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Group I Metabotropic Glutamate Receptors: A Role in Neurodevelopmental Disorders?

Maria Vincenza Catania · Simona D'Antoni · Carmela Maria Bonaccorso · Eleonora Aronica · Mark F. Bear · Ferdinando Nicoletti

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Abstract Group I metabotropic glutamate receptors (mGlu1 and mGlu5) are coupled to polyphosphoinositide hydrolysis and are involved in activity-dependent forms of synaptic plasticity, both during development and in the adult life. Group I mGlu receptors can also regulate proliferation, differentiation, and survival of neural stem/progenitor cells, which further support their role in brain development. An exaggerated response to activation of mGlu5 receptors may underlie synaptic dysfunction in Fragile X syndrome, the most common inherited form of mental retardation. In addition, group I mGlu receptors are overexpressed in dysplastic neurons of focal cortical dysplasia and hemimegaloencephaly, which are disorders of cortical development associated with chronic epilepsy. Drugs that block the activity of group I mGlu receptors (in particular, mGlu5 receptors) are potentially helpful for the treatment of Fragile X syndrome and perhaps other neurodevelopmental disorders.

Keywords Neural development · Plasticity · Metabotropic glutamate receptors · mGluRs · Fragile X syndrome · FRAX · Epilepsy · Malformation of cortical development

M. V. Catania (✉) · S. D'Antoni
Institute of Neurological Sciences,
National Research Council (CNR),
vl. Regina Margherita 6,
95123 Catania, Italy
e-mail: m.catania@isn.cnr.it

M. V. Catania · C. M. Bonaccorso
Laboratory of Molecular and Cellular Neurobiology,
Oasi Institute for Research on Mental
Retardation and Brain Aging (IRCCS),
Troina, Enna, Italy

E. Aronica
Department of (Neuro)Pathology, Academisch Medisch Centrum,
1105 AZ Amsterdam, The Netherlands

M. F. Bear
The Picower Institute, HHMI,
Massachusetts Institute of Technology,
Cambridge, MA, USA

F. Nicoletti
Department of Physiology and Pharmacology "V. Erspamer",
University of Rome "La Sapienza",
Rome, Italy

F. Nicoletti
INM Neuromed,
Pozzilli, Isernia, Italy

Activity-dependent mechanisms are critical for a proper development of the central nervous system (CNS). These mechanisms are largely mediated by the major excitatory neurotransmitter glutamate, which is known to activate both ligand-gated ion channels (ionotropic glutamate or iGlu receptors) and G-protein-coupled receptors (metabotropic glutamate or mGlu receptors). iGlu receptors, particularly α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartic acid (NMDA) receptors, mediate excitatory neurotransmission at most of the synapses in the CNS. mGlu receptors modulate excitatory synaptic transmission and are currently considered as novel targets for drugs of potential use in neurological and psychiatric disorders. However, a growing body of evidence indicates that mGlu receptors are involved in basic developmental processes that take place before synaptic formation, such as proliferation, differentiation, and survival of neural stem/progenitor cells [1–4]. Individual mGlu receptor subtypes are expressed by Cajal–Retzius cells [5], which are essential for laminar organization of the cerebral

cortex [6]. Because mGlu receptors are involved in activity-dependent and activity-independent processes occurring during early and late phases of CNS development (see below), it is reasonable to assume that a dysfunction of these receptors may contribute to the pathophysiology of neurodevelopmental disorders. In this study, we will focus on mGlu5 receptors in particular, which are developmentally regulated and are implicated in the pathophysiology of Fragile X syndrome (FRAX), which is the most frequent cause of inherited mental retardation ([7], for a recent review).

