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Metabotropic glutamate receptors: From the workbench to the bedside

F. Nicoletti[a,b,*], **J. Bockaert**[c], **G.L. Collingridge**[d], **P.J. Conn**[e], **F. Ferraguti**[f], **D.D. Schoepp**[g], **J.T. Wroblewski**[h], and **J.P. Pin**[c]

[a]Department of Physiology and Pharmacology, University of Rome, Sapienza, Piazzale Aldo Moro 5, 00185 Rome, Italy

[b]I.N.M. Neuromed, Pozzilli, Italy

[c]Institute of Functional Genomics, CNRS UMR 5203, INSERM U661, University of Montpellier 1 & 2, Montpellier, France

[d]MRC Centre for Synaptic Plasticity, Department of Anatomy, University of Bristol, Bristol, UK

[e]Department of Pharmacology, Vanderbilt Program in Drug Discovery, Vanderbilt University Medical Center, Nashville, TN, USA

[f]Department of Pharmacology, Innsbruck Medical University, Innsbruck, Austria

[g]Neuroscience, Merck and Company Inc., North Wales, NJ, USA

[h]Department of Pharmacology, Georgetown University Medical Centre, Washington, DC, USA

Abstract

Metabotropic glutamate (mGlu) receptors were discovered in the mid 1980s and originally described as glutamate receptors coupled to polyphosphoinositide hydrolysis. Almost 6500 articles have been published since then, and subtype-selective mGlu receptor ligands are now under clinical development for the treatment of a variety of disorders such as Fragile-X syndrome, schizophrenia, Parkinson's disease and L-DOPA-induced dyskinesias, generalized anxiety disorder, chronic pain, and gastroesophageal reflux disorder. Prof. Erminio Costa was linked to the early times of the mGlu receptor history, when a few research groups challenged the general belief that glutamate could only activate ionotropic receptors and all metabolic responses to glutamate were secondary to calcium entry. This review moves from those nostalgic times to the most recent advances in the physiology and pharmacology of mGlu receptors, and highlights the role of individual mGlu receptor subtypes in the pathophysiology of human disorders. This article is part of a Special Issue entitled 'Trends in Neuropharmacology: In Memory of Erminio Costa'.

Keywords

Metabotropic glutamate receptors; Receptor structure; mGlu receptor ligands; Clinical studies

1. Historical background

The evidence that quisqualate and glutamate stimulated inositol phosphate formation in cultured striatal neurons (Sladeczek et al., 1985) offered the first demonstration that

[*]Corresponding author. Department of Physiology and Pharmacology, University of Rome, Sapienza, Piazzale Aldo Moro 5, 00185 Rome, Italy. Tel.: +39 06 49912969; fax: +39 0865 927575, ferdinandonicoletti@hotmail.com (F. Nicoletti).

excitatory amino acids could activate receptors other than the classical ligand-gated ion channels (named NMDA, “quisqualate”and kainate receptors at that time). In the meantime, ibotenic acid, a heterocyclic amino acid naturally occurring in the mushrooms *Amanita muscaria* and *Amanita pantherina*, was found to stimulate inositol phosphate formation in hippocampal slices (Nicoletti et al., 1986a,b). Glutamate was virtually inactive in adult brain slices, but was able to stimulate polyphosphoinositide (PI) hydrolysis to a great extent (as much as 20 fold in some experiments) in slices from 7- to 9-day old rats (Nicoletti et al., 1986a). The latter findings were the product of the intuition, creativity, and long experience of Prof. Erminio Costa, who, at that time, was the Director of the Laboratory of Preclinical Pharmacology of NIMH, St. Elizabeth’s Hospital, Washington, DC. Independent work by Carl Cotman and his associates demonstrated that L-2-amino-4-phosphonobutanoate (L-AP4) and L-serine-O-phosphate (L-SOP), which at that time were considered as excitatory amino acid receptor *antagonists*, reduced excitatory synaptic transmission at mossy fibre/CA3 pyramidal cell synapses of the guinea pig hippocampus (Cotman et al., 1986), thus providing the first indirect evidence for the existence or presynaptic group-III mGlu autoreceptors (see below). In 1987, Prof. Sugyiama and his colleagues introduced the terminology of “metabotropic glutamate receptors” to indicate quisqualate-sensitive receptors expressed in *Xenopus* oocytes injected with rat brain mRNA (Sugiyama et al., 1987). The cloning of the first metabotropic glutamate subtypes (named mGluR1 or mGlu1 receptor) in the lab of Prof. Nakanishi (Masu et al., 1991) was the milestone for any further growth of the field. The eight mGlu receptor subtypes identified so far are divided into three groups, with group I including mGlu1 and mGlu5, group II including mGlu2 and mGlu3, and group III including mGlu4, mGlu6, mGlu7, and mGlu8. mGlu1 and mGlu5 receptors are coupled to Gq/G11, whereas all other subtypes are coupled to Gi/Go in heterologous expression systems (see below). The pharmacology of mGlu receptors has expanded dramatically in the last few years, and subtype-selective ligands are now under clinical development. As described above, quisqualate and ibotenic acid were the first reported molecules active at mGlu receptors coupled to PI hydrolysis. These molecules, however, are not selective and show activity at ionotropic glutamate receptors. The first breakthrough in the pharmacology of mGlu receptors was the discovery that trans-1-amino-cyclopentanedicarboxylic acid (trans-ACPD) could activate PI hydrolysis in brain slices with no effect at ionotropic glutamate receptors (Schoepp et al., 1991). One of the isomers of trans-ACPD, 1S,3R-ACPD, activates both group-I and group-II mGlu receptors (reviewed by Schoepp et al., 1999), and is still widely used as a non-selective mGlu receptor agonist. L-AP4, L-SOP and L-2-amino-3-phosphonopropionic acid (L-AP3) were described as antagonists of mGlu receptors coupled to PI hydrolysis in brain slices (Nicoletti et al., 1986a,b,c; Schoepp and Johnson, 1989). L-AP3 is now obsolete, whereas L-AP4 and L-SOP are considered as prototypical *agonists* of group-III mGlu receptors. Jeff Watkins and his associates introduced a series of phenylglycine derivatives as pharmacological tools for investigating the role of mGlu receptors in the CNS (Birse et al., 1993). One of these derivatives, R,S-α-methyl-4-carboxyphenylglycine (MCPG), has been widely used as a non-subtype-selective mGlu receptor antagonist (Eaton et al., 1993). The modern pharmacology of mGlu receptors coincides with the advent of orthosteric ligands bearing a cyclopropyl moiety in their structure. (2S,3S,4S)-2-(Carboxycyclopropyl)glycine (L-CCG-I) and (2S, 1′R,2′R,3′R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV), synthesized in the lab of Prof. Shinozaki (Shinozaki and Ishida, 1993), have been used for many years, and are still used, as potent mGlu2/3 receptor agonists. More recent compounds synthesized by Jim Monn at Eli Lilly, e.g. (1S,2S,5R,6S)-2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) and (1R,4R,5S,6R)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268), show nanomolar potency as mGlu2/3 receptor agonists and are systemically active (reviewed by Schoepp et al., 1999). Other drugs, including positive and negative allosteric modulators (PAMs and NAMs) of individual mGlu receptor subtypes, are described in the appropriate sections below. By definition, these drugs bind to mGlu

receptor sites distinct from the primary glutamate recognition site. No endogenous ligands ("endocoids") of these modulatory sites have been identified, as yet. Their existence is unlikely because the 7-transmembrane (7TM) region, which contains the binding sites of most PAMs and NAMs, is not highly conserved among the eight mGlu receptor subtypes. Now, after 25 years from the discovery of mGlu receptors, a number of potent and subtype-selective ligands of mGlu receptors are under clinical development and are among the most promising drugs in the treatment of neurological and psychiatric disorders.

2. Structure and activation mechanism of mGluRs

Sequence analysis of most class CG-protein coupled receptors (GPCRs), including the 8 mGlu receptor subtypes, the Ca^{2+}-sensing receptor, the taste T1R receptors, and the basic amino acid receptor GPCR6a, revealed that these receptors have a large extracellular domain made of a Venus Fly Trap (VFT) domain similar to the periplasmic bacterial leucine/isoleucine/valine binding protein (LIVBP) linked to the first TM domain *via* a cysteine-rich domain (CRD) containing 9 highly conserved cysteine residues (Fig. 1c). A number of 3D modeling studies (O'Hara et al., 1993), but most importantly, the resolution of a crystal structure of the mGlu1 extracellular domain (Kunishima et al., 2000; Tsuchiya et al., 2002) confirmed that the glutamate binding domain is structurally similar to LIVBP-like proteins (Fig. 1a). Later on, the structures of mGlu3 and mGlu7 receptor VFTs were reported (Muto et al., 2007). The VFT domain is composed of two lobes, each made of α-helices around a large β-sheet, with the glutamate binding site located in the cleft between the two lobes. Structural analysis of the binding pocket revealed 5 residues that directly contact the amino acid moiety and are conserved in a large variety of amino acid binding LIVBP-like proteins. The structure of the CRD was solved together with the VFT of the mGlu3 receptor (Muto et al., 2007), and revealed a domain made of two subdomains, each composed of 4 β-strands stabilized by 2 disulfide bridges. This domain is further linked to the VFT *via* an additional highly conserved disulfide bond, likely rigidifying the connection between the VFT and the CRD. The 7-TM domain of mGlu receptors shows very low sequence similarity with the 7-TM domain of other GPCRs. However, the 7-TM domains of mGlu receptors and other GPCRs share a similar general fold, with a relatively central helix 3, and a possible amphipathic helix 8 (Pin et al., 2003). Indeed, when the 7-TM domain alone is expressed in cells (after deletion of both the extra and intracellular parts), it folds correctly, and can be directly activated by ligands known as positive allosteric modulators (PAMs) of the full length receptors (Goudet et al., 2004), indicating that a change in conformation in such an isolated domain is sufficient for G-protein activation. In addition, as observed in many rhodopsin-like GPCRs, an ionic interaction between residues at the intracellular side of helices 3 and 6 is important to maintain the receptor in an inactive conformation (Binet et al., 2007). Lastly, as observed in other GPCRs, both the intracellular loops 2 and 3, as well as the helix 8 are important in G-protein coupling, being also involved in coupling selectivity (Pin et al., 2003).

Not only are mGlu receptors complex proteins because of the modular structural organization, but also because they form dimers stabilized by an intersubunit disulfide bond (Romano et al., 1996a). Such a dimeric organization was shown not only in transfected cells, but also in the brain. Using energy transfer technologies, together with systems to control receptor subunit composition, it was shown that mGlu receptors form dimers but not larger complexes, as opposed, for example, to the related $GABA_B$ receptor (Maurel et al., 2008). Early studies suggested that mGlu receptors only form homodimers, then limiting the number of possible mGlu receptors in the brain to the eight major subtypes (not taking into account the splice variants). However, a recent report by Doumazane et al. (2010) demonstrates that, similarly to $GABA_B$ receptors and sweet and umami taste receptors, mGlu receptor subtypes can form heterodimers. Subtypes of the same group of mGlu

receptors can form intragroup heterodimers (e.g., mGlu1 with mGlu5 and mGlu2 with mGlu3 receptors), and, interestingly, group-II and group-III mGlu receptors can form intergroup heterodimers (e.g., mGlu2 with mGlu4 receptors). No heterodimers can be formed between group-I and group-II/III mGlu receptors (e.g., mGlu1 and mGlu2 or mGlu4), suggesting that only mGlu receptor subtypes coupled to the same G protein can form heterodimers. Of interest, different mGlu receptor subunits have been colocalized in specific subdomains in neurons, suggesting the existence of mGlu receptor heterodimers in the brain. Further work is however necessary before the functional significance of such heterodimeric receptor entities is identified.

The dimeric organization of the mGlu receptors raises the question of how receptor function is infiuenced by ligand binding stoichiometry. Kniazeff et al. (2004a) have shown that a single agonist per dimer (i.e. a single VFT stabilized in the closed state) is sufficient for receptor activation, although the presence of two agonist molecules (i.e. both VFTs in the closed state) leads to a 3-fold higher coupling efficiency. It has even been suggested that the two states (one or two VFTs in the closed state) activate different signalling pathways, e.g. mGlu1 receptor coupling to Gs and Gq, respectively (Tateyama and Kubo, 2006). How can glutamate, by interacting into the cleft of the VFT, induce the necessary change in conformation at the 7-TM level to activate G-proteins? A first important step was discovered through the resolution of the VFT structure occupied either by an agonist or an antagonist (Fig. 1a, and Table 1) (Kunishima et al., 2000; Tsuchiya et al., 2002). Indeed, as observed for most LIVBP-like domains, ligand binding stabilizes the VFT domain in a closed conformation. This is well illustrated by the observation that many structures with bound agonists are in the closed form (Tables 1 and 2). Although open conformations with bound agonist have been identified for mGlu1 receptors, this may simply reflect the ability of this domain to oscillate between a closed and an open state, as already reported for many other LIVBP-like proteins. In contrast, all antagonist bound structures correspond to open VFTs. Of note, removing the steric or ionic hindrance that prevents VFT closure by site directed mutagenesis was found sufficient to convert the group-III mGlu receptor antagonists, (S)-2-amino-2-methyl-4-phosphonobutanoic acid (MAP4) and (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) into full agonists, consistent again with the close state corresponding to the active state (Bessis et al., 2002). As a further support to this conclusion, the fully activated state of the related $GABA_B$ receptor was obtained by inserting a disulfide bond expected to lock the VFT in its closed state (Kniazeff et al., 2004b).

The structures of mGlu1 VFT solved in the presence of agonists and antagonists suggested that the dimeric organization plays a pivotal role in the activation process. Indeed, an important reorientation of the VFTs in the dimer, from resting (R) to active (A) (Fig. 1b) was observed when at least one VFT was in a closed state (Fig. 1b) (Kunishima et al., 2000; Tsuchiya et al., 2002). However, recent new structures of dimeric mGlu VFTs cast some doubts on this proposed activation mechanism. Indeed, the active orientation was observed with the dimeric mGlu1 receptor VFTs bound with the antagonist, (2S)-2-amino-2-[(1S, 2S)-2-carboxycycloprop-1-yl]-3-(xanth-9-yl) propanoic acid (LY341495) (unpublished observation, pdb accession number 3KS9), and the resting orientation was systematically observed with the mGlu3 receptor VFT dimer bound with 5 different agonists (Muto et al., 2007). Although a change in the relative position between the VFTs is expected, as suggested by a study performed on the related $GABA_B$ receptor (Rondard et al., 2008), the movement may not necessarily be as important as that observed in the crystal structures. As shown in Fig. 1c, it is not possible to have both 7-TM domains of a dimeric mGlu receptor to be in close proximity according to the solved structure of the mGlu3 receptor extracellular domain composed of both the VFT and the CRD. This appears surprising and not consistent with the FRET data obtained with GFP fusion mGlu receptor subunits (Marcaggi et al.,

2009; Tateyama et al., 2004). A relative movement between the mGlu receptor subunits during activation is indeed supported by FRET measurements between their intracellular sides (Marcaggi et al., 2009; Tateyama et al., 2004). However, whether the change with FRET is solely due to a change in the distance between the fused GFPs, or to a change in their relative orientation due to conformational changes of the intracellular loops remains unclear. Whatever the real mechanism, it leads to the activation of only one 7TM within the dimer (Hlavackova et al., 2005), which strongly suggests a direct contact between the 7TMs in the dimer. Further work is necessary to understand how agonist binding leads to the activation of the 7TM.

