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Allosteric Modulation of Metabotropic Glutamate Receptors

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Abstract

The development of receptor subtype-selective ligands by targeting allosteric sites of G protein-coupled receptors (GPCRs) has proven highly successful in recent years. One GPCR family that has greatly benefited from this approach is the metabotropic glutamate receptors (mGlu). These family C GPCRs participate in the neuromodulatory actions of glutamate throughout the CNS, where they play a number of key roles in regulating synaptic transmission and neuronal excitability. A large number of mGlu subtype-selective allosteric modulators have been identified, the majority of which are thought to bind within the transmembrane regions of the receptor. These modulators can either enhance or inhibit mGlu functional responses and, together with mGlu knockout mice, have furthered the establishment of the physiologic roles of many mGlu subtypes. Numerous pharmacological and receptor mutagenesis studies have been aimed at providing a greater mechanistic understanding of the interaction of mGlu allosteric modulators with the receptor, which have revealed evidence for common allosteric binding sites across multiple mGlu subtypes and the presence for multiple allosteric sites within a single mGlu subtype. Recent data have also revealed that mGlu allosteric modulators can display functional selectivity toward particular signal transduction cascades downstream of an individual mGlu subtype. Studies continue to validate the therapeutic utility of mGlu allosteric modulators as a potential therapeutic approach for a number of disorders including anxiety, schizophrenia, Parkinson's disease, and Fragile X syndrome.

I. Introduction

Despite their tractability as drug targets, the majority of G protein-coupled receptor (GPCR)-based drug discovery programs have failed to yield highly selective compounds. Further, CNS disorders represent a therapeutic area with one of the highest rates of attrition in drug discovery (Kola & Landis, 2004). The traditional approach to targeting GPCRs in drug discovery has been to target the endogenous ligand (orthosteric)-binding site, to either mimic or block the actions of the endogenous neurotransmitter or hormone in a competitive manner. However, this approach has suffered from a lack of suitably subtype-selective ligands, both as tools to probe physiology and pathophysiology experimentally, and as therapeutic candidates. An alternative approach is to target allosteric sites that are

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topographically distinct from the orthosteric site, to either enhance (positive allosteric modulators, PAMs) or inhibit (negative allosteric modulators, NAMs) receptor activation. These allosteric modulators, offer a number of potential advantages over their orthosteric counterparts. In many cases, allosteric sites consist of regions on the receptor that show greater sequence divergence than orthosteric sites and as such have greater potential for subtype-selective ligand development. Further, in the case of an allosteric modulator that has no intrinsic activity, there is the capacity to “fine-tune” the response to the endogenous ligand, thereby retaining the spatial and temporal aspects of neurotransmission. Alternatively, allosteric modulators can also have intrinsic efficacy, activating the receptor alone (allosteric agonists) or neutral efficacy, having no effects on the receptor alone but competing with the activity of other allosteric modulators. Because the pharmacological effects of allosteric ligands are limited by their cooperativity, there is a ceiling level to their effect, which may provide greater margin of safety in the case of overdose. One disadvantage of allosteric modulators is that unlike orthosteric ligands, pure allosteric modulators with no intrinsic efficacy rely on the presence of endogenous ligand for efficacy.

Targeting allosteric sites to either enhance or inhibit receptor activation has proven to be highly successful for ligand-gated ion channels. For example, the mechanism of action of benzodiazepines is allosteric enhancement of GABA_A receptor activity, which provides a safe and effective treatment for anxiety and sleep disorders (Mohler et al., 2002). Two GPCR allosteric modulators have now entered the market, demonstrating the clinical validity of this approach. The first of these modulators, Cinacalcet, is a PAM of the calcium-sensing receptor (CaSR) and was approved in 2004 for the treatment of hyperparathyroidism, a disease associated with CaSR deficiency (Lindberg et al., 2005). The second, Maraviroc, stabilizes C–C chemokine receptor type 5 (CCR5) receptor conformations that have a lower affinity for the HIV virus, allosterically inhibiting CCR5-dependent entry of HIV-1 into cells (Dorr et al., 2005) and was approved for the treatment of HIV infections in 2007. Consequently, discovery and characterization of GPCR allosteric modulators have gained significant momentum in the past two decades and represent exciting novel means of targeting therapeutically relevant GPCRs. Arguably, one of the most well-studied GPCR families with respect to allosteric modulation are the metabotropic glutamate receptors (mGlu). Indeed, the full spectrum of allosteric ligands has been discovered for these receptors.

II. Metabotropic Glutamate Receptors

The neuromodulatory actions of the major neurotransmitter glutamate within the CNS are mediated by activation of the mGlu. There are eight mGlu subtypes, and with the exception of mGlu₆, which is primarily expressed in the retina, mGlu are expressed throughout the CNS. The individual subtypes show varied distribution in different brain areas, can be found both pre and postsynaptically (Fig. 1), participate in many different CNS processes, and are attractive therapeutic targets for a number of neurological and psychiatric diseases and disorders (Table I). The mGlu are family C GPCRs and the eight mGlu subtypes are generally classified into three groups based on sequence homology and pharmacology: Group I are mGlu₁ and mGlu₅, Group II are mGlu₂ and mGlu₃, and Group III are mGlu₄, mGlu₆, mGlu₇, mGlu₈. Within the same group, mGlu show ~70% sequence identity, whereas between groups, this conservation falls to ~45% (Niswender & Conn, 2010). The Group I mGlu preferentially couple to the G_{q/11} family of G proteins, activating phosphoinositide hydrolysis and calcium mobilization as their major signaling mechanism. In contrast, Group II and Group III mGlu preferentially couple to G_{i/o} and inhibit adenylyl cyclases.

A. Structural Features of Metabotropic Glutamate Receptors

GPCRs are predicted to share a common topology consisting of seven transmembrane-spanning α -helical domains, an extracellular N terminus, and intracellular C terminus. Additional structural features of mGluR include a large extracellular N-terminal domain, termed the venus flytrap domain (VFD), that contains the endogenous ligand-binding site (Pin et al., 2003) and a cysteine-rich domain that links the VFD to the trans-membrane-spanning α -helices by a conserved disulfide bridge (Fig. 2). Crystal structures of the N-terminal domains of mGlu₁, mGlu₃, and mGlu₇ have been solved and suggest that the VFD is made up of two lobes (Kunishima et al., 2000; Muto et al., 2007; Tsuchiya et al., 2002), forming a clam shell-shaped structure. Glutamate is thought to bind between the two lobes with the two globular domains closing into a stable conformation with glutamate inside (Bessis et al., 2000, 2002; Kunishima et al., 2000; Tsuchiya et al., 2002). Further, evidence suggests that the mGluR dimerize via interactions between their VFDs, and that activation of mGluR requires the binding of two glutamate molecules, one to each protomer (Kniazeff et al., 2011). Conformational changes induced by glutamate in the VFD are thought to be transmitted to the transmembrane spanning domains via the cysteine-rich domain to promote coupling to intracellular G proteins and activation of second messenger pathways (Liu et al., 2004; Muto et al., 2007; Rondard et al., 2006).

B. Localization and Functional Roles of the mGluR

1. Group I mGluR—Group I mGluR, comprising mGlu₁ and mGlu₅, are extensively expressed throughout the CNS in neurons, and mGlu₅ is expressed in both neurons and glia. mGlu₁ expression is most intense in Purkinje cells of the cerebellar cortex and the olfactory bulb with strong expression in neurons of the lateral septum, globus pallidus, ventral pallidum, most thalamic nuclei, as well as the substantia nigra. Localization of mGlu₅ is greatest in corticolimbic areas responsible for controlling higher cognitive function including the striatum, hippocampus, cerebral cortex, septal nuclei as well as the thalamus, and olfactory bulb (Ferraguti & Shigemoto, 2006). While Group I mGluR are predominantly found postsynaptically, where they increase neuronal excitability, it is important to note that Group I mGluR localized presynaptically can increase or decrease neurotransmitter release (Pinheiro & Mulle, 2008) (Fig. 1). Additionally, mGlu₁ and mGlu₅ subtypes can have differential functional roles within a single neuronal population as is the case in CA1 pyramidal cells (Mannaioni et al., 2001). The Group I mGluR play important roles in synaptic plasticity by facilitating both long-term depression (LTD) and potentiation (LTP) of synaptic strength as well as inducing nonsynaptic conductances leading to enhanced neuronal excitability (Anwyl, 1999; Bellone et al., 2008).

