

Metabotropic glutamate receptors (mGluRs) in epileptogenesis: an update on abnormal mGluRs signaling and its therapeutic implications

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Abstract

Epilepsy is a neurological disorder characterized by high morbidity, high recurrence, and drug resistance. Enhanced signaling through the excitatory neurotransmitter glutamate is intricately associated with epilepsy. Metabotropic glutamate receptors (mGluRs) are G protein-coupled receptors activated by glutamate and are key regulators of neuronal and synaptic plasticity. Dysregulated mGluR signaling has been associated with various neurological disorders, and numerous studies have shown a close relationship between mGluRs expression/activity and the development of epilepsy. In this review, we first introduce the three groups of mGluRs and their associated signaling pathways. Then, we detail how these receptors influence epilepsy by describing the signaling cascades triggered by their activation and their neuroprotective or detrimental roles in epileptogenesis. In addition, strategies for pharmacological manipulation of these receptors during the treatment of epilepsy in experimental studies is also summarized. We hope that this review will provide a foundation for future studies on the development of mGluR-targeted antiepileptic drugs.

Key Words: antiepileptic drugs; epileptogenesis; metabotropic glutamate receptors (mGluRs); signal pathways; therapeutic potentials

Introduction

Epilepsy is a devastating neurological and systemic disorder characterized by recurrent seizures that is likely to cause physical injury and death if not treated optimally. Epilepsy is estimated to affect about 65 million people worldwide, and its pathogenesis is thought to be related to a relative imbalance of excitatory and inhibitory neurotransmitters (Akyuz et al., 2021). Glutamate is present in the mammalian central nervous system (CNS) as an important excitatory neurotransmitter (Meldrum et al., 1999; Nicolo et al., 2019; Servaes et al., 2019) involved in the regulation of various neuronal and synaptic activities through the activation of two types of receptors, i.e. ionotropic and metabotropic glutamate receptors (mGluRs) (Luessen and Conn, 2022). Both receptor types are essential for the regulation of neuronal development, synaptic transmission, and overall brain function (Abd-Elrahman and Ferguson, 2022), therefore influencing sensory and motor processing, cognition, memory formation, pain, addiction, and behavior (Cleva and Olive, 2012; Guo et al., 2018; Seven et al., 2021; Liang et al., 2022). The mGluR family comprises membrane-bound proteins that transmit extracellular signals into cells; they have been shown to regulate, in addition to physiological processes, many aspects of tumor development and progression (Eddy et al., 2022). mGluRs are widely distributed on cell surfaces in all major regions of the brain, both in neuronal and non-neuronal cells, and regulate neuronal excitability and synaptic transmission primarily through the activation of G protein-regulated signal transduction mechanisms (Niswender and Conn, 2010; Pereira and Goudet, 2018; Alkadhi, 2021; Abd-Elrahman and Ferguson, 2022). The central importance of mGluRs in brain physiology and in neurological disorders such as stroke, epilepsy, schizophrenia, and neurodegenerative diseases is widely recognized (Maksymetz et al., 2017; Wang and Reddy, 2017; Fern and Matute, 2019; Roth, 2019; Zhang et al., 2019; Luo et al., 2023; Yeung and Kwakowsky, 2023).

Over time, it has become clear that mGluRs play an important role in epileptogenesis. In this review, we introduce and summarize the progress of research on mGluR signaling pathways, especially regarding how they affect the occurrence of epilepsy. We further provide a foundation for antiepileptic drug development by presenting an update on recent findings that substantiate the potential of mGluRs as drug targets.

Literature Search Strategy

A literature retrieval strategy was conducted on three online databases, i.e. PubMed, Web of Science, and ResearchGate. Full-text articles published in English from inception to January 5, 2023 were included in this narrative review. A combination of the following medical subject headings (MeSH) terms was used to maximize search specificity and sensitivity: "metabotropic glutamate receptors OR mGluRs", "epileptogenesis", "epilepsy", "seizure disorder" and "epilepsy therapy". The results were further screened by title and abstract, and only studies exploring the relationship between mGluRs and epilepsy were selected for this review.

Metabotropic Glutamate Receptor-Associated Signaling Pathways

mGluRs belong to the G-protein-coupled receptor superfamily. Eight mGluRs (mGluR1-8), each possessing seven structural transmembrane domains, have been identified, many of which presenting alternatively spliced isoforms. Structurally, mGluRs are characterized by a large extracellular N-terminal domain, which acts as a glutamate binding site, and a Venus flytrap domain (Abd-Elrahman and Ferguson, 2022; Zimmermann et al., 2022) linked to seven transmembrane α -helical domains through a cysteine-rich domain (Gregory and Goudet, 2021). VTFs exist as homodimers or heterodimers,

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with ligand binding influencing tight dimer interfaces to bring cysteine-rich domains closer together, resulting in a conformational change. Interactions between the cysteine-rich domain and the receptor's second extracellular loop rearrange the seven transmembrane domain to initiate the signaling process (Akanuma et al., 2015; Akanuma, 2020).

The eight mGluR subtypes are conventionally divided into three subgroups based on sequence homology, post-receptor signaling connections, and pharmacology (Mao et al., 2022; **Figure 1**). Group I members (mGluR1 and mGluR5) are typically postsynaptically localized and are coupled to the Gq signaling pathway (Hermans and Challiss, 2001; Azam et al., 2022; Dahl et al., 2022), which regulates neuronal excitability by stimulating the Gαq/Gα subunit to induce phosphatidylinositol 4,5-bisphosphate hydrolysis via phospholipase C (PLC) activation (Eddy et al., 2022). Another key feature of Group I mGluRs is also their enhancing effect on glutamate N-methyl-D-aspartate (NMDA) receptor activation (Carey et al., 2022; Kovalenko et al., 2022).

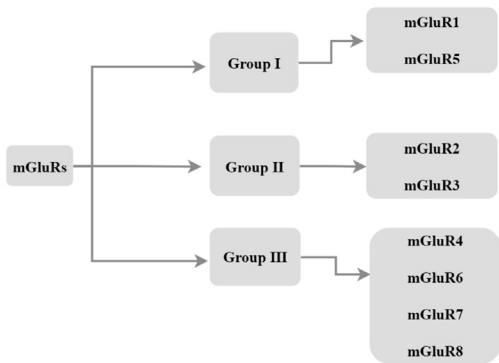


Figure 1 | Classification of mGluRs.
Created with diagrams.net. mGluR: Metabotropic glutamate receptor.

In contrast, Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) members are both presynaptically and postsynaptically localized, are coupled to the Gi/Go signaling pathway, and signal through adenylate cyclase pathway inhibition in heterologous expression systems (Guo et al., 2018). Of note, Group II receptor activation inhibits Ca²⁺ channels and activates K⁺ channels to mediate presynaptic inhibition of neurotransmitter release (Kovalenko et al., 2022). A summary of relevant characteristics and pathophysiological actions of members in the three mGluR groups is shown in **Table 1**.

