $G\alpha_s$ | PLC$\beta$ → IP3 + DAG hydrolysis phospholipase D MAPK/ERK mTOR/p70 S6 kinase | Activates NMDA receptors activates $Ca^{2+}$ channels (e.g., $Ca_{v2.1}$) activates CaMKII$\alpha$ |
| | $mGlu_5$ | Widespread in neurons | | | | |
| Group II | $mGlu_2$ | Widespread in neurons | Presynaptic and postsynaptic | Primarily $G\alpha_{i/0}$ | Inhibition of adenylyl cyclase MAPK/ERK IP3-PI3 kinase | Activation of $K^+$ channels inhibition of voltage-gated $Ca^{2+}$ channels (e.g., N- type) |
| | $mGlu_3$ | Widespread in neurons, astrocytes | | | | |
| Group III | $mGlu_4$ | Widespread in neurons, high in cerebellum | Predominantly presynaptic | Primarily $G\alpha_{i/0}$ noncanocial $G\alpha_{q/1}$ | Inhibition of adenylyl cylcase MAPK/ERK IP3 (mGlu7) stimulation of cGMP phosphodiesterase (mGlu6) | Activation of $K^+$ channels inhibition of $Ca^{2+}$ channels (P/Q subtype) |
| | $mGlu_6$ | Retina, select neuron populations, microglia | Postsynaptic in retinal cells | | | |
| | $mGlu_7$ | Widespread in neurons | Active zone of presynaptic terminals | | | |
| | $mGlu_8$ | Lower and more restricted expression than mGlu4/7 | Predominantly presynaptic | | | |

caMKII-alpha, Calcium/calmodulin-dependent kinase II; cGMP, cyclic guanosine monophosphate; DAG, diacyl-glycerol; G protein i/o alpha subunit; G protein Gs alpha subunit; G protein Gq alpha subunit; IP3, inositol 1,4,5-trisphosphate; MAPK/ERK, mitogen-activated protein kinase/extracellular receptor kinase; mTOR, mammalian target of rapamycin; PI3 kinase, phosphatidyl inositol 3-kinase; PLC$\beta$, phospholipase C$\beta$; *p70-S6 kinase, P70-S6; P/Q, P/Q-type calcium channel.*

subtypes predominantly couple to $G_{i/o}$ proteins, which classically inhibit adenylyl cyclases and downstream production of 3′,5′-cAMP. Group II mGlu receptors also directly regulate ion channels, including potassium ($K^+$) and calcium ($Ca^{2+}$) channels, and other downstream signaling components via G protein beta/gamma ($G\beta\gamma$) subunits (Niswender and Conn, 2010). Additionally, group II mGlu receptors can engage in a multitude of signal transduction pathways, including activation of phosphatidyl inositol 3-kinase and MAPK pathways (Muguruza et al., 2016), demonstrating the great complexity by which these receptors regulate neuronal signaling and synaptic plasticity.

The group III mGlu receptors consist of $mGlu_4$ (Tanabe et al., 1992), $mGlu_6$ (Nakajima et al., 1993), $mGlu_7$ (Saugstad et al., 1994), and $mGlu_8$ (Niswender and Conn, 2010). $mGlu_6$ receptors are largely expressed in the retina, however, these receptors have also been shown to be expressed in the CNS, including cortical areas, superior colliculus, the accessory olfactory bulb, and axons of the corpus callosum (Vardi et al., 2011; Palazzo et al., 2020). Alternatively, other group III mGlu receptors are largely expressed within the CNS (Nakajima et al., 1993). Group III mGlu receptors canonically signal via the $G\alpha_{i/o}$ subunits of the heterotrimeric G protein complex, resulting in inhibition of adenylyl cyclase and cAMP production (Niswender and Conn, 2010). Activation of group III mGlu receptors can also regulate a variety of ion channels and inhibition of vesicular fusion via $G\beta\gamma$ subunits (Cartmell and Schoepp, 2000). In addition to canonical $G_{\alpha i/o}$-mediated downstream signaling, group III mGlu receptors engage in a multitude of other signal transduction cascades. For instance, $mGlu_7$ has been shown to selectively inhibit P/Q-type (P/Q)-type $Ca^{2+}$ channels through a phospholipase C-dependent mechanism resulting in subsequent $Ca^{2+}$ release from intracellular stores and diacyl-glycerol—mediated activation of protein kinase C (Perroy et al., 2000). Furthermore, activation of $mGlu_4$ results in MAPK pathway signaling via $G\beta\gamma$ subunits (Iacovelli et al., 2004). Evidence suggests that the $mGlu_6$ receptor signals through $G\alpha_o$ to a cyclic guanosine monophosphate-preferring phosphodiesterase (Shiells and Falk, 1990; Thoreson and Miller, 1994; Nawy, 1999).

### *B. Metabotropic Glutamate Receptor Regulation of Neurotransmission and Synaptic Plasticity*

mGlu receptors are distributed widely throughout the CNS in a vast array of major brain regions and are localized at discrete synaptic and extrasynaptic sites in both neurons and glia. Based on their robust CNS expression and diverse signal transduction pathways, activation of mGlu receptors elicits a multitude of outcomes on synaptic transmission and contributes to many forms of synaptic plasticity (Crupi et al., 2019). These activity-dependent modifications of synaptic transmission are critical to learning and memory, for example and thus, represent important mechanisms underlying many neuropsychiatric disorders, such as schizophrenia and substance use disorders (SUDs). Here, we will briefly summarize select functional roles of mGlu receptor subtypes in neurotransmission and synaptic plasticity. In-depth discussion of the vast array of physiological roles of mGlu receptors has been presented in numerous previous reviews (Benarroch, 2008; Niswender and Conn, 2010; Mukherjee and Manahan-Vaughan, 2013; Maksymetz et al., 2017). mGlu receptors expressed presynaptically have the ability to increase or decrease neurotransmitter release at excitatory (glutamate), inhibitory (GABA), and neuromodulatory (i.e., monoamines, acetylcholine, peptides) synapses (Niswender and Conn, 2010). In most cases, mGlu receptor-mediated regulation of neurotransmitter release is mediated by mGlu receptors that are localized presynaptically; however, this can also occur via postsynaptic mGlu receptors and release of retrograde messengers, such as endocannabinoids (Yohn et al., 2020). mGlu receptor-mediated neuromodulation, in turn, has a wide array of downstream effects on neuronal activity and firing. For example, mGlu receptor-mediated inhibition of GABA transmission in the cerebellum results in a local reduction in inhibition, enhancing the efficacy of the more active fibers and accentuating the contrast between inputs with differential firing rates (Mitchell and Silver, 2000).

*1. Group I: Metabotropic Glutamate$_{1/5}$.* Group I mGlu receptors, which include $mGlu_1$ and $mGlu_5$, are heterogeneously expressed throughout the brain, with high levels in regions critical to cognition, reinforcement learning, and motivation, such as the nucleus accumbens (NAc), hippocampus, medial prefrontal cortex (mPFC), and thalamus (Cleva and Olive, 2012). Further studies have revealed that the vast majority of $mGlu_1$ and $mGlu_5$ receptors are located postsynaptically on dendritic spines (Olive, 2009) and on axon terminals in brain regions, such as the hippocampus (Romano et al., 1995) and cerebral cortex (Muly et al., 2003; Paquet and Smith, 2003). Additionally, group I mGlu receptors in globus pallidus of nonhuman primates are found in the main body of symmetric synaptic junctions established by striatal GABA terminals as well as perisynaptic to asymmetric glutamatergic synapses (Hanson and Smith, 1999). Their activation leads to cell depolarization and increases in neuronal excitability (Niswender and Conn, 2010). Group I mGlu receptor-mediated modulation of neuronal excitability is driven by regulation of numerous ion channels, which enable fine-tuning of neuronal excitability (Conn and Pin, 1997; Anwyl, 1999; Coutinho and Knöpfel, 2002; Valenti et al., 2002).

Activation of group I mGlu receptor subtypes leads to alterations in excitability and spontaneous synaptic

transmission in the mPFC and cornu ammonis (CA1) region of the hippocampus, among other brain regions (Zho et al., 2002; Yin and Niswender, 2014; Turner et al., 2018; Maksymetz et al., 2021). For example, activation of group I mGlu receptors by selective orthosteric agonists, such as (S)-3,5-dihydroxyphenylglycine (DHPG), results in direct excitatory effects on CA1 pyramidal cells, including increased cell firing and depolarization (Charpak et al., 1990; Desai and Conn, 1991; Pedarzani and Storm, 1993; Davies et al., 1995; Gereau and Conn, 1995; Mannaioni et al., 1999). These downstream effects are mediated by inhibition of $K^+$ currents and activation of both $Ca^{2+}$-dependent and independent conductance (Crépel et al., 1994; Guérineau et al., 1995). Additionally, recent studies have directly demonstrated for the first time that activation of $mGlu_1$ increases inhibitory transmission in the mPFC by excitation of somatostatin-expressing interneurons (SST-INs) (Maksymetz et al., 2021). Extensive evidence also supports the role of $mGlu_1$ and $mGlu_5$ receptor subtypes in numerous forms of long-term synaptic plasticity, including long-term depression (LTD) and long-term potentiation (LTP) of transmission. At excitatory synapses in hippocampal CA1, activation of $mGlu_{1/5}$ and subsequent $Ca^{2+}$ mobilization has been shown to induce LTP, a modality of synaptic plasticity thought to underlie learning and memory, at numerous glutamatergic synapses (Bashir et al., 1993; Frenguelli et al., 1993; Petrozzino and Connor, 1994; Balschun et al., 1999; Chevaleyre and Castillo, 2003; Gladding et al., 2009). However, there are mixed reports regarding the role of $mGlu_5$ in N-methyl-D-aspartate receptor (NMDAR)-dependent LTP (Fitzjohn et al., 1996, 1998; Lu et al., 1997; Francesconi and Duvoisin, 2004; Bortolotto et al., 2005; Neyman and Manahan-Vaughan, 2008). Several studies have also revealed that $mGlu_1$ and $mGlu_5$ subtypes regulate LTP in hippocampal SST-INs (McBain et al., 1994; Perez et al., 2001; Le Duigou and Kullmann, 2011; Pelkey et al., 2017). There is evidence for the role of group I mGlu receptors in regulation of LTP extrahippocampal brain regions. For instance, it has been reported that application of DHPG facilitated LTP of the evoked excitatory postsynaptic currents (EPSCs) in SST-INs of the prefrontal cortex (PFC) (Crowley and Joffe, 2021). Furthermore, a wealth of studies has shown that activation of group I mGlu receptors induces a LTD of synaptic transmission in rat hippocampal CA1 (Palmer et al., 1997; Chevaleyre and Castillo, 2003; Tan et al., 2003; Gladding et al., 2009) and dentate gyrus (O'Mara et al., 1995; Camodeca et al., 1999) among other brain regions (Kano and Kato, 1987; Kato, 1993; Conquet et al., 1994; Wang et al., 2015).

The development of mouse models with selective deletion of group I mGlu receptors have corroborated these findings. For instance, electrophysiological recordings from $mGlu_1^{-/-}$ mice show that these animals display impaired hippocampal LTP, which correlates with impairments in context-specific learning and impaired LTD in the cerebellum (Aiba et al., 1994a,b; Gil-Sanz et al., 2008). A wealth of studies using constitutive knockout models further confirmed the role of $mGlu_5$ in hippocampal LTP (Bashir et al., 1993; Lu et al., 1997). Using genetic deletion or pharmacological inhibition, it has been demonstrated that $mGlu_5$ reduces LTP at Shaffer collateral (SC)-CA1 synapses of the hippocampus in freely moving rats and ex vivo slice preparations (Lu et al., 1997; Francesconi et al., 2004; Shalin et al., 2006). In addition, LTP induction can be primed by DHPG (Cohen et al., 1998; Raymond et al., 2000), and multiple $mGlu_5$ positive allosteric modulators (PAMs) can induce LTP at SC-CA1 synapses (Ayala et al., 2009; Noetzel et al., 2013; Rook et al., 2015). More recently, studies using conditional knockout of Glutamate Metabotropic Receptor 5 gene (*GRM5*) in hippocampal CA1 pyramidal cells showed that loss of $mGlu_5$ in this cellular population impaired LTD of inhibitory synapses compared with wild-type control mice (Xu et al., 2014), suggesting a specific role of $mGlu_5$ in hippocampal CA1 pyramidal cells in metaplasticity by regulating inhibition. These findings are of particular importance as hippocampal LTP is known to be altered in models that recapitulate the physiologic and behavioral phenotypes associated with neuropsychriatic diseases, including schizophrenia. For example, subchronic phencyclidine (PCP) treatment in mice increases the threshold for LTP of CA1 excitatory synapses, and this effect is directly related to enhanced inhibitory input to CA1 pyramidal cells through increased activity of GABAergic neurons (Nomura et al., 2016). Therefore, the contributions of group I mGlu receptors in regulating LTP at excitatory synapses is critical for our understanding of the pathophysiology of neuropsychiatric diseases and development of novel treatments.

*2. Group II: Metabotropic Glutamate$_{2/3}$.* The group II mGlu receptor subtypes, $mGlu_2$ and $mGlu_3$, are expressed throughout the CNS, notably in brain regions central to motivation, learning, and memory (Moussawi and Kalivas, 2010; Muguruza et al., 2016). In some instances, they modulate synaptic transmission and alter neuroplasticity by acting at preterminal regions away from the active zone of on glutamatergic or GABAergic synapses (Nicoletti et al., 2011). $mGlu_{2/3}$ receptors located on the presynaptic membrane can be activated by substantial synaptic or astrocytic glutamate release (Muguruza et al., 2016; Maksymetz et al., 2017). Additionally, further evidence supports the existence of $mGlu_2$ and $mGlu_3$ expressed postsynaptically (Muguruza et al., 2016).