Each of the mGluR has been genetically deleted in mice. The phenotypes revealed by studies conducted with these mGluR knockout (KO) animals provide insight into the potential physiological roles of individual mGluR in a wide variety of brain systems as well as their potential as targets for novel therapeutic strategies. The first mGluR subtype deleted in mice was mGlu₁. While the overall gross brain morphology of these animals appears normal, they exhibit several phenotypes. As previously discussed, mGlu₁ is most abundantly expressed in Purkinje cells of the cerebellar cortex. Mice lacking mGlu₁ demonstrate cerebellar ataxic gait characterized by deficits in LTD in the cerebellum (Aiba et al., 1994b). Most adult Purkinje cells are individually innervated by a single climbing fiber as a consequence of developmental regulatory regression forming a strong excitatory synapse. Interestingly, mGlu₁-deficient mice have abnormal regression of climbing fibers, resulting in innervations of multiple climbing fibers onto single Purkinje cells, suggesting mGlu₁ is critical for guiding proper excitatory synapse formation in the cerebellum (Kano et al., 1997).

High levels of mGlu₁ expression are also found within the hippocampus, suggesting a potential role of this receptor in learning and memory. Electrophysiological studies in mGlu₁ KO mice reveal significantly reduced LTP in hippocampal slices. These studies also show impairment in the acquisition or retention of memory in a context-dependent fear conditioning task, suggesting deficits in hippocampal-mediated learning and memory (Aiba et al., 1994a). Recently, recordings at the CA3–CA1 synapse within the hippocampus during the acquisition of an associative learning task in mGlu₁ KO mice found impaired LTP as well as the inability of the animal to learn the task (Gil-Sanz et al., 2008).

Extensive studies using mGlu₅ KO mice implicate this receptor's role in cognition, addiction, anxiety, chronic pain, and obesity. Both mGlu₁ and mGlu₅ KO mice demonstrate deficits in prepulse inhibition (PPI) of the acoustic startle reflex, a measure of sensorimotor gating impaired in patients with schizophrenia (Brody et al., 2003, 2004b; Gray et al., 2009), which can be reversed by antipsychotic treatment (Brody et al., 2004a). Deletion of mGlu₅ also results in short-term spatial memory performance deficits in the Y-maze (Gray et al., 2009), a reduction in hippocampal CA1 LTP, and impaired performance in cognitive tasks (Lu et al., 1997). These studies, together with pharmacological studies demonstrating the involvement of mGlu₅ in synaptic plasticity, including LTP and LTD (Ayala et al., 2009), support a role for mGlu₅ in learning and memory (Homayoun & Moghaddam, 2010). In animal models of addiction, mGlu₅ KO mice do not self-administer cocaine and do not demonstrate hyperlocomotor activity following cocaine treatment (Chiamulera et al., 2001), demonstrating that mGlu₅ may play a role in addiction. Further, mGlu₅ KO mice also display attenuation of stress-induced hyperthermia, an animal model of anxiety (Brodtkin et al., 2002). Recently, deletion of mGlu₅ was also used to demonstrate the role of mGlu₅ signaling in the amygdala in the modulation of persistent pain due to peripheral inflammation (Kolber et al., 2010). Finally, mGlu₅ KO mice weigh less than littermate controls, eat less when challenged with food deprivation, and are resistant to weight gain and increased insulin levels induced by a high-fat diet (Bradbury et al., 2005) indicating a potential role of mGlu₅ in obesity.

2. Group II mGlu—The Group II mGlu, mGlu₂ and mGlu₃, are widely distributed in the CNS (Reviewed in Ferraguti & Shigemoto, 2006; Harrison et al., 2008) and in the periphery (Reviewed in Julio-Pieper et al., 2011). Generally, mGlu₂ and mGlu₃ are expressed presynaptically where they modulate neurotransmitter release (Fig. 1). In addition, they are also found at postsynaptic sites where they can induce hyperpolarization (Muly et al., 2007). In addition to these synaptic localizations, mGlu₃ is also expressed in glia (Mudo et al., 2007; Ohishi et al., 1993; Tamaru et al., 2001). Similar to the Group I mGlu, mGlu₂ and mGlu₃ KO mice have been heavily utilized in order to define the individual roles of the Group II mGlu in a variety of physiologic processes. For example, mGlu₂ KO mice show a loss of Group II agonist-induced reversal of PCP-induced hyperlocomotion (Spooren et al., 2000), loss of the anxiolytic effects of a Group II agonist (Linden et al., 2005), an enhanced responsiveness to cocaine (Morishima et al., 2005), alterations in synaptic transmission in a number of regions including the CA1 region of the hippocampus and the dentate gyrus (Kew et al., 2002; Yokoi et al., 1996), and loss of Group II agonist antipsychotic activity in numerous rodent models (Fell et al., 2008; Woolley et al., 2008). mGlu₃ KO mice also show decreased efficacy of Group II agonists in anxiolytic models (Linden et al., 2005), an increase in basal hippocampal c-Fos expression (Linden et al., 2006), and a loss of Group II agonist-induced neuroprotection by astrocytes against NMDA excitotoxicity (Corti et al., 2007).

3. Group III mGlu—The Group III mGlu (mGlu₄, mGlu₆, mGlu₇, and mGlu₈), with the exception of mGlu₆, which is localized postsynaptically on retinal ON bipolar cells (Nakajima et al., 1993), are mainly expressed presynaptically in neurons diffusely

distributed throughout the CNS (Fig. 1). mGlu₄ is highly expressed in the cerebellum, with lower levels of expression in the hippocampus, basal ganglia, and olfactory bulb (Lavreysen & Dautzenberg, 2008). mGlu₄ expression is also found peripherally in pancreatic islet cells (Uehara et al., 2004) and taste buds along with a shorter mGlu₄ splice variant (Toyono et al., 2002). Consistent with expression distribution, deleting the mGlu₄ gene results in mice with impaired cerebellar synaptic plasticity and deficits in learning of complicated motor tasks (Pekhletski et al., 1996) and spatial memory performance (Gerlai et al., 1998). mGlu₇ and mGlu₈ are widely distributed throughout the brain. In particular, mGlu₇ is localized to active zones of synapses and has an extremely low affinity for glutamate. Given this low glutamate affinity and localization, it has been proposed that mGlu₇ is only activated in the presence of very high glutamate levels and thus serves to prevent overstimulation by glutamate (Kinoshita et al., 1998; Shigemoto et al., 1997). This hypothesis is further supported by the epileptic phenotype of mGlu₇ KO mice (Sansig et al., 2001). Additionally, mice lacking mGlu₇ exhibit deficits in memory and learning (Bushell et al., 2002; Callaerts-Vegh et al., 2006; Goddyn et al., 2008; Holscher et al., 2004, 2005; Masugi et al., 1999) and have been implicated in disorders such as anxiety and depression (Cryan et al., 2003; Stachowicz et al., 2008). mGlu₈ is expressed broadly throughout the brain, albeit at lower levels than both mGlu₄ and mGlu₇. mGlu₈ KO mice displayed increased anxiety and weight gain (Duvoisin et al., 2005; Linden et al., 2002). mGlu₈ is also localized postsynaptically within the peripheral cells of the gut and pancreas and has been implicated in gastrointestinal motility and insulin secretion (Tong & Kirchgessner, 2003; Tong et al., 2002). Unlike other Group III subtypes, the mGlu₆ signaling cascade has been shown to involve G_o protein subunits (Dhingra et al., 2000). Mice lacking mGlu₆ demonstrate deficits in ON response to light stimulation (Masu et al., 1995; Sugihara et al., 1997).

