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Noncanonical Metabotropic Glutamate Receptor 5 Signaling in Alzheimer's Disease

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Abstract

Metabotropic glutamate receptor 5 (mGluR5) is ubiquitously expressed in brain regions responsible for memory and learning. It plays a key role in modulating rapid changes in synaptic transmission and plasticity. mGluR5 supports long-term changes in synaptic strength by regulating the transcription and translation of essential synaptic proteins. β-Amyloid 42 (Aβ42) oligomers interact with a mGluR5/cellular prion protein (PrP^C) complex to disrupt physiological mGluR5 signal transduction. Aberrant mGluR5 signaling and associated synaptic failure are considered an emerging pathophysiological mechanism of Alzheimer's disease (AD). Therefore, mGluR5 represents an attractive therapeutic target for AD, and recent studies continue to validate the efficacy of various mGluR5 allosteric modulators in improving memory deficits and mitigating disease pathology. However, sex-specific differences in the pharmacology of mGluR5 and activation of noncanonical signaling downstream of the receptor suggest that its utility as a therapeutic target in female AD patients needs to be reconsidered.

INTRODUCTION

Glutamate is an excitatory neurotransmitter in the brain that activates both ionotropic and metabotropic glutamate receptors (mGluRs), which are both essential for regulating integrative brain function, synaptic transmission, and neuronal development (1–6). mGluRs are widely distributed at the cell surface in major brain regions and expressed in both neuronal and nonneuronal cells to modulate neuronal excitation and synaptic transmission, primarily through the activation of G protein–regulated signal transduction mechanisms (1–6). Like other G protein–coupled receptors (GPCRs), mGluR5 activation leads to changes in receptor conformational structure that trigger the exchange of guanosine diphosphate for guanosine triphosphate (GTP) on the α subunit of the heterotrimeric (α, β, and γ subunits) G protein complex (7). The activated α and βγ G protein subunits then act as signal transducers to modulate the function of numerous effector proteins, including enzymes, ion channels, and transcription factors (1–6). mGluRs belong to a unique GPCR subfamily (family C), which is characterized by a large extracellular Venus flytrap–like N terminus that harbors the orthosteric glutamate binding site, and exist as homodimers or heterodimers (1–4, 8). Ligand binding at the Venus flytrap domain induces a conformational change that is associated with a compact dimer interface that brings the cysteine-rich domains into close proximity. The interaction of the cysteine-rich domains with the second extracellular loops of the receptor triggers the rearrangement of the receptor 7-transmembrane domains to initiate signaling (7). The C termini of mGluRs play a key role in regulating the coupling to G protein(s), are alternatively spliced, and interact with intracellular signaling and scaffolding proteins (1–4, 6). mGluR signaling can also be modulated by allosteric ligands that bind to an allosteric site located within the receptor 7-transmembrane domains (9). There are eight known mGluRs that are divided into three subgroups based on sequence homology, pharmacology, and signal transduction pathways: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4/6/7/8) receptors (1, 3, 4, 8).

mGluR5 is localized in the olfactory bulb, cerebral cortex, hippocampus, striatum, and nucleus accumbens of the basal ganglia and is predominately localized in the postsynaptic terminals but is also found presynaptically and in the nuclear membrane (10–12). The versatile pharmacology and signal transduction mechanisms triggered by mGluR5 make it a very attractive pharmacological target for the treatment of neurodegenerative, neurological, and psychiatric diseases (13, 14). In this review, we focus on mGluR5 and discuss its key role in neuronal synaptic plasticity and function essential for learning and memory and how aberrant cellular signaling downstream of mGluR5 contributes, at least in part, to the pathophysiology of Alzheimer's disease (AD).

MGLUR5 CANONICAL SIGNALING

mGluR5 exists as a homodimer and is coupled via $G\alpha_{q/11}$ to phospholipase Cβ (PLCβ), which hydrolyzes plasma membrane phosphoinositides into two classical secondary messenger molecules, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (1–6). This canonical signal transduction pathway leads to Ca^{2+} mobilization from intracellular stores in response to IP_3 binding to the IP_3 receptor, as well as the activation of protein kinase C (PKC) by both DAG and Ca^{2+}. Intracellular Ca^{2+} and activated PKC then modulate the function of a variety of substrates such as protein kinases, receptors, and ion channels important in the regulation of key brain functions, including memory and learning. In general, the termination of GPCR signaling is initiated by phosphorylation mediated by second messenger–dependent protein kinases activated downstream of the receptors and G protein–coupled receptor kinases (GRKs), which in combination with receptor activation facilitate β-arrestin recruitment to uncouple the receptor from G proteins and initiate receptor endocytosis (4, 6). Group I mGluR desensitization is distinct from other GPCRs, as the catalytic activity of GRK2 is not required for group I mGluR desensitization. Instead GRK2

uncouples mGluR5 from $G\alpha_{q/11}$ in a phosphorylation-independent manner via its amino terminal GRK2 regulator of G protein signaling homology (RH) domain (4). Additionally, PKC activated downstream of mGluR5 mediates a classical feedback phosphorylation of the first and second intracellular loop and the carboxyl-terminal domains of mGluR5 to terminate signaling (15).