3. Detailed description of mGlu receptor subtypes

3.1. mGlu1 receptor

Gene name: *GRM1* (human); *Grm1* (rat, mouse). Accession numbers: NP_000829 (human); NP_058707 (rat); NP_058672 (mouse). Chromosomal location: 6q24 (human); 1p13 (rat); 10A2 (mouse) (Masu et al., 1991; Kuramoto et al., 1994; Desai et al., 1995; Stephan et al., 1996).

3.1.1. Splice variants (Ferraguti et al., 2008—mGlu1α or mGlu1a (longest isoform): 1199 and 1194 amino acids in rodents and humans, respectively. C-terminus intracellular domain formed by 360 amino acids. mGlu1β1 or mGlu1b: 906 amino acids. C-terminus domain: 68 amino acids. mGlu1β2 or mGlu1f: 906 amino acids. C-terminus domain: 68 amino acids. mGlu1γ or mGlu1d: 908 amino acids. C-terminus domain: 70 amino acids. mGlu1δ or mGlu1E55: 321 amino acids. Possible secreted protein.

3.1.2. Receptor signalling and interacting proteins—mGlu1 receptors are primarily coupled to Gq/G11 proteins (Masu et al., 1991). Receptor activation stimulates phospholipase Cβ (PLCβ), the enzyme that cleaves phosphatidylinositol-4,5-bisphosphate with the ensuing formation of the intracellular second messengers, inositol-1,4,5-trisphosphate (Ins-1,4,5-P_3) and diacylglycerol (DAG). Ins-1,4,5-P_3 releases Ca^{2+} from intracellular stores, whereas DAG activates protein kinase C. Stimulation of cAMP formation, arachidonic acid release, the mitogen-activated protein kinase (MAPK) pathway, and L-type voltage-sensitive Ca^{2+} channels has also been reported in response to mGlu1 receptor activation (reviewed by Ferraguti et al., 2008). The mGlu1 receptor negatively modulates a variety of K^+ channels, including M-type voltage-gated K^+ channels (Ikeda et al., 1995) and the “tandem-pore” TASK and TREK K^+ channels (Talley et al., 2000; Chemin et al., 2003). In cultured neurons, mGlu1 (and mGlu5) receptors negatively modulate voltage-sensitive Ca^{2+} channels *via* mechanisms that involve pertussis toxin (PTX)-sensitive and PTX-insensitive G proteins and are regulated by Homer proteins (Choi and Lovinger, 1996; Kammermeier et al., 2000).

Different isoforms of G-protein coupled receptor kinases (GRKs), including GRK2, GRK4, and GRK5, mediate homologous desensitization of mGlu1 receptors (Dale et al., 2000; Sallese et al., 2000; Iacovelli et al., 2003). GRK4 is required for desensitization of native mGlu1 receptors in cerebellar Purkinje cells (Sallese et al., 2000). The *R*egulator of *G*-protein *S*ignalling, RGS-4, which increases the GTPase activity of $G\alpha_q$, inhibits mGlu1 receptor signalling (Saugstad et al., 1998).

A number of proteins have been shown to interact with mGlu1 receptors and to modify their surface expression and intracellular signal transduction. Homer proteins, which contain both PDZ (from *P*SD-95, *D*lgA, and *Z*o-1 proteins) and EVH-1 (from *E*na/*V*asp *H*omology-1) domains, bind to a proline-rich motif in the C-terminal tail of mGlu1a and mGlu5 receptors (Brakeman et al., 1997; Kato et al., 1998; Xiao et al., 1998; Tu et al., 1998). All members of

the Homer family, with the exception of Homer1a, contain a C-terminal coiled-coil domain, which allows multimerization (Kato et al., 1998; Tu et al., 1998). Thus, Homer proteins form a linking bridge between mGlu1α receptors and other proteins that are involved in receptor signalling, such as PLCβ3 and −4, the $InsP_3$ receptor, and the TrpC1 channel (reviewed by Ferraguti et al., 2008) (Fig. 2). The latter likely behaves as a store-operated channel, providing a potential route to restore intracellular Ca^{2+} stores after the opening of $InsP_3$-gated ion channels. mGlu1α receptors can also activate the phosphatidylinoisol-3-kinase (PtdIns-3-K) pathway *via* the interaction with Homer protein, and the PtdIns-3-K enhancer, PIKE-L (Rong et al., 2003) (Fig. 2). All these interactions are disrupted by the short Homer isoform, Homer1a, which is rapidly induced in response to synaptic activation and shares with other Homers the ability to interact with mGlu1α receptors, but cannot form multimeric complexes. mGlu1α receptors can also associate with tamaline (Kitano et al., 2002), the cytoskeletal protein, 4.1G (Lu et al., 2004), and the ubiquitin ligase, Siah-1A (Seven In Ansentia Homologue-1A) (Ishikawa et al., 1999; Kammermeier and Ikeda, 2001). The mGlu1 receptor co-immuno-precipitates and functionally interacts with ephrin-B2 (Calò et al., 2005), a member of the ephrin/Eph receptor family of trans-membrane proteins, which mediate processes of cell-to-cell interaction during development and in the adult life. Activation of ephrin-B2 by its receptor partner, Eph-B1, amplifies mGlu1 receptor signalling in brain tissue and cultured neurons. This interaction might have interesting implications for processes of developmental plasticity (Calò et al., 2005, 2006).

3.1.3. Functional anatomy—Expression of mGlu1 receptors is extensive in cerebellar Purkinje cells and in the mitral/tufted cells of the olfactory bulb. Strong expression is also found in the pars compacta of the substantia nigra, lateral septum, globus pallidum, and thalamic relay nuclei (Martin et al., 1992; Shigemoto et al., 1992; Baude et al., 1993). Neuroendocrine regions of the hypothalamus express higher levels of mGlu1β than mGlu1α receptors (Mateos et al., 1998; Van den Pol, 1994). The subcellular localization of the mGlu1 receptor has been consistently associated with postsynaptic specialization of excitatory synapses, where the receptor appears to be concentrated in perisynaptic and extrasynaptic areas. Thus, mGlu receptors are recruited by high concentrations of glutamate that escape the clearance mechanisms and spread to the sides of the synaptic cleft (Ferraguti et al., 2008 and references therein).

The function of the mGlu1 receptor has been most extensively studied in the cerebellar cortex, where receptor activation is required for the induction of long-term depression (LTD) of excitatory neurotransmission at parallel fibre-Purkinje cell synapses. This particular form of synaptic plasticity underlies motor learning, vestibulo-ocular reflex adaptation, and eye-blink conditioning (reviewed by Kano et al., 2008). Activation of mGlu1 receptors in Purkinje cells leads to formation of diacylglycerol, which is then cleaved by diacylglycerol lipase into 2-arachidonylglycerol (2-AG), the major endocannabinoid species of the CNS. 2-AG diffuses back to parallel fibre nerve terminals, where it activates type-1 cannabinoid receptors, thereby inhibiting glutamate release (reviewed by Kano et al., 2008). Gene-targeted deletion of mGlu1 receptors impairs LTD at parallel fibers-Purkinje cell synapses resulting into a severe motor incoordination (Aiba et al., 1994; Conquet et al., 1994). Selective re-introduction of mGlu1α receptors in Purkinje cells restores LTD and corrects motor impairment (Ichise et al., 2000). In addition, mice lacking mGlu1 receptors show a defect in the elimination of supranumerary climbing fibers innervating Purkinje cells that physiologically occurs in the developing cerebellum (Kano et al., 1997). Thus, the presence of mGlu1 receptors is essential for the correct development of the cerebellar cortex. In addition to a role in synaptic plasticity, mGlu1 receptors also mediate a slow EPSP at synapses made between parallel fibers and Purkinje cells (Batchelor et al., 1997). Therefore, mGlu1 receptors are involved in both acute and long-term regulation of synaptic transmission. While this synaptic response is induced by repetitive stimuli, it can be induced

by as few as 3 stimuli (Batchelor and Garthwaite, 1997) which demonstrates that synaptically released L-glutamate can readily access these receptors. The mGlu1-receptor mediated EPSC is subject to pronounced synaptic plasticity. Thus, it was shown that depolarization of Purkinje cells by climbing fibre stimulation elicits near complete inhibition of this synaptic current (Jin et al., 2007). These various functions of mGlu1 receptors (role in synaptic transmission, expression of synaptic plasticity, trigger for synaptic plasticity) could all contribute to the role of these receptors in physiological and pathological processes.

3.1.4. Pharmacology—3,5-Dihydroxyphenylglycine (DHPG) binds to the glutamate recognition site of mGlu1 receptors behaving as an orthosteric agonist. However, this drug is not subtype selective, and also activates mGlu5 receptors. To our knowledge, there are no orthosteric agonists selective for mGlu1 receptors. (S)-2-(4-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine (Ro67-7476), (9H-xanthene-9-carbonyl)-carbamic acid butyl ester (Ro-674853), diphenyl-acetyl-carbamic acid ethyl ester (Ro-01-6128), and 4-nitro-N-(1,4-diphenyl-1H-pyrazol-5-yl) benzamide (VU71) are examples of selective mGlu1 receptor PAMs (or “enhancers”), which require the presence of an orthosteric agonist to be active (reviewed by Niswender and Conn, 2010). These drugs, if given alone, exclusively recruit mGlu1 receptors that are activated by endogenous glutamate, i.e. their action is activity-dependent. 4-(Amino-carboxy-methyl)-3-methyl-benzoic acid (LY367385), 1-amino-indane-1,5,-dicarboxylic acid (AIDA), and its derivative, α-amino-5-carboxy-3-methyl-2-thiopheneacetic acid (3-MATIDA) are orthosteric antagonists of mGlu1 receptors with little or no activity at mGlu5 receptors (reviewed by Schoepp et al., 1999). 7-(Hydroxyimino) cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt) is the prototype of a growing list of drugs acting as negative allosteric modulators (NAMs) of mGlu1 receptors (reviewed by Niswender and Conn, 2010). Some of these drugs, including (3aS,6aS)-hexahydro-5-methylene-6a-(2-naphthalenylmethyl)-1H-cyclopenta[*c*]furan-1-one (BAY367620) (Carroll et al., 2001) and (3,4-dihydro-2H-pyrano[2,3-b] quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone (JNJ16259685) (Lavreysen et al., 2004), display high receptor affinity and are systemically active.

3.1.5. Relevance to human disorders

3.1.5.1. Inherited ataxia and autoimmune cerebellar disorders: Animal studies suggest that inherited ataxia can be associated with a defective expression or function of mGlu1 receptors in Purkinje cells. Ataxic transgenic mice show mutations of the *Grm1* gene or a reduced expression/activity of mGlu1 receptors or downstream effector molecules in Purkinje cells (Conti et al., 2006; Sachs et al., 2007; Kurnellas et al., 2007). Interestingly, in conditional spino-cerebellar ataxia type 1 (SCA1) mutant mice, recovery from the disease after stopping transgene expression correlates with localization of the mGlu1α receptor to the Purkinje cell-parallel fibre synapse (Zu et al., 2004). Although these data suggest that the GRM1 is a candidate gene for inherited cerebellar disorders, it should be highlighted that no causative mutations in the GRM1 gene have been found in children with idiopathic early-onset ataxia (Rossi et al., 2010). In three patients, cerebellar ataxia has been associated with the presence of autoantibodies directed against mGlu1 receptors. Two of these patients had Hodgkin’s lymphoma with paraneoplastic cerebellar ataxia (Sillevis Smitt et al., 2000). The third patient had a primary autoimmune disorder (Marignier et al., 2010). mGlu1 receptor PAMs are potential candidates for the treatment of those forms of ataxia that are associated with defective mGlu1 receptors. Mice developing experimental autoimmune encephalomyelitis (EAE) after immunization with the myelin oligodendrocyte glycoprotein (MOG) show a reduced expression of mGlu1α receptors in Purkinje cells and an impaired motor coordination at the rotarod test. Motor impairment is corrected by a systemic treatment with a selective mGlu1 receptor PAM (Fazio et al., 2008).

3.1.5.2. Malignant melanomas: Suzy Chen and her associates (Pollock et al., 2003) showed that insertional mutant mice predisposed to develop malignant melanomas had a deletion of 70 kb in intron 3 of *Grm1*, resulting into an ectopic expression of mGlu1 receptors in melanoma cells. Mutant mice in which expression of the *Grm1* gene is driven by the promoter of dopachrome tautomerase (an enzyme specifically expressed in melanocytes) also develop multiple melanomas. Expression of mGlu1 receptors has been detected in human melanomas, but not in benign nevi (Pollock et al., 2003). The oncogenic activity of mGlu1 receptors in melanoma cells depends on the activation of multiple transduction pathways that include PKC-ε, the MAPK pathway, and the PtdIns-3-K/Akt pathway (Marín et al., 2006; Shin et al., 2010). Treatment of human melanoma cells with mGlu1 receptor NAMs or with riluzole, which inhibits glutamate release, reduces cell proliferation (Namkoong et al., 2007). No clinical data with mGlu1 receptor antagonists are available, as yet. However, data from a phase 0 clinical trial show that a 14-day treatment with riluzole inhibits mGlu1 receptor signalling and metabolic activity in post-treatment tumor samples (Yip et al., 2009).

