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Metabotropic Glutamate 1 Receptor: Current Concepts and Perspectives

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Abstract——**Almost 25 years after the first report that glutamate can activate receptors coupled to heterotrimeric G-proteins, tremendous progress has been made in the field of metabotropic glutamate receptors. Now, eight members of this family of glutamate receptors, encoded by eight different genes that share distinctive structural features have been identified. The first cloned receptor, the metabotropic glutamate (mGlu) receptor mGlu1 has probably been the most extensively studied mGlu receptor, and in many respects it represents a prototypical subtype for this family of receptors. Its biochemical, anatomical, physiological, and pharmacological characteristics have been intensely investigated. Together with subtype 5, mGlu1 receptors constitute a subgroup of receptors that couple to phospholipase C and mobilize Ca^{2+} from intracellular stores. Several alternatively spliced variants of mGlu1 receptors, which differ primarily in the length of their C-terminal domain and anatomical localization, have been reported. Use of a number of genetic approaches and the recent development of selective antagonists have provided a means for clarifying the role played by this receptor in a number of neuronal systems. In this article we discuss recent advancements in the pharmacology and concepts about the intracellular transduction and pathophysiological role of mGlu1 receptors and review earlier data in view of these novel findings. The impact that this new and better understanding of the specific role of these receptors may have on novel treatment strategies for a variety of neurological and psychiatric disorders is considered.**

I. Introduction

The ability of the neurotransmitter glutamate to activate receptors coupled to heterotrimeric G-proteins was demonstrated in the mid-1980s by the evoked formation of inositol phosphates in cultured striatal neurons and brain slices (Sladeczek et al., 1985, 1988; Nicoletti et al., 1986b,c, 1987; Akiyama et al., 1987). The term metabotropic glutamate receptors (mGluRs; now mGlu[2] receptors according to the International Union of Pharmacology classification) was first introduced by Sugiyama et al. (1987) because of their coupling to G-proteins.

The earliest functional role described for these receptors came from Kano and Kato (1987), who demonstrated that a long-term modification of synaptic transmission efficacy in the cerebellar cortex, known as long-term depression (LTD), was selectively dependent on the activation of mGlu receptors present on Purkinje cell (PC) dendrites.

The recognition that brain mRNA could be used to express and measure metabotropic responses to glutamate in *Xenopus laevis* oocytes was instrumental for the cloning of mGlu receptors. In 1991, two independent laboratories (Houamed et al., 1991; Masu et al., 1991) cloned the first mGlu receptor, named mGlu1 (mGluR1 or Glu_GR in the original papers). Since then, eight different genes encoding for mGlu receptors have been identified (Abe et al., 1992; Tanabe et al., 1992; Nakajima et al., 1993; Okamoto et al., 1994; Saugstad et al.,