MGLUR5 NONCANONICAL SIGNALING

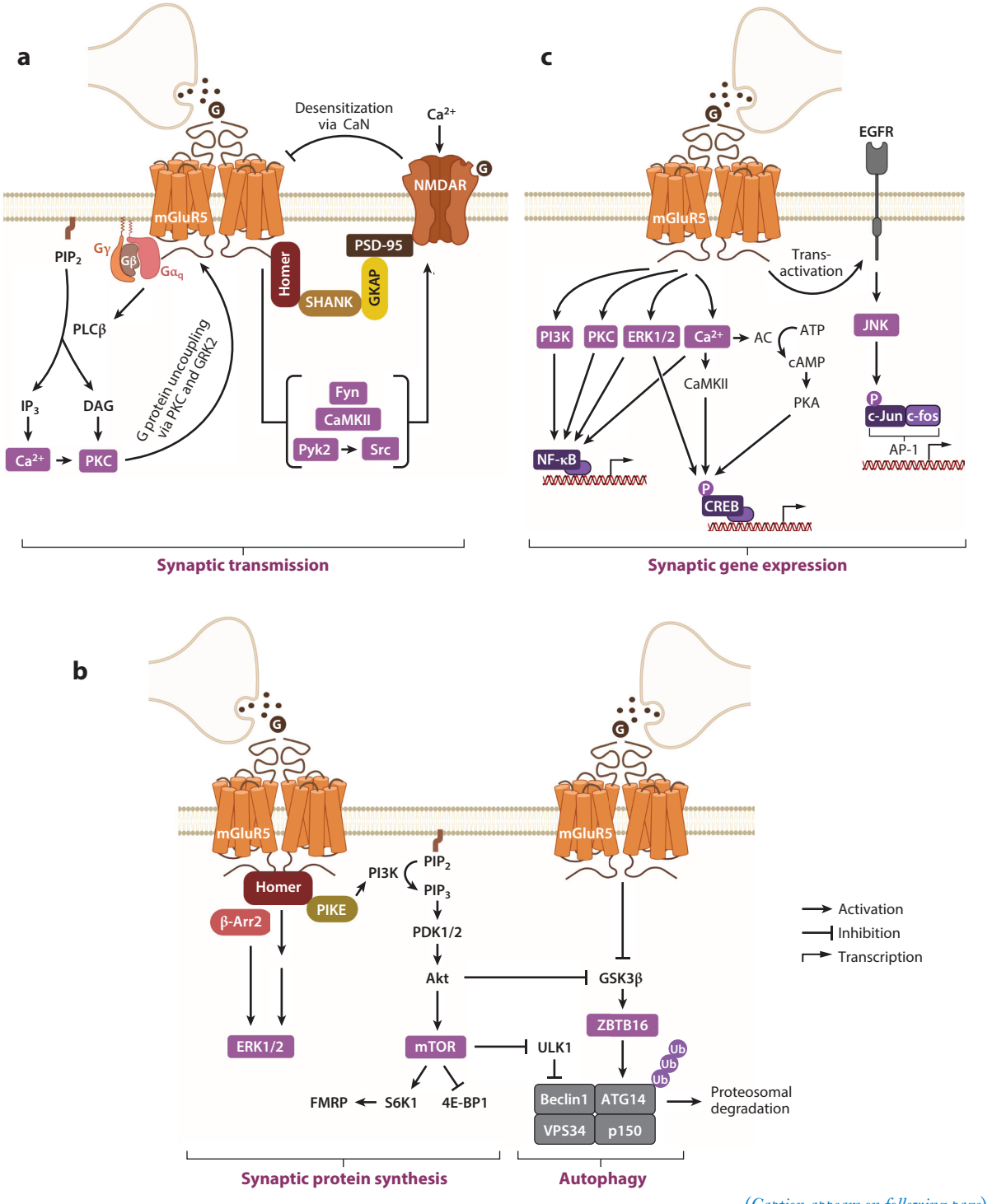
mGluR5-Mediated Activation of ERK1/2 Signaling

mGluR5 is coupled to a number of noncanonical signaling partners that orchestrate a variety of signaling events required for synaptic plasticity and neuronal adaptation. Extracellular signal-regulated kinase 1/2 (ERK1/2) is a critical downstream mediator of mGluR5-mediated synaptic plasticity and information storage by regulating gene transcription, messenger RNA (mRNA) translation, and rapid synaptic protein synthesis (16–19). Interestingly, mGluR5-mediated ERK1/2 activation in neurons occurs as the consequence of mechanisms that are insensitive to PKC and PLC inhibitors (20, 21). Specifically, group I mGluRs have been shown to utilize β-arrestin 2 to activate ERK1/2 and strengthen mGluR-dependent synaptic plasticity (18, 22). In addition to regulating GPCR desensitization and signaling, β-arrestins also function as scaffold proteins that recruit components of cytoplasmic signaling pathways such as ERK1/2 (6, 23). In fact, mGluR5-mediated activation of ERK1/2, synaptic protein synthesis, and long-term potentiation (LTP) are abolished in β-arrestin 2 knockout mice in the absence of alterations in $G\alpha_{q/11}$/PLCβ-mediated Ca^{2+} release (18, 22). However, it remains less clear whether the plasma membrane recruitment of β-arrestins to mGluR5 is required for β-arrestin-mediated ERK1/2 activation, similar to what is observed for most other $G\alpha_{q/11}$-coupled receptors (23).

Homer proteins represent a group of adaptor proteins that link mGluR5 to other cellular partners, such as ERK1/2, to regulate a variety of signaling cascades (24, 25). The N terminus of Homer proteins binds to a PP-x-FR motif in the distal part of the mGluR5 intracellular C-terminal tail and links the receptor to a variety of signaling partners. The disruption of Homer1 interactions with mGluR5 using either cell-permeable Tat-fusion peptides or Homer1b/c small interfering RNAs abolishes mGluR5-stimulated ERK1/2 phosphorylation (26). Although the role of Homer and β-arrestins in regulating mGluR5 signaling has been investigated in fragile X syndrome mice, the relative contribution of both adaptor proteins to mGluR5-activated ERK1/2 signaling in neurodegenerative diseases remains largely unclear (18, 27) (**Figure 1**).

mGluR5-Mediated Activation of PI3K/Akt/mTOR Signaling

Activation of phosphoinositide 3 kinase (PI3K)/mammalian target of rapamycin (mTOR) allows mGluR5 to promote rapid protein translation required for the induction of LTP (19, 28, 29). Pharmacological activation of group I mGluRs results in phosphorylation of mTOR and the mTOR downstream effectors, ribosomal protein S6 kinase-1 (S6K1) and eukaryotic initiation factor 4E–binding protein 1 (4E-BP1), to support mRNA translation (28, 30). This process is initiated at the receptor level by a mGluR5 scaffolded complex that includes Homer and the GTPase phosphoinositide 3 kinase enhancers (PIKEs). Upon agonist activation, mGluR5 increases Homer-PIKE association, leading to increased binding of PIKE to the p85 subunit of PI3K, and thereby enhances PI3K kinase activity (24, 31). mTOR signaling is initiated when activated PI3K promotes conversion of phosphatidylinositol-4,5-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PIP_3 activates phosphoinositide-dependent kinase 1/2 (PDK1/2), which in turn directly phosphorylates protein kinase B (Akt), leading to the activation of the mTOR signaling complex (32, 33). Disruption of the mGluR5/Homer/PIKE complex impairs both PI3K/mTOR signaling and protein synthesis required for synaptic plasticity (26, 30).



