



# Membrane trafficking and positioning of mGluRs at presynaptic and postsynaptic sites of excitatory synapses

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## ABSTRACT

The plethora of functions of glutamate in the brain are mediated by the complementary actions of ionotropic and metabotropic glutamate receptors (mGluRs). The ionotropic glutamate receptors carry most of the fast excitatory transmission, while mGluRs modulate transmission on longer timescales by triggering multiple intracellular signaling pathways. As such, mGluRs mediate critical aspects of synaptic transmission and plasticity. Interestingly, at synapses, mGluRs operate at both sides of the cleft, and thus bidirectionally exert the effects of glutamate. At postsynaptic sites, group I mGluRs act to modulate excitability and plasticity. At presynaptic sites, group II and III mGluRs act as auto-receptors, modulating release properties in an activity-dependent manner. Thus, synaptic mGluRs are essential signal integrators that functionally couple presynaptic and postsynaptic mechanisms of transmission and plasticity. Understanding how these receptors reach the membrane and are positioned relative to the presynaptic glutamate release site are therefore important aspects of synapse biology. In this review, we will discuss the currently known mechanisms underlying the trafficking and positioning of mGluRs at and around synapses, and how these mechanisms contribute to synaptic functioning. We will highlight outstanding questions and present an outlook on how recent technological developments will move this exciting research field forward.

## 1. Introduction

The actions of glutamate in the brain are mediated by a remarkable large variety of receptors. The fast actions of glutamate are mediated by ionotropic glutamate receptors: the AMPA, NMDA and KA-type receptors. These receptors are ligand-gated ion channels that allow fast excitatory synaptic transmission. The slower and long-lasting effects of glutamate are generally mediated by metabotropic glutamate receptors (mGluRs), a family of G-protein coupled receptors (GPCRs) that modulate various aspects of neuronal physiology, particularly excitability and plasticity (Reiner and Levitz, 2018; Scheefhals and MacGillavry, 2018).

Thus, these receptors are potent modulators of critical aspects of neuronal functioning and are broadly considered to be vital drug targets in treating mental disorders such as anxiety, Parkinson's, autism spectrum disorders, and drug abuse (Crupi et al., 2019).

mGluRs belong to the class C of GPCRs that also includes the metabotropic GABA B receptor subunits. Class C GPCRs contain a particularly large extracellular domain that contains the agonist-binding Venus fly trap (VFT) domain and, in the case of mGluRs, a cysteine-rich domain (CRD) that connects to the highly conserved seven-pass transmembrane domain (TMD) (Fig. 1A) (Pin and Bettler, 2016). Despite this common topology, the different mGluR subtypes are tremendously

**Abbreviations:** AC, adenylate cyclase; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AZ, active zone; CaM, calmodulin; CRD, cysteine-rich domain; DHPG, 3,5-dihydroxyphenylglycine; ECD, extracellular domain; ELFN, extracellular leucine-rich repeat and fibronectin type III domain-containing; EM, electron microscopy; EZ, endocytic zone; GA, Golgi apparatus; GABA, gamma-amino butyric acid; GAP, GTPase-activating proteins; GEF, guanine nucleotide exchange factor; GPCR, G-protein coupled receptor; GRK, G-protein coupled receptor kinase; HFS, high-frequency stimulation; KA, kainate; LTD, long-term depression; LTP, long-term potentiation; MF, mossy fiber; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; PAM, positive allosteric modulator; PFC, prefrontal cortex; PICK1, protein interacting with C kinase 1; PKA, protein kinase A; PKC, protein kinase C; PSD, postsynaptic density; RGS, regulators of G protein signalling; SC, Schaffer collateral; STED, stimulated emission depletion microscopy; SUMO, small ubiquitin-like modifier; TMD, transmembrane domain.

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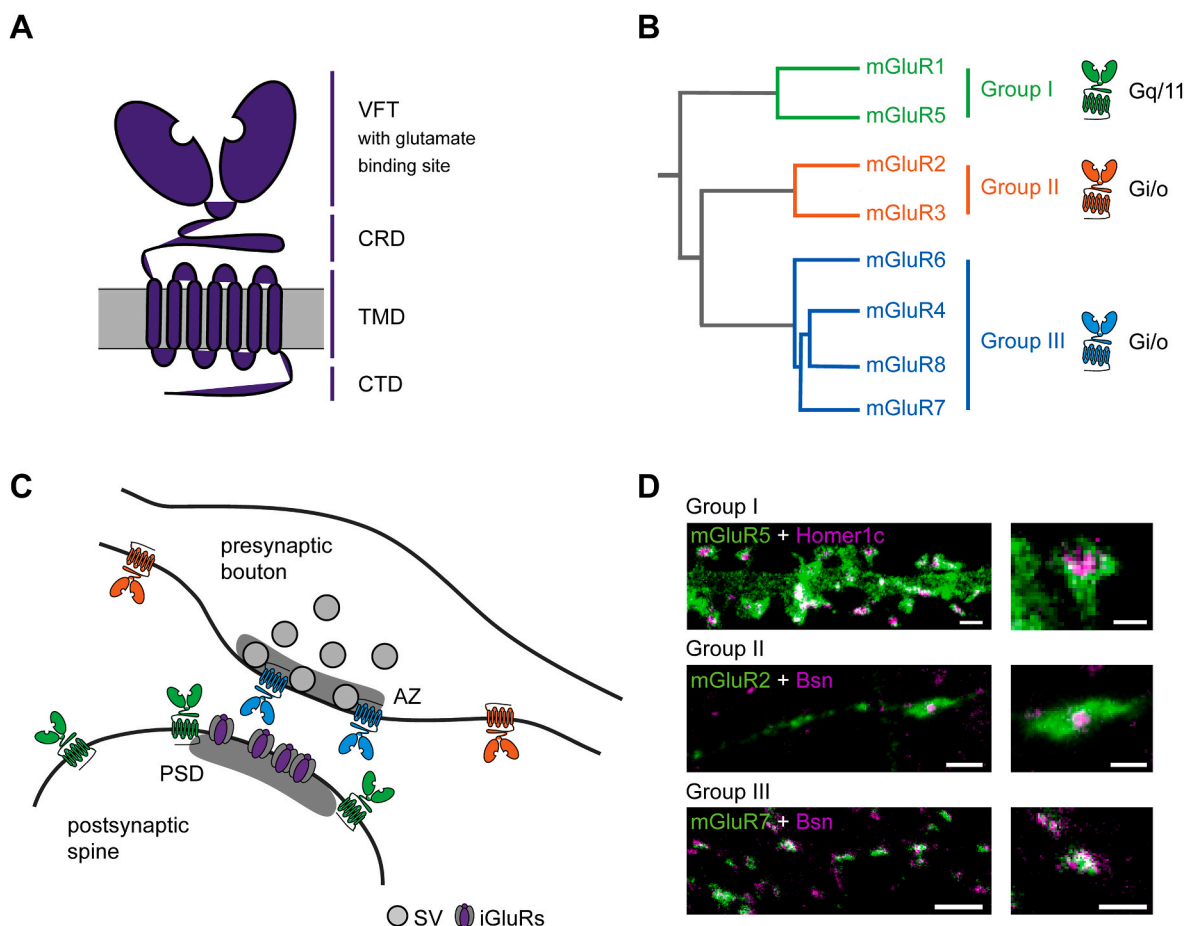
diversified in their biophysical properties, pharmacology, signaling profiles and expression patterns. Based on these characteristics, mGluRs can be divided in three main groups: group I mGluRs, (mGluR1 and 5) are coupled to  $G_{aq}$  proteins, group II mGluRs (mGluR2 and 3) and group III mGluRs (mGluR4, 6, 7 and 8) are coupled to inhibitory  $G_{ai/o}$  proteins (Fig. 1B) (Niswender and Conn, 2010). The molecular diversity of mGluRs is further broadened by alternative splicing, generating isoforms with unique properties. And, although mGluRs are typically homodimers, recent studies identified several heterodimeric receptor combinations that potentially have distinct functions and properties (Doumazane et al., 2011; Levitz et al., 2016).

mGluRs are widely expressed throughout the brain and are found at both presynaptic and postsynaptic sites of excitatory synapses. As such, mGluRs are ideally positioned to modulate virtually every aspect of synaptic transmission and plasticity. Here, we will discuss the current understanding of mGluR trafficking and positioning at excitatory synapses. Specifically, we will focus on how the precise (sub)synaptic distribution of mGluRs in neurons impacts their contribution to glutamatergic signaling in different ways. We will put particular emphasis on how mGluR trafficking and positioning contribute to synaptic functioning. This is important because although the biophysical properties of individual receptors principally dictate their activation kinetics, ultimately, the probability of receptor activation is determined by the distance these receptors are positioned relative to the release site of glutamate. Interestingly, while certain mGluRs are positioned close to, or even concentrated in the active zone, other receptors are localized

at distinct distances from, or even considerably far away from release sites, questioning how and when these receptors are activated. Additionally, for mGluRs the subcellular positioning, and the molecular environment of receptors largely influences their ability to engage local signaling effector molecules. For instance, while effectors close to the activated receptor can be modulated almost instantly, more distant effectors are less likely to contribute to the effects of receptor activation or respond with a delay. Thus, the mechanisms that control the trafficking and positioning of mGluRs at and around presynaptic and postsynaptic sites critically determine how this versatile group of glutamate receptors contributes to synaptic signaling and plasticity.

