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Metabotropic glutamate receptor trafficking

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Abstract

The metabotropic glutamate receptors (mGlu receptors) are G protein-coupled receptors that bind to the excitatory neurotransmitter glutamate and are important in the modulation of neuronal excitability, synaptic transmission, and plasticity in the central nervous system. Trafficking of mGlu receptors in and out of the synaptic plasma membrane is a fundamental mechanism modulating excitatory synaptic function through regulation of receptor abundance, desensitization, and signaling profiles. In this review, we cover the regulatory mechanisms determining surface expression and endocytosis of mGlu receptors, with particular focus on post-translational modifications and receptor-protein interactions. The literature we review broadens our insight into the precise events defining the expression of functional mGlu receptors at synapses, and will likely contribute to the successful development of novel therapeutic targets for a variety of developmental, neurological, and psychiatric disorders.

Keywords

metabotropic glutamate receptors; trafficking; endocytosis; protein-protein interaction; post-translational modification; phosphorylation

1. Introduction

Metabotropic glutamate receptors (mGlu receptors) are class C G protein-coupled receptors (GPCRs) that modulate synaptic transmission and plasticity throughout the CNS. Like all GPCRs, mGlu receptors consist of seven transmembrane domains (TMs) joined by three extracellular and three intracellular loops. The N-terminal extracellular domain (ECD) contains a glutamate-binding Venus flytrap domain (VFD) and a cysteine rich domain. The cytoplasmic C-terminal domain (CTD) modulates receptor signaling, trafficking and G protein coupling. This region is a major target of protein phosphorylation and a hub for protein-protein interactions.

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The nomenclature of mGlu receptors is numeric beginning with mGlu1, which was first isolated by expression cloning (Houamed et al., 1991; Masu et al., 1991). The cloning of subsequent mGlu receptors resulted in their sequential numbering. The mGlu receptors are divided into three sub-families based on sequence homology, second messenger coupling, and pharmacological properties. Group I (mGlu1 & mGlu5) receptors are coupled to G_q -like proteins and stimulate phospholipase C (PLC), leading to an elevation of intracellular Ca^{2+} and activation of protein kinase C (PKC). Group II (mGlu2 & mGlu3) and Group III (mGlu4, mGlu6, mGlu7 & mGlu8) receptors are coupled to G_i/G_o proteins and inhibit adenylate cyclase (AC), which leads to a reduction of cAMP and inactivation of protein kinase A (PKA). The signaling cascades of mGlu receptors are far more complex than these canonical pathways (Niswender and Conn, 2010; Willard and Koochekpour, 2013). Group I mGlu receptors, for example, can modulate unconventional signaling pathways involving $G_{i/o}$ and G_s (Aramori and Nakanishi, 1992; Francesconi and Duvoisin, 1998; Hermans et al., 2000; Thomsen, 1996). Furthermore, mGlu7 can stimulate PLC through the activation of a pertussis toxin (PTX)-sensitive or -resistant G protein (Martin et al., 2010; Perroy et al., 2000), and mGlu2 or mGlu4 can activate $G_{\alpha 15}$ and PLC (Gomez et al., 1996).

The distribution and subcellular localization differs between the subtypes of mGlu receptors. Most mGlu receptors are broadly expressed in the brain, except for mGlu6, which is restricted to the retina. Some mGlu receptors are additionally found in glial cells, such as mGlu3 and mGlu5 (Aronica et al., 2003; Schools and Kimelberg, 1999). Group I mGlu receptors are mainly localized at postsynaptic sites, whereas Group II and Group III mGlu receptors are preferentially expressed in presynaptic axon terminals. Group II mGlu receptors are located away from the glutamate release sites, whereas Group III mGlu receptors are typically localized at the presynaptic active zones (Pinheiro and Mulle, 2008; Shigemoto et al., 1997).

This review focuses on the mechanisms that regulate mGlu receptor trafficking, including phosphorylation, protein interactions, and differential endocytic sorting and degradation. As with other GPCRs, second messenger-dependent protein kinases, such as PKA, PKC, and Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), contribute to endocytosis and desensitization. Receptor phosphorylation additionally regulates binding to cytosolic proteins via their CTDs or intracellular loop (iL) domains (Dhami and Ferguson, 2006; Ritter and Hall, 2009). In this review, we discuss the current literature on mGlu receptor-specific binding partners that modulate surface expression and signaling.

2. Group I mGlu receptors

Group I mGlu receptors (mGlu1 and mGlu5) are $G_{\alpha q}$ -linked GPCRs, and binding of glutamate triggers a sequence of events: activation of $G_{\alpha q/11}$ proteins leading to PLC activity that generates inositol 1,4,5-trisphosphate (IP_3) and diacyl glycerol (DAG). IP_3 binds to IP_3 receptors leading to the release of intracellular Ca^{2+} from smooth endoplasmic reticulum (SER). DAG activates transient receptor potential canonical (TRPC)-mediated currents. Simultaneous binding of elevated Ca^{2+} and DAG activates PKC. mGlu1 and 5 are primarily expressed in the CNS and have distinct and sometimes overlapping distributions in different subtypes of neurons. Group I mGlu receptors are postsynaptic and are located in

perisynaptic regions of the postsynaptic membrane of the excitatory neurons. mGlu1 and mGlu5 receptors share about 70% sequence homology, and also share many conserved signaling pathways and trafficking routes. There are many factors that have an impact on the trafficking of Group I mGlu receptors.

2.1. Alternative splice variants

Both mGlu1 and mGlu5 receptors undergo alternative splicing (Ferraguti et al., 2008; Pin and Duvoisin, 1995), with mGlu1 being the most extensively studied vis a vis alternative splicing and protein trafficking. mGlu1 has eight isoforms with CTDs of differing lengths (mGlu1a–e, mGlu1g, mGlu1g-393, mGlu1g-620, and mGlu1h) and a truncated ECD (taste-mGlu1, (San Gabriel et al., 2005)). A rare ATD (amino terminal domain) form of mGlu1E55 cloned from a mouse brain cDNA library has also been found in brain and heart tissue (Zhu et al., 1999). The CTDs of Group I mGlu receptors include many signaling elements, phosphorylation sites, and protein binding motifs. The longest and most prevalent form of mGlu1 receptor is mGlu1a, which has a long intracellular CTD and displays a relatively higher affinity for agonists compared to the other short forms of mGlu1 (Flor et al., 1996). Like mGlu1a, the CTD splice variants of mGlu1 are expressed postsynaptically; however, there is some variability with some located further away from the postsynaptic density than mGlu1a (Mateos et al., 1998; Mateos et al., 2000). The shorter forms of mGlu1 are missing many conserved regulatory motifs and are therefore, not unexpectedly, traffic differently.

One splice variant, mGlu1b, is characterized by a shorter CTD that derives from the insertion of an 61-bp exon (exon 9) with an in-frame stop codon, which produces 20 unique amino acids instead of a long CTD (Ferraguti et al., 2008). While mGlu1a is robustly expressed on the cell surface, surface expression of mGlu1b is weaker (Chan et al., 2001). Chan *et al.* were able to identify four positively charged amino acids, ⁸⁷⁷-RRKK-⁸⁸⁰, as an ER retention motif in the CTD of both mGlu1a and mGlu1b (Chan et al., 2001). C-terminal end truncation experiments of mGlu1a were also used to successfully map the region (amino acids 975 to 1098) of the CTD that can effectively mask ER-retention signal of mGlu1a. Interestingly, the RRKK motif can also regulate the dimerization of the receptors. As this RRKK motif is not conserved in mGlu5, mGlu5a and mGlu5b can exist as a heterodimer. Hetero-dimerization of mGlu1b with mGlu1a is inhibited resulting in the aberrant intracellular accumulation of mGlu1b (Remelli et al., 2008). However, Kumpost *et al.* has found that the long CTD of mGlu1a might neutralize the RRKK motif of an adjacent mGlu1b, reporting that mGlu1a co-expressed with mGlu1b readily forms heterodimers and promotes trafficking of mGlu1b to the cell surface (Kumpost et al., 2008). mGlu1b is found preferentially in complexes with mGlu1a in the brain and redistributed from soma to dendritic compartments upon co-expression with mGlu1a in cortical neurons (Techlovská et al., 2014). These results indicate that the ER-retention motif in mGlu1 regulates membrane trafficking of mGlu1 isoforms with differential effects based on splice variants and heterodimerization.

2.2. Domain structure and receptor trafficking

Membrane trafficking of Group I mGlu receptors has been focused almost entirely on the CTD of the receptors (see Table 1), particularly regarding phosphorylation sites, ER

retention motifs, as well as a large number of protein binding sites as discussed in detail later in this review. Conversely, little attention has been focused on the ECD and the 7TM domains of mGlu receptors. It is worth noting that mGlu1 has many naturally occurring splice variants including a truncated form that consists of only the ECD. Like many other GPCRs, mGlu1 and 5 form stable, covalently and structurally linked homodimers with ligands bound to both dimer subunits (Kammermeier and Yun, 2005; Kniazeff et al., 2004). The closely related GABA_B receptors 1 and 2 can form heterodimers; however, whether mGlu1 and mGlu5 can form heterodimers is still a topic for debate (Chang and Roche, 2017; Doumazane et al., 2011; Romano et al., 1996). We recently utilized a truncated form of mGlu5 to study dimerization, trafficking and ligand binding. Taking advantage of the strong homodimer formation between the two ECDs of mGlu5, we used distinctly tagged ECDs to study its trafficking and dimerization (Chang and Roche, 2017). We first found that the CTD is not essential for mGlu5 surface expression, whereas the 7th TM appears to be a critical factor influencing its surface expression. We also showed that the mGlu5 ECD could form a dimer with mGlu1 in reciprocal co-IP experiments (Chang and Roche, 2017). It is important to note that consistent differences in membrane trafficking of truncated and ligand binding site mutants of mGlu5 was observed when receptors were expressed in HEK293 cells as opposed to neurons. For instance, one of the ligand binding deficient mutants, mGlu5 T174A, traffics to the plasma membrane in HEK293 cells similar to the WT, whereas the mutation almost abolishes surface expression when the receptor is expressed in neurons. Furthermore, dominant negative effects of the ECD upon co-expression with full-length mGlu5 are observed in HEK293 cells, but not in neurons. These results indicate that in some cases neurons are more sensitive to truncations and mutations. Therefore, it is always important to include analyses of receptor trafficking in neurons and not rely solely on expression in heterologous systems.

