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REVIEW ARTICLE

Metabotropic Glutamate Receptors in Glial Cells

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Abstract Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) and exerts its actions via a number of ionotropic glutamate receptors/channels and metabotropic glutamate (mGlu) receptors. In addition to being expressed in neurons, glutamate receptors are expressed in different types of glial cells including astrocytes, oligodendrocytes, and microglia. Astrocytes are now recognized as dynamic signaling elements actively integrating neuronal inputs. Synaptic activity can evoke calcium signals in astrocytes, resulting in the release of gliotransmitters, such as glutamate, ATP, and D-serine, which in turn modulate neuronal excitability and synaptic transmission. In addition, astrocytes, and microglia may play an important role in pathology such as brain trauma and neurodegeneration, limiting or amplifying the pathologic process leading to neuronal death. The present review will focus on recent advances on the role of mGlu receptors expressed in glial cells under physiologic and pathologic conditions.

Keywords Astrocytes · Gliosis · Metabotropic glutamate receptors · Gliotransmitter · Neurodegeneration · Glioma

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Introduction

Glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and its responses are mediated by ionotropic (iGlu) and metabotropic glutamate (mGlu) receptors. iGlu receptors mediate fast excitatory transmission and are cation-specific ion channels which are formed by a variable assembly of different subunits conferring specific properties to the different receptor-mediated membrane currents. There are three families of iGlu receptors defined by a specific pharmacology in α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. mGlu receptors are a family of G-protein-coupled, seven transmembrane domain receptors that exert a variety of effects on second messenger systems and ion channels. There are eight different subtypes (mGlu1–8) of mGlu receptors and three sub-groupings based on agonist pharmacology, coupling to specific signal transduction pathways, and sequence homology. Group I includes

mGlu1 and mGlu5 receptors, which are activated by quisqualate and (*S*)-3,5-dihydroxyphenylglycine (DHPG), and are coupled to inositol-(1, 4, 5)-trisphophate ($InsP_3$)/Ca^{2+} signal transduction via the Gq/11 family of G-proteins. Stimulation of mGlu1 and mGlu5 receptors activates phospholipase Cβ1, resulting in the formation of $InsP_3$, which acts to release calcium from intracellular stores, and production of diacylglycerol, which activates protein kinase C (PKC). Group II (mGlu2 and mGlu3) and group III (mGlu4, mGlu6, mGlu7, and mGlu8) receptors are quisqualate-insensitive and negatively coupled to adenylate cyclase through the Gi/o family of G-proteins [1]. mGlu receptors modulate synaptic transmission and are involved in activity-dependent modification of synaptic transmission such as long-term potentiation and long-term depression. Each receptor subtype exhibits a well-defined expression pattern in several brain regions. In neurons, mGlu1 and mGlu5 receptors are generally found in postsynaptic densities and modulate postsynaptic efficacy, whereas mGlu2, mGlu3, mGlu4, mGlu7, and mGlu8 receptors are mainly (but not exclusively) presynaptic and regulate neurotransmitter release [2]. mGlu receptors are also found in glial cells, where their activation exerts a variety of effects that are crucial for glial function and glial–neuronal interaction under physiologic and pathologic conditions.