mGlu receptors are members of class C G-protein-coupled receptor superfamily and are constituted by (1) a large N terminus region (containing the Venus fly trap domain where glutamate binds and a cystein-rich domain), (2) a heptahelical transmembrane domain involved in G protein activation, and (3) a C terminus intracellular domain that interacts with a number of adaptor and scaffolding proteins. mGlu receptors form functional dimers and require two molecules of orthosteric agonists (such as glutamate) for full activation [8–10]. For G protein activation, the heptahelical domain requires a closed conformation of the Venus fly trap that is facilitated by agonist binding. However, a constitutive activity of mGlu receptors has been described in heterologous expression system [11], suggesting that there are conditions in which mGlu receptors are functional in the absence of extracellular glutamate, including elevated extracellular calcium levels [12]. Positive and negative allosteric modulators bind directly to the heptahelical domain amplifying or inhibiting mGlu receptor function. Some, but not all, negative allosteric modulators also inhibit the constitutive activity of mGlu receptors acting as inverse agonists [13–15]. mGlu receptors form a family of eight subtypes subdivided into three groups on the basis of sequence similarities, pharmacological profile, and transduction pathways. Group I includes mGlu1 and mGlu5 receptors (splice variants: mGlu1a–d; mGlu5a, b), which are coupled to Gq protein. Their activation stimulates polyphosphoinositide hydrolysis with an ensuing formation of inositol-1,4,5-trisphosphate (InsP3) and diacylglicerol (DAG), which, in turn, triggers the release of intracellular Ca^{2+} and activates protein kinase C (PKC; reviewed in [16]). 3,5-Dihydroxyphenylglycine (DHPG) acts as a selective orthosteric agonist of mGlu1 and mGlu5 receptors. 7-(hydroxyimino) cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt) and 2-methyl-6-phenylethynyl pyridine hydrochloride (MPEP) are negative allosteric modulators of mGlu1 and mGlu5 receptors, respectively [13, 17]. MPEP can also inhibit the constitutive activity of mGlu5 receptors acting as an inverse agonist. Group II includes mGlu2 and mGlu3 receptors, which are coupled to Gi proteins and are potently activated by LY354740 and LY379268. Group III includes mGlu4, mGlu6, mGlu7, and mGlu8 receptors, which are also coupled to Gi protein and activated by L-2-amino-4-phosphonobutanoate (L-AP4). *N*-phenyl-7-(hydroxyimino) cyclopropa[b]chromen-1a-carboxamide (PHCCC) behaves as a selective positive allosteric modulator (enhancer) of mGlu4 receptors [18]. Whereas mGlu1 and mGlu5 receptors are generally found in postsynaptic densities and modulate postsynaptic efficacy, mGlu2, mGlu3, mGlu4, mGlu7, and mGlu8 receptors are mainly (but not exclusively) presynaptic and regulate neurotransmitter release [19, 20].

Although both mGlu1 and mGlu5 receptors are coupled to polyphosphoinositide hydrolysis, they differ for the pattern of intracellular Ca^{2+} release that they cause. Activation of mGlu1a receptors leads to a monophasic increase in $[Ca^{2+}]_i$, whereas activation of mGlu5 induces oscillatory increases in $[Ca^{2+}]_i$. This particular property of mGlu5 receptors depends on the presence of a threonine residue (Thr840) in the C terminus domain, which is phosphorylated by PKC [21]. The oscillatory pattern of $[Ca^{2+}]_i$ dynamics might be instrumental for an epigenetic control of gene expression during development [22]. Activation of group I mGlu receptors also stimulates the ERK1/2 MAP kinase pathway and the phosphatidylinositol-3-kinase (PI-3-K) pathways that are involved in cell proliferation, differentiation, and survival, as well as in processes of activity-dependent synaptic plasticity [23–25]. mGlu1a, mGlu5a, and mGlu5b receptors interact with the EVH1 domain of Homer proteins via a proline-rich motif of the C terminus domain. Long isoforms of Homer (Homer1b/c, Homer2, and Homer3) have a coiled–coil (CC) motif in their C-terminal region that mediates self-multimerization [26]. Long Homer isoforms link group I mGlu receptors with other adaptor or scaffolding proteins and membrane receptors including inositol-1,4,5-trisphosphate and ryanodine receptors (which release Ca^{2+} from intracellular stores) [27, 28]. The short inducible Homer1a, which lacks the CC motif, acts as a dominant negative modulator of mGlu receptor function by disrupting the interaction between group I mGlu receptors and long Homer isoforms [26]. Interaction with Homer proteins controls the constitutive activity of mGlu5 receptors [29], mGlu5 receptor trafficking and lateral mobility [30–32], and mGlu5 receptor coupling to ion channels [33], as well as to the MAPK and the PI-3-K pathways [25, 34]. mGlu5 receptors are physically linked to the NR2 subunit through a chain of anchoring proteins including PSD-95, SHANK, and Homer. Activation of mGlu5 receptors facilitates NMDA receptor function, whereas activation of NMDA receptors limits mGlu5 receptor desensitization through the Ca^{2+}-mediated stimulation of protein phosphatase 2B [35]. This reciprocal interaction between mGlu5 and NMDA receptors is involved in the induction process of activity-dependent forms of synaptic plasticity.