2.3. Protein Phosphorylation

2.3.1. PKC phosphorylation and CaM/Siah-1A binding—Group I mGlu receptor signaling is regulated by membrane trafficking events such as endocytosis, as well as posttranslational modifications such phosphorylation. Receptor desensitization is governed by the activity of a variety of serine/threonine protein kinases including PKC, PKA, mitogen-activated protein kinases (MAPKs), CaMKII, and GPCR kinases (GRKs) upon agonist exposure (Kim et al., 2008). Among them, PKC has been extensively characterized as a key kinase acting on both the intracellular loops and the CTD of Group I mGlu receptors. Multiple PKC consensus phosphorylation sites are found on the intracellular loop 1 (iL1) and iL2 in addition to the CTD of Group I mGlu receptors. Phosphorylation by PKC regulates the constitutive and agonist-induced desensitization of mGlu1 (Mao et al., 2008). Specifically, PKC phosphorylates mGlu1 at T695 (T681 on mGlu5), which is responsible for the agonist-induced rapid desensitization of mGlu1. PKC phosphorylation at T695 selectively desensitizes G_q-coupled signaling pathways resulting in IP₃ formation without affecting G_s-coupled cAMP signaling (Francesconi and Duvoisin, 2000). In the case of mGlu5, multiple potential PKC phosphorylation sites (T606, S613, T665, S881, and S890) play a role in the rapid desensitization of mGlu5. The T681A, non-phosphorylated, mutation of mGlu5 eliminates basal activity by a complete loss of PLC coupling, and T681

phosphorylation might therefore be responsible for the constitutive signaling or cell surface expression of mGlu5 (Gereau and Heinemann, 1998).

Both mGlu1a and mGlu5 activation leads to the release of Ca^{2+} from intracellular stores. However, mGlu1 induces a single transient peak of Ca^{2+} , whereas mGlu5 activation elicits high frequency Ca^{2+} oscillations that are PKC-dependent (Kim et al., 2008). An early study demonstrated that a single mutation within the mGlu5 CTD that swaps the threonine residue to the analogous amino acid in mGlu1 (mGlu5 T840D, a phospho-mimetic mutant) dramatically changed the mGlu5 phenotype to mimic mGlu1 Ca^{2+} signaling (Kawabata et al., 1996). The assumption was that T840 was the critical PKC phosphorylation site; however, subsequent investigation revealed that T840 itself is not phosphorylated by PKC, but serves a permissive role allowing the phosphorylation of the adjacent S839 residue. Indeed, the phosphorylation of mGlu5 at S839 by PKC is critical for the generation of mGlu5-dependent high frequency Ca^{2+} oscillations (Kim et al., 2005).

PKC-induced phosphorylation of mGlu5 also affects receptor endocytosis and binding of various intracellular molecules such as calmodulin (CaM) and Siah-1A (seven in absentia homolog-1A). In particular, S901 on mGlu5 was identified as a major PKC phosphorylation site in close proximity to the critical Ca^{2+} -CaM binding residue (Lee et al., 2008b). PKC-induced phosphorylation of S901 by agonist DHPG or PMA treatment increases the agonist-induced internalization of mGlu5 expressed in HeLa cells or endogenous mGlu5 in cultured hippocampal neurons. Agonist-induced internalization of mGlu5 is inversely regulated by CaM binding. Specifically, CaM inhibits the PKC-mediated S901 phosphorylation of mGlu5, whereas PKC-induced phosphorylation of S901 inhibits CaM binding to mGlu5. Thus, PKC phosphorylation and CaM reciprocally regulate mGlu5 trafficking in a Ca^{2+} -dependent manner (Lee et al., 2008b; Minakami et al., 1997) (Fig. 1). CaM binding appears to be the critical factor regulating surface expression of mGlu5 rather than S901 phosphorylation itself, given that the mGlu5 S901A mutant, which is typically stably expressed on the cell surface, can be efficiently internalized by agonist upon knocking down CaM. In addition, PKC phosphorylation of mGlu5 S901 regulates mGlu5 signaling by prolonging intracellular Ca^{2+} oscillations most likely through increased density of surface mGlu5 (Lee et al., 2008b). CaM can additionally regulate DHPG-stimulated activation of extracellular signal-regulated kinases 1/2 (ERK1/2) and p70-S6 kinase 1 (S6K1) in hippocampal neurons (Sethna et al., 2016). PKC-induced phosphorylation can also regulate the endocytosis of mGlu1. The distal CTD of mGlu1a is important for the PKC- or CaMKII-mediated mGlu1a internalization, because PKC or CaMKII inhibitors suppress the agonist-induced internalization of mGlu1a, but not that of mGlu1b or mGlu1a truncated at V893 (Ciruela and McIlhinney, 1997; Mundell et al., 2002; Mundell et al., 2003).

Ca^{2+} -CaM has long been known to bind to mGlu5 as characterized by *in vitro* binding assays (Minakami et al., 1997). For many years, it was assumed that mGlu1 would also bind to CaM. However, careful analyses demonstrated that CaM specifically binds to mGlu5, not mGlu1, and a single residue in mGlu5 (L896) is critical for CaM binding (Choi et al., 2011). The mGlu5 L896V mutant, which disrupts CaM binding, displays decreased surface expression. Conversely, the mGlu1 V909L mutation, which allows for CaM binding to mGlu1, results in increased surface expression of mGlu1 compared to wildtype (Choi et al.,

2011). CaM binding to mGlu receptors stabilizes and increases their own cell surface density, which enhances mGlu-mediated intracellular signaling that favors AMPA receptor endocytosis. DHPG triggers rapid endocytosis of AMPA receptors, within 15 min, resulting in mGlu receptor-mediated long-term depression (LTD). On a slower time course, DHPG then causes the internalization of mGlu receptors after 30–90 min (Choi et al., 2011; Palmer et al., 1997; Snyder et al., 2001). Thus agonist-induced internalization of Group I mGlu receptors is regulated by CaM binding as is mGlu receptor-mediated AMPA receptor endocytosis, which is enhanced by CaM binding to Group I mGlu receptors in hippocampal neurons (Choi et al., 2011) (Fig. 1).

Siah-1A is a member of the E3 ubiquitin ligase family containing a RING-finger protein motif and the first identified ubiquitin ligase that plays a crucial role in the trafficking of mGlu receptors. Siah-1A directly interacts with Group 1 mGlu receptors, and induces receptor ubiquitination at multiple lysine residues resulting in receptor degradation via the ubiquitin-proteasome pathway. The Siah-1A binding site is present in mGlu1a (amino acids K905–P932), and mGlu1b and truncated mGlu1a missing the Siah-interacting domain are not regulated by Siah1A co-expression (Moriyoshi et al., 2004). Importantly, the binding regions of Siah-1A and CaM within the mGlu5 CTD overlap. Studies show that Siah-1A competes with CaM for mGlu5 binding. S901 phosphorylation of mGlu5 favors Siah-1A binding by displacing CaM in a Ca^{2+} -dependent manner in hippocampal neurons (Ishikawa et al., 1999; Ko et al., 2012). Siah-1A binding decreases mGlu5 surface expression and increases agonist-induced endosomal trafficking, which leads to the lysosomal degradation of mGlu5 (Ko et al., 2012). Siah-1A-dependent ubiquitination is an important step regulating agonist-induced internalization of mGlu1a as well as mGlu5 in HEK293 cells and hippocampal neurons. In particular, K63-mediated polyubiquitination at K1112 in the mGlu1 CTD has been identified to be important in agonist-induced mGlu1a internalization (Gulia et al., 2017).

2.3.2. GRKs and β -arrestins—GPCR desensitization is the deactivation of GPCR-elicited signaling following prolonged or repeated agonist exposure. A major mechanism underlying desensitization is agonist-stimulated phosphorylation and subsequent endocytosis of the receptor. The second messenger-dependent protein kinases were originally regarded as the principal mediators of GPCR phosphorylation and desensitization. However, GRKs (originally called β -adrenoceptor kinases) have been shown to play a central role in the agonist-induced desensitization of many GPCRs since their discovery (Gurevich et al., 2012). The GRK family of serine/threonine kinases comprises seven members. Based on sequence homology, vertebrate GRKs are classified into three subfamilies: Visual or rhodopsin-kinases subfamily (GRK1 and GRK7), β -adrenergic receptor kinases subfamily (GRK2 and GRK3), and the GRK4 subfamily (GRK4, GRK5, and GRK6). The expression of GRK1 and 7 is restricted to the retina, whereas GRK4 is predominantly expressed in the testes, but has also been found in the brain. GRK2, 3, 5, and 6 are ubiquitously expressed. The GRK family members possess the N-terminal regulator of G protein signaling (RGS) homology (RH) domain implicated in GPCR binding, the catalytic domain containing S/T kinase activity, and the CTD responsible for plasma membrane targeting. GRK2 and GRK3

contain pleckstrin homology (PH) domains that interact with $G_{\beta\gamma}$ subunits (Sato et al., 2015).