mGlu Receptors Expression in Glial Cells

The presence of mGlu receptors in glial cells was initially inferred by a number of actions of glutamate in cultured astrocytes, including the accumulation of inositol phosphate [3, 4], the increase in intracellular Ca^{2+} [5], the inhibition of cyclic AMP formation [6] and the induction of immediate early gene expression [7]. The expression of mGlu receptors in glial cells was subsequently investigated by reverse transcription polymerase chain reaction (RT-PCR), immunohistochemistry, and immunoblotting. In general, most of the reports showed the presence of mGlu3 and mGlu5 receptors in astrocytes, whereas a few studies suggest the presence of other receptor subtypes. Both mGlu3 and mGlu5 receptors have been detected by RT-PCR in hippocampal astrocytes acutely isolated from young [8] and adult rats [9]. The expression of mGlu5 receptors in astrocytes exhibits a decremental profile during development, which is more evident for the mGlu5a receptor splice variants [9], similarly to what reported in neurons [10, 11]. The expression of mGlu3 and mGlu5 receptors in the intact brain has been studied by both immunohistochemistry and in situ hybridization. While the expression of the mGlu5 receptor protein has been detected in astrocytes [12, 13], the transcripts of both mGlu5a and mGlu5b splice variants have never been found in glial cells of CNS by in situ hybridization [14–16]. In contrast, both mGlu5 receptor protein and mRNA are consistently detected in cultured astrocytes. It is possible that expression of mGlu5 receptors in glial cells is below detection levels under resting conditions. In cultured astrocytes, the expression of mGlu5 receptors is modulated by extracellular signals, being low in astrocytes grown in conventional serum-containing medium and up-regulated when astrocytes are shifted to astrocyte-defined medium (ADM) containing growth factors such as basic fibroblast growth factor, epidermal growth factor, or transforming growth factor-α [17–19]. It has been proposed that morphological changes induced by exposure to these growth factors mimic the activation of astrocytes occurring in reactive gliosis. Accordingly, the expression of mGlu5 receptors in reactive astrocytes surrounding a lesion or induced by epileptic seizures has been found to be higher than in non-activated astrocytes when investigated by immunohistochemistry [20–22]. The mGlu1a receptor has not been detected in cultured cortical astrocytes grown in conventional medium or ADM at both mRNA and protein level [17, 18, 23–26]. In contrast, about 10% of cultured astrocytes prepared from the spinal cord are immunoreactive for mGlu1a receptors [27]. These data are in line with data obtained in the human spinal cord from patients affected by amyotrophic lateral sclerosis (ALS) [28] and rat spinal cord after emisection or traumatic injury [29, 30]. mGlu5 receptor mRNA has been detected in cultured microglia by RT-PCR analysis, but has not been found in resident microglia by in situ hybridization [16]. It is not clear whether mGlu5 receptors are expressed by oligodendrocytes or microglial cells in vivo.

The presence of mGlu3, but not mGlu2 receptors, in astrocytes and oligodendrocytes in vivo, has been shown by several techniques [16, 31–33]. Cultured astrocytes express the transcripts for mGlu3 receptors [15, 24, 34], but are not easily labelled by mGlu2/3 antibodies [19, 25, 34, 35]. Similarly to mGlu5 receptors, mGlu3 receptors are up-regulated in response to growth factors in cultured astrocytes [19, 36]. Interestingly, while mGlu3 mRNA has not been found in the microglia of intact rat brain [16], mGlu2/3 immunoreactivity has been observed in microglia/macrophages in autoptic brain samples from patients with multiple sclerosis [37]. Cultured microglia have been found to express both mGlu2 and mGlu3 mRNA and proteins [38], but see Ref. [15] for contrasting results.

The mGlu4 receptor has been detected in primary cultures of rat and mouse cortical astrocytes by RT-PCR and immunoblotting in some studies [39], but not in others [15, 25], whereas neither mGlu6 nor mGlu7 receptors are found in cultured astrocytes [25]. It has been suggested that mGlu7 receptors are not expressed by glial cells [40]. The transcript of mGlu8 receptor is not detectable in cortical

astrocytes grown in conventional medium, but it becomes detectable in astrocytes grown in ADM medium; however, the mGlu8 receptor protein expression is never found in cultured astrocytes [34]. mGlu4, mGlu6, mGlu8 (but not mGlu7) receptor mRNA and protein are detectable in cultured microglia [41]; but see also Ref. [15] for contrasting results.

Cultured oligodendrocytes prepared from neonatal rats are immunoreactive for mGlu1a, mGlu2/3, mGlu4, and mGlu5 receptors. Expression of all these receptor subtypes is developmentally regulated, being high in early and late oligodendrocyte precursors, and low or absent in immature and mature oligodendrocytes [42]. Maturational stages of oligodendrocyte precursors can be identified by the selective expression of stage-specific markers such as A2B5 (early precursors), O4 (late precursors), O1 (immature oligodendrocytes), MBP (mature oligodendrocytes). Rat O4- and O1-positive and A2B5-positive early precursors from adult human brain express both mGlu3 and mGlu5 receptor proteins [43, 44]. mGlu3 and mGlu5 receptors are also found in neural stem cells, i.e., in partially committed stem cells isolated from the fetal brain or neurogenic zones of the adult brain that give rise to neurons, astrocytes, and oligodendrocytes [45].

mGlu Receptors are Coupled to Multiple Signal Transduction Pathways in Glial Cells