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Canonical and noncanonical metabotropic glutamate receptor 5 (mGluR5) signaling. (*a*) Glutamate binds to mGluR5 dimers and activates $G\alpha_q$ to trigger phospholipase β (PLCβ) to lyse membrane phosphatidylinositol 4,5-bisphosphate (PIP_2) and generate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 triggers the release of Ca^{2+} from intracellular stores and along with DAG activates protein kinase C (PKC). Receptor signaling is terminated when the G protein is uncoupled from the receptor by PKC and G protein–coupled receptor kinase 2 (GRK2). mGluR5 physically associates with *N*-methyl-D-aspartic acid receptor (NMDAR) via a complex involving Homer, SH3 and multiple ankyrin repeat domains (SHANK) protein, guanylate kinase-associated protein (GKAP), and postsynaptic density-95 (PSD-95). mGluR5 activates Fyn, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and Pyk2, which then activates the Src kinase that facilitates Ca^{2+} entry via NMDAR. Ca^{2+} entering via NMDAR activates calcineurin (CaN), which reduces the desensitization of mGluR5. mGluR5 and NMDAR-dependent signaling are both essential for synaptic transmission. (*b*) Homer and β-arrestin 2 (β-Arr2) are essential for activation of mGluR5-mediated extracellular signal-regulated kinase 1/2 (ERK1/2), which is required for synaptic protein synthesis. Glutamate increases Homer phosphoinositide 3 kinase enhancer (PIKE) association, leading to enhanced phosphoinositide 3 kinase (PI3K) activity. PI3K converts membrane PIP_2 to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3). PIP_3 then activates phosphoinositide-dependent kinase 1/2 (PDK1/2), which directly phosphorylates protein kinase B (Akt), leading to the activation of the mammalian target of rapamycin (mTOR) signaling complex. mTOR can activate ribosomal protein S6 kinase 1 (S6K1) and inhibit eukaryotic initiation factor 4E–binding protein 1 (4E-BP1) to support synaptic protein synthesis. S6K1 can also phosphorylate and activate fragile X mental retardation protein (FMRP) to modulate protein synthesis. mTOR can also phosphorylate unc-51-like kinase 1 (ULK1) and suppress its catalytic activity to abolish the ULK1-mediated Beclin1 phosphorylation required for autophagy induction by proautophagy vacuolar protein sorting 34 (VPS34) complexes. mGluR5 directly, or via Akt, inhibits glycogen synthesis kinase 3β (GSK3β)-mediated phosphorylation and degradation of zinc finger and BTB domain–containing protein 16 (ZBTB16). This enhances the ubiquitination and proteasomal degradation of autophagy-related 14 (ATG14) and disrupts the VPS34 complex to inhibit autophagic flux. (*c*) Ca^{2+} activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) that phosphorylates the transcription factor cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB). Ca^{2+} activates adenyl cyclase (AC) to convert ATP to cAMP and activate protein kinase A (PKA), which can then activate CREB. ERK1/2 can also directly phosphorylate and activate CREB. mGluR5-mediated activation of PI3K, ERK1/2, and PKC can promote the translocation of the nuclear factor κB (NF-κB) to the nucleus. Transactivation of membrane epidermal growth factor receptors (EGFRs) by mGluR5 activates c-Jun N-terminal kinase (JNK), which phosphorylates c-Jun, a component of the transcriptional activator protein-1 (AP-1), along with c-fos. CREB, NF-κB, and AP-1 regulate synaptic gene expression. Figure adapted from images created using BioRender.com.

Of special interest is the fragile X mental retardation protein (FMRP), an essential RNA binding protein that suppresses protein translation by stalling ribosomes, which contributes to the signal cascade coupling mGluR5 to mTOR-dependent protein translation. Specifically, activated S6K can phosphorylate FMRP at a serine residue required for RNA binding and therefore inhibit protein translation (34) (**Figure 1**).

The mTOR pathway is also a master regulator of autophagy, a catabolic process that plays a key role in degrading and recycling cellular cargoes via lysosomal degradation when a cell is challenged (35). The ULK1 autophagy complex is regulated by mTOR and is required for initiation of autophagosome formation (36). The complex consists of ULK1, autophagy-related protein 13 (ATG13), focal adhesion kinase family interacting protein of 200 kDa (FIP200), and autophagy-related protein 101 (ATG101) (37). Phosphorylation of ULK1 at S757 by mTOR complex suppresses its catalytic activity and abolishes ULK1-mediated Beclin1 phosphorylation, which is required for autophagy induction and maturation by proautophagy vacuolar protein sorting 34 (VPS34) complexes (36, 38, 39). In fact, enhanced mGluR5 signaling is associated with impaired unc-51-like kinase 1 (ULK1)-dependent autophagy in mouse models of AD and Huntington's disease (HD) (40, 41). Thus, it is reasonable to predict that mGluR5-dependent mTOR signaling will also regulate autophagy along with protein translation to ensure an optimal availability of synaptic proteins by modulating protein synthesis and degradation machineries (**Figure 1**).

mGluR5-Mediated Activation of ZBTB16 Signaling

Another newly discovered mechanism by which mGluR5 can regulate autophagy in neurons is the zinc finger and BTB domain–containing protein 16 (ZBTB16)-dependent pathway (40–42).

ZBTB16 is a key element in multiple cullin-RING-based E3 ubiquitin–protein ligase complexes and is phosphorylated in the center domain at S184/T282 by glycogen synthesis kinase 3β (GSK3β) (43). The phosphorylation of ZBTB16 triggers its autoubiquitination and lysosomal degradation, leading to a reduction in the ubiquitination activity of the E3 ubiquitin–protein ligase complex. Moreover, GSK3β-mediated phosphorylation of S184/T282 also disrupts the binding of ZBTB16 to the autophagy-related 14 (ATG14) and thereby reduces the ubiquitination and degradation of ATG14, a core component in the vacuolar protein sorting 34 (VPS34) autophagic complex initiating autophagosome formation (39, 43). Therefore, GSK3β plays a crucial role in orchestrating the expression and function of ZBTB16 and eventually the ubiquitination of key autophagy adaptor proteins. Recently, mGluR5 has been found to be coupled to GSK3β to regulate the proteasomal degradation of ZBTB16 and ATG14. Specifically, mGluR5 overactivation in mouse models of AD and HD is associated with increased phospho-GSK3β at S9, resulting in the inhibition of its activity, which subsequently leads to the accumulation of ZBTB16 and suppression of autophagy (40–42). While it remains less clear how mGluR5 directly regulates GSK3β phosphorylation, the most plausible candidate is PI3K. As discussed earlier, the PI3K/Akt pathway is also activated by mGluR5, and Akt is known to phosphorylate GSK3β at S9 to inhibit its catalytic activity (44, 45). Therefore, mGluR5-mediated activation of the PI3K/Akt pathway inhibits autophagy via two convergent signaling mechanisms, the mTOR- and ZBTB16-dependent mechanisms. Interestingly, β-arrestin 2 forms a signaling complex with Akt downstream of the D2 dopamine receptor, suggesting that β-arrestin 2 may also contribute to the regulation of this novel autophagy pathway (45, 46). Thus, mGluR5-regulated autophagy plays a crucial role in balancing the levels of synaptic proteins required to support plasticity changes, as well as clearing toxic cargos from synapses (**Figure 1**).