The canonical mechanism for GPCR desensitization involves phosphorylation of receptors by GRKs and subsequent recruitment of β -arrestins, which sterically hinders further heterotrimeric G protein activation (Dhami and Ferguson, 2006). β -arrestin-bound receptors initiate G protein-independent signaling and are subject to clathrin-mediated endocytosis (CME) and are sorted for receptor degradation or receptor recycling (Sato et al., 2015). β -arrestins were initially regarded as negative regulators of GPCRs by inducing receptor endocytosis and attenuation of receptor signaling. However, there is accumulating evidence that β -arrestins also contribute to the formation of fully engaged GPCR–G protein– β -arrestin supercomplexes that mediate sustained G protein activation from internalized receptors in endosomes (Ranjan et al., 2017). At the end of GPCR cycles, RGS acts as GTPase activating proteins (GAPs), leading to GTP hydrolysis and reversing the receptor to an initial resting state (Sato et al., 2015).

Different GRK subtypes combined with the action of β -arrestins can contribute to the endocytosis of Group I mGlu receptors in an agonist-dependent manner; however, the results are inconsistent (reviewed in Refs: (Iacovelli et al., 2013; Kim et al., 2008)). Both GRK2 and GRK4 facilitate the agonist-induced internalization of mGlu1a, which appears to require GRK2-mediated phosphorylation of the S869–V893 region of mGlu1a when expressed in HEK293 cells (Dale et al., 2001a; Iacovelli et al., 2003; Mundell et al., 2003; Sallese et al., 2000). These agonist-induced internalization processes are β -arrestin 1/2 and dynamin-dependent (Mundell et al., 2002; Mundell et al., 2001; Mundell et al., 2003). β -arrestin 1 appears to be important in mGlu1 endocytosis; however, the agonist-stimulated internalization of mGlu1a is observed only when β -arrestin 1 is co-expressed with either GRK2 or GRK5 in HEK293 cells. GRK2, GRK5, β -arrestin 1, or β -arrestin 2 individually has no significant effect on the internalization of mGlu1a (Dale et al., 2001a). The constitutive internalization of mGlu1a does not require GRK2 nor β -arrestin 1, but occurs by a clathrin-coated vesicle-mediated pathway (Dale et al., 2001a). In other studies, GRK4 has been shown to be critical for the rapid internalization of mGlu1a in HEK293 cells and in cerebellar Purkinje neurons (Iacovelli et al., 2003; Sallese et al., 2000). In this case, β -arrestin 1 does not seem to be essential for the agonist-induced internalization of mGlu1a (Iacovelli et al., 2003).

Much less is known about the role of GRKs in mGlu5 signaling and trafficking. GRK2 and GRK3, but not GRK4, GRK5 or GRK6, regulate mGlu5 signaling in a kinase-activity dependent manner, when mGlu5 signaling was monitored by measuring GIRK channel currents following DHPG application in transfected HEK293 cells (Sorensen and Conn, 2003). The membrane-proximal domain near G847, in particular S839, might contribute to mGlu5 signaling, since the T840A mutation alone did not reverse the effect of GRK2 (Sorensen and Conn, 2003). Recently it was reported that β -arrestin 2, not β -arrestin 1, is required for specific forms of mGlu receptor-dependent synaptic plasticity in the hippocampus. Specifically, endogenous mGlu1 and mGlu5 were shown to physically interact with β -arrestin 2 in hippocampus and cortex, but surface expression of mGlu5 was not altered in β -arrestin 2 knockout (KO) animals (Eng et al., 2016).

2.3.3. Other kinases and phosphatases

PKA: PKA potentiates constitutive (agonist-independent) signaling of mGlu1a by increasing IP₃ formation in HEK293 cells, but does not alter the basal activity of mGlu1b (Francesconi and Duvoisin, 2000; Mundell et al., 2004). PKA increases the agonist-stimulated IP₃ accumulation in mGlu1a- or mGlu1b-expressing HEK293 cells (Mundell et al., 2004). For receptor trafficking, PKA inhibits the agonist-induced internalization of both mGlu1a and mGlu1b by primarily acting on the domain spanning region S869–A886 through a mechanism that inhibits the agonist-induced association of receptors and GRK2/β-arrestin 1. In addition, PKA increases constitutive surface expression of mGlu1a, but not mGlu1b, in HEK293 cells (Mundell et al., 2004). An early study showed that PKA activation does not contribute to the agonist-induced desensitization of mGlu5 expressed in oocytes (Gereau and Heinemann, 1998). A recent study revealed that PKA directly phosphorylates S870 on mGlu5 in *in vitro* assays and in the neostriatum. PKA-mediated phosphorylation on mGlu5 S870 is necessary for agonist-triggered ERK1/2 activation and Ca²⁺ oscillations without altering receptor surface expression levels (Uematsu et al., 2015).

CaMKII: CaMKIIα increases the agonist-induced endocytosis of mGlu1 and mGlu5 (Jin et al., 2013a; Mundell et al., 2002; Raka et al., 2015). CaMKIIα directly binds to the membrane-proximal CTD region of mGlu1a (amino acids K841–N885) and promotes the phosphorylation of mGlu1a T871, which is part of a consensus CaMKII phosphorylation sequence (R/KXXS/T) (Jin et al., 2013a). In addition, CaMKIIα can bind to the iL2 region of Group I mGlu receptors *in vitro* (Raka et al., 2015). Agonist-induced activation of mGlu1a triggers a Ca²⁺-dependent activation of CaMKIIα and potentiates CaMKIIα binding to mGlu1a. CaMKIIα then desensitizes the mGlu1-mediated IP₃ accumulation in striatal neurons (Jin et al., 2013a). In the case of mGlu5, there is evidence that inactive forms of CaMKIIα bind constitutively to the proximal CTD (amino acids L875–K917), which overlaps with the CaM binding region. Following mGlu5-stimulated Ca²⁺ release from intracellular calcium stores, CaMKIIα dissociates from mGlu5 in competition with CaM. The dissociated active CaMKIIα is subsequently recruited to the NMDA receptor where it can phosphorylate the GluN2B subunit (Jin et al., 2013b). CaMKIIα selectively attenuates the mGlu5a-stimulated ERK1/2 activation in a kinase activity-dependent manner in transfected HEK293 cells, but has no effect on mGlu1a-mediated ERK1/2 phosphorylation (Raka et al., 2015).

CaMKIIβ can regulate Group I mGlu receptor-mediated dendritic spine dynamics through its interaction with α-Actinin-4 (Actn4). Although Actn4 does not affect surface expression of Group I mGlu receptors, it is implicated in mGlu receptor-mediated dynamic remodeling of dendritic protrusions through the interaction with CaMKII (Kalinowska et al., 2015). Actn1, another α-actinin family protein, is associated with mGlu5b via a region that is conserved between mGlu5a and 5b (amino acids R931–A1002 of rat mGlu5b) in HEK293 cells and striatum. Actn1 increases the cell surface expression of mGlu5b and agonist-induced ERK1/2 phosphorylation in HEK293 cells (Cabello et al., 2007).

MAPK-ERK: MAPKs are serine/threonine kinases that include three subclasses: ERK1/2, c-Jun N-terminal kinases/stress-activated protein kinases (JNK/SAPK), and p38 MAPKs.

Among these kinases, ERK has been demonstrated to phosphorylate Group I mGlu receptors directly and modulate synaptic transmission and plasticity (Mao and Wang, 2016). ERK1/2 are associated with the CTD of Group I mGlu receptors *in vitro* and in cerebellar neurons. The ERK2 binding site is a membrane-proximal region (amino acids K841–N885) in the mGlu1a CTD (Yang et al., 2016). As a proline-directed kinase, ERK phosphorylates mGlu1a (S1154) and mGlu5 (S1126) at a consensus phosphorylation motif (S/T-P) as detected in cortical and cerebellar neurons. The phosphorylation site is located within a conserved Homer binding motif (-PPSPF-), but is distant from the ERK binding region of mGlu1a (Mao and Wang, 2016; Yang et al., 2016). Because the Group I agonist DHPG increases ERK phosphorylation and activated ERK phosphorylates mGlu5 S1126 in an activity-dependent manner, mGlu receptor-ERK constitutes a positive feedback loop. The phosphorylation of mGlu5 at S1126 increases the affinity of Homer-1, and mGlu5 surface expression in striatal neurons (Park et al., 2013). ERK also positively stabilizes mGlu1a on the cell surface in cerebellar neurons, whereas inhibition of ERK by U0126 reduces mGlu1a surface expression (Yang et al., 2016).

Cdk5: Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine kinase involved in neuronal development and synaptic plasticity. Cdk5 phosphorylates S/T residues within the Homer binding domain of mGlu5 in an *in vitro* kinase assay. CDK5-mediated phosphorylation of mGlu5 at T1123 and S1126 enhances its association with Homer, and appears to stabilize the receptor on cell surface (Orlando et al., 2009; Park et al., 2013).

Fyn: Fyn is a member of the Src family of nonreceptor tyrosine kinases and has been implicated in the direct phosphorylation, channel activity, and trafficking of GluN2B-containing NMDA receptors (Trepanier et al., 2012). Fyn also regulates mGlu1a by directly binding to the distal CTD (amino acids N925–T1000) of mGlu1a in GST pulldown assays and in cerebellar neurons. Fyn increases the surface expression of mGlu1a and agonist-stimulated IP₃ production by phosphorylation of mGlu1a Y937 (Jin et al., 2017).