Expression and Function of Group I mGlu Receptors During CNS Development

The expression of mGlu receptors during postnatal development was initially studied at the messenger RNA (mRNA) level by in situ hybridization [36]. Individual mGlu receptor subtypes differ in cell-specific distribution and developmental pattern of expression in the rodent brain. The transcript of mGlu1 receptors is low at birth and progressively increases during postnatal development, whereas the transcript of mGlu5 receptors is highly expressed early after birth and progressively decreases afterwards [36]. The developmental pattern of the mGlu5 reflects changes in the expression of the mGlu5a splice variant, whereas the transcript of mGlu5b receptors, which incorporates a sequence for a 32-aa insert in the 7-TM region, increases with age in the cerebral cortex, hippocampus, and corpus striatum [37, 38]. Interestingly, the expression of mGlu5a mRNA remains high in the adult olfactory bulb, where a neurogenetic pathway originating from the subventricular zone (SVZ) is active across the entire lifespan [37, 38]. Studies on the expression of mGlu1a and mGlu5 receptors at protein level have been largely consistent. Expression of mGlu5 receptors is high and widespread in the first 2 weeks of postnatal life [38–43], when the polyphosphoinositide (PI) response to group I mGlu receptor agonists in brain slices is substantial [41, 44, 45]. A much lower receptor response is detected in hippocampal, cortical, or striatal slices of adult rats, where only agonists endowed with high intrinsic efficacy (and resistant to local metabolism and/or transport, such as ibotenic acid or 1S,3R-ACPD) can stimulate PI hydrolysis [41, 44–48]. More recent studies have shown that mGlu5 receptors are expressed in the embryonic brain and, particularly, in zones of active neurogenesis [4]. The mGlu1a receptor protein is highly expressed in discrete regions of the adult brain including the cerebellum, olfactory bulb, thalamus, and pars compacta of the substantia nigra and is barely detectable during early development [5].