Activation of mGlu5 receptors in astrocytes stimulates polyphosphoinositide (PI) hydrolysis [18, 46] and generates oscillatory increases in intracellular calcium [15, 47]. This results into the release of glutamate and other gliotransmitters, which can evoke synaptic responses in neighbor neurons [48, 49, next paragraph]. Activation of group I mGlu receptors has been shown to increase the open probability of two types of Ca^{2+}- activated K^+ channels in hippocampal astrocytes through a mechanism mediated by PLC activation [50]. In addition, activation of group I mGlu receptors by DHPG stimulates mitogen-activated protein (MAP) kinase pathways [35]. Interestingly, while DHPG-induced PI hydrolysis and calcium responses are inhibited by PKC inhibitors, activation of MAP kinases in astrocytes is PKC-independent [51], and instead requires the transactivation of the epidermal growth factor receptor and the activation of a Src family tyrosine kinase [52]. Stimulation of phospholipase D mediated by activation of mGlu5 receptors has also been reported in cultured astrocytes from cortex and hippocampus, but not from cerebellum [53].

mGlu2 and mGlu3 receptors are negatively coupled to adenylate cyclase. In cultured murine astrocytes, activation of group II mGlu receptors by the selective agonist LY379268 reduces forskolin-stimulated cAMP formation in the absence of extracellular calcium, but enhances cAMP formation in the presence of calcium [54]. This dual regulation of cAMP formation is peculiar of cultured astrocytes, being absent in cultured neurons [54]. In addition, pharmacological activation of group II mGlu receptors amplifies the stimulation of cAMP formation mediated by β2-adrenergic receptor, and the combined activation of group II mGlu receptors and β2-adrenergic receptors stimulates adenosine release in cultured astrocytes [55]. Extracellular adenosine may be critical for the overall effect of mGlu2/3 receptor activation in astrocytes [54]. Activation of mGlu2/3 receptors also stimulates the MAP/ERK kinase and PI-3-kinase pathways in cultured mouse and human astrocytes [19, 56]. Both pathways mediate the increased formation of transforming growth factor-β (TGF-β) from astrocytes in response to mGlu3 receptor activation in astrocytes [56], an effect that mediates a particular form of neuroprotection based on a mechanism of glial–neuronal interaction [57]. Stimulation of MAP kinase and PI-3-kinase also underlies the protective effects of group II mGlu receptor agonists against astrocytic damage caused by oxygen/glucose deprivation in culture [58]. Finally, activation of mGlu3 receptors enhances the formation of nerve growth factors and S-100beta protein in cultured astrocytes [59].

mGlu receptors have been implicated in the control of astrocyte proliferation [4, 60, 61], with the activation of mGlu5 receptors increasing and activation of mGlu3 receptors decreasing cell proliferation [25]. The functional significance of this regulation is unknown.

mGlu Receptors and the Release of Gliotransmitters

During the last decade the concept that glial cells actively participate to synaptic transmission has been corroborated by several observations. Astrocytes can regulate neuronal excitability and information processing by controlling the levels of extracellular glutamate at synapses and by responding to neurotransmitters with the release of gliotransmitters, which in turn can modulate neuronal responses. mGlu receptors expressed in astrocytes are implicated in both mechanisms. Astrocytes respond to neurotransmitters with an increase of intracellular Ca^{2+} and an ensuing release of gliotransmitters such as glutamate, ATP, and D-serine, which in turn can modulate neuronal excitability and promote neuronal synchrony [49, 62]. The glutamate released from astrocytes in response to mGlu5 receptor activation induces a slow inward current in neurons mediated by extrasynaptic NR2B-containing NMDA receptors, which indicates that glutamate released from astrocytes can have access to extrasynaptic sites [63, 64]. This mechanism promotes synchronized activation of

groups of neurons as shown in the hippocampus [63], and can therefore be involved in a form of slow, long distance information processing. The mGlu5 receptor-mediated glutamate release in astrocytes has also been implicated in processes relevant to drug addiction, such as cocaine self-administration and drug-seeking behavior [65].

The number of studies on the effects of mGlu receptor activation on the release of gliotransmitters other than glutamate is limited. Activation of mGlu receptors by the mixed agonist trans-ACPD is only slightly effective in promoting ATP release [66]. However, ATP release can be elicited by the activation of mGlu receptors in spinal cord astrocytes treated with glutamate in the presence of substance P [67]. ATP is a key spinal cord neurotransmitter and an important regulator of inflammatory and neuropathic pain. Group I mGlu receptors are strongly expressed in the dorsal horn of spinal cord and are implicated in the increased excitability of dorsal horn neurons induced by a persistent noxious stimulus [68]; however, the role of astrocytic mGluRs in nociceptive sensitization awaits further elucidation. D-Serine, one of the endogenous ligand at the glycine site of NMDA receptors, is released from astrocytes upon AMPA/kainate and mGlu receptor stimulation though a calcium-dependent and SNARE protein-dependent mechanism [69].

