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Group I Metabotropic Glutamate Receptor Interacting Proteins: Fine-Tuning Receptor Functions in Health and Disease

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Abstract: Group I metabotropic glutamate receptors mediate slow excitatory neurotransmission in the central nervous system and are critical to activity-dependent synaptic plasticity, a cellular substrate of learning and memory. Dysregulated receptor signaling is implicated in neuropsychiatric conditions ranging from neurodevelopmental to neurodegenerative disorders. Importantly, group I metabotropic glutamate receptor signaling functions can be modulated by interacting proteins that mediate receptor trafficking, expression and coupling efficiency to signaling effectors. These interactions afford cell- or pathway-specific modulation to fine-tune receptor function, thus representing a potential target for pharmacological interventions in pathological conditions.

Keywords: Amyloid-β, CaMKIIα, caveolin-1, homer, mGluR, norbin, PrP^c, synaptic plasticity.

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1. INTRODUCTION

In the central nervous system (CNS) the excitatory neurotransmitter glutamate acts on two receptor classes: ionotropic receptors, which are ligand-gated cation channels, and metabotropic receptors that are linked *via* heterotrimeric G proteins to second messenger signaling pathways. Metabotropic glutamate receptors belong to class C of the G-protein coupled receptor (GPCR) superfamily and are further classified into three groups (I through III) based on sequence homology and signal transduction modality. Group I metabotropic glutamate receptors (Gp1 mGluRs hereafter), which include mGlu1 and mGlu5, play critical functions in forms of activity-dependent synaptic plasticity, including long-term depression (LTD) and long-term potentiation (LTP), in different brain regions such as cerebellum, hippocampus, ventral tegmental area (VTA) and striatum [1-3]. Importantly, Gp1 mGluRs are emerging molecular targets for treatment of neuropsychiatric disorders including Fragile X syndrome [4] and Alzheimer's disease [5], and are implicated in the pathophysiology of pain [6, 7], anxiety [8, 9], schizophrenia [10, 11] and drug addiction [12].

Gp1 mGluRs couple to $G\alpha_{q/11}$ to stimulate phospholipase Cβ (PLC) that cleaves membrane phosphatidylinositol 4,5-bisphosphate (PIP2) to release second messengers inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) to induce mobilization of Ca^{2+} from intracellular stores and activation of protein kinase C (PKC). As for other GPCRs, Gp1 mGluRs can regulate ion channel opening *via* membrane delimited-functions dependent on Gβγ subunits or potentially *via* indirect or direct molecular interactions as reviewed elsewhere [13-15]. In addition to canonical $G\alpha_{q/11}$-dependent signaling, Gp1 mGluRs activate extracellular signal-regulated kinase (ERK) [16] and phosphatidylinositol-3-kinase(PI3K)/Akt/mammalian target of rapamycin (mTOR) [17] pathways linked to control of protein translation initiation [18]. Importantly, the capacity to elicit *de novo* protein synthesis is critical to several forms of Gp1 mGluR-dependent synaptic plasticity [19-22].

Interacting proteins can modify signaling efficiency by exerting scaffolding functions that enable receptors to be physically and functionally integrated in macromolecular signaling complexes [23]. Thus, receptor interacting proteins can help defining temporo-spatial specificity and efficiency of signaling to control net functional output. Gp1 mGluRs interacting partners have been shown to modulate receptor signaling *via* canonical G protein-dependent or G protein-independent pathways or alternatively to modulate receptor targeting to specific subcellular compartments. Examples of interacting partners that regulate Gp1 mGluR signaling *via* G proteins include G protein–coupled receptor kinases (GRK) [24-26] that participate in receptor signaling and desensitization through binding of arrestin and subsequent clathrin-dependent internalization. The role of GRK-arrestin in Gp1 mGluR desensitization and internalization and the function of a number of other Gp1 mGluR interacting partners (Table **1**) has been extensively reviewed elsewhere [27]. This Minireview will focus on Gp1 mGluR interacting proteins that were identified in recent years and shown to modulate receptor expression and/or signaling *in vivo* and discuss their impact on Gp1 mGluR physiological functions with emphasis on synaptic plasticity and implications in pathological conditions (Fig. **1**).

2. ROLE OF GROUP I MGLUR INTERACTING PROTEINS IN SYNAPTIC PLASTICITY

Gp1 mGluRs are widely expressed in the CNS and present at excitatory synapses where mGlu1 and mGlu5

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Table 1. Gp1 mGluR interacting proteins.