## 2. Cellular and subcellular distribution of mGluRs in neurons

The expression pattern and precise subcellular positioning of mGluRs are important determinants for their function. In situ hybridization and immunolabeling EM studies have been instrumental in mapping and quantifying the cellular and subcellular distribution of mGluRs in the brain at high resolution. These studies led to the general notion that different mGluR types are often co-expressed by individual neurons, but that the distribution within neurons is highly compartmentalized with different types of receptors targeted to different subcellular domains (Ferraguti and Shigemoto, 2006). Of note, mGluRs are also expressed by glia cells (Petralia et al., 1996) and can as such also be intricate components of the tripartite synapse regulating several aspects of synaptic transmission and plasticity. This will however not be discussed in this



**Fig. 1. Structure organization and distribution of mGluRs.** (A) Domain organization of mGluRs. ECD – extracellular domain, VFT - Venus fly trap domain with glutamate binding site, CRD – cysteine rich domain, TMD – transmembrane domain, ICD – intracellular domain. (B) Phylogenetic tree of the mGluR groups. (C) Schematic diagram of the distribution of mGluR types at the synapse. AZ – the active zone, iGluR – ionotropic glutamate receptors, PSD – the postsynaptic density, SV – synaptic vesicles. (D) STED images of mGluR distribution in hippocampal neurons. Group I mGluR5 co-stained with marker of postsynaptic density - Homer1c. Group II mGluR2 and group III mGluR7 co-stained with marker of the active zone – Bassoon (Bsn). Scale bar: 1  $\mu$ m, zooms: 500 nm.

review.

Throughout the adult central nervous system, group I mGluRs have been found to localize almost exclusively at postsynaptic sites (Lujan et al., 1996, 1997; Martin et al., 1992; Shigemoto et al., 1993, 1997), although mGluR5 labeling has been found at presynaptic sites too (Romano et al., 1995). Strikingly, in dendritic spines the concentration of immunolabeling for both mGluR1 and mGluR5 is highest within an annular region (~100 nm) around the postsynaptic density (PSD), the perisynaptic domain, and rapidly drops further away in the extrasynaptic region (Baude et al., 1993; Lujan et al., 1996; Nusser et al., 1994). This perisynaptic enrichment seems more pronounced for mGluR1 than for mGluR5, with an estimated perisynaptic pool of 50% for mGluR1 compared to 25% for mGluR5 (Lujan et al., 1997). In hippocampal CA1 neurons the size of the perisynaptic pool of mGluR5 is highly heterogeneous across individual spines, with varying levels of perisynaptic enrichment and a significant population of spines lacking mGluR5 labeling (Lujan et al., 1997). The particular perisynaptic distribution likely has important consequences for receptor function. First, the concentration of glutamate is significantly lower in the perisynaptic region than in the center of the synapse. Second, being either in or just outside of the PSD could have tremendous consequences for a receptor's ability to connect to downstream effectors. Particularly, in the PSD numerous receptor types, scaffolds and signaling proteins are enriched within a sharply defined region. mGluR5 has also been found to localize in the nuclear membrane of neurons, regulating nuclear calcium signaling (Jong et al., 2005; O'Malley et al., 2003).

The expression patterns of the Group II mGluRs overlap and are both expressed in a number of brain regions and cell types, including Golgi cells of the cerebellum, dentate gyrus granule cells, the olfactory bulb, thalamus and cortex (Ohishi et al., 1993a, b; Petralia et al., 1996). mGluR2 and mGluR3 are found both in axons and dendrites of GABAergic Golgi cells in the cerebellum and in the olfactory bulb (Hayashi et al., 1993; Neki et al., 1996a, b; Ohishi et al., 1994), but in the hippocampus mGluR2 and mGluR3 predominantly labeled axons (Petralia et al., 1996; Shigemoto et al., 1997; Tamaru et al., 2001). In axons, mGluR2/3 labeling was found along the axon but largely excluded from presynaptic terminals (Shigemoto et al., 1997; Yokoi et al., 1996).

Group III receptors are expressed throughout the brain and are consistently found at presynaptic sites, enriched at the active zone (AZ) of glutamatergic synapses (Bradley et al., 1996, 1998; Corti et al., 2002; Kinoshita et al., 1996; Shigemoto et al., 1996, 1997). An exception is mGluR6 which is exclusively expressed by ON-bipolar cells in the retina and is enriched at dendritic tips contacting photoreceptors (Nomura et al., 1994). mGluR4 and mGluR7 expression patterns in the brain seem to complement each other, with mGluR7 being the most widespread receptor in the adult nervous system. mGluR4 expression is abundant in granule cells in the cerebellum and the olfactory bulb, where mGluR7 levels are undetectable (Ohishi et al., 1995). mGluR7 expression is high in the cortex, hippocampus and several other forebrain regions (Kinzie et al., 1995). The expression pattern of mGluR8 seems to complement the pattern of mGluR2 in CA3 area and dentate gyrus (Shigemoto et al., 1997). The strong enrichment of mGluR4 and mGluR7 at the AZ suggests that specific anchors at the synapse position these receptors close to the release site. Additionally, mGluR4, mGluR7 and mGluR8 have also been found enriched in a subset of GABAergic synapses in the hippocampus (Corti et al., 2002; Ferraguti et al., 2005; Somogyi et al., 2003; Summa et al., 2013).

Altogether, these studies provide a general model where mGluRs are positioned in defined subcellular compartments (Fig. 1C). In dendritic spines, group I mGluRs accumulate around the PSD, positioned to respond to strong synaptic stimulation protocols and modulate postsynaptic mechanisms of transmission and plasticity. In axons, group II mGluRs are widely distributed, but seemingly excluded from the AZ, while group III mGluRs are strongly enriched at the AZ. This suggests that group II and group III mGluRs likely respond differentially to

glutamate release and can have differential effects on transmission.

### 2.1. Super-resolution studies of nanoscale mGluR distribution and dynamics

Apart from EM studies, single-molecule tracking (Aloisi et al., 2017; Goncalves et al., 2020; Renner et al., 2010; Sergé et al., 2002) and super-resolution techniques (Klotz et al., 2019; Siddig et al., 2020) provide additional insight in the mechanisms that underlie mGluR dynamics and distribution. In hippocampal neurons, a study using 3D structured illumination microscopy (3D-SIM) also revealed the perisynaptic enrichment of mGluR5, co-localizing with the mGluR5 accessory protein Norbin (Westin, 2014). In seemingly contrast with this study and immuno-EM studies (Lujan et al., 1996), a study using direct stochastic optical reconstruction microscopy (dSTORM) found a homogeneous distribution of mGluR5 at the synaptic surface (Goncalves, 2020). Moreover, a single-molecule tracking (SMT) study revealed that mGluR5 alternates between diffusive and confined states regulated by receptor activation and the scaffolding protein Homer (Sergé et al., 2002), but nevertheless mGluR5 was found to be highly mobile in both dendrites and spines (Goncalves, 2020). Other SMT studies did reveal slower diffusion of mGluR5 at synaptic sites compared to extrasynaptic sites, and disrupted mGluR5 mobility was implicated in the pathology of Alzheimer's disease and Fragile X syndrome (Renner, 2010; Aloisi, 2017). A recent study using stimulated emission depletion (STED) microscopy showed the exclusive postsynaptic localization of mGluR2 in ribbon synapses of inner hair cells in the cochlea (Klotz et al., 2019). Co-localization with the PSD marker PSD-95 revealed that mGluR2 is preferentially localized outside the PSD, while mGluR4 and mGluR8b co-localized strongly with the AZ marker CtBP2/RIBEYE. The subsynaptic localization of mGluR4 was studied in great detail in cerebellar granule cells using quantitative single-molecule localization microscopy (SMLM) (Siddig et al., 2020). This study found a high degree of enrichment of mGluR4 in the AZ and estimated that on average an AZ contains ~35 mGluR4 subunits. Within AZs, mGluR4 was found to be in close proximity to key molecular components regulating neurotransmitter release: Munc-18 (~30 nm coupling distance) and the Ca<sup>2+</sup> channel CaV2.1 (~65 nm coupling distance), indicating that mGluR4 can directly or indirectly interact and modulate these AZ components. Super-resolution STED imaging of the subsynaptic distribution of presynaptic mGluRs in hippocampal neurons showed that mGluR2 localizes to the axon shaft and presynaptic boutons but was excluded from the AZ. In contrast, mGluR7 was found almost exclusively in the AZ (Fig. 1D) (Bodzeta et al., 2020). Furthermore, SMT revealed that while mGluR2 was highly dynamic throughout the axon, mGluR7 was preferentially immobilized at AZs. Using domain-swapping experiments it was found that while intracellular interactions modulate mGluR2 mobility, mGluR7 seemed stabilized by its extracellular domain (Bodzeta et al., 2020).

Altogether, the overall distribution patterns for each of the different mGluR subtypes and their positioning in distinct subcellular compartments has been studied extensively in fixed preparations. Excitingly, recent advances in super-resolution technologies now allow live-cell investigation of receptor distribution and dynamics in neurons which will be important for extending our understanding of mGluR biology. Particularly, these directions will be of importance to reveal the mechanisms that underlie the dynamic organization of mGluRs at subsynaptic sites.

### 3. Secretory trafficking of mGluRs

Transmembrane proteins are synthesized, assembled, and processed through an ordered sequence of events along the secretory pathway. All mGluRs contain a signal peptide that drives the co-translational insertion of the newly formed receptor into the ER membrane. After adapting its proper conformation, the nascent receptor then exits the ER through

the classic secretory system consisting of a series of organelles: the ER/Golgi intermediate compartment (ERGIC), *cis*-Golgi, Golgi apparatus (GA) and *trans*-Golgi network (TGN). Transport vesicles emanating from the Golgi then traffic to their destination by cytoskeleton-based transport to reach the membrane via exocytosis. The complex morphology of neurons imposes various challenges to this traditional organization. Unlike other cells, the secretory system in neurons has to correctly sort and distribute membrane proteins throughout its long, extended axon and the highly arborized somatodendritic compartment, putting unique demands on the organization of the secretory system (Kennedy and Hanus, 2019). Intriguingly, although neurons contain the same secretory compartments as other cells, the secretory system is organized differently. Neurons are equipped with a highly elaborate ER network that is continuous throughout the soma, axon and dendrites (Cui-Wang et al., 2012; Spacek and Harris, 1997). The Golgi compartment, however, is almost exclusively found in the soma, suggesting that newly synthesized receptors emanate primarily from the soma (Horton and Ehlers, 2003), or through Golgi-like structures, termed Golgi outposts, present in dendrites (Horton and Ehlers, 2003; Mikhaylova et al., 2016; Pierce et al., 2001). Whether such elements are present in axons remains untested.