mGluR5-Mediated Regulation of NMDAR Function

The *N*-methyl-D-aspartic acid receptor (NMDAR) is a ligand-gated ion channel that enhances Ca^{2+} permeability in response to glutamate binding and membrane depolarization at excitatory synapses and plays a pivotal role in synaptic function and plasticity (47). The interaction between mGluR5 and NMDARs was first described almost three decades ago and is known to be crucial for neuronal excitability and LTP (48–51). A physical link exists between NMDAR and mGluR5 that involves Homer, SH3 and multiple ankyrin repeat domains (SHANK), guanylate kinase-associated protein (GKAP), and postsynaptic density-95 (PSD-95) (25). mGluR5 activation potentiates NMDAR-mediated responses in a $G\alpha_{q/11}$-dependent manner via a signal transduction cascade that involves the sequential activation of PKC and Src protein tyrosine kinase (1, 47, 51, 52). The mechanism by which mGluR5 activates Src involves Pyk2, a focal adhesion tyrosine kinase, which is activated by PKC and Ca^{2+}, and Pyk2 can directly interact with group I mGluRs (53). Pyk2 is abundantly localized within the postsynaptic density and is also a component of the NMDAR complex, and the activation of Pyk2 facilitates the binding and the activation of Src to potentiate NMDAR currents (54, 55). Fyn is another Src tyrosine kinase family member that modulates NMDAR activity in response to mGluR5 activation via phosphorylation of the NR2B subunit of the NMDAR (56, 57). Thus, it is evident that the potentiation of NMDAR currents following mGluR5 activation can be initiated by canonical $G\alpha_{q/11}$-coupled signaling and involves the Pyk2/Src/NMDAR complex (**Figure 1**).

Ca^{2+}/calmodulin-dependent kinase IIα (CamKIIα) is reported to bind directly to the intracellular C-terminal tail and the second intracellular loop of mGluR5 (58, 59). mGluR5-stimulated Ca^{2+} release triggers dissociation of CamKIIα from the mGluR5 complex that can then associate with and phosphorylate NR2B to potentiate NMDAR current. The dissociation of CamKIIα is driven by the ability of Ca^{2+}-bound calmodulin to interact with mGluR5 at a region

overlapping with the CaMKIIα binding site. Thus, Ca^{2+}-bound calmodulin can competitively inhibit CaMKIIα binding to mGluR5. This positive coupling between mGluR5 and NMDAR is important for the regulation of synaptic transmission (59). Additionally, the activation of NMDAR also reduces mGluR5 desensitization to further potentiate mGluR5 signaling. This feedforward mechanism is mediated by protein phosphatase 2B (PP2B)/calcineurin (CaN) that is activated by Ca^{2+} entering via NMDARs. Specifically, CaN directly dephosphorylates mGluR5 at PKC phosphorylation sites required for receptor desensitization and thereby enhances mGluR5 signaling (60) (**Figure 1**).

mGluR5-Mediated Regulation of Gene Expression

Along with the ability of mGluR5 to induce synaptic plastic changes via membrane-bound and intracellular mechanisms, mGluR5 can also regulate gene transcription to support long-term changes in synaptic function and neuronal differentiation (61, 62). mGluR5 regulates synaptic protein expression via three key transcription factors, cyclic adenosine monophosphate (cAMP)-responsive element binding protein (CREB), nuclear factor κB (NF-κB), and c-Jun. CREB regulates the expression of transcription factors essential for synaptic plasticity and memory (63). CREB target genes include the immediate early genes: *Arc*, *c-fos*, and *erg1* (61). Arc is a postsynaptic density enriched protein that contributes to multiple forms of neuronal plasticity such as long-term depression (LTD) (64). c-fos is a transcription factor, and its role in synaptic plasticity has been attributed to its ability to tightly regulate the expression of many genes, including brain-derived neurotrophic factor, which promotes synaptic efficacy required for learning and memory (65, 66). Erg1 is the most widely studied member of the Erg family and is key to modulating the transcriptome required for the transition from short- to long-term synaptic plasticity and the consolidation of long-term memory (67). Pharmacological activation of extracellular and intracellular mGluR5 triggers a rapid and transient increase in CREB phosphorylation at S133 via Ca^{2+}/calmodulin-dependent activation of adenyl cyclase 1, CaMKII, and ERK1/2, resulting in parallel induction in *c-fos*, *erg1*, and *Arc* expression (61, 63, 68–72).

NF-κB is a member of a family of dimeric transcription factors expressed in both neuronal and glial cells. It exists in a dormant state in the cell cytoplasm bound to the inhibitor κB (IκB) that prevents the nuclear translocation and signaling of the NF-κB complex. When the pathway is activated, the NF-κB dimer is released from the IκB complex to translocate into the nucleus, where it interacts with the κB DNA binding sequences (73). NF-κB regulates the transcription of a variety of genes involved in myriad neuronal functions, including inflammation, apoptosis, and LTP-mediated synaptic plasticity (73, 74). mGluR5 activation enhances both NF-κB nuclear accumulation and DNA binding, an effect that is dependent on PI3K, PKC, and ERK1/2 signaling (75, 76). It is likely that Ca^{2+}, PI3K, PKC, and ERK1/2 activated downstream of mGluR5 enhance the activity of the IκB kinase (IKK) complex, leading to the phosphorylation and degradation of IκB to allow the nuclear translocation of NF-κB (77, 78).

c-Jun is a component of the transcriptional activator protein AP-1 along with c-fos and is activated by c-Jun N-terminal kinase (JNK). c-Jun is phosphorylated by JNK on its N-terminal transactivation domain to enhance the transcriptional capacity of AP-1 and the expression of genes required for synaptic plasticity and function (79, 80). mGluR5 activates JNK via a mechanism that requires the transactivation of the epidermal growth factor receptor (EGFR) (80). Moreover, JNK can directly regulate synaptic strength by phosphorylating synaptic proteins such as PSD-95 to adjust its synaptic availability (81). Taken together, it is evident that mGluR5-mediated regulation of the transcription factors CREB, NF-κB, and c-Jun is essential for synaptic plasticity and can be triggered by G protein–dependent and independent mechanisms (**Figure 1**).