Protein	Binding Region	Signaling Pathway	Receptor Expression	Impact *in vivo*	References
Actinin-1	C-tail	ERK	Increases surface expression (*in vitro*)	-	[80]
CAIN	i2 (C-tail)	PLC	Stabilizes surface expression (*in vitro*)	-	[81]
Calmodulin	C-tail	$Ca2+_i$	Stabilizes surface expression (*in vitro*)	-	[35]
CaMKIIα	C-tail	protein synthesis	-	*Pharmacological inhibition* - Sch-CA1 synapses: Reduced mGluR-LTD	[30, 31, 33]
Caveolin-1	i1, i3	PLC Ca2+i ERK	Stabilizes surface expression (*in vitro*) KO mice: no change (*in vivo*)	*KO mice* - Sch-CA1 synapses: Reduced mGluR-LTD -Enhanced sensitivity to PCP -Resistance to atypical antipsychotics	[38, 39, 45]
GRK2	i2	PLC	Promotes internalization (*in vitro*)	*cKO mice* - D1R+ neurons: Increased cocaine sensitivity - D2R+ neurons: Reduced cocaine sensitivity	[25, 82]
Homer-1	C-tail	ERK mTOR PI3K $Ca2+_i$	Reduces surface expression (*in vitro*) KO mice: no change (*in vivo*)	*KO mice* - Impaired pre-pulse inhibition - Increased behavioral despair - Increased sensitivity to MK-801, methamphetamine and cocaine *Homer1a KO* - Decreased inflammatory pain - Reduced cocaine sensitization *Binding competition w/ peptides* Sch-CA1 synapses: Reduced mGluR-LTD	[56, 62, 79, 83-85]
Homer-2	C-tail	PI3K $Ca2+_i$	KO mice: no change (*in vivo*)	*KO mice* - Increased sensitivity to MK-801, methamphetamine and cocaine - Reduced sensitivity to EtOH	[86, 87]
Homer-3	C-tail		Reduces surface expression (*in vitro*)		[88]
NHERF2	C-tail	$Ca2+_i$	-	-	[89]
Norbin	C-tail	PLC $Ca2+_i$ ERK	Stabilizes surface expression (*in vitro*) cKO mice: reduced expression (*in vivo*)	*Forebrain cKO mice* - Sch-CA1 synapses: Reduced mGluR-LTD Reduced HFS-LTP -PPI deficits - Increased sensitivity to MK-801 (locomotor activity)	[47]
Optineurin	C-tail	PLC	No effect	*OPTN mutations in human:* Associated with glaucoma	[76, 90]
Pin1	C-tail		-	$Grm5^{TS/AA}Pin1^{+/-}$ *mice* - Reduced cocaine sensitization	[62]
Preso1	C-tail	$Ca2+_i$	-	*KO mice* - Increased inflammatory pain response	[79]

Table 1. contd….

Protein	Binding Region	Signaling Pathway	Receptor Expression	Impact *in vivo*	References
PrP^{C}	-	$Ca2+_i$ protein synthesis	-	Aβo co-receptor complex	[70]
Pyk2	i2 C-tail	PLC ERK	No effect	-	[91]
Rab8	C-tail	PLC $Ca2+_i$	Stabilizes surface expression (*in vitro*)	-	[92]
Siah-1A	C-tail	-	Increases turnover (*in vitro*)	-	[93]
Tamalin	C-tail		Stabilizes surface expression (*in vitro*)	*KO mice* - Decreased sensitivity to morphine, cocaine - Hippocampal DG: Loss of LTP after ECS	[94-96]

Listed are proteins shown to directly interact with Gp1 mGluRs. Indicated in the table are receptor domains involved in the interaction and signaling pathways downstream of Gp1 mGluRs that are modulated by corresponding interacting proteins. Also indicated is impact of interacting proteins on Gp1 mGluR expression and relevant phenotype of mouse mutants or in human for corresponding gene. Highlighted in bold are interacting proteins specifically discussed in this Minireview. Sch-CA1, Schaffer collateral-CA1 synapses; i2-3, intracellular loops 1 through 3; C-tail, carboxyl terminal tail; D1R, D2R, Dopamine D1/2 receptors;ECS, Electroconvulsive shock.