Proper regulation of each of these steps through the secretory pathway is essential for the correct delivery of functional receptors to the plasma membrane. However, while these processes have been well characterized for many synaptic transmembrane proteins, how mGluRs traffic through this intricate network of secretory organelles remains largely unknown. We will next discuss each of the steps in more detail and review what is currently known for mGluRs.

### 3.1. Protein folding and glycosylation

Newly synthesized transmembrane proteins are often glycosylated through a process termed N-linked glycosylation. Proper glycosylation is important for the correct folding, subsequent trafficking and ultimately the function of the protein (Helenius and Aebi, 2001). In this process, first a precursor mannose-rich oligosaccharide is attached to specific extracellular Asn residues. Then, mannose residues are trimmed before the protein can exit the ER and transit to the Golgi. In the Golgi, additional sugar chains are added to give rise to mature, complex glycan structures. For only a few mGluRs glycosylation and its effects on receptor function have been studied. For mGluR1 and mGluR5 a number of potential glycosylation sites were proposed. mGluR1b isolated from rat brain was indeed found to be fully glycosylated (Chan et al., 2001), but the exact sites of glycosylation have not been identified and although disruption of glycosylation severely diminished signaling downstream of mGluR1, surface expression was not affected (Mody et al., 1999). For mGluR5 six potential glycosylation consensus sites have been predicted. Initially only a single glycosylated site was confirmed biochemically (Bhave et al., 2003), but a more recent study indicated that five sites in the VFT domain are glycosylated and that glycosylation is critical for surface expression of mGluR5 (Nasrallah et al., 2018). Also, for mGluR3 several residues seem to be glycosylated (Muto et al., 2009), but the significance of glycosylation for the surface expression and function of group II mGluRs remains untested.

A recent study characterized the glycosylation of mGluR7 in great detail (Park et al., 2020). This study identified four Asn residues in the ECD that are linked to glycans and were found to be essential for the proper surface expression of mGluR7. Disruption of mGluR7 glycosylation led to the retention of the receptor in the ER. Conventionally, misfolded ER proteins are targeted for degradation by the ER-associated protein degradation pathway. However, deglycosylated mGluR7 was found to be targeted to the autophagolysosomal degradation pathway, that is independent of the ubiquitin proteasome system. Interestingly, two of these glycosylated residues were found to promote the interaction of mGluR7 with the adhesion molecule ELFN1, facilitating the correct localization of mGluR7 at presynaptic sites (Park et al., 2020). Thus,

N-glycosylation seems to be a general feature of mGluRs and can have an important impact on receptor function but remains poorly characterized for most mGluR subtypes. It will be important to more systematically characterize the glycosylation patterns of individual mGluR subtypes and study the contribution of glycosylation to receptor trafficking and function in neurons.

### 3.2. Receptor dimerization

Dimerization of mGluRs has been studied using many different experimental approaches. Traditional biochemical studies (Ray and Hauschild, 2000; Romano et al., 1996, 2001; Tsuji et al., 2000), time-resolved FRET assays in live cells (Doumazane et al., 2011), as well as quantitative fluorescence-based counting experiments (Lee et al., 2020; Levitz et al., 2016; Moller et al., 2018; Moreno Delgado et al., 2017) all consistently indicate that mGluRs form stable, disulphide-linked dimers on the plasma membrane. Dimerization is a requirement for full receptor activation (El Moustaine et al., 2012; Kammermeier and Yun, 2005). In the resting state of the receptor, dimers of mGluRs are in an open conformation. In the active state, after binding of glutamate, dimers change conformation to a closed state (Kniazeff et al., 2004; Levitz et al., 2016; Marcaggi et al., 2009). Generally, proper receptor dimerization is a requirement to pass the quality control system in the ER to transit along the secretory pathway. The assembly process of protomers into functional dimers remains poorly understood, but high-resolution mGluR structures and mutational analyses suggest that dimerization relies primarily on interactions between the hydrophobic interfaces of the VFT and interactions between the TMDs (El Moustaine et al., 2012; Koehl et al., 2019; Kunishima et al., 2000; Levitz et al., 2016). Interestingly, interactions between the TMDs play a predominant role in homodimerization of mGluR2 while for other mGluRs TMD interactions play only a moderate role in receptor dimerization (Gutzeit et al., 2019; Thibado et al., 2021). While mGluRs were long thought to be strict homodimeric receptors, a number of recent studies indicate that mGluRs are also able to form various heterodimer combinations (Doumazane et al., 2011; Habrian et al., 2019; Kammermeier, 2012; Lee et al., 2020; Levitz et al., 2016; Moreno Delgado et al., 2017; Pandya et al., 2016; Werthmann et al., 2020; Yin et al., 2014). Based on these studies, mostly in heterologous cells, it can be concluded that functional heterodimers form preferentially within group I, II or III mGluRs, but heterodimerization between group II and III mGluRs has also been found to occur. The functional relevance of these heterodimers for synaptic physiology remains to be explored, but a recent pharmacological study in the medial PFC (mPFC) showed that mGluR2/mGluR4 heterodimers selectively modulate synaptic transmission at specific thalamo-mPFC synapses but not at hippocampus-mPFC or amygdala-mPFC synapses (Xiang et al., 2021). A systematic single-cell sequencing study revealed that co-expression of mGluR subtypes is prevalent in the cortex (Lee et al., 2020), indicating that synapse-specific modulation of synaptic transmission by mGluR heterodimers could be a widespread phenomenon in the brain. Additionally, mGluRs can heterodimerize with other GPCR types e.g., mGluR2 can form dimers with the serotonin receptor (Gonzalez-Maeso et al., 2008), and mGluR5 was shown to interact with the dopamine receptor D1 (Sebastianutto et al., 2020).

### 3.3. ER export

ER exit is rate limiting for many receptors, including GPCRs (Petaja-Repo et al., 2000). For mGluRs, ER export has been best studied for group I mGluRs. mGluR1 dimerization was shown to take place in the ER and is independent of glycosylation (Robbins et al., 1999). Both the long and short isoforms of mGluR1 (mGluR1a and mGluR1b) contain a C-terminal ER retention signal (RRKK) (Chan et al., 2001). This sequence has a dominant effect on the surface trafficking and signaling capabilities of the short mGluR1b isoform (Chan et al., 2001);



Francesconi and Duvoisin, 2002; Mary et al., 1998), but has little effect on the trafficking of the long mGluR1a isoform. Mutation analysis indicated that a region downstream of the retention signal in the long intracellular tail of mGluR1a neutralizes the retention signal, overcoming ER retention (Chan et al., 2001). Additionally, when mGluR1a associates with mGluR1b, this region seems to also neutralize the retention motif in mGluR1b promoting the formation and surface trafficking of mGluR1a/b heterodimers (Kumpost et al., 2008; Techlovska et al., 2014), although see also (Remelli et al., 2008). Indeed, in the brain, mGluR1a is preferentially found in complex with mGluR1b, particularly in synaptic membranes (Techlovska et al., 2014). In contrast, for mGluR5 does not share a similar ER retention signal. In fact, although C-terminal interactions modulate mGluR5 ER exit and surface expression (Coutinho et al., 2001; Roche et al., 1999), these interactions do not seem to be dominant in controlling mGluR5 ER export (Chang and Roche, 2017). Rather the seventh transmembrane helix seems to be strictly required for surface expression of mGluR5 in both heterologous cell and neurons (Chang and Roche, 2017), further indicating that neurons evolved diversified mechanisms to control the secretory trafficking of mGluR subtypes and isoforms.

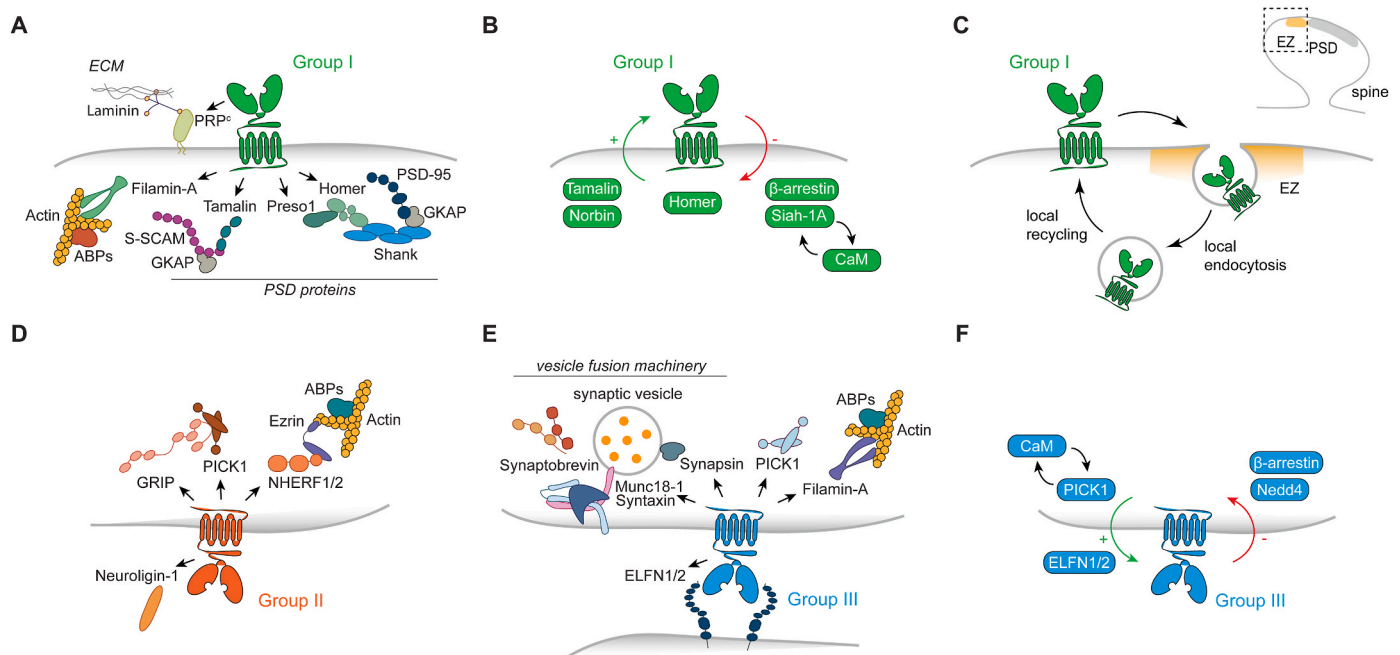
Once released from the ER, most receptors will be further processed by the somatic GA, or through non-somatic Golgi-like structures, and distributed throughout the cell in endosomes via long-range transport. Usually, long-range, directed transport is mediated by members of the kinesin superfamily that can selectively transport various cargoes via adaptor proteins (Kapitein and Hoogenraad, 2015). Indeed, mGluR1 has been shown to be transported by the molecular motor KIF5 (kinesin-1 heavy chain) in complex with the adaptor protein SNAP-23 along dendritic microtubules in hippocampal neurons (Raynaud et al., 2018).