The activation of mGluRs is modulated by some ions, notably Cl⁻ (Tora et al., 2015) and Ca²⁺ (Zou et al., 2017), and exerts physiological functions through G protein-coupled or G protein-independent intracellular signaling (Ribeiro et al., 2017). Cl⁻ behaves as a positive allosteric regulator of mGluRs, and is necessary for the activation of glutamate in many mGluRs. Similarly, extracellular Ca²⁺ play an essential regulatory role in the signaling pathway of mGluRs as allosteric regulators and second messengers of mGluRs. Additionally, it is important to note that glutamate concentrations in the brain are primarily regulated by glial cells. Glial cells control glutamate uptake via glutamate transporters (GLUT receptors), followed by the conversion of glutamate to glutamine in a process known as the glutamate/glutamine cycle (Evans et al., 2022). Upon activation, mGluRs crucially influence synaptic transmission and plasticity by modulating cell excitability, ionic conductance, and neurotransmitter release (Gubellini et al., 2004), typically triggering multiple long-lasting intracellular signaling pathways (Bodzeta et al., 2021; **Figure 2**). Accordingly, several CNS pathologies, such as epilepsy and Alzheimer's disease, may be associated with abnormal signaling through mGluRs (Edfawy et al., 2019; Carey et al., 2022).

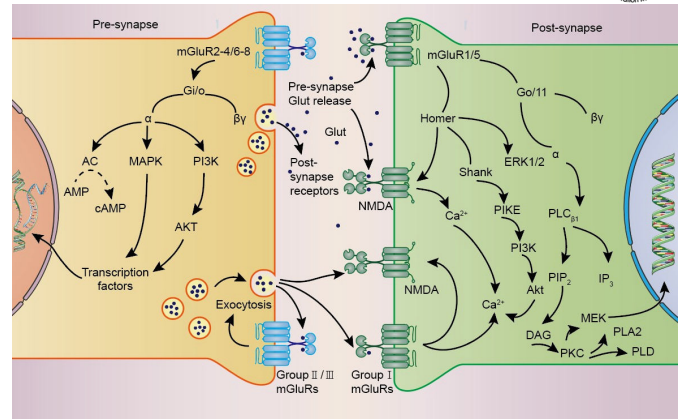


Figure 2 | Signaling pathways mediated by mGluRs.
Schematic depiction of the synaptic localization of mGluRs and their signaling cascades. Relevant signaling pathways involve mainly MAPK, PI3K, Akt, PLC, IP₃, mTOR, and ERK. A continuous line represents a physical interaction between elements, and the direction of signal conduction is indicated by arrows. Reduced activity is represented by dashed lines. Created with Adobe Illustrator (version 27.5). AMP: Adenosine monophosphate; ERK: extracellular signal-regulated kinase; GLUT: glucose transporters; IP₃: inositol 1,4,5-trisphosphate; MAPK: mitogen-activated protein kinase; mGluRs: metabotropic glutamate receptors; mTOR: mechanistic target of rapamycin; NMDA: N-methyl-D-aspartic acid; PI3K: phosphoinositide 3-kinase; PIKE: PI 3-kinase enhancer; PLC: phospholipase C.

A classical view is that Group I mGluRs couple to Gαq/11 and activate phospholipase Cβ1, leading to phosphoinositide hydrolysis for inositol 1,4,5-trisphosphate (InsP₃) and diacylglycerol generation, and calcium mobilization and protein kinase C (PKC) activation (Niswender and Conn, 2010; Ribeiro et al., 2017). Group II and Group III mGluRs primarily couple to Gi/Go proteins, with consequent downstream inhibition of adenylate cyclase activity leading to decreased cyclic adenosine monophosphate (cAMP) levels. In addition, Group III mGluR signaling through Gβγ subunits regulates ionic conductances in neurons, limiting presynaptic glutamate or gamma-aminobutyric acid (GABA) release by inhibiting voltage-dependent Ca²⁺ channels and promoting the activation of inwardly rectifying K⁺ channels (Schoepp, 2001; Niswender and Conn, 2010; Ribeiro et al., 2017; Vahidinia et al., 2021; Li et al., 2022).

Although the mGluR-associated second messenger system involved in phosphoinositide 3-kinase (PI3K)/Akt, mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NF-κB), phospholipase C (PLC), mammalian target of rapamycin (mTOR), protein interacting with C kinase-1 (PICK1), and Ca²⁺/calmodulin-dependent protein kinase (Ca/CaM) signaling activation has been described in detail (Willard and Koochekpour, 2013; Dalley et al., 2018; Sadananda and Subramaniam, 2021), studies have identified new roles for mGluRs in other signaling pathways. For example, some Group I mGluR-mediated signaling pathways were shown to be associated with acid-sensing ion channel sensitization in dorsal root ganglion neurons; specifically, enhanced proton-gated currents induced by selective Group I mGluR agonism via (S)-3,5-dihydroxyphenylglycine (DHPG) were shown to fade after suppressing intracellular Gq/11, PLCβ, PKC, or PICK1 signaling (Gan et al., 2016).

Long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission are the two most common forms of synaptic plasticity (Malenka and Bear, 2004). In this regard, the role of mGluR1 in LTD signal processing has garnered considerable attention. LTD has been associated with numerous signaling cascades involving MAPK, protein tyrosine phosphatases, proteases, endocannabinoids, and PI3K/Akt-mTOR signaling (Gladding et al., 2009). By analyzing Ca²⁺ imaging results from Purkinje cells in slices of

Table 1 | mGluRs groups, common agonists and antagonists and effects

Receptor	Localization	Common agonist	Common antagonist	Convulsive seizures	Neurotransmitter release	Reference
mGlu1, mGlu5	Postsynaptic neurons, presynaptic terminals, glial cells	Nonselective (1S, 3R)-ACPD, (R,S)-CHPG, (S)-3,5-dihydroxy-phenylglycine, L-quisqualic acid	(S)-MCPG, (T) AIDA, (U) (S)-4CPG	Proconvulsive	Enhancement	Thomsen and Dalby, 1998; Tang et al., 2009; Gregory and Goudet, 2021
mGlu2, mGlu3	Presynaptic membranes, postsynaptic membranes, glial cells	Nonselective (1S, 3R)-ACPD, DCG-IV, pomaglumetad (S)-4-carboxy-3-hydroxyphenylglycine	CPPG, (S)-MCPG, (T) L-serine-O-phosphate	Anticonvulsant	Reduction	Folbergrova et al., 2001; Alexander and Godwin, 2006; Gregory and Goudet, 2021
mGlu4, mGlu6, mGlu7, mGlu8	Presynaptic membranes, presynaptic membranes, glutamatergic and GABAergic neurons, glial cells	ACPT-1, cinnabarinic acid, L-serine-O-phosphate' (RS)-PPG, cyclobutylene AP5	CPPG, (S)-MCPG, (T) MSOP	Mixed responses	Reduction	Thomsen and Dalby, 1998; Folbergrova et al., 2001; Gregory and Goudet, 2021