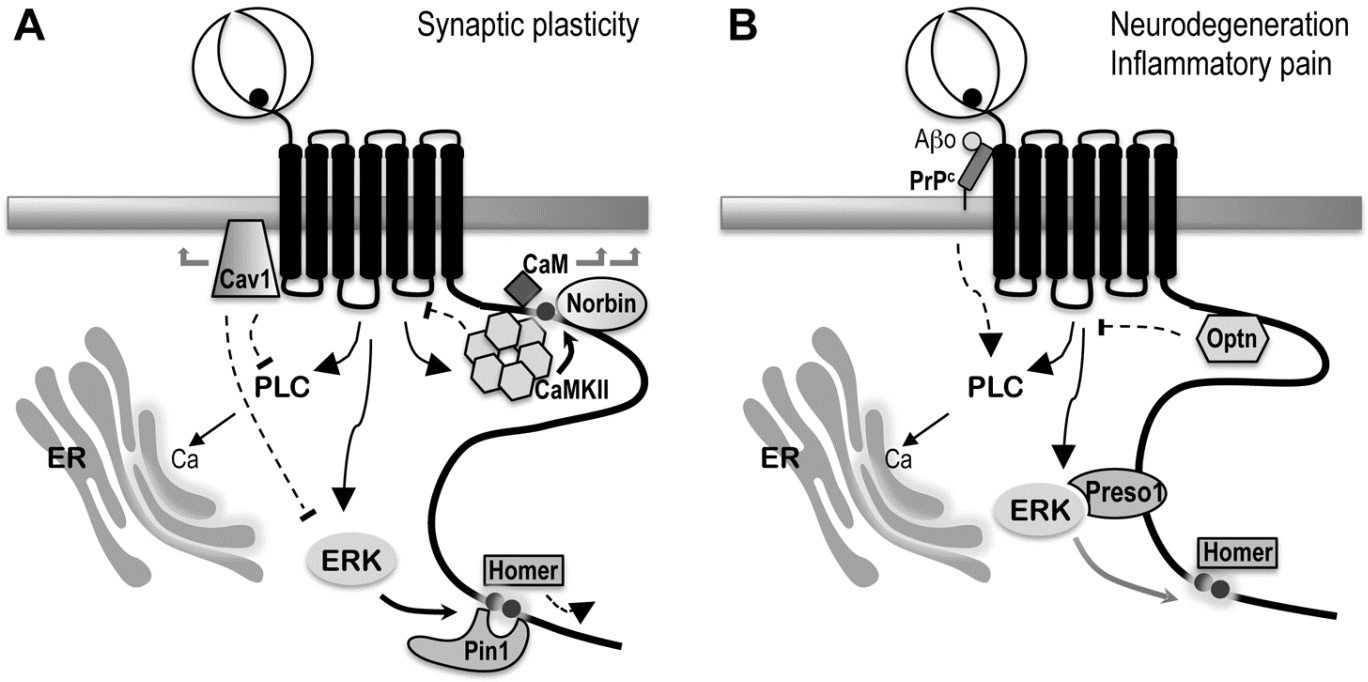

Fig. (1). Schematic representation that summarizes proposed molecular functions and binding sites of Gp1 mGluR-interacting proteins. **A**) Proteins that play a role in various forms of Gp1 mGluR-dependent synaptic plasticity. Gray upward arrows indicate effect on receptor surface expression as reported for caveolin-1 (Cav1), calmodulin (CaM) and norbin. Dots mark phosphorylation sites. ER endoplasmic reticulum, Ca calcium, PLC phospholipase C, ERK extracellular signal-regulated kinases. **B**) MGluR-interacting proteins that are implicated in pathological conditions including neurodegenerative disorders and inflammatory pain. Precise binding regions in Gp1 mGluRs for optineurin (Optn) and PrP^{c} remain undefined and relative locations in the scheme are based on limited available information on relevant protein properties.

predominantly localize to the *annulus* of the postsynaptic density [28]. Gp1 mGluRs are prevalently activated by strong synaptic stimulation leading to glutamate spillover from synaptic cleft through which they drive different forms of synaptic plasticity, including LTD and LTP, in several brain regions. Here, we will focus on the role of Gp1 mGluR interacting proteins in the cellular and molecular mechanisms underlying Gp1 mGluR-dependent LTD (mGluR-LTD) [2] a

form of synaptic plasticity that is altered in disease conditions such as Fragile X syndrome, autism and addiction.