A basic role for the mGlu5 receptor in cell development is suggested by the evidence that this is the only mGlu receptor subtype expressed by embryonic stem cells in vitro, and its activation is required for the maintenance of the undifferentiated state of stem cells [3, 49]. mGlu5 receptors are also found in neural stem cells, i.e., in partially committed stem cells that are present in the CNS and give rise to neurons, astrocytes, and oligodendrocytes. Genetic deletion of mGlu5 receptors or receptor blockade with MPEP inhibits proliferation of neural stem cells and reduces neurogenesis in the SVZ and hippocampal dentate gyrus [50]. Interestingly, mGlu5 receptors are transiently expressed by Cajal–Retzius cells of the rat hippocampus and cerebral cortex at E18, whereas the same cells express mGlu1a receptors at later developmental stages (between PND1 and 10) [5]. Cajal–Retzius cells are present in rodents in the early stages of neocorticogenesis before disappearing around the end of the second postnatal week and are critical for brain development because they direct the laminar organization of neocortex through the release of the glycoprotein reelin [51]. An attractive hypothesis is that a sequential activation of mGlu5 and mGlu1a receptors in Cajal–Retzius cells regulates the production and/or secretion of reelin by increasing the levels of intracellular free Ca^{2+} [52]. Activation of group I mGlu receptors increases reelin mRNA levels in cultured cerebellar neurons [53]. Mechanisms of cell death and survival are critical for the process of neuronal selection during CNS development, when supranumerary neurons that are not engaged into functional circuitries develop apoptotic death. Cultured cerebellar granule cells provide a model for the study of developmental apoptosis. These cultures are usually grown in a medium containing depolarizing concentrations of K^+, which promote cell survival by mimicking the excitatory drive of mossy fibers in the intact cerebellum. When cultures are grown in low-K^+ containing medium, granule cells die after 4 days in vitro (DIV), when expression of mGlu5 receptors begins to decline. Pharmacological activation of mGlu5 receptors promotes granule cell survival, whereas receptor blockade or knockdown accelerates apoptotic death [54, 55]. Similar data are found in cerebellar cultures containing both granule cells and Purkinje cells, where mGlu5 and mGlu1 receptors support the survival of granule cells and Purkinje cells, respectively. These receptors are also involved in the regulation of morphogenesis because their blockade reduces dendritic arborization of Purkinje cells in vitro and in vivo [56]. The mechanism(s) whereby activation of group I mGlu receptors supports cell survival has been explored in cultured hippocampal neurons, where activation of mGlu5 receptors stimulates the PI-3-K/Akt pathway by a chain of anchoring proteins that include Homer 1c and the long isoform of PIKE (phosphoinositide 3 kinase enhancer) [25].

Role for Group-I mGlu Receptors in Experience-Dependent Forms of Developmental Plasticity

Hebbian-like mechanisms of synaptic plasticity underlie processes of synaptic stabilization or elimination that ultimately lead to the formation of functional circuitries within a defined neuronal network. In the early development, a long-lasting increase in synaptic strength called long-term potentiation (LTP) seems to be important for retaining nascent synapses, whereas long-term depression (LTD) is important for synaptic elimination. The same

mechanisms contribute to associative learning in the adult life [57–60]. Activation of group I mGlu receptors is involved in the induction of LTP and LTD at different types of excitatory synapses in the CNS [60–64]. Mice lacking mGlu5 receptors show impaired learning and reduced LTP in the hippocampal CA1 region [65].

Induction of LTD in the hippocampus usually requires the activation of NMDA receptors. However, there is a mechanistically distinct form of LTD that instead requires the activation of group I mGlu receptors (reviewed in [66]). This form of LTD has been extensively characterized at the parallel fiber–Purkinje cell synapses of the cerebellar cortex, where it requires the activation of mGlu1 receptors [67–69]. Cerebellar LTD is induced by the combined activation of parallel and climbing fibers, and is considered as a substrate for motor learning. Purkinje cells of mGlu1 knockout mice are innervated by multiple climbing fibers because regression of supernumerary climbing fibers ceases about 1 week earlier than in normal mice [70]. This extends the involvement of mGlu1 receptors to processes of early synaptogenesis within the cerebellar cortex. mGlu1 is critically involved in the developmental pruning of supernumerary connections between climbing fibers and Purkinje cells [70]. The analysis of mGlu receptor-dependent LTD in the hippocampus and cerebellum shows that LTD depends on dendritic protein synthesis and follows the activation of the extracellular signal-regulated protein kinase (ERK) pathway (reviewed in [66]). Inhibitors of mRNA translation prevent (1) the induction of mGlu receptor-dependent LTD in hippocampal slices [71, 72], (2) DHPG-induced loss of postsynaptic AMPA receptors in hippocampal neurons [73], and (3) LTD at parallel fiber–Purkinje cell synapses in cerebellar slices [74].