(R, S)-PPG: (R,S)-4-phosphonophenylglycine; 1S,3R-ACPD: 1S,3R-1-aminocyclopentane-1,3-dicarboxylic acid; ACPT-1: (1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid; AIDA: 1-aminoindan-1,5-dicarboxylic acid; CHPG: (R,S)-2-chloro-5-hydroxyphenylglycine; CPPG: α-cyclopropyl-4-phosphonophenylglycine; Cyclobutylene AP5: (RS)-1-amino-3-(phosphonomethylene) cyclobutene-carboxylic acid; DCG IV: (2S,2'R,3'R)-2-(2',3'-dicarboxycyclopropyl)glycine; MCPG: α-methyl-4-carboxyphenylglycine; mGluR: metabotropic glutamate receptor; M-SOP: α-methylserine-O-phosphate; S-3,4-DCPG: (S)-3,4-dicarboxyphenylglycine. (S), (U), (T) represent the different relative configurations of the chiral centres.

juvenile rat cerebella, Jin et al. showed that mGluR1-induced LTD results from activation of a slow excitatory post-synaptic current and PLC/IP3-mediated dendritic Ca^{2+} mobilization (Jin et al., 2007). Furthermore, it has been shown that mGluRs-induced LTD involves two interacting Ca^{2+} sensors, NCS-1 and PICK1 (Ghasemi et al., 2021).

In a recent study, Dasgupta et al. (2020) revealed that Group III mGluR4 and mGluR7 inhibition results in potentiation of LTP-resistant Schaffer collateral-CA2 synapses via ERK/MAPK signaling activation and striatal-enriched protein tyrosine phosphatase (STEP) downregulation, transforming a transient potentiation of the entorhinal cortical (EC)-CA2 synapses into a sustained, stable LTP pattern. Meanwhile, Kelly et al. (2009) discovered that in cerebellar stellate cells, GABA-dependent synaptic plasticity mediated by switching of GluR2-lacking Ca^{2+} -permeable α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (CP-AMPA) receptor subunits and subsequent loss of Ca^{2+} permeability requires mGluR activation. This mechanism was shown to differ, in turn, from those described to mediate mGluR-induced LTD in CA1 neurons and parallel fiber-Purkinje cell synapses. These findings have significantly contributed to our understanding of the participation of mGluRs in various neurological disorders, including epilepsy, as discussed below.

Some neural circuit study tools contributed also to elucidate mGluR-related signaling pathways involved in the regulation of neuronal excitability. For example, Xiang et al. (2021) reported on mGluR2/mGluR4 heterodimers in brain slices through electrophysiology and optogenetic methods; these proteins are essential in excitatory synapse transmission within the rodent medial prefrontal cortex (mPFC) and may inhibit glutamatergic signaling at thalamus-mPFC synapses. These and several other techniques have greatly assisted precise localization of mGluR-related signaling pathways and are expected to promote this field's development. A detailed picture of the multiple mGluRs-mediated signaling pathways will deepen our understanding of the molecular mechanisms underlying neuronal disorders and facilitate targeted drug development.

Potential Mechanisms Underlying Metabotropic Glutamate Receptor Regulation of Epileptogenesis

Group I mGluRs

Group I mGluR subtypes (mGluR1 and mGluR5) are primarily expressed postsynaptically but exist also in presynaptic terminals of GABA and glutamatergic neurons (Luessen and Conn, 2022). The roles of Group I mGluRs in epileptogenesis and epilepsy persistence have been studied for over two decades (Table 2). Focal cortical dysplasia is a substantial intractable epilepsy factor. Immunocytochemistry analysis of epilepsy patient samples showed that mGluR1 α and mGluR5 are highly expressed in dysplastic neurons, suggesting that Group I mGluRs may trigger high epileptogenicity (Turati et al., 2022). In turn, analysis of mGluR expression in epileptic dentate gyrus granule cells from different mouse strains evidenced reduced excitatory group I mGluRs expression in correlation with a diminished epileptic phenotype (Chen et al., 2005; Lukawski et al., 2018; Celli et al., 2019). Attesting at the importance of glial mGluR activity in epilepsy, in mouse astrocytes mGluR5 expression is suppressed ~3 weeks after birth but its re-expression occurs during induction of epileptogenesis (Salvati and Beenhakker, 2019). More recently, it was also demonstrated that seizure-induced mGluR5 upregulation in reactive astrocytes is associated with increased TGF- β production (Mazzitelli et al., 2022).

Although the association between high Group I mGluR expression and seizure susceptibility is well-established, a causal relationship has not yet been fully determined. It has been proposed that mGluR5 upregulation in surviving neurons is likely a consequence of seizure activity and may lead to hippocampal hyperexcitability in patients with pharmaco-resistant temporal lobe epilepsy (TLE), suggesting that mGluR5 signaling is a potential target for new antiepileptic drugs (Zimmermann et al., 2022). Along these lines, Sanon et al. reported that epileptiform burst discharges in hippocampal stratum oriens-alveus interneurons (O/A-INs) are partially mGluR5-dependent. Postsynaptic O/A-IN currents include different components, with mGluR5 contributing to slow and fast components and mGluR1 α contributing to slow ones only. These findings indicate that differential mGluR1 α and mGluR5 expression may influence cell type-specific epileptiform activity (Sanon et al., 2010; Govindaiah et al., 2018).

The development of pharmacological inhibitors of Group I mGluRs is a topic of great interest in epilepsy research and treatment. As early as 1995, McBain found that the mGluR antagonist (+)-2-methyl-4-carboxyphenylglycine reversibly abolished the periodic inward current elicited by high K^+ in stratum oriens interneurons, thereby inhibiting epileptiform activity (McBain, 1995). Subsequently, Micheli reported on the development of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), a selective, systemically active non-competitive mGluR5 antagonist with epilepsy treatment potential that effectively inhibited phosphoinositide hydrolysis (Micheli, 2000). Subsequently, Borowicz and collaborators proposed a new therapeutic approach focused on SIB 1893, a non-competitive Group I mGluRs antagonist, and conventional antiepileptic drug combinations (Borowicz et al., 2003, 2004). Aided by gene expression technology, Gass and Olive (2008) found that mGluR5 antagonism can mediate expression changes in a wide range of genes. Their analyses showed that repeated administration of the mGluR5 antagonists MPEP and 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine (MTEP) to rats influenced

frontal cortex's transcriptional profiling, differentially altering the expression of 63 genes.

Homer proteins are postsynaptic scaffolding proteins that act as molecular adaptors of Group I mGluRs and other proteins. Homer-1a expression during seizures can reduce seizure susceptibility, and intracellular Homer-1a protein injection reduces membrane excitability (Bockaert et al., 2021). Interactions between Homer proteins and mGluR1 and mGluR5 can fine-tune synaptic strength, thus modulating epileptic activity (Gurgone et al., 2022). Cavarsan et al. (2012) confirmed a significant increase in Homer-1a protein expression in the hippocampus, amygdala, and piriform and entorhinal cortices 24 hours after pilocarpine-induced epilepsy onset, coinciding with a significant decrease in mGluR5 protein expression in the same areas.