Similar information for other mGluRs is however lacking.

#### 4. Membrane trafficking and anchoring of mGluRs

Ultimately, surface expression determines the density of receptors available for activation and the mechanisms that control the surface expression of mGluRs have been studied extensively (Suh et al., 2018). Particularly, the intracellular C-tails of mGluRs contain numerous interaction motifs and phosphorylation sites that are involved in receptor surface expression and trafficking (Enz, 2012), but recent evidence suggests that other receptor domains, most notably the extracellular domain are also involved in regulating receptor trafficking and function (Dunn et al., 2019a) (Fig. 2).

The intracellular tail of mGluR5 contains several binding motifs that have been characterized to great extent. Perhaps the best studied group I mGluR-interacting protein is its adaptor protein Homer. The EVH1 domain of Homer binds to the proline-rich motif (PPxxFR) within the distal C terminus of group I mGluRs (Brakeman et al., 1997; Kato et al., 1998; Tu et al., 1999; Xiao et al., 1998). The short Homer1a isoform was first identified as an immediate early gene, whose expression is rapidly increased upon strong excitation or during LTP induction (Brakeman et al., 1997; Kato et al., 1997). The constitutively expressed long Homer isoforms (Homer1b/c, 2, and 3) contain a C-terminal coiled-coil multimerization domain that allows Homers to couple other PSD proteins, most notable Shank proteins, forming a large assembly platform in the PSD (Hayashi et al., 2009). In addition, the Homer EVH1 domain links group I mGluRs to effector proteins, such as the IP3 and ryanodine receptors modulating basal mGluR activity (Ango et al., 2001; Tu et al., 1998; Yuan et al., 2003), but also co-assembles mGluRs and NMDARs in



**Fig. 2.** Spatial regulation of mGluRs. **(A)** Proteins that directly interact with group I mGluRs (green shaded) provide opportunities for bridging with different complexes potentially anchoring group I mGluRs (postsynaptic proteins: Filamin-A – Actin cytoskeleton – Actin binding proteins (ABPs), Tamalin – S-SCAM – GKAP, Preso1 – Homer – Shank – GKAP – PSD-95; and extracellular proteins: cellular prion protein (PRPc) – Laminin – extracellular matrix (ECM)). **(B)** Proteins that regulate group I mGluR surface expression; Tamalin and Norbin increase mGluR surface expression (green arrow),  $\beta$ -arrestin, Siah-1A binding and Calmodulin (CaM) unbinding decrease mGluR surface expression (red arrow), and Homer has been found to both increase and decrease mGluR surface expression. **(C)** The endocytic zone (EZ) is a compartmentalized receptor trafficking mechanism in spines, coupled to the PSD, that facilitates the local endocytosis and recycling of group I mGluRs to regulate receptor content. **(D)** Proteins that directly interact with group II mGluRs (orange shaded) provide opportunities for bridging with different complexes potentially anchoring group II mGluRs (presynaptic proteins: GRIP – PICK1, NHERF1/2 – Actin cytoskeleton – ABPs; and extracellular protein: Neuroigin-1) **(E)** Proteins that directly interact with group III mGluRs (blue shaded) provide opportunities for bridging with different complexes potentially anchoring group III mGluRs (presynaptic proteins: Munc18 – Syntaxin – Synaptobrevin – synaptic vesicle, Synapsin – synaptic vesicle, Filamin-A – Actin cytoskeleton – ABPs; and postsynaptic protein: ELFN1/2) **(F)** Proteins that regulate group III surface expression; ELFN1/2, PICK1 binding and CaM unbinding increase mGluR surface expression (green arrow), and Nedd4 and  $\beta$ -arrestin decrease mGluR surface expression (red arrow).

the same complex (Moutin et al., 2012; Naisbitt et al., 1999). Homer1a lacks this coiled-coil domain and functions as a dominant negative regulator of mGluR signaling by disrupting the binding between long Homer isoforms and mGluRs (Brakeman et al., 1997; Moutin et al., 2012; Xiao et al., 1998). As such, the Homer family of proteins modulate several aspects of group I mGluR biology, although findings have been contradictory. Long Homer isoforms were found to depress surface expression of mGluR1 and mGluR5 and retain receptors in intracellular clusters (Ango et al., 2002; Coutinho et al., 2001; Roche et al., 1999; Sergé et al., 2002), but other studies found that long Homer isoforms promote surface expression and synaptic targeting (Ango et al., 2000; Ciruela et al., 2000; Kammermeier, 2006; Tadokoro et al., 1999). Although studies do not unanimously agree, long Homer isoforms are generally proposed as the proteins regulating group I mGluR membrane trafficking and anchoring at postsynaptic sites (Fig. 2A). Homer1a seems to have a relatively small effect on surface expression, but rather functions to acutely uncouple mGluRs from downstream signaling effectors (Sergé et al., 2002; Xiao et al., 1998).

Tamalin, Norbin and Preso1 are critical regulators of mGluR signaling and trafficking through interactions with the mGluR C-tail (Matosin et al., 2015a, 2015b). The scaffold protein Tamalin is auto-inhibited through self-assembly of its PDZ domain and intrinsic ligand, which is disrupted by the presence and competitive binding of group I mGluRs (Kitano et al., 2002). The binding of the mGluR C-terminal SSSSL motif to the Tamalin PDZ domain liberates the intrinsic ligand for the motor protein receptor S-SCAM, facilitating mGluR cell surface trafficking and ligand-dependent internalization (Pandey et al., 2020; Sugi et al., 2007). Additionally, Tamalin links mGluRs to a complex of other proteins involved in postsynaptic organization and protein trafficking, including the ARF-specific guanine nucleotide exchange factor (GEF), that play a key role in the cell-surface expression and intracellular trafficking of group I mGluRs (Kitano et al., 2002, 2003). However, even though Tamalin functions as a scaffolding molecule interacting with PDZ binding motifs of SAP90/PSD-95-associated proteins and likely assembles within the PSD (Kitano et al., 2003), Tamalin could be a candidate, but is thus far unknown to play a role in anchoring group I mGluRs. Rather, Tamalin has been proposed to play a critical role in mGluR trafficking to control the spatiotemporal surface expression modulating mGluR-dependent synaptic plasticity (Neyman et al., 2019; Pandey et al., 2020) (Fig. 2A and B).

Norbin binds to the proximal C-terminal part of mGluR5, but does not interfere with Homer binding to mGluR5. Norbin is an mGluR5 accessory protein and promotes mGluR5 surface expression and downstream signaling (Wang et al., 2009) (Fig. 2B). Interestingly, using 3D-SIM and STED microscopy Norbin was found to localize to the perisynaptic domain, co-localizing with mGluR5 (Westin et al., 2014). However, whether the large degree of colocalization between Norbin and mGluR5 goes beyond underlining the importance of Norbin as a modulator of mGluR activity, and plays a role in mGluR anchoring, remains unknown.

Preso1 is a multidomain scaffolding protein that can bind to group I mGluRs, as well as Homer and proline-directed kinases. The Preso1 binding to mGluR C-terminus is upstream of the Homer binding site, however the Preso1-mGluR interaction does depend on the Homer binding site. Preso1 facilitates the binding of proline-directed kinases, such as CDK5/p35 and MEK/ERK, to mGluRs resulting in the phosphorylation of the Homer binding site in mGluR. In turn, Preso1-dependent phosphorylation enhances mGluR-Homer binding, resulting in the negative regulation of activity-dependent mGluR signaling (Hu et al., 2012). In contrast to Tamalin and Norbin, Preso1 does not affect mGluR surface expression, but rather dynamically modulates the mGluR-Homer binding through anchoring proline-directed kinases in the vicinity of mGluRs that negatively regulate activity-dependent mGluR signaling (Fig. 2A). Finally, Filamin-A, a large structural protein that crosslinks actin filaments, has been found to interact with several mGluRs, including mGluR5 and mGluR7 (Enz, 2002). Filamin-A

could be an interesting candidate to position group I mGluRs in the perisynaptic domain by coupling receptors to the actin cytoskeleton that is prominent in spines (Fig. 2A).