III. Pharmacological Profiles of mGlu Allosteric Modulators

A. Group I mGlu

The first mGlu allosteric modulator was identified when the selective mGlu₁ antagonist CPCCOEt (Annoura et al., 1996) was determined to act via a noncompetitive mechanism (Litschig et al., 1999), which marked a major advance in supporting the rationale of targeting allosteric sites for discovery of highly subtype-selective mGlu antagonists. Several structurally distinct mGlu₁ NAMs with nanomolar potencies have been published since, including Bay 36-7620 (Carroll et al., 2001), JNJ16259685 (Lavreysen et al., 2003), YM298198 (Kohara et al., 2005), and FTIDC (Suzuki et al., 2007a), which possess adequate pharmacokinetic properties for *in vivo* characterization. Highly selective mGlu₁ PAMs have also been developed and among these compounds are Ro 67-7476 and VU71 (Hemstapat et al., 2006; Knoflach et al., 2001).

The other Group I receptor, mGlu₅, has been extensively investigated, and several potent and selective NAMs are known. SIB-1757 and SIB-1893 were originally reported (Varney et al., 1999), with the subsequent structural analogs MPEP (Gasparini et al., 1999) and MTEP (Cosford et al., 2003b) providing increased potency and selectivity as well as brain penetration as compared to their predecessors. While many potent, highly selective mGlu₅ NAMs have now been reported, MTEP and MPEP remain the most commonly used antagonists for *in vivo* characterization of this receptor. However, Rodriguez et al. (2010) recently reported discovery of VU0285683 as a potent, *in vivo* active, mGlu₅ NAM with improved pharmacokinetic properties for systemic dosing.

In addition to mGlu₅ NAMs, many mGlu₅ PAMs have been identified. These include DFB, CPPHA, CDPPB, VU29, and ADX47273 (Conn et al., 2009). Although DFB and CPPHA do not have suitable potencies or solubility in physiological buffers for systemic administration and assessment of mGlu₅ function *in vivo*, newer generation PAMs are

proving highly useful in evaluating the role of mGlu₅ in animal models. Most recently, VU0360172 was reported as a potent, selective mGlu₅ PAM with properties that are much more favorable for *in vivo* studies than was the case for earlier mGlu₅ PAMs (Rodriguez et al., 2010). Another pharmacological tool utilized for evaluating the physiological role of mGlu₅ is the neutral ligand, 5MPEP, which binds to the MPEP site but has no effects alone. However, 5MPEP blocks the effects of both the allosteric antagonist MPEP and potentiators DFB and CDPBB (Rodriguez et al., 2005).

B. Group II mGlu

Numerous mGlu₂ PAMs have been identified, the majority of which are structurally related to BINA and LY487379 (Reviewed in Rudd & McCauley, 2005). Unfortunately, there are currently no reports of selective mGlu₃ PAMs. Interestingly, a single report of an mGlu₂ PAM displaying mGlu₃ PAM activity in a GTP S binding assay (Govek et al., 2005) has shown that discovery of mGlu₃ PAMs may be on the horizon. Compared to the mGlu₂ PAMs, only a limited number of Group II NAMs, which are nonselective between mGlu₂ and mGlu₃ (Hemstapat et al., 2007), have been reported. Chemically, the majority of these Group II NAMs are benzo-diazepinones structurally related to MNI-137 (Hemstapat et al., 2007), with some newer compounds in this series demonstrating improved oral bioavailability in rodents (Woltering et al., 2010). Interestingly, LY2389575, an mGlu₃ selective NAM, was recently reported (Caraci et al., 2010), providing a key tool compound that will allow further investigation of mGlu₃'s physiological function.

C. Group III mGlu

Relative to Group I and Group II mGlu, the pharmacology of Group III mGlu has been the least investigated, due in large part to the difficulty in developing subtype-selective compounds. While several orthosteric compounds selective for Group III receptors have been identified, generally these compounds do not discriminate between subtypes and have relatively low potencies (Schoepp et al., 1999). However, exciting new progress has been made in developing subtype-selective Group III mGlu allosteric modulators with the development of mGlu₄ and mGlu₇ subtype-selective compounds. PHCCC is a pure positive allosteric modulator of mGlu₄, potentiating the potency of glutamate at mGlu₄ with no direct agonist activity alone (Maj et al., 2003; Marino et al., 2003). Additionally, the mGlu₅ NAMs SIB-1893 and MPEP possess mGlu₄ PAM activity, although at significantly lower potencies and efficacies (Mathiesen et al., 2003). Recently, two structurally distinct mGlu₄ PAMs, VU0155041 and VU0080421, have been identified (Niswender et al., 2008a,b). Significant improvements in potency and selectivity for mGlu₄ have been achieved with VU0155041, which is a mixed allosteric agonist/PAM. Moreover, VU0155041 exhibits increased solubility in physiological buffers, providing the opportunity to examine the role of mGlu₄ in animal models of various disease states (Niswender et al., 2008a).

AMN082 has been reported as a selective mGlu₇ allosteric agonist and is extensively used as an *in vivo* tool compound (Mitsukawa et al., 2005). Recent studies demonstrating varying activity suggest that the pharmacology of this compound is complex. Reports have shown that AMN082 does not induce calcium mobilization in a cell line coexpressing mGlu₇ and a promiscuous G protein (Suzuki et al., 2007b), mGlu₇-mediated activation of GIRK potassium channels in human embryonic kidney cells (Ayala et al., 2008), or activation of mGlu₇ at the Schaffer collateral-CA1 synapse (Ayala et al., 2008). Therefore, AMN082-mediated activation of mGlu₇ may be highly dependent upon specific signaling pathways activated and the system involved. A novel mGlu₇ NAM, MMPIP, displays similar nuisances in determining its activity at mGlu₇, exhibiting permissive antagonism, varying antagonist ability contingent upon the signaling pathway being investigated (Kenakin, 2005; Niswender, 2008).

IV. Quantifying Allosteric Interactions

The binding of an allosteric modulator has the potential to modulate, either in a positive or negative manner, the binding affinity and/or signaling efficacy of an orthosteric ligand. This is a consequence of changes in the conformation of the receptor when it is simultaneously bound by more than one ligand, resulting in altered “geography” of the orthosteric site and also receptor/protein interfaces. The simplest model of GPCR allosteric interactions, referred to as the allosteric ternary complex model (ATCM; Fig. 3), assumes that allosteric modulator binding to its site changes only the affinity of the orthosteric ligand and vice versa. Within this model, the interaction is governed by the concentration of each ligand, the equilibrium dissociation constants of the orthosteric and allosteric ligands (K_A and K_B , respectively), and the “cooperativity factor” α , a measure of the magnitude and direction of the allosteric interaction between the two conformationally linked sites (Ehlert, 1988; Stockton et al., 1983). This model has been sufficient to describe the behavior of allosteric modulators for class A GPCRs, however, there is increasing evidence of allosteric modulators that alter signaling efficacy in addition to, or independently of, any effects on orthosteric ligand binding affinity.