[2] Abbreviations: 3,5-DHPG, 3,5-dyhydroxyphenylglycine; 3-MATIDA, derivative of aminothiophene dicarboxylic acid; 3-NP, 3-nitropropionic acid; 4CPG 4-carboxyphenylglycine; 5-HT, 5-hydroxytryptamine, serotonin; A-841720, 9-dimethylamino-3-(*N*-hexamethyleneiminyl)-3*H*-5-thia-1,3,6-triazafluoren-4-one; AIDA, (*RS*)-1-aminoindan-1,5-dicarboxylic acid; AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP3 2-amino-3-phosphonopropionic acid; APDC, 2*R*,4*R*-aminopiperidindicarboxylic acid; BAY 36-7620, (3a*S*,6a*S*)-6a-naphtalan-2-ylmethyl-5-methyliden-hexahydro-cyclopenta[*c*]furan-1-one; bp, base pair(s); CaR, Ca^{2+}-sensing receptor; CB1, cannabinoid receptor 1; CF, climbing fibers; CHO, Chinese hamster ovary; CPCCOEt 7-(hydroxyimino)-cyclopropan[*b*]chromen-1*a*-carboxylate ethylester; CRD, cysteine-rich domain; DA, dopamine; DAergic, dopaminergic; DAG, diacylglycerol, IP_3, inositol triphosphate; EM-TBPC, 1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile; EPSC, excitatory postsynaptic current, RyR, ryanodine receptor; ERK, extracellular signal-regulated kinases; GPCR, G-protein coupled receptor; GRK, G-protein-coupled receptor kinase; GW398171X, 3-methyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester; R214127, 1-(3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-phenyl-1-ethanone; IPSC, inhibitory postsynaptic current; IS, interneuron selective interneuron; JNJ16259865, 3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl(*cis*-4-methoxycyclohexyl)-methanone; KA, kainic acid; kb, kilobase(s); KO, knockout; LBD, ligand binding domain; LTD, long-term depression; LTP, long-term potentiation; LY367366, α-thioxanthyl-9-methylanalogue of *S*-4-CPG; LY367385, (+)-2-methyl-4-carboxyphenylglycine; MAPK, mitogen-activated protein kinases; MCPG, α-methyl-4-carboxyphenylglycine; mGlu, metabotropic glutamate; NMDA, *N*-methyl-D-aspartic acid; NPS 2390, 2-quinoxaline-carboxamide-*N*-adamantan-1-yl; NPS 2407, quinoxaline-2-carboxylic acid (1,1-dimethyl-2-phenyethyl)amide; NPS 3018, 2-quinoxaline ester; nt, nucleotides; O-Bi, oriens-bistratified; O-LM, oriens-lacunosum moleculare; PC, Purkinje cell; PF, parallel fiber; PI, polyphosphoinositide; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C, PSD, postsynaptic density; PL, phospholipase; PPI, prepulse inhibition; PTX, pertussis toxin; RGS, regulators of G-protein signaling; Ro 01-6128, ethyl diphenylacetylcarbamate; Ro 67-4853, butyl (9*H*-xanthene-9-carbonyl)carbamate; Ro 67-7476, (*S*)-2-(4-fluorophenyl)-1-(toluene-4-sulfonyl)pyrrolidine; SCA1, spinocerebellar ataxia type 1; SCG, superior cervical ganglion; Siah, member of the mammalian seven in absentia homologs; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; TMD, transmembrane domain; TRP, transient receptor potential; TRPC, TRP channel; UBC, unipolar brush cells; VFTM, Venus flytrap module; VSCC, voltage-sensitive calcium channel; YM-202074, *N*-cyclohexyl-6-*N*-methylthiazolo[3,2-*a*]benzimidazole-2-carboxamide.

1994; Duvoisin et al., 1995). Nakanishi (1992) proposed the current classification of mGlu receptor subtypes into three groups on the basis of their amino acid sequence, intracellular coupling mechanisms, and relative pharmacology; this classification is substantiated also by phylogenetic analyses (Joost and Methner, 2002; Pin et al., 2003). Group I includes mGlu1 and mGlu5 receptors, which are coupled to G_q proteins and are selectively activated by 3,5-dihydroxyphenylglycine (3,5-DHPG), group II includes mGlu2 and mGlu3 receptors that are coupled to G_i proteins and are activated by 2*R*,4*R*-aminopiperidindicarboxylic acid, and group III consists of mGlu4, mGlu6, mGlu7, and mGlu8 receptors, which are coupled to G_i proteins in recombinant systems and are activated by 2-amino-4-phosphonobutyrate.

The generation of mice carrying gene-targeted deletion of mGlu1 receptors (Aiba et al., 1994b; Conquet et al., 1994) and the development of potent, selective, and systemically active antagonists has allowed great progress in the understanding of the physiological and pathophysiological role of these receptors in many neuronal systems. In addition, the resolution of the three-dimensional structure of the extracellular N-terminal domain of mGlu1 receptors, containing the ligand-binding site (Kunishima et al., 2000), has provided the ground for the generation of models of receptor activation.

