

Metabotropic Glutamate Receptors: Physiology, Pharmacology, and Disease

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Key Words

G-protein-coupled receptors, neuromodulation, allosterism, synaptic plasticity

Abstract

The metabotropic glutamate receptors (mGluRs) are family C G-protein-coupled receptors that participate in the modulation of synaptic transmission and neuronal excitability throughout the central nervous system. The mGluRs bind glutamate within a large extracellular domain and transmit signals through the receptor protein to intracellular signaling partners. A great deal of progress has been made in determining the mechanisms by which mGluRs are activated, proteins with which they interact, and orthosteric and allosteric ligands that can modulate receptor activity. The widespread expression of mGluRs makes these receptors particularly attractive drug targets, and recent studies continue to validate the therapeutic utility of mGluR ligands in neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, anxiety, depression, and schizophrenia.

INTRODUCTION

L-glutamate serves as the neurotransmitter at the majority of excitatory synapses in the mammalian central nervous system (CNS). The existence of neuromodulatory glutamate receptors, called metabotropic glutamate receptors (mGluRs), provides a mechanism by which glutamate can modulate cell excitability and synaptic transmission via second messenger signaling pathways. The widespread distribution of mGluR proteins suggests that these neuromodulatory receptors have the ability to participate in numerous functions throughout the CNS and may represent ideal targets for therapeutic intervention in a wide variety of CNS disorders.

STRUCTURAL FEATURES OF mGluRs

mGluRs are members of the G-protein-coupled receptor (GPCR) superfamily, the most abundant receptor gene family in the human genome. GPCRs are membrane-bound proteins that are activated by extracellular ligands such as light, peptides, and neurotransmitters, and transduce intracellular signals via interactions with G proteins. The resulting change in conformation of the GPCR induced by ligand binding activates the G protein, which is composed of a heterotrimeric complex of α , β , and γ subunits. In their inactive state, G proteins are bound to guanosine 5'-diphosphate (GDP); activation of the G protein causes the exchange of guanosine 5'-triphosphate (GTP) for GDP within the α subunit. Activated G protein subunits then modulate the function of various effector molecules such as enzymes, ion channels, and transcription factors. Inactivation of the G protein occurs when the bound GTP is hydrolyzed to GDP, resulting in reassembly of the heterotrimer.

The GPCR family contains several subgroupings, and the majority of classical neurotransmitter GPCRs belong to family A. These receptors are often termed the rhodopsin-like GPCRs and are structurally similar in that they consist of an extracellular N-terminal domain, seven transmembrane-spanning domains, and an intracellular C-terminus. In contrast to family A receptors, mGluRs belong to class C GPCRs. These receptors are distinguished from their family A relatives by the presence of a large extracellular N-terminal domain that contains the endogenous ligand-binding site, discussed in more detail below. Family C GPCRs also include GABA_B receptors, calcium-sensing receptors, pheromone receptors, and taste receptors (1). Genes encoding eight mGluR subtypes have been identified, many with multiple splice variants that are differentially expressed in distinct cell types throughout the CNS. mGluRs are subclassified into three groups based on sequence homology, G-protein coupling, and ligand selectivity. Group I includes mGluRs 1 and 5, Group II includes mGluRs 2 and 3, and Group III includes mGluRs, 4, 6, 7, and 8 (Table 1).

The Venus Flytrap Domain

As mentioned above, mGluRs contain a large extracellular N-terminal domain, termed the Venus flytrap domain (VFD), which contains the glutamate-binding site (1) (Figure 1). The examination of crystal structures of N-terminal domains of mGluR1 (2, 3), mGluR3, and mGluR7 (4) reveals that each VFD consists of two lobes that sit one atop the other and bind glutamate in a cleft between them. Evidence suggests that two VFDs dimerize together, back to back, and large conformational changes are induced when agonists bind to one or both VFDs (5). Three main states of the VFD dimer exist: open-open, open-closed, and closed-closed (Figure 1). The open-open (inactive) conformation is stabilized by antagonists; the open-closed and closed-closed conformations are induced by the binding of ligand to one or two protomers. The mutation of

Table 1 Key features of mGluRs

Group	Receptor/splice variants	CNS expression	Synaptic localization	Signaling pathways of group
Group I	mGluR1 a,b,c,d,e,f Taste mGluR1	Widespread in neurons Taste buds	Predominantly postsynaptic	Phospholipase C stimulation Stimulation of adenylyl cyclase (some systems) MAP kinase phosphorylation
	mGluR5 a,b	Widespread in neurons, astrocytes		
Group II	mGluR2	Widespread in neurons	Presynaptic and postsynaptic	Inhibition of adenylyl cyclase Activation of K ⁺ channels Inhibition of Ca ⁺⁺ channels
	mGluR3 GRM3Δ2 GRM3Δ4 GRM3Δ2Δ3	Widespread in neurons, astrocytes		
Group III	mGluR4 Taste mGluR4	Widespread in neurons, High in cerebellum Taste buds	Predominantly presynaptic	Inhibition of adenylyl cyclase Activation of K ⁺ channels Inhibition of Ca ⁺⁺ channels
	mGluR6 a,b,c	Retina	Postsynaptic in ON-bipolar retinal cells	Stimulation of cGMP phosphodiesterase (mGluR6)
	mGluR7 a,b,c,d,e	Widespread in neurons	Active zone of presynaptic terminals	
	mGluR8 a,b,c	Lower and more restricted expression than mGluR4/7	Predominantly presynaptic	

residues that prevent closure of the VFD can switch the pharmacology of antagonists to agonists (6), indicating that the relative orientation of these domains is important for receptor activation. For glutamate binding, several conserved residues span lobes 1 and 2 and make critical contacts with the glutamate molecule (1, 7, 8). In addition to binding glutamate, VFDs also bind divalent cations such as magnesium and calcium, which can potentiate or activate the receptor (3, 9, 10).

Cysteine-Rich Domains

Conformational changes induced by ligand binding are propagated from the VFD via cysteine-rich domains (CRDs) to the heptahelical domain (HD)–C-terminal tail. The CRD contains nine critical cysteine residues, eight of which are linked by disulfide bridges (4). Crystallization and mutagenesis studies have shown that the signal induced by ligand binding is transmitted from the VFDs through the CRDs, in part because of a disulfide bridge formed by the ninth CRD cysteine with a cysteine in lobe 2 of the VFD (4, 11). Rondard et al. (11) recently showed that mutation of Cys234 in the VFD of mGluR2 resulted in a receptor that could be expressed at the surface, dimerize, and bind ligands appropriately but could not induce intracellular signaling. The receptor was still functional, however, as shown by normal signal transduction induced by an allosteric ligand that bound within the HD rather than the VFD. Further studies identified the CRD-located Cys518 as the partner of Cys234, and similar results were shown using homologous cysteines within mGluR5. These results suggest that a disulfide bridge linking the CRD and the VFD may be globally involved in propagation of signals induced by orthosteric agonist binding to mGluRs.