A role for group I mGlu receptors in experience-dependent forms of developmental plasticity was originally proposed by Dudek and Bear [75], who showed that the peak of mGlu-receptor mediated PI hydrolysis in the kitten striate cortex coincides with the critical period of ocular dominance plasticity. Moreover, both the PI response to excitatory amino acids and the expression of mGluR5 is altered in dark-reared animals [75, 76]. This hypothesis was challenged by the findings that, although the old-generation, broad-spectrum mGlu receptor antagonist, (S)-α-methyl-4-carboxyphenylglycine (MCPG), prevented LTP reversal (depotentiation) in mouse visual cortex, it failed to affect ocular dominance plasticity in kitten visual cortex [77]. However, it is noteworthy that MCPG, the compound that has generated most of the controversies in the mGlu field, fails to antagonize glutamate-stimulated PI turnover in the visual cortex [78] or affect NMDA receptor-dependent LTD [79]. Involvement of mGluR5 in ocular dominance plasticity, therefore, remains an open question.

Although the gross anatomy of mGlu5 knockout mice is normal, these animals have a defect in the formation of barrels in the somatosensory cortex and a partial segregation in the pattern of thalamic innervation [80]. The altered formation of the barrel field in mGlu5 knockout mice might be directly related to a reduced stimulation of PI hydrolysis because mice lacking PLCβ1, which couples mGlu receptors to PI hydrolysis, show the same deficit [80]. In contrast, a reduced PI hydrolysis might not account for the defective thalamic innervation of mGlu5 knockout mice because segregation of thalamic afferents to the somatosensory cortex is intact in PLCβ1 knockout mice [80]. The mGlu5–PLCβ1 system might also be critical for dendritic spine maturation because PLCβ1 knockout mice show a reduced proportion of mature mushroom-shaped spines in the somatosensory cortex [81], and activation of group I mGlu receptors affects spine morphology in cultures neurons [56, 82]. Abnormal spine morphogenesis is associated with cognitive deficit in different developmental disorders including FRAX (see below) and might be related to an abnormal synthesis of synaptic proteins such as PSD-95, Shank, Homer, CamKII [83].

An Exaggerated Response to Activation of mGlu5 Receptors May Underlie Synaptic Dysfunction in FRAX

A growing number of studies support a role of mGlu5 in the pathophysiology of FRAX, a common inherited neurodevelopmental disorder, which is caused by the transcriptional silencing of the *Fmr1* gene encoding the Fragile X mental retardation protein (FMRP) [84]. FRAX is characterized by mental retardation, seizures, autistic-like behaviors, attention-deficit hyperactivity disorder, macroorchidism, facial abnormalities, and connective tissue dysfunction [85]. The brains of FRAX patients or *Fmr1* knockout mice are macroscopically normal, but neurons have an increased density of long and tortuous dendritic spines, suggesting a role for FMRP in synaptic maturation and spine pruning [86–89].

The first indication for a link between mGlu receptors and FRAX was the evidence that activation of group I mGlu receptors stimulates the synthesis of FMRP in synaptoneurosomes [90]. FMRP is a RNA-binding protein associated with polyribosomal ribonucleoparticles, which is found in dendrites and dendritic spines [90–95]. FMRP is involved in the transport of subsets of mRNAs along the dendrites to actively translating ribosomes of dendritic spines [91, 96] and regulates local protein synthesis at synapses [95, 97]. Interestingly, activation of group I mGlu receptors is necessary for FMRP trafficking from the cell body into dendrites, but diminishes FMRP localization at synapses [92]. It is believed that FMRP functions as a negative regulator of protein synthesis [98–100]. Protein