Protein phosphatases: Protein phosphatase 2A (PP2A) has been shown to regulate recycling of both mGlu1 and mGlu5. DHPG-induced internalization of mGlu1/5 occurs within 5 min, and increases over time in HEK293 and neuronal cell lines. Subsequent to ligand-dependent internalization, mGlu1 is localized in Rab11-positive recycling endosomes with low abundance in LAMP1-positive lysosomal compartments. Internalized mGlu1/5 is then recycled to the cell surface upon DHPG application, and recycling is abolished by PP2A inhibition (Mahato et al., 2015; Pandey et al., 2014). The constitutively internalized mGlu5 is also reported to recycle to the cell surface in HEK293 cells, without entering lysosomes (Trivedi and Bhattacharyya, 2012). Serine/threonine protein phosphatase 1γ1 (PP1γ1) binds to Group I mGlu receptors through KSVTW residues in their CTD (amino acids 891–895 in mGlu1a; 880–884 in mGlu5) as well as mGlu7 by GST pulldown and yeast two-hybrid assays. However, functional consequences of their binding remain unknown (Crocì et al., 2003). The calcineurin inhibitor protein (CAIN) interacts with the iL2 and distal CTD of Group I mGlu receptors. CAIN inhibits the endocytosis of Group I mGlu receptors in transfected HEK293 cells, and attenuates mGlu1a signaling by disrupting G^{αq/11}-coupling to the receptor (Ferreira et al., 2009).

2.4. Binding proteins

2.4.1. Homer—Homer, also known as Vesl (VASP/Ena-related protein induced during Seizure and LTP), is a postsynaptic scaffold protein bridging Group I mGlu receptors and intracellular signaling molecules or receptors at excitatory synapses. Homer-1a was first discovered as an immediate early gene, whose expression is rapidly induced by synaptic activation such as seizures or long-term potentiation (LTP) stimulation (Brakeman et al., 1997). Homer-1, 2, and 3 proteins are encoded by three independent mammalian genes, and alternative spliced variants from those genes give rise to Homer family members that share a similar structure. The N-terminal region of Homer isoforms contains an enabled/VASP homology 1 (EVH1) domain that interacts with a consensus binding motif of **PPSPFR** present on the CTD of mGlu1a and mGlu5 (Beneken et al., 2000; Brakeman et al., 1997; Tu et al., 1998). Unlike Homer-1a, long-form isoforms are expressed constitutively and contain a cytoplasmic domain of coiled-coil (CC) structure, which allows multimerization and links the CTD of Group I mGlu receptors to the IP₃ receptors or ryanodine receptors (Feng et al., 2002; Kato et al., 1998; Rong et al., 2003; Tadokoro et al., 1999; Tu et al., 1998; Xiao et al., 1998; Xiao et al., 2000). The short-form Homer-1a lacks a CC domain and consequently cannot form multimers or interact with IP₃ or ryanodine receptors, thereby functioning as a natural dominant negative. (Xiao et al., 1998). There is a direct competition between endogenous long Homers and short Homer-1a for mGlu1a binding (Ango et al., 2001). Disruption of long Homer-mGlu receptors interaction or expression of endogenous Homer-1a induces agonist-independent activation of Group I mGlu receptors (Ango et al., 2001) (Fig. 2). It was recently shown that Homer-1a and long Homers competitively interact with mGlu5 receptor to control NMDA-mGlu5 receptor cross talk and synaptic excitability in dendritic spines (Moutin et al., 2012).

Homer organizes the trafficking and membrane clustering of Group I mGlu receptors. Homer-1b/c acts to decrease cell surface expression of Group I mGlu receptors. Homer-1b inhibits surface expression of mGlu5 or mGlu1a and retains the receptors within the ER via a direct protein-protein interaction in HeLa cells and cultured cerebellar granule cells (Ango et al., 2002; Hayashi et al., 2006; Roche et al., 1999). Homer-1c, but not Homer-1a diminishes surface expression of mGlu5 or mGlu1a and increases the formation of intracellular clusters of the receptors expressed in HEK293 cells (Abe et al., 2003; Coutinho et al., 2001). The reduction of Homer-3 increases surface expression of mGlu1a, and the degradation of mGlu1a can be facilitated by Homer-3 which binds to the S8 ATPase of the 26S proteasome in differentiated PC12 cells (Rezvani et al., 2012). Unlike long form Homers, Homer-1a has a relatively small effect on cell surface expression and clustering of Group I mGlu receptors (Ango et al., 2000; Ango et al., 2001; Ango et al., 2002; Ciruela et al., 1999; Roche et al., 1999). Homer-1a expression induced by neuronal activation reverses the intracellular retention of mGlu5 mediated by Homer-1b and promotes cell surface targeting of mGlu5 (Ango et al., 2002). Induction of Homer-1a expression by conditioning depolarization reduces the internalization and increases surface expression of mGlu1 in MAPK-dependent manner in HEK293 cells and cerebellar Purkinje neurons (Minami et al., 2003) (Fig. 2).

In contrast, Homer-1b/c has been shown, in some preparations, to increase cell surface expression and dendritic clustering of mGlu1a and mGlu5 in HEK293 cells and neurons, which are inhibited by overexpression of Homer-1a (Ciruela et al., 2000; Gama et al., 2001; Kammermeier, 2006; Serge et al., 2002; Tadokoro et al., 1999). Similarly, long Homer proteins, but not short Homer-1a, can induce surface clustering of Group I mGlu receptors and inhibit Group I mGlu receptor coupling to calcium channels in superior cervical ganglion (SCG) neurons (Beqollari and Kammermeier, 2013; Kammermeier, 2006; Kammermeier et al., 2000). Surface expression of mGlu5 increases in Homer-1a KO cortical neurons and a rescue expression of Homer-1a downregulates surface levels of mGlu5 (Hu et al., 2010).

Homer-dependent regulation of Group I mGlu receptor trafficking is also implicated in pathways involved in addiction. Homer-1 or Homer-2 KO mice, but not Homer-3 KO, display sensitized behavioral responses to cocaine (Szumlinski et al., 2004). Homer-2 deletion reduces total mGlu1a expression levels without altering mGlu5 levels in the Nucleus accumbens (NAc) (Szumlinski et al., 2004). Cocaine administration decreases surface expression of mGlu5 by elevating long Homers in the NAc (Fourgeaud et al., 2004). In contrast, a single dose of cocaine specifically induces Homer-1a, not long Homers, in the striatum and cocaine withdrawal leads to the reduction in the long Homer-1b/c and mGlu5 levels in the medial NAc (Swanson et al., 2001). Furthermore, upregulated Homer-1b/c in the NAc after extinction training reduces the surface expression of mGlu5 (Knackstedt et al., 2010). Overall, Homer has been demonstrated to play an important role in mGlu receptor trafficking with varying effects.

2.4.2. Other interactors

Tamalin: Tamalin (also termed GRP1-associated scaffold protein) has been isolated as a binding partner to the cytoplasmic domain of Group I mGlu receptors as well as mGlu2/3 by yeast two-hybrid screening (Kitano et al., 2002). Tamalin is a scaffolding protein composed of a PDZ domain, a leucine-zipper domain, four YXXL motifs involved in CME, a proline-rich region, and a carboxyl-terminal PDZ binding motif (Kitano et al., 2002; Kitano et al., 2003). The PDZ domain of tamalin interacts with Group I and II mGlu receptor CTDs and SAP90/PSD-95-associated protein (SAPAP) 1/3. A leucine-zipper domain of tamalin binds to guanine nucleotide exchange factor cytohesin-2, which promote surface trafficking of Group I mGlu receptors in heterologous cells and neurons (Kitano et al., 2002). The crystal structure of tamalin has revealed that tamalin undergoes the auto-inhibited self-assembly through its PDZ domain and C-terminus, which is converted to the released form by competitive binding of mGlu receptor CTD. This interaction liberates C-terminal PDZ binding domain of tamalin and facilitates the association with S-SCAM, and their association promotes mGlu receptor cell-surface trafficking (Sugi et al., 2007).

Band 4.1G: Band 4.1G cytoskeletal protein directly interacts with the mGlu1a CTD at the negatively charged glutamic acid-rich region (amino acids E1131–D1135), but not with mGlu1b in HEK293 cells and the cerebral cortex (Tateyama and Kubo, 2007). Band 4.1G co-localizes with mGlu1a and promotes mGlu1a surface expression in primary hippocampal neurons (Lu et al., 2004).

GluD2: The GluD2 receptor has roles in cerebellar LTD and synaptogenesis. It is a homologous protein to ionotropic glutamate receptors, but has long been considered as an orphan receptor without known endogenous ligands (Schmid and Hollmann, 2008). However, recent studies have demonstrated that GluD2 is indirectly gated by glutamate through mGlu1 receptor activation, and D-serine and Cbln1 (cerebellin 1 precursor) are endogenous ligands for GluD2 (Ady et al., 2014; Dadak et al., 2017; Yuzaki and Aricescu, 2017). The ECD of GluD2 interacts with neurexin through the secreted synapse organizer Cbln1 (Matsuda et al., 2010; Uemura et al., 2010). The mGlu1, PKC γ , and TRPC3 protein complex interact with GluD2 in the cerebellum. Loss of GluD2 increases surface expression of mGlu1b (Kato et al., 2012).

Norbin: Norbin (also known as Neurochondrin) has been identified as an mGlu5 binding molecule in a yeast two-hybrid screen, and increases cell surface expression and signaling of mGlu5 (Wang et al., 2009). Norbin physically interacts with the membrane proximal region of the CTD that overlaps with the calmodulin-binding site in mGlu5. CaM disrupts Norbin binding for mGlu5, but Norbin binding does not appear to affect CaM binding to mGlu5. Norbin positively regulates mGlu5-mediated IP₃ formation and ERK1/2 phosphorylation, and prolongs mGlu5-elicited Ca²⁺ oscillations in HEK293 cells. The cell surface expression of mGlu5 increases upon co-expression of Norbin in N2a cells and is reduced in Norbin KO or knockdown cortical neurons. In addition, Norbin KO mice display the impaired mGlu5-dependent synaptic plasticity in the hippocampus and depressive-like behaviors (Wang et al., 2015; Wang et al., 2009).