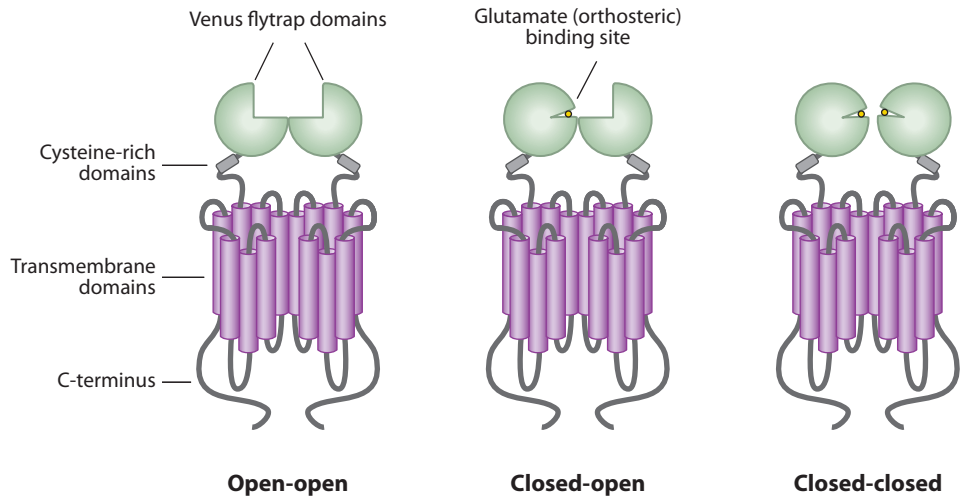


Figure 1

Schematic diagram of the mGluR dimer in different activity states. mGluR dimers contain two large extracellular domains called the Venus flytrap domains (VFDs), which bind glutamate and other orthosteric ligands. The cysteine-rich domain links the VFDs to seven transmembrane-spanning domains; the C-terminus faces intracellularly and is often subject to alternative splicing to generate different C-terminal protein tails. The open-open state (*left*) is the inactive state and can be stabilized by antagonists. Either one or two VFDs can then bind glutamate, resulting in active receptor conformations.

Heptahelical Domain and Intracellular Loops

mGluR HDs share very low homology to family A GPCRs, and it has been proposed that the second intracellular loop (i2) of mGluRs may play a role similar to that of the i3 loop in rhodopsin-related receptors in regulating G protein coupling specificity (12, 13). The i2 loop is also a site for regulation by kinases, including G-protein-coupled receptor kinase 2 (14). The majority of characterized allosteric modulators of mGluRs that positively and negatively affect glutamate activity bind within the HD (reviewed in 15). Positive allosteric modulators (PAMs) do not activate the receptor directly in most systems but potentiate the response of the receptor to orthosteric agonists (**Figure 2**, left). Allosteric agonists bind to a site other than the orthosteric site and directly activate the receptor. Negative allosteric modulators (NAMs) antagonize the activity of agonists in a noncompetitive fashion by binding to a site other than the agonist, in this case glutamate, binding site (**Figure 2**, right). Interestingly, truncation of the N-terminal domain of mGluR5 results in a receptor that can be directly activated by PAMs (16). This suggests that there is a conformational restraint induced by the VFD-CRD region that prevents PAMs from acting as agonists until glutamate is bound.

C-Terminus

The C-termini of mGluRs are important regions for modulating G protein coupling. Additionally, this region of several of the mGluRs is subject to alternative splicing, regulation by phosphorylation, and modulatory protein-protein interactions. These issues are discussed in more detail in the following sections.

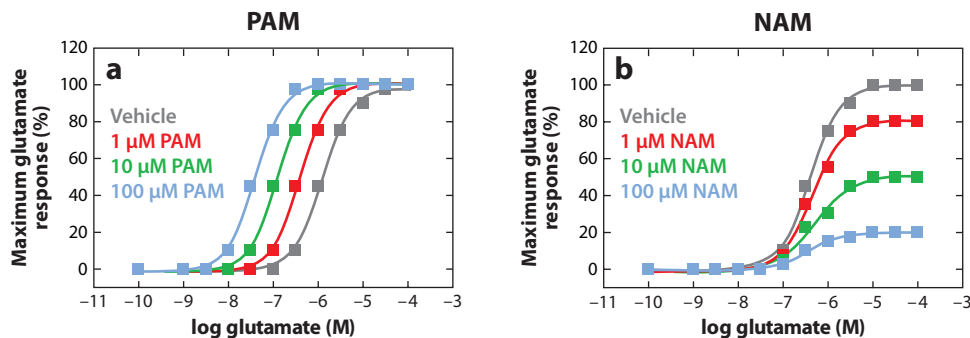


Figure 2

Simple schematic representation of the positive allosteric regulator (PAM) and negative allosteric regulator (NAM) activity using an in vitro functional assay. (a) Monitoring of a functional assay such as calcium mobilization shows that increasing PAM concentrations progressively shift the glutamate concentration response for an mGluR to the left. Depending on the assay used, PAMs can also cause an increase in the maximal agonist response. (b) Increasing NAM concentrations progressively shift the magnitude of the concentration response curve and produce little change in potency, indicating a noncompetitive form of antagonism.

SIGNAL TRANSDUCTION

mGluR Activation

mGluRs, and other family C GPCRs, are constitutive dimers (reviewed in 1). There is some controversy as to whether binding of glutamate to only one protomer within the dimer is sufficient to activate the entire complex. In the case of the GABA_B receptor, which is a heterodimer consisting of GABA_{B1} and GABA_{B2} subunits, ligand binding to GABA_{B1} is sufficient to activate the receptor (17). This may not be the case for mGluRs, however. For example, glutamate was unable to activate dimers formed by one wild-type and one mutant form of mGluR1, suggesting that glutamate binding to one protomer is not sufficient for activation (18). In contrast, Kniazeff et al. (19) showed that one glutamate molecule can activate mGluR5 homodimers but that occupation of both VFDs with ligand is more effective. Suzuki et al. showed that glutamate binding to one protomer exerts negative cooperativity for binding to the second protomer (20), suggesting that glutamate binds to both dimers but that this binding can induce complexities in receptor pharmacology.

General Signaling Profiles

In general, group I mGluRs couple to G_q/G₁₁ and activate phospholipase C_β, resulting in the hydrolysis of phosphoinositides and generation of inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (Table 1). This classical pathway leads to calcium mobilization and activation of protein kinase C (PKC). However, it is now recognized that these receptors can modulate additional signaling pathways including other cascades downstream of G_q as well as pathways stemming from G_{i/o}, G_s, and other molecules independent of G proteins (21). Depending on the cell type or neuronal population, group I mGluRs can activate a range of downstream effectors, including phospholipase D, protein kinase pathways such as casein kinase 1, cyclin-dependent protein kinase 5, Jun kinase, components of the mitogen-activated protein kinase/extracellular receptor kinase (MAPK/ERK) pathway, and the mammalian target of rapamycin (MTOR)/p70 S6 kinase

pathway (22–25). The latter pathways, MAPK/ERK and MTOR/p70 S6 kinase, are thought to be particularly important for the regulation of synaptic plasticity by group I mGluRs.

In contrast to group I mGluRs, group II and III mGluRs are coupled predominantly to $G_{i/o}$ proteins. $G_{i/o}$ linked receptors are classically coupled to the inhibition of adenylyl cyclase and directly regulate ion channels and other downstream signaling partners via liberation of $G_{\beta\gamma}$ subunits. As with group I mGluRs, it is becoming increasingly appreciated that group II and group III mGluRs also couple to other signaling pathways, including activation of MAPK and phosphatidyl inositol 3-kinase PI3 kinase pathways (26), providing further complexity regarding the mechanisms by which these receptors can regulate synaptic transmission.