ABERRANT MGLUR5 SIGNALING IN ALZHEIMER'S DISEASE

AD is an age-related progressive neurodegenerative disease that is the leading cause of dementia and is characterized by memory loss and cognitive impairments that are associated with both profound behavioral and personality changes. The neuropathological hallmarks of AD are the presence of extracellular senile β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau (82, 83). As a consequence of the ubiquitous expression of mGluR5 in all brain regions considered to be responsible for memory and learning, along with its key role in regulating neuronal transmission and synaptic strength, aberrant mGluR5 signaling is suggested to be implicated in mediating multiple aspects of the cognitive deficits associated with AD (84–86). A number of studies have reported conflicting results regarding changes in mGluR5 expression using positron emission tomography imaging techniques in both AD patients and mouse models (87–91). While the significance of these opposing observations remains unclear, it is possible that there is a biphasic change in mGluR5 expression along the disease course that warrants performing longitudinal studies in different models of the disease. It is also important to consider changes in the cell surface of the receptor when examining the significance of altered mGluR5 expression and pharmacology in AD, as an increase in mGluR5 cell surface expression was detected in two AD mouse models without a change in total expression (41, 92).

Soluble Aβ42 oligomers are 39- to 43–amino acid–long peptide precursors of Aβ42 plaques that are formed by the sequential proteolytic cleavage of the membrane-anchored glycoprotein amyloid precursor protein (APP) by β- and γ-secretases. Physiologically, APP is cleaved by the α-secretase pathway to produce soluble APPα, which is neurotrophic (93, 94). Aβ42 oligomers are also normally found in the brain as a soluble protein at low picomolar levels and are proposed to support synaptic plasticity, neurogenesis, and neuronal survival (95). However, pathological overproduction of Aβ42 (nanomolar range) triggers its aggregation and associated neurotoxicity, and thus Aβ42 aggregates represent one of the potential primary causes of AD (96–98). Aβ42-mediated synaptic dysfunction is primarily attributed to impairment in both LTP and LTD and in vitro, ex vivo, and in vivo data from both AD rodent models and patients suggest that soluble oligomeric Aβ42 represents the most synaptotoxic form of β-amyloid (97, 98).

Tau is a microtubule-associated protein predominantly found in neuronal axons, where it plays a key role in maintaining the stability of microtubules. Physiologically, tau phosphorylation reduces its affinity for microtubules and supports its dynamic properties essential for shuttling cellular cargos that support neuronal transmission (99). However, pathological hyperphosphorylation of tau triggers its aggregation, which is associated with gain of toxic functions. Specifically, hyperphosphorylated tau impairs the anterograde axonal transport of cellular cargoes such as mitochondria (100). Moreover, hyperphosphorylated tau alters chromatin structure and destabilizes microtubular structure, resulting in reduced neuronal excitability, and ultimately causes axonal degeneration (101). Next, we discuss the evidence linking aberrant mGluR5 signaling to Aβ42 and hyperphosphorylated tau and its contribution to synaptic dysfunction in AD (**Figure 2**).

mGluR5/PrP^C/Aβ42 Signaling Complex

There is mounting evidence that Aβ42 signaling via mGluR5 leads to the loss of synaptic transmission in AD, making mGluR5 a potential therapeutic target for the treatment of AD. Renner et al. (102) have reported that Aβ42 binds to mGluR5 to reduce its lateral diffusion and enhances receptor clustering and localization at the synapses. This results in enhanced mGluR5-specific signaling that leads to elevated intracellular Ca^{2+} and neuronal hyperexcitability, causing synaptic loss. The increase in excitotoxic cell death of neurons that is observed following mGluR5 activation may well be due to localized elevations in intracellular Ca^{2+} at the synapse, resulting in

mGluR5-mediated potentiation of NMDAR function (103). These findings are further supported by the study by Rammes et al. (104) showing that antagonists for either NR2B or mGluR5 can restore LTP and prevent Aβ42-induced synaptic toxicity. Aβ42 also interferes with neuronal Ca^{2+} homeostasis by impairing store-operated Ca^{2+} entry, which is rescued by pharmacological blockade of mGluR5 (105, 106).

The molecular nature of the interaction between Aβ42 and mGluR5 may be best explained by studies performed by the Strittmatter laboratory (56, 107), whose work provides convincing