At many synapses, $mGlu_{2/3}$ receptor activation decreases spontaneous excitatory transmission (Marek et al., 2000;

Kiritoshi and Neugebauer, 2015; Bocchio et al., 2019). Studies have shown that group II mGlu receptor agonist LY 354740 decreases frequency, but not amplitude, of miniature EPSCs in the presence of tetrodotoxin, which suggests that the site of action is primarily presynaptic on the glutamatergic terminals (Han et al., 2006; Kiritoshi and Neugebauer, 2015). In the infralimbic mPFC, electrophysiology experiments in rat brain slices showed that group II mGlu receptor subtypes decrease the output of layer V pyramidal cells as the result of an inhibitory action on glutamatergic synapses (Kiritoshi and Neugebauer, 2015; Thompson and Neugebauer, 2017). More specifically, LY379268, a selective group II mGlu receptor agonist, regulates activity of pyramidal cells by modulating glutamate-driven feedforward inhibitory transmission (inhibitory postsynaptic currents) in addition to direct EPSCs. In addition to regulation of neurotransmitter release and short-term plasticity, group II mGlu receptors play important roles in long-term synaptic plasticity, which underlies many cognitive and behavioral processes disrupted in neuropsychiatric disease. Activation of either $mGlu_2$ or $mGlu_3$ receptor subtypes induces a robust, postsynaptic LTD of evoked synaptic responses in the PFC. Interestingly, $mGlu_2$ and $mGlu_3$ receptors induce LTD by divergent presynaptic and postsynaptic mechanisms, respectively (Walker et al., 2015; Joffe et al., 2019a,b). At mossy fiber pyramidal cell synapses, prolonged low-frequency stimulation results in a presynaptic form of LTD that is absent in $mGlu_2$-deficient mice and blocked by a nonselective group II antagonist. At this synapse, the activation of $mGlu_2$ induces LTD selectively when it is coupled to a synaptically-driven increase in presynaptic $Ca^{2+}$. Additionally, mossy fiber LTP is reversible by low-frequency stimulation via the activation of group II mGlu receptors (Chen et al., 2001). Finally, exciting recent reports have demonstrated that activation of $mGlu_3$ induces metaplastic changes, biasing stimulation of afferents to induce LTP through an $mGlu_5$ receptor-dependent, endocannabinoid-mediated mechanism of action (Dogra et al., 2021). In this same study, targeted genetic deletion of $mGlu_3$ from hippocampal pyramidal cells prevented the LTP-inducing effects of $mGlu_3$ activation, revealing a novel avenue by which $mGlu_3$ regulates long-term hippocampal synaptic plasticity.

*3. Group III: Metabotropic Glutamate$_{4/6/7/8}$.* Group III mGlu receptors are differentially expressed in the CNS and peripheral nervous system. $mGlu_4$ and $mGlu_8$ subtypes are expressed in the brain but in a restricted manner (Pilc et al., 2008; Julio-Pieper et al., 2011). Although $mGlu_4$ is primarily found in the cerebellum (Kinoshita et al., 1996b; Shigemoto et al., 1997), expression has also been reported in the cerebral cortex, striatum, olfactory bulb, pontine nuclei, lateral septum, hippocampus, thalamic nuclei, and dorsal horn (Fotuhi et al., 1994; Azkue et al., 2001). Within the CNS, $mGlu_8$ is found presynaptically in the hippocampus, cerebellum, olfactory bulb, and cortical areas (Ferraguti and Shigemoto, 2006). Although $mGlu_7$ is expressed widely throughout the brain, $mGlu_6$ only exhibits limited expression in the retina (Crupi et al., 2019). $mGlu_7$ expression has been reported in the amygdala, hypothalamus, hippocampus, thalamus, and locus coeruleus (Ngomba et al., 2011). Similar to group II mGlu receptors, group III mGlu receptor subtypes are most commonly located in or near presynaptic active zones of GABAergic and glutamatergic neuronal cells (Shigemoto et al., 1997; Ferraguti and Shigemoto, 2006). Activation of group III mGlu receptors inhibits the release of neurotransmitters, such as glutamate, GABA, and dopamine, via modulation of a variety of ion channels and G$\beta\gamma$ subunit-dependent inhibition of vesicular fusion (Cartmell and Schoepp, 2000).

Until recent advances in group III mGlu receptor subtype-selective pharmacological compounds, most of the research pertaining to group III mGlu receptors used the broad-spectrum agonist, L-2-amino-4-phosphonobutyric acid (L-AP4). A multitude of studies have shown that L-AP4 reduces excitatory transmission in numerous brain regions, including the hippocampus, amygdala, striatum, globus pallidus, thalamus, hypothalamus, cerebellum, NAc, and substantia nigra (Mercier and Lodge, 2014). Application of L-AP4 typically increases paired-pulse ratio (Harris and Cotman, 1983; Manzoni et al., 1997; Lorez et al., 2003), and its application has also been shown to reduce the frequency, but not the amplitude, of miniature excitatory postsynaptic events (Harris and Cotman, 1983; Gereau and Conn, 1995; Manzoni et al., 1997; Schoppa and Westbrook, 1997; Schrader and Tasker, 1997), both of which indicate the role of group III mGlu receptors as presynaptic autoreceptors in the CNS. Group III mGlu receptors are also involved in the regulation of GABA and monoamine neurotransmission (Cartmell and Schoepp, 2000; Schoepp, 2001). In addition to its ability to regulate glutamate release, L-AP4 has been found to reduce inhibitory transmission in many brain regions, including the midbrain, globus pallidus, striatum, thalamus, and hippocampus (Mercier and Lodge, 2014). Importantly, hippocampal electrophysiological studies bolstered evidence for the localization of group III mGlu receptors on both glutamate and GABA terminals, such that L-AP4 has reduced both excitatory and inhibitory transmission onto hippocampal interneurons and pyramidal cells (Semyanov and Kullmann, 2000; Kogo et al., 2004; Klar et al., 2015). The critical role of group III mGlu receptors on interneurons highlights their utility in regulating the balance of excitation and inhibition of these cells, thus regulating overall network excitability (Ferraguti and Shigemoto, 2006; Klar et al., 2015).

A multitude of studies have leveraged selective pharmacological tools and transgenic knockout lines to determine the roles of group III mGlu receptors in long-term synaptic plasticity. For instance, application of α-Cyclopropyl-4-phosphonophenylglycine (CPPG), the group III mGlu receptor antagonist, prevents LTD, but not LTP, in the CA1 region of mice (Altinbilek and Manahan-Vaughan, 2007). However, the development of selective pharmacological and genetic tools has provided additional insight to the role of Group III mGlu receptor subtypes in long-term synaptic plasticity. A recent study shows that inhibition of group III mGlu receptors elicit an NMDA receptor-dependent LTP in SC-CA2 synapses (Dasgupta et al., 2020). Further, disinhibition produced by activation of $mGlu_7$ induces LTP at SC-CA1 synapses in the hippocampus (Klar et al., 2015). Interestingly, one study using $mGlu_4$ knockout mice found enhanced LTP in hippocampal CA1 region but not in the PFC compared with wild-type controls (Iscru et al., 2013). Other studies have shown that mGlu receptor-dependent LTD can be induced after activation of $mGlu_7$ (Bellone et al., 2008). Together, these demonstrate critical roles of group III mGlu receptor subtypes in regulating various forms of long-term synaptic plasticity in brain regions and circuits dysregulated in neuropsychiatric disease.

## II. Targeting Metabotropic Glutamate Receptors for the Treatment of Neuropsychiatric Disease

### *A. Metabotropic Glutamate Receptor Allosteric Modulators*

The vast diversity and distribution of mGlu receptors provides an unparalleled opportunity for selective targeting of individual mGlu receptor subtypes as novel treatment strategies for neuropsychiatric and neurologic disorders. However, longstanding efforts to develop ligands that target mGlu receptors have largely focused on agonists and antagonists that interact with the orthosteric glutamate binding sites of these receptors to mimic or block the endogenous actions of glutamate. Although this strategy has proven to be somewhat fruitful, the high conservation of orthosteric binding sites across receptor subtypes has served as a critical barrier to the development of subtype-selective orthosteric ligands. To address this issue, recent efforts have been focused on developing allosteric modulators for mGlu receptor subtypes. Allosteric modulators act by altering the receptor conformational state by binding a topographically distinct nonorthosteric site, typically found within the HD of mGlu receptors (Wu et al., 2014). Thus, allosteric modulators potentiate or attenuate the response to the endogenous orthosteric ligand (i.e., glutamate for mGlu receptors) without activating the receptor directly. Allosteric modulators can be categorized based on the direction that they modulate the response to the orthosteric agonist. For instance, allosteric modulators that increase the functional response to an orthosteric agonist are referred to as "positive allosteric modulators." In contrast, those that attenuate the functional response to the orthosteric agonist are coined "negative allosteric modulators" (NAMs). If a compound binds to an orthosteric site without inducing effects on the response of the receptor, it is called a "neutral allosteric ligand" (Conn et al., 2009). In functional assays, such as those that measure calcium mobilization or downstream signaling (e.g., cAMP accumulation), the presence of a PAM often induces a leftward shift of the agonist concentration–response curve, whereas a NAM decreases the maximal effect of the response. In addition to this modulatory activity, a subset of allosteric modulators possesses intrinsic activity and can both potentiate agonist responses and directly activate the receptor (ago-PAMs). In sum, allosteric modulators display a number of the following pharmacological properties: 1) efficacy modulation, the signaling capacity (or "intrinsic efficacy") of an orthosteric agent can be modified via alterations in intracellular responses; 2) affinity modulation, the conformational change induced by binding of the allosteric ligand alters the binding pocket and association/dissociation rates of orthosteric ligands; and 3) agonism/inverse agonism, receptor signaling is altered either positively (agonism) or negatively (inverse agonism) by the allosteric modulator, irrespective of the presence or absence of an orthosteric ligand.

### *B. Advantages of Metabotropic Glutamate Allosteric Modulators*

Allosteric modulators provide several advantages as potential pharmacotherapies and experimental tools in comparison with orthosteric ligands. For example, orthosteric ligand binding sites often possess a high degree of sequence homology, which presents a challenge for the development of receptor subtype-specific ligands. In contrast, allosteric ligand binding sites are often less highly conserved than orthosteric sites, allowing for the development of highly selective allosteric modulators for receptor subtypes that, formerly, have been intractable using traditional approaches (Conn et al., 2009; Nussinov et al., 2011). Additionally, differential receptor cooperativity serves as a means of subtype selectivity. The cooperativity between orthosteric and allosteric sites is not correlated with the affinity of allosteric modulators for their binding sites, and, thus, allows some allosteric modulators to bind to more than one receptor subtype with similar affinities but elicit effects through distinct cooperativity between receptor subtypes (Boehr et al., 2009; Tsai et al., 2009).

One shortcoming of orthosteric agonists targeting mGlu receptors is the risk of receptor overactivation,

which can disrupt brain circuit modulation and result in adverse side effects (Sendt et al., 2012; Rook et al., 2013). This challenge is more effectively circumvented by allosteric modulators with their ability to fine-tune active synapses versus nonphysiological activation of synapses that display low glutamatergic tone. This allows for regulation of receptor responses in brain areas where the endogenous agonist exerts its physiologic effect, reducing the risk for off target or overactivation. For instance, $mGlu_5$ agonists can induce epileptic seizure activity (Tizzano et al., 1995) This effect is also observed with allosteric agonists but is mitigated by administration of $mGlu_5$ PAMs that lack agonist activity (Rook et al., 2015; Gould et al., 2016). This requirement for the presence of the endogenous agonist provides spatial and temporal control of allosteric modulators and provide a sizable therapeutic edge by allowing for physiologically appropriate modulation of synaptic signaling and transmission.

In addition to serving as novel treatment strategies, these ligands are essential to driving fundamental investigation into the roles of specific signaling pathways and distinct receptors in modulating identified neural circuits and behavior under physiologic and pathologic conditions. Allosteric modulators of mGlu receptor subtypes are now being pursued as potential drug candidates for numerous neuropsychiatric diseases, including Alzheimer's disease, Parkinson's disease, dystonia, schizophrenia, SUDs, and other brain diseases (Conn et al., 2009; O'Brien and Conn, 2016; Foster and Conn, 2017; Maksymetz et al., 2017; Joffe and Conn, 2019; Stansley and Conn, 2019). The present review will summarize the current findings on the efficacy of mGlu receptor subtype PAMs/NAMs for the treatment of neuropsychiatric diseases, with particular focus on schizophrenia and SUDs.

## III. Potential of Allosteric Modulators of Metabotropic Glutamate Receptors for Treating Neuropsychiatric Disease

### *A. Schizophrenia*

Schizophrenia is a chronic neuropsychiatric disorder that affects approximately 1% of the world population (GBD 2019 Diseases and Injuries Collaborators, 2020). The disease is characterized by three primary clusters of symptoms: positive (auditory/visual hallucinations), negative (amotivation, anhedonia, social withdrawal), and cognitive deficits (working memory, executive function, attention). Current antipsychotic medications effectively treat the positive symptoms of the disease, such as auditory and visual hallucinations, disorganized thoughts, and delusions; however, they do not improve the negative or cognitive symptoms. Negative symptoms (e.g., flattened affect, social withdrawal) and cognitive symptoms (e.g., deficits in attention, working memory, and cognitive flexibility) are believed to be the best predictors of long-term treatment outcome (Green, 1996; Bobes et al., 2007; McEvoy, 2007). Furthermore, many patients discontinue treatment due to adverse effects, such as extrapyramidal side effects (EPS) (i.e., tardive dyskinesia, tremor, dystonia, and bradykinesia) induced by typical antipsychotics as well as a host of metabolic side effects (i.e., weight gain, hyperlipidosis, and type II diabetes) elicited most commonly by atypical antipsychotics (Lieberman et al., 2005; Meltzer, 2013; Lally and MacCabe, 2015). Therefore, development of improved therapeutic options that mitigate a broader range of symptoms of schizophrenia and are devoid of EPS is of great need.