3.1.5.3. Neurodegeneration/neuroprotection: mGlu1 receptor antagonists protect hippocampal neurons against “post-ischemic” degeneration in both hippocampal slices exposed to oxygen–glucose deprivation and *in vivo* models of transient global ischemia (reviewed by Pellegrini-Giampietro, 2003). Pharmacological blockade of mGlu1 receptors enhances GABAergic transmission in the hippocampus by preventing the mGlu1-receptor mediated formation of endocannabinoids and the ensuing activation of inhibitory CB1 receptors localized on GABAergic nerve terminals (Landucci et al., 2009). In contrast, it is the activation of mGlu1 receptors that mediates the mechanism of ischemic tolerance observed with the paradigm of “ischemic preconditioning” in hippocampal slices (Werner et al., 2007), whereas activation of both mGlu1 and mGlu5 receptors mediates mechanisms of “ischemic post-conditioning” (Scartabelli et al., 2008). In cultured neurons challenged with excitotoxins mGlu1 receptor antagonists are consistently neuroprotective, whereas agonists can be neurotoxic or neuroprotective depending on the experimental paradigm (reviewed by Nicoletti et al., 1999). Michel Baudry and his associates have shown that mGlu1α receptors activate two pathways that differentially affect neurodegeneration: (i) a protective pathway mediated by the activation of PtdIns-3-K; and (ii) a toxic pathway mediated by intracellular Ca^{2+} release. The calpain-mediated truncation of mGlu1α receptors prevents the activation of the PtdIns-3-K pathway, leaving the Ca^{2+}pathway intact (Xu et al., 2007). Recent evidence also indicates that mGlu1α may produce dual neuroprotective and neurotoxic signalling in cerebellar and cortical neurons (Pshenichkin et al., 2008) exhibiting the properties of a dependence receptor by inducing apoptosis in the absence of glutamate, while promoting neuronal survival in its presence. The mechanism of the proapoptotic action has not been elucidated, but, similarly to other dependence receptors, it may involve an agonist-independent interaction of the C-terminal receptor domain with intracellular targets. Instead, the prosurvival action of mGlu1 occurs *via* a novel, G-protein independent, mechanism mediated by β-arrestin1-dependent, persistent, activation of the MAPK pathway (Emery et al., 2010) with a pharmacology indicating the presence of a ligand bias whereby glutamate, but not quisqualate can activate the signal transduction mechanism. This suggests a role for receptor desensitization and internalization – that critically depend on the extent and duration of agonist exposure – in mechanisms of neurodegeneration/neuroprotection. Moreover, the proapoptotic action of mGlu1α may play a role in developmental apoptosis in the CNS.

3.1.5.4. Schizophrenia: Recent evidence corroborates the hypothesis that inhibition of mGlu1 receptors could be a novel treatment for schizophrenia. Indeed, mGlu1 receptor antagonists were shown to selectively improve prepulse inhibition in DBA/2J mice (Hikichi

et al., 2010), an animal model for impaired sensorimotor gating. Sensorimotor gating is a fundamental form of information processing that is deficient in patients with schizophrenia (Braff et al., 1992) and which can be modeled in animals using acoustic pre-pulse inhibition of the startle (PPI). Deficits in PPI were also observed in mice with gene-targeted deletion of the mGlu1 receptor, which was evident as early as 6 weeks postnatal and remained impaired till adulthood (Brody et al., 2003). Moreover, allosteric mGlu1 receptor antagonists reduced methamphetamine-induced hyperlocomotion (Satow et al., 2009) and behave similarly to the atypical antipsychotic, clozapine, in activating neurons in the nucleus accumbens and medial prefrontal cortex (Suzuki et al., 2010). Although these findings are still at a relatively early stage, mGlu1 receptor antagonists hold promise as novel putative antipsychotic drugs.

3.2. mGlu5 receptor

Gene name: *GRM5* (human); *Grm5* (rat, mouse). Accession numbers: NP_000833 (human); NP_058708 (rat); NP_001074883 (mouse). Chromosomal location: 11q14.2 (human); 1q32 (rat); 7D3 (mouse) (Abe et al., 1992; Kuramoto et al., 1994).

3.2.1. Splice variants—mGlu5a: 1212 amino acids in humans; 1203 amino acids in rats; highly and diffusely expressed in the rat brain during early postnatal development (Romano et al., 1996b).

mGlu5b: a variant that contains a 32 amino acid fragment inserted into the cytoplasmic tail 50 residues after the 7th TM; more abundant in the adult brain (Joly et al., 1995; Minakami et al., 1995; Romano et al., 1996b).

mGlu5d: identified in human cerebellum and hippocampus; C-terminus domain 267 amino acids shorter than human mGlu5a receptors (Malherbe et al., 2002).

3.2.2. Receptor signalling and interacting proteins—The mGlu5 receptor is coupled to Gq/G11 protein and its activation stimulates PI hydrolysis. In recombinant cells, activation of mGlu5 receptors induces oscillatory increases in intracellular Ca^{2+} release, as a result of a PKC-mediated receptor phosphorylation (Kawabata et al., 1996). Both mGlu5a and mGlu5b receptors are characterized by a long C-terminus domain that allows the interaction with Homer proteins similarly to mGlu1α receptors. In the postsynaptic elements, mGlu5 receptors are physically linked to the NR2 subunit of NMDA receptors *via* a chain of interacting proteins, which include PSD-95, Shank, and Homer (Tu et al., 1999) (Fig. 2). Calcium ions that enter the cell *via* the NMDA-gated ion channel activate protein phosphatase 2B, which dephosphorylates mGlu5 receptors thereby limiting mGlu5-receptor desensitization (Alagarsamy et al., 2005). In addition, a large body of evidence indicates that activation of mGlu5 receptors enhances NMDA receptor function (Doherty et al., 1997; Ugolini et al., 1999; Awad et al., 2000; Attucci et al., 2001; Mannaioni et al., 2001; Pisani et al., 2001). The neuron-specific protein, Norbin, physically interacts with mGlu5 receptors *in vivo* and increases both membrane localization and signalling of mGlu5 receptors (Wang et al., 2009). The mGlu5 receptors are selectively desensitized by members of the GRK2 family (GRK2 and GRK3), through a mechanism that involves phosphorylation of the Threo 840 residue (Sorensen and Conn, 2003).

3.2.3. Functional anatomy—The mGlu5a receptor is highly expressed in the CNS during early postnatal life, and likely mediates the robust PI response to excitatory amino acids found in all brain regions early after birth (Casabona et al., 1997). The mGlu5b receptor is abundant in the adult hippocampus, corpus striatum, and cerebral cortex (Romano et al., 1996b), and is therefore the main target for pharmacological intervention in the adult brain. Partly, because of their functional interaction with NMDA receptors (Collett

and Collingridge, 2004), mGlu5 receptors are involved in the regulation of synaptic plasticity (Bortolotto et al., 2005; Manahan-Vaughan and Braunewell, 2005; Bikbaev et al., 2008). Mice with genetic deletion of mGlu5 receptors show a mild deficit in long-term potentiation (LTP) in the hippocampus and an impaired spatial learning (Jia et al., 1998). However, pharmacological inhibition of mGlu5 receptors does not affect LTP in this pathway, suggesting that the deficit in the knockout has a developmental origin (Bortolotto et al., 2005).

Pharmacological activation of mGlu5 receptors induces a robust form of LTD at the Schaffer collateral-CA1 pyramidal cell synapse in the hippocampus (Palmer et al., 1997). This form of synaptic plasticity can also be induced by synaptic activity and has been shown to be dependent on dendritic protein synthesis under certain circumstances (Huber et al., 2000) but independent of protein synthesis under others (Moult et al., 2008). A selective amplification of mGlu5-receptor mediated LTD in the hippocampus has been suggested to underlie cognitive dysfunction in Fragile-X mutant mice and represents a promising target for therapeutic intervention (see below). A variety of different signalling mechanisms have been found to be involved in mGluR-LTD in the hippocampus, including the activation of p38 MAPK (Bolshakov et al., 2000; Rush et al., 2002) and tyrosine phosphatases (Moult et al., 2008), including the *St*riatal *E*nriched tyrosine *P*hosphatase, STEP (Zhang et al., 2008a,b).

In addition to direct roles in LTP and LTD at CA1 synapses, mGlu5 receptors have been demonstrated to play a crucial role in some forms of metaplasticity. Metaplasticity is the plasticity of synaptic plasticity and comes in many varieties (Abraham, 2008). One rather unusual manifestation of metaplasticity has been termed the molecular switch, whereby the induction of LTP makes the induction of subsequent LTP at the same pathway resistant to inhibition by α-methyl-4-carboxyphenylglycine (MCPG) (Bortolotto et al., 1994). This conditioning effect of the first tetanus relies on activation of mGlu5 receptors since it is blocked by 2-methyl-6-(phenyl-ethynyl)-pyridine (MPEP) and is absent in the mGlu5 knockout mouse (Bortolotto et al., 2005). Like the activation of the slow EPSC in cerebellar Purkinje cells described above, the setting of the molecular switch by activation of mGlu5 receptors can be achieved by very few synaptic responses (Bortolotto et al., 2008). This once again demonstrates that mGlu receptors can be activated relatively easily, despite their more peripheral location at synapses. A second form of metaplasticity at these synapses, that may utilise similar mechanism, is where prior stimulation of group-I mGlu receptors leads to a greater magnitude LTP (Cohen et al., 1998). The mechanisms by which activation of mGlu5 results is metaplasticity are not fully understood but might involve both Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) (Bortolotto and Collingridge, 1998) and PKC (Bortolotto and Collingridge, 2000).

The expression and function of mGlu5 receptors in the basal ganglia motor circuits and in the pain neuraxis is described below. Interestingly, mGlu5 receptors are also expressed in non-neuronal cells, including astrocytes, oligodendrocytes, and microglia, stem-progenitor cells, and a variety of peripheral cells. Expression and function of mGlu5 receptors in astrocytes is highly plastic and changes dramatically in response to cell activation or under pathological conditions (Miller et al., 1996; Balázs et al., 1997; Aronica et al., 2000, 2003; Geurts et al., 2003). Mice expressing a mutated form of human superoxide dismutase associated with amyotrophic lateral sclerosis (ALS) show astrocytic degeneration in the ventral horns of the spinal cord, which likely depends on the activation of mGlu5 receptors by endogenous glutamate. Blocking mGlu5 receptors *in vivo* delays the onset of motor neuron disease and increases survival of these mice (Rossi et al., 2008). Embryonic stem (ES) cells (pluripotent stem cells derived from the inner mass of the blastocysts) grown under proliferating conditions express mGlu5 receptor and no other mGlu receptor subtypes.

Pharmacological blockade of mGlu5 receptors inhibits self-renewal of ES cells and promotes cell differentiation towards mesoderm and endoderm lineages (Cappuccio et al., 2005). mGlu5 receptors are also expressed by neural stem cells, i.e. stem cells resident in the CNS, which can give rise to neurons, astrocytes, and oligodendrocytes. Mice lacking mGlu5 receptors have a lower number of proliferating neuroprogenitors in zones of active neurogenesis of the adult brain (Di Giorgi-Gerevini et al., 2005). A recent review (Julio-Pieper et al., in press) highlights the role of mGlu receptors in peripheral organs. The regulation of the lower esophageal sphincter by mGlu5 receptor is of great relevance from a therapeutical standpoint (see below). mGlu5 receptors are also found in the liver, and hepatocytes lacking mGlu5 receptors are less sensitive to hypoxic damage (Storto et al., 2004). In addition, pharmacological blockade of mGlu5 receptors reduces liver damage caused by lipopolysaccharide (Jesse et al., 2009) or acetaminophen (Storto et al., 2003). mGlu5 receptors are expressed in many other peripheral cells, including cells of the male germinal line, insulinoma cell lines, immune cells, and brain endothelial cells, where their precise function remains to be determined (Julio-Pieper et al., in press).

3.2.4. Pharmacology—There are no selective orthosteric agonists of mGlu5 receptors with the exception of (RS)-2-chloro-5-hydroxyphenylglycine (CHPG), which displays low affinity and is active in the high micromolar range (reviewed by Schoepp et al., 1999). A number of mGlu5-receptor enhancers have been developed, which include [(3-fluorophenyl) methylene]hydrazone-3-fluorobenzaldehyde (DFB), N-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl}-2-hydrox-ybenzamide (CPPHA), (S)-(4-fluorophenyl)-(3-[3-(4-fluoro-phenyl)-[1,2,4]-oxadiazol-5-yl]piperidin-1-yl)methanone (ADX47273), 3-cy-ano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (CDPPB), 4-nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (VU29), and ADX63365 behave as mGlu5-receptor enhancers (reviewed by Niswender and Conn, 2010), whereas MPEP, 3-((2-methyl-1,3-thiazol-4-yl)ethynyl) pyridine hydrochloride (MTEP), 6-methyl-2-(phenylazo)-3-pyridinol (SIB-1757), and (E)-2-methyl-6-(2-phenylethenyl)pyridine (SIB-1893) are the prototypes of a growing list of mGlu5 receptors NAMs, which also includes fenobam, AFQ056, AZD2516, AZD2066, STX107, ADX10059, and ADX48621. Many of these drugs are systemically active and are under clinical development.

3.2.5. Relevance to human disorders and clinical perspectives

3.2.5.1. Fragile-X syndrome (FXS): FXS is the most frequent inherited cause of mental retardation (incidence = 1:3600 in males and 1:4000–6000 in females) caused by the transcriptional silencing of the *FMR1* gene, which encodes the fragile X mental retardation protein (FMRP) (Pieretti et al., 1991). Prominent signs and symptoms include cognitive dysfunction, autism, behavioural problems, seizures, dysmorphic features, and macroorchidism. Current medications include antipsychotic, anticonvulsant, antidepressant, and psychostimulant drugs, which, however, do not correct cognitive impairment associated with FXS (reviewed by Dölen and Bear, 2008). *Fmr1* knockout mice show a selective amplification of mGlu5-receptor mediated LTD in the Schaffer collateral-CA1 pyramidal cell synapses in the hippocampus. Remarkably, other forms of synaptic plasticity, including the more classical NMDA-receptor dependent LTD, show no abnormalities in the hippocampus of *Fmr1* knockout mice (Huber et al., 2002; reviewed by Waung and Huber, 2009). The mGlu5-receptor mediated LTD is, under certain circumstances, dependent of protein synthesis occurring in the dendrites of CA1 pyramidal neurons as a result of local mRNA translation. FMRP is one of the dendritic proteins synthesized in response to mGlu5-receptor activation and has the specific function of acting as a translational suppressor of other LTD-associated proteins, such as *P*ost*S*ynaptic *D*ensity-95 (PSD-95), the amyloid precursor protein, microtubule-associated protein 1b (MAP1b), the elongation factor 1a, and the cytoskeleton-associated protein, Arc. In the absence of FMRP, these proteins are

constitutively and highly expressed, and this makes the mGlu5-receptor mediated LTD insensitive to protein synthesis inhibitors (reviewed by Waung and Huber, 2009). A series of recent elegant studies have characterized the signalling pathways leading to dendritic protein synthesis in response to mGlu5-receptor activation. This includes the association of mGlu5 receptors with Homer proteins, and the activation of upstream regulators of dendritic mRNA translation, such as the ERK/MAPK-interacting kinase (Mnk1)/eukaryotic initiation factor 4E (eIF4E) pathway, and the PtdIns-3-K/mammalian target of rapamycin (mTOR)/p70S6K pathway. Many steps along these pathways are abnormal in *Fmr1* knockout mice (Giuffrida et al., 2005; Ronesi and Huber, 2008; Sharma et al., 2010). The lack of one of the two *Grm5* alleles as well as systemic treatment with MPEP or other mGlu5-receptor antagonists corrects most of the phenotypes associated with the lack of FMRP, including cognitive dysfunction, epileptic seizures, and morphological abnormalities (Yan et al., 2005; Tucker et al., 2006; Dölen et al., 2007; de Vrij et al., 2008). Most of the mGlu5-receptor NAMs listed in the previous paragraph are under clinical development for the treatment of FXS. Interestingly, non-sedative doses of MPEP block repetitive self-grooming behavior in BTBR T + tfJ mice, which show multiple behavioural traits with face validity for the diagnostic symptoms of autism (Silverman et al., 2010). This raises the possibility that forms of autism other than FXS may be amenable of treatment with mGlu5-receptor antagonists.