ALTERNATIVE SPLICING

Several mGluR subtypes undergo alternative splicing; in many cases, this generates different C-terminal tails (**Table 1**). The gene for mGluR1a encodes four main distinct C-terminal splice variants: mGluR1a, b, c, and d; of these, mGluR1a is the longest (reviewed in 21) (**Table 1**). mGluR1e encodes an inactive form of mGluR1 that terminates before the transmembrane domains (27). In rats, another splice variant termed mGluR1f encodes a protein with a sequence identical to that of mGluR1b (28). mGluR5 exists as two main splice variants: mGluR5a and mGluR5b (29, 30). Whereas no splicing events have been reported for mGluR2, mGluR3 RNA has recently been shown to undergo alternative splicing to yield at least four variants: full length mGluR3, GRM3 Δ 2 (missing exon 2), GRM3 Δ 4 (missing exon 4), and GRM3 Δ 2 Δ 3 (missing exons 2 and 3) (31); GRM3 Δ 4 appears to be the most abundant. This variant lacks the transmembrane domain of the receptor but can be translated in cell lines and in vivo, suggesting that it may function as a unique glutamate receptor. As with mGluR3, three mGluR6 splice variants can be generated, and two of these terminate within the N-terminal domain [mGluR6b and mGluR6c (32)]. Additionally, an isoform of mGluR8 in human brain, mGluR8c, is also predicted to encode only the N-terminal region of the receptor (33). It has been postulated that these short N-terminal proteins may be secreted and could serve as soluble receptors for glutamate or as dominant negative receptor variants (32, 33).

The C-terminal tails of mGluRs 7 and 8 also serve as key regions for alternative splicing. For example, five C-terminal isoforms of mGluR7 (mGluR7a–e) have been identified, and two distinct isoforms of mGluR8 have been cloned (mGluR8a and mGluR8b) that differ at their C-termini (34, 35). Although an mGluR4b splice variant has been reported (36), other accounts have been unable to replicate this finding (37). Interestingly, there are isoforms of mGluR1 and 4 that lack approximately half of the amino terminus. These receptor variants, known as taste mGluR1 and taste mGluR4, are located in taste buds (38–40). Owing to the lack of much of the traditional glutamate-binding domain, glutamate exhibits lower potency when inducing signaling via these truncated receptors compared with their full-length counterparts; nevertheless, these isoforms have an emerging role in mediating the taste of monosodium glutamate, or umami (reviewed in (41).

PROTEIN-PROTEIN INTERACTIONS

Multiple proteins interact directly with the C-terminal tails of each of the mGluR subtypes and play important roles in regulating mGluR signaling. The most well-characterized are Homer proteins, which contain PDZ 1 (post-synaptic density 95, discs large, zona occludens 1) domains that interact with the last several amino acids, PPxxF, of mGluR1a, mGluR5a, and mGluR5b (42–44). Distinct Homer gene and splice variants can differentially regulate localization of mGluR1 and mGluR5 receptors in transfected cells and neurons (42, 45). Homer proteins also participate in the assembly

of protein complexes at the C-terminal tails of mGluRs that are critical for receptor activity or that mediate functional responses downstream of receptors. For example, the long isoform of protein PI3 kinase enhancer (PIKE-L) associates with mGluR5 via Homer interactions, allowing agonist activity at mGluR5 to prevent apoptosis when certain Homer isoforms are present (46).

Although protein-protein interactions between group II receptors and other proteins have not been as extensively characterized as interactions occurring with group I mGluRs, calmodulin and protein phosphatase 2C (PP2C) have recently been shown to interact with the C-terminus of mGluR3 (47). Interestingly, binding of PP2C is inhibited by phosphorylation of serine 845 by protein kinase A (PKA), and PP2C can dephosphorylate this site (47). This suggests that there is a dynamic regulation of phosphorylation/dephosphorylation of mGluR3 that is regulated by binding of PKA/PP2C. Another protein, Ran binding protein in the microtubule-organizing center (RanBPM), binds to group II and certain group III mGluR splice variants in the retina and may localize these mGluRs to specific synaptic locations in neurons (48). Isoforms of mGluR8 also interact with proteins in the retina called Band 4.1 proteins, and this interaction facilitates cell surface expression of receptors and reduces their ability to inhibit cAMP accumulation (49).

C-terminal tails of mGluR7 splice variants bind to a variety of interacting proteins such as the PDZ domain clustering protein PICK1 (protein interacting with C kinase 1) (50–53). PICK1 also binds protein kinase $C\alpha$ (PKC α), and the three proteins form a complex at active zones of presynaptic terminals (52). The C-terminus of mGluR7a also interacts with Ca^{2+} -calmodulin, G protein $\beta\gamma$ subunits, and the protein MacMARCKS (macrophage myristoylated alanine rich C kinase substrate; MacM) (54), creating a complex interplay of signaling downstream of mGluR7 (**Figure 3**). To add further complexity, it has been shown that PKC phosphorylation of serine 862 inhibits the binding of G $\beta\gamma$ subunits and Ca^{2+} -calmodulin. This complex signaling system

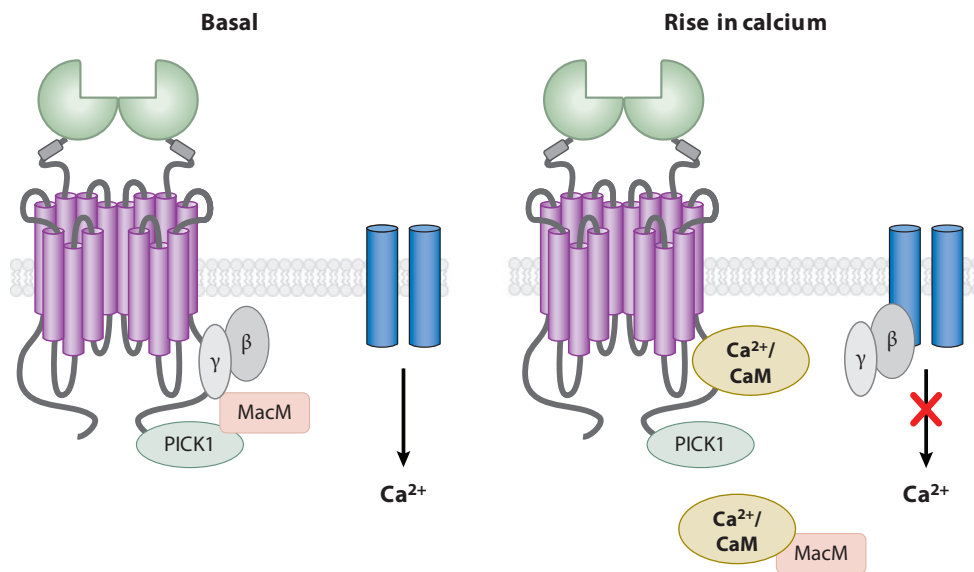


Figure 3

Protein-protein interactions mediating the activity of mGluR7. It is proposed that in the resting state, mGluR7 binds PICK1, MacMARCKS (MacM), and G $\beta\gamma$ subunits; this binding prevents G $\beta\gamma$ subunits from inhibiting voltage-sensitive calcium channels (VSCCs; blue). Rises in calcium induce displacement of MacMARCKS and G $\beta\gamma$ subunits by calcium-calmodulin (Ca^{2+} -CaM), promoting G $\beta\gamma$ subunit inhibition of VSCCs. Adapted from (52, 54).

may provide a way in which mGluR7, which is highly localized to presynaptic active zones, has extremely low affinity for glutamate and is predicted to only be activated during periods of intense synaptic activity, can serve as an integrator of multiple presynaptic signaling events including rises in intracellular calcium.

Recently, an elegant set of studies was performed in which the mGluR7a-PICK1 interaction was disrupted by employing a viral vector in which the last nine amino acids of the C-terminus of mGluR7 were used as bait to compete with full-length mGluR7 for the binding of PICK1 (55). Infection of neurons with this construct *in vivo* inhibited mGluR7-PICK1 interactions and led to absence seizures and waveform changes specifically within thalamo-cortical brain regions, areas thought to mediate absence epilepsy phenotypes. Furthermore, knock-in mice in which the amino acids within the mGluR7 C-terminus that interact with PICK1 were mutated (56) exhibited spontaneous absence seizures (55), further substantiating that the interaction of mGluR7 and PICK1 is important for regulating mGluR7 signaling and that this protein-protein interaction may underlie certain disease states.