Substantial research has focused on the mechanisms linking Group I mGluR activities and epileptogenesis. D'Amore et al. (2013) reported that changes in mGluR5 expression might be central to the absence-seizure prone phenotype of WAG/Rij rats. This study showed that pharmacological mGluR5 activation reduced spike-and-wave discharge (SWD) number and duration in WAG/Rij rats, thus highlighting mGluR5 enhancers as potential drug candidates for treatment of absence epilepsy. Similarly, supporting a protective role for mGluR5 in TLE, Kandratavicius et al. proposed that mGluR5 upregulation in TLE may represent a postsynaptic adaptation to control hyperexcitability and excessive glutamate release (Kandratavicius et al., 2013). Moreover, Potter et al. (2013) concluded that increased mGluR5 contributes to epileptiform seizure activity and leads to LTD in the CA1 hippocampus in a mouse model of tuberous sclerosis complex (TSC). Interestingly, the pro-apoptotic effect of mGluR5 upregulation in glial cells, linked to intracellular Ca^{2+} overload and observed during brain hypoxia, epilepsy, and some neurodegenerative conditions, has been substantiated by several studies (Paquet et al., 2013; Hu et al., 2022).

Imaging technology has also advanced our knowledge regarding the involvement of Group I mGluRs in epilepsy. Choi et al. (2014) applied [^{11}C] ABP688 micro positron emission tomography (PET)/CT to investigate mGluR5 expression *in vivo*, confirming regional mGluR5 non-displaceable binding potential (BP_{ND}) changes in a pilocarpine-induced epilepsy rat model. Using the same technique, DuBois et al. (2016) introduced *in vivo* evidence of reduced mGluR5 availability in focal cortical dysplasia in epilepsy patients, suggesting focal glutamatergic alterations in epilepsy-associated cortical developmental malformations. Applying also [^{11}C]ABP688-PET to assess mGluR5 activity in mesial TLE patients, Lam et al. (2019) quantified [^{11}C] ABP688 BP_{ND} and determined that mGluR5 was locally reduced in the epileptic hippocampal head and amygdala. This evidence likely reflected receptor internalization or conformational changes in response to excess extracellular glutamate, and suggested that mGluR5 is a potential therapeutic target for mesial TLE treatment. Using electrophysiology and two-photon microscopy, Ding et al. (2007) showed that in mice with pilocarpine-induced status epilepticus (SE), mGluR5 activation triggers astrocytic Ca^{2+} transients that promote neuronal hyperactivity and death by mediating the release of glial-derived glutamate and activating GluN2B-subunit containing NMDAR-mediated neuronal currents. The astrocyte hyperexcitability and altered glial transmission induced by this pathway are vital in controlling the excitability balance required to set lower seizure thresholds in epileptic circuits (Alcoreza et al., 2021).

Abnormal depolarization-induced suppression of excitation (DSE) was reported in animal epilepsy models. During chronic inflammatory pain, increased nociception due to reduced DSE in the anterior cingulate cortex may be associated with reduced mGluR5 protein levels and function (Guo et al., 2018). Extensive data have established mGluR1's critical role in the transition of interictal bursts into ictal activity and development of sustained, synchronized discharges. Using a rat model, Postnikova et al. (2019) reported that NMDA-dependent LTP was inhibited during pentylentetrazole (PTZ)-induced SE, and underwent a transient switching to mGluR1-dependent potentiation. One day after SE induction, the mGluR1 antagonist FTIDS completely blocked LTP in hippocampal slices from PTZ-treated animals, and mGluR1-dependent LTP was expressed postsynaptically without NMDA receptor activation. Thus, mGluR1 antagonists hold therapeutic promise for novel epilepsy syndrome treatments.

Drugs targeting mGluR1 and mGluR5 are considered to have great potential for the treatment of epilepsy (Anovadiya et al., 2012; Hanak et al., 2019; DuBois et al., 2021). Allosteric mGluR modulators are well studied and provide robust foundations for both basic research and therapeutic drug development. D'Amore et al. (2014) compared the effects of allosteric activators of mGluR1 and mGluR5 in the WAG/Rij rat models of absence epilepsy. They showed that the antiepileptogenic effect of VU0360172, a positive allosteric modulator (PAM) of mGluR5, largely persisted over time, with only minor tolerance signs. In contrast, that of mGluR1 PAM RO0711401 ceased over a relatively short period (D'Amore et al., 2014). These results hence support the development of mGluR5 PAMs as potential symptomatic agents for the treatment of chronic absence epilepsy (D'Amore et al., 2014; Celli et al., 2019; Brown et al., 2022). In subsequent experiments, some researchers locally injected VU0360172 and RO0711401 into the thalamus and cortex of WAG/Rij rats and found that both agents attenuated absence seizures by enhancing cortical GABAergic inhibition and reducing thalamic tonic GABAergic inhibition (D'Amore et al., 2015; Gedikli et al., 2023). Further research in this rat model concluded that VU0360172 elicited long-lasting antiabsence effects when used in conjunction with ethosuximide, the first-choice medication for the treatment of patients with absence seizures (D'Amore et al., 2016). Hanak et al. (2019) used a