synthesis is constitutively increased in the brain of *Fmr1* knockout mice [101] and levels of synaptic proteins, such as CamKII, Arc, and MAP1B, are increased in the absence of FMRP [97, 102]. However, activation of group-I mGlu receptors stimulates further synthesis of synaptic proteins to a lesser extent when FMRP is lacking [103, 104]. This suggests that increased constitutive protein synthesis in the absence of FMRP occludes stimulated protein synthesis. One possible scenario is that FMRP normally sequesters certain mRNAs, and, following mGlu receptor activation, it releases these trapped mRNAs thus allowing their translation [104]. Mechanisms of phosphorylation/dephosphorylation regulate the association between FMRP and actively translating polyribosomes [105]. Interestingly, expression of the catalytic subunit of protein phosphatase 2A (PP2A) is increased in the absence of FMRP [106], and PP2A activity is negatively regulated by mGlu5 receptors [107]. Thus, mGlu5 receptors may influence the phosphorylation state of FMRP via an action on PP2A [7, 108].

The lack of FMRP interferes with mechanisms underlying mGlu receptor-dependent LTD [109] and epileptogenesis [110]. mGlu5 receptor-dependent LTD in the hippocampus is amplified in the absence of FMRP, whereas NMDA receptor-dependent LTD is not [109, 111]. mGlu5 receptor-dependent LTP is instead reduced in the cerebral cortex of FMR1 KO mice [112].

The mGlu5 receptor-dependent LTD found in animal models of FRAX, unlike that found in control animals, is insensitive to inhibitors of protein synthesis [113, 114]. One possibility is that the constitutive abnormality in the expression of synaptic proteins alters long-term responses to mGlu5 receptor activation in FRAX. It is noteworthy that mGlu5 receptors are less associated to Homer protein in the brain of *Fmr1* knockout mice, which is suggestive of an important alteration in receptor signalling [115].

Hippocampal epileptogenesis is another form of synaptic plasticity that depends on group I mGlu receptor activation and protein synthesis and is altered in *Fmr1* knockout mice. In wild types, long-term modification of excitability occurs only in response to activation of group I mGluRs and subsequent protein synthesis. In the knockouts, however, the excitability increases occur spontaneously. The increased excitability in the absence of FMRP can be reversibly blocked by MPEP, suggesting elevated constitutive mGlu5 receptor activation. Interestingly, epileptogenesis mediated by group I mGlu receptors requires an ERK-dependent protein synthesis [110]. Thus, the absence of FMRP causes an abnormal expression of dendritic proteins leading to the amplification of long-term responses to mGlu5 receptor activation that include LTD or epileptiform discharges triggered by synaptic glutamate. The identity of these proteins, which may be critical for the pathophysiology of synaptic dysfunction in FRAX, is unknown.

The notion that mGluR5 antagonists might be therapeutically useful for FRAX [116] has received support from studies using the mGlu5 receptor antagonist MPEP in both Drosophila and mouse models. Remarkably, MPEP rescues synaptic plasticity, courtship behaviour, and mushroom body defects in a Drosophila model of FRAX [117], and reduces susceptibility to audiogenic seizure and abnormalities in exploratory behaviour in a mouse model of FRAX [118].

mGlu Receptors and Malformations of Cortical Development

Malformations of cortical development (MCD) are a recognized cause of mental retardation and chronic epilepsy [119–121]. Chronic epilepsy has deleterious effects on the CNS, especially in the case of a developing child, and can significantly affect health and quality of life of the child and family. Epilepsy is particularly difficult to manage in these patients, and surgical resection improves seizure control in a limited number of cases [121–124] Thus, development of new treatment strategies aimed at controlling the occurrence of seizures and, most important, at preventing the development of these malformations is necessary.