PHARMACOLOGICAL PROFILES OF METABOTROPIC GLUTAMATE RECEPTORS

Group I mGluRs

The first selective orthosteric agonist at group I mGluRs, (S)-3,5-dihydroxyphenylglycine [(S)-3,5-DHPG], has similar potencies at mGluR1 and mGluR5 and remains the most selective group I mGluR agonist. Most other group I mGluR agonists have activity at ionotropic glutamate receptors (i.e., quisqualate) or other mGluR subtypes [(1S,3R)-ACPD] (57). A related compound, 2-chloro-5-hydroxyphenylglycine (CHPG), is a selective orthosteric agonist of mGluR5 but has limited utility because of its relatively weak potency and efficacy. Multiple orthosteric antagonists for group I mGluRs, including MCPG and related phenylglycine derivatives, are of low potency but have been widely used in electrophysiology and other studies. More recently, more potent and selective orthosteric antagonists of group I mGluRs have emerged from further optimization of the 4-carboxyphenylglycine scaffold. These include compounds with improved potencies such as LY367385, which is highly useful as a selective antagonist of mGluR1 relative to mGluR5 (57).

A major advance in the identification of highly selective ligands for group I mGluRs came with the discovery of CPCCOEt as the first highly selective mGluR1 NAM (58). CPCCOEt acts in the HD and provided a major breakthrough in demonstrating the utility of targeting allosteric sites for discovery of highly subtype-selective mGluR antagonists. A large number of structurally distinct mGluR1-selective NAMs have become available, including Bay 36-7620 (59), JNJ16259685 (60), FTIDC (61), YM 298198 (62), and others (63). Many of these compounds have nanomolar potencies and are useful for *in vivo* studies.

Varney et al. reported the discovery of two highly selective mGluR5 NAMs: SIB-1757 and SIB-1893 (64). Subsequent structural analogs MPEP (65) and MTEP (66) provided increased potency, selectivity, and brain penetration (67). Many structurally distinct and highly selective mGluR5 NAMs have now been reported, including compounds that have unique properties such as selective partial antagonists of mGluR5 (68). MTEP and MPEP, however, remain the most commonly used and selective mGluR5 antagonists for probing the function of this receptor in the CNS.

Highly selective PAMs have also been developed for each of these group I mGluR subtypes. These compounds do not activate the mGluR directly but act at an allosteric site in the HD to potentiate the response to glutamate, inducing robust leftward shifts of the glutamate concentration

response relationship. Ro 67-7476, Ro 67-4853, and VU71 are selective mGluR1 PAMs (69, 70). Additionally, multiple mGluR5-selective PAMs have been identified including DFB, CPPHA, CDDPB, VU29, and ADX47273 (reviewed in 71). Whereas DFB and CPPHA are not sufficiently potent or soluble in physiological buffers to make them useful for studies of mGluR5 function, other mGluR5 PAMs are proving highly useful for assessment of the functional roles of mGluR5 in the CNS (72, 73).

Group II mGluRs

DCG-IV and (2*R*,4*R*)-APDC (abbreviations of all compounds, along with targets and mode of pharmacology, are defined in **Table 2**) were the first selective group II mGluR agonists (57). More recently, systemically active and highly selective agonists of group II mGluRs have been developed, providing valuable insights into the *in vitro* and *in vivo* functions of these receptors. The prototypical molecule in this series is LY354740, which has been followed by more recent compounds, including LY379268, now a commonly used tool for studies of group II mGluR function (57). These compounds are highly selective for group II mGluRs relative to other mGluR subtypes but do not differentiate between mGluR2 and mGluR3. Recently, an analog of LY354740 was reported that had mGluR2 agonist and mGluR3 antagonist activity (74). Thus far, no orthosteric antagonists have been discovered that are entirely specific for group II mGluRs among other family members, although LY341495 provides relatively high selectivity with nanomolar potency as a group II mGluR antagonist with submicromolar to micromolar potencies at all other mGluR subtypes (57).

Multiple selective PAMs of mGluR2 have now been identified, with the majority being structurally related to either LY487379 or BINA, two prototypical mGluR2 PAMs (71, 75). Many of these compounds are highly selective for mGluR2 and do not potentiate responses to activation of mGluR3 or any other mGluR subtype. In addition, group II mGluR NAMs have been reported that block both mGluR2 and mGluR3 (76–78). As with group I mGluR allosteric modulators, mutation analysis and molecular pharmacology studies have revealed that these compounds interact with the receptor in the HD (76, 79, 80).

Group III mGluRs

The prototypical orthosteric agonist of group III mGluRs is L-AP4, which is highly selective for group III mGluRs relative to other mGluRs or ionotropic glutamate receptors (57). L-AP4 has submicromolar to low micromolar potencies at mGluRs 4, 6, and 8 but submillimolar to millimolar potency at mGluR7 (57). Multiple related compounds have provided additional group III mGluR agonists, but most have the same selectivity profile as L-AP4 (57, 81, 82). (*S*)-3,4-DCPG has recently emerged as a novel agonist with 100-fold selectivity for mGluR8 over mGluR4 (83, 84). Additionally, several L-AP4 analogs, including Z-cyclopentyl AP4, have been shown to have some selectivity for mGluR4 compared with other group III mGluRs (85–87). Several orthosteric antagonists have been reported to have high selectivity for group III mGluRs (i.e., CPPG, MAP4, and others) (57). However, these compounds exhibit low potencies for antagonizing group III mGluRs, and in some cases have no effect even at high concentrations (88). In cell lines expressing the cloned rat receptors, the group II–preferring antagonist LY341495 has been shown to be the most potent antagonist across group III mGluRs, followed by CPPG (88).

As with group I and group II mGluRs, exciting progress has been made in identifying selective allosteric modulators of group III mGluRs. PHCCC is an mGluR4 PAM (89, 90) that has no direct agonist activity at mGluR4 but increases the potency of glutamate at mGluR4. Two mGluR5 NAMs, SIB-1893 and MPEP, also possess mGluR4 PAM activity (91), although these compounds