Our current understanding of the neurochemical alterations driving the symptoms associated with schizophrenia is largely attributed to two major lines of research that are driven by the dopamine and glutamate hypotheses of schizophrenia-related dysfunction (Howes et al., 2015; McCutcheon et al., 2019). The dopamine hypothesis posits that the positive symptoms of the disease are largely driven by aberrant dopamine signaling. This notion is supported by evidence that amphetamine and other dopamine-releasing agents induce symptoms that resemble those of the positive symptoms of schizophrenia (Steeds et al., 2015; Kesby et al., 2018). Further, currently available antipsychotic medications largely target the dopamine system and act, in part, by inhibiting dopamine D2 subtype of dopamine receptors (Meltzer, 2013). In support of this model, in vivo neuroimaging studies show increased subcortical dopamine release after amphetamine challenge in individuals with schizophrenia (Laruelle et al., 1996; Breier et al., 1997; Abi-Dargham et al., 1998). However, since amphetamine exposure exacerbates only the positive symptoms of schizophrenia and dopamine-targeting antipsychotic medications only alleviate positive symptoms, dopaminergic hyperactivity alone cannot account for the negative symptoms or cognitive disturbances observed in patients with schizophrenia (Carlsson, 1988).

Another prominent line of research suggests that disruption of glutamate signaling underlies numerous symptoms of schizophrenia. This notion is derived from extensive evidence that NMDA antagonists, such as PCP, ketamine and dizocilpine (MK-801), induce symptoms closely resembling those of schizophrenia (Javitt and Zukin, 1991). In addition, administration of NMDAR antagonists exacerbates or induces controlled symptoms when administered to schizophrenia patients (Krystal et al., 1994). These findings, in addition to a wealth of preclinical evidence, support the hypothesis that NMDAR hypofunction contributes to the pathophysiology underlying schizophrenia. Thus, pharmacological agents that enhance NMDAR function represent a potential

TABLE 2
Summary of preclinical efficacy of group I mGlu receptor allosteric modulators in schizophrenia-related deficits

| Receptor | Type | Compound | Positive Symptom Models | Negative Symptoms Models | Cognitive Models | References |
|---|---|---|---|---|---|---|
| $mGlu_1$ | PAM | VU0483605 | No effect on AHL | | | Cho et al., 2014 |
| | | VU6004909 | Attenuates AMPH-induced hyperlocomotion and disruptions in PPI | No effect on PR | | Yohn et al., 2020 |
| | NAM | FTIDC | Attenuates MHL and PPI deficits | | | Satow et al., 2009 |
| | | CFMTI | Reduced MHL and NMDAR antagonist-induced hyperlocomotion (NMDAR-HL)<br>Ameliorated METH and ketamine-disrupted PPI | Reversal of MK-801-disrupted social interaction | No effect on object location memory | Satow et al., 2008 |
| $mGlu_5$ | PAM | CDPPB | Attenuated AMPH-induced hyperlocomotion and deficits in PPI[a,b] | Attenuated MK-801-induced decrease in sucrose preference[c] | ↑Morris water maze learning[d]<br>↓MK-801 deficits in cognitive flexibility[e]<br>↓PCP deficits in NOR[f] | (See footnotes.) |
| | | 5PAM523 | Reduced AHL[g,h] and NMDAR-HL[h] | | ↑Contextual CF[2]<br>↑NOR[h] | (See footnotes.) |
| | | VU0409551 | Reverses MK-801-induced hyperlocomotion | | ↑Working memory/ executive function in the DNMTP task<br>↑contextual CF deficits in $SR^{-/-}$ mice | Rook et al., 2015 |

AHL, amphetamine-induced hyperlocomotion; AMPH, amphetamine; CF, fear conditioning; DNMTP, delayed nonmatching to position; HL, hyperlocomotion; METH, methamphetamine; MHL, METH-induced hyperlocomotion; NOR, novel object recognition; SR, serine racemase-deficient.
[a]Kinney et al., 2003.
[b]Lindsley et al., 2005.
[c]Vardigan et al., 2010.
[d]Ayala et al., 2009.
[e]Stefani and Moghaddam, 2010.
[f]Horio et al., 2013.
[g]Parmentier-Batteur et al., 2014.
[h]Rook et al., 2015.

strategy that could provide therapeutic benefits to patients with schizophrenia. However, a primary obstacle is that overactivation of NMDARs using traditional orthosteric agonists induces adverse effects, such as excitotoxicity and seizures (Zeron et al., 2002; Kaufman et al., 2012; Monaghan et al., 2012; Puddifoot et al., 2012). Importantly, mGlu receptors are critical modulators of NMDAR function and regulate glutamate and GABA neurotransmission throughout the CNS (Niswender and Conn, 2010; Maksymetz et al., 2017). Therefore, pharmacological modulation of mGlu receptors holds the potential to alter NMDAR function and restore excitatory and inhibitory neurotransmission to provide therapeutic benefit in patients with schizophrenia. To this end, allosteric modulators targeting all three groups of mGlu receptors have been pursued as putative targets for novel antipsychotics (Tables 2–4).

*I. Group I: Metabotropic Glutamate$_{1/5}$.* The $mGlu_1$ receptor subtype shows promise as a potential therapeutic target for treating schizophrenia. Genetic studies in humans reveal an association of the human gene encoding $mGlu_1$ (*GRM1*) and, specifically, loss of function single nucleotide polymorphisms in *GRM1* with schizophrenia, raising the possibility that $mGlu_1$ signaling is critical to the function of brain circuits underlying symptoms associated with this disorder (Ayalew et al., 2012; Ayoub et al., 2012; Cho et al., 2014). Numerous studies have characterized the pivotal role of $mGlu_1$ in regulating GABA and glutamate signaling in the PFC as well as striatal dopamine dynamics. The development of $mGlu_1$ PAMs and transgenic mouse lines have allowed for these discoveries. Potent first-generation $mGlu_1$ PAMs were developed in the early 2000s; however, they displayed poor pharmacokinetic and metabolic profiles, limiting their use in preclinical studies (Knoflach et al., 2001; Vieira et al., 2005). More recent efforts yielded $mGlu_1$ PAMs, such as VU 6000799, VU6000790, and VU6004909 as potent, highly selective $mGlu_1$ PAMs with improved drug metabolism and pharmacokinetic (DMPK) properties and brain penetrance and are therefore better suited for in vivo studies (Garcia-Barrantes et al., 2015, 2016a,b,c). Recent studies have leveraged these improved $mGlu_1$ PAMs and have yielded promising results. For instance, Yohn et al., showed that activation of $mGlu_1$ negatively regulates striatal dopamine release through an intricate mechanism involving coactivation of

TABLE 3
Summary of preclinical efficacy of group II mGlu receptor allosteric modulators in schizophrenia-related deficits

| Receptor | Type | Compound | Positive Symptom Models | Negative Symptoms Models | Cognitive Models | References |
|---|---|---|---|---|---|---|
| $mGlu_2$ | PAM | LY487379 | Reduced NMDAR-HL and AHL;[a] attenuated AMPH but not PCP-disrupted PPI[a] | Reduced PCP-induced deficits in social interaction[b] | Promoted cognitive flexibility in ASST[c] | (See footnotes.) |
| | | BINA | Reduced NMDAR-HL;[d,f] no effect on AHL;[d] reduced PCP-disrupted PPI;[d] reduced DOB-induced head twitches[e] | Reduced MK-801-induced increased immobility in the FST[f] | | (See footnotes.) |
| | | TASP0443294 | Reduced MHL[g] and NMDAR-HL[h] | Rescued MK-801-induced social memory deficits[g] | | (See footnotes.) |
| | | JNJ-40411813/ ADX71149 | Reduced NMDAR-HL; no effect on AHL; inhibited DOM-induced head twitches | | | Lavreysen et al., 2015 |
| | | SAR 218645 | No effect on NMDAR-HL or AHL; no effect on hyperactivity in $DAT^{-/-}$ and NR1neo $^{-/-}$ mice; reduced DOI-induced head twitches | | Reversed MK-801-induced deficits in NOR; attenuated working memory deficits in Y-maze test in $NR1neo^{-/-}$ mice | Griebel et al., 2016 |
| $mGlu_3$ | NAM | VU0477950 | | | Dose-dependent impairment in extinction learning | Walker et al., 2015 |
| | | VU0650786 | | | Blocked the ability of mGlu2/3 agonists to restore trace fear conditioning after PCP administration | Dogra et al., 2021 |

AHL, amphetamine-induced hyperlocomotion; AMPH, amphetamine; ASST, attentional set-shift task; DAT, dopamine transporter; DOB, dimethoxy-bromoamphetamine; HL, hyperlocomotion; METH, methamphetamine; MHL, METH-induced hyperlocomotion; NOR, novel object recognition; NR1neo, NR1 subunit reduced expression.
[a]Galici et al., 2005.
[b]Harich et al., 2007.
[c]Nikiforuk et al., 2010.
[d]Galici et al., 2006.
[e]Benneyworth et al., 2007.
[f]Kawaura et al., 2016.
[g]Hikichi et al., 2015.
[h]Lavreysen et al., 2015.

muscarinic acetylcholine subtype 4 (M4) receptors and retrograde endocannabinoid signaling (Yohn et al., 2020). Additionally, a recent study has characterized the critical role of $mGlu_1$ receptors located on SST-INs of the prelimbic PFC in regulating inhibitory output onto glutamatergic pyramidal cells, highlighting $mGlu_1$ as a critical determinant of inhibitory/excitatory balance in the PFC (Maksymetz et al., 2021). The ability to normalize both dopamine and GABA dysfunction highlights $mGlu_1$ as a promising target to comprehensively treat symptomology associated with schizophrenia. Importantly, $mGlu_1$ PAMs show robust antipsychotic-like efficacy in rodent models. Specifically, the $mGlu_1$ PAM VU6004909 reverses amphetamine-induced hyperlocomotion and deficits in prepulse inhibition (PPI) induced by amphetamine treatment (Yohn et al., 2020). Furthermore, $mGu_1$ PAMs show promising cognitive-restoring effects in rodent models. A recent study demonstrates that $mGlu_1$ PAM VU6004909 reverses deficits in spatial working memory induced by NMDAR antagonist, MK-801 (Maksymetz et al., 2021). In addition to the potential of $mGlu_1$ PAMs in treating schizophrenia, $mGlu_1$ NAMs 4-[1-(2-fluoropyridin-3-yl)-5-methyl-1H-1,2,3-triazol-4-yl]-N-isopropyl-N-methyl-3,6-dihydropyridine-1(2H)-carboxamide (FTIDC) and 2-cyclopropyl-5-[1-(2-fluoro-3-pyridinyl)-5-methyl-1H-1,2,3-triazol-4-yl]-2,3-dihydro-1H-isoindol-1-one (CFMTI) have displayed efficacy in animal models of antipsychotic activity (Table 2), such as decreasing NMDAR antagonist and psychostimulant-induced hyperlocomotion and deficits in PPI as well as reversing social interaction deficits elicited by MK-801, an NMDAR antagonist, in rats (Satow et al., 2008, 2009). The contrasting findings of $mGlu_1$ PAMs and NAMs illustrate the potential complexity of $mGlu_1$-targeting ligands and suggest that $mGlu_1$ PAMs may primarily be effective in patients carrying *GRM1* mutations. Considering these exciting findings, continued interrogation is

TABLE 4
Summary of preclinical efficacy of group III mGlu receptor allosteric modulators in schizophrenia-related deficits

| Receptor | Type | Compound | Positive Symptom Models | Negative Symptoms Models | Cognitive Models | References |
|---|---|---|---|---|---|---|
| $mGlu_4$ | PAM | ADX88178 | Reduced NMDAR-HL; reduced DOI-induced head twitches | Reduced immobility in FST | | Kalinichev et al., 2014 |
| | | Lu AF21934 | Reduced NMDAR-HL and AHL;[a] reduced DOI-induced head twitches[a] | Reduced MK-801-induced deficits in social interaction[a] | Rescued MK-801-induced deficits in the delayed spatial alternation task;[a] reduced MK-801-induced deficits in NOR | (See footnotes.) |
| | | Lu AF32615 | Reduced NMDAR-HL and AHL; reduced DOI-induced head twitches | Reversed MK-801-induced deficits in social interaction | Reversed MK-801-induced deficits in the delayed spatial alternation task | Sławińska et al., 2013 |
| $mGlu_7$ | Ago-PAM | AMN082 | No effect on AHL; exacerbated NMDAR-HL;[b] exacerbated DOI-induced head twitches[c] | | | (See footnotes.) |
| | NAM | MMPIP ADX71743 | Inhibited MK-801-induced hyperactivity and reversed deficits in PPI | | Reversed MK-801-induced deficits in NOR and spatial delayed alternation | Cieślik et al., 2018 |

AHL, amphetamine-induced hyperlocomotion; HL, hyperlocomotion; NOR, novel object recognition.
[a]Sławińska et al., 2013.
[b]Mitsukawa et al., 2005.
[c]Wierońska et al., 2012a.

required to determine the efficacy of $mGlu_1$ PAMs and NAMs in nonhuman primate and clinical studies.