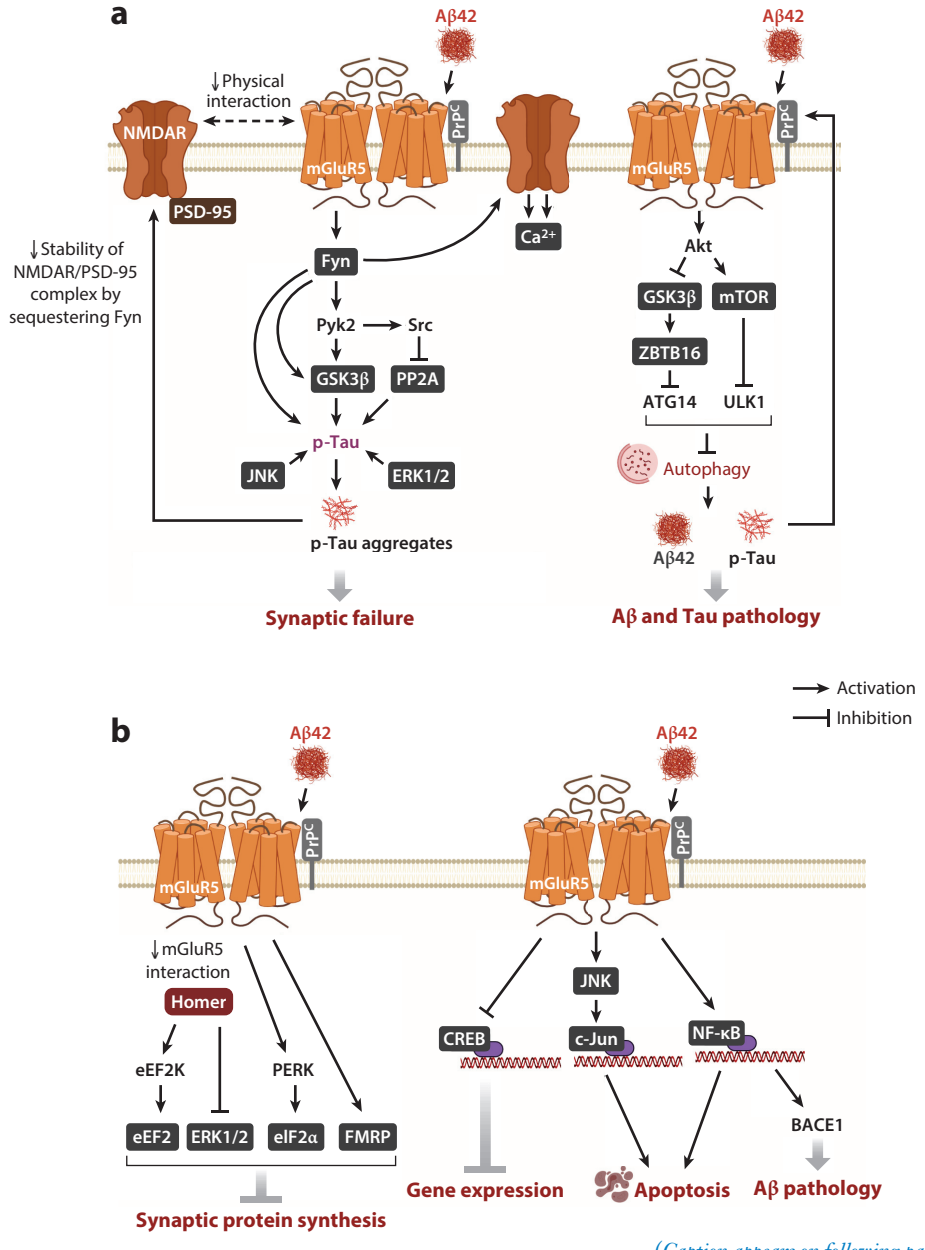


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Figure 2 (*Figure appears on preceding page*)

Pathological metabotropic glutamate receptor 5 (mGluR5) signaling triggered by β-amyloid 42 (Aβ42). (*a*) Aβ42 binds to mGluR5 in the presence of cellular prion protein (PrP^C) to trigger the pathological signaling of mGluR5. Aβ42 via mGluR5 activates Fyn, which can then stimulate Pyk2 or both Pyk2 and Fyn to induce tyrosine phosphorylation of glycogen synthesis kinase 3β (GSK3β), which phosphorylates tau, leading to tau aggregation. Pyk2 can activate the Src kinase that inhibits protein phosphatase 2 (PP2A), contributing to accumulation of p-tau. Fyn can directly phosphorylate tau and *N*-methyl-D-aspartic acid receptor (NMDAR) to potentiate tau pathology and Ca^{2+} entry, respectively. p-tau sequesters Fyn and reduces the stability of the NMDAR/postsynaptic density-95 (PSD-95) complex, possibly disrupting the physical interaction between mGluR5 and NMDAR and contributing to synaptic failure. Activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) by Aβ42 can contribute to tau phosphorylation. This altered signaling of mGluR5 and NMDAR disrupts synaptic transmission and leads to synaptic failure. Aβ42 may also enhance protein kinase B (Akt) activity, leading to activation of mammalian target of rapamycin (mTOR), which induces the inhibitory phosphorylation of unc-51-like kinase 1 (ULK1) and suppresses autophagy. Akt can also inhibit GSK3β-mediated phosphorylation and degradation of zinc finger and BTB domain–containing protein 16 (ZBTB16). This enhances the proteasomal degradation of autophagy-related 14 (ATG14) and inhibits autophagic flux. Inhibition of autophagy enhances the accumulation of Aβ42 and p-tau oligomers and exacerbates pathology. p-tau can bind to PrP^C similar to Aβ42 and may contribute to the pathological signaling of mGluR5. (*b*) Aβ42 disrupts Homer interactions with the receptor, leading to increased eukaryotic elongation factor 2 (eEF2) phosphorylation via eukaryotic elongation factor 2 kinase (eEF2K) and impaired ERK1/2 phosphorylation. Aβ42 binding to mGluR5 enhances the phosphorylation of eukaryotic initiation factor 2α (eIF2α) via RNA-like endoplasmic reticulum kinase (PERK) and increases fragile X mental retardation protein (FMRP) expression, which, along with altered eEF2 and ERK1/2 signaling, impairs synaptic protein translation. Aβ42 impairs CREB and JNK-dependent gene transcription and enhances the expression of proapoptotic genes downstream of c-Jun and nuclear factor κB (NF-κB). Aβ42 activates β-secretase 1 (BACE1) in a NF-κB-dependent manner to exacerbate Aβ pathology. Figure adapted from images created using BioRender.com.

evidence that Aβ42 utilizes both mGluR5 and the membrane-anchored glycoprotein cellular prion protein (PrP^C) to mediate pathological signaling. This ground-breaking work shows that Aβ42 forms a complex with PrP^C and this Aβ42/PrP^C complex utilizes mGluR5 as a receptor to signal via Fyn kinase (108, 109). This observation is further supported by binding studies using both soluble Aβ42 oligomers obtained from human AD brains that exhibit high affinity for PrP^C and antibodies directed to antagonize the primary binding site for Aβ42 on PrP^C (110, 111). Thus, it is clear from these studies that the Aβ42/PrP^C/mGluR5 complex adopts a conformation within the plasma membrane that not only elicits pathological signaling but also disrupts physiological glutamate signaling (112) (**Figure 2**).