Table 2 Names, abbreviations, and actions of the drugs mentioned in text

Nonselective Ligands			
Compound	Chemical name	Target	Activity
L-glutamate	(S)-1-Aminopropane-1,3-dicarboxylic acid	Group I/Group II> Group III	Orthosteric agonist
(1S,3R)-ACPD	(1S,3R)-1-Aminocyclopentane-1,3-dicarboxylic acid	Group I/II> Group III	Orthosteric agonist
LY341495	(2S)-2-Amino-2-[(1S,2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid	Group II> Group III> Group I	Orthosteric antagonist
Group I preferring ligands			
Compound	Chemical name	Target	Activity
(S)-3,5-DHPG	(S)-3,5-dihydroxyphenylglycine	mGluR1/5	Orthosteric agonist
L-quisqualate	(L)-(+)- α -Amino-3,5-dioxo-1,2,4-oxadiazolidine-2-propanoic acid	mGluR1/5/glutamatergic ion channels	Orthosteric agonist
CHPG	(RS)-2-chloro-5-hydroxyphenylglycine	mGluR5	Orthosteric agonist
(S)-MCPG	(S)- α -Methyl-4-carboxyphenylglycine	Group I/II	Orthosteric antagonist
LY367385	(S)-(+)- α -Amino-4-carboxy-2-methylbenzeneacetic acid	mGluR1	Orthosteric antagonist
CPCCOEt	7-(Hydroxyimino)cyclopropa[b]chromen-1 α -carboxylate ethyl ester	mGluR1	NAM
Bay 36-7620	(3 <i>aS</i> ,6 <i>aS</i>)-Hexahydro-5-methylene-6 <i>a</i> -(2-naphthalenylmethyl)-1H-cyclopenta[c]furan-1-one	mGluR1	NAM
JNJ16259685	3-4-Dihydro-2 <i>H</i> -pyrano[2,3- <i>b</i>]quinolin-7-yl-(cis-4-methoxycyclohexyl)-methanone	mGluR1	NAM
FTIDC	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	mGluR1	NAM
YM 298198	6-Amino- <i>N</i> -cyclohexyl- <i>N</i> ,3-dimethylthiazolo[3,2- <i>a</i>]benzimidazole-2-carboxamide	mGluR1	NAM
SIB-1757	6-Methyl-2-(phenylazo)-3-pyridinol	mGluR5	NAM
SIB-1893	2-Methyl-6-(2-phenylethenyl)pyridine	mGluR5/mGluR4	NAM/PAM
MPEP	2-Methyl-6-(phenylethynyl)pyridine	mGluR5/mGluR4	NAM/PAM
MTEP	3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine	mGluR5	NAM
Ro 67-7476	(S)-2-(4-fluorophenyl)-1-(toluene-4-sulfonyl)pyrrolidine	mGluR1	PAM
Ro 67-4853	Butyl (9 <i>H</i> -xanthene-9-carbonyl)carbamate	mGluR1	PAM
VU71	4-nitro- <i>N</i> -(1,4-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide	mGluR1	PAM
DFB	[(3-Fluorophenyl)methylene]hydrazone-3-fluorobenzaldehyde	mGluR5	PAM
CPPHA	<i>N</i> -(4-chloro-2-[(1,3-dioxo-1,3-dihydro-2 <i>H</i> -isoindol-2-yl)methyl]phenyl)-2-hydroxybenzamide	mGluR5	PAM
CDDPB	3-cyano- <i>N</i> -(1,3-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide	mGluR5	PAM
VU29	4-nitro- <i>N</i> -(1,3-diphenyl-1 <i>H</i> -pyrazol-5-yl)benzamide	mGluR5	PAM
ADX47273	[S-(4-fluoro-phenyl)]-(3-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazol-5-yl]-piperidin-1-yl)-methanone]	mGluR5	PAM

Group II preferring ligands			
Compound	Chemical name	Target	Activity
DCG-IV	(2 <i>S</i> ,2' <i>R</i> ,3' <i>R</i>)-2-(2'-(2',3')-Dicarboxycyclopropyl)glycine	Group II	Orthosteric agonist
(2 <i>R</i> ,4 <i>R</i>)-APDC	(2 <i>R</i> ,4 <i>R</i>)-4-Aminopyrrolidine-2,4-dicarboxylate	Group II	Orthosteric agonist
LY354740	(1 <i>S</i> ,2 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid	Group II	Orthosteric agonist
LY379268	(1 <i>R</i> ,4 <i>R</i> ,5 <i>S</i> ,6 <i>R</i>)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid	Group II	Orthosteric agonist
LY487379	2,2,2-Trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl)ethanesulfonamide	mGluR2	PAM
BINA	Biphenyl-indanone A	mGluR2	PAM
Group III preferring ligands			
Compound	Chemical name	Target	Activity
L-AP4	L-(+)-2-Amino-4-phosphonobutyric acid	mGluR4,6,8>mGluR7	Orthosteric agonist
(<i>S</i>)-3,4-DCPG	(<i>S</i>)-3,4-Dicarboxyphenylglycine	mGluR8>mGluR4/6	Orthosteric agonist
Z-cyclopentyl AP4	cis-(±)-1-Amino-3-phosphonocyclopentane carboxylic acid	mGluR4>other Group III receptors	Orthosteric agonist
CPPG	(<i>RS</i>)-a-Cyclopropyl-4-phosphonophenylglycine	Group III	Orthosteric antagonist
MAP4	(<i>S</i>)-2-Amino-2-methyl-4-phosphonobutanoic acid	Group III	Orthosteric antagonist
PHCCC	N-Phenyl-7-(hydroxyimino)cyclopropa[<i>b</i>]chromen-1 <i>a</i> -carboxamide	mGluR4	PAM
VU0155041	cis-2-[(3,5-Dichlorophenyl)amino]carbonyl cyclohexanecarboxylic acid	mGluR4	PAM
AMN082	N,N'-Bis(diphenylmethyl)-1,2-ethanediamine	mGluR7	Allosteric agonist
MMPIP	6-(4-Methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo [4,5- <i>c</i>]pyridin-4(5 <i>H</i>)-one hydrochloride	mGluR7	NAM

have relatively low potency and efficacy at mGluR4. Recently, a high-throughput screening approach identified VU0155041 and VU0080421 as structurally distinct mGluR4 PAMs (92, 93). VU0155041 exhibits significant improvements in aqueous solubility, potency, and selectivity for mGluR4 relative to PHCCC. Additionally, in contrast to PHCCC, VU0155041 exhibits allosteric agonist activity at mGluR4 when assessed in vitro (92), suggesting that these two ligands may induce potentiation of mGluR4 in mechanistically distinct ways.

AMN082 has been reported as a selective allosteric agonist of mGluR7 (94). Whereas AMN082 is becoming widely used as a putative mGluR7 agonist in vivo, subsequent studies suggest that the activity of this compound is complex. For instance, in contrast to L-AP4, AMN082 does not induce calcium mobilization downstream of mGluR7 in a cell line coexpressing the receptor with a promiscuous G protein (95), does not induce mGluR7-mediated activation of GIRK potassium channels in human embryonic kidney (HEK) cells (87), and does not activate mGluR7 at the Shaffer collateral-CA1 synapse (87). Thus, activity of AMN082 on mGluR7 may be context-specific and may only be observed in some systems, perhaps depending on the specific signaling pathways engaged.

Similar complexities have been observed with recently discovered mGluR7 NAMs. MMPiP is an mGluR7-selective NAM that inhibits L-AP4-induced calcium mobilization in cells expressing mGluR7 and $G_{\alpha 15}$ (95, 96). Interestingly, MMPiP does not appear to effectively block coupling of mGluR7 to inhibition of cAMP accumulation, activation of G-protein-activated inwardly rectifying potassium channels (GIRK) potassium channels, or L-AP4-mediated inhibition of synaptic transmission at the Shaffer collateral-CA1 synapse (96). Thus, as with AMN082, MMPiP may only have activity on mGluR7 in some cellular contexts or may block specific signaling pathways while permitting signaling through others, an idea recently coined permissive antagonism (97).

FUNCTIONAL ROLES OF mGluRs

mGluRs are broadly distributed throughout the CNS and are specifically localized at discrete synaptic and extrasynaptic sites in both neurons and glia in virtually every major brain region. Activation of mGluRs results in diverse actions on neuronal excitability and synaptic transmission by modulation of a variety of ion channels and other regulatory and signaling proteins. Discussion of the physiological roles of mGluRs has been presented in detail in multiple previous reviews (98–103). While broad generalizations should be avoided, there are common roles for the major subgroups of mGluRs. Group I mGluRs are often localized postsynaptically, and their activation often leads to cell depolarization and increases in neuronal excitability (**Table 1; Figure 4**). Modulation of neuronal excitability results from modulation of a number of ion channels and can range from robust excitation to more subtle changes in patterns or frequency of cell firing or responses to excitatory inputs (98–101). In contrast, group II and group III mGluRs are often localized on presynaptic terminals or preterminal axons where they inhibit neurotransmitter release (**Figure 4**). This occurs at excitatory (glutamatergic), inhibitory (GABAergic), and neuromodulatory (i.e., monoamines, ACh, peptides) synapses.