2.1. CaMKIIα

Calcium/calmodulin-dependent protein kinase II (CaMKII) is a serine/threonine kinase highly enriched at excitatory synapses where it plays important functions in synaptic plasticity [29]. CaMKIIα binds *via* its N-terminal catalytic domain to the membrane proximal segment of the carboxyl tail of mGlu1 [30] and mGlu5 [31]. CaMKII is activated by Ca^{2+}/calmodulin binding, upon which it phosphorylates substrate proteins and concurrently undergoes intersubunit autophosphorylation that renders it constitutively active [32]. Active, autophosphorylated (Thr286) CaMKIIα binds mGlu1 with higher affinity and phosphorylates the receptor at Thr871, a residue situated within the CaMKIIα binding region in the mGlu1 tail. CaMKII-dependent phosphorylation in turn leads to desensitization of mGlu1-dependent activation of the PLC pathways, thus establishing a feedback mechanism relevant to regulation of mGlu1 activity in the striatum [30]. CaMKIIα binding region in mGlu5 partly overlaps with the calmodulin-binding site present in the receptor (see below, Section *2.2*) and in contrast to mGlu1, activated/ autophosphorylated CaMKIIα has reduced affinity for mGlu5 whereby CaMKIIα interaction with the receptor is occluded by calmodulin competition for the shared binding site [31]. Interestingly, in striatal neurons mGlu5 stimulation is sufficient to promote CaMKIIα activation, whereby the activated kinase is released from mGlu5 and recruited to the GluN2B subunit of NMDA receptors [31]. Gp1 mGluR stimulation with the selective agonist DHPG was also shown to transiently induce phosphorylation/activation of CaMKIIα in the hippocampus [33], although whether mGlu1 or mGlu5 or both drive this process and whether regulatory mechanisms observed in the striatum also operate in the hippocampus remains unknown. At hippocampal Schaffer collateral-CA1 synapses (Sch-CA1), activation of Gp1 mGluRs with DHPG or by synaptic stimulation with paired-pulse low frequency stimulation induces long-term depression of synaptic transmission (mGluR-LTD) by a mechanism that requires *de novo* protein synthesis [20]. Of note, CaMKII inhibitors impair expression of mGluR-LTD - both chemically or synaptically induced - while concurrently inhibiting *de novo* protein synthesis elicited by Gp1 mGluRs [33] thus indicating that synaptic signaling by Gp1 mGluRs to CaMKII – potentially mediated *via* their physical interaction – is critical for efficient expression of synaptic plasticity.

2.2. Calmodulin

Calmodulin is a ubiquitously expressed Ca^{2+}-binding protein that acts as calcium sensor and signaling protein. As sensor of intracellular Ca^{2+} levels calmodulin plays a critical role in both LTP and LTD [34]. Calmodulin selectively binds to mGlu5 carboxyl tail within a membrane proximal segment that shares a high degree of sequence similarity with mGlu1. Selectivity of calmodulin interaction is conferred by one amino acid, Leu896, in mGlu5 whereby mutation of this single critical residue (Leu896Val) abrogates calmodulin binding [35]: conversely, mutation of the corresponding residue Val909 present in mGlu1 (Val909Leu) confers binding. Calmodulin binding was shown to enhance mGlu5 surface expression, potentially by reducing constitutive internalization, and control the rate of mGlu5 internalization in response to stimulation by agonist [35]. By increasing the density of surface receptors, calmodulin was also shown to regulate the frequency of Ca^{2+} oscillations induced by mGlu5 and the efficiency of mGlu5-dependent internalization of AMPA receptors, at least *ex vivo*. Thus, by stabilizing mGlu5 receptors at the cell surface calmodulin can selectively modify the efficacy of receptor signaling to downstream effectors.