Epilepsy-associated MCD are frequently encountered in surgical epilepsy programs. The access of clinically well-characterized neurosurgical material has provided the unique opportunity to study a variety of developmental focal lesions related to seizures, combining functional in vivo studies with structural, molecular, and neurophysiological analysis of the resected tissue. Neuropathological evaluation of surgical specimens from patients with epilepsy-associated developmental lesions reveals two major pathologies: focal cortical dysplasia (FCD) and low-grade neurodevelopmental tumors (glioneuronal tumors, GNT) [125]. Hemimegalencephaly (HMEG) is another MCD associated with severe and intractable epilepsy, characterized by unilateral enlargement of the cerebral hemisphere, which requires prompt neurosurgical intervention [126]. HMEG can occur as isolated malformation or associated with several syndromes [127, 128], and epilepsy surgery in patients with HMEG has modest post-surgery seizure and cognitive outcomes [129].

MCD refer to a group of disorders caused by alteration of the normal development of the cortex and are histologically characterized by regions of abnormal cortical cytoarchitecture, with dislaminated cortical layers and cytological abnormalities involving both glial and neuronal cells [125, 130]. Immature neurons, giant neurons, dysmorphic neurons, and glioneuronal balloon cells are encountered within the dysplasic cortex in both FCD and HMEG. GNT are composed of a mixture of tumor glial cells and abnormal

neuronal elements. A recent classification scheme for MCD, based on the possible pathogenetic mechanisms involved in specific MCD, includes FCD and GNT, and HMEG among the disorders of proliferation (with abnormal cell types) [120]. Intraoperative electrocorticography supports the intrinsic and high epileptogenicity of MCD, such as FCD and GNT [123, 131]. In addition, several electrophysiological studies performed in tissues of patients undergoing surgery for intractable epilepsy indicate the presence of a hyperexcitable neuronal component functionally integrated with excitatory pathways (for reviews, see [125, 132]). The cellular mechanism(s) underlying the epileptogenicity of MCD remain, however, largely unknown. Recent work suggests the existence of developmental alterations of the balance between excitation and inhibition in the pathogenesis of epileptic discharges in patients with MCD. In particular, attention has been focussed on detection of alterations of postsynaptic ionotropic glutamate receptors, including NMDA receptor subunits [119, 132].

Group I mGlu receptor subtypes have also been suggested to have a proconvulsant action and may be considered as a potential target for treatment of epilepsy [133, 134]. An increased expression of group I mGlu receptors has been shown in dysplastic neurons of GNT, FCD, and HMEG specimens ([135, 136] and unpublished results). In particular, the mGlu5 receptor was observed in a higher proportion of dysplastic neurons and balloon cells in FCD, compared to the mGlu1a receptor [136]. These observations point to the expression of this receptor subtype as a common feature of epileptogenic developmental lesions. The presence of mGlu5 receptor immunoreactivity may indicate an immature immunophenotype.

Whether the strong neuronal expression of group I mGlu receptors in MCD is constitutive or induced is still unclear. Epileptic activity has been shown to regulate the expression of neuronal mGlu receptors [137–139]. However, no significant differences in the expression of neuronal group I mGlu receptors were observed in normal cortex adjacent to the dysplastic region when compared to the control tissue from patients with no history of seizures [135, 136].

In contrast to the convulsant action of group I mGlu receptors, activation of group II mGlu receptors has been shown to decrease epileptiform activity in different experimental models [133, 134]. Interestingly, a lower expression of mGlu2/3 receptors was observed in dysplastic neurons [135, 136].

Glial cells are also an important component in MCD, including GNT, FCD, and HMEG [125]. Expression of both mGlu5 and mGlu2/3 receptors in glial cells with the morphology of reactive astrocytes was observed in GNT, FCD, and HMEG ([135, 136] and unpublished results). Glial mGlu receptors regulate different cell functions, including glial–neuronal interactions [140], regulation of brain microcirculation [141], glial cell proliferation [142], and production and release of different growth factors and cytokines [143–146]. In addition, activation of mGlu receptors regulates the expression of glial glutamate transporter protein [147], possibly controlling the extracellular levels of glutamate [148].

Hopefully, the detection of mGlu receptors within the complex excitatory network of MCD will lead to future therapeutic approaches in patients with developmental disorders associated with epilepsy.

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