Numb: Numb is a cell fate determinant maintaining neural stem cells during asymmetric cell division. Numb has been proposed as an endocytic protein because it locates at various endocytic organelles and co-traffics with the internalized receptors (Santolini et al., 2000). Numb appears to regulate mGlu1 trafficking in the cerebellar Purkinje neurons. Numb KO mice exhibit reduced synaptic expression of mGlu1 by altering agonist-induced internalization and recycling of mGlu1 in cerebellar Purkinje neurons, and display impaired motor coordination (Zhou et al., 2015).

Optineurin and Rab8: Optineurin (OPTN) is co-localized with huntingtin (Htt) in the Golgi apparatus, forms a complex with Rab8, and participates in the regulation of post-Golgi protein transport (del Toro et al., 2009; Esseltine and Ferguson, 2013). OPTN has been identified as a binding molecule to the mGlu1a CTD in a yeast two-hybrid screen (Anborgh et al., 2005). Rab8 functions in concert with OPTN to attenuate both mGlu1a internalization and G protein coupling. Rab8 is associated with mGlu1a, but not with mGlu1b. Agonist treatment increases their association and co-localization in HEK293 cells and hippocampal neurons. Rab8 attenuates the agonist-induced endocytosis of mGlu1a and increases cell surface receptor expression (Esseltine et al., 2012).

p11: p11 (also known as S100A10) is a Ca²⁺-insensitive multifunctional protein implicated in serotonin receptor signaling and depression (Svenningsson et al., 2013). p11 interacts directly with the membrane-proximal region of mGlu5 (amino acids F836–M844) through a consensus binding motif for p11 (S/T-S/T-V) (Lee et al., 2015). Co-expression of p11

increases the cell surface expression of mGlu5 and agonist-induced Ca^{2+} oscillations in HEK293 cells, whereas knockdown or KO of p11 decreases the surface availability of mGlu5 (Lee et al., 2015).

Preso1: Preso1 is a multi-domain scaffolding protein that contains WW, PDZ, FERM, Homer ligand, and PDZ ligand binding domains. Preso1 was first identified as a PSD-95-interacting protein (Lee et al., 2008a) and later a Homer-binding protein by yeast two-hybrid screening (Hu et al., 2012). In addition to binding to proline-directed kinases such as CDK5 and ERK, Preso1 also binds to the membrane-proximal region of Group I mGlu receptor CTD (K920–S1020) via its FERM domain. The Homer binding site on mGlu5 is additionally required for complete binding affinity for Preso1. Preso1 increases constitutive and agonist-induced mGlu5 S1126 phosphorylation and enhances Homer-mGlu5 binding by facilitating the association of proline-directed kinases with mGlu5. Preso1 inhibits Group I mGlu receptor coupling to L-type voltage-sensitive Ca^{2+} channels like the action of long Homer proteins (Hu et al., 2012). Although Preso1 stabilizes the interaction among Group I mGlu receptors, Homer, and proline-directed kinases, surface and total expression of mGlu5 was not altered in Preso1 KO mice or upon knockdown (Hu et al., 2012; Luo et al., 2013).

Spinophilin: Spinophilin is a multifunctional synaptic scaffolding protein that interacts with protein phosphatases and F-actin. Spinophilin reduces the agonist-induced internalization of Group I mGlu receptors and ERK1/2 phosphorylation via its association with the PDZ binding motif of the receptors in HEK293 cells and cortical neurons. Spinophilin KO mice exhibit enhanced agonist-induced endocytosis of mGlu5 in cortical neurons and a deficit of mGlu receptor-dependent LTD in the CA1 hippocampus (Di Sebastiano et al., 2016).

2.5. Trafficking pathways

2.5.1. Endocytic trafficking—Many GPCRs undergo both constitutive (agonist-independent) or regulated (agonist-induced) internalization. The subsequent endocytosis can be clathrin-dependent or clathrin-independent. CME is the most extensively characterized endocytic pathway, and it involves the formation of clathrin-coated pits composed of clathrin and adaptor protein complexes. In contrast, clathrin-independent endocytosis (CIE) is caveolin-dependent endocytosis that involves the formation of caveolae by caveolins and cavins. Caveolae are flask-shaped invaginated plasma membrane domains enriched in cholesterol and sphingolipids. Dynamin, a membrane scission GTPase, mediates fission at the neck of both clathrin- and caveolin-coated pits upon GTP hydrolysis. CLIC/GEEC (clathrin-independent carriers/GPI-anchored protein enriched early endosomal compartment) is an uncoated tubular shaped structure, which mediates clathrin- and caveolin-independent pathways. CLIC/GEEC endocytosis is regulated by Cdc42 and delivers glycosylphosphatidylinositol (GPI)-anchored proteins and CD44 as specific cargos. Another type of CIE is a MHCI/CD59/Arf6-positive pathway that might overlap with the CLIC/GEEC pathway (Johannes et al., 2015).

Group I mGlu receptors appear to use multiple endocytic pathways that act together for regulating the internalization and recycling of the receptors. Studies using a dominant negative (DN) mutant of Eps15 (E 95/295), which has been extensively regarded as a

marker of CME, have revealed that the constitutive internalization of mGlu1a occurs via a clathrin-dependent pathway, whereas constitutive mGlu5 internalization occurs in a clathrin-independent pathway in heterologous cells and neurons (Dale et al., 2001a; Fourgeaud et al., 2003; Pula et al., 2004). However, constitutive endocytosis of both mGlu1a and mGlu5 were also shown to occur in a clathrin-dependent manner by Ral, a small GTP-binding protein in a complex with RalGDS (Ral guanine nucleotide dissociation stimulator), and PLD2 (phospholipase D2). The Ral/RalGDS/PLD2 complex are constitutively associated with mGlu1a and mGlu5, and are co-localized in clathrin-positive intracellular vesicles together with internalized mGlu1a or mGlu5 in HEK293 cells and neurons (Bhattacharya et al., 2004).

Agonist-independent endocytosis of Group I mGlu receptors might also be regulated by caveolin and a lipid raft-dependent process. Group I mGlu receptors co-fractionate in a detergent-resistant lipid raft-rich membrane (DRM) fraction and bind directly with caveolins via two caveolin-1 binding motifs present in the junction of iL1/3 and TM domains. The internalized Group I mGlu receptors co-localize with caveolin-1 and cholera toxin B, markers of the caveolar/raft pathway in neurons (Burgueno et al., 2004; Francesconi et al., 2009; Kumari et al., 2013). Caveolin-1 stabilizes mGlu1 at the cell surface, and disruption of caveolin-1 binding to mGlu1 drives rapid internalization of receptor in HEK293 cells and neurons. Depletion of membrane cholesterol also leads to the impairment of constitutive endocytosis of Group I mGlu receptors (Francesconi et al., 2009). However, a subsequent study reported that constitutive surface expression of Group I mGlu receptors is not altered in caveolin-1 KO hippocampus maybe due to the presence of compensatory trafficking mechanisms (Takayasu et al., 2010).

Agonist-induced endocytosis of Group I mGlu receptors involves both clathrin-dependent and caveolin-dependent pathways (Hong et al., 2009; Kumari et al., 2013; Luis Albasanz et al., 2002; Mundell et al., 2002; Mundell et al., 2001). As internalized mGlu1a was found in transferrin-positive endosomes in HEK293 cells, mGlu1a is probably endocytosed by clathrin-coated pits (Mundell et al., 2002; Mundell et al., 2001). Caveolar and lipid raft-dependent pathways also contribute to the agonist-induced internalization of mGlu1a; however, the role of caveolin itself is reported as inconsistent (see (Francesconi et al., 2009; Hong et al., 2009)). In particular, caveolin is phosphorylated and binds more to mGlu1a upon agonist stimulation, and then enhances internalization of mGlu1a rather than stabilizing the receptor on the cell surface (Hong et al., 2009). In a more recent study, agonist stimulation was shown to increase the association of Group I mGlu receptors with lipid rafts, which is dependent on membrane cholesterol content, not on caveolin-1 in HEK293 cells and cortical neurons (Kumari et al., 2013).

2.5.2. Nuclear trafficking—Nuclear entry of cell surface receptors has been reported for receptor tyrosine kinases (RTKs) such as EGFR and ErbB-2 and is thought to be important for some functions of those RTKs (Carpenter and Liao, 2013). It is well known that the intracellular CTD of these cell surface receptors is responsible for regulating receptor activity as well as subcellular localization. In fact, a nuclear localization signal (NLS) has been identified in the CTD of EGFR and ErbB-2 RTKs. Intriguingly, the CTD of one glutamate receptor, the NMDA receptor GluN1 subunit, has been reported to be present in

the nucleus when expressed alone. And, another study has identified a bi-partite nuclear localization sequence in the C1 region of GluN1 (Holmes et al., 2002). There is also evidence that mGlu receptors can traffic to the nucleus. For example, mGlu2 has been found on the nuclear envelope of Golgi cells by immunogold electron microscopy (Lujan et al., 1997). Using immunocytochemical, ultrastructural, subcellular fractionation and intracellular Ca^{2+} -measuring techniques, O'Malley, K.L. *et al.* were among the first to demonstrate that mGlu5 not only exists on the nuclear membrane but can be activated with rapid oscillatory Ca^{2+} elevations in response to 1 mM glutamate (O'Malley et al., 2003). Activation of intracellular, but not cell surface, mGlu5 was found to be responsible for the increased phosphorylation of ERK1/2 in a downstream signaling study (Jong et al., 2009).