2.3. Caveolin-1

Caveolin-1 is an adaptor protein that binds cholesterol, associates with lipid rafts and plays critical functions in orchestrating signal transduction. Caveolin-1 organizes macromolecular signaling complexes by interacting through its scaffolding domain with an array of effector proteins including, but not limited to, G protein α subunits, PLC and PKC [36]. Moreover, caveolin-1 can regulate signal transduction strength and duration through the actions of its scaffolding domain that inhibits the enzymatic activity of caveolin-1 interacting partners [37]. Caveolin-1 binds to mGlu1/5 intracellular loop regions (i1 and i3: Table **1**) [38] to control the rate of receptor constitutive internalization such that mutations that abrogate receptor binding to caveolin-1 result in decreased receptor density at the neuronal surface [38]. However, in mice lacking caveolin-1 expression of native Gp1 mGluRs is not significantly compromised suggesting the existence of compensatory mechanisms [39]. Although Gp1 mGluRs associate with lipid rafts, caveolin-1 is not required for receptor recruitment to raft domains that is instead promoted by intrinsic affinity of the receptors for cholesterol [40], a principal component of raft membranes. In heterologous cells, caveolin-1 overexpression decreases mGlu1 internalization and concomitantly leads to reduced mGlu1-mediated activation of ERK1/2 in response to glutamate [38], an observation consistent with findings that revealed that receptor internalization enables sustained mGlu1 signaling to ERK [41]. In mice lacking caveolin-1, basal MEK and ERK1/2 phosphorylation – indicative of active state - are abnormally elevated such that the capacity of the Gp1 mGluR agonist DHPG to induce further phosphorylation/activation is blunted [39]. Enhanced basal activity of diverse signaling effectors was previously observed in different cell types and tissues from caveolin-1 knockout mice and is likely to arise from inability to effectively terminate signaling in absence of the inhibitory actions imposed by the caveolin-1 scaffolding domain [36]. Consistent with dysregulated signaling to ERK, caveolin-1 knockout mice exhibit impaired induction of mGluR-LTD at hippocampal Sch-CA1 synapses [39]. Involvement of the mGlu1-caveolin-1-ERK signaling axis in synaptic plasticity is further underscored by findings that 17β-estradiol-dependent enhancement of hippocampal spatial memory consolidation involves non-classical signaling by membrane estrogen receptors α/β (ERα,β) to the mGlu1-ERK pathway [42] in a caveolin-1 dependent-manner [43]. In human subjects, disruption of the *CAV1* gene encoding caveolin-1 was identified as a rare structural genomic variant linked to

schizophrenia [44] and caveolin-1 knockout mice show enhanced sensitivity to the psychotomimetic drug phencyclidine – an NMDA receptor antagonist - and resistance to atypical antipsychotics [45]. Thus, regulation of Gp1 mGluR-caveolin-1 interaction may provide a potential target for modulation of metabotropic functions in neuro-psychiatric disorders including autism and schizophrenia.

2.4. Norbin

Norbin, also known as neurochondrin, is a leucine-rich cytoplasmic protein with expression restricted to CNS, bone and chondral tissue, and targeted deletion of which results in embryonic lethality [46]. In the adult murine CNS, norbin is broadly expressed and particularly abundant in hippocampus, amygdala, septum, and nucleus accumbens [47]. Within neurons, at least *ex vivo*, norbin is prevalently enriched in the somatodendritic compartment and virtually absent from axons [48]. Norbin was shown to interact with the membrane proximal segment of the carboxyl tail of mGlu5a/b and mGlu1a (Table **1**), within a region that partly overlaps with the calmodulin binding site (see Section *2.2*). Studies in heterologous cells demonstrated that norbin over-expression potentiates agonist-dependent mGlu5 signaling to PLC and ERK pathways, potentially by enhancing receptor density at the cell surface. Consistent with a critical function in receptor trafficking, mGlu5 surface expression is compromised in the forebrain of adult mice in which norbin was conditionally deleted [47]. In support of a selective function in the metabotropic component of glutamatergic transmission, mice lacking norbin display normal basal synaptic transmission but reduced mGluR-LTD and impaired LTP induced by high frequency stimulation (HSF) at Sch-CA1 synapses [47]. Norbin cKO mice exhibit sensorimotor gating abnormalities as indicated by deficits in pre-pulse inhibition - which are similarly present in mGlu1 [49] and mGlu5 [50] null mice - and enhanced locomotor activity in response to the NMDA antagonist MK-801 [47]. Together, these findings indicate that Gp1 mGluR-norbin interactions are relevant to understanding and pharmacologically targeting metabotropic signaling dysfunctions in the context of neuropsychiatric conditions such as schizophrenia.