Table 2 | Roles of Group I mGluRs in epileptogenesis

Receptor	Mechanism	Signaling pathway	Model organism	Epilepsy inducer	Reference
mGluR5	Initiation of fast ripples	phospholipase C β 1 \uparrow \rightarrow intracellular Ca $^{2+}$ \uparrow	Male Wistar rats	KA (0.8 μ g/0.5 μ L)	Medina-Ceja and Garcia-Barba, 2017
mGluR5	Increased astrocytic glutamate uptake	Changes in synaptic contact: IP3 signaling \uparrow \rightarrow number of Schaffer collateral synapses \uparrow \rightarrow enhanced glutamate uptake/GLT-1 expression/PKC-dependent phosphorylation	Adult male and female mice	KA (2 mg/mL)	Umpierre et al., 2019
mGluR5	Synthesis of amyloid-beta protein precursor	mGluR5/FMRP signaling (influenced by A β /PrPC/mGluR5 interactions)	3 \times Tg-AD mice	Auditory stimuli (5 min, high-pitched siren, 120 dB)	Kazim et al., 2017; Westmark, 2019
mGluR1/5	Initiating SWDs	mGluR \downarrow \rightarrow GAT-1 protein \downarrow /GABA uptake \downarrow \rightarrow SWDs \uparrow	Male spontaneously epileptic WAG/Rij rats, age-matched Wistar rats, Sprague-Dawley rats		Celli et al., 2020
mGluR5	Decreasing tumor necrosis factor α expression in immune cells (microglia and macrophages)	Enhanced innate immune response \rightarrow proinflammatory cytokine secretion \rightarrow seizure development	Male WAG/Rij rats, male non-epileptic control Wistar rats		Crans et al., 2020
mGluR5			C57BL/6J inbred male mice	DA strain of TMEV	Hanak et al., 2019
mGluR5			C57BL/6J inbred male mice, MyD88-deficient mice	2 DA strain of TMEV	Kirkman et al., 2010
mGluR1/5	mGluR5-dependent calcium transients	Gq-PLC-IP3 signaling \rightarrow calcium transients/activity of PKC \uparrow \rightarrow epileptogenesis	Long Evans rats and genetic absence epilepsy rats from Strasbourg model		Neyer et al., 2016
mGluR1/5	Eliciting epileptiform discharges	PLC β 1 signaling: G α q/11 subunit \rightarrow PLC β pathway \rightarrow IP3	Ten-week-old F1 homozygous and wild-type littermates from crosses of C57BL/6J(N8)PLC β 1 $^{+/+}$ and 129S4/SvJae(N8)PLC β 1 $^{-/-}$		Chuang et al., 2001
mGluR5	NMDA receptor activation	Activated glutamatergic synapses/ <i>in vivo</i> kindling \rightarrow activated group I mGluRs \rightarrow epileptogenesis	Male Wistar rats	Tramadol (150 mg/kg)	Valian et al., 2021
mGluR5		NMDA receptor \uparrow \rightarrow epileptogenesis/maintenance of seizures	Male Wistar rats (7–8-wk-old)	Pilocarpine (10 mg/kg with 30 min intervals)	Kovalenko et al., 2022
mGluR5	Reducing CaMKII activity	Protein kinase C mediated CaMKII phosphorylation at Ser901 \rightarrow CaMKII \downarrow \rightarrow limbic epilepsy	Embryonic neurons; HEK293T cells		McNamara et al., 2006; Park et al., 2008
mGluR1/5	Contributing to the paroxysmal burst of multiple unit activities in CA1 region	Exogenous activation of mGluR \rightarrow extrasynaptic NMDAR/suprathreshold depolarization \rightarrow paroxysmal burst	P5–P7 Wistar rats	TBOA (DL-threo- β -benzyloxyaspartic acid, 100 μ M)	Molinari et al., 2012
mGluR1/5	Elevation of spontaneous spike frequency in cortical neurons	Group I mGluRs \downarrow \rightarrow Anaphase-promoting complex/cyclosome \uparrow /casein kinase I \uparrow \rightarrow Mdm2 \downarrow \rightarrow p53 \uparrow \rightarrow proteasomal degradation of Akt	p53 $^{fl/+}$ -Emx1-Cre $^{+}$ mouse neurons		Liu et al., 2020
mGluR5	Co-localization with norbin in neurons of epileptic brain	Norbin \downarrow \rightarrow mGluR5 signaling \downarrow /CaMKII \uparrow	Adult male Sprague-Dawley rats	Pilocarpine hydrochloride (30 mg/kg)	Xu et al., 2017
mGluR1	DNA methylation	Hypermethylation of mGluR1 gene \rightarrow prolonged febrile seizure \uparrow	Adult Sprague-Dawley rats	KA (1.83 mg/kg)	Alese and Mabandla, 2019
mGluR1/5	Altering efficacy of synaptic connections	\uparrow mGluR1 α in TLE \rightarrow intracellular calcium \uparrow \rightarrow altered efficacy of synaptic connections	Male Sprague-Dawley rats/TLE patients	KA (12.5 mg/kg)	Blumcke et al., 2000

CaMKII: Calcium/calmodulin-dependent protein kinase II; FMRP: fragile X mental retardation protein; GLT-1: glutamate transporter-1; IP3: Inositol 1,4,5-trisphosphate; KA: kainic acid; mGluR: metabotropic glutamate receptor; NMDA: N-methyl-D-aspartic acid; PKC: protein kinase C; PLC: phospholipase C; SWD: spike-and-wave discharges; TMEV: Theiler's murine encephalomyelitis virus.

Theiler's murine encephalomyelitis virus (TMEV)-induced TLE mouse model to demonstrate that VU0360172 reduced acute seizures and tumor necrosis factor α -producing microglia and macrophage abundance by three days post-infection. Furthermore, VU0360172 treatment did not alter viral antigen levels, suggesting that it does not affect viral clearance. In turn, Kelly et al. (2018) reported that treating a Tsc2 mutant mouse model with the mGluR5 PAM RO6807794 exacerbated seizures and hyperactivity. This finding suggests that mGluR5 inhibition might serve to effectively correct the disease's core phenotype, characterized by seizures and hyperactivity.

Vijaya Prabhu and Singh (2019) developed an energy-optimized pharmacophore model to identify in the eMolecules database potent negative allosteric modulators (NAMs) of mGluR5 by obtaining variable conformation sites for docking targets. After validating the model through enrichment calculations, specific amino acid interactions with receptor metastable binding sites for the candidate compounds were analyzed via molecular dynamics simulations. Within the binding regions, TRP785 and TYR659 were identified as critical determinants of hydrophobic bonds, whereas SER809 critically influenced hydrogen bonding interactions.

The potential of plant-derived therapeutic agents to modulate mGluR5 expression and/or activity has been suggested by some studies. Krishnakumar et al. (2015) reported that *Bacopa monnieri* extract ameliorated pilocarpine-induced TLE in rats at least in part by downregulating mGluR5 expression. Similarly, behavioral and physiological assays conducted by Li et al. (2017) showed that fermented Pu-erh tea significantly reduced mGluR5 transcription and translation and alleviated pilocarpine-induced epilepsy in rats.

Alese et al. (2020) demonstrated marked downregulation of mGluR5 expression in hippocampi from PTZ-treated rats with a history of LPS-induced prolonged febrile seizures compared to PTZ-treated controls without prolonged febrile seizure history, an effect probably related to increased glutamate concentrations in the epileptic brain. Of note, these experiments

demonstrated also an association between epilepsy and depressive-like behavior regardless of background prolonged febrile seizure history.

There are however conflicting reports about whether mGluR5 antagonists can prevent epilepsy. Dyomina et al. (2022) showed that administration to rats of the selective mGluR5 antagonist MTEP during the latent phase of pilocarpine-induced SE did not prevent SE development nor symptoms, but completely prevented neuronal loss and partially attenuated astrogliosis in the hippocampus. They speculated that the neuroprotective effect of MTEP may result from short-term glial activation and enhanced glial glutamate reuptake secondary to prevention of excitatory amino-acid transporter 2 protein downregulation in astrocytes.

There is evidence that mGluR5 can also act in concert with other molecules and signaling pathways to affect epilepsy. For example, Wang et al. (2016) reported that CB1 receptor antagonist application early during PTZ-induced epileptogenesis after brain injury attenuated hyperexcitability by reversing mGluR5 overexpression in the hippocampus. Xu et al. (2017) demonstrated that norbin, a prominent endogenous mGluR5 signaling regulator co-expressed with mGluR5 in brain tissues, is downregulated in the temporal lobes of TLE patients and in the hippocampus of rats with pilocarpine-induced epilepsy. A connection between reduced norbin expression, possibly linked to mGluR activation, and epileptogenesis was therefore theorized. In turn, Medina-Ceja and Garcia-Barba (2017) found that blocking the mGluR5 receptor in KA-treated rats temporarily reduced the number of fast ripples (high-frequency oscillations of 250–600 Hz) associated with epilepsy.

The activities of mGluR1 and mGluR5 affect as well other proteins and pathways. Celli et al. (2020) described the regulation of thalamic GABA transmission by mGluR5 activation, indicated by increased GABA uptake in the thalamus of absence epileptic WAG/Rij rats. This was consistent with results from previous studies in various preclinical absence epilepsy models indicating that defective GABA uptake is associated with SWD pathophysiology (Yalcin,

2012; Kovacs et al., 2022). Drugs that enhance synaptic and extrasynaptic GABA levels, such as tiagabine and vigabatrin, exacerbate akinetic seizures and hold promise for treating akinetic epilepsy (Celli et al., 2020).