With the continued discovery and characterization of allosteric modulators for a plethora of GPCRs, it is becoming more and more evident that in addition to, or independently of, modulating affinity and/or efficacy, allosteric ligands can act as agonists in their own right (Langmead & Christopoulos, 2006). Referred to as allosteric agonists, these compounds represent additional therapeutic development options and yet another level of complexity. Further, it is conceivable that an allosteric modulator can possess more than one of these properties concurrently, for example, positive or inverse agonism along with enhancement or inhibition of orthosteric agonist affinity/efficacy, or even have opposing effects on affinity and efficacy (May et al., 2007; Schwartz & Holst, 2007). Such a phenomenon is prevalent within the ion channel field, defined as use-dependent blockade, where an antagonist is more potent at blocking the active firing channel (Winqvist et al., 2005). For GPCRs, an example of this is the cannabinoid CB₁ receptor allosteric modulator, Org27569, which is a positive allosteric modulator of [³H]CP 55940 binding but a NAM of CP 55940 function (Price et al., 2005). The ATCM has been extended into an allosteric “two-state” model (ATSM) to account for such allosteric effects on efficacy (Hall, 2000). Further, Parmentier et al. (2002) have suggested an alternate extension of the ATCM that accounts for the fact that class C GPCRs have very distinct ligand binding and effector coupling domains and proposes an allosteric interaction between these two domains (Parmentier et al., 2002). Indeed, mGlu allosteric modulators are generally efficacy modulators only, most likely due to the fact that the orthosteric and allosteric binding sites are in very separate domains of the receptor.

While the ATSM and the model proposed by Parmentier and colleagues describe the multitude of effects an allosteric modulator may have on ligand–receptor interactions and functional properties, due to the large number of parameters, they are not amenable to fitting experimental biological data. To this end, an operational model of allosterism (Fig. 3) was recently reported that incorporates allosteric agonism as well as the capacity to modulate both efficacy and affinity (Leach et al., 2007; May et al., 2007). In this model, two cooperativity parameters describe the cooperativity between two interacting ligands, (α affinity) and (β efficacy). For each set of ligands, these parameters should be constant regardless of the measure of GPCR function, unless there is pathway specific modulation occurring, in which case the α values will change. Clearly, allosteric interactions can be considerably complex presenting challenges with respect to detection strategies and subsequent data interpretation.

V. Structural Determinants of mGlu Allosteric Modulator Binding

Through the use of chimeric and truncated receptor constructs, all currently identified allosteric modulators of mGlu are known to bind within the transmembrane-spanning regions of the receptor (Brauner-Osborne et al., 1999; Carroll et al., 2001; Gasparini et al., 2001; Goudet et al., 2004; Knoflach et al., 2001; Litschig et al., 1999; Maj et al., 2003; Mitsukawa et al., 2005; Pagano et al., 2000). Interestingly, truncation of the N-terminal extracellular VFD, but retention of an intact transmembrane region and a functional C terminus, yields a receptor that couples to G proteins and can be positively or negatively regulated by ligands, like any class A GPCR (Goudet et al., 2004), but which no longer responds to orthosteric ligands. Importantly, allosteric modulators retain activity in cells expressing the truncated receptor, PAMs are agonists, and NAMs become inverse agonists (Chen et al., 2007, 2008; Suzuki et al., 2007a). In the absence of a crystal structure of the transmembrane spanning regions of a class C GPCR, experimental evidence suggests that this region consists of seven transmembrane-spanning α -helices (Bhave et al., 2003), despite the low sequence identity (less than 20%) between the different classes of GPCRs. This predicted common architecture between the class A and class C GPCRs has provided the basis for the use of class A crystal structures as templates for homology models of the transmembrane-spanning region of class C GPCRs. Given the lack of sequence identity between classes, homology models cannot provide structural information at atomic resolution, therefore modeling best occurs synergistically alongside experimental studies of allosteric modulators (Ballesteros & Palczewski, 2001). With the growing number of mammalian GPCR crystal structures to use as templates (Cherezov et al., 2007; Chien et al., 2010; Jaakola et al., 2008; Palczewski et al., 2000; Rasmussen et al., 2007; Rosenbaum et al., 2007; Wu et al., 2010), a number of homology models of mGlu have been published revealing possible binding modes of known allosteric modulators within the top half of the α -helical transmembrane domains (TMs) (Gregory et al., 2010; Malherbe et al., 2003a, 2003b; Miedlich et al., 2004; Ott et al., 2000; Vanejevs et al., 2008). The availability of multiple templates has sparked development of high-throughput homology modeling of GPCRs (Yarnitzky et al., 2010), which has the potential to enrich our understanding of the transmembrane region of these receptors.

A. Common Allosteric Sites on the mGlu

One of the continuing challenges faced in drug discovery in general and for mGlu in particular is establishing suitably subtype-selective ligands. For the most part, mGlu allosteric modulators have displayed better specificity than orthosteric ligands. However, there are a number of examples of allosteric modulators that interact with more than one subtype: MPEP, an mGlu₅ NAM, is an mGlu₄ PAM (Mathiesen et al., 2003); DFB and CPPHA (mGlu₅ PAMs) are also weak mGlu₄ NAMs (O'Brien et al., 2003, 2004); PHCCC, an mGlu₄ PAM, is also an mGlu₁ NAM (Annoura et al., 1996). This lack of selectivity across mGlu from different groups suggests similarities within the allosteric binding pockets. Initial studies seeking to identify allosteric modulator binding sites of mGlu hypothesized that it would resemble the orthosteric site of class A GPCRs, located within the top third of the TMs. Indeed, it was shown that several residues critical for retinal-rhodopsin binding corresponded to important residues for allosteric modulator binding (Malherbe et al., 2003a, 2003b). To date, mutagenesis studies have exclusively investigated the determinants of allosteric modulator binding and cooperativity at mGlu₁, mGlu₂, and mGlu₅ (see Gregory et al., 2010 for review). Specifically, for Group I mGlu, important residues have been identified on the top half of TMs 3, 5, 6, and 7 on the inside faces of helices. Studies performing substitution of nonconserved residues from one mGlu subtype to another have provided further evidence for commonalities in the location of allosteric sites. For example, swapping residues known to be important for allosteric modulation by the

selective mGlu₁ compounds CPCCOEt and Ro 67-7476 onto mGlu₅ result in a gain of function of these compounds at mGlu₅ (Knoflach et al., 2001; Litschig et al., 1999). Similarly, exchange of residues important for binding of the mGlu₅ NAM, MPEP, onto mGlu₁ results in the gain of [³H]MPEP binding (Pagano et al., 2000). Interestingly, molecules from structurally distinct chemical scaffolds including both NAMs and PAMs have shown a tendency to cluster in overlapping binding sites. The mGlu₅ neutral MPEP site ligand, 5MPEP, displays a competitive interaction with PAMs from the CDPPB series, which are also able to displace [³H]methoxyPEPy binding (Chen et al., 2007). Clearly, despite the availability of selective allosteric modulators for Group I mGlu, there is evidence that the location of at least one allosteric site is very similar. For mGlu₂, important residues for interactions with PAMs have been identified in both TM4 and TM5, and exchange of the equivalent residues onto mGlu₃ results in a gain of mGlu₂ PAM activity (Hemstapat et al., 2007; Rowe et al., 2008; Schaffhauser et al., 2003). Those residues important for mGlu₂ PAM function in TM5 appear to cluster near the Group I mGlu common allosteric site, however, the residues in TM4 do not. It is important to note that mutagenesis data for mGlu₂ rely entirely upon functional assays, so it remains to be determined whether these residues are required for binding or for the transmission of cooperativity. Therefore, mapping of residues to TM4 does not necessarily suggest a different localization of an allosteric binding pocket on mGlu₂ relative to Group I mGlu.