Whereas these generalizations hold in many instances, there are many exceptions, and the physiological roles of different mGluR subtypes are highly specific to the neuronal population and even subcellular localization. For instance, activation of mGluR1 induces hyperpolarization of some neuronal populations such as midbrain dopamine neurons (101). Also, group I mGluRs can act presynaptically to either increase or decrease neurotransmitter release. In some cases, this is mediated by postsynaptic group I mGluRs and release of retrograde messengers, such as endocannabinoids. However, in others, it is likely mediated by group I mGluRs that are localized presynaptically (100, 102, 103). Also, different group I mGluR subtypes often have different

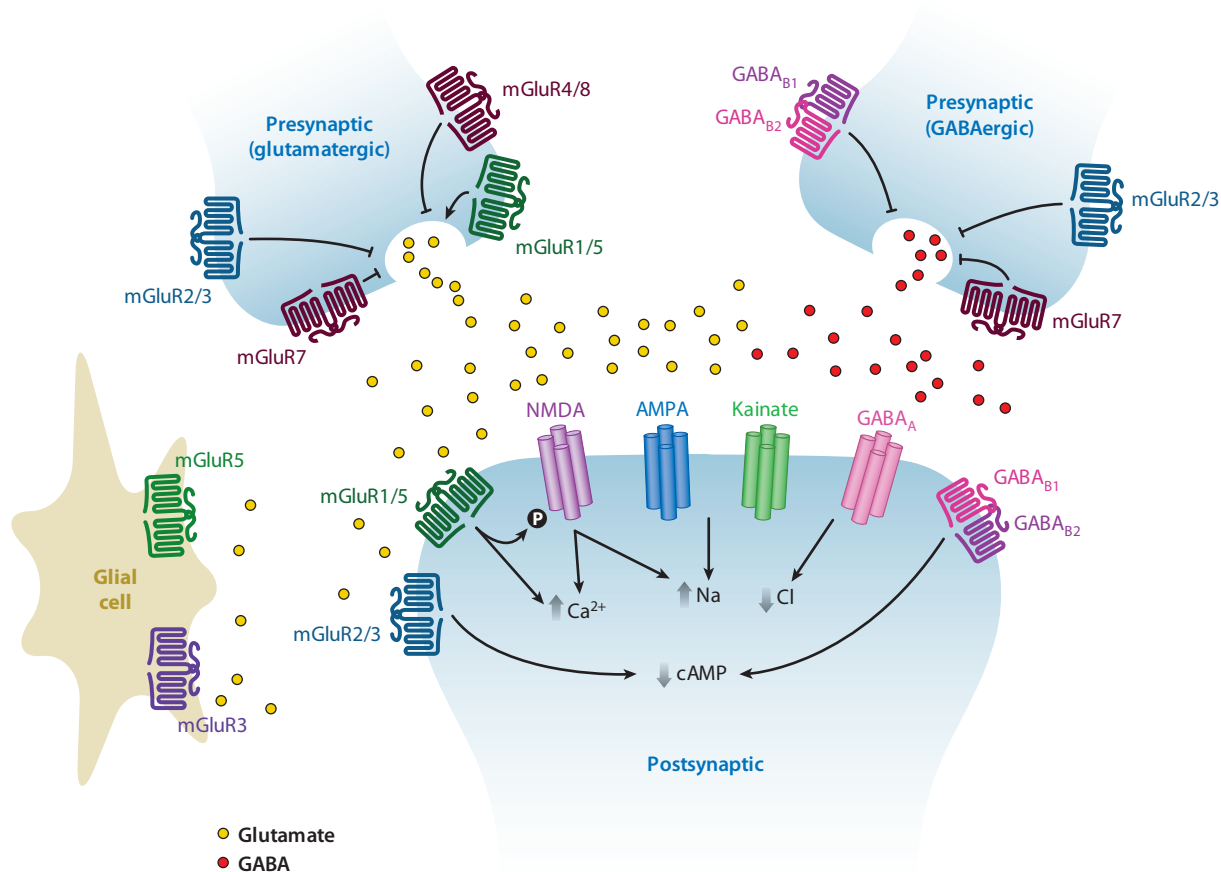


Figure 4

Schematic representation of mGluRs at the synapse. In general, group I mGluRs (green) are localized postsynaptically, and group II (blue) and III (red) receptors are localized in presynaptic locations, although exceptions occur. In presynaptic locations, mGluRs 2, 3, 4, and 8 are generally found in extrasynaptic locations, and mGluR7 is highly localized to the active zone (136). Group II and III receptors inhibit release of glutamate (left, yellow circles) or GABA (right, red circles), whereas group I receptors promote release when present. At the postsynaptic terminal, the glutamate gated ion channels N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) and kainate respond to glutamate with increases in intracellular sodium or calcium, promoting cell excitability. Group I mGluRs signal via G_q proteins to increase intracellular calcium; additionally, mGluR5 and NMDA receptors are closely linked signaling partners reciprocally regulated by phosphorylation (black circle) (71). Postsynaptic mGluR2/3 and GABA_{B1/2} receptors couple to cAMP inhibition. GABA_A chloride channels (pink) modulate intracellular chloride. Expression of mGluR3 and mGluR5 on glia is now emerging as another key site for mGluR regulation of synaptic activity, although the signaling pathways and consequences of receptor activation on these cells are not presently well understood.

physiological roles in a single neuronal population. For instance, in CA1 pyramidal cells mGluR1 activation leads to somatic calcium transients and neuronal depolarization, whereas mGluR5 activation inhibits I_{AHP} (slow after hyperpolarization potential) potassium currents and potentiates NMDA receptor currents (104). Group I mGluRs also play important roles in induction of long-lasting forms of synaptic plasticity, including long-term depression (LTD) and long-term potentiation (LTP) of transmission at multiple glutamatergic synapses and induce long-lasting changes in neuronal excitability (87, 100, 102, 105).

All of the mGluRs have been genetically deleted in mice. Results of studies with these animals have revealed potential roles for each of the receptors in cell function and in various disease states. mGluR1 was the first mGluR to be knocked out in mice. These animals show normal gross brain morphology but exhibit several phenotypes. For example, the high expression of mGluR1 in the hippocampus points to a potential role in learning and memory. Indeed, electrophysiological recordings from mGluR1 $-/-$ mice show that these animals exhibit abnormal induction of long-term potentiation and that this phenotype correlates with deficits in context-specific learning (106). Recently, Gil-Sanz et al. recorded activity occurring at hippocampal CA3-CA1 synapses in mice as the animals were learning an associative task (107). These studies revealed that mGluR1 knockout mice were unable to learn this task and showed significant impairments in the ability to induce LTP.