2.5. Homer Proteins

Homer proteins [51] are postsynaptic scaffolding proteins that bind a proline-rich motif within the distal segment of the carboxyl tail of mGlu1a and mGlu5 (Table **1**). Homer-1b/c, -2 and -3, termed 'long homers', possess an N-terminal EVH1 domain that binds Gp1 mGluRs and a C-terminal coiled-coil domain that mediates dimerization, cross-linking and interaction with other synaptic proteins. In contrast, Homer1a - encoded by an immediate early gene – is a 'short' isoform lacking the coiled-coil domain and is endowed with dominant negative functional properties as it can disrupt interactions of long homers with Gp1 mGluRs thereby inducing constitutive receptor activity [52]. The multiple functions of Homer proteins in the regulation of Gp1 mGluR expression and coupling to ion channels and their functional implications have been extensively reviewed elsewhere [53]. In addition, due to space constraints we will not discuss the role of Homer–mGluR5 interaction in Fragile X syndrome as there are exhaustive reviews on the subject [54]. Here we will focus on Homer functions in coupling Gp1 mGluRs to ERK and PI3K/Akt/mTOR pathways and their impact on mGluR-LTD and homeostatic plasticity. Binding of mGlu5 to long Homer proteins is required to induce activation of ERK in striatal neurons [55] and of PI3K in the hippocampus suggesting brain region specific differences in Gp1 mGluR signaling. Whereas in the hippocampus blocking mGlu5-Homer1 interaction by peptide competition has no effect on ERK induction, signaling to PI3K is impaired as shown by reduced phosphorylation/activation of PI3K downstream effectors phosphoinositide-dependent kinase 1 (PDK1), mTOR, p70 ribosomal S6 kinase (S6K) and translation initiation factor 4EBP [56, 57]. Disruption of the mGlu5-Homer1 complex also results in increased phosphorylation of elongation factor 2 (eF2), which leads to inhibition of global protein synthesis rates while enabling translation of mGluR-LTD specific target mRNAs including Arc and Camk2a [57]. Consistent with this, disruption of the mGlu5-Homer1 complex with competing peptides inhibits mGluR-LTD. Thus Homer proteins link Gp1 mGluRs to activation of multiple signaling pathways for the control of protein synthesis and enable expression of Gp1 mGluR-dependent synaptic plasticity.

In addition to input-specific synaptic plasticity, mGluR signaling was shown to regulate homeostatic synaptic scaling by which cell-wide changes in synaptic strength maintain overall neuronal firing in response to global changes in activity [58]. Gp1 mGluR function in homeostatic scaling is dependent on receptor constitutive activity that is in turn regulated by interaction with Homer1a, the 'short' Homer isoform (see above)[59]. In a paradigm of homeostatic scaling, chronic administration of the $GABA_A$ receptor antagonist bicuculline increases network activity that is compensated by cell-wide endocytosis of AMPA receptors. Bicuculline-induced synaptic scaling is blocked by Gp1 mGluR inverse agonists but not by competitive or neutral antagonists and requires activity-induced Homer1a expression since it is abrogated in Homer1a knockout neurons [59]. Altogether, interaction of Gp1 mGluRs with Homer proteins is emerging as a critical nodal point for regulation of diverse forms of Gp1 mGluR-dependent synaptic plasticity and thus represents an important target for pharmacological interventions aimed to modulate Gp1 mGluR function in pathological settings including Fragile X syndrome and autism.

2.6. Pin1

Addictive drugs target the mesocorticolimbic dopaminergic system and lead to increased dopamine concentration and modification of synaptic transmission, including at glutamatergic synapses [60]. Gp1 mGluRs critically participate to mechanisms underlying development of addiction and underlying molecular mechanisms are being uncovered [61]. Cocaine was shown to induce mGlu5 phosphorylation at two residues (Thr1123, Ser1126) located within the Homer-binding motif in the distal segment of the receptor carboxyl tail: post-translational modification of the motif by phosphorylation enables direct binding of the prolyl-isomerase Pin1[62]. Binding of Pin1 to mGlu5 is