GPCR signaling at the nucleus is an emerging paradigm given several subsequent studies indicating that other GPCRs can also be expressed and function in the mitochondria, ER membrane, lysosomes, and on the nuclear membrane (Benard et al., 2012; Branco and Allen, 2015; Gobeil et al., 2006; Irannejad and von Zastrow, 2014; Oksche et al., 2000; Tadevosyan et al., 2012). In attempts to identify the NLS for mGlu5, Sergin, I. *et al.* have focused on the mGlu5 CTD and mapped a region of 25 amino acids (amino acids S852–S876) as important for inner nuclear membrane insertion, and mGlu5 appears to interact with chromatin directly (Sergin et al., 2017). As the NLS is thought to overlap with the Ca^{2+} -CaM and Norbin binding sites, its regulation of mGlu5 entry to the nucleus may be far more complicated than originally thought since these sites have been proven to be involved with surface expression of the receptor (Chang and Roche, 2017; Choi et al., 2011; Kim et al., 2008; Ko et al., 2012; Lee et al., 2008b). Nevertheless, reports of nuclear trafficking of mGlu5 suggest mGlu5 is a membrane-crossing and multi-functional receptor, and its role in regulating and interacting with nuclear matrix proteins remains to be investigated.

3. Group II and III mGlu receptors

Activation of either Group II or III mGlu receptors inhibits AC activity via PTX-sensitive $\text{G}_{i/o}$, which leads to the inhibition of forskolin-stimulated cAMP formation, and activates the MAPK-ERK pathway. Although these receptors share a common signaling pathway, they differ in their expression patterns and subcellular distribution. For example, mGlu3 and mGlu7 are widely expressed (Ferraguti and Shigemoto, 2006), whereas mGlu6 is restricted to the retina. Group II and Group III mGlu receptors are known substrates for phosphorylation, both the second messenger-dependent protein kinases and GRKs, and phosphorylation affects receptor signaling and desensitization (reviewed in (Iacovelli et al., 2013)). However, very few studies demonstrate clear effects of phosphorylation on trafficking, with the exception of mGlu7. In this section we will discuss trafficking of Group II and III mGlu receptors with a major focus on the mechanisms underlying synaptic expression and endocytosis of mGlu7 (Table 2).

3.1. Group II mGlu receptors

Both mGlu2 and mGlu3 receptors are phosphorylated by PKA, and in vitro phosphorylation assays showed that PKA directly phosphorylates mGlu2 and mGlu3 at a single site (S843 and S845, respectively) within the CTD. There is another putative PKA consensus site

(S675) on the iL2 of mGlu2, but assays reveal only weak phosphorylation by PKA, compared to the robust phosphorylation of S843 (Cai et al., 2001; Schaffhauser et al., 2000). S845 on mGlu3 is dephosphorylated by the serine/threonine protein phosphatase 2C (PP2C), which specifically binds to the membrane-proximal region of the mGlu3 CTD (amino acids T836–Q855), but does not bind to other mGlu receptors (Flajolet et al., 2003). Because S843 on mGlu2, S845 on mGlu3, S859 on mGlu4, S862 on mGlu7, and S855 on mGlu8 are conserved PKA phosphorylation sites (Cai et al., 2001), PKA may similarly contribute to the function of most Group II and Group III receptors. However, a direct role of PKA-induced phosphorylation in surface expression and trafficking of Group II/III mGlu receptors has not yet been addressed.

Group I and Group II mGlu receptors possess a common (S/T)x(V/L) motif that belongs to the class I PDZ binding motif, whereas Group III mGlu receptors contain PDZ binding motifs similar to the class II-IV (Hirbec et al., 2002; Songyang et al., 1997). PDZ domain-containing proteins act as scaffolds for the assembly of protein complexes via multiple protein-protein interacting PDZ domains. They play an important role in the regulation of trafficking, signaling, and clustering of GPCRs (Dunn and Ferguson, 2015; Sheng and Sala, 2001). Specifically, PDZ proteins such as PICK1 (Protein Interacting with C-Kinase), syntenin, and GRIP (glutamate receptor interacting protein) interact with Group II and III mGlu receptors in various affinities in *in vitro* binding assays (Hirbec et al., 2002). Tamalin and NHERF1/2 (Na⁺/H⁺ exchanger regulatory factors 1/2) were also identified as PDZ-dependent binding partners with mGlu2/3, as well as for Group I mGlu receptors (Kitano et al., 2002; Paquet et al., 2006; Ritter-Makinson et al., 2017). However, direct roles of these PDZ-containing proteins in regulating mGlu2/3 surface expression and trafficking remain unknown. Furthermore, phosphorylation has been shown to dramatically regulate protein interactions via PDZ binding domains, but this has also not been reported for these receptors.

3.2. Group III mGlu receptors

There has been a sustained effort by the pharmaceutical industry to make selective compounds to either activate or block distinct subtypes of mGlu receptors. In fact, the identification of agonists, antagonists and allosteric modulators has led to better insights into the varied functions of mGlu receptors. L-AP4 is a prototypical orthosteric agonist of Group III mGlu receptors. As mGlu7 is activated only by high concentrations of glutamate or L-AP4, mGlu7 becomes active only under conditions of sustained synaptic activity, thereby acting as an autoreceptor to inhibit further glutamate release (Niswender and Conn, 2010). However, recent studies suggest a different role for Group III mGlu receptors, namely the facilitation of presynaptic release following agonist-exposure. This switch from inhibition to facilitation might be mediated by agonist-induced receptor endocytosis, an altered signaling pathway, or the competitive interaction among the receptors, Ca²⁺-activated CaM, and the exocytic machinery (Ferrero et al., 2016; Martin et al., 2010; Mochida, 2011; Nakajima et al., 2009; Pelkey et al., 2008) (Fig. 1).

3.2.1. mGlu4 receptor—The internalization and desensitization of mGlu4 are independent of agonist treatment, but can be induced by PKC activation. Mathiesen and

Ramirez found that L-AP4 fails to induce mGlu4 internalization even after a 60 min treatment in HEK293 cells, but rather slightly increases surface expression of mGlu4. However, mGlu4 is robustly internalized and desensitized when PKC pathways are activated in HEK293 cells (Mathiesen and Ramirez, 2006). It should be noted that another study successfully detected an agonist-induced, rapid and reversible internalization of mGlu4 in the same HEK293 cells by a GRK2-independent mechanism (Iacovelli et al., 2004).

Native mGlu4 is reported to interact with exocytic proteins such as Munc18-1, syntaxin, SNAP-25, and synapsin I and II in rat cerebellar lysates (Nakajima et al., 2009; Ramos et al., 2012). Munc18-1 binds to the membrane-proximal portion of mGlu4 CTD (amino acids E851–N871) that overlaps with the binding region of CaM. As Munc18-1 promotes soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-mediated vesicle fusion, mGlu4 might facilitate synaptic vesicle release by regulating SNARE complex assembly through the competitive association between CaM and Munc18-1. Munc18-1 is sequestered by mGlu4 during basal transmission. After an action potential, Ca^{2+} -activated CaM can liberate Munc18-1 from mGlu4, causing short-term synaptic facilitation (Mochida, 2011; Nakajima et al., 2009). Ca^{2+} -activated CaM that can compete with exocytotic proteins for binding to Group III mGlu receptors has emerged as the likely molecule responsible for presynaptic facilitation and is reviewed elsewhere (Mochida, 2011).

3.2.2. mGlu7 receptor— Ca^{2+} -CaM has been shown to bind to Group I and Group III mGlu receptors (except mGlu6), but not to Group II mGlu receptors (El Far et al., 2001; Lidwell et al., 2004). The minimal CaM binding consensus motif in mGlu7 (amino acids K858–M872) is conserved in Group III mGlu receptors other than mGlu6 (El Far et al., 2001; O'Connor et al., 1999). The heterotrimeric G protein $\beta\gamma$ subunits are associated with the membrane-proximal region (amino acids Q857–F863) that partially overlaps with CaM binding domain in mGlu7 CTD. While the S862E, phospho-mimetic mutation in mGlu7 reduces binding of both $\text{G}_{\beta\gamma}$ and CaM (El Far et al., 2001), the binding of $\text{G}_{\beta\gamma}$ and CaM to mGlu7 is mutually exclusive such that CaM binding to the mGlu7 CTD displaces $\text{G}_{\beta\gamma}$ from mGlu7 and liberates $\text{G}_{\beta\gamma}$ subunits more available for a direct inhibition of P/Q-type Ca^{2+} channels or for further receptor signaling to regulate neurotransmitter release (Fagni et al., 2004; O'Connor et al., 1999). This competitive displacement of $\text{G}_{\beta\gamma}$ subunits by CaM might be a general mechanism for regulating $\text{G}_{\beta\gamma}$ signaling among presynaptic Group III mGlu receptors.

Ca^{2+} -CaM binding to mGlu7 is regulated by the phosphorylation status of mGlu7 S862. This residue is located within the CaM-binding domain of mGlu7 and is phosphorylated by PKC, PKA, or PKG (Airas et al., 2001; Cai et al., 2001; Sorensen et al., 2002). S862 is the singular PKC phosphorylation site in mGlu7. When S862 is phosphorylated by PKC or mutated to a phospho-mimetic Glu(E) residue, CaM binding to mGlu7 is abolished. Conversely, overexpression of CaM reduces PKC-induced phosphorylation of mGlu7 S862 in an *in vitro* kinase assay or in transfected HeLa cells (Airas et al., 2001; Nakajima et al., 1999; Suh et al., 2008). In addition, CaM facilitates endocytosis of mGlu7 when bound to the CTD unphosphorylated at S862 (Suh et al., 2008). The phosphorylation of mGlu7 S862 critically regulates both constitutive and agonist-dependent mGlu7 trafficking along with the PDZ binding domain at the end of the mGlu7 CTD. The endocytosis of mGlu7 is markedly

enhanced for mGlu7 S862A, whereas endocytosis is reduced for mGlu7 S862E (Suh et al., 2008). Phosphorylation of mGlu7 S862 and subsequent endocytosis of mGlu7 is regulated by the agonist L-AP4, the allosteric modulator AMN082, or neuronal activation (Pelkey et al., 2005; Pelkey et al., 2007; Suh et al., 2013; Suh et al., 2008). mGlu7 also undergoes constitutive endocytosis via a clathrin-independent pathway and is accumulated in ADP-ribosylation factor 6 (ARF6) positive endosomes, distinct from the transferrin receptor (Lavezzari and Roche, 2007).