In this review, we have tried to integrate and summarize the current literature related to the structure and function of mGlu1 receptors and to critically discuss the existing controversies. In addition, we will comment on the role of mGlu1 receptors in physiology and pathology, discussing the pros and cons of the use of mGlu1 receptor ligands in human disorders. We apologize for omissions in our coverage of the existing literature (~2500 papers dealing directly or indirectly with mGlu1 receptors) because of space limitations.

II. Genomic Organization of the Metabotropic Glutamate 1 Receptor

A. Chromosomal Localization and Organization of the Metabotropic Glutamate 1 Receptor Gene

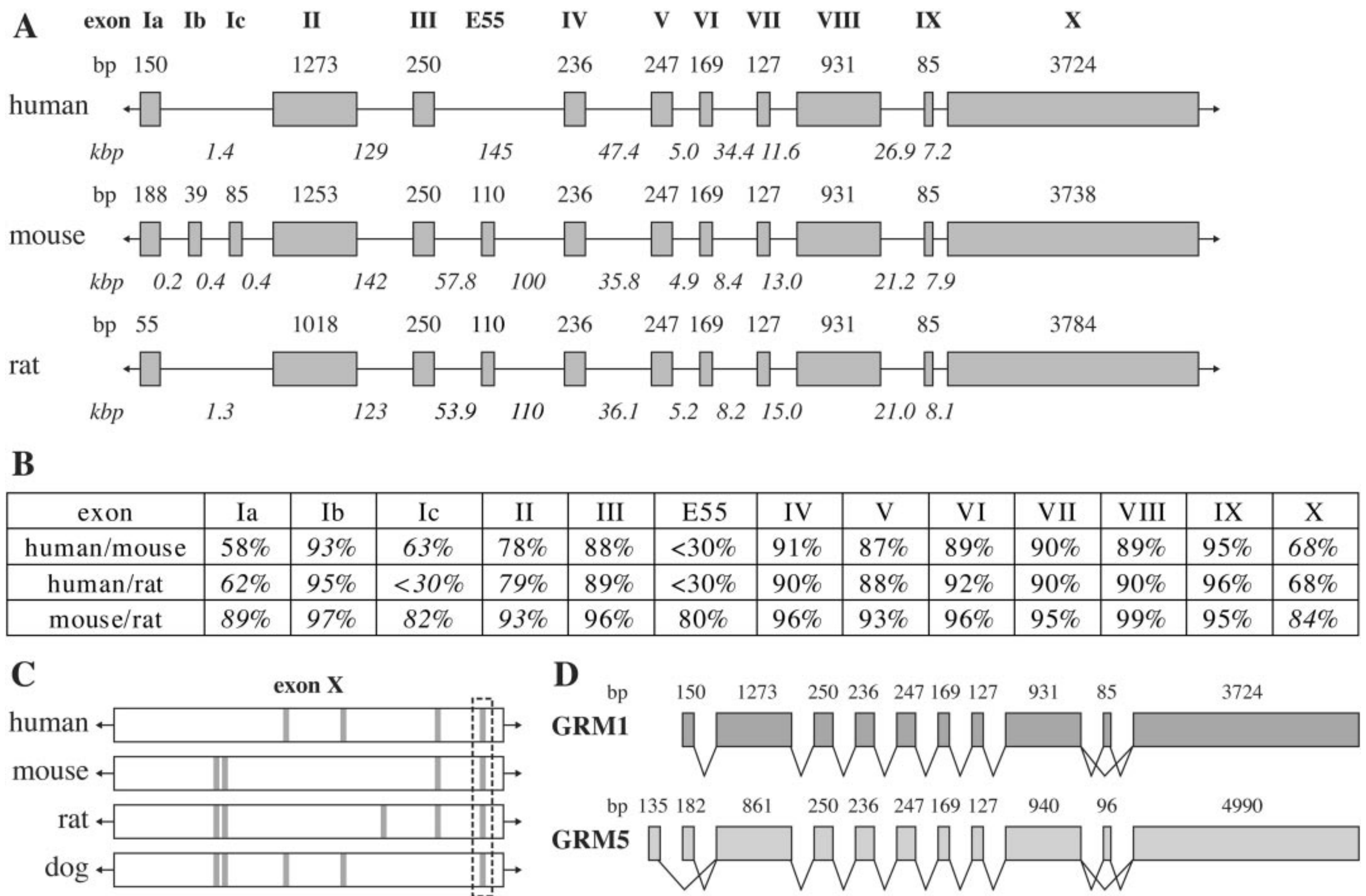
The gene encoding for the mGlu1 receptor (locus name: *GRM1* in humans and *Grm1* in other species) has been mapped to chromosome 6q24 in humans (Stephan et al., 1996; Ganesh et al., 2000), chromosome 1p13 in rats (Kuramoto et al., 1994), and chromosome 10, band 10a1, in mice (http://www.ncbi.nlm.nih.gov/unigene).