competed by native long Homer proteins and enhanced by Homer1a expression: accordingly, Pin1 and mGlu5 interaction is increased in mice lacking all three long Homer proteins (Homer1$^{-/-}$Homer2$^{-/-}$Homer3$^{-/-}$ triple knockout mice) and by cocaine-induced mGlu5 phosphorylation. When bound to mGlu5, Pin1 isomerase activity efficiently catalyzes isomerization of the phospho-Ser1126-proline bond, an intramolecular reaction that is facilitated by Homer1a expression by virtue of its ability to displace long Homer isoforms [62]. In a paradigm of behavioral sensitization established to model addiction, repeated administration of cocaine to wild type mice increases locomotor activity in response to subsequent doses: strikingly, cocaine-induced motor sensitization is strongly attenuated in Homer1a null mice or GRM5 knockin mice in which Thr1123 and Ser1126 cannot be phosphorylated (GRM5$^{AA/AA}$ mice) a phenotype also exhibited by mice with a single copy of Pin1 and GRM5$^{TS/AA}$ mutation (GRM5$^{TS/AA}$/Pin1$^{+/-}$ mice) [62]. This novel and sophisticated mechanism of activity-dependent regulation of protein interactions within assembled macromolecular signaling complexes represents an attractive target for pharmacological tuning of metabotropic functions.

3. ROLE OF GROUP I MGLUR INTERACTING PROTEINS IN NEURODEGENERATIVE DISORDERS

Neurodegenerative disorders are characterized by progressive accumulation of abnormal protein aggregates that form inclusion bodies and plaques, cell toxicity and widespread neuronal death. Although protein aggregates and plaques are a hallmark of a number of neurodegenerative conditions [63], their causative role in neurodegeneration has been challenged by observations that they do not always correlate with disease progression [64]. For example, plaque accumulation in the brain of Alzheimer's disease patients does not correlate with cognitive impairment [65] and synaptic dysfunctions in Huntington's disease are observed long before onset of cell death [66, 67]. Recent studies suggest that aggregating proteins function at synapses and abnormal synaptic plasticity and synapse loss are salient causal features of disease process [65]. Here, we will focus on the functional role of Gp1 mGluR interaction with Cellular Prion Protein (PrP^{c}) and mutant huntingtin protein and potential implications for the pathology of Alzheimer's disease and Huntington's disease, respectively.

3.1. PrP^{C}

Cellular Prion Protein (PrP^{C}) is a GPI-anchored protein present in lipid rafts [68] that acts as high-affinity cell surface receptor for soluble Amyloid-β peptide oligomers (Aβo) [69], a process through which it mediates synaptic dysfunctions induced by Aβo . PrP^{C} interacts with mGlu5 *in vitro* and *in vivo* although the precise site(s) in the receptor that mediate the interaction remain unclear [70]. Interaction between PrP^{C} and mGlu5 occurs in lipid rafts, where mGlu5 is enriched [38, 40] and is regulated by the receptor conformational state, whereby mGlu5 agonists (*e.g.* DHPG) and to some extent positive allosteric modulators (*e.g.* ADX-47273) promote the interaction whereas negative allosteric modulators (*e.g.* MTEP) weaken it [71]. Mechanistically, mGlu5 acts together with PrP^{C} as Aβo co-receptor and thus provides a direct functional link for Aβo-induced activation of non-receptor protein tyrosine-kinase Fyn and mobilization of intracellular calcium [70]. These findings establish a critical link between mGlu5 and Aβo–induced activation of Fyn that underlies reduced NMDAR surface expression, dendritic spine loss and cell toxicity [70, 72]. Furthermore, the PrP^{C}-mGluR5 co-receptor complex enables Aβo to regulate protein synthesis *via* phosphorylation of eukaryotic elongation factor 2 (eEF2), in an mGlu5-dependent manner, thereby enabling local translation of Arc/Arg3.1 mRNA [73]. Consistent with these findings, Aβo-induced disruption of synaptic plasticity, including LTP and NMDAR-independent LTD, is mediated *via* mGlu5 [74]. Thus the Aβo-PrP^{C}-mGlu5 macromolecular complex is a core mediator of cellular and synaptic dysfunctions in Alzheimer's disease and represents a promising pharmacological target for treatment of not only Alzheimer's but other forms of dementia and cognitive impairment associated with aging.