3.2.5.2. Parkinson's disease and L-DOPA-induced dyskinesia: mGlu5 receptors are highly expressed in the basal ganglia motor circuit and are involved in the regulation of motor behavior (Smith et al., 2000; Paquet and Smith, 2003; reviewed by Conn et al., 2005). Seminal work by the groups of David Lovinger and Paolo Calabresi, Antonio Pisani and other associates have shed lights into the role of group-I mGlu receptors in processes of striatal synaptic plasticity underlying habit memory and motor learning (reviewed by Gubellini et al., 2004; Bonsi et al., 2008; Lovinger, 2010). The neostriatum (caudate nucleus and putamen), which is the primary input region of the basal ganglia, is connected to output nuclei (internal globus pallidus and substantia nigra pars reticulata) by a "direct" inhibitory GABAergic pathway, and by an "indirect" pathway, which includes a striatal GABAergic projection to the external globus pallidus, an additional GABAergic projection from the external globus pallidus to the subthalamic nucleus, and an excitatory glutamatergic projection from the subthalamic nucleus to the output nuclei. Dopamine released from the nigro-striatal pathway stimulates the direct pathway acting at D1 receptors and inhibits the indirect pathway acting at D2 receptors. The progressive loss of nigro-striatal neurons associated with Parkinson's disease leads to a decreased activity of the direct pathway and an increased activity of the indirect pathway, which lead to inhibition of thalamocortical neurons and motor dysfunction (bradykinesia, rigidity, and resting tremor). Dopamine replacement therapy with L-3,4-dihydroxyphenylalanine (L-DOPA) is highly effective in relieving parkinsonian symptoms in the first few years of treatment (the "honeymoon"). Afterwards, L-DOPA treatment is complicated by loss of efficacy and the occurrence of stereotyped involuntary movements (monophasic and diphasic L-DOPA-induced dyskinesias), which likely depends on a hyperactivity of the direct pathway (Cenci, 2007). mGlu5 receptors are expressed in the neostriatum by medium spiny projection neurons and interneurons (Smith et al., 2000), and are also found in output nuclei and in nuclei of the indirect pathway (reviewed by Conn et al., 2005). In striatal projection neurons of the indirect pathway, mGlu5 receptors are functionally linked to NMDA receptors and A_{2A} adenosine receptors, forming a receptor complex that counteracts the activity of D2 receptors (Ferré et al., 2002; Nishi et al., 2003). In striatal projection neurons of the direct pathway, mGlu5 receptors affect synaptic responses to dopamine by modulating the activity of dopamine-and cAMP-regulated phosphoprotein, DARPP-32 (Liu et al., 2001). mGlu5 receptors inhibit neurons of the external globus pallidus by a mechanism of cross-desensitization with mGlu1 receptors (Poisik et al., 2003), whereas their activation produces

membrane depolarization and an increase in burst firing in neurons of the subthalamic nucleus (Awad et al., 2000). A growing body of evidence indicates that systemic treatment with mGlu5-receptor NAMs is highly effective in relieving motor symptoms and L-DOPA-induced dyskinesias in rodent and primate models of parkinsonism (Breysse et al., 2002, 2003; Mela et al., 2007; Yamamoto and Soghomonian, 2009; Ouattara et al., 2009; Ambrosi et al., 2010; Johnston et al., 2010; Rylander et al., 2010). The mGlu5 NAMs, AFQ056, AZD2516, and ADX48621, are currently in phase I/II of clinical development for the treatment of Parkinson's disease and L-DOPA-induced dyskinesias. Remarkably, genetic deletion of mGlu5 receptors or systemic treatment with mGlu5-receptor blockers is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine mouse models of toxicological parkinsonism (Battaglia et al., 2002, 2004). Although these are acute models of nigro-striatal degeneration, the possibility that mGlu5-receptor blockade attenuates the progressive loss of nigral neurons associated with Parkinson's disease is attractive and warrants further investigation.

3.2.5.3. Chronic pain: Chronicization of pain reflects the development of "nociceptive sensitization", i.e. the amplification of pain transmission that occurs along the entire pain neuraxis and underlies the hallmark features of chronic pain, such as primary and secondary hyperalgesia, mechanical and thermal allodynia, and spontaneous pain (reviewed by Basbaum et al., 2009). All mGlu receptor subtypes (with the exception of mGlu6 receptors) are widely distributed in pain centers of the brain and spinal cord, and are implicated in the induction, expression, and maintenance of nociceptive sensitization (Neugebauer, 2001; Varney and Gereau, 2002; Goudet et al., 2009; Chiechio et al., 2010). In peripheral nociceptors (the peripheral terminals of dorsal root ganglia neurons) mGlu1 and mGlu5 receptors respond to ambient glutamate by triggering a cascade of reactions leading to sensitization of TrpV1 channels, which sense noxious heat and also respond to inflammatory molecules and capsaicin (Bhave et al., 2001; Hu et al., 2002). In nociceptive neurons of the dorsal horns of the spinal cord, the mGlu5 receptor is activated by glutamate released from primary afferent fibers or by local excitatory interneurons expressing PKC-γ. Activation of mGlu5 receptors leads to inhibition of Kv4.2 voltage-sensitive potassium channels *via* a phosphorylation mechanism mediated by the MAPK pathway (Hu et al., 2007). The resulting increase in neuronal excitability contributes to nociceptive sensitization in spinal cord neurons. mGlu5 receptors are also found in supraspinal brain centers, such as dorsal raphe nuclei and amygdala, where their activation sustains chronic pain (de Novellis et al., 2005; Ansah et al., 2009, 2010). Pharmacological blockade of mGlu5 receptors is analgesic in models of inflammatory and neuropathic pain, and inhibits the development of tolerance to the analgesic activity of morphine (Fisher et al., 2002; Kozela et al., 2003; de Novellis et al., 2004; Smith et al., 2004; Varty et al., 2005; Han and Neugebauer, 2005; Sevostianova and Danysz, 2006; Osikowicz et al., 2008; Montana et al., 2009). Based on these preclinical data, mGlu5-receptor NAMs such as AZD2516 and AZD2066 are under clinical development for the treatment of neuropathic pain (pain originating from structural or functional lesions of the pain pathways). In a phase IIa clinical trial, the mGlu5-receptor NAM, ADX100159, has shown better efficacy than placebo in the treatment of acute pain associated with migraine.

3.2.5.4. Drug addiction: Drug addiction or "substance dependence" (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, 1994) is a chronic, relapsing disorder characterized by compulsive drugs seeking behavior, loss of control in taking the drug, and emergence of a negative emotional state when access to the drug is prevented (reviewed by Koob and Le Moal, 2008). From a therapeutic standpoint, it is helpful to subdivide the addiction process into three phases: (i) an "intoxication phase" (e.g. a cocaine binge), dominated by the reinforcing properties of the drug; (ii) an abstinence phase, in which

mechanisms of negative reinforcement sustain drug craving; and (iii) a phase of enduring vulnerability to drug intake, in which drug reinstatement may be induced by stress, drug priming, or environmental cues previously paired with drug intake. Activation of the dopaminergic mesolimbic system, projecting from the ventral tegmental area (VTA) to the shell of nucleus accumbens, mediates the reinforcing properties of drugs of abuse (Di Chiara and Imperato,1988), whereas a dysregulation of synaptic plasticity in the nucleus accumbens contributes to the phase of enduring vulnerability to drug intake (reviewed by Kauer and Malenka, 2007; Kalivas, 2009). Chiamulera et al. (2001) have shown that mice lacking mGlu5 receptors fail to self-administer cocaine without showing a defect in the ability of cocaine to increase extracellular dopamine levels in the nucleus accumbens. Data obtained with MPEP in experimental paradigms measuring acute drug reward (e.g., self-administration of drugs of abuse, measurements of brain reward thresholds, and conditioned-place preference) indicate that activation of mGlu5 receptors is required for incentive motivation for the reinforcer (reviewed by Kenny and Markou, 2004; Kenny et al., 2005). mGlu5-receptor NAMs exert anti-reinforcing effects at multiple levels including VTA neurons, where group-I mGlu receptors are involved in mechanisms of synaptic plasticity underlying reward-based conditioning and the development of drug addiction (Kauer and Malenka, 2007; Ahn et al., 2010). Accordingly, cocaine-mediated synaptic potentiation is absent in VTA neurons from mGlu5-defient mice (Bird et al., 2010). mGlu5-receptor blockade in the nucleus accumbens is effective in preventing relapse to drug seeking as well as neurochemical changes associated with drug reinstatement (Bespalov et al., 2005; Schroeder et al., 2008). mGlu5-receptor NAMs hold promise in the treatment of drug addiction, and AFQ056 is under clinical development for the treatment of tobacco smoking (Kenny, 2009). However, it should be highlighted that mGlu5-receptor blockade increases somatic signs and reward deficits associated with nicotine withdrawal (Liechti and Markou, 2006), suggesting that mGlu5-receptor NAMs should be associated with drugs that lower the reward threshold (e.g., bupropion) in the acute phase of nicotine withdrawal.

3.2.5.5. Anxiety: Drugs that block mGlu5 receptors consistently show anxiolytic-like activity in a variety of animal models such as fear potentiated startle, contextual fear conditioning, elevated plus maze, conflict tests, and stress-induced hyperthermia (Spooren et al., 2000; Tatarczyńska et al., 2001; Busse et al., 2004; Roppe et al., 2004; Pietraszek et al., 2005; Stachowicz et al., 2007; Spanka et al., 2010). Mice lacking mGlu5 receptors also show a reduced stress-induced hyperthermia (Brodkin et al., 2002). Remarkably, fenobam, a clinically validated anxiolytic drug, behaves as a potent and selective mGlu5-receptor NAM (Porter et al., 2005). A critical issue is whether mGlu5-receptor antagonists show a better profile of safety and tolerability than benzodiazepines and selective serotonin reuptake inhibitors (SSRIs), which are widely prescribed for the treatment of generalized anxiety disorders and panic attacks. A potential advantage with respect to benzodiaze-pines is that, at least in preclinical models, mGlu5-receptor NAMs retain their anxiolytic activity after repeated dosing (i.e. there is no development of tolerance) (Nordquist et al., 2007). As opposed to diazepam, MPEP produces a robust anxiolytic effect in rat conflict tests at doses that do not impair working memory and spatial learning (Ballard et al., 2005). Fenobam, however, was shown in one study to produce anxiolytic activity at doses that impaired spatial learning (Jacob et al., 2009). Finally, little is known on the interaction between mGlu5-receptor NAMs and drug metabolizing enzymes (e.g. the various isotypes of cytochrome-P450) and drug efflux pumps. Thus, the development of mGlu5-receptor NAMs as novel anxiolytic agents warrants further investigations.

3.2.5.6. Schizophrenia: The interest for mGlu5 receptors in schizophrenia stems from the evidence that mGlu5-receptor knockout mice show a disruption in PPI, which reflects a defect in sensory-motor gating (Kinney et al., 2003; Brody et al., 2004). mGlu5-receptor

blockade enhances the psychotomimetic effect of phencyclidine (Campbell et al., 2004), and mice with genetic deletion of Norbin, which enhances mGlu5-receptor signalling, also show a defect in PPI (Wang et al., 2009). GRM5 has been mapped to 11q15 neighbouring a translocation that segregates with schizophrenia in a large Scottish family (Devon et al., 2001). mGlu5 and NMDA receptors may act synergistically in regulating neuronal activity in the prefrontal cortex, a region that is critically involved in the pathophysiology of cognitive dysfunction in schizophrenic patients. Accordingly, pretreatment with a selective mGlu5-receptor enhancer prevents the abnormality in neuronal firing induced by NMDA receptor blockade in the medial prefrontal cortex (Lecourtier et al., 2007). The prediction that amplification of mGlu5-receptor function could be beneficial in the treatment of schizophrenia led to the development of a series of mGlu5-receptor PAMs (reviewed by Conn et al., 2009). Among these, CDPPB and ADX47273 are active in preclinical models that predict efficacy in the treatment of positive symptoms and cognitive dysfunction associated with schizophrenia (Liu et al., 2008; Schlumberger et al., 2009a,b; Vardigan et al., 2010), and ADX63365 is currently developed for the treatment of schizophrenia. It should be highlighted that the therapeutic activity of conventional antipsychotics on cognitive dysfunction associated with schizophrenia is negligible, and therefore, the use of mGlu5-receptor PAMs may represent a new avenue in the treatment of schizophrenic syndromes.