$mGlu_5$ also represents an exciting target for the treatment of schizophrenia and improving cognitive function in multiple brain disorders (Foster and Conn, 2017; Nicoletti et al., 2019). Extensive research supports a bidirectional interaction between $mGlu_5$ and NMDARs, such that activation of $mGlu_5$ receptors facilitates NMDAR function (Doherty et al., 1997; Ugolini et al., 1999; Awad et al., 2000; Attucci et al., 2001; Mannaioni et al., 2001; Pisani et al., 2001), whereas activation of NMDARs amplifies $mGlu_5$ receptor activity by restraining receptor desensitization (Alagarsamy et al., 2005). These observations serve as a foundation for the development of $mGlu_5$ PAMs for the treatment of schizophrenia. A number of $mGlu_5$ PAMs have demonstrated efficacy in rodent models used to predict antipsychotic efficacy and the treatment of cognitive disturbances (Kinney et al., 2003; Lecourtier et al., 2007; Liu et al., 2008; Conn et al., 2009; Stefani and Moghaddam, 2010; Vardigan et al., 2010; Gastambide et al., 2013; Horio et al., 2013; Nicoletti et al., 2019). However, one caveat of $mGlu_5$ PAMs includes excitotoxicity mediated by the enhanced NMDAR activity, as high doses of $mGlu_5$ receptor PAMs have been shown to induce seizures and neurotoxicity in rodents (Parmentier-Batteur et al., 2014; Rook et al., 2015; Conde-Ceide et al., 2016). To circumvent these adverse side effects, biased $mGlu_5$ receptor PAMs have been developed to amplify receptor function without recruiting NMDA receptors (Rook et al., 2013, 2015). Interestingly, these biased $mGlu_5$ PAMs have robust efficacy in animal models without potentiating NMDA receptor signaling (Rook et al., 2015; Gould et al., 2016), suggesting that efficacy of these compounds is not mediated by potentiation of NMDA receptor currents. Thus, leveraging this biased $mGlu_5$ PAM, VU0409551, Rook et al. have shown antipsychotic-like activity and precognitive efficacy without activating NMDA receptors and without inducing the adverse effects of nonbiased $mGlu_5$ PAMs (Rook et al., 2015).

*II. Group II: Metabotropic Glutamate$_{2/3}$.* Based on evidence that activation of group II mGlu receptor subtypes, $mGlu_2$ and $mGlu_3$, produce robust antipsychotic-like effects in preclinical models (Chaki et al., 2004; Pilc et al., 2008; Conn et al., 2009; Dhanya et al., 2014; Muguruza et al., 2016), longstanding efforts have been aimed at optimizing $mGlu_2$ and $mGlu_3$ agonists for the treatment of schizophrenia. Despite group II mGlu receptor agonists showing efficacy in improving positive and negative symptoms in an initial phase II trial (Patil et al., 2007), larger clinical studies did not demonstrate significant efficacy of these compounds compared with placebo (Kinon et al., 2011). The development of highly selective allosteric modulators of $mGlu_2$ and $mGlu_3$ have allowed for delineation of the role of these receptor subtypes in the physiologic and behavioral deficits associated with schizophrenia (Table 3)

with hopes of developing improved treatments for schizophrenia. Interestingly, preclinical studies have alluded to $mGlu_2$ activation being sufficient to provide therapeutic benefit, such that the antipsychotic-like activity of group II mGlu receptor agonists are absent in $mGlu_2$, but not $mGlu_3$, receptor knockout mice (Spooren et al., 2000). These observations have been bolstered by the discovery of $mGlu_2$-selective PAMs, which allowed for direct interrogation of this hypothesis. Several $mGlu_2$ PAMs demonstrated antipsychotic-like efficacy as well as precognitive and social effects in multiple preclinical models (Galici et al., 2005, 2006; Harich et al., 2007; Nikiforuk et al., 2010; Griebel et al., 2016). For example, administration of the $mGlu_2$ PAM, potassium 3′-([(2-cyclopentyl-6-7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl l-4-carboxylate (BINA), reduced dimethoxy-bromoamphetamine–induced head twitches and reversed MK-801-induced immobility in the forced swim test (FST) (Benneyworth et al., 2007; Kawaura et al., 2016). Additionally, (2S)-5-methyl-2-{[4-(1,1,1-trifluoro-2-methylpropan-2-yl)phenoxy]methyl}-2,3-dihydroimidazo[2,1-b][1,3]oxazole-6-carboxamid (TASP0443294), another $mGlu_2$ PAM, showed efficacy in reducing methamphetamine and NMDAR antagonist-induced hyperlocomotion as well as reversed social memory deficits induced by MK-801 administration in mice (Hikichi et al., 2015; Lavreysen et al., 2015). Two primary $mGlu_2$ PAMs moved forward to clinical testing; however, the $mGlu_2$ PAM AZD 8529 did not significantly improve positive or negative symptoms in patients with schizophrenia when administered as a monotherapy (Litman et al., 2016). Alternatively, another $mGlu_2$ PAM, JNJ-40411813/ADX71149, showed beneficial effects in patients with residual negative symptoms (Hopkins, 2013) and potential efficacy in reversing select cognitive deficits and negative symptoms after administration of ketamine in healthy volunteers (Salih et al., 2015). However, negative phase 2 schizophrenia clinical trials with JNJ-40411813/AZD8529 has tempered expectations on the utility of $mGlu_2$ PAMs for the treatment of schizophrenia. The ongoing efficacy of this compound in large-scale clinical trials remains to be seen.

In addition to the wealth of research on $mGlu_2$-selective PAMs, numerous studies have indicated a relationship between decreased performance PFC-dependent cognitive tasks and single nucleotide polymorphisms in the human gene encoding $mGlu_3$ (*GRM3*) (Egan et al., 2004; Tan et al., 2007; Harrison et al., 2008), identifying *GRM3* as a risk locus for schizophrenia in genome-wide association studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). After the discovery of highly selective $mGlu_3$ NAMs, studies in mice revealed that $mGlu_3$ mediates distinct aspects of PFC synaptic plasticity and procognitive effects in rodents (Walker et al., 2015; Dogra et al., 2021). In agreement with these findings, studies in nonhuman primates have demonstrated that $mGlu_{2/3}$ agonists elicit postsynaptic effects in the dorsolateral PFC that improve cognitive function (Jin et al., 2017). Together, these studies highlight $mGlu_3$ as a novel regulator of PFC-mediated cognitive processes. Additional investigation using current and next-generation group II mGlu receptor PAMs/NAMs is essential for expanding our understanding of these receptors and their potential utility in treating schizophrenia.

*III. Group III: Metabotropic Glutamate$_{4/6/7/8}$.* Like group II mGlu receptors, the therapeutic promise of group III mGlu receptors arose from evidence of their ability to improve the hyperglutamatergic state believed to take place in schizophrenia and modulate behavioral processes dysregulated in the disease, including cognition and motivation. For instance, mice lacking $mGlu_4$ display impairments in spatial reversal and long-term memory (Gerlai et al., 1998), suggesting a critical role of $mGlu_4$ in cognitive flexibility and associative learning, both of which are known to be impaired in patients with schizophrenia. Previous studies also suggest that $mGlu_4$ activation may elicit antipsychotic-like effects in rodent models. In one study, the group III agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) reduced PCP- and amphetamine-induced hyperlocomotion in addition to head twitching in response to 2,5-Dimethoxy-4-iodoamphetamine (DOI) (Pałucha-Poniewiera et al., 2008). Similar actions of ACPT-I administration are also observed with $mGlu_4$-selective orthosteric agonists, LSP 1-2111 (Wierońska et al., 2012a) and LSP4-2022 (Woźniak et al., 2016). Activation of $mGlu_4$ receptors with these compounds also improves behavioral deficits associated with negative and cognitive symptoms of schizophrenia (Wierońska et al., 2012a; Woźniak et al., 2016). More recently, $mGlu_4$ PAMs Lu AF 21934 (Bennouar et al., 2013), Lu AF32615 (East et al., 2010), and ADX88178 (Le Poul et al., 2012) have also displayed similar outcomes in models of representing all three symptom clusters of schizophrenia (Table 4). For example, ADX88178, an $mGlu_4$ PAM, was shown to reduce NMDAR antagonist-induced hyperlocomotion and DOI-induced head twitches while also reducing immobility time in FST (Kalinichev et al., 2014). Alternatively, the $mGlu_4$ PAMs, Lu AF21934 and Lu AF32615, showed efficacy in restoring social interaction, reducing hyperlocomotion induced by amphetamine and NMDAR antagonists, and rescuing MK-801-induced deficits in spatial working memory and novel object recognition (Wierońska et al., 2012a; Sławińska et al., 2013a). Together, these studies highlight the potential therapeutic utility of selective $mGlu_4$ activators for schizophrenia.

Despite limited studies focusing on the $mGlu_7$ receptor subtype as a potential therapeutic target for schizophrenia, a polymorphism in the *GRM7* gene encoding $mGlu_7$ that decreased transcription in vitro was positively

correlated with schizophrenia in a large Japanese cohort (Ohtsuki et al., 2008). These findings suggest that hypofunction of $mGlu_7$ may contribute to the pathophysiology of schizophrenia. Because activation of $mGlu_7$ reduces glutamatergic neurotransmission (Baskys and Malenka, 1991; Ayala et al., 2008) and acts as a heteroreceptor to modulate GABA release and the induction of LTP in brain regions, such as the hippocampus (Klar et al., 2015), it is plausible that selective activators of $mGlu_7$ may enhance aspects of hippocampal-dependent cognitive function. However, some preclinical studies refute this hypothesis such that the $mGlu_7$ allosteric agonist N,N'-dibenzhydrylethane-1,2-diamine dihydrochloride (AMN082) exacerbates MK-801-induced hyperlocomotion (Mitsukawa et al., 2005) and DOI-induced head twitches (Wierońska et al., 2012a). Although these findings may be driven by off-target effects of AMN082 in vivo (Sukoff Rizzo et al., 2011), it has been shown that the psychotic-enhancing effects were occluded in $mGlu_7$ knockout (KO) mice (Wierońska et al., 2012a), implying that they may be $mGlu_7$ receptor-dependent. At this time, future studies must further confirm if the use of selective PAMs may show more promise of $mGlu_7$ activation in schizophrenia-related models.

Although expressed at fairly low levels in the brain, the $mGlu_8$ receptor subtype is expressed in the presynaptic active zone of mainly glutamatergic synapses (Kinoshita et al., 1996a; Shigemoto et al., 1997) where it functions to modulate neurotransmitter release and gates glutamatergic transmission into the hippocampus (Zhai et al., 2002). In line with this function, $mGlu_8$ KO mice display deficits in hippocampal-dependent learning (Gerlai et al., 2002), suggesting that activating $mGlu_8$ with selective ligands could treat the cognitive impairments in patients with schizophrenia. In studies determining the antipsychotic efficacy of $mGlu_8$-targeting ligands, two studies have found that the relatively selective orthosteric $mGlu_8$ agonist (S)-3,4-dichlorophenyl glycine ((S)-3, 4-DCPG) was unable to reverse amphetamine or PCP-induced hyperactivity in Sprague-Dawley rats (Thomas et al., 2001; Robbins et al., 2007). Additionally, $mGlu_8$ KO mice do not display significant deficits in PPI of acoustic startle; thus, it appears to be unlikely that $mGlu_8$ is a promising target for a novel antipsychotic (Robbins et al., 2007). Despite lacking evidence for antipsychotic efficacy, continued studies are required to determine the utility of $mGlu_8$-targeting compounds as cognitive enhancers.

### *B. Substance Use Disorders*

SUD is a multifaceted chronically relapsing disorder characterized by excessive drug intake, repeated unsuccessful attempts to reduce or stop drug use, enhanced drug-seeking and self-administration, the emergence of drug tolerance and withdrawal, and continued drug intake despite negative consequences (Koob and Volkow, 2010). SUD represents a serious public health problem with devastating consequences to society. However, there is a lack of pharmacological agents approved to treat the disease. Drugs of abuse exert their effects by altering the signaling of numerous neurotransmitter systems and brain circuits, which serves as a challenge for developing efficacious treatments. Ongoing research highlights detrimental adaptations in GABA and glutamate neurotransmission in SUD (Tzschentke and Schmidt, 2003; Cruz et al., 2008). Drugs of abuse alter glutamate transmission through a diverse array of mechanisms. For example, cocaine increases glutamate transmission indirectly through dopamine transporter-mediated dopamine release (Ritz et al., 1987). Alternatively, it has been reported that alcohol inhibits postsynaptic NMDAR- and non-NMDAR-mediated glutamate transmission and release, possibly via inhibition of GABA interneurons (Lovinger et al., 1989, 1990; Carta et al., 2003; Hendricson et al., 2003, 2004). Notably, imbalance of glutamate and GABA systems in brain regions, such as the PFC, is associated with physiologic and behavioral aspects of SUDs, including impulsivity, reinforcement learning, and executive function. For instance, a recent clinical study using hydrogen ($^1$H)-magnetic resonance spectroscopy revealed significantly higher glutamate levels and lower GABA levels in patients with opioid use disorder compared with healthy controls (Li et al., 2020). Additionally, this study showed that higher impulsivity and cognitive impairment were associated with lower GABA and higher glutamate levels. Furthermore, exposure to pharmacological agents that block glutamate transmission attenuate the reinforcing effects of drugs of abuse. For instance, systemic administration of NMDAR antagonists attenuates self-administration of alcohol (Shelton and Balster, 1997), cocaine (Pierce et al., 1997; Pulvirenti et al., 1997; Hyytiä et al., 1999; Blokhina et al., 2005), and nicotine (Kenny et al., 2009). Therefore, restoring GABA and glutamate balance in PFC, among other brain regions, represents a promising therapeutic strategy for treating SUD.