B. Multiple Allosteric Sites Within a mGlu Subtype

In addition to evidence of common allosteric sites utilized by both PAMs and NAMs at a single mGlu subtype, a number of studies have described allosteric ligands that do not appear to compete with common allosteric sites. The most striking example of this being CPPHA, a Group I PAM, which displaces neither [³H]methoxyPEPy at mGlu₅ nor [³H]R214127 at mGlu₁ (Chen et al., 2008; O'Brien et al., 2004). Moreover, 5MPEP noncompetitively inhibits CPPHA potentiation of glutamate at mGlu₅, suggesting that not only does CPPHA bind to a distinct allosteric site, but also that these two allosteric sites can allosterically regulate one another (Chen et al., 2008). Preliminary site-directed mutagenesis identified a single point mutation at the top of TM1 (F585I/mGlu₅; F599I/mGlu₁) that abolished potentiation of orthosteric agonists by CPPHA (Chen et al., 2008). Further, residues known to perturb modulators that compete at the common Group I allosteric site (A809V/mGlu₅ and V757L/mGlu₁) had no effect on CPPHA potentiation. Similarly, two mGlu₁ selective PAMs, VU48 and VU71, which are noncompetitive with [³H]R214127 and insensitive to mutations known to affect NAMs that bind the common Group I mGlu allosteric site, have been reported (Hemstapat et al., 2006). Collectively, these data suggest the presence of multiple distinct allosteric sites on Group I mGlu that can be targeted by PAMs. Although limited mutagenesis studies have been performed regarding mGlu_{2/3} NAMs, mutation of a residue important for mGlu₂ PAM functional activity, N735 in TM5, does not affect the functional responses of the mGlu_{2/3} NAM MNI-137, implying that mGlu_{2/3} NAMs may occupy a separate allosteric site from the mGlu₂ PAMs (Hemstapat et al., 2007). However, as noted earlier, as this study relies upon functional assays alone, it is not evident whether or not this point mutation perturbs PAM affinity or cooperativity. Therefore, an alternative conclusion is that this particular residue is important for positive cooperativity or receptor activation; if this is the case, it is not surprising that this residue would have no effect on a NAM. Although less conclusive, there is evidence in support of multiple allosteric binding pockets for mGlu₄ PAMs. The presence of PHCCC, an mGlu₄ PAM, does not affect the potentiation concentration–response curve of VU0155041, a structurally distinct PAM, suggesting that these two ligands are not competitive for the same allosteric site (Niswender et al., 2008a).

VI. Functional Selectivity of mGlu Allosteric Modulation

Within the GPCR field, it is becoming increasingly evident that the consequences of receptor activation are not limited to G protein-coupling alone, with the overall cellular response to GPCR activation arising from a myriad of receptor-effector interactions. Indeed, it is now well established that ligand pharmacology is dependent upon the measure of receptor activation employed, a phenomenon referred to by many names including “stimulus trafficking,” “biased agonism,” and “functional selectivity” (Galandrin et al., 2007; Kenakin, 2007; Urban et al., 2007). With multiple binding pockets to exploit and diverse chemical scaffolds being tolerated within common mGlu allosteric binding sites, it is conceivable that allosteric modulators may have the capacity to differentially modulate signaling to different effector pathways. Indeed, in rat cortical astrocytes, CPPHA potentiates signaling to phosphorylation of ERK1/2 versus inositol phosphate turnover differentially, while other PAMs such as VU-29 have similar effects on both pathways (Zhang et al., 2005). Also, MMPIP, an mGlu₇ NAM, has differential effects on the receptor activation depending upon the measure of receptor activation and cellular background (Niswender et al., 2010). Further, Ro 67-4853 and other structurally related mGlu₁ PAMs potentiate mGlu₁-mediated calcium mobilization but act as allosteric agonists for mGlu₁-mediated ERK1/2 phosphorylation and stimulation of cAMP (Sheffler & Conn, 2008). Such diversity in functional coupling of allosteric modulator-bound receptors has important implications with respect to the development of therapeutics, particularly for selection of screening assays and lead compounds. If the pathophysiology of a disease of therapeutic end-point can be attributed to the activation or inactivation of a particular pathway, then selective modulation by allosteric ligand may represent a novel, more selective means of therapeutic intervention.

VII. Therapeutic Potential of mGlu Allosteric Modulators

A. mGlu₁ NAMs for Pain

Multiple studies have demonstrated the efficacy of mGlu₁ NAMs in models of analgesia. For example, the mGlu₁ NAM YM-298198 is analgesic in the streptozotocin-induced hyperalgesia mouse model (Kohara et al., 2005), and FTIDC displays analgesic effects in the formalin test (Satow et al., 2008). In addition, the mGlu₁ NAM CPCCOEt dose-dependently reversed capsaicin-induced sensitization in spinothalamic tract cells *in vivo* demonstrating the potential utility of mGlu₁-selective NAMs for the treatment of persistent pain associated with spinal sensitization (Neugebauer et al., 1999). Although mGlu₁ NAM development has largely focused on potential in pain, mGlu₁ NAMs have also demonstrated efficacy in models of anxiety (Satow et al., 2008), antipsychotic activity (Satow et al., 2008), and addiction (Xie et al., 2010).

B. mGlu₅ NAMs for Anxiety, Depression, and Fragile X Syndrome

Several preclinical studies suggest a role for mGlu₅ NAMs as a therapeutic approach for the treatment of anxiety. MPEP, a selective mGlu₅ NAM, demonstrates anxiolytic activity in several rodent behavioral models including marble burying, elevated plus maze, fear-potentiated startle, social exploration, stress-induced hyperthermia, ultrasonic vocalizations, and the Vogel conflict test (Spooren & Gasparini, 2004). Further, Fenobam, a nonbenzodiazepine anxiolytic, was recently found to be a selective negative modulator of mGlu₅ (Porter et al., 2005). Fenobam has not only been shown to be efficacious in preclinical model of anxiety (Patel et al., 1982) but also in clinical trials (Pecknold et al., 1982) establishing efficacy of mGlu₅ NAMs in the treatment of anxiety. Recent studies have also linked antagonism of mGlu₅ with antidepressant activity. MPEP and MTEP exhibit antidepressant activity in multiple animal behavioral models of depression, including the tail suspension test (Tatarczynska et al., 2001) and forced swim test (Li et al., 2006) in mice, as

well as passive-learning in olfactory bulbectomized rats (Wieronska et al., 2002). While further testing in chronic depression models is needed, these data suggest exciting new potential in mGlu₅ NAMs as novel antidepressants. Although mGlu₅ NAM development has largely focused on anxiety disorders, additional studies suggest that mGlu₅ NAMs have therapeutic potential in the treatment of addiction, chronic pain, migraine, Alzheimer's disease, gastroesophageal reflux (GERD), as well as fragile X syndrome (FXS) (Alexander & Godwin, 2006; Goudet et al., 2009; Keywood et al., 2009; Lehmann, 2008; Slassi et al., 2005; Thathiah & De Strooper, 2011; Ure et al., 2006; Varney & Gereau, 2002).

In particular, the potential for mGlu₅ NAMs for the treatment of FXS has gained momentum through recent preclinical and clinical studies. FXS is the most common inherited form of mental retardation and autism, which is caused by the transcriptional silencing of the *FMR1* gene due to an expansion of a CGG repeat. The *FMR1* gene product, fragile X mental retardation protein (FMRP), negatively regulates local protein synthesis in neuronal dendrites responsible for promoting LTD. In its absence, overabundance of these proteins results in reduced synaptic strength due to AMPA receptor trafficking abnormalities that lead, at least in part, to the fragile X phenotype (Bear, 2005; Dolen et al., 2010). Importantly, multiple studies have demonstrated that increased mGlu₅ signaling occurs in FXS (Bear, 2005; Ronesi & Huber, 2008), a reduction in mGlu₅ expression rescues FXS phenotypes (Dolen et al., 2010), and that FXS mice demonstrate diminished FXS phenotypes, such as anxiety and seizures, when treated with MPEP (Yan et al., 2005). These preclinical studies have validated the use of mGlu₅ NAMs as a potential therapeutic strategy for FXS. AFQ056, a NAM of mGlu₅, is currently in phase 2 clinical trials in adults with FXS and has demonstrated improvement in several patients with full *FMR1* promoter methylation and no detectable *FMR1* messenger RNA (Jacquemont et al., 2010).