3.2.5.7. Gastroesophageal reflux disorder (GERD): GERD is a common disorder affecting 3–7% of the U.S. population, which is caused by an abnormal reflux of stomach acid to the esophagus due to a transient relaxation of the lower esophageal sphincter (LES). The most common symptoms are regurgitation, heartburn, and dysphagia. In some cases, GERD causes injury of the esophageal epithelium leading to esophagitis, esophageal strictures, metaplastic changes in the esophageal epithelium (Barrett's esophagus), and esophageal adenocarcinoma. Proton pump inhibitors are commonly used in the treatment of GERD. These drugs, however, inhibit acid secretion without affecting LES tone. Interestingly, glutamate is a potent activator of the vagal pathway mediating LES relaxation (Partosoedarso and Blackshaw, 2000), and mGlu receptors, including mGlu5, are expressed by gastric vagal afferents (Page et al., 2005). Preclinical studies have shown that mGlu5-receptor NAMs such as MPEP and MTEP increase basal LES pressure and inhibit LES relaxation (Frisby et al., 2005; Jensen et al., 2005). In a clinical study, treatment with the mGlu5 NAM, ADX100159, reduced the number and duration of symptomatic reflux episodes as well as nocturnal and postprandial esophageal acid exposure (Keywood et al., 2009). A modified release formulation of ADX100159 showed a better profile of tolerability and is therefore particular suitable for long-term treatments in patients with GERD (Zerbib et al., 2010).

3.3. mGlu2 and mGlu3 receptors

3.3.1. mGlu2 receptor—Gene name: *GRM2* (human); *Grm2* (rat, mouse). Accession numbers: NP_000830 (human); NP_001099181 (rat); NP_001153825 (mouse). Chromosomal location: 3q21.31 (human); 8q32 (rat); 9 (mouse) (Tanabe et al., 1992; Kuramoto et al., 1994; Flor et al., 1995a; Martí et al., 2002).

3.3.2. mGlu3 receptor—Gene name: *GRM3* (human); *Grm3* (rat, mouse). Accession numbers: NP_000831 (human); NP_001099182 (rat); NP_862898 (mouse). Chromosomal location: 7q21.1–q21.2 (human); 4q32 (rat); 5A1-h (mouse) (Tanabe et al., 1992; Kuramoto et al., 1994; Scherer et al., 1996; Emile et al., 1996; Corti et al., 2000).

3.3.2.1. Splice variants: Three splice variants of GRM3 have been reported in human brain and B lymphoblasts. The most abundant variant lacks exon 4 (GRM3Δ4) and encodes for a 60 kDa protein lacking the 7-TM domain of mGlu3 receptors (Sartorius et al., 2006).

3.3.2.2. Signal transduction and interacting proteins: mGlu2 and mGlu3 receptors are coupled to Gi/Go proteins in heterologous expression systems (reviewed by Tanabe et al., 1992). Their activation inhibits cAMP formation, inhibits voltage-sensitive Ca^{2+} channels, activates K^+ channels, and can also activate the MAPK and PtdIns-3-K pathways (reviewed by Pin and Duvoisin, 1995). mGlu2/3 receptor agonists do not stimulate PI hydrolysis on their own, but amplify the stimulation of PI hydrolysis mediated by mGlu1/5 receptors in brain slices (Genazzani et al., 1994; Schoepp et al., 1996). Recent findings suggest that mGlu2 and mGlu3 receptors show a different sensitivity to processes of homologous desensitization mediated by GRK2/β-arrestin, with mGlu2 receptors being resistant to desensitization. However, this difference is visible only when inhibition of cAMP formation is measured as a read-out of mGlu2/3 receptor activation (Iacovelli et al., 2009). Group-II mGlu receptors were shown to interact with calmodulin, protein phosphatase 2C, and the Ran binding protein in the microtubule-organizing center (RanBPM) (reviewed by Niswender and Conn, 2010).

3.3.2.3. Functional anatomy: mGlu2 and mGlu3 receptors are diffusely expressed in the CNS. mGlu2 receptors are uniquely localized in neurons and particularly in the pre-terminal region of axons, far from the active zone of neurotransmitter release (Luján et al., 1997; Tamaru et al., 2001), whereas mGlu3 receptors are found at both presynaptic and postsynaptic sites as well as in glial cells (Ohishi et al., 1993a,b; 1994; Neki et al., 1996; Petralia et al., 1996; Ferraguti and Shigemoto, 2006). Presynaptic mGlu2/3 receptors can be activated by an excess of synaptic glutamate, or, alternatively, by the glutamate released from astrocytes *via* the cystine–glutamate membrane antiporter (see Kalivas, 2009) (Fig. 3). Changes in the expression and/or activity of the cystine–glutamate antiporter may affect the function of mGlu2/3 receptors in brain regions that are critically involved in drug addiction (see below). A major function of presynaptic mGlu2/3 receptor is to inhibit neurotransmitter release. Both receptors have an established role in the regulation of synaptic plasticity, particularly in the induction of LTD of excitatory synaptic transmission (Yokoi et al., 1996; Manahan-Vaughan, 1998; Kahn et al., 2001; Kilbride et al., 2001; Renger et al., 2002; Robbe et al., 2002; Grueter and Winder, 2005; Nicholls et al., 2006; Altinbilek and Manahan-Vaughan, 2009).

A particular form of synaptic plasticity has been described in the mouse accessory olfactory bulb, where activation of mGlu2 receptors relieves the GABAergic inhibition of mitral cells, thus permitting the formation of a specific olfactory memory that faithfully reflects the memory of male pheromones formed at mating (Hayashi et al., 1993; Kaba et al., 1994). mGlu3 receptors were also found in embryonic stem cells and glioma-initiating cells, where their activation limits cell differentiation by negatively regulating type-4 bone-morphogenetic protein (BMP-4) receptor signalling (reviewed by Melchiorri et al., 2007).

3.3.2.4. Pharmacology: There are no marketed orthosteric agonists or antagonists that can differentiate between mGlu2 and mGlu3 receptors, with the exception of N-acetylaspartateglutamate (NAAG), which selectively activates mGlu3 receptors (Wroblewska et al.,1997; but see also Chopra et al., 2009). Orthosteric agonists of mGlu2 and mGlu3 receptors include 2R,4R-APDC, and the carboxycyclopropylglycine derivatives, DGC-IV and L-CCG-I. DCG-IV is active in the nanomolar range, but lacks specificity because it also activates NMDA receptors. L-CCG-I also activates group-I mGlu receptors (reviewed by Schoepp et al., 1999). LY354740 and LY379268 are conformationally constrained glutamate analogues in which the glutamate backbone is locked into a fully

extended state by incorporation into a bicycle[3.1.0] hexane ring system. Both compounds behave as potent mGlu2/3 receptor agonists and are systemically active (reviewed by Schoepp et al., 1999). (−)-(1R,4S,5S,6S)-4-Amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY404-039), which is pharmacologically similar to LY379268, is under clinical development for the treatment of schizophrenia (see below). LY341495 is an orthosteric antagonist with nanomolar affinity for mGlu2 and mGlu3 receptors, but is not subtype selective and may recruit other mGlu receptor subtypes (reviewed by Schoepp et al., 1999). (3-(3,4-Dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0] hexane-2,6-dicarboxylic acid) MGS0039 (Nakazato et al., 2004), is a potent and selective mGlu2/3 receptor antagonist, which holds promise as a potential antidepressant drug (see below). 2,2,2-Trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl) ethanesulfonamide hydrochloride (LY487379) and 3′-([(2-cyclo-pentyl-6-7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methy-l)biphenyl l-4-carboxylate (BINA) are prototypes of selective mGlu2 receptor PAMs (reviewed by Niswender and Conn, 2010), which are also under development in the treatment of schizophrenia (see below). No mGlu3 receptor enhancers are currently available.

3.3.2.5. Relevance to human disorders and clinical perspectives

3.3.2.5.1. Anxiety: mGlu2/3 receptors regulate synaptic transmission and plasticity in the amygdala (Wang and Gean, 1999; Lin et al., 2000, 2005), a brain region that encodes fear memory and is critically involved in the pathophysiology of anxiety disorders. Systemic treatment with the mGlu2/3 receptor agonist, LY354740, enhances Fos protein expression – a non-specific marker of cell activation – in GABAergic neurons of the lateral portion of central amygdala (CeL) (Linden et al., 2005, 2006). Thus, activation of mGlu2/3 receptors inhibits GABA release at basolateral amygdala (BLA)-CeL synapses, leading to an increased activity of GABAergic interneurons in the CeL. This, in turn, reduces the activity of output neurons in the medial central amygdala, which project to brain regions mediating the motor, autonomic, and endocrine features of anxiety. Treatment with LY354740 is highly effective in several animal models of anxiety and panic disorders with no reductions of activity on repeated dosing (reviewed by Swanson et al., 2005). The anxiolytic activity of LY354740 requires the presence of both mGlu2 and mGlu3 receptors (Linden et al., 2005), and, as predicted by the above mechanism, is reversed by the benzodiazepine antagonist, flumazenil (Ferris et al., 2001). LY354740 has progressed into phase II clinical trials with demonstration of good efficacy in the treatment of generalized anxiety disorder before discontinuation based on findings of convulsions in preclinical studies (Dunayevich et al., 2008). If convulsions represent an off-target effect of LY354740 or rather develop as a result of chronic activation (or desensitization) of mGlu2 or mGlu3 receptors remains to be determined.

3.3.2.5.2. Schizophrenia: The development of mGlu2/3 receptor agonists as antipsychotic drugs moved from the observation that LY354740 inhibits glutamate release (Battaglia et al., 1997), allowing for testing the hyperglutamatergic theory in schizophrenia (Aghajanian and Marek, 1999). Moghaddam and Adams (1998) found that LY354740 attenuates the disruptive effect of phencyclidine on working memory, locomotion, stereotypies, and cortical glutamate efflux. Since then, a number of mGlu2/3 receptor agonists have shown robust activity in models that are used to predict efficacy of potential antipsychotic agents (Schoepp and Marek, 2002; Conn et al., 2008, 2009). A pioneer phase II clinical study has shown that the a 21-day treatment with LY2140023, the oral prodrug of the potent and selective mGlu2/3 receptor agonist, LY404039, was nearly as effective as treatment with the antipsychotic olanzapine in reducing both positive and negative symptoms in schizophrenic patients (Patil et al., 2007). As opposed to olanzapine, LY2140023 did not increase body weight and blood triglyceride levels, two effects that seriously limit the use of atypical

antipsychotic drugs in the treatment of schizophrenia (Patil et al., 2007). The antipsychotic activity of mGlu2/3 receptor agonists has been proposed to involve a negative interaction between mGlu2/3 receptors and 5-HT_{2A} receptors. 5-HT_{2A} receptors are activated by hallucinogenic drugs, such as lysergic acid diethylamide, psilocin, and (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and are antagonized by clozapine and other atypical antipsychotics. Pharmacological activation of mGlu2/3 receptors attenuates 5-HT_{2A}-receptor-mediated excitatory post-synaptic currents recorded in layer V pyramidal neurons of the prefrontal cortex (Marek et al., 2000), and reduces electrophysiological and behavioural effects of hallucinogens (Gewirtz and Marek, 2000; Winter et al., 2004; Kłodzinska et al., 2002; Zhai et al., 2003; Benneyworth et al., 2007). Variations in the GRM3 gene (encoding human mGlu3 receptors) have been consistently associated with the risk of schizophrenia as well as with the response to antipsychotic medication (Egan et al., 2004; Bishop et al., 2005, 2007; Nicodemus et al., 2007; Fijal et al., 2009; Jönsson et al., 2009). However, preclinical studies suggest that it is the mGlu2 receptor that specifically mediates the antipsychotic activity of mGlu2/3 receptor agonists. González-Maeso et al. (2008) have shown that mGlu2 and 5-HT_{2A} receptors form a heterodimeric complex in the cell membrane, and that activation of mGlu2 receptors inhibits a particular signalling pathway activated by 5- HT_{2A} receptors in response to hallucinogens. In addition, selective mGlu2 receptor PAMs mimic the action of mGlu2/3 receptor agonists in inhibiting 5-HT_{2A} receptor function (Zhai et al., 2003; Benneyworth et al., 2007). In one paper, however, the ability of mGlu2/3 agonists to inhibit DOI-stimulated PI hydrolysis *in vivo* is preserved in both mGlu2 and mGlu3 receptor knockout mice, although it is lost in double mGlu2/3 knockout mice (Molinaro et al., 2009). In line with these findings, an altered dimerization of mGlu3 receptors was detected in the prefrontal of schizophrenic patients (Corti et al., 2007a). Whether or not dual mGlu2/3 receptor agonists and selective mGlu2 receptor PAMs are comparable in terms of efficacy and tolerability in the treatment of schizophrenia is an interesting issue that warrants further investigation.

3.3.2.5.3. Depression: Multiple classes of drugs are available in the treatment of major depression, yet no drug has a fast onset of antidepressant activity, and a substantial percentage of depressed patients are resistant to medication. Dr. Chaki and his associates have shown that systemic treatment with the selective mGlu2/3 receptor antagonist, MGS0039, exerts antidepressant effects in models that are predictive of clinical efficacy, such as the learned helplessness paradigm, the forced swim test, and the tail suspension test (Chaki et al., 2004; Yoshimizu et al., 2006; reviewed by Pilc et al., 2008). Treatment with MGS0039 increases dopamine release in the nucleus accumbens and neurogenesis in the hippocampal dentate gyrus (Yoshimizu and Chaki, 2004; Karasawa et al., 2006), two effects that are consistent with an antidepressant activity. In combination studies, low doses of the mGlu2/3 receptor agonist, LY379268, shorten the temporal latency of classical antidepressants in reducing the expression of β1-adrenergic receptors in the hippocampus (a classical biochemical marker of antidepressant-induced neuroadaptation) and reducing the immobility time in the forced swim test (Matrisciano et al., 2005, 2007). Whether repeated dosing of LY379268 potentiate the activity of classical antidepressants by desensitizing mGlu2/3 receptors remains to be determined.