Additionally, these mice showed cerebellar gait problems; in contrast to the effects seen in the hippocampus, mGluR1 deficiency leads to deficits in long-term depression in the cerebellum (108). A recent extension of this initial work showed that mice deficient in mGluR1 showed abnormal levels of regression of climbing fibers from cerebellar Purkinje cells (109). Normally, these fibers regress during development such that one fiber maintains a strong excitatory input to an individual Purkinje cell, and the remaining cells regress. The authors suggest a critical role for mGluR1 in maintaining proper levels of innervations of cerebellar neurons. Interestingly, it has recently been shown that several spontaneous mutations giving rise to spontaneous ataxia in mice genetically map to the mGluR1 locus (110). These mutations alter the ligand-binding domain of mGluR1, suggesting that mGluR1 function is critical for this ataxic phenotype.

mGluR5 knockout mice have been intensely studied in models of learning and memory, addiction, motor regulation, and obesity. Most recently, mGluR5 has emerged as a novel player in the treatment of fragile X syndrome based, in part, on studies with knockout animals (discussed further in the following section). Both mGluR1 and mGluR5 knockout animals show deficits in prepulse inhibition (111, 112), which is a measure of sensorimotor gating that is impaired in schizophrenic patients and can be reversed by antipsychotic agents. In models of drug abuse and addiction, mGluR5 knockout mice do not self-administer cocaine or increase their locomotor activity after cocaine administration (113). mGluR5 knockout mice weigh less than littermate controls, eat less than control mice when challenged with a starvation and refeeding paradigm, and are resistant to effects induced by a high-fat diet such as weight gain and increases in plasma insulin and leptin levels (114).

The physiological roles of group II and group III mGluRs are also more complex than a simple role in acute presynaptic regulation of neurotransmitter release. Group II mGluRs can be localized postsynaptically where they can induce hyperpolarization (115), and mGluR4 and -8 have also both been shown to be expressed postsynaptically in certain areas such as the hippocampus and retina (116, 117). Both group II and group III mGluRs play important roles in induction of LTD (102, 103). In addition to their roles in regulating neuronal excitability and synaptic transmission, mGluRs play other important roles, including regulation of metabolism, gene transcription, and multiple aspects of glial function and glial-neuronal communication.

Both mGluR2 and mGluR3 have been separately deleted from the mouse genome, and these animals are critically important for several reasons. For example, the high conservation of mGluR2 and mGluR3 makes it difficult to develop selective ligands that can be used to differentiate the function of one receptor versus the other, although the emergence of more selective allosteric modulators is helping to define the roles of these receptors. In terms of functional correlates of learning and memory, mGluR2 knockout mice show normal regulation of basal synaptic transmission and LTP at mossy fiber-CA3 synapses in the hippocampus, but these animals are severely impaired in terms of LTD induced by low-frequency stimulation at this synapse (118). In other

studies using knockout mice combined with other pharmacological tools, mGluR2 activation has been postulated to result in cognitive impairment, suggesting a potential role for mGluR2 antagonists in cognitive disorders (119). mGluR2 has also been implicated in addiction to drugs of abuse because mGluR2 knockout mice show increased responsiveness to cocaine (120), and this receptor has also been shown to selectively mediate the beneficial effects of group II agonists in rodent models of psychosis (121, 122).

A potentially important role for mGluR3 in astrocytes is emerging from studies with knockout animals. For example, mixed cultures of cortical neurons and astrocytes from wild-type, mGluR2, and mGluR3 knockout mice have shown that an agonist of group II receptors, LY379268, is neuroprotective when cultures are challenged with NMDA (123). This neuroprotection is lost, however, if mGluR3 is missing from astrocytes in the culture. In these same experiments, the authors found that activation of mGluR2 might actually be harmful in terms of excitotoxicity (123).

Each of the group III mGluRs has also been genetically deleted in mice, and these animals show several interesting phenotypes. mGluR6 exhibits the most restricted expression of all of the mGluRs and is found primarily in retinal ON bipolar cells (124). The mGluR6 activation cascade has been shown to involve Go protein subunits (125). When mGluR6 is deleted from mice, bipolar cells from homozygous mutants show deficits in ON responses to light, which appears to be manifested by a delayed and decreased ON response to light stimulation (126, 127).

mGluR4 is very highly expressed in the cerebellum, with lower levels of expression in the hippocampus, basal ganglia, and olfactory bulb (reviewed in 128 and references therein). mGluR4 is predominantly expressed presynaptically (37, 129). As mentioned above, a splice variant of mGluR4, termed taste mGluR4, is located in taste buds, and the longer, brain version of mGluR4 is also expressed in this location (130). mGluR4 protein is also expressed peripherally in tissues such as pancreatic islets (131). Consistent with the high expression of mGluR4 in cerebellum, mice lacking this receptor show impairments in cerebellar synaptic plasticity and in learning complicated motor tasks (132). These animals also show impaired abilities in spatial memory performance (133). mGluR4 has also been shown to modulate GABA(A) receptor-mediated seizure activity (134), and mGluR4^{-/-} mice also lack motor stimulatory effects induced by ethanol (135).

mGluR7 exhibits a wide distribution throughout the entire brain. mGluR7 has an extremely low affinity for glutamate and is highly localized to the active zones of synapses (136, 137). It has been proposed that mGluR7 serves a low pass filter role in neurotransmission, only becoming active when glutamate levels are very high and thus serving as a brake for overstimulation by glutamate. In support of this hypothesis, knockout of mGluR7 results in animals with an epileptic phenotype (138). mGluR7^{-/-} mice also show abnormalities in learning tasks (139–144), and mGluR7 function appears to be particularly important in mediating amygdala-dependent learning (139). Additionally, these mice have revealed roles for mGluR7 in CNS disorders such as anxiety and depression (144–146).

mGluR8 is expressed at lower levels than mGluR4 and mGluR7 but is widely distributed in the brain. As for mGluR4, mGluR8 has been localized predominantly presynaptically but has been identified in some postsynaptic locations and in the periphery (reviewed in 128). The mGluR8 gene is exceptionally large, spanning approximately 1000 kilobases of genomic DNA in a region that maps to the same location as mutations causing two human disorders, Smith-Lemli-Optiz syndrome and retinitis pigmentosa (147). mGluR8 knockout mice show enhanced anxiety and weight gain compared to controls (148–150), suggesting that mGluR8 activators may be of benefit in anxiety disorders. Additionally, expression and function of mGluR8 in peripheral locations such as the gut and pancreas suggests that this receptor is involved in gastrointestinal motility and insulin secretion *in vivo* (151, 152).

THERAPEUTIC POTENTIAL OF mGluRs

The wide diversity and heterogeneous distribution of mGluR subtypes provides an opportunity for selectively targeting individual mGluR subtypes involved in only one or a limited number of CNS functions for the development of novel treatment strategies for psychiatric and neurological disorders. A large body of preclinical studies now suggests that ligands for specific mGluR subtypes have potential for the treatment of multiple CNS disorders, including depression (153), anxiety disorders (154), schizophrenia (71, 155), pain syndromes (156), epilepsy (157), Alzheimer's disease (158), and Parkinson's disease (159), among others. Data from clinical studies with mGluR ligands are beginning to emerge and are providing strong proof of concept for clinical efficacy of some of these compounds. Whereas each of these therapeutic areas has been extensively reviewed, several exciting advances are especially noteworthy and are discussed here.

Allosteric Modulators of mGluR5

A major focus of many efforts to discover novel mGluR5 ligands has been the discovery of mGluR5 antagonists for the treatment of anxiety disorders. This receptor increases neuronal excitability and NMDA receptor currents in brain regions thought to be involved in anxiety, such as the amygdala (160), leading to the hypothesis that an antagonist of mGluR5 might dampen the hyperactivity of glutamatergic transmission believed to underlie anxiety disorders. Consistent with this, MPEP and related mGluR5 NAMs have robust efficacy in several animal models of anxiolytic activity (154), and the clinically validated anxiolytic agent fenobam (161) acts as a selective mGluR5 NAM (162). Animal studies suggest that selective mGluR5 NAMs also have potential utility in the treatment of fragile X syndrome (FXS) (163–165) as well as chronic pain, addictive disorders, depression, gastroesophageal reflux (GERD), migraine, and some neurodegenerative disorders (166). Exciting new clinical studies have now established the efficacy of mGluR5 NAMs in treatment of GERD (167) and migraine (168).