C. mGlu₅ PAMs for Schizophrenia

Positive allosteric modulation of mGlu₅ has also emerged as a novel therapeutic target for the treatment of schizophrenia and cognitive disorders. Early clinical findings demonstrated that noncompetitive, use-dependent *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP) and ketamine, produce a state of psychosis in humans that is not clinically distinguishable from that observed in schizophrenic patients (Luby et al., 1959). Moreover, administration of NMDA receptor function-enhancing agents, such as agonists at the glycine binding site of the NMDA receptor, results in a symptomatic improvement in schizophrenic patients (Heresco-Levy & Javitt, 2004; Heresco-Levy et al., 1999, 2005; Javitt et al., 1997). Based on these clinical studies, enhancement of glutamatergic neurotransmission via increased NMDA receptor activity has been proposed as a potential treatment for the psychotic symptoms and cognitive deficits associated with many neurological disorders.

Numerous studies suggest that mGlu₅ is a closely associated signaling partner with the NMDA receptor and may play an integral role in regulating NMDA receptor function in various forebrain regions implicated in the pathology of schizophrenia (Homayoun et al., 2004; Marino & Conn, 2002). Consistently, activation of mGlu₅ receptors results in the potentiation of NMDA receptor currents in hippocampal pyramidal cells, suggesting a role of mGlu₅ in cognitive function (Mannaioni et al., 2001). Therefore, selective activation of mGlu₅ and subsequent enhancement of NMDA receptor activity may provide a novel approach to the treatment of not only the positive symptoms but also the negative symptoms and cognitive deficits afflicting patients with schizophrenia. Multiple mGlu₅ PAMs have been identified and potentiate mGlu₅-mediated electrophysiological responses in midbrain and forebrain circuits, including NMDA receptor currents (Ayala et al., 2009; Chen et al., 2007; O'Brien et al., 2004). Further, the positive modulators of mGlu₅, CDPPB, ADX47273, and VU0360172 demonstrate robust efficacy in models predictive of

antipsychotic activity and cognition enhancement (Kinney et al., 2005; Liu et al., 2008; Rodriguez et al., 2010; Stefani & Moghaddam, 2010). These findings present exciting evidence for the use of mGlu₅ potentiators in the treatment of schizophrenia. Extensive discovery efforts to develop a selective mGlu₅ PAM for clinical trials are ongoing.

D. mGlu₂ PAMs for Schizophrenia, Anxiety Disorders, and Drug Dependence

There is a tremendous volume of clinical and preclinical evidence that Group II mGlu activators have potential as a novel approach for the treatment of schizophrenia and anxiety disorders. Many brain regions relevant to schizophrenia and anxiety express Group II mGlu (Lindsley et al., 2006; Schoepp & Marek, 2002), and Group II agonists reduce neurotransmission in these regions (Chavez-Noriega et al., 2005; Doherty et al., 2004; Macek et al., 1996; Nicholls et al., 2006). Further, the effects of psychotomimetics on thalamocortical glutamatergic neurotransmission, a region postulated to play a role in the pathophysiology of schizophrenia (Chavez-Noriega et al., 2005; Lorrain et al., 2003; Moghaddam, 2004), are blocked by Group II mGlu agonists (Marek et al., 2000). Numerous studies have further demonstrated that Group II agonists have activity in multiple animal models of anxiolytic (Swanson et al., 2005) and antipsychotic (Marek, 2010) drug action, including reversal of PCP-induced hyperlocomotor activity, stereotyped behaviors, and working memory deficits in rats (Cartmell et al., 1999; Moghaddam & Adams, 1998). In addition, Group II agonists inhibit PCP-(Moghaddam & Adams, 1998) or ketamine-induced (Lorrain et al., 2003) glutamate release in prefrontal cortex and nucleus accumbens, two regions of the brain thought to be relevant for antipsychotic drug action. Importantly, LY2140023, the prodrug of the Group II agonist LY404039, recently demonstrated antipsychotic efficacy in a clinical trial, with schizophrenic patients showing improvements in multiple symptom clusters (Patil et al., 2007).

The efficacy of Group II agonists in anxiolytic and antipsychotic models has paved the way for evaluation of mGlu₂ selective PAMs as an alternative therapeutic route. Similar to the Group II agonists, numerous mGlu₂ PAMs have demonstrated efficacy in reversing PCP- or ketamine-induced hyperlocomotion in rodents (Galici et al., 2005, 2006; Govek et al., 2005; Hackler et al., 2010; Johnson et al., 2005; Pinkerton et al., 2004, 2005). mGlu₂ PAMs have also been demonstrated to inhibit ketamine-induced neurotransmitter release in brain regions relevant for the antipsychotic action of Group II agonists, including norepinephrine release in the ventral hippocampus (Pinkerton et al., 2004) and histamine release in the medial prefrontal cortex (mPFC; Fell et al., 2010). Further, two distinct mGlu₂ PAMs, BINA and LY487379, have been evaluated in PPI, an animal model of sensorimotor gating that is disrupted in schizophrenic patients. Although Group II agonists have no effect on PPI, LY487379 reversed amphetamine-, but not PCP-, induced disruptions of PPI (Galici et al., 2005), whereas BINA reversed PCP-induced disruptions of PPI (Galici et al., 2006). Together, these studies suggest that mGlu₂ PAMs may provide a novel approach toward the sensorimotor gating deficits associated with schizophrenia. In addition to these models of antipsychotic drug action, multiple mGlu₂ PAMs have demonstrated efficacy in several models of anxiolytic action, including stress-induced hyperthermia (Fell et al., 2011; Galici et al., 2006), marble burying (Fell et al., 2011), fear-potentiated startle (Johnson et al., 2003, 2005), and in the elevated plus maze (Galici et al., 2006). Together, these studies raise the possibility that selective mGlu₂ PAMs might provide a novel approach to the treatment of schizophrenia and anxiety disorders.

In addition to anxiety and schizophrenia, Group II agonists have also been suggested for the treatment of drug addiction and relapse (Moussawi & Kalivas, 2010). In animal models, Group II agonists attenuate cocaine self-administration (Adewale et al., 2006; Baptista et al., 2004; Kim et al., 2005) and cocaine-seeking behavior (Baptista et al., 2004; Peters & Kalivas, 2006). In addition to their effects on cocaine, Group II agonists also inhibit heroin-

seeking (Bossert et al., 2005, 2006) and alcohol-seeking (Backstrom & Hyttia, 2005) behaviors. Although these studies are promising, Group II agonists have also been demonstrated to decrease food-seeking behavior (Baptista et al., 2004; Jin et al., 2010; Peters & Kalivas, 2006), implying that Group II agonists decrease responses to both drug and natural rewards. Alternatively, recent studies with the mGlu₂ PAM BINA have demonstrated attenuation of cocaine-self administration and cocaine-seeking without an effect on food responding, implying that mGlu₂ PAMs may provide a better therapeutic approach to drug addiction than direct acting agonists (Dhanya et al., 2011; Jin et al., 2010).