Crans et al. (2020) utilized a systemic kainic acid (KA) TLE model to demonstrate mGluR5 protein downregulation in the late latency and exponential growth phases post-SE, primarily in the hippocampal CA1 region. Furthermore, their data suggested a relationship between Homer-1b/c downregulation and seizure rate in the SE model, potentially indicating an endogenous neuroprotective mechanism. In addition, Di Cicco et al. determined that mGluR5 and Homer protein expression changes in symptomatic WAG/Rij rats significantly reduced mGluR1- and mGluR5-mediated LTD at Schaffer collateral-CA1 (SC-CA1) synapses, pointing that hippocampal mGluR5-dependent synaptic plasticity is associated with a pathological phenotype in these animals (Di Cicco et al., 2021). Previously, it had been suggested that mGluR1 and mGluR5 activation underly the attenuating effect of low-frequency stimulation on neuronal hyperexcitability produced by epileptiform activity in hippocampal CA1 pyramidal neurons (Neyman and Manahan-Vaughan, 2008). These findings corroborate long-term inhibition and shock absorption as low-frequency stimulation anti-epileptiform activity effects *in vitro* (Ghasemi et al., 2021). However, further studies are needed to fully elucidate the underlying cellular and molecular mechanisms involved in the antiepileptic effects of low-frequency stimulation.

Groups II–III mGluRs

Several studies corroborated that Group II and Group III mGluRs are located at glutamatergic neurons' presynaptic ends and reduce glutamate release (Ure et al., 2006), which makes them potential targets for antiseizure drug development. However, compared with Group I mGluRs, relatively little research has focused on Groups II and III mGluRs in recent years (Tables 3 and 4). Several studies (Davidson et al., 2016; Bocchio et al., 2018; Li et al., 2020; Bodzeta et al., 2021; Miller et al., 2022) have explored Group II mGluRs' influence on epilepsy and neuron excitability regulation. Das et al. examined mGluR changes in resected human hippocampus through immunohistochemical staining and western blotting (Das et al., 2012). Their study detected significant mGluR2 and mGluR3 upregulation and astrocyte activation in brain tissue from TLE patients, concluding that mGluR2 deregulation might play an essential role in TLE development. However, the authors failed to confirm whether this phenomenon is a compensatory mechanism to decrease neuronal activity.

Evidence for such a negative feedback was obtained by experiments showing that mGluR2 gene mutation increases motor neuron excitability by disrupting autocrine glutamate-mediated negative feedback and preventing PI3K activation (Liu et al., 2021). These results suggest that neuron excitability disruption may induce CNS disorders, including epilepsy (Lima et al., 2020). The interactions between mGluRs and synaptic circuits within the human brain are garnering increasing attention. Bocchio et al. (2018) reported that most Group II mGluRs are autoreceptors that inhibit glutamate delivery to pyramidal cerebral cortex neurons to mediate presynaptic inhibition of excitatory transmission. Their study provided new methodological tactics for revealing antiseizure drug mechanisms.

Extensive research in rodent models has proven that inadequate glutamate uptake can induce seizures through mechanisms resembling those of some human epilepsy syndromes (Pajarillo et al., 2019). However, the cellular mechanisms linking glutamate transporter dysfunction with pathological cortical activity remain elusive. Shedding light on the involvement of amino acid transporters' abnormalities in epilepsy, Molinari et al. (2012) showed that

application of the amino acid transporter inhibitor TBOA to the CA1 region of hippocampal slices lead to insufficient extracellular glutamate buffering, which allowed Group I/II mGluRs and NMDAR interconversion. This interaction initiates hippocampal network hyperexcitability, promotes seizure-like activity generation during glutamate release, and reduces afterhyperpolarization currents.

In vivo experiments demonstrated that Group III mGluRs activation may aid in preventing and treating epilepsy through the excess extracellular glutamate spillover, excitotoxicity inhibition, and seizure suppression (Vera and Tapia, 2012; Lazo-Gomez and Tapia, 2016). However, a previous study had suggested that during seizure kindling, Group III mGluRs may mediate a shift in the balance between neurotransmitters toward increased excitatory amino acid production (Maciejak et al., 2009). Kovalenko et al. (2022) reported decreased Group III mGluR gene expression in the hippocampus and temporal cortex of rats during the latent and chronic stages of pilocarpine-induced epilepsy. Additionally, they showed that while most changes in mGluR expression detected in the latent phase were absent in the chronic phase, mGluR8 mRNA downregulation persisted during the latter. These finding led the authors to suggest that Group III mGluRs agonists are the most suitable targets for epilepsy prevention.

Several studies indicated that G-alpha-interacting protein (GAIP) is crucial for receptor transport and expression (Shaw et al., 2019; Liu et al., 2021, 2022b), but its role in epilepsy is still uncertain. Liu et al. (2022a) detected a reduction in GAIP interacting protein C-terminus 1 (GIPC1) expression in both TLE patients and in mice with KA-induced epilepsy. They further showed that GIPC1 colocalized with mGluR7 and its overexpression counteracted epileptogenesis through mGluR7 upregulation. Dammann et al. (2018) reported that mGluR4 and mGluR6 downregulation in associational-commissural-CA3 synapses occurred concomitantly with mGluR8 upregulation in SC-CA1 synapses in pilocarpine-treated epileptic mice, concluding that a bidirectional shift in the transcription of Group III mGluRs modulates synaptic depression in the hippocampus of chronically epileptic mice. Evidence for divergent roles for Group I and Group III mGluRs in epilepsy was in turn produced using pilocarpine-treated mGluR4-KO and mGluR1-overexpressing mice. For each mouse type, increased seizure frequency was observed, respectively, during the acute and the chronic stages of SE, while enhanced hippocampal neuronal loss was only evident in mGluR4-KO mice (Pitsch et al., 2007; Pohlentz et al., 2022). Meanwhile, the ongoing debate regarding mGluR3 expression levels in TLE patients (Berger et al., 2020; Peterson and Binder, 2020) highlights the need for further investigation in larger sample sizes, as well as more comprehensive basic research.

Protein interactions between extracellular leucine-rich repeat fibronectin domain-containing family proteins (Efn1 and Efn2) and Group III mGluRs have been described in recent studies (Matsunaga and Aruga, 2021). Efn2-KO mice exhibit various behavioral abnormalities, including increased seizure susceptibility, hyperactivity, and anxiety. Dunn et al. (2019) showed that administering the mGluR4-selective PAM VU0155041 rescued these behavioral abnormalities in Efn2-KO mice. Due to its low glutamate affinity, mGluR7 is speculated to act as a brake against excessive glutamate levels (Niswender and Conn, 2010), which may help explain increased seizure incidence in mGluR7-deficient animals (Sansig et al., 2001). In this regard, the Dunn et al. (2019) report pointed to mGluR7 downregulation as a determinant factor of the epilepsy-like phenotype of Efn2-KO mice. Complementing mechanistic studies like those above with proteomic and genomic studies will further our understanding of the defining roles of mGluRs in epilepsy and foster the development of novel treatments.