Numerous medications targeting GABA and/or glutamate receptors have been under longstanding investigation for the treatment of SUD, including baclofen, topiramate, and gabapentin. However, to date, there has been mixed evidence for their efficacy in clinical trials for various types of SUDs, including alcohol, nicotine, cocaine, and methamphetamine (Addolorato et al., 2012). One of the well-studied candidates, baclofen, a $GABA_B$ agonist, has yielded findings in preclinical and clinical studies suggesting its potential utility in treating alcohol use disorder. Baclofen acts presynaptically to hyperpolarize synaptic terminals, inhibits calcium influx, and prevents the release of the excitatory neurotransmitters glutamate and aspartate

(Davidoff, 1985). Preclinical studies show that baclofen effectively mitigates the reinforcing properties of alcohol in addition to suppressing acquisition and maintenance of alcohol drinking behavior and relapse-like drinking in rats and mice (Cousins et al., 2002; Maccioni and Colombo, 2009). Alternatively, baclofen has also been tested as a treatment of cocaine use disorder. A human brain imaging study found that baclofen reduces the activation of limbic brain regions that occurs in response to cocaine-related cues (Brebner et al., 2002). Baclofen has undergone numerous clinical trials for the treatment of cocaine use disorder; however, these studies have yielded mixed results with the first human open-label study showing a trend toward reduced cocaine craving and self-reported cocaine consumption (Ling et al., 1998), but subsequent, larger studies have not identified statistically significant effects of baclofen on craving or cocaine intake (Shoptaw et al., 2003). In addition to the studies detailed here, baclofen and other GABA-targeting drugs, such as gabapentin, have been tested for efficacy in treating nicotine and methamphetamine use disorders. Together, these studies shed light on the potential utility of activating GABA systems for the treatment of SUDs; however, more effective compounds are required to better achieve this goal.

A wealth of studies using ligands targeting mGlu receptors has demonstrated the utility of targeting these receptors as an alternative approach to mitigate SUD-induced imbalances in glutamate and GABA signaling. For example, systemic administration of LY379268, an $mGlu_{2/3}$ orthosteric agonist, decreases self-administration of cocaine (Baptista et al., 2004; Adewale et al., 2006; Xi et al., 2010), nicotine (Liechti et al., 2007), and alcohol (Bäckström and Hyytiä, 2005; Sidhpura et al., 2010). However, excessive glutamate release, a potential consequence direct activation of mGlu receptors, including $mGlu_5$, elicits excitotoxicity via NMDAR-mediated mechanisms, limiting the utility of orthosteric mGlu-targeting compounds (Reiner and Levitz, 2018). Thus, allosteric modulators of mGlu receptors represent a novel avenue for restoring homeostasis of GABA and glutamate systems while exerting receptor subtype selects effects and circumventing EPS.

*I. Group I: Metabotropic Glutamate$_{1/5}$.* Group I mGlu receptor subtypes, $mGlu_1$ and $mGlu_5$, have been extensively studied in terms of behavioral effects in animal models of SUD. Both $mGlu_1$ and $mGlu_5$ are robustly expressed in brain regions known to be critical to SUD pathophysiology, including the NAc, dorsal striatum, ventral midbrain and PFC (Niswender and Conn, 2010). Repeated exposure to drugs of abuse can dysregulate $mGlu_1$ and $mGlu_5$ expression and function. For example, chronic alcohol consumption in rodents reduces $mGlu_{1/5}$ mRNA levels in various subregions of the hippocampus and increases $mGlu_{1/5}$ expression in the NAc core and central nucleus of the amygdala (Simonyi et al., 2004; Obara et al., 2009). Nicotine exposure increases expression of $mGlu_1$ mRNA in the ventral tegmental area (VTA) and amygdala (Kane et al., 2005). Further, repeated cocaine exposure disrupts mGlu1 receptor-mediated signaling in the NAc (Swanson et al., 2001). Finally, prolonged withdrawal from extended-access cocaine self-administration decreases total protein and surface expression levels of $mGlu_1$ in the NAc compared with drug-naıve rats (Loweth et al., 2014). Alternatively, the total and surface levels of $mGlu_1$ is unchanged in the NAc following shorter abstinence periods or during cocaine administration (Ary and Szumlinski, 2007; Loweth et al., 2014). Withdrawal time-dependent reductions in $mGlu_{1/5}$ expression within ventromedial PFC have also been reported for following extended-access cocaine self-administration following extinction testing compared with drug-naıve animals (Ben-Shahar et al., 2013). Additionally, extinction of cocaine-seeking decreases the surface expression of $mGlu_5$ receptors in the NAc (Knackstedt et al., 2010). Thus, there is extensive evidence that $mGlu_1$ and $mGlu_5$ receptor subtypes may be involved in drug-related behaviors and the pathophysiology of SUDs.

Notably, $mGlu_1$ and $mGlu_5$ have both also been implicated as regulators of drug self-administration behavior. Early studies reported that mice carrying a null mutation for the gene encoding the $mGlu_5$ receptor lack cocaine-induced hyperlocomotion and did not acquire intravenous self-administration of cocaine (Chiamulera et al., 2001). Furthermore, genetic inactivation or pharmacological inhibition of $mGlu_5$ receptors decreases self-administration of alcohol, cocaine, heroin, nicotine, methamphetamine and ketamine and reduces breakpoints for reinforcement for various drugs of abuse in a progressive ratio (PR) paradigm (Cleva and Olive, 2012). $mGlu_1$ antagonist JNJ16259685 reduces alcohol self-administration and breakpoints for alcohol reinforcement under a PR schedule (Besheer et al., 2008a,b). However, other studies have shown that acquisition and fixed ratio operant responding for psychostimulants, such as cocaine and methamphetamine, is intact in mice lacking $mGlu5^{-/-}$; however, deletion of $mGlu_5$ enhanced responding on a progressive ratio schedule and impaired extinction of drug-seeking behaviors (Chesworth et al., 2013; Bird et al., 2014). These findings suggest that $mGlu_5$ may play distinct roles in drug reinforcement and instrumental extinction learning. Furthermore, $mGlu_1$ and $mGlu_5$ play an important role in reinstatement of drug seeking. Numerous studies have reported that pharmacological blockade of $mGlu_5$ attenuates the reinstatement of drug-seeking behavior induced by drug-associated cues, stress and drug priming (Bespalov et al., 2005; Bäckström and Hyytiä, 2007; Platt et al., 2008; Schroeder et al., 2008; Kumaresan et al., 2009; Martin-Fardon et al., 2009).

Additionally, $mGlu_1$ antagonism attenuates the reinstatement of nicotine and cocaine-seeking behavior elicited by drug-associated cues (Dravolina et al., 2007). A wealth of additional research supports the roles of $mGlu_1$ and $mGlu_5$ in various other drug-related behaviors, including conditioned place preference and interoceptive drug effects. These findings have been elegantly detailed in reviews elsewhere (Olive, 2009; Cleva and Olive, 2012; Caprioli et al., 2018; Niedzielska-Andres et al., 2021).

The extensive evidence that $mGlu_1$ and $mGlu_5$ play critical roles in behavioral deficits associated with SUD raises the question of whether targeting group I mGlu receptors is a promising therapeutic approach for the treatment of SUD. The development of $mGlu_1$ and $mGlu_5$ allosteric modulators have allowed researchers to directly test this question. Studies have investigated the efficacy of $mGlu_1$ allosteric modulators within the context of SUD (Caprioli et al., 2018). These studies have been summarized in Table 5. Specifically, repeated administration of selective $mGlu_1$ PAMs, SYN119 or Ro0711401, blocks incubation of cue-induced cocaine craving following extended-access cocaine self-administration and prolonged withdrawal in rats (Loweth et al., 2014). Interestingly, administration of $mGlu_1$ PAMs during withdrawal from methamphetamine self-administration did not block incubation of methamphetamine craving. The efficacy of $mGlu_1$ PAMs in reducing incubation of cocaine craving may be driven by $mGlu_1$-mediated blockade of calcium permeable amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor accumulation and synaptic transmission, which is known to be a critical mechanism driving cue-induced drug craving and cocaine seeking (McCutcheon et al., 2011; Loweth et al., 2014; Ruan and Yao, 2021). However, there is evidence that $mGlu_1$ does not regulate calcium permeable amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor accumulation during methamphetamine withdrawal (Murray et al., 2019), further supporting divergent mechanisms underlying incubation of craving for psychostimulants and selective roles of $mGlu_1$. These studies leveraging $mGlu_1$ PAMs provide further support that selective activation of $mGlu_1$ is able to reduce the impact of drug-induced adaptation in $mGlu_1$ function, which drives cocaine-seeking behavior (Halbout et al., 2014) and modulates a number of critical forms of synaptic plasticity, such as cocaine-induced plasticity in the VTA (Mameli et al., 2009) and $mGlu_1$-LTD and synaptic potentiation in the PFC (Ruan and Yao, 2021).

$mGlu_1$ NAMs have been shown to decrease alcohol self-administration in some studies but not others. In alcohol self-administration studies in alcohol-preferring P rats, JNJ16259685, an $mGlu_1$ NAM, decreased responding under fixed ratio and PR schedules (Besheer et al., 2008a; b), but also decreased locomotor activity and lever-pressing for sucrose, suggesting nonspecific motor effects. Similar observations were reported in additional studies looking at the effect of (−)-ethyl (7E)-7-hydroxyimino-1,7a-dihydrocyclopropa[b]chromene-1a-carboxylate (CPCCOEt), another $mGlu_1$ NAM, on alcohol self-administration in alcohol-preferring (P)-rats or C57BL/6J mice (Casabona et al., 1997; Schroeder et al., 2005; Hodge et al., 2006). In another study, CPCCOEt reduced ethanol reinforcement, consumption, and expression of ethanol conditioned place preference while facilitating the motor-impairing effects of ethanol (Casabona et al., 1997; Lominac et al., 2006). Importantly, CPCCOEt was able to block the acute effects of ethanol on extracellular levels of dopamine and glutamate in the NAc, while potentiating the effects of acute ethanol on extracellular GABA in this region. Leveraging another $mGlu_1$ NAM, JNJ16259685, one study reported decreased psychostimulant (cocaine and methamphetamine) administration under a second-order reinforcement schedule of reinforcement fixed interval 5-10 (FI5-FR10) (Achat-Mendes et al., 2012). In this same study, JNJ16259685 had no effect on food-reinforced responding but exerted motoric effects. The efficacy of $mGlu_1$ NAMs in nicotine use has also been studied. The selective $mGlu_1$ NAM EMQMCM (5 mg/kg) inhibited cue and nicotine-induced reinstatement of nicotine-seeking behavior, albeit when administered at higher doses EMQMCM reduced cue-induced reinstatement of food-seeking, indicating that high doses of this compound may have general inhibitory effects on appetitive responding (Dravolina et al., 2007). Furthermore, EMQMCM has been shown to inhibit the expression of locomotor sensitization to both morphine and cocaine (Dravolina et al., 2006; Kotlinska and Bochenski, 2007). Another study showed that intra-NAc injections of $mGlu_1$ NAM, 6-amino-N-cyclohexyl-N,3-dimethylthiazolo[3,2-a]benzimidazole-2-carboxamide (YM298198), decreases reinstatement of cocaine seeking in rats following cocaine priming (Schmidt et al., 2015). Together, these studies highlight the potential utility of $mGlu_1$ allosteric modulators for the treatment of various SUDs but also highlight the need for continued studies with improved formulations.

$mGlu_5$ allosteric modulators have been of particular interest as therapeutic options for the treatment of SUDs. A summary of these studies has been included in Table 5. Due to the abundance of reports, we have focused on summarizing the effects of $mGlu_5$ allosteric modulators on drug self-administration and reinstatement. Details on the efficacy of $mGlu_5$ PAM/NAMs in other drug-related behaviors have been reviewed previously (Olive, 2009; Cleva and Olive, 2012; Caprioli et al., 2018). A subset of classically studied $mGlu_5$ NAMs include the compounds 2-Methyl-6-(phenylethynyl)pyridine (MPEP) and 3-((2-Methyl-4-thiazolyl)ethynyl)pyridine (MTEP). MPEP and MTEP have been shown to attenuate intravenous self-administration of

TABLE 5.
Summary of preclinical efficacy of group I mGlu receptor allosteric modulators in substance use disorder models

| Receptor | Type | Compound | Drug of Abuse | Behavioral Effect | References |
|---|---|---|---|---|---|
| $mGlu_1$ | PAM | SYN119/Ro0711401 | Cocaine | Blocks incubation of cue-induced cocaine craving after extended-access self-administration | Loweth et al., 2014 |
| | | | Methamphetamine | No effect on incubation of methamphetamine craving after extended-access self-administration and withdrawal | Murray et al., 2019 |
| | NAM | JNJ-16259685 | Alcohol | Decreased responding under FR/PR schedules | Besheer et al., 2008a,b |
| | | | Cocaine and methamphetamine | Decreased self-administration under a second-order reinforcement schedule of reinforcement (FI5-FR10) | Achat-Mendes et al., 2012 |
| | | CPCCOEt | Alcohol | Decreased self-administration under FR and PR schedules of reinforcement in alcohol-preferring P-rats or C57BL/6J mice;[a,b,c] reduced ethanol reinforcement, consumption, and expression of ethanol CPP[d] | [1] (See footnotes.) |
| | | EMQMCM | Nicotine | Inhibited cue and nicotine-induced reinstatement of nicotine-seeking behavior | Dravolina et al., 2007 |
| | | | Morphine and cocaine | Inhibited the expression of locomotor sensitization | Dravolina et al., 2006; Kotlinska and Bochenski, 2007 |
| | | YM298198 | Cocaine | Decreased cocaine-primed reinstatement of cocaine seeking | Schmidt et al., 2015 |
| $mGlu_5$ | NAM | MPEP/MTEP | Cocaine, nicotine, heroin, and alcohol | Attenuates self-administration (intravenous or oral) | Ombelet et al., 1994; Kenny et al., 2003, 2005; Paterson et al., 2003; Bäckström et al., 2004; Tessari et al., 2004; Bespalov et al., 2005; Cowen et al., 2005, 2007; Lee et al., 2005; McMillen et al., 2005; Olive et al., 2005; Hodge et al., 2006; Lominac et al., 2006; Liechti and Markou, 2007; Besheer et al., 2008b; Palmatier et al., 2008; |
| | | | Cocaine | Attenuated cue-induced reinstatement of cocaine seeking | Bäckström and Hyytiä, 2007; Knackstedt et al., 2014; Knackstedt and Schwendt, 2016 |
| | | | Alcohol, cocaine, and nicotine | Reduced breakpoints under PR reinforcement schedule | Paterson et al., 2003; Besheer et al., 2008b |
| | | | Methamphetamine | Reduced incubated methamphetamine seeking; decreased self-administration under FR and PR schedules of reinforcement | Gass et al., 2009; Murray et al., 2021 |
| | Partial NAM | M-5MPEP/Br-5MPEPy | Cocaine | Decreased self-administration and attenuated the discriminative stimulus effects of cocaine | Gould et al., 2016 |