3.2. Optineurin

In Huntington's disease, abnormal expansion of a CAG tri-nucleotide repeat within exon 1 of the *HTT* gene encoding huntingtin (Htt) results in synthesis of mutant proteins harboring abnormally long polyglutamine tracts (> 35) in their N-terminal region. Mutant forms of huntingtin tend to aggregate and cytoplasmic aggregates and nuclear inclusions are deposited throughout the brain [75]. Whether this property is causal to neurodegeneration associated with the disease is currently debated. Although the precise functions of wild type huntingtin remain unclear, identification of its numerous interacting partners is beginning to shed light on its impact on many cellular processes. Optineurin is a coiled-coil containing protein that interacts with huntingtin and was shown to directly bind the carboxyl terminal tail of mGlu1a and promote formation of a complex with mGlu1a and huntingtin in a model cell system whereas interaction of optineurin with mGlu5 was demonstrated in striatal cells [76]. Optineurin was shown to regulate Gp1 mGluR signaling by competing with GRK2 for mGlu1a binding to reduce receptor-induced activation of the PLC pathway and IP3 production. Of note, mutant (Htt^{Q138}) but not wild type huntingtin further exacerbates optineurin-dependent attenuation of mGlu1a signaling, an observation that is buttressed by findings that Gp1 mGluR-dependent signaling to the PLC pathway is impaired in striatal cell lines derived from Hdh$^{Q111/Q111}$ knockin mice, a mouse model of Huntington's disease [76]. Importantly, Gp1 mGluR capacity to induce IP3 production is blunted in the striatum of Hdh$^{Q111/Q111}$ mice at pre-symptomatic ages [77]. Together these findings indicate that metabotropic glutamatergic functions are altered in Huntington's disease before full onset of symptoms and thus provide a window of advanced therapeutic opportunity.

4. ROLE OF GROUP I MGLUR INTERACTING PROTEINS IN INFLAMMATORY PAIN

Gp1 mGluRs modulate nociception in the spinal cord whereby their activation enhances pain sensitivity to certain stimuli whereas antagonism was shown to attenuate inflammatory pain [78]. Recent advances provide evidence that the Gp1 mGluR interacting protein Preso1 plays a critical role in mediating receptor functions in responses to inflammatory pain [79].

4.1. Preso1

Preso1 is a multidomain synaptic scaffold protein that interacts with mGlu1 and mGlu5 carboxyl terminal tails *via* a FERM domain and with Homer proteins (Homer1/3) *via* a conserved Homer binding site. Moreover, Preso1 constitutively associates with proline-directed kinases, including CDK5 and ERK1/2, an interaction by which it promotes phosphorylation of Gp1 mGluRs at the Homer-binding site leading to enhanced interaction of the receptors with Homer. Consistent with a function of Preso1 as molecular scaffold supporting dynamic formation of macromolecular complexes, mGlu5 phosphorylation and association with Homer are decreased in brain cortex and spinal cord of Preso1 null mice. Thus upon induction of CDK5 and ERK1/2 activation by Gp1 mGluR stimulation, Preso1 enables homologous desensitization of receptor signaling. Disruption of this feedback mechanism results in enhanced inflammatory pain response in Preso1 null mice, that can be counteracted by inhibition of mGlu5 signaling with the inverse agonist MPEP [79]. Whether Preso1 functions are broadly conserved at synapses in other brain regions is as yet unknown: however Preso1 scaffolding properties represent a potentially powerful mechanism for activity-dependent tuning of metabotropic signaling.

CONCLUSIONS

A major challenge to the development of mGluR-based therapies is presented by the fact that orthosteric agents, acting on the conserved extracellular glutamate-binding site, can cause unwanted adverse effects due to excessive receptor stimulation and profound desensitization. Recent advances in the development of allosteric compounds, such as NAMs and PAMs, have extended the repertoire of drugs that can be used to effectively modify mGluR activity. Conceivably, we could further expand the landscape of pharmacological targets in the receptors by regarding receptor-interacting proteins as endogenous allosteric ligands. If we consider the regions of mGluRs that engage in coupling to G proteins as the "active" sites, we can postulate that a change in the conformation and activity of mGluRs can be brought forth by binding of a protein to receptor domains other than the active site. By this definition mGluR-interacting proteins may be viewed as allosteric ligands endowed with the capacity to fine-tune receptor functional output. Characterization of the impact of interacting proteins on mGluR function and of the underlying mechanisms may allow the development of peptides or small molecule compounds - "signaling modulators" - that could compete or promote such interactions thereby selectively modifying mGluR activity.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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LIST OF ABBREVIATIONS

cKO = conditional knockout

DHPG = 3,5-Dihydroxyphenylglycine

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