Relatively little is known about interactions with the C-tail of group II mGluRs. The intracellular domains of mGluR2 and mGluR3 have high sequence homology and contain a type I PDZ binding motif. However, yeast-two-hybrid and pull-down assays showed that PICK1 and glutamate receptor-interacting protein (GRIP) can interact via the PDZ binding motif only with mGluR3, but not mGluR2 (Hirbec et al., 2002). Another study using GST-pull down screening revealed interactions of group II mGluRs with the Na<sup>+</sup>/H<sup>+</sup> exchanger regulatory factor 1 and 2 (NHERF-1 and -2) (Ritter-Makinson et al., 2017). Interestingly, NHERFs can interact with actin and could thus link mGluRs to the actin cytoskeleton, perhaps to anchor receptors at specific sites (Fig. 2D). The apparent exclusion of mGluR2 from the presynaptic AZ suggests that specific mechanisms underlie receptor localization, but further studies are necessary to elucidate which molecular interactions contribute to group II mGluR positioning.

C-terminal interactions of group III mGluRs were studied in more detail. The C-tail of mGluR4 interacts with several exocytotic proteins such as Munc18-1, synapsins and syntaxins (Ramos et al., 2012). An early study using overexpression of mGluR7 suggested a dominant role for the C-tail of mGluR7 in axonal targeting (Stowell and Craig, 1999). Additionally, interactions between mGluR7 and PICK1 via PDZ binding motifs was shown to be important for targeting and clustering mGluR7 at presynaptic sites (Boudin et al., 2000) (Fig. 2E). However, a study using a knock-in mouse with mGluR7 lacking the PDZ motif (Zhang et al., 2008) showed that the PDZ binding motif and interaction with PICK1 were not necessary for synaptic clustering but were essential for receptor function. A number of recent studies provided evidence that group III mGluRs interact *in trans* with the postsynaptic adhesion molecules ELFN1 and ELFN2 (Dunn et al., 2018, 2019b; Tomioka et al., 2014). These interactions were shown to be important for the cell surface expression of mGluR7 (Dunn et al., 2019b; Tomioka et al., 2014) and interestingly, ELFNs act as allosteric modulators of group III receptor activity (Dunn et al., 2018; Stachniak et al., 2019) (Fig. 2E and F). A recent study showed that a mutation in the VFT of mGluR7 associated with neurodevelopmental disorders reduces surface expression of the receptor in primary cortical neurons (Song et al., 2021). Altogether, there is growing number of evidence that ECD plays crucial role in surface expression of mGluR7.

#### 4.1. Desensitization and endocytosis of mGluRs

In general, prolonged or repetitive activation of GPCRs leads to the rapid desensitization to prevent overactivation of the receptor. Central in this process are the receptor-associated GPCR kinases (GRKs) that phosphorylate and terminate receptor activation in response to ligand binding (Gurevich and Gurevich, 2019). Receptor phosphorylation triggers the recruitment of  $\beta$ -arrestin which prevents further G-protein activation but also acts as an adaptor for components of the endocytic machinery (AP-2 and clathrin), leading to the sequestration and internalization of the receptor (Ferguson et al., 1996; Goodman et al., 1996; Laporte et al., 1999). For mGluRs, several other kinases have been shown to regulate receptor desensitization, including PKA, ERK, CaMKII, and PKC (Dhami and Ferguson, 2006). Finally, regulators of G protein signalling (RGS) act as GTPase activating proteins (GAPs) on G $\alpha$  proteins to terminate signaling (Saugstad et al., 1998).

##### 4.1.1. Agonist-induced endocytosis of group I mGluRs

Agonist stimulation induces the rapid internalization of group I mGluRs that is primarily mediated by clathrin and dynamin (Dale et al., 2001; Mundell et al., 2001, 2002), but can be modulated by a myriad of processes. First, GRK-mediated phosphorylation and  $\beta$ -arrestin recruitment trigger the recruitment of endocytic adaptor proteins that initiate clathrin-mediated endocytosis (Fig. 2B). Several GRKs were shown to

promote the desensitization and internalization of group I mGluRs in heterologous cells (Dale et al., 2000; Sallèse et al., 2000; Sorensen and Conn, 2003). But, particularly GRK4, seems to have a physiological role in cerebellar neurons, where knockdown of GRK4 disrupted agonist-induced internalization of mGluR1 (Iacovelli et al., 2003; Sallèse et al., 2000). Second, mGluR5 endocytosis was found to be modulated by the regulated binding of calmodulin (CaM) in the mGluR5 C-tail (Minakami et al., 1997). Upon activation, mGluR5 triggers the activation of PKC that phosphorylates the CaM binding site, promoting the unbinding of CaM and subsequent endocytosis of mGluR5 (Choi et al., 2011; Lee et al., 2008). Interestingly, this regulatory feedback mechanism seems specific for mGluR5, as mGluR1 does not bind CaM (Choi et al., 2011). Third, the E3 ubiquitin ligase, seven in absentia homolog 1A (Siah-1A) competes with CaM for binding mGluR5 (Ishikawa et al., 1999) such that PKC phosphorylation of mGluR5 promotes Siah-1A binding by displacing CaM, leading to decreased mGluR5 surface expression (Ko et al., 2012; Moriyoshi et al., 2004) (Fig. 2B). Furthermore, Siah-1A regulates mGluR5 trafficking through the endosomal pathway and accelerates lysosomal degradation of mGluR5 (Ko et al., 2012). Siah-1A was shown to indeed act as an E3 ubiquitin ligase for both mGluR1 and mGluR5, and ubiquitination underlies the efficient internalization of group I mGluRs (Gulia et al., 2017). Finally, the calcium-dependent kinase CaMKII was found to interact with mGluR5 and CaMKII-mediated phosphorylation promotes mGluR5 endocytosis (Jin et al., 2013a, 2013b; Raka et al., 2015).

#### 4.1.2. Constitutive trafficking of group I mGluRs

Apart from activity-dependent or ligand-induced endocytosis, receptors also undergo constitutive endocytosis in the absence of activity (Fourgeaud et al., 2003). The exact physiological function of this process remains unknown but might be required for maintaining a surface pool of 'fresh', resensitized receptors. Constitutive trafficking of mGluR5 in heterologous cells occurs at quite a high rate: almost the complete pool of receptors is recycled in ~3.5 h (Trivedi and Bhattacharyya, 2012). Constitutive endocytosis of group I mGluRs was found to be independent of clathrin and dynamin (Fourgeaud et al., 2003; Mundell et al., 2001) and is instead mediated by caveolae (Francesconi et al., 2009) and dependent on Ral and PLD2 signaling (Bhattacharya et al., 2004). In neurons, agonist-independent internalization of mGluR5 was observed in both the dendritic spine and shaft and was also found to be independent of dynamin (Scheefhals et al., 2019)

#### 4.1.3. Post-endocytic trafficking

After internalization, receptors enter the endosomal system, a complex system of different intracellular compartments that direct receptors to either undergo recycling to the cell surface or to late endosomes and lysosomes for degradation. In cell lines, it was shown that after agonist-induced internalization mGluR1 was preferentially targeted to recycling endosomes, and less to lysosomes (Pandey et al., 2014). Interestingly, receptor recycling was dependent on PP2A activity, indicating that receptor resensitization is a requirement for proper recycling to the cell surface (Pandey et al., 2014). Similarly, in hippocampal neurons, after agonist-induced internalization mGluR5 traffics preferentially through early endosomes to the recycling compartment before returning to the surface. Here, a small fraction of the internalized mGluR5 pool was targeted to lysosomes via late endosomes, suggesting the targeted breakdown of a subpopulation of internalized receptors (Scheefhals et al., 2019)

#### 4.1.4. Endocytic trafficking of group II and III mGluRs

In contrast to group I and III mGluRs, far less is known about the trafficking of group II mGluRs. Of interest, it was shown that in response to activation, mGluR3, but not mGluR2, desensitized the cAMP response in a GRK-dependent manner (Iacovelli et al., 2009; Lennon et al., 2010). The resistance of mGluR2 to desensitization is a unique feature shared only by a few other GPCRs, including mGluR4 (Mathiesen and Ramirez,

2006), and is potentially relevant for mGluR2-mediated processes at presynaptic sites.

Constitutive and activity-dependent trafficking of group III mGluRs was studied most extensively for mGluR7. Studies from heterologous cells and neurons show that mGluR7 undergoes clathrin-independent, constitutive endocytosis and after internalization, mGluR7 is accumulated in Arf6-positive recycling endosomes (Lavezzari and Roche, 2007). Agonist stimulation induces the rapid internalization of mGluR7 (Pelkey et al., 2007; Suh et al., 2008) and many posttranslational modifications of mGluR7 have been reported that regulate mGluR7 trafficking and surface expression. Particularly, phosphorylation of mGluR7 by PKC is important for the stable expression of the receptor at the cell surface and its interaction with PICK1 and CaM (Suh et al., 2008). Reversely, activity-dependent dephosphorylation by protein phosphatase 1 (PP1) causes receptor internalization (Suh et al., 2013). Recently, Nedd4 and  $\beta$ -arrestin-dependent ubiquitination of mGluR7 were shown to regulate agonist-induced endocytosis (Lee et al., 2019) (Fig. 2F). In addition, the covalent attachment of small ubiquitin-like modifiers (SUMO), or SUMOylation of mGluR7 has been suggested to be involved in activity-dependent receptor trafficking (Choi et al., 2016). Similarly, mGluR8 was also found to be a target of SUMOylation (Tang et al., 2005). However, a more recent study found that mGluR7 was not SUMO1-conjugated *in vivo* (Daniel et al., 2017). The exact relevance of these findings for synaptic functioning thus remain to be tested.