mGlu Receptors Regulate Glutamate Transport in Glial Cells

Synaptic cleft glutamate is rapidly cleared from the extracellular space by high-affinity glutamate transporters present in both neurons and astrocytes. This mechanism maintains glutamate concentration below excitotoxic levels and prevents glutamate from spreading outside the synaptic cleft. Of the five different isoforms of glutamate transporters, GLAST (EEAT1) and GLT1 (EEAT2) are expressed almost exclusively by astrocytes, with GLT1 being the most abundant and accounting for more than 80% of glutamate uptake in the brain. Recent evidence suggests that activation of mGlu receptors modulates the expression and function of glutamate transporter proteins in astrocytes. GLT1 and GLAST, which are expressed at very low levels in cultured astrocytes grown in serum-containing medium, are strongly induced by the presence of neurons or by a chemically defined medium containing growth factors [19, 70, 71]. Under the latter conditions, an acute stimulation of mGlu5 receptors rapidly enhances glutamate uptake by GLT1, through a mechanism that involves PLC and PKC [71]. In contrast, a long-term treatment with the group I mGluR agonist, DHPG, produces opposite effects in cultured rat and human astrocytes [19, 70]. While the increased activity of GLT-1 induced by the acute stimulation of mGlu5 may contribute to restrict the glutamate signal to the synaptic territory, the functional significance of the opposite regulation of glutamate transporter proteins by a sustained activation of mGlu3 and mGlu5 receptors is less clear. It has been reported that activation of group II and group III mGlu receptors in astrocytes enhances glutamate uptake, thus protecting neurons against 1-methyl-4-phenylpyridinium toxicity in midbrain cultures [72]. However, it is possible that mechanisms controlling mGlu receptor-dependent regulation of glutamate uptake are disrupted under pathologic condition involving reactive gliosis and neuroinflammation.

Glial mGlu Receptors and Diseases

The expression of mGlu receptors in glial cells is highly dynamic and modulated in response to different types of experimental brain injuries. In humans, mGlu3 and mGlu5 receptors have been found to be diffusely up-regulated in reactive astrocytes in pathologic specimens of ALS [28], glioneuronal tumors [73], and multiple sclerosis (MS) [37]. mGlu2/3 immunoreactivity is found in activated microglia in brain tissue of patients with MS, but not in ALS. mGlu4 and mGlu8 receptors are not found in resting astrocytes and microglia, but are detectable in reactive astrocytes and microglia of MS lesions, respectively [74].

mGlu receptors modulate excitatory synaptic transmission and are currently considered as novel targets for drugs of potential use in neurological and psychiatric disorders [75]. A great deal of work has been done to clarify the role of mGlu receptors in excitotoxic neuronal death. Although data are not univocal, group II and group III mGlu receptors are generally considered as neuroprotective receptors, whereas activation of mGlu1 and mGlu5 receptors may either amplify or attenuate excitotoxicity depending on the experimental paradigms [75]. Neuroprotection mediated by mGlu3 receptors involves a mechanism of glial–neuronal interaction. The medium collected from cultured astrocytes challenged with mGlu3 receptor agonists protects neurons against excitotoxic death because it contains TGF-β and, perhaps other neurotrophic factors [56, 57, 76]. Neuroprotection is lost when cultured astrocytes are prepared from mGlu3 knockout mice [77]. Activation of mGlu4 receptors can instead reduce the production of the chemiokine RANTES in cultured astrocytes exposed to proinflammatory cytokines. This mechanism suggests a potential use of mGlu4 receptor enhancers in neuroinflammatory disorders [39]. The role of glial mGlu5 receptors in neurotoxicity is currently under investigation. An enhanced release of glutamate induced by the activation of glial mGlu5 receptors contributes to glutamate-mediated neuronal death after status epilepticus [78].