E. mGlu₃ PAMs for Neuroprotection

Numerous mGlu₃ have been suggested as a target for neurodegenerative disorders (Nicoletti et al., 1996). In particular, a number of studies have demonstrated that Group II mGlu agonists are neuroprotective when mixed cultures of cortical neurons and astrocytes are challenged with NMDA (Bruno et al., 1997, 1998) via a glial-neuronal mechanism involving transforming growth factor (Bruno et al., 1998). Studies with mGlu₂ and mGlu₃ KO mice have shown that mGlu₃ expressed on the astrocytes are necessary for this effect and that, in the absence of mGlu₃, the activation of neuronally expressed mGlu₂ may further contribute to excitotoxicity (Corti et al., 2007). Recently, LY2389575, an mGlu₃ selective NAM, was utilized in combination with mGlu₃ KO mice to further demonstrate that activation of glial mGlu₃ receptors was protective against amyloid neurotoxicity (Caraci et al., 2010). Together, these studies suggest that mGlu₃ selective PAMs may have efficacy as neuroprotective agents and potentially novel targets for the treatment of Alzheimer's disease.

F. Group II NAMs for Cognitive Enhancement

Group II agonists (Spinelli et al., 2005) and muscarinic antagonists, such as scopolamine (Dunnett, 1993), induce deficits in the delayed match to position (DMTP) task in rodents, a measure of working memory. Recently, a Group II NAM has been shown to reverse Group II agonist or scopolamine-induced working memory deficits in the DMTP task (Woltering et al., 2010). Additional studies by this group demonstrated a synergistic reversal of scopolamine-induced deficits in DMTP when low doses of a Group II NAM were combined with a threshold dose of the acetylcholinesterase inhibitor donepezil (Woltering et al., 2010). Given the efficacy of donepezil and other acetylcholinesterase inhibitors in the treatment of the cognitive impairments in Alzheimer's disease (Tsuno, 2009), Group II NAMs may have efficacy as cognitive enhancers.

G. mGlu₄ PAMs for Parkinson's Disease

mGlu₄ is expressed on GABAergic fibers within the indirect pathway of motor control in the basal ganglia circuit. Activation of these receptors decreases GABA release at the striatopallidal synapse, which is overactive after the loss of dopamine neurons in Parkinson's disease (PD) (Macinnes & Duty, 2008; Matsui & Kita, 2003; Valenti et al., 2003). Disinhibition of thalamocortical neurons is believed to alleviate Parkinsonian symptoms and is the basis for targeting mGlu₄ for the treatment of PD (Conn et al., 2005). PHCCC, a selective mGlu₄ PAM, potentiates mGlu₄-mediated inhibition at the striatopallidal synapse (Marino et al., 2003). In addition, PHCCC, as well as VU0155041, demonstrates antiparkinsonian effects in preclinical models, such as reversal of haloperidol-induced catalepsy and reserpine-induced akinesia (Marino et al., 2003; Niswender et al., 2008a). PHCCC also exhibits neuroprotective properties and has been shown to decrease dopamine neuron degeneration in the substantia nigra in a MPTP model of PD, providing evidence of mGlu₄ PAMs' ability to potentially slow progression of PD by reducing excitotoxicity of dopamine neurons resulting from excessive excitatory stimulation (Battaglia et al., 2006; Valenti et al., 2005).

Group III mGluRs demonstrate potential for the treatment of several other CNS disorders. mGlu₄ KO mice are resistant to characteristics attributed to alcohol addiction (Blednov et al., 2004); injection of the mGlu₇ allosteric agonist, AMN082, into the nucleus accumbens and ventral pallidum inhibits cocaine self-administration (Li et al., 2009); and mGlu₈ expression is altered by cocaine and amphetamine administration (Parelkar & Wang, 2008; Zhang et al., 2009), suggesting a role for Group III receptors in addiction. Pharmacological and genetic studies implicate mGlu₄ and mGlu₇ in the regulation of seizures (Ngomba et al., 2008; Sansig et al., 2001; Snead et al., 2000). Additional research proposes roles of Group III mGluRs in anxiety and depression (Klak et al., 2007; Palucha et al., 2007; Stachowicz et al., 2004, 2006, 2008), and neuroblastoma (Iacovelli et al., 2006).

VIII. Conclusion

Within the past 15 years, selective allosteric modulators have been developed for the vast majority of the mGluRs. This advance, together with the development of mGlu KO mice, has greatly led to our better understanding of the roles of individual mGlu subtypes in a number of systems. Within this time, the mGlu allosteric modulators field has also made significant advances in the understanding of how and where these compounds interact with the receptor. These studies have suggested commonalities among mGlu allosteric sites, and that individual mGlu subtypes can have multiple allosteric sites. However, given the inherent complexity of allosteric interactions, there remains a great need to further investigate these mechanisms. In particular, numerous mGlu allosteric modulators have been demonstrated to display functional selectivity. Thus, allosteric modulators have the potential to engender unique receptor conformations that may have different functional consequences than regular competitive ligands. This possibility suggests that evaluation of mGlu allosteric modulators across multiple functional outputs is key to a greater understanding of how a given modulator may function *in vivo*. It remains to be determined whether pure modulation or both modulator and agonist properties, that is, inverse agonist/NAMs or agonist/PAMs, will be required to treat diseases with mGlu allosteric ligands. In all likelihood, each therapeutic intervention will require a different drug profile. Regardless, numerous preclinical and clinical studies continue to provide validity for utilizing mGlu allosteric ligands as a therapeutic approach, and it is likely that these studies will pave the way for additional utilization of mGlu allosteric modulators for the treatment of numerous neurological and psychiatric disorders in the coming years.

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Abbreviations

5MPEP	5-methyl-6-(phenylethynyl)-pyridine
ADX47273	<i>S</i> -(4-fluorophenyl)-{3-[3-(4-fluorophenyl)-[1,2,4] oxadiazol-5-yl]-piperidin-1-yl}-methanone
AMN082	<i>N,N</i> -bis(diphenylmethyl)-1,2-ethanediamine
ATCM	allosteric ternary complex model
Bay 36-7620	(3 <i>aS</i> ,6 <i>aS</i>)-hexahydro-5-methylene-6 <i>a</i> -(2-naphthalenylmethyl)-1 <i>H</i> -cyclopenta[<i>c</i>]furan-1-one
BINA	Biphenyl-indanone A

cAMP	cyclic adenosine monophosphate
CaSR	calcium-sensing receptor
CCR5	C–C chemokine receptor type 5
CDPPB	3-cyano- <i>N</i> -(1,3-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide
CPCCOEt	7-(hydroxyimino)cyclopropa[<i>b</i>]chromen-1 <i>a</i> -carboxylate ethyl ester
CPPHA	<i>N</i> -{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2 <i>H</i> -isoindol-2-yl)methyl]phenyl}-2-hydroxybenzamide
DFB	[(3-fluorophenyl)methylene]hydrazone-3-fluorobenzaldehyde
DMTP	delayed match to position
ERK1/2	extracellular signal-regulated kinases 1 and 2
FMRP	fragile X mental retardation protein
FTDC	4-[1-(2-fluoropyridin-3-yl)-5-methyl-1 <i>H</i> -1,2,3-triazol-4-yl]- <i>N</i> -isopropyl- <i>N</i> -methyl-3,6-dihydropyridine-1(2 <i>H</i>)-carboxamide
FXS	fragile X syndrome
GERD	gastroesophageal reflux
GPCR	G protein-coupled receptor
JNJ16259685	(3,4-dihydro-2 <i>H</i> -pyrano[2,3- <i>b</i>]quinolin-7-yl)-(cis-4-methoxycyclohexyl)-methanone
KO	knockout
LTD	long-term depression
LTP	long-term potentiation
LY2389575	(3 <i>S</i>)-1-(5-bromopyrimidin-2-yl)- <i>N</i> -(2,4-dichlorobenzyl) pyrrolidin-3-amine methanesulfonate hydrate
LY404039	(–)-(1 <i>R</i> ,4 <i>S</i> ,5 <i>S</i> ,6 <i>S</i>)-4-amino-2-sulfonylbicyclo[3.1.0] hexane-4,6-dicarboxylic acid
LY487379	2,2,2-trifluoro- <i>N</i> -[4-(2-methoxyphenoxy) phenyl]- <i>N</i> -(3-pyridinylmethyl)ethanesulfonamide
mGlu	metabotropic glutamate receptor
MMPIP	6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo [4,5- <i>c</i>]pyridine-4(5 <i>H</i>)-one hydrochloride
MNI-137	4-(7-bromo-4-oxo-4,5-dihydro-3 <i>H</i> -benzo[1,4]diazepin-2-yl)-pyridine-2-carbonitrile
MPEP	2-methyl-6-(phenylethynyl)pyridine
mPFC	medial prefrontal cortex
MTEP	3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine
NAM	negative allosteric modulator
NMDA	<i>N</i> -methyl-D-aspartate
Org27569	5-chloro-3-ethyl- <i>N</i> -[2-[4-(1-piperidinyl)phenyl]ethyl]-1 <i>H</i> -indole-2-carboxamide