#### 4.2. Local trafficking mechanisms at synapses

A wealth of information is available on the post-translational events and interactors that modulate mGluR trafficking. Nevertheless, many of these findings are based on overexpression studies in neurons and heterologous cells which could influence the trafficking pathways of receptors and surprisingly little is known about which of these mechanisms act locally at synaptic sites in neurons. Nevertheless, insight in the compartmentalized regulation of receptor trafficking is likely very important for a better understanding of how receptor surface levels and positioning are regulated at synapses. Local regulation of receptor trafficking has been studied most extensively in dendritic spines. Intriguingly, at postsynaptic sites clathrin-coated structures laterally coupled to the PSD mark the endocytic zone (EZ) (Blanpied et al., 2002). The EZ is physically coupled to the PSD via interactions with Homer, Dynamin and Shank proteins to facilitate the local uptake of synaptic receptors (Blanpied et al., 2002; Lu et al., 2007; Rácz et al., 2004; Scheefhals, 2019). Ionotropic AMPA-type glutamate receptors have been shown to traffic through the EZ and disrupting the PSD-EZ interaction severely affected AMPA receptor levels at synapses (Petrini et al., 2009; Rosendale et al., 2017). The EZ is therefore generally thought to be a critical component in the regulation of synaptic transmission and plasticity and allows the synapse to autonomously control receptor content (Czondor et al., 2012). Once internalized at the EZ, glutamate receptors enter the local recycling mechanism that retains receptors in intracellular pools that can recycle back to the synaptic membrane in an activity-dependent manner (Park et al., 2006). Indeed, the local recycling of receptors via the EZ is essential for synaptic plasticity as uncoupling the EZ from the PSD depletes synaptic AMPA receptors and aborts activity-induced trafficking of receptors to the synaptic membrane during long-term potentiation (Lu et al., 2007; Petrini et al., 2009). While the EZ has been studied almost exclusively in the context of AMPAR trafficking, more recently it was shown that also postsynaptic endocytosis and recycling of group I mGluRs relies on coupling of the EZ to the PSD (Scheefhals et al., 2019). Disrupting the PSD-EZ interaction reduced mGluR surface levels at synapses resulting in severely decreased mGluR5-mediated calcium responses and ERK1/2 activation (Scheefhals et al., 2019). These findings suggest that the postsynaptic EZ is an important mechanism to compartmentalize receptor recycling and locally balance the density of group I mGluRs to modulate neuronal functioning (Fig. 2C). Even though the EZ plays such a central role in



postsynaptic glutamate receptor trafficking, and disruptions in this structure might underlie cognitive deficits, insight in the molecular architecture and dynamics of this local trafficking mechanisms remain to be gained. A recent live-cell and super-resolution imaging study revealed that the EZ is remarkably long-lived and is assembled from a number of other key endocytic proteins that are dynamically organized at and around the clathrin lattice (Catsburg et al., 2021).

At presynaptic sites, receptor internalization has not been studied extensively. The G-protein coupled mu-opioid receptor was shown to undergo rapid ligand-induced internalization in axons and accumulated in a distinct population of endosomes marked by the retromer (Jullie et al., 2020). These retromer-marked endosomes were found to be enriched at synaptic boutons and provided a means of rapid receptor re-insertion in the axonal membrane. This vesicle cycle operates independently of the neurotransmitter vesicle cycle, indicating the existence of a dedicated machinery for the endosomal trafficking of presynaptic GPCRs that is mediated by the retromer complex. Further delineation of these processes would be of interest to determine how local trafficking mechanisms are organized in presynaptic boutons to sustain localized surface expression of receptors.

## 5. Functional roles of synaptic mGluRs

### 5.1. Role of presynaptic mGluRs in modulating neurotransmitter release

Presynaptic mechanisms that modulate the efficiency of neurotransmitter release are critical for the fine tuning of synaptic transmission. In this regard, presynaptic mGluRs are considered as essential auto-receptors that act as negative-feedback elements to depress glutamate release (Pinheiro and Mulle, 2008). Although group I mGluRs have been ascribed to modulate neurotransmitter release in different synapse types in the nervous system (Giribaldi et al., 2013; Luccini et al., 2007; Pittaluga, 2016), the group II and III mGluRs are studied most extensively in this context. The presynaptic group II and III mGluRs both couple to inhibitory G-proteins ( $G_{i/o}$ ) (Tanabe et al., 1992). Activation of presynaptic mGluRs can depress synaptic transmission via several pathways: inhibition of voltage-gated  $Ca^{2+}$ -channels (VGCC), activation of  $K^+$  channels, or by direct modulation of components of the release machinery such as Munc13, Munc18 and RIM-1 (de Jong and Verhage, 2009). Release can also be inhibited by action of  $G\beta\gamma$  subunits that act on vesicular fusion machinery (Anwyll, 1999). Consequently, these receptors have been implicated in the acute, transient regulation of transmission as well as persistent forms of plasticity such as long-term depression (LTD) and long-term potentiation (LTP).

#### 5.1.1. Determinants of activation for presynaptic mGluRs

Although both group II and group III mGluRs are co-expressed at presynaptic sites and can in principle couple to the same signaling pathways, the distribution of group II and III receptor relative to the presynaptic release site is highly segregated. Notably this distribution seems aligned with the differences in affinity of these receptors for glutamate. mGluR2 for instance has a moderate to high affinity for glutamate (0.5–20  $\mu$ M) but is found primarily in the axonal shaft and at perisynaptic sites. The affinity of most group III mGluRs is somewhat lower (5–40  $\mu$ M), however the EC50 of mGluR7 for glutamate is exceptionally low (>500  $\mu$ M) (Schoepp et al., 1999). Single release events produce only brief, 1–3 mM peaks in glutamate concentration in the synaptic cleft that rapidly decay in space and time. As a result, it has been proposed that presynaptic mGluRs preferentially respond to strong, high-frequency stimulation (HFS) patterns that result in high cleft concentration of glutamate or even spill-over activating perisynaptic receptors (Scanziani et al., 1997). However, there is a surprising scarcity of quantitative information on the activation kinetics of mGluRs in response to physiological synaptic stimuli.

#### 5.1.2. Presynaptic actions of group II mGluRs

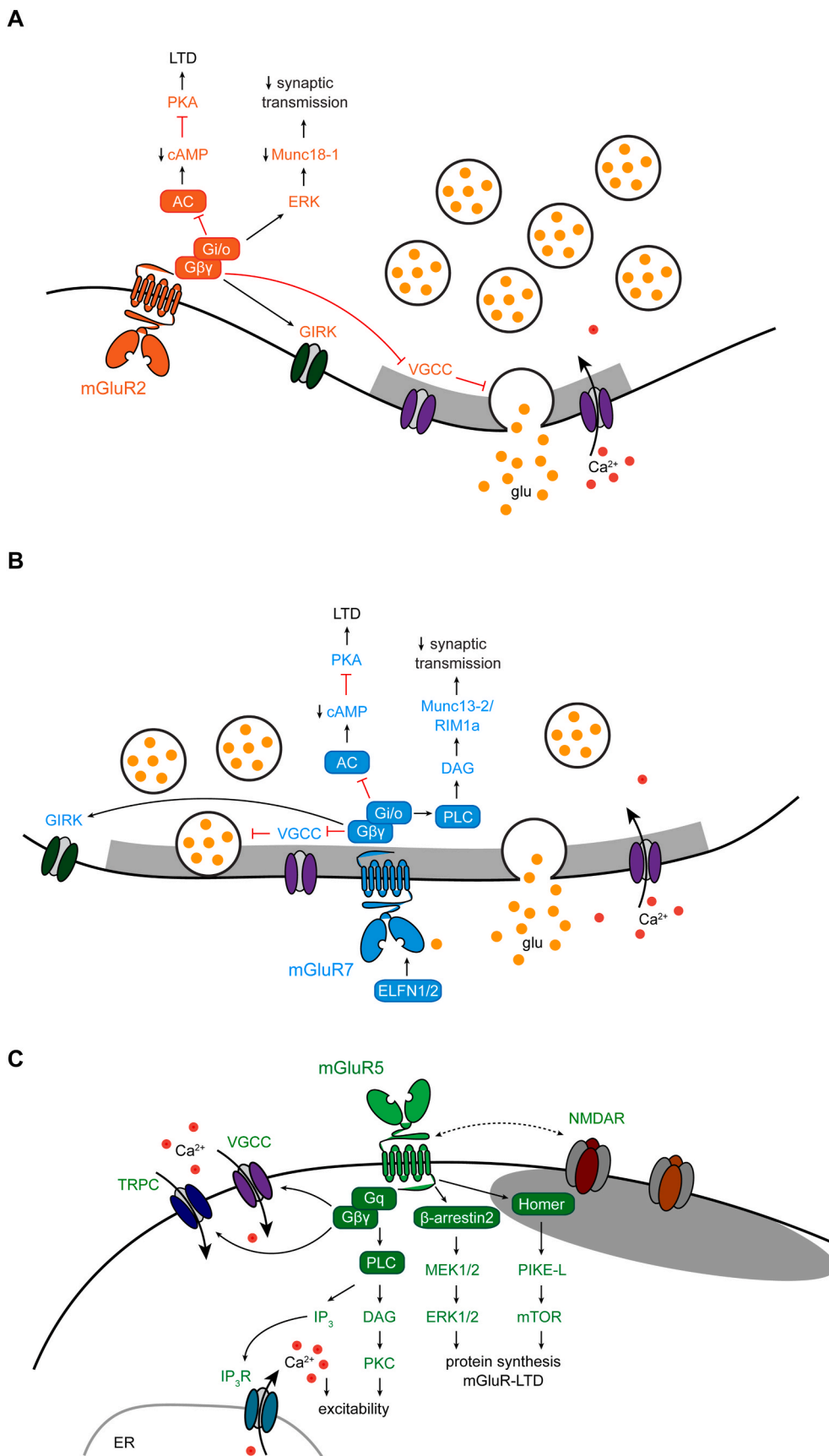
The depressing actions of mGluR2/3 activation on neurotransmitter release are primarily mediated by inhibition of adenylate cyclase (AC) activity and consequently reduced cAMP-mediated PKA activation (Nicholls et al., 2006; Tzounopoulos et al., 1998). In addition, mGluR2/3 activation also stimulates ERK-dependent pathways that lead for instance to phosphorylation of Munc18-1, directly impacting the release machinery (Schmitz et al., 2016) (Fig. 3A). Stimulation of group II mGluRs with selective agonists acutely depresses transmission at excitatory synapses throughout the brain (Bushnell et al., 1996; Capogna, 2004; Kilbride et al., 1998; Lovinger and McCool, 1995; Price et al., 2005). A role for group II mGluRs in persistent presynaptic LTD has also been found and has been most intensely studied at mossy fiber (MF)-CA3 synapses (Kobayashi et al., 1996; Yokoi et al., 1996). This form of LTD relies on a mGluR-dependent reduction in cAMP and decrease in PKA activity, but additionally requires the activity-dependent influx of presynaptic calcium (Tzounopoulos et al., 1998). The exact targets of PKA at presynaptic sites remain elusive, but the induction of LTD was blocked in Rab3a knock-out mice (Tzounopoulos et al., 1998), suggesting that PKA acts on targets that directly regulate transmitter release. However, the absolute requirement for group II mGluRs for mossy fiber LTD was recently challenged by findings that LTD was unaltered by a new selective and highly potent group II mGluR antagonist (Wostrack and Dietrich, 2009) and remained intact in mGluR2/3 double-knockout mice (Lyon et al., 2011).