3.3.2.5.4. Drug addiction: mGlu2 receptors negatively regulates the activity of the reward pathway (i.e. the mesolimbic dopaminergic system) as shown by the increased reinforcing properties of cocaine shown by mGlu2 receptor knockout mice (Morishima et al., 2005). As predicted from this finding, pharmacological activation of mGlu2/3 receptors reduces self-administration of nicotine and cocaine (Liechti and Markou, 2006; Adewale et al., 2006), but precipitates the deficit in brain reward function associated with nicotine withdrawal (Kenny et al., 2003). Thus, mGlu2/3 receptor agonists may be valuable in the treatment of

the "intoxication" phase of nicotine or cocaine addiction, but may increase drug craving during the early phase of drug withdrawal. Interestingly, however, mGlu2/3 receptor agonists reduce the somatic signs of opiate withdrawal and the associated hyperactivity of locus coeruleus neurons (Fundytus and Coderre, 1997; Vandergriff and Rasmussen, 1999), suggesting that activation of mGlu2/3 receptors differentially affects various aspects of drug withdrawal (reviewed by Kenny and Markou, 2004). An elegant series of experiments by Peter Kalivas and his associates has linked a defective activation of mGlu2/3 receptors to abnormalities of synaptic plasticity in the core of nucleus accumbens underlying the enduring vulnerability to drug reinstatement in addiction (reviewed by Kalivas, 2009). Rats withdrawn from chronic cocaine self-administration fail to develop LTP in the nucleus accumbens core after *in vivo* stimulation of the prefrontal cortex because of a pre-existing potentiation of synaptic transmission, which results form a reduced ability of presynaptic mGlu2/3 receptors to negatively regulate glutamate release. This derives (i) from a reduced expression of the xCT subunit of the glial cystine–glutamate antiporter transport system X_c^-, which releases the glutamate necessary for the activation of presynaptic mGlu2/3 receptors, and (ii) from a reduced expression of type-3 Activator of G-protein Signalling (AGS3), which, in spite of its name, negatively regulates mGlu2/3 receptor signalling. Treatment with N-acetylcysteine, which provides the cystine substrate for residual cystine–glutamate exchangers, restores synaptic plasticity in the nucleus accumbens core and prevents cocaine relapse *via* the activation of mGlu2/3 receptors (Moran et al., 2005; Moussawi et al., 2009; reviewed by Kalivas, 2009). N-Acetylcysteine is under clinical development for the treatment of nicotine and cocaine addiction (LaRowe et al., 2006, 2007; Mardikian et al., 2007; Karila et al., 2008; Knackstedt et al., 2009). Curiously, N-acetylcysteine is marketed as an expectorant, and is also helpful in improving bronchial secretions associated with tobacco smoking.

3.3.2.5.5. Chronic pain: mGlu2/3 receptors are found in many stations of the pain neuraxis, from peripheral nociceptors to the amygdala, which encodes the emotional aspects of pain. In nociceptors, activation of mGlu2/3 receptors negatively regulate TrpV1 channels *via* the inhibition of cAMP formation (Yang and Gereau 4th, 2002; Carlton et al., 2009), whereas activation of presynaptic mGlu2/3 receptors localized on primary afferent fibers inhibits neurotransmitter release in the dorsal horns of the spinal cord (review by Chiechio et al., 2010). Systemic treatment with mGlu2/3 receptor agonists consistently produces analgesia in animal models of acute and chronic pain, but their use is limited by the development of tolerance in response to repeated dosing (Jones et al., 2005). This limitation can be overcome by a novel analgesic strategy based on the transcriptional activation of the *Grm2* gene. L-Acetylcarnitine (LAC), a drug marketed for the treatment of neuropathic pain, induces the expression of mGlu2 receptors in dorsal root ganglia and in the dorsal horns of the spinal cord by enhancing acetylation of the p65/Rel subunit of the NFκB family of transcription factors. Remarkably, LAC-induced analgesia requires multiple dosing and is abolished by the mGlu2/3 receptor antagonist, LY341495 (Chiechio et al., 2002, 2006). Identical results are obtained with inhibitors of histone deacetylase, which also cause analgesia by inducing mGlu2 receptors in the spinal cord (Chiechio et al., 2009). Transcriptional regulation of mGlu2 receptors has been highlighted as an epigenetic path to novel treatments for chronic pain (Chiechio et al., 2010).

3.3.2.5.6. Brain tumors: Grade III and IV gliomas (anaplastic astrocytoma and glioblastoma multiforme, respectively) are highly infiltrating malignant brain tumors that represent the 3rd largest cause of all cancer-related deaths. It is generally believed that glioblastoma multiforme arises from a particular population of transformed neural stem cells named "glioma stem cells", which sustain tumor growth and are intrinsically resistant to radiotherapy and chemotherapy (reviewed by Stiles and Rowitch, 2008). Purified glioma

stem cells express mGlu3 receptors, the activation of which restrains the pro-differentiating activity of type-4 bone-morphogenetic protein (BMP-4) *via* a mechanism of receptor–receptor interaction. Systemic treatment with the preferential mGlu2/3 receptor antagonist, LY341495, reduces the growth of brain tumors originating from U87MG glioma cells (Arcella et al., 2005) or human glioma stem cells (Ciceroni et al., 2008) in mice. More recent findings suggest that mGlu3 receptor antagonists act synergistically with DNA-alkylating agents in killing glioma stem cells (Ciceroni C. et al., unpublished). The possibility that mGlu3 receptor blockade is used as a strategy for the treatment of malignant gliomas is attractive and warrants further investigation.

3.3.2.5.7. Neurodegenerative disorders: The role of mGlu2/3 receptors in mechanisms of neurodegeneration/neuroprotection is highlighted in a previous review (Bruno et al., 2001). It is disappointing that the robust neuroprotective activity of mGlu2/3 receptor agonists found in cell cultures (Bruno et al., 1995; Copani et al., 1995) is only partially seen in *in vivo* models of acute or chronic neurodegenerative disorders (Bond et al., 1999, 2000; Murray et al., 2002; Battaglia et al., 2003). The use of knockout mice unravelled distinct roles for mGlu2 and mGlu3 receptors in mechanisms of neurodegeneration/neuroprotection, with neuroprotection being entirely mediated by glial mGlu3 receptors in cultures challenged with mGlu2/3 receptor agonists (Corti et al., 2007b). In contrast, the lack of mGlu2 receptors in neurons attenuates excitotoxic death (Corti et al., 2007b), and treatment of neuronal cultures with a selective mGlu2 receptor enhancer amplifies β-amyloid toxicity (Caraci F. et al., unpublished). Activation of glial mGlu3 receptors enhances the production of transforming growth-factor-β (TGF-β) (Fig. 3), which acts as a paracrine protective factor on neighbour neurons (Bruno et al., 1998; D'Onofrio et al., 2001). Interestingly, systemic treatment with the mGlu2/3 receptor agonist, LY379268, prevents neurodegeneration and increases the expression of TGF-β2 in the entorhinal cortex of rats exposed to an alcohol binge (Cippitelli et al., 2010). Glial mGlu3 receptors are promising targets for the treatment of Alzheimer's disease (AD) because TGF-β protects neurons against β-amyloid toxicity (reviewed by Caraci et al., 2009), and type-2 TGF-β receptors are defective in the AD brain (Tesseur et al., 2006). In addition, abnormalities in the mGlu3/TGF-β axis might contribute to the pathophysiology of Huntington's disease (HD) because TGF-β1 levels are reduced in the plasma and brain tissue of HD patients, and activation of mGlu3 receptors fails to enhance the production of TGF-β1 in brain tissue of HD mutant mice (Battaglia et al., 2010). Production of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial-derived neurotrophic factor (GDNF) is also positively regulated by mGlu3 receptors (Ciccarelli et al., 1999; Battaglia et al., 2009; Di Liberto et al., 2010). GDNF is a potent prosurvival factor for nigral dopaminergic neurons (Lin et al., 1993), and intraputaminal infusion of GDNF attenuated parkinsonian symptoms in two phase-I clinical trials (Gill et al., 2003; Slevin et al., 2005). Thus, drugs that selectively activate mGlu3 receptors might produce neuroprotective effects in all major neurodegenerative disorders of the CNS.

3.4. mGlu4, mGlu7, and mGlu8 receptors

3.4.1. mGlu4 receptor—Gene name: *GRM4* (human); *Grm4* (rat, mouse). Accession numbers: NP_000832 (human); NP_073157 (rat); NP_001013403 (mouse). Chromosomal location: 6p21.3 (human); 20p12 (rat); 17A3.3 (mouse) (Tanabe et al., 1992; Kuramoto et al., 1994; Flor et al., 1995b; Barbon et al., 2000a).

3.4.2. mGlu7 receptor—Gene name: *GRM7* (human); *Grm7* (rat, mouse). Accession numbers: NP_000835 (human); NP_112302 (rat); NP_796302 (mouse). Chromosomal location: 3p26.1–p25-1 (human); 4q42 (rat); 6E3 (mouse) (Okamoto et al., 1994; Saugstad et al., 1994; Barbon et al., 2000b).

3.4.3. mGlu8 receptor—Gene name: *GRM8* (human); *Grm8* (rat, mouse). Accession numbers: NP_000836 (human); NP_071538 (rat); NP_032200 (mouse). Chromosomal location: 7q31.3–q32 (human); 4q22 (rat); 6A3 (mouse) (Duvoisin et al., 1995; Saugstad et al., 1997; Scherer et al., 1996, 1997).

3.4.3.1. Splice variants: There are no variants of mGlu4 receptors. Five splice variants of mGlu7 receptors have been described so far (mGlu7a–e). In mGlu7b, alternative splice originates from an out-of-frame insertion in the C-terminus domain, which results in the replacement of the last 16 amino acids of mGlu7a with 23 amino acids (Flor et al., 1997; Corti et al., 1998). Expression of mGlu7 receptors in non-neuronal tissue (see below) is restricted to variants mGlu7c and mGlu7d (Schulz et al., 2002). A splice variant of mGlu8 receptors (mGlu8b) has been described in rats and humans, in which an out-of-frame insertion of 55 bp results in the substitution of the last 16 amino acids of mGlu8a with 16 different amino acids (Corti et al., 1998; Malherbe et al., 1999). An additional variant has been described in the human mGlu8 receptor, in which an insertion of 74 bp introduces a frame shift in the predicted translation resulting in termination of the polypeptide before the 7-TM region (Malherbe et al., 1999).

3.4.3.2. Signal transduction and interacting proteins: mGlu4, mGlu7, and mGlu8 receptors are coupled to Gi/Go proteins in heterologous expression systems (reviewed by Pin and Duvoisin, 1995; Niswender and Conn, 2010). Activation of the MAPK and PtdIns-3-K pathways mediated by native mGlu4 receptors has been reported in cultured cerebellar granule cells (Iacovelli et al., 2002). mGlu7 receptors bind to a number of interacting proteins that include filamin A, protein phosphatase 1C, protein interacting with protein kinase C 1 (PICK1), syntenin, the βγ subunits of G proteins, and MacMARCKS (macrophage myristoylated alanine rich C kinase substrate) (Boudin et al., 2000; El Far et al., 2001; Enz and Croci, 2003; Bertaso et al., 2006). Proteins interacting with mGlu8 receptors include Band 4.1, which facilitates cell surface receptor expression and inhibits mGlu8-receptor signalling (Rose et al., 2008), and Pias-1 and other proteins of the sumoylation cascade (Tang et al., 2005).

3.4.3.3. Functional anatomy: mGlu4, mGlu7, and mGlu8 receptors are localized presynaptically at the active zone of neurotransmitter release. Synaptic glutamate can therefore activate all three receptor subtypes, thus negatively regulating its own release (reviewed by Niswender and Conn, 2010). However, glutamate binds with relatively high affinity to mGlu4 and mGlu8 receptors, but displays very low affinity for mGlu7 receptors (reviewed by Schoepp et al., 1999). This suggests that mGlu7 receptors can only be recruited by high concentrations of glutamate released under conditions of high synaptic activity. Not surprisingly, mice lacking mGlu7 receptors show an increased susceptibility to epileptic seizures (Sansig et al., 2001). A presynaptic integration exists among mGlu7 receptors, $GABA_B$ receptors and A1 adenosine receptors, which functionally interact in reducing glutamate release mediated by N-type voltage-sensitive Ca^{2+} channels (Martín et al., 2008). However, repeated agonist exposure discloses a facilitatory mGlu7 signal on glutamate release, which is mediated by stimulation of PI hydrolysis and translocation of munc-13-1, a protein that is essential for priming of synaptic vesicles (Martín et al., 2010). Thus, the regulation of glutamate release by mGlu7 receptors is not univocal and is strictly activity-dependent.

The mGlu4 receptor is highly expressed in the cerebellum, where its activation inhibits glutamate release at the synapse between parallel fibers (the axons of cerebellar granule cells) and Purkinje cells. High-to-moderate levels of expression are also found in the thalamus, basal ganglia, and olfactory bulb. mGlu4 receptors found in nerve terminals of striatal projection neurons innervating the external globus pallidus are particularly relevant

from a clinical standpoint (see below). A truncated form of mGlu4 receptors lacking a great portion of the glutamate binding domain has been found in taste buds (Chaudhari et al., 2009). mGlu4 receptors were also present in medulloblastoma cells (Iacovelli et al., 2006), immune cells (see below), and in pancreatic α-cells, where they inhibit glucagons secretion (Uehara et al., 2004). mGlu7 are highly expressed in the CNS, and are also found in peripheral organs. mGlu7 receptors are found in hair cells and in spiral ganglion cells of the inner ear, and common single nucleotide polymorphisms (SNPs) of GRM7 are strongly associated with the risk of developing age-related hearing impairment (presbycusis), the most prevalent sensory impairment in the elderly (Friedman et al., 2009). Recent findings suggest that mGlu7 receptors are expressed in the colon mucosa, where receptor activation increases fecal water content in a stress-induced defecation paradigm (Julio-Pieper et al., in press). It has been suggested that mGlu7 receptors play a role in functional disorders of the gut, such as the irritable bowel syndrome (IBS), which are often associated with chronic stress.

The mGlu8 receptor is widely, but unevenly, distributed in the CNS. For example, mGlu8-receptor expressing nerve terminals target specific subsets of GABAergic neurons in the hippocampus (Ferraguti et al., 2005).

3.4.3.4. Pharmacology: L-AP4 and L-SOP (an endogenous product of phospholipids cleavage which accumulates in the Alzheimer's brain) are the prototypical, non-subtype-selective orthosteric agonists of group-III mGlu receptors (reviewed by Schoepp et al., 1999). As outlined in the Historical background, these two compounds are also able to block excitatory amino acid-stimulated PI hydrolysis in brain slices (Nicoletti et al., 1986a). Whether this particular effect derives from an interaction between group-I and group-III mGlu receptors is unknown. (1S,3R,4S)-1-Amino-cyclopentane-1,3,4-tricarboxylic acid ACTP-I and (R,S)-4-phosphonophenylglycine (PPG) also behave as non-subtype-selective orthosteric agonists of group-III mGlu receptors (reviewed by Schoepp et al., 1999). In spite of the new insights into the activation mechanisms of group-III mGlu receptors (Selvam et al., 2007; Frauli et al., 2007), there are only a few orthosteric agonists that can discriminate between mGlu4 and mGlu8 receptors. (S)-3,4-dicarboxyphenylglycine (DCPG) has ≥100 fold greater affinity for mGlu8 receptors than for all other group-III mGlu receptor subtypes (Thomas et al., 2001), and is widely used as a tool to selectively activate mGlu8 receptors. The available orthosteric antagonists of group-III mGlu receptors display low receptor affinity or lack specificity. For example, (R,S)-α-cyclopropyl-4-phosphonophenylglycine (CPPG), which is often used as an orthosteric antagonist of group-III mGlu receptors, can also antagonize group-II mGlu receptors with nanomolar affinity (Toms et al., 1996). N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC) is the prototype of a growing list of selective mGlu4 receptor PAMs that hold promise for the treatment of Parkinson's disease and other disorders (reviewed by Niswender and Conn, 2010). Because of its structure similarity with CPCCOEt, PHCCC can also have off-target effects by blocking mGlu1 receptors at high concentrations. The mGlu5-receptor NAMs, MPEP and SIB1893, also behave as mGlu4 receptor PAMs in the high micromolar range (Mathiesen et al., 2003). Only few drugs behave as selective ligands of mGlu7 receptors. These include the "allosteric agonist" N,N′-Bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride (AMN082), which directly activate mGlu7 receptors by interacting with a site different from the glutamate binding site, and the putative mGlu7 receptor NAM, 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo [4,5]pyridine-4(5H)-one (MMPIP) (Mitsukawa et al., 2005; Suzuki et al., 2007). A bias inherent to the use of AMN082 is that the drug induces a rapid internalization of mGlu7 receptors (Pelkey et al., 2007). This may partly explain some unexpected findings in experiments using AMN082 (see below).