Aβ42-Dependent mGluR5 Signaling via Fyn and CaMKII

The Aβ42/PrP^C/mGluR5 complex triggers multiple pathological signaling cascades, but the activation of the tyrosine kinase Fyn plays a central role in Aβ42-mediated synaptic toxicity (56, 109). Specifically, Aβ42-mediated activation of Fyn drives the tyrosine phosphorylation of the NR2B subunit of NMDA receptors, leading to increased surface expression and impaired synaptic transmission (56, 109). Moreover, Aβ42-mediated activation of Fyn represents the plausible link between Aβ42 and tau pathologies, and the relationship between tau and Fyn is bidirectional. Specifically, Fyn physically associates and directly phosphorylates tau at multiple tyrosine residues, leading to tauopathy (113). Additionally, Fyn and Pyk2 directly interact with mGluR5, and exposure to Aβ42 activates Fyn to trigger Pyk2 activity. Both Fyn and Pyk2 can phosphorylate GSK3β, a key kinase in tauopathy, at Y216, leading to its activation and consequently tau hyperphosphorylation (53, 114–116). The association between PrP^C and Pyk2 in brains from $APP/PS1^+$ mice and AD patients has been reported to be reduced, and thus it is possible that

Aβ42 impairs the mGluR5-Pyk2 interaction that facilitates its aberrant signaling upon Fyn activation (112). Interestingly, functional tau is required for synaptic targeting of Fyn to the NMDAR, and Fyn-mediated phosphorylation of NR2B facilitates the interaction of NMDARs with PSD-95, thereby increasing the stability of NMDARs within the postsynaptic density by inhibiting NMDAR endocytosis (117). Hyperphosphorylated tau has a higher binding affinity for Fyn and reduces postsynaptic delivery of Fyn, impairing the stability of NMDAR/PSD-95 complexes, and possibly disrupts the physical interaction with mGluR5, contributing to synaptic dysfunction (118).

The potent inhibition of LTP by Aβ42 may also be due in part to the inability of CaMKII to dissociate from mGluR5 upon Aβ42 binding to the mGluR5/PrP^C complex. Specifically, Aβ42 treatment enhances the association between CaMKII and mGluR5, thereby promoting CaMKII activity (58, 112). CaMKII is activated by acute Aβ42 stimulation but becomes deactivated following prolonged Aβ42 exposure (112). Given the crucial role of CaMKII in regulating multiple pathways required for synaptic transmission, including NMDAR signaling and gene expression, Aβ42-mediated impairment in CaMKII signaling via mGluR5 likely plays a crucial role in synaptic failure in AD (**Figure 2**).

Aβ42- and mGluR5-Dependent Gene Transcription and Protein Translation

At the level of gene transcription, Aβ42 reduces CREB phosphorylation, resulting in impaired CREB-mediated gene transcription and synaptic transmission (119). Moreover, Aβ42-mediated inhibition of LTP induction involves pathological activation of JNK, which impairs c-Jun-dependent gene expression, while also potentially inducing a JNK-mediated inflammatory response and apoptosis (80, 120). Aβ42 can induce proinflammatory and apoptotic genes as well as β-secretase 1 activity in a NF-κB-dependent manner (78, 121, 122). Because mGluR5 functions as a receptor for Aβ42, it is likely that the abovementioned alterations in gene transcription are mediated at least in part by mGluR5.

In addition to gene transcription, mGluR5 also regulates synaptic protein synthesis at the translational level. Specifically, the eukaryotic elongation factor 2 kinase (eEF2K) is a CaMK that binds mGluR5 via Homer and dissociates following mGluR5 activation to phosphorylate eEF2 at T56, which inhibits the elongation step of protein translation (123). Aβ42 impairs synaptic plasticity by promoting eukaryotic elongation factor 2 (eEF2) phosphorylation in the hippocampus of $APP/PS1^+$ mice and postmortem AD patient brains (124, 125). The enhanced activity of eEF2 kinase may be attributed to a reduction in Homer interactions with mGluR5/Aβ42/PrP^C protein complex (125). It is likely that a loss of Homer binding to mGluR5 impairs other Homer-dependent signaling mechanisms such as ERK1/2, PI3K, and NMDAR signaling. Activation of mGluR5 also enhances the phosphorylation of eukaryotic initiation factor 2α (eIF2α) via RNA-like endoplasmic reticulum kinase (PERK) and causes a decrease in translation initiation (126). Aβ42-activated mGluR5 signaling increases eIF2α phosphorylation, resulting in a general inhibition of protein synthesis that leads to severe impairment of synaptic plasticity and memory function. The suppression of eIF2α kinase activity, either pharmacologically or genetically, improves synaptic plasticity and memory deficits in AD mice (126–128). Moreover, overexpression of FMRP, which couples mGluR5 to protein translation, is detected in APPswe/PS1ΔE9 mice, and genetic deletion of mGluR5 both normalizes FMRP levels and improves cognitive function (92). This suggests that Aβ42 enhances the expression of FMRP to stall the translation of proteins required for long-term synaptic changes in a mGluR5-dependent manner. However, the molecular mechanism underlying this increase in FMRP expression remains unknown (**Figure 2**).

Aβ42- and mGluR5-Dependent Regulation of Autophagy

Genetic deletion and pharmacological inhibition of mGluR5 using a selective negative allosteric modulator (NAM) rescues learning deficits and induces autophagic clearance of Aβ aggregates in male APPswe/PS1ΔE9 AD mice (92, 129). These studies reveal that Aβ42 inhibits mGluR5-regulated autophagy via ZBTB16 and mTOR-dependent pathways. Specifically, Aβ42 activation of the PrP^C/mGluR5 complex triggers the phosphorylation (inactivation) of GSK3β, leading to the accumulation of ZBTB16 and inhibition of autophagic clearance of Aβ42 oligomers (33, 40–42, 130). Moreover, Aβ42 via mGluR5 also activates the PI3K/Akt/mTOR pathway, resulting in reduced ULK1 activity and impaired autophagy (41, 42). Aβ42-mediated phosphorylation of GSK3β via mGluR5 is likely mediated by the PI3K/Akt pathway and may provide a plausible link between ZBTB16 and mTOR-dependent autophagy downstream of mGluR5 (44, 98, 131). This inhibition of autophagic clearance of Aβ42 by mGluR5 may represent a key step in the pathophysiology of AD, resulting in the further accumulation of Aβ42 and potentially other synaptotoxic proteins that further exacerbate synaptic failure (**Figure 2**).