Table 3 | Roles of Group II mGluRs in epileptogenesis

Receptor	Mechanism	Signaling pathway	Model organism	Epilepsy inducer	Reference
mGluR2	Astrogliosis, cellular hypertrophy, water homeostasis, inflammation, modulation of excitatory neurotransmission	GluR2 receptor and KA receptor ↓→Ca ²⁺ ↑	TLE patients		Das et al., 2012
mGluR2/3	Excitatory synaptic transmission	Group II mGluRs↑→release of glutamate onto pyramidal neurons ↓→epileptogenesis	Pyramidal neurons of cortical layers 2–3 in acute slices derived from surgically removed cortical tissue of people with epilepsy		Bocchio et al., 2018
mGluR2/3	Disruption of glutamate-mediated homeostasis of neuronal excitability	Drosophila GluRA mutations→PI3K activation↓, FOXO↑→neuronal excitability	Drosophila (UAS-PI3K DN and UAS-PI3K-CAAX transgenes)	Electrical stimulation (10 Hz)	Howlett et al., 2008; Lovisari et al., 2021
mGluR2/3	Involvement in the generation and propagation of epilepsy in the entorhinal cortex	LY354740→K ⁺ conductance↑→Na ⁺ -permeable channel↓→neuronal excitability and epileptiform activity↓	Sprague-Dawley rats	PTX (100 mM)	Zhang et al., 2015
mGluR3	Seizure-induced upregulation of mGluR3	Mesial temporal lobe epilepsy→mGluR3↑→TGF-β↑	Male Sprague-Dawley rats	Intermittent electrical stimulation (10-s trains of 50 Hz biphasic square pulses); max. stimulus intensity: 500 μA)	Aronica et al., 2000; Kovalenko et al., 2022; Celli et al., 2023
mGluR2	Synergistic interactions with the antiseizure drug levetiracetam and the positive allosteric modulator JNJ-46356479		Adult male CF-1 mice	Electrical stimulation (6 Hz, 32 or 44 mA)	Metcalf et al., 2018

FoxO: Forkhead box O; LY354740: hexane-2,6-dicarboxylic acid; mGluR: metabotropic glutamate receptor; PI3K: phosphoinositide 3-kinase; PTX: Picro-toxin; TLE: temporal lobe epilepsy.

Table 4 | Roles of Group III mGluRs in epileptogenesis

Receptor	Mechanism	Signaling pathway	Model organism	Epilepsy inducer	Reference
mGluR7	Antagonism of mGluR7	GIPIC1↓→mGluR7↓→more and longer abnormal brain discharges in LFP	TLE patients and adult male C57BL/6 mice	KA (50 nL of a 20 mM solution)	Liu et al., 2022a
mGluR4	mGluR4 knock-down	mGluR4↓→excitatory activity and seizure-associated vulnerability of hippocampal neurons↑→severe seizure activity↑	mGluR4-KO mice		Kumar et al., 2022
mGluR4, mGluR6, mGluR8	Divergent patterns of associational-commissural-CA3 and SC-CA1 synapse depression in SE	mGluR4, mGluR6↓, mGluR8↑→synaptic depression→chronic epilepsy	Male Wistar rats	Pilocarpine hydrochloride (340 mg/kg)	Dammann et al., 2018
Group III mGluRs	Excitotoxic action of 4-aminopyridine	Extracellular glutamate↑→mGluR III↑→seizure↓	Male Wistar rats	4-aminopyridine (7 mM)	Vera and Tapia, 2012
Group III mGluRs	Neurotransmitter shift towards increased production of excitatory amino acids	mGluR III↓→GABA, alanine, taurine, and glutamine/GABA ratio↑→seizure	Adult male Wistar rats	PTZ (35 mg/kg)	Zhai et al., 2021; Zhao et al., 2022
mGluR7	Interaction between mGluR7 and PDZ proteins	Targeted mutation of the mGluR7a C terminus→disrupted interaction with PDZ proteins→EEG discharges	Adult Sprague-Dawley rats		Liu et al., 2022b; Tuduri et al., 2022
Group III mGluRs	Selective downregulation of group III mGluRs and dysregulated glutamatergic synaptic transmission	Elfn2 knockout→selective downregulation of group III mGluRs and dysregulated glutamatergic synaptic transmission→seizure susceptibility↑	HEK 293T/17 cells		Dunn et al., 2019
Group III mGluRs	Decreased expression of group III genes in the hippocampus and temporal cortex	Group III genes↓→mGluRs III expression↓→epileptogenesis	Male Wistar rats	Pilocarpine (20–40 mg/kg)	Kovalenko et al., 2022
mGluR7	Interactions between extracellular leucine-rich repeat fibronectin domain-containing family proteins (Elfn1 and Elfn2) and mGluRs	Activation of mGluR7 by Elfn1→glutamate levels↓	Elfn1/2-KO mice		Matsunaga and Aruga, 2021

EEG: Electroencephalography; GABA: gamma aminobutyric acid; KA: kainic acid; KO: knockout; LFP: local field potential; mGluRs: metabotropic glutamate receptors; TLE: temporal lobe epilepsy.

Therapeutic Potential of Metabotropic Glutamate Receptors in Epilepsy

Epilepsy has become one of the most common neurological disorders. Although its exact etiology is still unclear, many researchers believe there is potential for antiepileptic treatment targeting mGluRs (Malik et al., 2017). mGluRs have three primary advantages in epilepsy-targeting drug development (Vijaya Prabhu and Singh, 2019; Dyomina et al., 2022; Witkin et al., 2022): (i) they generally modulate slow synaptic responses and have low inference in individual synaptic release events; (ii) they are only active under high neuronal activity conditions, which determines selectivity and thus favors their utility as drug targets; and (iii) the activation of mGluRs-related pathways usually produces long-lasting effects and can be further modulated by targeting associated G-proteins and downstream second messengers.

mGluR5 is a prominent calcium-dependent glutamate release mediator in astrocytes that promotes neuronal excitability. Elevated mGluR5 levels in hippocampal tissue of TLE patients suggest that its overexpression induces abnormal neuronal firing. In contrast, mGluR2 and mGluR3 are located both in astrocytes and in presynaptic terminals, and negatively regulate excitatory neurotransmission through alterations in intracellular cAMP levels. Intriguingly, the expression of both mGluR2 and mGluR3 is also significantly increased in the hippocampus of TLE patients, which may represent a compensatory response to counteract pathological neuronal activity (Das et al., 2012). In this regard, it has been shown that administration of a highly selective Group II mGluR agonist, (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC), significantly suppresses behavioral seizures in rats with pilocarpine-induced SE (Yao et al., 2015). This agent conferred not only anticonvulsant effects, but also neuroprotective ones, by reducing SE-induced neurogenesis in the dentate gyrus. Meanwhile, both 2R,4R-APDC and the Group III mGluR8 agonist (S)-3,4-DPCPG were shown to provide neuroprotection in animal models of epilepsy by significantly reducing or completely eliminating superoxide anion formation in the brain (Folbergrova et al., 2012).