3.4.3.5. Relevance to human disorders and clinical perspectives

3.4.3.5.1. Parkinson's disease: Activation of mGlu4 receptors inhibits GABA release at the synapse between stratial projection neurons and neurons of the external globus pallidus. This is the first synapse of the indirect pathway of the basal ganglia motor circuit, which is overactive in Parkinson's disease (reviewed by Conn et al., 2005). Drugs that activate mGlu4 receptors including orthosteric agonists and selective PAMs cause a robust depression of inhibitory synaptic transmission in the external globus pallidus and relieve motor symptoms in animal models of parkinsonism (Marino et al., 2003; Valenti et al., 2003; Niswender et al., 2008; Beurrier et al., 2009). Because the inhibitory action of mGlu4 receptors on synaptic transmission in the external globus pallidus is not affected by dopamine loss, one can predict that mGlu4 receptor agonists retain their therapeutic activity in Parkinsonian patients for a long time without causing dyskinesias or other motor side effects that typically develop in response to L-DOPA or other dopaminergic drugs. It is now believed that during the early "compensated" phase of Parkinson's disease a number of mechanisms reduce the activity of the indirect pathway. These include an increased production of endogenous opioids, which suppress synaptic transmission in the external globus pallidus by activating presynaptic μ opioid receptors (Sandyk, 1988; Schroeder and Schneider, 2002). Whether mGlu4 receptors undergo plastic modification in this specific setting is unknown. An early treatment with mGlu4 receptor agonists might reinforce the defensive mechanisms in the early phases of Parkinson's disease, thus delaying the clinical onset of the disorder. Activation of mGlu4 receptors might produce a dual benefit in Parkinson's disease by relieving motor symptoms and attenuating the progressive degeneration of nigro-striatal dopa-minergic neurons at the same time. In mice challenged with the toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), systemic treatment with PHCCC reduces the degeneration of nigro-striatal dopaminergic neurons. PHCCC retains its protective activity when locally injected in the external globus pallidus, suggesting that inhibition of synaptic transmission in the external globus pallidus leads to a reduced activity of excitatory neurons of the subthalamic nucleus, thereby inducing neuroprotection (Battaglia et al., 2004). However, mGlu4 receptors also reduce excitatory synaptic transmission in the pars compacta of the substantia nigra, a mechanism that may contribute to restrain excitotoxic death of nigral dopaminergic neurons (Valenti et al., 2005). Finally, preclinical data raise the interesting possibility that mGlu4 receptor agonists may be helpful for the prophylaxis of drug-induced parkinsonism occurring in schizophrenic patients receiving first-generation antipsychotic drugs. These patients are usually treated with anticholinergic drugs, which, however, cause autonomic adverse effects and cognitive dysfunctions.

3.4.3.5.2. Absence epilepsy: Absence seizures, which are characterized by synchronous spike-and-wave discharges (SWDs) at the EEG, are generated by an abnormal oscillatory activity of a thalamocortical loop that comprises ventrobasal thalamic nuclei, the cerebral cortex, and the reticular thalamic nucleus (RTN) (reviewed by Blumenfeld, 2005). Drugs that block T-type voltage-sensitive Ca^{2+} channels, such as ethosuximide and valproate, as well as clonazepam and lamotrigine are commonly used in the treatment of absence epilepsy; however, these drugs cause class-related adverse effects as sedation and ataxia, and >20% of patients with absence seizures are resistant to medication. Recent evidence suggests that mGlu receptors in general, and group-III mGlu receptors in particular, are novel potential targets for treatment of absence epilepsy. Genetic deletion of mGlu4 receptors or intra-RTN injection of a group-III mGlu receptor antagonist protects mice against absence seizures induced by low doses of pentylentetrazol (Snead et al., 2000). In addition, WAG/Rij rats, which spontaneously develop SWDs after 2–3 months of age, show an increased expression of mGlu4 receptors in the RTN, and respond to pharmacological activation of mGlu4 receptors with an increased frequency of absence seizures (Ngomba et

al., 2008). Interestingly, the GRM4 gene is localized within the EJM1 susceptibility focus for juvenile myoclonic epilepsy (Wong et al., 2001; Izzi et al., 2003), which is characterized by absence seizures combined with myoclonic and tonic–clonic seizures. These data stimulate the search for molecules that selectively antagonize mGlu4 receptors as potential anti-absence drugs.

Recent evidence indicates that absence seizures develop in mice under conditions that disrupt the interaction of mGlu7 receptors with PICK1 (Bertaso et al., 2008). In addition, mutant mice lacking the PDZ domain in mGlu7 receptors (necessary for the interaction with PICK1 and other proteins) are more sensitive to pentylentetrazol-induced absence seizures (Zhang et al., 2008a,b). This suggests that interaction between mGlu7 receptors and PICK1 is protective against paroxysmal activity of the thalamocortical network underlying absence seizures.

3.4.3.5.3. Pain: Recent evidence suggests that group-III mGlu receptors regulate pain transmission and are potential targets for analgesic drugs (reviewed by Goudet et al., 2009). However, the individual role of mGlu4, mGlu7, and mGlu8 receptors in the regulation of pain threshold is not univocal. Intrathecal injection of PHCCC causes analgesia in models of inflammatory or neuropathic pain (Goudet et al., 2008), suggesting that mGlu4 receptors in the spinal cord negatively modulate pain transmission. The role of mGlu7 and mGlu8 receptors has been investigated by experiments with microinfusion of subtype-selective ligands in two supraspinal centers that lie along the pain neuraxis, i.e. the amygdala and the periaqueductal grey. In both regions, activation of mGlu7 receptors with the “allosteric agonist” AMN082 amplifies nocifensive behavior, whereas selective activation of mGlu8 receptors with DCPG produces opposite effects (Marabese et al., 2007a; Palazzo et al., 2008). Systemic treatment with DCPG also causes analgesia (Marabese et al., 2007b). Thus, compounds that activate mGlu4 and mGlu8 receptors but have no activity at mGlu7 receptors can be developed as novel analgesic drugs.

3.4.3.5.4. Anxiety: A role for group-IIII mGlu receptors in anxiety was suggested by the evidence that intrahippocampal injection of the non-subtype-selective agonist, L-SOP, had an anticonflict effect in the rat Vogel test (Tatarczyńska et al., 2001). Both mGlu8 and mGlu4 receptors appear to negatively modulate anxiety in rodents. mGlu8-receptor knockout mice exposed to the elevated plus maze test showed anxiety-related behavior and a higher number of c-Fos-positive neurons in the centromedial thalamic nucleus as compared to wild-type mice (Linden et al., 2002, 2003; Duvoisin et al., 2005). In addition, the mGlu8-receptor agonist, DCPG, and the novel mGlu8-receptor enhancer, AZ12216052, reduced anxiety-like behavior in mice (Duvoisin et al., 2010; see Stachowicz et al., 2005 for contrasting data). Selective activation of mGlu4 receptors in the rat amygdala produced an anticonflict effect in the Vogel test (see Linden and Schoepp, 2006 for a comprehensive review). The role of mGlu7 receptors in anxiety is uncertain because treatment with the mGlu7 receptor agonist, AMN082, relieves anxiety and genetic deletion of mGlu7 receptors also relieves anxiety (reviewed by Lavreysen and Dautzenberg, 2008). Functional antagonism of mGlu7 receptors by AMN082 resulting from receptor internalization (see above) may help reconcile these contrasting findings.

3.4.3.5.5. Neuroinflammation and regulation of the immune system: A report by Fallarino et al. (2010) discloses a new mechanism that highlights the cross-talk between the nervous and immune systems. These authors have shown that activation of mGlu4 receptors expressed on dendritic cells, a cell type crucial for supporting an immune response, drives the differentiation of antigen-specific T cells into T regulatory (T_{reg}) cells at the expenses of autoreactive T_H17 cells, thus reinforcing mechanisms of immune tolerance. Mice lacking mGlu4 receptors immunized with a myelin-specific antigen develop a more severe

experimental autoimmune encephalomyelitis (EAE), whereas wild-type mice treated with the mGlu4 receptor PAM, PHCCC, are protected against EAE. Remarkably, PHCCC administered at the onset of motor symptoms reduces the frequency and severity of relapses in a relapsing-remitting model of EAE. These data are particularly relevant to the treatment of relapsing-remitting multiple sclerosis, a demyelinating disorder of the CNS mediated *inter alia* by autoreactive clones of and T_H17 cells. The central role of mGlu4 receptors in the immunological synapses between dendritic cells and T lymphocytes (Fallarino et al., 2010; see also Hansen and Caspi, 2010) suggests a therapeutic activity of mGlu4 receptor enhancers in autoimmune disorders other than multiple sclerosis.

3.4.3.5.6. Smith–Lemli–Opitz syndrome and retinitis pigmentosa: GRM8, the human gene encoding the mGlu8 receptor, encompasses approximately 1000 kb of DNA at the boundary of the q31.3–q32.1 bands of chromosome 7, the same region where the Smith–Lemli–Opitz syndrome and an autosomal form of retinite pigmentosa (Scherer et al., 1997). The Smith–Lemli–Opitz syndrome is a relatively rare developmental disorder due to deficiency of the enzyme 7-dehydrocholesterol reductase. Retinite pigmentosa is a group of genetic eye disorders characterized by abnormalities of photoreceptors or retinal pigment epithelium. It should be highlighted that the mGlu8 receptor has been first identified in the retina (Duvoisin et al., 1995), where it shows multiple localizations (Quraishi et al., 2007). Interestingly, mGlu8 receptors are found in photoreceptor nerve terminals, where they modulate neurotransmitter release by interacting with calcium channels (Koulen et al., 1999, 2005). Whether abnormalities of mGlu8 receptors are related to the progressive blindness associated with autosomal retinite pigmentosa remains to be established.

3.5. mGlu6 receptor

Gene name: *GRM6* (human); *Grm6* (rat, mouse). Accession numbers: NP_000834 (human); NP_075209 (rat); NP_775548 (mouse). Chromosomal location: 5q35 (human); 10 (rat); 11B1.3 (mouse) (Nakajima et al., 1993; Hashimoto et al., 1997; Laurie et al., 1997).

3.5.1. Splice variants—mGlu6 receptor variants have been identified in rats and humans. The rat receptor variant is characterized by an additional exon of 88 nucleotides which contains an in frame stop codon, resulting in a truncated protein of 508 amino acids. The two human variants lack 97 nucleotides of exon 6 and include 5 nucleotides of intron 5, respectively. mRNAs of these two variants encode truncated proteins of 425 and 405 amino acids, respectively. All truncated variants lack the 7-TM and the C-terminus domain of the receptor (Valerio et al., 2001).

3.5.2. Pharmacology—The mGlu6 receptor exhibits the same pharmacological profile as other group-III mGlu receptors, being activated by L-AP4, L-SOP, and PPG, and antagonized by CPPG, (RS)-α-methylserine-O-phosphate (MSOP), and (S)-2-amino-2-methyl-4-phosphonobutanoic acid (MAP4).

3.5.3. Functional anatomy and relevance to human disorders—The mGlu6 receptor is exclusively localized in the dendrites of ON-bipolar cells of the retina and responds to glutamate released from rod and cone photoreceptor cells in the dark (Nakajima et al., 1993; Nomura et al., 1994; Vardi et al., 2000). Activation of mGlu6 receptors reduces excitability of ON-bipolar cells by negatively regulating a membrane non-selective cation channel, which likely corresponds to the TrpM1 channel (Shen et al., 2009; Morgans et al., 2009; Koike et al., 2010). This effect is mediated by a Go protein-dependent activation of the Ca^{2+}-stimulated protein phosphatase, calcineurin (Dhingra et al., 2004; Nawy, 1999, 2000) (Fig. 4). Light reduces glutamate stimulation of mGlu6 receptors, leading to opening of cation channels and depolarization of ON-bipolar cells. The effect of light is amplified by

inactivation of the mGlu6 receptor signalling mediated by the transmembrane protein R9AP, which facilitates the GTPase activity of RGS11 complexed with the $G\beta_5$ subunit of Go (Cao et al., 2009; Masuho et al., 2010; Zhang et al., 2010). mGlu6 receptor knockout mice show a loss of ON responses but an unchanged response to light (Masu et al., 1995), and a mouse screened for the lack of the b-wave at the electroretinogram showed a splice error in the *Grm6* and the lack of mGlu6 receptors in the retina (Maddox et al., 2008). The b-wave of the electroretinogram reflects the light-induced depolarization of ON-bipolar cells (Stockton and Slaughter, 1989). Interestingly, mutations in the gene encoding the mGlu6 receptor is associated with autosomal recessive congenital stationary night blindness characterized by abnormal electroretinogram ON responses in humans (Dryja et al., 2005; Zeitz et al., 2005; O'Connor et al., 2006). Mutations of the TrpM1 gene are also associated with autosomal recessive congenital stationary night blindness (Van Genderen et al., 2009). In conclusion, these are exciting times for mGlu receptors. After 25 years we can truly believe that subtype-selective mGlu receptor ligands will soon enter the clinic. Perhaps the treatment of FXS will be the launching platform for the use of mGlu drugs in highly prevalent disorders, such as schizophrenia, Parkinson's disease, chronic pain, and drug addiction. It is sad that Prof. Costa will not be a witness of the clinical era of mGlu receptors.