The last three C-terminal amino acids of mGlu7 are essential for its interaction with the PDZ domain of PICK1 (Boudin and Craig, 2001; Dev et al., 2000; El Far et al., 2000; Enz and Croci, 2003; Hirbec et al., 2002; Perroy et al., 2002). This PDZ binding domain is important not only in the clustering of the receptor at the presynaptic active zone in hippocampal neurons (Boudin et al., 2000), but also in the control of mGlu7 endocytosis (Suh et al., 2008). As PICK1 recruits and interacts with PKC α , PICK1 augments the PKC-induced S862 phosphorylation of mGlu7, and enhances stable surface expression of mGlu7 (Suh et al., 2008). Interestingly, although S862 is ~50 amino acids away from the PDZ binding domain, PICK1 competes with CaM for binding to mGlu7 and regulates mGlu7 receptor trafficking (Fig. 1).

Agonist-induced dephosphorylation of S862 is primarily mediated by PP1 γ 1 in cortical and hippocampal neurons (Suh et al., 2013). The inhibition of PP1 increases constitutive receptor surface expression by promoting S862 phosphorylation, and the overexpression of PP1 γ 1 D95N, a catalytically inactive mutant, inhibits constitutive and L-AP4-induced internalization of mGlu7a. It has been shown that PP1 γ 1 binds only to the mGlu7b, but not to mGlu7a, through KSVTW residues (amino acids 911–915) in *in vitro* assays (Croci et al., 2003; Enz, 2002; Enz and Croci, 2003). However, it was reported that both mGlu7a and mGlu7b are co-immunoprecipitated with PP1 γ 1 and phosphorylated upon treatment with a PP1 inhibitor in HEK293 cells. Thus, PP1 γ 1 plays a role in S862 phosphorylation and receptor trafficking for both mGlu7a and 7b (Suh et al., 2013).

Agonist-induced mGlu7 endocytosis has been proposed as a key mechanism regulating a metaplastic switch at the mossy fiber-CA3 interneuron (MF-SLIN) synapses such that the presence or absence of mGlu7 on the presynaptic surface dictates LTD or LTP in response to high-frequency stimulation (HFS), respectively (Pelkey et al., 2005; Pelkey and McBain, 2007, 2008). At naive MF-SLIN synapses, HFS or L-AP4 treatment triggers presynaptic LTD by mGlu7 activation and subsequent inhibition of P/Q-type Ca²⁺ channels. This mGlu7-mediated LTD is lost in PICK1 KO mice (Pelkey et al., 2005; Suh et al., 2008). Following L-AP4-induced activation and internalization of mGlu7, the same HFS produces presynaptic LTP, which requires the activation of the AC-cAMP-PKA pathway and subsequent action of RIM1 α released from mGlu7b (Pelkey et al., 2008). In addition, prolonged mGlu7 activation by L-AP4 pretreatment can switch mGlu7 signaling pathways from inhibition to potentiation of glutamate release. This pathway is dependent on a PTX-resistant G protein-PLC-PKC pathway and requires mGlu7-bound Munc13-1 translocation to promote interactions with RIM1 α , thereby enhancing synaptic vesicle exocytosis and glutamate release (Ferrero et al., 2016; Martin et al., 2010).

Trafficking of mGlu7 is also implicated in synaptic dysfunction. The proper surface expression of mGlu7 appears to be required for blocking epilepsy, as disruption of the interaction between mGlu7a and PICK1 results in absence-like seizures and increased susceptibility to PTZ (pentylentetrazole), a convulsant agent (Bertaso et al., 2008; Bockaert et al., 2010; Zhang et al., 2008). In addition, Elfn1, a cell adhesion protein that localizes to postsynaptic sites of somatostatin-positive interneurons, binds to mGlu7 *in trans* in the hippocampus. Elfn1 KO mice that have deficits in mGlu7 recruitment to synaptic sites display seizure-prone phenotypes (Tomioka et al., 2014).

Protein SUMOylation is a posttranslational modification that occurs most often at lysine residues within a consensus motif, Φ KX[D/E] (Φ , hydrophobic; X, any amino acid). All Group III mGlu receptors, except mGlu6, share a conserved SUMOylation motif. In addition, several PIAS (protein inhibitors of activated STATs) proteins that serve as SUMO E3 ligases, and Ubc9, an E2 enzyme have been found to interact with Group III mGlu receptor CTDs (Dutting et al., 2011; Tang et al., 2005). In addition, these SUMOylation machinery proteins are co-localized with mGlu8b in the retina (Dutting et al., 2011). All Group III mGlu receptors and mGlu2 have been found to be SUMOylated in a bacterial SUMOylation assay, whereas Group I mGlu receptors and mGlu3 were not SUMOylated (Dutting et al., 2011; Wilkinson and Henley, 2011; Wilkinson et al., 2008). Subsequent studies have identified K882/K903 on mGlu8b and K889 on mGlu7 as targets for SUMOylation in heterologous cells when Pias1 and/or Ubc9 are co-expressed (Choi et al., 2016; Dutting et al., 2011). SUMO-modifications participate in the stable surface expression of mGlu7. Endogenous mGlu7 is SUMOylated in hippocampus and cortical neurons, and SUMOylation of mGlu7 is reduced by the treatment of L-AP4. When mGlu7 is deSUMOylated, mGlu7 is internalized in hippocampal neurons. Furthermore, there is an interplay between SUMOylation and phosphorylation of receptor such that S862 phosphorylation of mGlu7 facilitates the SUMO conjugation of mGlu7 at K889 (Choi et al., 2016).

3.2.3. mGlu8 receptor—The membrane proximal region of the mGlu8 CTD is highly conserved with mGlu7, thus both receptors might be expected to share common trafficking mechanisms related to serine phosphorylation, $G_{\beta\gamma}$ association, and Ca^{2+} -CaM binding. As described above, S855 is a unique PKA phosphorylation site within mGlu8 (Cai et al., 2001) and mGlu8a signaling is inhibited by S855 phosphorylation in the hippocampus. However, the underlying molecular mechanism, for example receptor endocytosis, has not been analyzed (Cai et al., 2001). It is reported that PPG, an mGlu8 agonist, increases mGlu8 endocytosis in the enteric nervous system (Tong and Kirchgeßner, 2003).

Band 4.1 proteins (4.1B, 4.1G, 4.1N, 4.1R) interact with the cytoplasmic domain of mGlu8a/b, but not with other Group III mGlu receptors in GST pulldown assays. The Band 4.1 protein family functions as adaptor proteins, linking membrane proteins to the actin cytoskeleton. Band 4.1B is co-localized with mGlu8, facilitates mGlu8 cell surface expression, and reduces mGlu8 receptor-mediated intracellular cAMP levels in HEK293 cells and hippocampal neurons (Rose et al., 2008). Band 4.1B binds to KRKR residues (amino acids K851–R854) in the membrane-proximal region of mGlu8, which is a possible consensus sequence for 4.1 binding partners (Rose et al., 2008). This region partially

overlaps with the CaM and G $\beta\gamma$ binding region of mGlu7, but their competitive binding has not been analyzed.

Cannabinoid receptor interacting protein 1a (CRIP1a) is a binding partner of the CB1 receptor and negatively regulates endocytosis of CB1 receptors and mGlu8 coordinately. CRIP1a binding on the distal CTD (amino acids N892–T898) reduces the constitutive endocytosis of mGlu8a, but not of mGlu8b in HEK293 cells. The S894 residue on mGlu8a is responsible for the negative regulation of receptor endocytosis and protein-protein interactions (Mascia et al., 2017).

4. Conclusion

In conclusion, over the last two decades there has been a lot of progress in elucidating the mechanisms underlying mGlu receptor trafficking and functional regulation. The primary mechanisms identified are posttranslational modifications, such as phosphorylation, and C-terminal binding proteins that mediate synaptic expression of receptors. Although the majority of studies are focused on Group I mGlu receptors, many of the same themes apply to the Group II and Group III receptors.