#### 5.1.3. Presynaptic actions of group III mGluRs

The inhibitory action of group III mGluRs on glutamate release has been shown in a broad variety of preparations. Stimulation of group III mGluRs blocks the stimulated release of glutamate from isolated nerve endings or synaptosomes (Millan et al., 2002; Rodriguez-Moreno et al., 1998) and autapses (O'Connor et al., 1999), depresses cAMP-induced vesicle cycling (Chavis et al., 1998), induces the PKC-dependent blockade of P/Q-type channels (Martin et al., 2007; Perroy et al., 2000) (Fig. 3B), and potently depresses synaptic transmission at CA3-CA1 synapses in the hippocampus (Ayala et al., 2008; Baskys and Malenka, 1991; Gereau and Conn, 1995), as well as other synapses in the central nervous system (Pelkey et al., 2005; Perroy et al., 2002; Zhang et al., 2008). Also, short-term plasticity is significantly altered short-term plasticity at CA3-CA1 synapses in mGluR7 knockout mice (Bushnell et al., 2002). Thus, all these lines of evidence are consistent with the notion that these receptors act as autoreceptors at excitatory synapses. However, mGluR7 has also been suggested to be a heteroreceptor acting at inhibitory synapses in the CA1 region of the hippocampus to indirectly regulate excitatory drive in the hippocampus (Klar et al., 2015). Activation of group III mGluRs has also been found to potentiate transmission through activation of PKC and recruitment of Munc-13 (Martin et al., 2010) (Fig. 3B). It was proposed that mGluR7 activation bidirectionally regulates transmission, inducing a rapid, short-lasting potentiation followed by a longer-lasting depression of synaptic responses (Martin et al., 2018).

At MF-stratum lucidum interneurons HFS or transient application of L-AP4 induces a prominent presynaptic form of LTD that is mediated by mGluR7 and the subsequent persistent downregulation of P/Q-type VGCCs (Pelkey et al., 2005, 2006). Interestingly, however, when induced after L-AP4 application, this same HFS protocol induces potentiation, or de-depression of synaptic responses that required cAMP-PKA signaling. Since L-AP4 induces the rapid internalization of mGluR7, it is thought that the surface expression of mGluR7 dictates the direction of plasticity, acting as a metaplastic switch at MF-SLIN synapses (Pelkey et al., 2005, 2008; Suh et al., 2008). Interestingly, a recent study in SC-CA2 synapses similarly suggested a gating role for group III mGluRs, based on findings that group III mGluR antagonists allow the induction of NMDAR-dependent LTP that is normally absent at these synapses (Dasgupta et al., 2020).





**Fig. 3. Main signaling pathways of mGluRs.** (A–C) Main molecular components involved in the regulation of synaptic transmission by presynaptic group II mGluR2 (A) and group III mGluR7 (B) and postsynaptic group I mGluR5 (C). AC – adenylyl cyclase, glu – glutamate, GIRK – G-protein-coupled inwardly-rectifying potassium channel, VGCC – voltage-gated calcium channel.

#### 5.1.4. Transsynaptic control of mGluR activity

Of interest for the regulation of group III mGluR function at synapses is the increasing evidence that the extracellular domain of mGluRs forms a critical point of regulation, allowing for interactions with structural proteins that act as structural and allosteric modulators of GPCR activity (Dunn et al., 2019a). For example, the adhesion molecules ELFN1 and ELFN2 bind selectively to all group III mGluRs in trans and act as allosteric modulators of mGluR activity (Dunn et al., 2018, 2019b; Tomioka et al., 2014). At synapses, ELFN proteins generally seem to stimulate mGluR activity, even under resting conditions of synaptic activity, providing constitutive depression of release (Dunn et al., 2019b; Stachniak et al., 2019; Sylwestrak and Ghosh, 2012). These actions of ELFNs are probably mediated by maintaining sufficient surface expression levels of mGluR7 and increasing its apparent affinity for glutamate (Dunn et al., 2019b). It is tempting to speculate that extracellular interactions are a more general mechanism regulating different aspects of mGluR biology, including (subsynaptic) positioning, mobility, and receptor activity. Recent evidence for extrasynaptic interactions has been reported for mGluR2, which was shown to interact with neuroligin 1 (Gjørnlund et al., 2017), and for group I mGluRs that were shown to transduce intracellular signaling triggered by the laminin-bound prion protein (Beraldo et al., 2011). Additionally, prion proteins are suggested to form a dynamic platform for signaling modules to assemble at the surface, spatially restricting group I mGluRs and compartmentalizing downstream responses (Linden, 2017) (Fig. 2A, D).

#### 5.2. Role of postsynaptic mGluRs in synaptic transmission and plasticity

The particular perisynaptic partitioning of group I mGluRs, puts these receptors at a considerable distance away from the release site, effectively lowering the probability that these receptors become activated by synaptic release events. Nevertheless, postsynaptic mGluR signaling has been found to be involved in a plethora of processes that regulate basal synaptic transmission and long-term plasticity. Once activated, group I mGluRs can trigger a wide variety of signaling pathways. Canonically, group I mGluRs couple to  $G_{aq/11}$  proteins that activate the PLC pathway, leading to release of  $Ca^{2+}$  from internal stores and stimulation of PKC (Niswender and Conn, 2010). Apart from this principal pathway, group I mGluRs can engage a wide range of other effector proteins, including casein kinase 1, Cdk 5, as well as the PI3K-mTOR signaling and ERK-signaling pathways that stimulate protein translation (Banko et al., 2006; Hou and Klann, 2004; Liu et al., 2001; Ronesi and Huber, 2008). The ability of group I mGluRs to activate these G-protein-independent signaling pathways relies on specific adaptor proteins that differentially recruit signaling components. For instance, Homer proteins can recruit PIKE-L (phosphoinositide PI3-kinase enhancer) that couples to the PI3K-AKT-mTOR pathway (Rong et al., 2003), and  $\beta$ -arrestin2 couples mGluR5 to the ERK signaling pathway (Stoppel et al., 2017) (Fig. 3C). Group I mGluRs also modulate several ion channels including  $K^+$  channels (Chrapak et al., 1990), voltage-gated calcium channels (Kato et al., 2012), TRP channels (Gee et al., 2003), generally leading to an increased excitability (Anwyl, 1999; Fagni et al., 2000). Through these actions group I mGluRs can have broad and lasting effects on the excitability of a neuron but depending on the context, these receptors can also modulate local synaptic processes that lead to long-term changes in synaptic efficacy.

##### 5.2.1. Modulation of NMDA receptors by group I mGluRs

Early studies in *Xenopus* oocytes demonstrated that group I mGluR activation can potentiate NMDAR activity (Kelso et al., 1992), presumably through an increase in NMDAR exocytosis (Lan et al., 2001b). Similarly, stimulation of group I mGluRs also potentiates NMDAR responses in the hippocampus (Aniksztejn et al., 1992; Benquet et al., 2002; Fitzjohn et al., 1996; Harvey and Collingridge, 1993; O'Connor et al., 1994) as well as other brain regions (Awad et al., 2000). In contrast, in other studies group I mGluRs were shown to depress NMDAR

activity (Bertaso et al., 2010; Moutin et al., 2012; Perroy et al., 2008; Snyder et al., 2001; Wang et al., 1998; Yu et al., 1997). A clear explanation for these contradicting findings is still lacking but the effect of mGluR activity on NMDAR function seems to be highly dependent on the context, i.e., related to the synapse type that is investigated, interacting scaffolds and access to signaling pathways. For instance, group I mGluR activation potentiates NMDARs in the hippocampal CA1 region, but has a depressing effect on NMDAR currents in CA3 neurons (Grishin et al., 2004).