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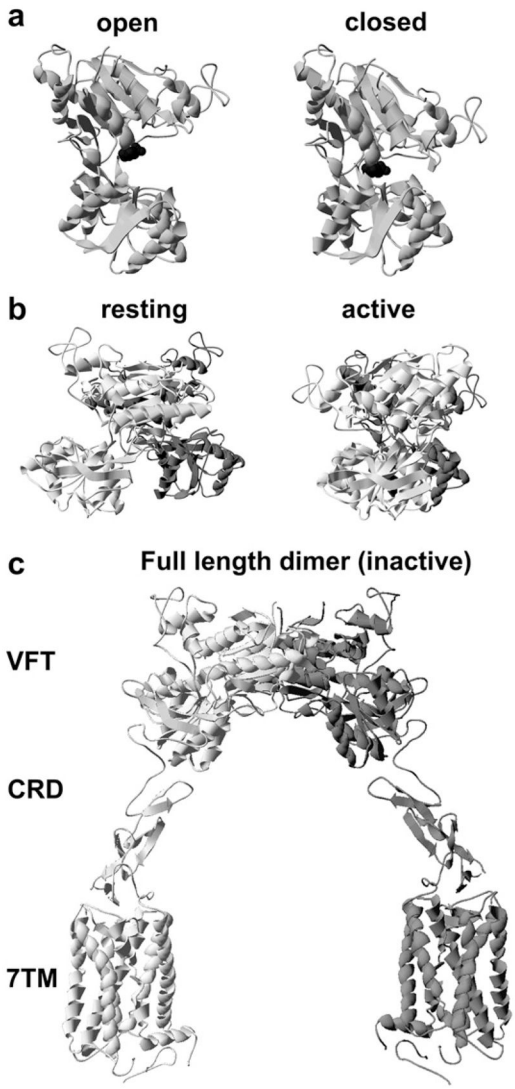

Fig. 1.

Modular structure of mGlu receptors. a) Ribbon view of the open (left) and closed (right) mGlu1 receptor Venus Fly Trap (VFT) bound with glutamate (back). Images were prepared using the coordinates of the glutamate-bound mGlu1 receptor VFT dimer (pdb 1EWK), in which one VFT is closed while the other is open. b) Side view of the mGlu1 receptor dimer bearing the VFT in its empty “resting” state (left) (pdb 1EWT), or agonist occupied “active” orientation (right) (pdb 1EWK). The front VFT is in light grey, while the one in the back is black. c) General organization of an mGlu receptor deduced from the structure of the dimeric mGlu3 extracellular domain (VFT + CRD) (pdb 1E4U) associated with two rhodopsinlike 7-TM domains.

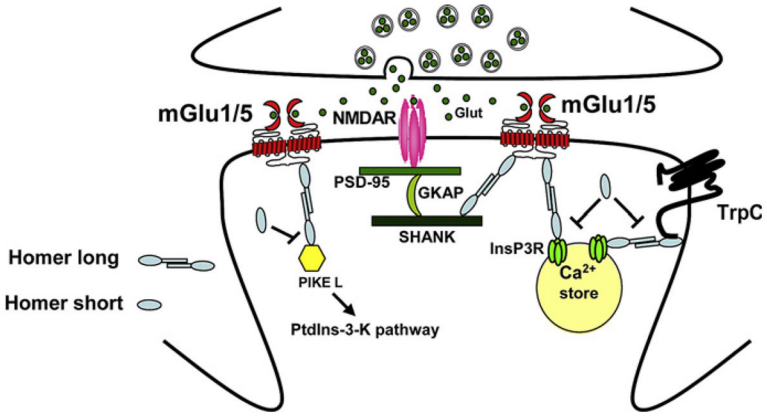

Fig. 2.

Protein–protein interactions involving group-I mGlu receptors in the post-synaptic densities. Long isoforms of Homer proteins allows the formation of multi-molecular complexes including mGlu1 and mGlu5 receptors. Interactions with NMDA receptors, TrpC ion channels, inositol-1,4,5-trisphosphate receptors (InsP3R), or PIKE-L are shown. Short Homer1a lacking the coiled-coil domain disrupts the formation of the multimolecular complex, thereby affecting mGlu1/5 receptor signalling.

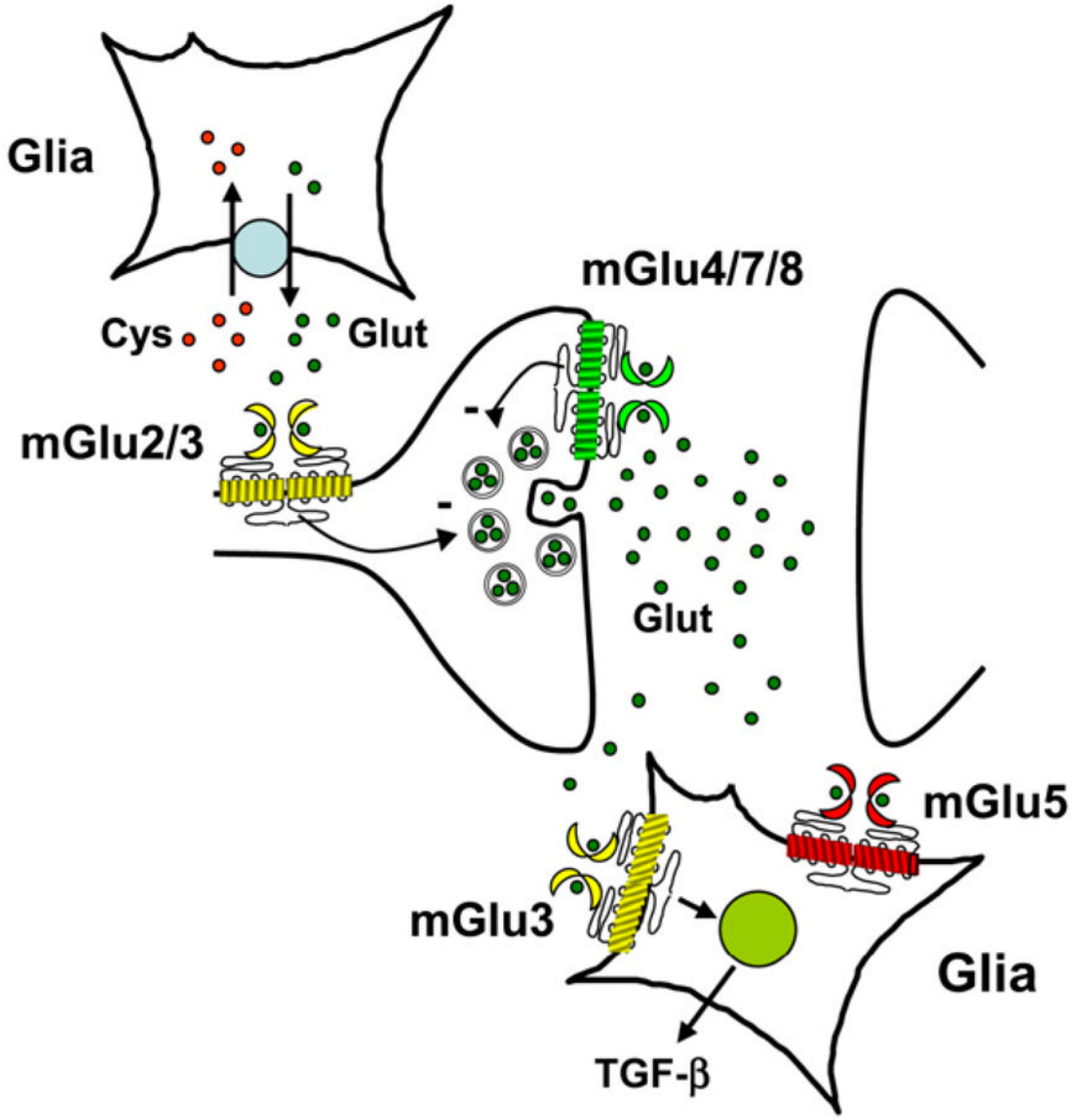

Fig. 3.

Synaptic distribution of group-II and group-III mGlu receptors. Note that presynaptic mGlu2/3 receptors are located in the pre-terminal regions of the axons, where they can be activated by glutamate released from astrocytes *via* the cystine/ glutamate antiporter. In contrast, presynaptic mGlu4/7/8 receptors are located near to the active zone of neurotransmitter release. Glial mGlu3 receptors induce the formation and secretion of TGF-β. The presence of mGlu5 receptors in glial cells is also shown.

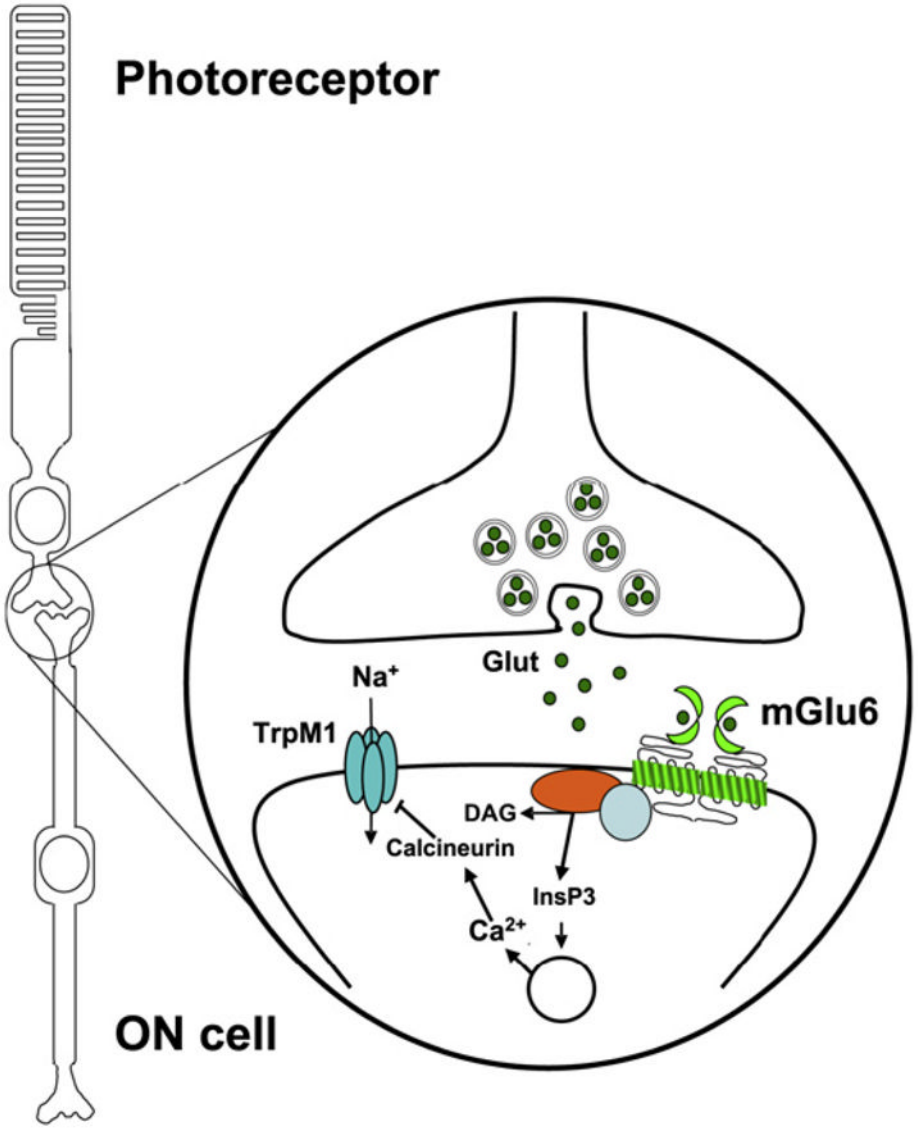

Fig. 4.

Localization and function of mGlu6 receptors in retinal ON-bipolar cells. mGlu6 receptors are present in the dendrites of the ON-bipolar cells of the retina, where their activation negatively modulates TrpM1 channels through a chain of events that include intracellular calcium release and activation of the protein phosphatase, calcineurin.

Table 1

Conformations of the Venus Fly Traps of mGlu receptor subtypes bound to agonists or antagonists.

Receptor	Ligand	Ligand activity	Conformation	PDB entry
mGlu1	–	–	Dimer Roo	1EWT
	–	–	Dimer Aco	1EWV
	Glu	Agonist	Dimer Aco	1EWK
	Glu + Gd^{3+}	Agonist	Dimer Acc	1ISR
	MCPG	Antagonist	Dimer Roo	1ISS
	LY341495	Antagonist	Dimer Aoo	3KS9
mGlu5	Glu	Agonist	Dimer Acc	3LMK
mGlu3	Glu	Agonist	Dimer Rcc	2E4U
	DCG-IV	Agonist	Dimer Rcc	2E4V
	1S,3S-ACPD	Agonist	Dimer Rcc	2E4W
	1S,3R-ACPD	Agonist	Dimer Rcc	2E4X
	2R,4R-APDC	Agonist	Dimer Rcc	2E4Y
mGlu7	–	–	Dimer Roo	2E4Z
	LY341495	Antagonist	Monomer open	3MQ4

Glu = Glutamate; R = resting; A = active; o = open; c = closed.

Table 2

Subtype-selective mGlu receptor ligands.

Subtype	Orthosteric agonists	Orthosteric antagonists	PAMs	NAMs
mGlu1	DHPG (group-selective)	LY367385, AIDA, MATIDA	Ro-0711401, Ro-674853, Ro-677476, VU71	CPCCOEt, BAY367620, JNJ6259685
mGlu5	DHPG (group-selective)	None	DFB, CPPHA, CDPPB, VU29	MPEP, SIB1757, SIB1893, Fenobam, AFQ056, AZD2516, AZD2066, STX107, ADX10059, ADX48621
	CHPG		ADX47273, ADX63365	
mGlu2	LY354740, LY379268, LY404039	LY341495, MGS0039	LY566332, LY487379, BINA	
mGlu3	MCPG	Antagonist	Dimer Roo	1ISS
	LY341495	Antagonist	Dimer Aoo	3KS9
mGlu5	Glu	Agonist	Dimer Acc	3LMK
mGlu3	Glu	Agonist	Dimer Rcc	2E4U
	DCG-IV	Agonist	Dimer Rcc	2E4V
	1S,3S-ACPD	Agonist	Dimer Rcc	2E4W
	1S,3R-ACPD	Agonist	Dimer Rcc	2E4X
	2R,4R-APDC	Agonist	Dimer Rcc	2E4Y
mGlu7	–	–	Dimer Roo	2E4Z
	LY341495	Antagonist	Monomer open	3MQ4