Tau and mGluR5 Signaling

The molecular interplay between hyperphosphorylated tau and pathological mGluR5 signaling is not well investigated. However, it is evident that many of the signaling mechanisms leading to tauopathy in AD can be initiated by Aβ42-mediated activation of mGluR5, and both pathological tau and Aβ42 oligomers act together to impair neuronal circuits and disrupt synaptic transmission (132). Interestingly, soluble forms of hyperphosphorylated tau can translocate across the plasma membrane either via sulfated proteoglycans or extracellular vesicles, resulting in the spread of the tau pathology (132, 133). Moreover, soluble forms of hyperphosphorylated tau can interact with PrP^C similar to Aβ42 and trigger pathological signaling and synaptic dysfunction, possibly in a mGluR5-dependent manner (134). It is noteworthy that abnormal activation of Src downstream of mGluR5 is associated with an increase in the inhibitory phosphorylation of PP2A, thereby reducing tau dephosphorylation (135). Therefore, it is possible that Aβ42-stimulated, mGluR5-dependent Src activation contributes to hyperphosphorylated tau accumulation and synaptic failure. Additionally, Fyn and Pyk2 can elicit tau hyperphosphorylation mediated by GSK3β in response to mGluR5 activation by Aβ42 (98, 115, 116, 119, 136). Aβ42 also activates mGluR5 to stimulate both ERK1/2 and JNK, which are also known tau kinases (58, 80, 119, 137). Therefore, mGluR5 may play a central role in regulating both Aβ42 and tau pathological signaling (**Figure 2**).

MGLUR5 AS A THERAPEUTIC TARGET FOR ALZHEIMER'S DISEASE

The pathology of AD was first described more than 100 years ago, and despite the extensive preclinical and clinical research efforts, no US Food and Drug Administration–approved drugs exhibit robust disease-modifying properties (138, 139). However, mGluR5 has represented an attractive target for AD therapeutics for at least two reasons. First, unlike ionotropic glutamate receptors, targeting mGluR5 can fine-tune glutamate signaling without impairing fast glutaminergic synaptic transmission. Second, mGluR5 is a key receptor for Aβ42 and possibly hyperphosphorylated tau, and therefore targeting mGluR5 could effectively interrupt the pathological signaling triggered by Aβ42 and tau to halt disease progression. A seemingly attractive approach for targeting mGluR5 is the use of modulators that target the allosteric site of the receptor, a topographically distinct site from the orthosteric glutamate binding site, to either enhance or inhibit receptor signaling. Along with their superior selectivity, allosteric modulators (AMs) possess a versatile pharmacokinetic and pharmacodynamic profile that can further enhance their therapeutic applicability (140). AMs of mGluR5 are subdivided into positive allosteric modulators (PAMs), NAMs, and

silent allosteric modulators (SAMs). PAMs and NAMs can respectively enhance and reduce the efficacy of glutamate-induced receptor activation and Ca^{2+} mobilization. In contrast, SAMs do not alter glutamate-induced Ca^{2+} signaling or mobilization (141). The mGluR5 SAM, BMS-984923, has been shown to reduce pathological signaling induced by Aβ42 binding to mGluR5 binding, while maintaining physiological glutamate signaling. However, BMS-984923 rescues memory deficits but not Aβ42 pathology in the AD mice (142). The fact that this SAM does not alter normal glutamate-mediated mGluR5 signaling has led to the suggestion that this drug represents the superior choice for the pharmacological treatment of AD. In contrast, the mGluR5 PAM, CDPPB, increases neuronal viability and reduces neurogliosis, but it fails to improve memory deficits in aged AD mice (143). The mGluR5 NAM, CTEP, has proven to be the most effective mGluR5 ligand in improving memory function, reducing increased mGluR5 surface expression and ameliorating Aβ42 pathology in male AD mouse models (41, 42, 129, 130). Therefore, mGluR5 NAMs represent an attractive class of mGluR5-selective ligands that may be potentially repurposed to rescue memory impairment in AD.

SEX-SPECIFIC Aβ42-ACTIVATED MGLUR5 SIGNALING

The general utility of mGluR5 as a target for the treatment of AD in both men and women has been diminished by a recent study showing that mGluR5 exhibits distinct sex-dependent pharmacological profiles that dictate its contribution to Aβ42-mediated pathology (130). Specifically, the ternary complex between mGluR5, Aβ oligomer, and PrP^C that triggers pathological signaling is found to be formed in male, but not female, mouse brain. Thus, Aβ42 oligomers exhibit no specific binding to mGluR5 in either female mouse or human cortical brain autopsy tissue, indicating that the biophysical properties of Aβ42 oligomer binding to mGluR5 significantly differ between the sexes. These sex-specific differences in Aβ42-activated mGluR5 signaling translate into in vivo differences in mGluR5-dependent pathological signaling via the ZBTB16 autophagic pathway between male and female APPswe/PS1ΔE9 mice. Therefore, the mGluR5 NAM, CTEP, is effective in improving cognitive performance and reducing disease pathology in male, but not female, mice. Interestingly, CTEP improves cognitive improvement and reduces disease progression in male AD mice following treatment for either 3 or 6 months but is no longer effective following 9 months of treatment, suggesting that older male AD mice respond in a similar manner to younger female AD mice (42). This highlights the complexity of the interaction between Aβ42 and mGluR5 and suggests that more efforts should be directed toward delineating sex-specific receptor pharmacodynamics. It is also clear that there is a priority to identify novel receptor targets to treat AD in women.

CONCLUSIONS AND FUTURE PERSPECTIVES

Mounting evidence has demonstrated the obligatory role of mGluR5 signaling in synaptic plasticity. Indeed, mGluR5 signaling via G protein–dependent and G protein–independent mechanisms modulates synaptic transmission and supports the structural changes required for long-term synaptic modifications, such as LTP and LTD, that lead to the formation and removal of memories. Furthermore, mGluR5 serves as a receptor for Aβ42 and potentially hyperphosphorylated tau and can transduce their detrimental signals into the synapses, leading to synaptic failure. This is paralleled by an increase in the expression of mGluR5 in various mouse models of AD as well as in human AD patients. Therefore, mGluR5 represents an attractive target for the treatment of AD, as mGluR5 SAMs and NAMs are both capable of improving symptoms, although only NAMs appear to modify disease pathology in preclinical male models of AD. A number of mGluR5 NAMs, including the humanized analog of CTEP, basimglurant, are now in clinical

trials for the treatment of many neurodevelopmental, psychiatric, and neurodegenerative diseases such as fragile X syndrome, major depressive disorder, and Parkinson's disease with minimal reported adverse effects (144–148). However, recent findings indicate that pathological mGluR5 signaling triggered by Aβ42 is sex dependent. Therefore, the potential of mGluR5 antagonism to treat male-specific AD requires serious consideration, and additional efforts need to be directed toward understanding the biology underlying the sex-specific contribution of mGluR5 to the pathology of AD and possibly other neurodevelopmental and neurodegenerative diseases.

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AUTHOR CONTRIBUTIONS

K.S.A.-E. performed the literature review, drafted the manuscript, and generated the figures. S.S.G.F. edited and reviewed the manuscript. Both authors approved the submitted version.

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