Potential for mGluR5 NAMs for the treatment of FXS also has a strong clinical basis because the primary mutation giving rise to the disorder leads to increased mGluR5 signaling (163, 169). FXS is the most common inherited form of mental retardation and a leading cause of autism (170). FXS is caused by genetic defects in the gene encoding the fragile X mental retardation protein (FMRP), a translational repressor that regulates local protein translation in neuronal dendrites; these proteins promote LTD. In mouse models of FXS, the group I mGluR-dependent LTD is excessive, suggesting that antagonists of mGluR1 or mGluR5 might represent novel mechanisms for FXS treatment (163). Consistent with this, studies examining the phenotypes of FXS mice interbred with mGluR5 knockout animals have revealed that many of the phenotypes of FXS can be rescued when mGluR5 levels are reduced (164). Early work with the mGluR5 NAM MPEP has also validated the use of mGluR5 antagonists as a possible treatment for FXS; MPEP administration can suppress several phenotypes, such as seizures and anxiety, present in FXS mice (165). Intense efforts are now underway to develop highly selective mGluR5 antagonists for clinical trials in FXS patients.

In addition to the utility of mGluR5 NAMs, mGluR5 PAMs may have potential utility in the treatment of schizophrenia and other disorders that involve impaired cognitive function (71, 155). Multiple mGluR5 PAMs have been identified and can potentiate mGluR5-mediated electrophysiological responses in midbrain and forebrain circuits, including potentiation of NMDA receptor currents (68, 171, 172), a response that is thought to be relevant for schizophrenia and cognitive function. Furthermore, two mGluR5 PAMs, CDPPB and ADX47273, have robust antipsychotic-like effects and improve cognitive function in animal models (72, 73, 173). Although lacking the clinical validation of mGluR5 NAMs, these exciting findings suggest that mGluR5 PAMs have potential utility as novel antipsychotic and cognition-enhancing agents.

Agonists and PAMs of Group II mGluRs

Preclinical and clinical studies provide strong evidence that agonists of group II mGluRs have potential as a novel approach for the treatment of anxiety disorders and schizophrenia. Selective group II mGluR agonists such as LY354740 and related compounds have robust anxiolytic (154, 174) and antipsychotic-like effects in animal models (175), and clinical studies reveal that group II mGluR agonists have efficacy in treatment of both anxiety and schizophrenia (71, 154). Group II mGluR agonists also have robust efficacy in human models of panic attacks and fear-potentiated startle and improve symptoms of generalized anxiety disorder (154, 176). Furthermore, a selective group II mGluR agonist improves positive and negative symptoms in patients suffering from schizophrenia (177). These clinical findings represent a major breakthrough and could ultimately lead to the introduction of group II mGluR activators as a fundamentally novel approach to the treatment of anxiety disorders and schizophrenia. Interestingly, the effects of mGluR2 and -3 agonists in animal models of anxiety disorders and schizophrenia can be observed with highly selective mGluR2 PAMs (reviewed in 71). These studies raise the possibility that selective mGluR2 PAMs may also provide a novel approach to the treatment of these disorders.

Recently, a direct interaction between mGluR2 and the serotonin 5-HT_{2A} receptor has been proposed as providing a mechanism for antipsychotic effects of mGluR2 agonists (178). 5-HT_{2A} receptors are activated by hallucinogens such as lysergic acid diethylamide (LSD) and inhibited by atypical antipsychotics such as clozapine. Activation of 5-HT_{2A} receptors induces a dramatic increase in spontaneous excitatory postsynaptic potentials at thalamo-cortical synapses in the medial prefrontal cortex (179), and increased spontaneous activity at this synapse has been postulated to participate in some aspects of schizophrenia (155, 179). Interestingly, it has been shown that 5HT_{2A} receptors can heterodimerize with mGluR2 (178), and activation of mGluR2 dramatically reduces serotonin-stimulated increases in spontaneous excitatory postsynaptic potentials at thalamocortical synapses (179, 180). Based on this, it is possible that heterodimerization and functional interactions between 5HT_{2A} receptors and mGluR2 may be important for the antipsychotic activity of group II mGluR agonists. Additionally, this raises the possibility that more examples of heterodimers between mGluRs and other GPCRs exist, providing further complexity to mGluR biology.

In addition to schizophrenia and anxiety, ligands at group II mGluRs have also been suggested as therapeutic directions for other CNS disorders, including mGluR2 and mGluR3 agonists and mGluR2 PAMs for treatment of pain, addictive disorders, depression, and epilepsy (reviewed in 181). Whereas less is known about the potential utility of mGluR3-selective compounds, agonists of these receptors appear to be neuroprotective, and this effect has been attributed to mGluR3 with the use of knockout animals (123). The future development of more selective compounds that differentiate between mGluR2 and mGluR3 is anticipated to advance the understanding of the individual roles of these receptors in various disease states.

mGluR4 PAMs

Another mGluR subtype, mGluR4, has emerged as an exciting new target for the treatment of Parkinson's disease (PD) (159). Activation of mGluR4 reduces GABAergic transmission at the striato-pallidal synapse (182–184), a synapse that is overactive after the loss of dopamine neurons in patients suffering from PD (185). Agonists of group III mGluRs have robust efficacy in rodent models of PD (182, 186–190). Furthermore, a highly selective mGluR4 PAM, PHCCC, potentiates mGluR4 responses at the striato-pallidal synapse (90), and intracerebroventricular injection of PHCCC as well as several other mGluR4 PAMs have antiparkinsonian effects in

rodent models (90, 92, 191, 192). In addition to providing symptomatic relief for PD patients, a number of studies suggest that mGluR4 activation could also provide a neuroprotective effect and slow disease progression by reducing excessive excitatory drive onto dopamine neurons and potential excitotoxicity, which may contribute to loss of these neurons (193, 194).

Group III mGluRs also have potential for the treatment of other CNS disorders. For example, mGluR4 knockout animals appear to be resistant to several of the features of alcohol addiction (135), and mGluR8 levels are regulated by cocaine and amphetamine administration, suggesting roles for group III receptors in drug abuse (195, 196). mGluR7 appears to have a role in mediating seizures based on studies with knockout mice (138) as well as mouse models examining interacting proteins (55). Additionally, emerging studies suggest roles of group III mGluRs in depression and anxiety (153), neuroblastoma (197), and neuronal differentiation (198).

SUMMARY AND CONCLUSIONS

Our understanding of the mGluR field has grown exponentially within the past decade. Novel insights into the mechanism of activation of receptors, detailed studies regarding interacting proteins that modulate receptor function, and the identification of many new ligands available to probe receptor biology have all contributed to the growth of this area from both basic science and therapeutic perspectives. Advances in selective compound discovery, spanning orthosteric and allosteric binding sites, have promoted the development of highly selective tools and, in some cases, compounds that can be tested in the clinical setting. It is anticipated that the fast-paced development in the mGluR field will continue to enhance our understanding of CNS function and will soon open additional possibilities for treatments of neurological and psychiatric disorders.

DISCLOSURE STATEMENT

Dr. Conn has served as a consultant over the past year for Epix Pharmaceuticals, Evotec Inc., Seaside Therapeutics, Merck Serono, AstraZeneca USA, NeurOp Inc., Millipore Corp., Genentech, Abbott Laboratories, AMRI, and PureTech. Dr. Conn and Dr. Niswender receive research support that includes salary support from The Michael J. Fox Foundation, Seaside Therapeutics, and Johnson and Johnson.

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