Interestingly, the mGlu5 receptor-mediated up-regulation of glutamate transport is lost in chemically activated astrocytes prepared from a G93A SOD1 rat model of ALS [79]. In addition, because the expression of mGlu3 and mGlu5 receptors is increased in reactive astrocytes, changes in the ratio of these receptor subtypes might influence the levels of extracellular glutamate in neurological disorders associated with reactive gliosis. In this context, a role for microglia should also be considered. In fact, although most of the reports suggest an up-regulation of both mGlu3 and mGlu5 receptors in reactive astrocytes, a down-regulation of mGlu5 receptors has been shown in cultured astrocytes treated with interleukin-1beta, tumor necrosis factor-α (TNFα) and with a conditioned medium collected from lipopolysaccharide-activated microglia [80, 81]. In contrast, an up-regulation of mGlu5 has been observed after a treatment with NO donor and prostaglandin E2 [81]. These data indicate that the interaction between astrocytes and microglia might influence responses mediated by mGlu receptors under pathologic conditions characterized by neuroinflammation. In microglia, activation of mGlu2 receptors induces mitochondrial depolarization and apoptosis or, alternatively, induces an activated phenotype, which underlies microglia-mediated neurotoxicity [38, 82]. This is mediated by the secretion of TNFα and Fas ligand from activated microglia [82]. In contrast, activation of group III mGlu receptors does not induce microglial apoptosis, or TNFα release, and appears to be protective against microglia-mediated neurotoxicity [41, 82]. A scheme showing the complex interaction between microglia and astrocytes in neuroinflammation is depicted in Fig. 1.

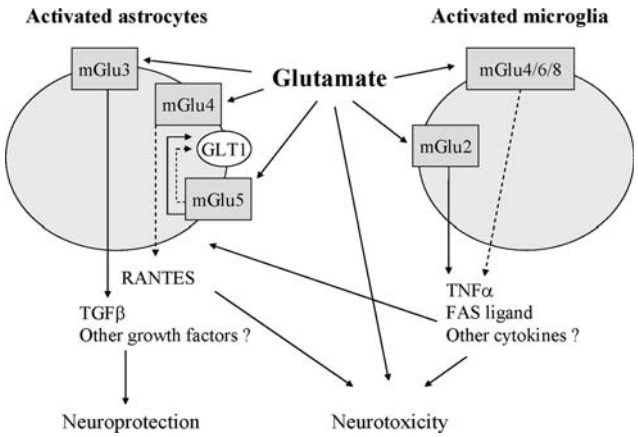

Fig. 1 A complex crosstalk between activated astrocytes and activated microglia results in neurotoxic and neuroprotective cascades whose balance might influence the progress of neurological disorders characterized by an inflammatory component. See text for a description of mGlu-dependent effects. Solid arrows represent causative or activating effects. Dashed arrows represent inhibitory effects

Recent evidence supports a role for AMPA/kainate iGlu receptors in the pathophysiology of oligodendroglial death in demyelinating diseases. Oligodendroglial cells are highly vulnerable to glutamate-mediated toxicity both in vitro and in vivo [83]. Interestingly, activation of both mGlu1 and mGlu5 receptors attenuates excitotoxic damage of oligodendrocyte precursors, but is not protective against excitotoxicity on mature oligodendrocytes, reflecting the developmental pattern of mGlu receptor expression across the oligodendroglial lineage [42, 84]. More recently, activation of mGlu5 receptors has been shown to completely protect oligodendrocyte precursors and partially protect mature oligodendrocytes against staurosporine-induced apoptosis [85]. Thus, agonists of group I mGlu receptors are potentially helpful in the treatment of neurological disorders that primarily involves oligodendrocyte precursors, such as periventricular leukomalacia, the predominant form of hypoxic-ischemic brain injury in premature infants [42]. Oligodendrocyte precursors persist in the adult brain and trigger the remyelination process following injury to white matter. mGlu receptors might be involved in the regulation of remyelination and might be viewed as novel pharmacological target for therapeutic intervention in MS and other demyelinating conditions.

Interestingly, mGlu5 receptors are expressed in enteric glial cells, which bear similarities to astrocytes and are the most numerous cells in the enteric nervous system. The expression of mGlu5 receptors in enteric glial cells is increased in colitis suggesting a potential role for mGlu5 receptors in the pathophysiology of this disorder [86].

mGlu receptors are expressed in glioma cell lines, as well as in cells isolated from malignant gliomas [19, 24, 87, 88]. In contrast to what observed in cultured astrocytes, activation of mGlu3 receptors supports proliferation of glioma cells [87]. Accordingly, a chronic treatment with group II mGlu receptor antagonists reduces the growth of glioma cells in vivo, indicating that mGlu2/3 antagonists are of potential use in the experimental treatment of malignant gliomas [88]. The possible use of drugs acting at mGlu receptors in the therapy of cancer, including gliomas has been recently discussed elsewhere [89].

Future Direction

Drugs acting at mGlu receptors are currently proposed as potential therapeutical agents for the treatment of several neurological and psychiatric disorders. In the light of this, future experiments will be fundamental to further define the role of glial mGlu receptors in gliotransmitter-dependent information processing and in the complex interplay between microglia, astrocytes, and neurons occurring in neurological disease characterized by neuroinflammation.

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