CPP, conditioned place preference; FI, fixed interval ;FR, fixed ratio; P, preferring; SYN119, mGlu1 PAM.
[a]Casabona et al., 1997.
[b]Hodge et al., 2006.
[c]Schroeder et al., 2005.
[d]Lominac et al., 2006.

numerous drugs of abuse, including cocaine, nicotine, methamphetamine, and heroin (Ombelet et al., 1994; Kenny et al., 2003, 2005; Paterson et al., 2003; Tessari et al., 2004; Bespalov et al., 2005; Lee et al., 2005; Liechti and Markou, 2007; Palmatier et al., 2008; Gass et al., 2009) and ethanol in a variety of rodent strains (Bäckström et al., 2004; Cowen et al., 2005; McMillen et al., 2005; Olive et al., 2005; Hodge et al., 2006; Lominac et al., 2006; Cowen et al., 2007; Besheer et al., 2008b ) without altering the reinforcing properties of natural reward or food (Paterson et al., 2003; Tessari et al., 2004; Bespalov et al., 2005; Liechti and Markou, 2007; Gass et al., 2009). These compounds have also demonstrated the ability to modulate the motivational properties of many drugs. For instance, MPEP reduces breakpoints for ethanol, cocaine, and nicotine under PR schedules of reinforcement (Paterson et al., 2003; Besheer et al., 2008b). Furthermore, administration of MTEP has been shown to reduce the reinforcing efficacy of methamphetamine as reflected by reduced breakpoints under a PR schedule off reinforcement (Gass et al., 2009). In addition to modulating the rewarding and motivational properties of drugs, MPEP and MTEP have also been shown to prevent cue and drug-induced priming of reinstatement of cocaine, nicotine or ethanol-seeking behavior (Bäckström et al., 2004; Tessari et al., 2004; Lee et al., 2005; Bäckström and Hyytiä, 2006; Iso et al., 2006; Murray et al., 2021). For instance, a recent study showed that systemic administration of MTEP reduces incubated methamphetamine seeking following self-administration and prolonged withdrawal (Murray et al., 2021), elucidating the role of $mGlu_5$ in the incubation of methamphetamine craving and delineating distinct mechanisms from that of incubation of cocaine craving. Interestingly, cue-induced reinstatement of cocaine-seeking behavior is attenuated in response to local infusion of MPEP or MTEP into the NAc (Bäckström and Hyytiä, 2007; Knackstedt et al., 2014), while local infusion of MTEP into the dorsolateral striatum at time of context-induced relapse testing attenuated extinction learning (Knackstedt et al., 2014; Knackstedt and Schwendt, 2016). This finding was paralleled by reduced $mGlu_5$ surface expression and LTD in brain slices of animals during prolonged abstinence from cocaine which could be reversed by bath application of the $mGlu_5$ PAM VU-29, suggesting brain-region specific subpopulations of $mGlu_5$ receptors may play distinct roles in regulating extinction learning and reinstatement of cocaine-seeking.

Despite the promising results of these studies, it has also been reported that MPEP and MTEP can attenuate breakpoints for food (Paterson et al., 2003), enhance the sedative properties of ethanol (Sharko and Hodge, 2008) and elicit general behavioral reduction, including decreases in inactive lever responding (Murray et al., 2021). To this end, partial $mGlu_5$ NAMs have been developed, which feature submaximal but saturable levels of blockade and may represent an additional avenue to broaden the therapeutic window of $mGlu_5$ NAMs. One study evaluated the efficacy of partial mGlu5 NAMs, 2-[2-(3-methoxyphenyl) ethynyl]-5-methylpyridine (M-5MPEP) and bromo-2-[2-(3-methoxyphenyl)ethynyl]-5-methylpyridine (Br-5MPEPy), in comparison with the full mGlu5 NAM MTEP in models of SUD. Gould et al., found that M-5MPEP, Br-5MPEPy, and MTEP dose-dependently decreased cocaine self-administration and attenuated the discriminative stimulus effects of cocaine, suggesting that partial $mGlu_5$ NAM activity is sufficient to elicit therapeutic effects comparable to full $mGlu_5$ NAMs (Gould et al., 2016). In sum, full and partial $mGlu_5$ NAMs may represent a promising therapeutic option for the treatment of numerous SUDs; however, continued exploration of novel $mGlu_5$ NAMs with improved therapeutic window and reduced side effects is required.

*II. Group II: Metabotropic Glutamate$_{2/3}$.* Decades of research support a critical role of group II mGlu receptors in SUDs. $mGlu_2$ and $mGlu_3$ regulate neurotransmission in brain regions implicated in SUDs, including the PFC and NAc. In the PFC, $mGlu_{2/3}$ receptors are tonically activated by endogenous glutamate and infusion of a selective $mGlu_{2/3}$ receptor antagonist, LY341495, increases glutamate levels (Melendez et al., 2005; Xie and Steketee, 2008). Within the NAc, numerous studies suggest that endogenous glutamatergic tone on group II mGlu receptors regulating both glutamate and dopamine levels. In vivo microdialysis studies have demonstrated increased glutamate release after perfusion of selective antagonist LY143495 into the NAc and decreased extracellular glutamate levels in response to agonist (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (APDC) (Xi et al., 2002). Further, electrophysiological recordings from NAc slices reveal that $mGlu_{2/3}$ receptors can act as presynaptic autoreceptors to control glutamate release. Specifically, increased paired pulse ratios and reduced miniature EPSC frequency were observed after bath application of selective agonists (S)-4-carboxy-3-hydroxyphenylglycine ((1S,3S)-ACPD) and (2S,1'S,2'S)-2-(2'-carboxycyclopropyl)-glycine (L-CCG1) (Manzoni et al., 1997). Evidence also supports that $mGlu_{2/3}$ receptors regulate glutamate release in VTA (Manzoni and Williams, 1999), bed nucleus of stria terminalis (Grueter and Winder, 2005), and hippocampus (Capogna, 2004), among other brain regions within the motivational circuit (Poisik et al., 2005).

The expression and function of $mGlu_{2/3}$ receptor subtypes are also altered by chronic use of drugs, such as alcohol, cocaine, opioids, and nicotine. The effects of drugs of abuse on $mGlu_{2/3}$ receptor function have been detailed in greater detail previously (Moussawi and Kalivas, 2010). In brief, it has been reported that ethanol-dependent rats have decreased PFC

*GRM2* mRNA levels and $mGlu_{2/3}$ autoreceptor function in the NAc shell compared with control rats (Meinhardt et al., 2013). In addition, drinking-induced decreases in $mGlu_{2/3}$ autoreceptor function have also been observed in the VTA (Ding et al., 2017). Alternatively, enhanced physiologic and behavioral sensitivity to $mGlu_{2/3}$ agonists is observed in the central nucleus of the amygdala and bed nucleus of stria terminalis of ethanol-dependent rats (Kufahl et al., 2011). In addition to sensitivity to the effects of ethanol, $mGlu_{2/3}$ receptors are altered by chronic exposure to other drugs of abuse. A recent study revealed that 12 days cocaine self-administration followed by 6 to 10 days of extinction training resulted in a decreased in $mGlu_2$ expression in the NAc core of male and female rats (Logan et al., 2020). Further, the inhibitory effects of $mGlu_{2/3}$ receptors on excitatory transmission in the VTA and NAc are enhanced in rodents during early withdrawal from chronic morphine (Manzoni and Williams, 1999; Martin et al., 1999). Interestingly, genetic variation in the $mGlu_2$ gene, *Grm2*, has also been associated with alcohol preference and consumption in rodents, such that the presence of an abnormal stop codon preventing expression of the *Grm2* results in increased alcohol preference and intake as measured by a two-bottle choice paradigm (Zhou et al., 2013; Wood et al., 2017).

Notably, $mGlu_{2/3}$ receptor-dependent plasticity is impaired after exposure to drugs of abuse. For example, chronic morphine impairs $mGlu_{2/3}$ receptor induced LTD at excitatory synapses in NAc medium spiny neurons (Robbe et al., 2002) and chronic cocaine exposure impairs $mGlu_{2/3}$ receptor-dependent LTD in PFC pyramidal cells (Huang et al., 2007). More recently, it was shown that NAc LTP induced by high frequency stimulation of the PFC was abolished after withdrawal from self-administered cocaine via reduced $mGlu_{2/3}$ receptor stimulation (Moussawi et al., 2009). Given the importance of neuroplasticity in cognition, reinforcement learning, and updating behaviors after changes in environmental contingencies (Malenka and Bear, 2004; Whitlock et al., 2006; De Roo et al., 2008) and evidence of drug-induced plasticity impairments, $mGlu_{2/3}$ receptors may be a critical target underlying drug-induced deficits in synaptic plasticity. Thus, potentiating the function of $mGlu_{2/3}$ may represent a promising approach to mitigate drug intake and cognitive deficits in individuals with SUD by restoring neurotransmitter homeostasis and neuroplasticity.

Early studies using the prototypical group II mGlu agonist LY379268 demonstrate decreased reinstatement of alcohol, cocaine, methamphetamine, and heroin seeking induced by cues previously associated with drug self-administration (Acri et al., 2017). Administration of LY379268 has also been shown to decrease cue- and drug priming-induced reinstatement of cocaine self-administration in nonhuman primates (Adewale et al., 2006; Justinova et al., 2016) and incubation of cocaine, methamphetamine, or nicotine self-administration in rats (Liechti et al., 2007; Crawford et al., 2013). Although less abundant than studies on group I mGlu receptor PAM/NAMs, a few studies have looked at the efficacy of $mGlu_{2/3}$ allosteric modulators in behavioral models of SUD (Table 6). One study used the selective and brain penetrant $mGlu_2$ PAM BINA in a model of intravenous cocaine self-administration and cocaine-seeking behavior in rats that had short (1 h, ShA) or long (6 h, LgA) access to cocaine. In this study, BINA decreased cocaine self-administration in both ShA and LgA rats, with no effect on food self-administration (Jin et al., 2010). Additionally, this study showed that BINA decreased cue-induced reinstatement of cocaine seeking without altering food seeking, suggesting that $mGlu_2$ allosteric modulators may have potential as treatments for cocaine use disorder and possibly other drugs of abuse.

$mGlu_2$ PAMs, AZD8418 and AZD8529, underwent preclinical and clinical evaluation for their efficacy in nicotine use disorder. Acute treatment with AZD8418 (0.37, 1.12, 3.73, 7.46, and 14.92 mg/kg) and AZD8529 (1.75, 5.83, 17.5, and 58.3 mg/kg) deceased nicotine self-administration and blocked cue-induced reinstatement of nicotine- and food-seeking behavior but did not significantly affect food-maintained responding in rats (Li et al., 2016). Chronic treatment with AZD8418 attenuated nicotine self-administration but resulted in tolerance to this effect. The inhibitory effects of chronic AZD8529 administration on nicotine self-administration persisted throughout the 14 days of treatment; however, chronic treatment with these PAMs inhibited food self-administration. The $mGlu_2$ PAM AZD8529 has since been tested in clinical trials including a 19-week, multicenter, randomized, phase 2 clinical study comparing the efficacy of two different doses of AZD8529 (1.5 and 40 mg) in smoking cessation in female smokers. However, this trial was completed in 2017 and reported only ~10% of either the low- or high-dose AZD8529 groups meeting the primary outcome of abstinence during the course of the 13-week study (Lassi et al., 2016).

*III. Group III: Metabotropic Glutamate$_{4/6/7/8}$.* The group III mGlu receptor subtypes have also garnered attention as potential targets for the treatment of SUD. A multitude of studies have reported group III mGlu receptor subtypes are sensitive to the effects of drugs of abuse, including psychostimulants and alcohol. For instance, repeated amphetamine exposure increases $mGlu_8$ mRNA levels in the dorsal striatum and NAc (Parelkar and Wang, 2008). Chronic alcohol consumption has been shown to reduce $mGlu_7$ mRNA levels in numerous hippocampal subregions, whereas

TABLE 6
Summary of preclinical efficacy of group II/III mGlu receptor allosteric modulators in substance use disorder models

| Group | Receptor | Type | Compound | Drug of Abuse | Behavioral Effect | References |
|---|---|---|---|---|---|---|
| II | $mGlu_2$ | PAM | BINA | Cocaine | Decreased cocaine self-administration in both short-access (1 h) and long-access (6 h) in rats; decreased cue-induced reinstatement of cocaine seeking without altering food seeking | Jin et al., 2010 |
| | | | AZD8418/AZD8529 | Nicotine | Deceased nicotine self-administration and blocked cue-induced reinstatement of nicotine- and food-seeking behavior | Li et al., 2016 |
| III | $mGlu_7$ | Ago-PAM | AMN082 | Cocaine | Reduced self-administration under an FR2 schedule of reinforcement; lowered PR breakpoints in rats | Li et al., 2009, 2013 |
| | | | | Cocaine | Attenuates cocaine-primed reinstatement of cocaine-seeking behavior | Li et al., 2010 |
| | | | | Alcohol and heroin | Inhibited self-administration and preference | Salling et al., 2008; Bahi et al., 2012 |

FR, fixed ratio; PR, progressive ratio

$mGlu_8$ mRNA levels were unchanged (Simonyi et al., 2004). Additionally, expression levels of the gene encoding the $mGlu_7$ receptor is associated with higher levels of alcohol consumption (Vadasz et al., 2007). The development of selective compounds targeting group III mGlu receptor subtypes have allowed for delineation of the distinct roles of these receptors in the physiologic and behavioral effects of drugs of abuse. For example, treatment with AMN082, a selective $mGlu_7$ allosteric agonist, attenuates cocaine-induced decreases of ventral pallidum GABA release in both naıve rats and cocaine self-administering rats (Li et al., 2009). These findings suggest a novel role of $mGlu_7$ receptors in regulating the effects of cocaine on NAc-ventral pallidum GABA transmission, which is one mechanism proposed to underlie the rewarding and motivational effects of cocaine. Furthermore, microinjection of L-AP4, a nonselective agonist of group III mGlu receptors, into the dorsal striatum reduced amphetamine or cocaine-induced hyperlocomotion in rats (Mao and Wang, 2000). Importantly, L-AP4 attenuated amphetamine-stimulated dopamine release in the dorsal striatum (Mao et al., 2000), suggesting that group III mGlu receptors may be involved in the acute effects of psychostimulant exposure by inhibiting dopamine release. Striatal glutamate has long been recognized to facilitate dopamine release (Mao et al., 2000). Thus, inhibition of glutamate release by group III autoreceptors may result in this inhibition of dopamine release. A study by Xi et al., showed that L-AP4 decreased extracellular glutamate levels, whereas the group III receptor antagonist (R, S)-α-methylserine-O-phosphate increased extracellular glutamate levels in the NAc of rats, respectively (Xi et al., 2003). In addition to the presynaptic roles of group III mGlu receptors in regulating drug-associated neurotransmission, $mGlu_7$ is expressed postsynaptically on both striatopallidal and striatonigral medium spiny neurons (Kosinski et al., 1999). To this end, L-AP4 inhibits evoked synaptic responses in the NAc, in part, through a postsynaptic mechanism (Martin et al., 1997). This putative postsynaptic mechanism likely works in concert with group III mGlu receptor subtype-mediated presynaptic modulation to control synaptic responses to drugs of abuse like cocaine.