PAM	positive allosteric modulator
PCP	phencyclidine
PD	Parkinson's disease
PHCCC	<i>N</i> -Phenyl-7-(hydroxyimino)cyclopropa[<i>b</i>] chromen-1a-carboxamide
PPI	prepulse inhibition
Ro 67-4853	(9 <i>H</i> -xanthene-9-carbonyl)-carbamic acid butyl ester
Ro 67-7476	(<i>S</i>)-2-(4-fluorophenyl)-1-(toluene-4-sulfonyl)-pyrrolidine
SIB-1757	6-methyl-2-(phenylazo)-3-pyridinol
SIB-1893	2-methyl-6-(2-phenylethenyl)pyridine
TM	transmembrane domain
VFD	venus flytrap domain
VU0155041	<i>cis</i> -2-{[(3,5-dichlorophenyl)amino]carbonyl} cyclohexanecarboxylic acid
VU0285683	3-fluoro-5-(3-(pyridine-2-yl)-1,2,4-oxadiazol-5-yl) benzonitrile
VU0360172	<i>N</i> -cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide
VU29	4-nitro- <i>N</i> -(1,3-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide
VU48	4-nitro- <i>N</i> -(1-(2-bromophenyl)-3-phenyl-1 <i>H</i> -pyrazol-5-yl) benzamide
VU71	4-nitro- <i>N</i> -(1,4-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide
YM298198	6-amino- <i>N</i> -cyclohexyl- <i>N</i> ,3-dimethylthiazolo[3,2-] benzimidazole-2-carboxamide

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FIGURE 1.

Schematic representation of mGluR at the synapse. Group I mGluR, mGlu₁ and mGlu₅, are generally localized postsynaptically, while Group II mGluR (mGlu₂ and mGlu₃) and Group III mGluR (mGlu₄, mGlu₇, and mGlu₈) are localized in presynaptic locations, although exceptions occur. mGlu₆ is not shown in this figure as it is only found localized postsynaptically in the retina. On presynaptic terminals, Group II and III receptors often function to inhibit neurotransmitter release, whereas Group I mGluR promote release when present. Postsynaptically, Group I mGluR signal via G_q proteins to increase intracellular calcium, whereas Group II mGluR signal via $G_{i/o}$ proteins to inhibit cAMP production. mGlu₅ activation also can potentiate *N*-methyl-D-aspartate (NMDA) glutamate receptor currents. In addition to the NMDA receptor, the other ionotropic glutamate receptors, the α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and kainate receptors, respond to glutamate with increases in intracellular sodium or calcium, promoting cell excitability. In the CNS, mGlu₃ and mGlu₅ have also been found to be expressed on glia.

FIGURE 2.

Representation of the mGlu structure. mGlu possess a large N-terminal extracellular domain that contains the orthosteric binding site of the endogenous ligand glutamate, referred to as the venus flytrap domain (VFD). The extracellular VFD is connected to seven transmembrane (7TM) domains via a cysteine-rich domain. Allosteric ligands bind to sites other than the orthosteric glutamate binding site, such as within the 7TM domain. Group I mGlu couple to G_{q/11} proteins, whereas the Group II and Group III mGlu couple to G_{i/o} proteins.

FIGURE 3.

Models of allosteric interactions. (A) Allosteric ternary complex model (ACTM), (B) Operational model of allosterism. In these models, the affinity (equilibrium dissociation constant) of the orthosteric ligand (A) for the receptor (R) is defined as K_A , while the affinity of the allosteric modulator (B) is K_B . α is the affinity cooperativity parameter, denoting the direction and magnitude of the allosteric interaction. The pharmacological effect or stimulus arising from the orthosteric agonist occupied receptor is S_A , whereas that arising from the modulator occupied receptor is S_B . β is the efficacy cooperativity parameter, describing the change in S_A when both orthosteric and allosteric sites are occupied. α denotes the coupling efficiency of the orthosteric ligand, E_m represents the maximal system response, while n is the slope factor that links occupancy to response.

TABLE I
Representative Allosteric Modulators of mGlu and Their Potential Therapeutic Applications

mGlu subtype	Intervention	Therapeutic indication	Representative modulators	<i>In vitro</i> potency (nM)	<i>In vitro</i> affinity (nM)	Reference(s)
1	NAM	Pain, anxiety, drug abuse	CPCCOEt	3400–6500	4900	Ott et al. (2000), Litschig et al. (1999), Suzuki et al. (2007a)
2	Agonist/PAM	Anxiety, drug abuse, schizophrenia	FTDC BINA LY487379	6 98–347 270–1700	2	Suzuki et al. (2007a, 2009) Galici et al. (2006), Jin et al. (2010) Johnson et al. (2003), Schaffhauser et al. (2003)
3	Agonist/PAM	Neuroprotection	None reported			
4	Agonist/PAM	Movement disorders, Parkinson's disease	PHCCC ^a	4100–6000		Maj et al. (2003), Marino et al. (2003), Niswender et al. (2008a)
5	NAM	Anxiety, chronic pain, depression, fragile X Syndrome, GERD, migraine, drug abuse	VU0155041 MPEP ^b	693–798 2–36	3–12	Niswender et al. (2008a) Malherbe et al. (2006, 2003a), Gasparini et al. (1999), Cosford et al. (2003a, 2003b), Rodriguez et al. (2005), Porter et al. (2005)
5	PAM	Cognition disorders, schizophrenia	MTEP Fenobam VU0285683 ADX47273	5–47 38–58 24 170–479	5–16 31–61 17 4300	Malherbe et al. (2006), Cosford et al. (2003a, 2003b), Porter et al. (2005) Ceccarelli et al. (2007), Porter et al. (2005) Rodriguez et al. (2010) de Paulis et al. (2006), Liu et al. (2008), Bradley et al. (2009), Rosenbrock et al. (2010)
7	NAM	Depression, anxiety	CDPPB CPPHA ^c VU0360172	27–347 239–810 16	1300–3800	Kinney et al. (2005), de Paulis et al. (2006), Chen et al. (2007), Bradley et al. (2009) O'Brien et al. (2004), Zhang et al. (2005), Chen et al. (2008) Rodriguez et al. (2010)
7	Agonist/PAM	Anxiety, depression, epilepsy, drug abuse	MMPIP AMN082	26–718 64–240		Suzuki et al. (2007b), Niswender et al. (2010) Suzuki et al. (2007b), Mitsukawa et al. (2005), Fendt et al. (2008)
8	Agonist/PAM	Anxiety, drug abuse, epilepsy, pain	No selective allosteric ligands reported			

^aPHCCC is also a weak mGlu1 NAM (Annoura et al., 1996) and an mGlu6 agonist (Begollari & Kammermeier, 2008).

^b MPEP is also a weak mGlu₄ PAM (Mathiesen et al., 2003).

^c CPPHA is also a weak mGlu₄ and mGlu₈ NAM (O'Brien et al., 2004) and an mGlu₁ PAM (Chen et al., 2008).