Group I mGluRs

Current studies on mGluR1 and mGluR5 mostly focus on the effects of their positive and negative modulators, to identify pharmacological strategies aimed at attenuating the pro-convulsive effects of these mGluRs (Anovadiya et al., 2012; Su et al., 2022). Preclinical studies have shown that Group I mGluR negative modulators are among the most efficacious antiepileptic drugs. Kelly et al. (2018) determined that NAM-mediated chronic mGluR5 inhibition corrected overactivity, reduced seizure frequency and duration, and elevated *de novo* synaptic protein synthesis in TSC model mice.

Dyomina et al. (2022) demonstrated potential neuroprotection for the selective mGluR5 antagonist MTEP, which prevented neuronal loss and excitotoxicity in pilocarpine-treated rats. However, the ability of MTEP to prevent epilepsy development and attenuate its symptoms and manifestations has not been investigated. The latter study suggested that it is essential to focus on the actions of epilepsy-specific target molecules when developing antiepileptic drugs, and that not all mGluR5 inhibitors will have equal efficacy against epilepsy. The authors pointed however to a therapeutic opportunity, by implying that specific Group I mGluR NAMs may aid in epilepsy treatments

as part of drug combinations. Along those lines, a previous investigation had showed that MPEP, an mGluR5 NAM, reduced fast ripple events in KA-treated rats only during the first hour post-application, without altering oscillation frequency nor duration for each FR event (Medina-Ceja and Garcia-Barba, 2017). Meanwhile, Westmark et al. (2021) demonstrated that MPEP attenuated sensitivity to audiogenic-evoked seizures in a mouse model of fragile X syndrome mice, implying that NAMs effects may vary in relation to epileptogenesis mechanisms and types. These findings thus support the notion that Group I mGluR NAMs are promising antiepileptic drugs and thus merit more in-depth research.

Although Group I mGluR PAMs are often shown to cause epilepsy or to exacerbate the epileptic phenotype, there is evidence that they may instead be beneficial for epilepsy treatment. Celli et al. (2020) showed that systemic mGluR5 PAM VU0360172 injection increased GABA uptake both in the thalamus and in synaptosomes *in vitro* in the WAG/Rij model of absence epilepsy. D'Amore et al. (2014) had previously demonstrated that although both VU0360172 and RO0711401 (an mGluR1-selective PAM) were able to decrease SWD frequency, tolerance to RO0711401, but not VU0360172, developed after 3 days of treatment in WAG/Rij rats. Moreover, Hanak et al. (2019) noted that attenuated seizure activity after positive mGluR5 regulation was correlated with reduced brain levels of the proinflammatory cytokines IL-6 and tumor necrosis factor α in a TMEV-induced TLE mouse model. Thus, although there are conflicting conclusions and ongoing controversies, studying the therapeutic effects of Group I mGluR PAMs is still imperative as they have remarkable potential for epilepsy prevention and treatment.

mGluR-interacting proteins are also promising drug targets. For example, Homer proteins can physically connect glutamate receptors to intracellular calcium stores to regulate signaling cascades coupled to Group I mGluRs. In hippocampal cells, the scaffold protein tamalin regulates cell surface mGluR1a expression and the targeting of mGluR5 to neurons and may promote homodimerization of mGluRs (Pandey et al., 2020). Besides tamalin, calmodulin, and protein phosphatases 1 and 2, among others, were also shown to interact with mGluRs and regulate their effects (Enz, 2012).

Group II–III mGluRs

Many drugs based on Group II and III mGluRs were designed for treating neurological disorders including epilepsy. Currently available mGluR II agonists include (2R,4R)-APDC, DHPG, and (2S, 2'R, 3'R)-2-(2',3'-dicarboxycyclopropyl) glycine, shown to alleviate audiogenic seizures in rats susceptible to hereditary epilepsy, and LY379268 and LY389795, shown to reduce absence seizures in lethargic (*lh/lh*) mutant mice (Thomsen et al., 1994; Attwell et al., 1998; Qian and Tang, 2016). Similarly, Zhang et al. (2015) reported that the selective Group II mGluR agonist LY354740 notably inhibited epileptiform activity in Horizontal brain slices from 13- to 20-day-old Sprague-Dawley rats. Their study further showed that application of the G $\beta\gamma$ inhibitor gallein significantly reduced LY354740-induced hyperpolarization of entorhinal neurons, indicating that mGluRs II activation reduced neuronal excitability via G $\beta\gamma$. A study conducted by Yao et al. (2015) revealed that 2R,4R-APDC exerted a neuroprotective effect against hyperexcitability by reducing the amount of ectopic nascent dentate granule cells, which contributes to abnormal network reorganization in the adult rat hippocampus. However, elucidating the exact mechanism(s) responsible for this effect requires further investigation.

mGluRs III agonists, including L-(+)-2-amino-4-phosphonobutyric acid (Watanabe et al., 2011), L-serine-O-phosphate (Qian and Tang, 2016), (R, S)-4-phosphonophenylglycine (Selvam et al., 2018), and (1S,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid (Selvam et al., 2018), have anticonvulsant actions in models of generalized epilepsy in mice. Unfortunately, relatively few antiepileptic drugs based on Group III mGluRs have been so far developed.

Limitations

This review has certain limitations. First, since epilepsy has attracted the attention of a large number of investigators in the field of neurosciences, there has been a wealth of research output over the years. Hence, in the process of literature retrieval and screening, researchers may inevitably miss some excellent or innovative studies. Additionally, in the summary of the signaling pathways involving mGluRs, it is difficult to provide an in-depth and exhaustive description due to the complex molecular mechanisms and various physicochemical factors involved. Moreover, the authors' bias in selecting articles may also have an impact on the review.

Conclusion and Perspective

The mGluR family is vital in epilepsy onset and progression. Group I mGluRs (mGluR1 and mGluR5) are mainly involved in physiological G protein-coupled signaling pathway activities, intracellular calcium regulation, and neuronal firing. Group II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7, and mGluR8) mGluRs characteristically mediate adenylate cyclase activity inhibition and neurotransmitter release regulation. This review summarizes the involvement of the three mGluR groups in epilepsy, in the hope that it will further the identification of molecular markers and therapeutic drug targets. In light of the beneficial effects demonstrated for mGluR agonists and antagonists in preclinical models of epilepsy, their use as part of novel drug combination therapies may prove to be a highly effective clinical approach to optimize efficacy and delay or prevent drug resistance.

This review emphasized that factors related to the complex regulatory networks established between mGluRs and their numerous interacting proteins, mGluR agonist/antagonists dosages, and epilepsy stage may significantly influence therapeutic effects (Gregory and Goudet, 2021; Zhai et al., 2021). Thus, specific therapies targeting different pathogenic mechanisms also merit further investigation. Although several molecules, such as AMPA receptors, protein kinases, and mGluRs, are possible drug targets for epilepsy treatment, most related pharmacological interventions have only been animal-tested, and their potential use and safety in human epilepsy remain to be demonstrated in clinical trials.

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