Importantly, group III mGlu receptors have been shown to be important in drug self-administration in preclinical studies in rodents. For instance, Blednov and Harris demonstrated that $mGlu_4$ knockout mice showed normal levels of ethanol consumption but are devoid of a locomotor stimulant effect of low doses of alcohol (Blednov and Harris, 2008). Furthermore, administration of the $mGlu_8$ agonist (S)-3,4-DCPG suppressed alcohol self-administration and cue-induced reinstatement of alcohol-seeking behavior (Bäckström and Hyytiä, 2005). The $mGlu_7$ subtype has also been established to be critical to drug self-administration and reinstatement of drug-seeking. The development of group III mGlu selective ligands and allosteric modulators has allowed for rigorous characterization of their roles in various SUDs (Table 6). Stimulation of presynaptic $mGlu_7$ receptors with AMN082 significantly reduced cocaine self-administration under a fixed ratio 2 (FR2) schedule of reinforcement and lowered PR breakpoints for cocaine self-administration in rats (Li et al., 2009, 2013). These effects were replicable when AMN082 was directly infused the NAc or ventral pallidum. Additionally, systemic administration of AMN082 has been shown to attenuate cocaine-primed reinstatement of cocaine-seeking behavior (Li et al., 2010). Consistent with the literature on cocaine self-administration, AMN082 administration has also been shown to significantly inhibit heroin and ethanol self-administration and preference in rodents (Salling et al., 2008; Bahi et al., 2012). Together, these findings provide evidence that the $mGlu_7$ receptor is a promising target for the treatment of SUD. Continued studies leveraging using AMN082 or $mGlu_7$ PAMs are required to further evaluate their efficacy novel pharmacotherapies in nonhuman primates and clinical studies.

TABLE 7
Summary of preclinical efficacy of group I/II mGlu receptor allosteric modulators in stress-related deficits

| Group | Receptor | Type | Compound | Behavioral Effect | References |
|---|---|---|---|---|---|
| I | $mGlu_5$ | PAM | CDPPB | Facilitated the extinction of contextual fear memory; enhanced the initial fear memory formation and had no effect on memory retrieval | Sethna and Wang, 2014 |
| | | NAM | MPEP/MTEP | Antidepressant-like activity in the tail TST and FST[a, b] | (See footnotes.) |
| | | | DSR-98776 | Produces antidepressant-like actions in rats | Kato et al., 2015 |
| | | Partial NAM | M-5MPEP/Br-5MPEPy | Demonstrate antidepressant- and anxiolytic-like activity in FST, TST, SIH and marble burying tests | Gould et al., 2016 |
| | | | VU0477573 | Dose-dependent efficacy in marble-burying test | Nickols et al., 2016 |
| II | $mGlu_2$ | PAM | BINA | Anxiolytic-like effects on SIH and EPM tests in mice | Galici et al., 2006 |
| | | | THIIC | Anxiolytic-like efficacy in SIH assay in rats and stress-induced marble-burying assay in mice | Fell et al., 2011 |
| | | | LY487379/LY379268 | Anxiolytic-like efficacy in SIH assay in mice | Wierońska et al., 2012b |
| | $mGlu_2$ | NAM | VU6001966 | Reverse passive coping behavior in the FST | Joffe et al., 2020 |
| | $mGlu_3$ | NAM | VU0650786 | Antidepressant-like and anxiolytic-like effects as measured by FST and marble-burying tests | Engers et al., 2015 |
| | | | | Reverse passive coping behavior in the FST; reduce stress-induced deficits in motivation | Joffe et al., 2020 |
| | | | | Blocked LY379268-induced trace fear conditioning enhancement in mice | Dogra et al., 2021 |

BR-5MPEPy, bromo-2-[2-(3 methoxyphenyl)ethynyl]-5-methylpyridine; M-5MPEP, 2-[2-(3 methoxyphenyl)ethynyl]-5-methylpyridine; THIIC, (trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1H-imidazole-4-carboxamide; TST, tail suspension test.
[a]Li et al., 2006.
[b]Belozertseva et al., 2007.

### *C. Stress-Related Disorders*

Stress-related disorders, including anxiety, are incredibly pervasive psychiatric conditions and represent an enormous worldwide health concern. Chronic psychosocial stressors have been implicated as some of the most common risk factors for the development of stress-related disorders, which also have high comorbidity with other neuropsychiatric diseases, including depression and SUDs (Risch et al., 2009; Duric et al., 2016). However, our understanding of the mechanisms driving the development and persistence of stress-related disorders is still unclear. Stress-related disorders have been associated with aberrant brain excitability within critical neural circuits and disruption of excitatory and inhibitory transmission has been increasingly implicated as a crucial determinant of the pathophysiology of these diseases (Nuss, 2015; Jie et al., 2018). Mood and stress-related disorders involve both bottom-up and top-down control, primarily by limbic regions of the brain. As such, exposure to various stressors is known to dysregulate transmission of both glutamatergic and GABAergic systems (Nemeroff, 2003; Popoli et al., 2011; Jie et al., 2018). For example, clinical studies using proton magnetic resonance spectroscopy to measure endogenous brain metabolites, such as glutamate, in the brain have demonstrated a positive correlation between frontal cortex glutamate levels and state anxiety levels in healthy subjects (Grachev and Apkarian, 2000). Additionally, patients with social anxiety show higher glutamate levels in brain regions, such as the anterior cingulate cortex, compared with healthy control subjects who positively correlated with the severity of their social anxiety symptoms (Phan et al., 2005). These findings, among many others, suggest that restoring the balance between glutamatergic and GABAergic transmission represents a promising therapeutic strategy for alleviating symptoms of stress-related disorders.

A wide variety of pharmacotherapeutics targeting glutamate and/or GABA systems have been under ongoing investigation for their efficacy in treating stress-related disorders, including ketamine, memantine, gabapentinoids, tiagabine, valproic acid, and

TABLE 8
Summary of preclinical efficacy of group III mGlu receptor allosteric modulators in stress-related deficits

| Receptor | Type | Compound | Behavioral Effect | References |
|---|---|---|---|---|
| $mGlu_4$ | PAM | PHCCC | Antidepressant-like effects in rats;[a] intra-BLA administration elicits anticonflict effects in rats subjected to the Vogel conflict test[b] | (See footnotes.) |
| | | ADX88178 | Reduced duration of immobility in the FST; attenuated conditioned freezing in the acquisition phase of the fear conditioning | Kalinichev et al., 2014 |
| | | Lu AF21934 | Anxiolytic, but not antidepressant-like, effects as measured by SIH, four-plate, marble-burying, and Vogel's conflict tests | Sławińska et al., 2013b |
| $mGlu_7$ | NAM | ADX71743 | Dose-dependent reduction in the number of buried marbles and increasing open arm exploration in EPM and marble-burying assays | Kalinichev et al., 2013 |

[a]Kłak et al., 2007.
[b]Stachowicz et al., 2004.
BLA, basolateral amygdala

topiramate (Nasir et al., 2020). For example, the NMDA antagonist ketamine, which first showed efficacy in treating symptoms of depression in 2000 (Berman et al., 2000), has shown some efficacy in the treatment of post-traumatic stress disorder and anxiety disorders (Feder et al., 2014; Liriano et al., 2019; Banov et al., 2020). In addition, benzodiazepines, which act on $GABA_A$ receptors, have historically been used for the treatment of anxiety and other stress-related disorders. However, their utility has been limited by adverse side effects and high abuse liability (Tan et al., 2011). Therefore, particular interest has been focused on the development of subtype-selective drugs that will achieve specific therapeutic benefits by balancing glutamate and GABA transmission while limiting undesirable side effects. To this end, the mGlu receptors are in prime locations within these brain regions and neural circuits to normalize excitatory/inhibitory transmission, thus modulating stress responses and serving as a promising therapeutic approach for the treatment of stress-related disorders.

*I. Group I: Metabotropic Glutamate$_{1/5}$.* Group I mGlu receptors subtypes have been strongly implicated in the pathophysiology of stress-related disorders. For example, clinical studies leveraging positron emission tomography (PET) imaging have demonstrated a strong association between the $mGlu_5$ receptor subtype and anxiety, obsessive compulsive disorder, and depression (Terbeck et al., 2015). Positive correlations have been reported between $mGlu_5$ binding in regions of the amygdala, anterior cingulate cortex, and medial orbitofrontal cortex and obsessive compulsive disorder severity as assessed by the Yale-Brown Obsessive-Compulsive Scale (Akkus et al., 2014). Furthermore, mice exposed to social isolation stress exhibited selectively reduced $mGlu_1$ levels in the PFC (Ieraci et al., 2016). Prenatal stress models have also shown robust changes in mRNA and protein levels as well as gene methylation levels of $mGlu_1$ and $mGlu_5$ receptor subtypes expressed in the hippocampus of offspring rats that exhibit depression-like behavior (Lin et al., 2018). Several studies leveraging genetic deletion or pharmacological manipulation of group I mGlu receptors subtypes have further substantiated the notion that these receptors may be viable targets for treating stress-related disorders (Li et al., 2006; Shin et al., 2015; Zangrandi et al., 2021). For instance, $mGlu_5$ knockout mice or mice that received the $mGlu_5$ NAM, MTEP, displayed detriments in stress coping mechanisms (Li et al., 2006; Shin et al., 2015; Zangrandi et al., 2021). A recent study showed that mice with conditional knockout of $mGlu_5$ in dopamine receptor $D_1$ neurons demonstrated divergent coping mechanisms in response to acute escapable or inescapable stress compared with littermate controls, such that $mGlu_5$ conditional knockout mice showed enhanced active stress coping upon exposure to escapable stress task and higher levels of passive strategy in response to inescapable stress (Zangrandi et al., 2021). Numerous studies also implicate the $mGlu_1$ receptor subtype in the mechanisms underlying stress and anxiety. One study demonstrated that administration of the $mGlu_1$ antagonist, JNJ16259685, produced an anxiolytic phenotype in mice (Steckler et al., 2005). These findings

provide strong support for the potential utility of group I mGlu receptor allosteric modulators for the treatment of stress-related disorders.

The development of $mGlu_1$ and $mGlu_5$ allosteric modulators have greatly advanced our understanding of the physiologic and behavioral role of these receptor subtypes in stress and anxiety disorders. For example, intrahippocampal injection of MTEP impairs fear extinction by blocking hippocampal metaplasticity mechanisms that lead to enhanced LTP (Stansley et al., 2018), suggesting a potential utility of $mGlu_5$ PAMs for the treatment of stress-related disorders. As such, preclinical work has demonstrated efficacy of $mGlu_5$ PAM enhancement of fear extinction (Sethna and Wang, 2014). Additionally, MTEP displays antidepressant-like activity in the tail suspension test and FST (Palucha et al., 2005, 2007; Belozertseva et al., 2007). Furthermore, the $mGlu_5$ receptor NAM, DSR-98776, was shown to produce rapid antidepressant-like actions in rats (Kato et al., 2015). Leveraging partial $mGlu_5$ receptor NAMs, studies have also demonstrated antidepressant- and anxiolytic-like effects without inducing sedation (Gould et al., 2016; Nickols et al., 2016). Together, these studies support the possibility that $mGlu_5$ receptor NAMs may provide fast-acting antidepressant activity. Based on extensive preclinical evidence and clinical imaging studies, $mGlu_5$ receptor NAMs were tested in clinical trials for their efficacy to treat depressive symptoms. However, two $mGlu_5$ receptor NAMs, AZD2066 and Basimglurant (RG7090, RO4917523) have been tested in Phase II clinical trials and failed to show any efficacy over the placebo control (ClinicalTrials.gov Identifier: NCT01145755) (Quiroz et al., 2016). Nonetheless, higher doses significantly improved secondary outcomes (Quiroz et al., 2016). In combination with an improved tolerability profile, these findings warrant need for further investigation of $mGlu_5$ receptor NAMs for the treatment of depressive disorders. In contrast to the wealth of literature supporting the utility of $mGlu_5$ receptor allosteric modulators for the treatment of stress-related disorders, little is known about the utility of $mGlu_1$ receptor subtype-targeting allosteric modulators for mitigating stress and anxiety phenotypes. However, several studies using $mGlu_1$ receptor antagonists provide a strong foundation for future studies characterizing $mGlu_1$ allosteric modulators in stress-related disorder. For example, $mGlu_1$ receptor antagonists LY456236, 1-Aminoindan-1,5-dicarboxylic acid (AIDA), and JNJ-16259685 elicit anxiolytic-like effects in rodents (Tatarczyńska et al., 2001; Kłodzińska et al., 2004; Varty et al., 2005; Lima et al., 2008; Lavreysen et al., 2015). In addition to reported anxiolytic-like effects, one study showed antidepressant potential of $mGlu_1$ receptor antagoni,sts such that administration of JNJ-16567083 decreased immobility time in the tail suspension test (Belozertseva et al., 2007). However, further studies are needed to evaluate the potential anxiolytic activity of $mGlu_1$ receptor allosteric modulators in the context of stress physiology.