Likely related to these conflicting results, how group I mGluRs exert their modulatory effects on NMDAR activity remains poorly understood. Various modes of crosstalk between group I mGluRs and NMDARs have been described that could in principle mediate these effects. For instance, G-protein-mediated activation of PKC and Src were shown to be involved in modulating the gating properties and trafficking of NMDARs (Aniksztejn et al., 1992; Benquet et al., 2002; Harvey and Collingridge, 1993; Heidinger et al., 2002; Lan et al., 2001a). Another potential mode of crosstalk is through modulation of the Homer scaffold proteins. The interaction of Homer with Shank proteins (Tu et al., 1999) links group I mGluRs to the NMDAR that couples to Shank via its interaction with PSD-95. Interestingly, the activity-regulated short Homer1a isoform, lacks the coiled-coil domain and acts as a dominant-negative monomer that disrupts the structural link between mGluRs and NMDARs. Overexpression of Homer1a abolishes the potentiating effects of mGluRs on NMDAR activity (Sylantsev et al., 2013), suggesting there could be a direct modulatory impact of mGluRs on NMDARs through this structural interaction (O'Neill et al., 2018). In an alternative, seemingly conflicting model, the Homer-Shank scaffold interaction prevents mGluR1/5 from exerting a modulatory role on the synaptic NMDAR and Homer1a-mediated disruption of this complex is required to allow crosstalk (Bertaso et al., 2010). Support for this notion comes from studies that show that Homer1a uncouples mGluR5 from perisynaptic sites, allowing direct interaction of mGluR5 with the NMDAR in the PSD (Aloisi et al., 2017; Moutin et al., 2012; Perroy et al., 2008). These seemingly conflicting mechanisms might in fact overlap at different time scales with the outcome being dependent on the properties of the particular cell and/or synapse type (O'Neill et al., 2018).

##### 5.2.2. Modulation of NMDAR-dependent plasticity by mGluRs

At hippocampal SC-CA1 synapses, the most well-studied forms of long-term plasticity, LTD and LTP, are induced by the activation of NMDARs. Thus, the modulatory effects of group I mGluRs on NMDAR function suggest that mGluRs can also influence the expression of NMDAR-mediated forms of plasticity. Several studies have indeed implicated group I mGluRs in the regulation of NMDAR-dependent LTP in SC-CA1 synapses. Prior stimulation of mGluRs with agonists primes LTP induction (Bashir et al., 1993b; Bortolotto et al., 1994; Cohen and Abraham, 1996; Cohen et al., 1998), and PAMs enhance LTP at hippocampal SC-CA1 synapses (Ayala et al., 2009). Reversely, pharmacological blockade of group I mGluRs (Balschun and Wetzels, 2002; Bashir et al., 1993a; Bortolotto et al., 1994; Francesconi et al., 2004; Neyman and Manahan-Vaughan, 2008) and genetic deletion of mGluR5 (Jia et al., 1998; Lu et al., 1997) strongly reduce hippocampal LTP. Thus, co-activation of postsynaptic group I mGluRs and NMDARs seems to underlie the induction of LTP, and chemical co-activation of these receptors has even been found sufficient to induce LTP (Kotecha et al., 2003). In a recent, careful analysis evaluating the plasticity-inducing rules at SC-CA1 synapses it was shown that time-correlated pre- and postsynaptic spiking induced strong potentiation that was dependent on the coordinated calcium influx through NMDARs and VGCCs in spines and required group I mGluRs (Tigret et al., 2016). Here, group I mGluRs were shown to be required for depressing SK channels that negatively affect NMDAR activity. Thus, also under more physiological synaptic stimulation protocols, mGluRs seem to work in close synergy with synaptic NMDARs to orchestrate synaptic transmission and plasticity.

### 5.2.3. Group I mGluR-dependent long-term depression

Activation of group I mGluRs by prolonged low-frequency stimulation protocols or direct application of DHPG, induces a persistent form of LTD: mGluR-LTD (Luscher and Huber, 2010). Interestingly, this form of LTD is mechanistically distinct from NMDAR-dependent LTD (Oliet et al., 1997). Most importantly, unlike NMDAR-LTD, mGluR-LTD relies on the rapid and local synthesis of new proteins in dendrites (Huber et al., 2000) that promote the internalization of AMPARs (Park et al., 2008; Waung et al., 2008). mGluR-LTD induction is dependent on the activation of  $G_{aq}$  signalling (Kleppisch et al., 2001), PI3K/mTOR signaling (Hou and Klann, 2004), ERK (Gallagher et al., 2004) and  $\beta$ -arrestins (Stoppel et al., 2017) that converge on local cap-dependent translation. Interestingly, the efficacy of mGluR-mediated LTD seems strongly determined by the availability of effectors. Using local glutamate uncaging protocols that induce mGluR-dependent LTD at individual spines it was shown that only spines containing an ER were able to undergo LTD (Holbro et al., 2009).

### 5.2.4. Role of group I mGluRs in non-Hebbian plasticity

Apart from Hebbian, input-specific forms of plasticity, group I mGluRs have been found to play a dominant role in forms of non-Hebbian plasticity such as homeostatic scaling of synaptic strength and metaplasticity (Bockaert et al., 2021). This was first shown in dissociated cortical neurons, where synaptic downscaling by a chronic increase in network activity was prevented by pharmacological inhibition of group I mGluRs (Hu et al., 2010). Interestingly, this study showed that mGluR1/5-driven scaling was not initiated by synaptically released glutamate but was stimulated by the activity-induced increase in Homer1a expression (Hu et al., 2010), consistent with earlier observations that Homer1a expression stimulates agonist-independent signaling pathways downstream of mGluR5 (Ango et al., 2001). In a physiological context, downscaling of synapses is prominent during sleep, which is thought to desaturate synaptic strength and allow further learning during the awake phase. In a recent comprehensive study, it was shown that excitatory synapses undergo extensive remodeling during sleep, which was primarily driven by targeting of Homer1a to the synapse, and the consequent stimulation of group I mGluR activity (Diering et al., 2017). Homer1a-driven stimulation of mGluR1/5 activity was also shown to regulate visual experience-dependent weakening of synapses in the visual cortex (Chokshi et al., 2019), and has been extensively investigated in the context of reward-directed learning in drug addiction (Marton et al., 2015), as well as other psychiatric disorders (Szumlinski et al., 2006). Promisingly, stimulating constitutive activation of mGluR1/5 activity by introducing cell-permeable Homer1a was recently shown to have anti-depressant effects (Holz et al., 2019). This induction mechanism of mGluR1/5 signaling by intracellular Homer1a thus seems to be a particularly important mechanism in non-Hebbian forms of synaptic plasticity that has clear relevance for understanding physiological and pathological conditions.

### 5.2.5. Postsynaptic actions of group II mGluRs

Of note, group II mGluRs have also been reported to have postsynaptic effects. Group II agonists were shown to strongly enhance neuronal excitability in CA3 neurons (Ster et al., 2011). Moreover, stimulation of group II mGluRs induced the stable potentiation of SC-CA1 synapses that was mediated by modulation of NMDAR activity (Rosenberg et al., 2016). Interestingly, this form of mGluR-dependent LTP seemed to be independent of the classic form of HFS-induced SC-CA1 LTP. Rather, the activation of mGluR2/3 potentiated NMDARs and was proposed to act as a metaplasticity switch that gates the subsequent induction of NMDAR-mediated LTP (Rosenberg et al., 2016). Group II mGluRs were also shown to potentiate postsynaptic mGluR5 function in the prefrontal cortex (PFC) (Di Menna et al., 2018) and regulate AMPA receptor trafficking in PFC neurons (Wang et al., 2013). Interestingly, disruptions in mGluR3-mGluR5 crosstalk were found to underlie stress-induced cognitive deficits (Joffe et al., 2019), and

stimulation of mGluR3 enhanced cognitive performance of mice in an mGluR5-dependent manner (Dogra et al., 2021), highlighting the relevance of this emerging notion of mGluR crosstalk for understanding psychiatric disorders. It thus seems that several mGluRs impact NMDAR-dependent processes and it would be important to further dissect the extent of glutamate receptor crosstalk at postsynaptic sites and unravel the mechanisms that mediate glutamate receptor cooperativity.

## 6. Conclusions and future directions for the field

Since the initial cloning of metabotropic glutamate receptors, tremendous efforts have led to an astonishing progress in our understanding of how mGluRs are trafficked and targeted to their subcellular destination in neurons. This fascinating family of glutamate receptors has evolved to fulfil a broad palette of cellular functions and regulate key aspects of neuronal functioning. We here discussed the various actions of these receptors at pre- and postsynaptic sites that are key for the regulation of synaptic transmission and plasticity, but it is important to note is that these receptors also signal in various other subcellular compartments, including the nucleus, and fulfil key roles in glial cells. This striking diversity in biological functions is determined by the various signaling pathways, heterodimerization with family members and other GPCRs, subcellular localization and crosstalk with ionotropic receptors. Grasping this functional complexity and incorporating this into existing models of synaptic transmission is one of the largest challenges of the moment and will greatly benefit from computational modeling efforts that can integrate different levels of complexity and make quantitative predictions. Moreover, defining the activation and deactivation kinetics of receptors in intact neuronal networks is important to connect the pharmacology and molecular biology of mGluRs to a circuit level understanding of brain functioning and animal behavior. This is for instance exemplified by the recent discovery of endogenous allosteric modulators such as the ELFN proteins, that significantly alter the pharmacological and functional profile of mGluRs at native synapses in the brain. To accurately probe receptor function within their native environment it will be important to continue ongoing exciting developments in fluorescence live-cell and super-resolution microscopy to study the nanoscale distribution and dynamics of glutamate receptors (Groc and Choquet, 2020). These techniques in turn will benefit from the development of optical sensors of receptor activation (Villardaga et al., 2003), optogenetic tools to control receptor activation (Levitz et al., 2013, 2017) or localization (Sinnen et al., 2017) and CRISPR/Cas9 technologies to label endogenous receptor complexes (Willems et al., 2020). Continuing research in these directions will provide a firm understanding of the dynamic processes that underlie the actions of mGluRs at and around synapses. This will not only result in a deeper insight in the regulatory roles of mGluRs in synaptic transmission and plasticity but will also reveal critical points in these processes that can be targeted in therapeutic approaches to treat neurological disorders.

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