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Abbreviations

AC	adenylate cyclase
Actn4	α -Actinin-4
ARF6	ADP-ribosylation factor 6
ATD	amino terminal domain
CAIN	calcineurin inhibitor protein
CaM	calmodulin
CaMKII	Ca ²⁺ /calmodulin-dependent protein kinase II
Cbln1	cerebellin 1 precursor
CC	coiled-coil
Cdk5	Cyclin-dependent kinase 5
CIE	clathrin-independent endocytosis
CLIC/GEEC	clathrin-independent carriers/GPI-anchored protein enriched early endosomal compartment
CME	clathrin-mediated endocytosis

CRIP1a	cannabinoid receptor interacting protein 1a
CTD	C-terminal domain
DAG	diacyl glycerol
DN	dominant negative
DRM	detergent-resistant lipid raft-rich membrane
ECD	extracellular domain
ERK1/2	extracellular signal-regulated kinases 1/2
EVH1	enabled/VASP homology 1
GAP	GTPase activating protein
GPCR	G protein-coupled receptor
GPI	glycosylphosphatidylinositol
GRIP	glutamate receptor interacting protein
GRK	GPCR kinase
HFS	high-frequency stimulation
Htt	huntingtin
iL	intracellular loop
IP₃	inositol 1,4,5-trisphosphate
JNK/SAPK	c-Jun N-terminal kinases/stress-activated protein kinase
KO	knockout
LTD	long-term depression
LTP	long-term potentiation
MAPK	mitogen-activated protein kinase
MF-SLIN	mossy fiber-CA3 interneuron
mGlu receptor	metabotropic glutamate receptor
NAc	Nucleus accumbens
NECAB2	neuronal Ca ²⁺ binding 2
NHERF1/2	Na ⁺ /H ⁺ exchanger regulatory factors 1/2
NLS	nuclear localization signal
OPTN	optineurin

PH	pleckstrin homology
PICK1	Protein Interacting with C-Kinase
PKA	protein kinase A
PKC	protein kinase C
PLC	phospholipase C
PLD2	phospholipase D2
PP1γ1	protein phosphatase 1 γ 1
PP2A	protein phosphatase 2A
PP2C	serine/threonine protein phosphatase 2C
PTX	pertussis toxin
PTZ	pentylentetrazole
RalGDS	Ral guanine nucleotide dissociation stimulator
RGS	regulator of G protein signaling
S6K1	p70-S6 kinase 1
SAPAP	SAP90/PSD-95-associated protein
SCG	superior cervical ganglion
SER	smooth endoplasmic reticulum
Siah-1A	seven in absentia homolog-1A
SNARE	soluble N-ethylmaleimide-sensitive factor attachment protein receptor
TM	transmembrane domain
TRPC	transient receptor potential canonical
Ves1	VASP/Ena-related protein induced during Seizure and LTP
VFD	Venus flytrap domain

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Highlights

- Metabotropic glutamate receptors (mGlu receptors) undergo constitutive and agonist-induced endocytosis.
- The surface expression and endocytosis of mGlu receptors are regulated by receptor phosphorylation and protein-protein interactions.
- Many proteins involved in mGlu receptor trafficking bind to the intracellular C-terminus or cytoplasmic loop domains of mGlu receptors.
- The intracellular trafficking pathways of mGlu receptors are remarkably diverse.

Fig. 1.

Ca^{2+} -activated CaM differentially regulates trafficking of mGlu5 versus mGlu7 receptors. In the postsynaptic compartments, Ca^{2+} -CaM binds to mGlu5 at a single critical residue, L896, and stabilizes mGlu5 on the postsynaptic plasma membrane. Treatment with the agonist DHPG or PKC activation dissociates CaM binding, increases S901 phosphorylation of mGlu5, and induces mGlu5 endocytosis (Choi et al., 2011; Ko et al., 2012; Lee et al., 2008b). Siah-1A competes with CaM for mGlu5 binding, increases agonist-induced endosomal trafficking, and degrades mGlu5 in lysosomes (Ishikawa et al., 1999; Ko et al.,

2012). CaMKII α dissociates from mGlu5 in competition with CaM and increases agonist-induced receptor endocytosis upon mGlu5-stimulated Ca²⁺ release (Jin et al., 2013b; Raka et al., 2015). In the presynaptic compartment, CaM reduces PKC-induced phosphorylation of mGlu7 S862 and facilitates endocytosis of mGlu7. PICK1 augments the PKC-induced S862 phosphorylation of mGlu7, enhances stable surface expression of mGlu7, and competes with CaM for binding to mGlu7. PP1 γ 1 inhibits constitutive and agonist L-AP4-induced internalization of mGlu7 (Suh et al., 2013; Suh et al., 2008). At resting state, RIM1 α and munc13-1 are sequestered by mGlu7. After prolonged mGlu7 activation, munc13-1, which may compete with CaM, is translocated from mGlu7 to associate with RIM1 α and enhance synaptic vesicle exocytosis (Ferrero et al., 2016; Martin et al., 2010; Mochida, 2011; Pelkey et al., 2008). CaM also competes with G $\beta\gamma$, CaBP1, MacMARCKS, MAP1B, and Norbin (Bertaso et al., 2006; Moritz et al., 2009; Nakajima, 2011; O'Connor et al., 1999; Wang et al., 2009).

Fig. 2.

Homer regulates trafficking of Group I mGlu receptors.

Long-form Homer proteins (CC-Homers) are postsynaptic scaffolds bridging Group I mGlu receptors and IP₃/ryanodine receptors, Shank, or F-actin cytoskeleton, *et cetera*. They arguably act to decrease cell surface expression of Group I mGlu receptors (Ango et al., 2002; Hayashi et al., 2006; Roche et al., 1999). Following synaptic activation, Homer-1a, a short-form lacking a CC domain, is rapidly induced, competes with CC-Homers, and stabilizes cell surface targeting of mGlu1a (Ciruela et al., 1999; Minami et al., 2003). ERK and CDK5 phosphorylate S/T residues within a conserved Homer binding motif in Group I mGlu receptors, which leads to an increase in the affinity of Homer-1 and the stabilization of receptors on cell surface (Orlando et al., 2009; Park et al., 2013; Yang et al., 2016).

Table 1

A list of Group I mGlu receptor-interacting proteins that regulate cell surface expression of receptors.

Subtypes	Effect on surface expression	Interacting proteins	Interacting regions ^a	References
mGlu1	Stabilize	Band4.1G	E1131–D1135	(Lu et al., 2004; Tateyama and Kubo, 2007)
		CAIN	N887–L1199, iL2	(Ferreira et al., 2009)
		Caveolin	F609–Y617, F781–F789	(Francesconi et al., 2009)
		ERK2	K841–N885	(Yang et al., 2016)
		Fyn	N925–T1000 (Y937)	(Jin et al., 2017)
		Homer-1a	P1152–R1157	(Ciruela et al., 1999; Minami et al., 2003)
		Homer-1c	P1152–R1157	(Ciruela et al., 2000; Gama et al., 2001)
		PKA	S869–A886	(Mundell et al., 2004)
		PP2A	n/d ^b	(Pandey et al., 2014)
		Rab8	N887–L1199	(Esseltine et al., 2012)
		Spinophilin	S1197–L1199, K891–W895, iL2	(Di Sebastiano et al., 2016)
		Tamalin	S1197–L1199	(Kitano et al., 2002)
	Decrease	ARRB1	S869–V893	(Dale et al., 2001b; Iacovelli et al., 2003; Mundell et al., 2002; Mundell et al., 2001; Mundell et al., 2003; Pula et al., 2004)
		ARRB2	S869–V893	(Mundell et al., 2002; Mundell et al., 2001; Mundell et al., 2003)
		GluD2	n/d (mGlu1b-specific)	(Kato et al., 2012)
		CaMKIIα	K841–N885 (T871), iL2	(Jin et al., 2013a; Mundell et al., 2002; Raka et al., 2015)
		Caveolin	F609–Y617, F781–F789	(Hong et al., 2009)
		GRK2	S869–V893	(Mundell et al., 2003)
		GRK4	n/d	(Iacovelli et al., 2003; Sallese et al., 2000)
		Homer-1b	P1152–R1157	(Hayashi et al., 2006; Roche et al., 1999)
		Homer-1c	P1152–R1157	(Abe et al., 2003)
		Homer-3	P1152–R1157	(Rezvani et al., 2012)
		Ral/PLD2	n/d	(Bhattacharya et al., 2004)
		Numb	n/d	(Zhou et al., 2015)
		PKC	S894–L1199	(Ciruela and McIlhinney, 1997; Mundell et al., 2002; Mundell et al., 2003)
		Siah-1A	K905–P932, K1112	(Gulia et al., 2017; Moriyoshi et al., 2004)
mGlu5	Stabilize	Actn1	R931–A1002 (mGlu5b)	(Cabello et al., 2007)
		CAIN	n/d	(Ferreira et al., 2009)
		CaM	E888–L896 (L896)	(Choi et al., 2011; Lee et al., 2008b)
		CDK5	T1123, S1126	(Orlando et al., 2009; Park et al., 2013)

Subtypes	Effect on surface expression	Interacting proteins	Interacting regions ^a	References
		ERK	S1126	(Park et al., 2013)
		Norbin	R857–R867, L896–L900	(Wang et al., 2009)
		p11	F836–M844	(Lee et al., 2015)
		PP2A	n/d	(Mahato et al., 2015)
		Spinophilin	n/d	(Di Sebastiano et al., 2016)
	Decrease	CaMKII α	L875–K917, iL2	(Jin et al., 2013b; Raka et al., 2015)
		Homer-1a	P1152–R1157	(Hu et al., 2010)
		Homer-1b	P1152–R1157	(Ango et al., 2002; Roche et al., 1999)
		Homer-1c	P1152–R1157	(Coutinho et al., 2001)
		PKC	S901	(Lee et al., 2008b)
		Ral/PLD2	n/d	(Bhattacharya et al., 2004)
		Siah-1A	R892–P918	(Ko et al., 2012)

^a All amino acid numbering was based on the rat protein sequences. GenBank accession numbers used are NP_058707 (Grm1), NP_058708 (Grm5).

^b n/d, not determined

Table 2

A list of Group III mGlu receptor-interacting proteins that regulate cell surface expression of receptors.

Subtypes	Effect on surface expression	Interacting proteins	Interacting regions ^a	References
mGlu4	Decrease	PKC	S859(?)	(Mathiesen and Ramirez, 2006)
mGlu7	Stabilize	PICK	L913–I915, S862	(Suh et al., 2008)
		PKC	S862	(Suh et al., 2008)
		SUMO1/3	K889	(Choi et al., 2016)
	Decrease	CaM	K858–M872	(Suh et al., 2008)
		PP1 γ 1	K911–W915 (mGlu7b), S862	(Suh et al., 2013)
mGlu8	Stabilize	Band4.1B	K851–R854	(Rose et al., 2008)
		CRIP1a	N892–T898 (mGlu8a)	(Mascia et al., 2017)

^a All amino acid numbering is based on the rat protein sequences. GenBank accession numbers used are NP_073157 (Grm4), NP_112302 (Grm7), and NP_071538 (Grm8).