*II. Group II: Metabotropic Glutamate$_{2/3}$.* Substantial preclinical and clinical evidence supports the role of group II mGlu receptor subtypes in the etiology and maintenance of stress-related disorders (Dogra and Conn, 2021). For example, expression changes in $mGlu_2$ and $mGlu_3$ receptor subtypes are observed in numerous models of anxiety and depression. Elevation in group II mGlu receptor expression in the hippocampus and PFC has been observed in the mice reared under isolated conditions (Kawasaki et al., 2011). Further, increased levels of $mGlu_{2/3}$ receptors have been observed in the postmortem PFC tissue from patients with depression (Feyissa et al., 2010), providing evidence that increased $mGlu_{2/3}$ receptor function may contribute to the etiology of depression. To this end, several studies have reported anxiolytic effects with $mGlu_{2/3}$ agonists (Helton et al., 1998; Shekhar and Keim, 2000; Schoepp et al., 2003; Linden et al., 2005, 2018). A multitude of studies have also leveraged transgenic mouse lines featuring deletion of $mGlu_2$ and/or $mGlu_3$ to parse out the individual contributions of these receptor subtypes in stress-related disorders. However, these studies have yielded mixed results. One study reported that the anxiolytic efficacy of $mGlu_{2/3}$ agonists is reduced or absent in single $GRM2^{-/-}$ and $GRM3^{-/-}$ mice compared with littermate controls (Linden et al., 2005). Alternatively, several studies have reported that mice lacking either $mGlu_2$ or $mGlu_3$ alone did not display altered anxiety phenotypes (Morishima et al., 2005; Fujioka et al., 2014; De Filippis et al., 2015). Nonetheless, because the anxiolytic efficacy of $mGlu_{2/3}$ agonists has been observed across a variety of species, including humans and rodents, the lack of an anxiety phenotype in the transgenic mice may be due to species differences or compensatory changes.

As such, selective $mGlu_2$ and $mGlu_3$ receptor allosteric modulators have been investigated for their efficacy in treating symptomology of stress-related disorders (Table 7). $mGlu_3$ receptor NAMs have been shown to elicit antidepressant-like and anxiolytic-like effects as measured by FST and marble-burying tests, respectively (Engers et al., 2015). Further, recent studies show that $mGlu_2$ and $mGlu_3$ receptor NAMs reverse passive coping behavior in the FST (Joffe et al., 2020) and $mGlu_3$ receptor NAMs reverse motivational deficits and changes in the amygdalo-cortical plasticity induced by acute stress (Joffe et al., 2019a). Other studies using $mGlu_2$ receptor PAMs, BINA, N-(4-((2-(trifluoromethyl)-3-hydroxy-4-(isobutyryl)phenoxy)methyl)benzyl)-1-methyl-1H-imidazole-4-carboxamide, and LY487379, have demonstrated anxiolytic-like efficacy in multiple assays of rodent stress

response and also displayed antidepressive-like efficacy (Galici et al., 2006; Fell et al., 2011; Wierońska et al., 2012b). A recent study also reported that administration of the selective $mGlu_3$ NAM VU0650786 blocked the LY379268-induced trace fear conditioning enhancement in mice (Dogra et al., 2021). Together, these studies provide strong evidence that $mGlu_2$ and $mGlu_3$ allosteric modulators may also be a promising novel treatment strategy for stress-related disorders.

*III. Group III: Metabotropic Glutamate$_{4/6/7/8}$.* Group III mGlu receptor subtypes have garnered attention as potential therapeutic targets for the treatment of stress-related disorders. Initial studies using nonselective group III mGlu receptor agonists have aimed to determine the role of these receptors in stress-related phenotypes. For instance, Tatarczynska et al. showed that intrahippocampal administration of the group III mGlu receptor agonist ACPT-I elicits anxiolytic- and antidepressant-like effects in mice (Tatarczyńska et al., 2001). Other studies also found anxiolytic-like effects of ACPT-I as measured by stress-induced hypothermia (SIH), elevated plus-maze (EPM) tests in mice, and the Vogel test in rats (Pałucha et al., 2004; Stachowicz et al., 2009). However, until recently, a lack of selective compounds has largely limited our current understanding of the specific contribution of each group III mGlu receptor subtype in the pathophysiology of stress-related disorders. The development of transgenic rodent models and selective pharmacological agents has allowed us to gain insights on the role of group III mGlu receptor subtypes in stress-related phenotypes. For example, $mGlu_7$-selective antagonist 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one, which inhibits lateral amygdala LTP, reduces innate anxiety and freezing during acquisition of Pavlovian fear in mice (Gee et al., 2014). Additionally, $mGluR_7^{-/-}$ mice displayed anxiolytic efficacy in a battery of behavioral tasks, including the staircase test, EPM, light-dark box, and SIH (Cryan et al., 2003). Interestingly, $mGluR_7^{-/-}$ mice also show an increase in glucocorticoid-dependent feedback suppression of the hypothalamic–pituitary–adrenal axis and increases hippocampal brain-derived neurotrophic factor (BDNF) levels compared with wild-type littermate controls (Mitsukawa et al., 2006), further bolstering the hypothesis that $mGlu_7$ receptors are critical in stress physiology. In support of this notion, a wealth of literature reports anxiolytic- and antidepressant-like efficacy of the $mGlu_7$ agonist, AMN082 (Palucha et al., 2007; Palazzo et al., 2008; Pałucha-Poniewiera et al., 2010, 2014; Bradley et al., 2012; O'Connor and Cryan, 2013; Pałucha-Poniewiera and Pilc, 2013). Alternatively, mice lacking the $mGlu_4$ receptor subtype exhibited increased anxiety in the open-field and EPM test as well as improvements in cued-fear conditioning (Davis et al., 2013). Studies using the orthosteric $mGlu_8$ agonist, DCPG, showed that $mGlu_8$ stimulation reduced anxiety-like behavior in open field and EPM tests while also attenuating the expression of contextual fear (Fendt et al., 2013). Together, these studies have begun to elucidate the role of each receptor subtype in the pathophysiology of stress-related disorders.

Based on this evidence, studies have focused on the potential utility of allosteric modulators of group III mGlu receptor subtypes for the treatment of stress-related disorders (Table 8). Studies have leveraged $mGlu_4$ PAMs and shown anxiolytic- and antidepressant-like activity in rodents. For example, a study by Klak et al. reported that administration of the $mGlu_4$-selective PAM 7-hydroxyimino-N-phenyl-1,7 adihydrocyclopropa[b]chromene-1a-carboxamide (PHCCC) in combination with a subeffective dose of (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid produced antidepressant-like effects in rats (Kłak et al., 2007). Intra-basolateral amygdala (BLA) administration of PHCCC was reported to elicit anticonflict effects in rats subjected to the Vogel conflict test (Stachowicz et al., 2004). Another $mGlu_4$ PAM, ADX88178, dose-dependently reduced duration of immobility in the forced swim test and attenuated conditioned freezing in the acquisition phase of the fear conditioning test without altering freezing propensity in the expression phase of the task (Kalinichev et al., 2014). Furthermore, Sławińska et al. also showed that administration of the $mGlu_4$ PAM, Lu AF21934, produced anxiolytic- but not antidepressant-like effects as measured by SIH, four-plate, marble-burying, and Vogel's conflict tests (Sławińska et al., 2013b). In addition to promising evidence of the anxiolytic efficacy of $mGlu_4$ allosteric modulators, another study reported an anxiolytic-like profile of $mGlu_7$ NAMs. Specifically, the $mGlu_7$ NAM, ADX71743, produced a robust anxiolytic-like phenotype as evidenced by dose-dependent reduction in the number of buried marbles and increasing open arm exploration in EPM and marble burying assays, respectively (Kalinichev et al., 2013).

## IV. Future Directions/Concluding Remarks

A wealth of preclinical literature over the past decade supports the potential utility of allosteric modulators of mGlu receptors as promising therapeutic options to treat multiple neuropsychiatric diseases, including schizophrenia, SUDs, and stress-related disorders, which currently have limited or no effective treatments. Thus far, investigation of mGlu receptor allosteric modulators has yielded important insights into the neuropharmacology of these diseases, and surely more discoveries are yet to be discovered. However, many outstanding questions remain that the field is primed to address and that will propel research on allosteric modulators forward. One important outstanding question involves the utility of mGlu allosteric modulators as novel cognitive enhancers. Neuropsychiatric conditions, such as schizophrenia, SUDs, and stress-related disorders, are known to produce marked deficits in cognitive behavior (Gould

et al., 2012; Robinson et al., 2013; Tripathi et al., 2018; Lukasik et al., 2019). Extensive literature supports the notion that many cognitive deficits associated with neuropsychiatric diseases (working memory, attention, executive function, etc.), such as schizophrenia and SUD, are driven by aberrant glutamate and GABA signaling and associated detriments in synaptic plasticity (Logue and Gould, 2014; Guidi et al., 2015). Based on the well-established and critical role of mGlu receptor subtypes in regulating glutamate/GABA transmission and synaptic plasticity (see *Metabotropic Glutamate Receptor Regulation of Neurotransmission and Synaptic Plasticity*), allosteric modulators of mGlu receptors are promising targets to reverse disease-related cognitive deficits, a major unmet need of numerous neuropsychiatric diseases. For example, by leveraging $mGlu_5$-mediated regulation of cortical and hippocampal plasticity, $mGlu_5$ PAMs show excellent potential as cognitive enhancers. Recent work demonstrates that $mGlu_1$ PAMs regulate spatial working memory via regulation of PFC SST-IN function in mice (Maksymetz et al., 2021). Furthermore, $mGlu_5$ PAM VU0092273 enhances trace fear conditioning in wild-type mice but not in $mGlu_5$-CA1-KO mice (Xiang et al., 2019). Further supporting this notion, the biased $mGlu_5$ PAM VU0409551 demonstrated robust cognition enhancement as measured by enhancement of contextual fear conditioning acquisition and an increase in recognition memory in the novel object recognition task in rats, both commonly used rodent learning and memory assays dependent upon hippocampal function (Rook et al., 2015). In the same study, VU0409551 also enhanced working memory performance in rats, such that systemic administration increased accuracy in a delayed non-match-to-sample task.

Several studies have also provided evidence for the cognitive-enhancing abilities of group II mGlu receptor subtype allosteric modulators. For example, $mGlu_2$ PAM SAR 218645 improved learning and memory in rodent models of schizophrenia (Griebel et al., 2016). In line with their ability to enhance hippocampal LTP, selective activation of $mGlu_3$ has been shown to improve cognition in hippocampal dependent temporal associative tasks in rodents (Stansley and Conn, 2019). Interestingly, the functional interplay between $mGlu_3$ and $mGlu_5$ receptor subtypes and the involvement of $mGlu_3$ in cortical plasticity further suggests that $mGlu_3$ PAMs may also exert cognition-enhancing effects. Lastly, group III mGlu receptors may be a promising cognition-enhancing approach to mitigate neuropsychiatric-related deficits. This notion is further evidenced by preclinical cognition-enhancement observed with $mGlu_7$ NAMs. Specifically, the $mGlu_7$ NAM, ADX71743, reverses MK-801-induced deficits in novel object recognition and delayed spatial alternation in mice (Cieślik et al., 2018). Ongoing studies are required to evaluate the procognitive utility of mGlu receptor allosteric modulators for other cognitive processes and neuropsychiatric disease models.

Lastly, questions remain about pharmacological refinement of next-generation allosteric modulators of mGlu receptor subtypes. Allosteric-related factors, such as heterodimer engagement and signal bias, are essential to the translation of these compounds into the clinical setting. Expanding our understanding of allosteric modulator signal biases and interaction with heterodimer complexes, for example, will allow us to optimize treatments to restore normal physiology within the circuits underlying specific disease states. Several compounds targeting mGlu receptor subtypes display biased allosteric modulation or "functional selectivity" (Zhang et al., 2005; Sheffler and Conn, 2008; Rook et al., 2015). For example, the gadolinium ion, an allosteric modulator of the mGlu1$\alpha$ receptor subtype, inhibits $G\alpha_{q/11}$-linked $Ca^{2+}$ mobilization but also stimulates $G\alpha_s$-mediated cAMP production when administered with glutamate (Tateyama and Kubo, 2006). Recent reports have also shown that signal bias can have crucial implications for therapeutic efficacy, as evidenced by $\beta$-arrestin-biased $mGlu_5$ NAMs in models of Fragile X (Stoppel et al., 2017) or $mGlu_5$ PAMs biased away from NMDAR modulation for schizophrenia (Rook et al., 2015; Gould et al., 2016). Moving forward, efforts will determine how to translate these pharmacological properties to emerging drug candidates through different systems and species to avoid context-dependent pharmacology that has the potential to hinder efficacy. Accounting for these pharmacological factors, among others, throughout model systems will likely increase the competitiveness and effectiveness of future drug candidates for the treatment of neuropsychiatric disease.

**Authorship Contributions**

*Wrote or contributed to the writing of the manuscript:* Luessen, Conn.

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