Exon/intron boundaries were determined by comparing cDNA, mRNA, and expressed sequence tags retrievable from public databases or present in literature, with genomic nucleotide sequences (Crepaldi et al., 2007). The human *GRM1* spans ~410 kilobase pairs and consists of 10 exons and 9 introns. Exons vary from 85 (exon IX) to 3724 bp (exon X) in size, whereas intron sizes range from 149 to 1.3 kilobase pairs (Fig. 1A). Intron/exon splice junctions conformed to the GT-AG rule of splice donor/acceptor sites (Burset et al., 2000). Despite the highly similar genomic structure of *Grm1* observed in humans and rodents (Fig. 1, A and B), some divergences were detected, such as the presence in mouse of two additional exons between exons I and II (indicated by Ib and Ic) and the absence in human *GRM1* of exon E55 (Zhu et al., 1999) (see section II.C). Within the group I mGlu family, comparison of the genomic structures of *GRM1* with *GRM5* reveals a high degree of similarity in terms of exon/intron arrangement, strongly suggesting that group I mGlu receptors have been generated by gene duplication from a common ancestor (Fig. 1D).

On the basis of public cDNA sequences, available expressed sequence tags and genomic data, we could identify several putative polyadenylation consensus sequences (AATAAA). However, only one of these signals, located 3707 bp downstream from the 5′ of human *GRM1* exon X, is conserved across the mGlu1 genes of several other species including mouse, rat, and dog (Fig. 1C). Therefore, this site is likely to be the main signal used to terminate transcription. This consensus sequence is located within a ~150-bp region highly conserved among these four species. Northern hybridization analysis of brain mRNA revealed the existence of transcripts of ~7 kb in length in human brain areas (Stephan et al., 1996). In contrast, two transcripts of ~4 and ~7 kb were detected in rodent brain (Houamed et al., 1991; Masu et al., 1991; Kerner et al., 1997; Zhu et al., 1999). An ~6-kb transcript has been reported in mouse heart (Zhu et al., 1999). These differences can be explained by considering the two additional polyadenylation signals present in rodents, located 1236 and 1249 nt downstream from the 5′-end of rat exon X, which could generate the ~4-kb transcript (Fig. 1C). On the other hand, the polyadenylation signal conserved among humans, dogs, and rodents, which in the rat is located 3758 nt downstream from the 5′-end of exon X, is likely to be involved in the generation of the ~7-kb transcript.

B. Transcriptional Regulation

Transcriptional regulation of the mGlu1 receptor gene, both in humans and mice, is driven by at least two alternative promoters located upstream from exons Ia and II, with the latter encoding the transcription initiation codon (Crepaldi et al., 2007). According to 5′ rapid amplification of cDNA ends analyses, approximately 70% of mGlu1 transcripts start within exon Ia. Although at very low levels, transcripts encoding for exons Ib or Ic are present in mouse. Functional analysis of the promoter region located upstream of exon Ia reveals the presence of a 57-bp core promoter encompassing −68 to −11 bp, relative to the first transcription initiation site. Within this core promoter region, two elements critically regulate mGlu1 transcription, binding, respectively, thyroid transcription factor 1 and the CCAAT/enhancer binding protein β. These proximal elements probably



exon	Ia	Ib	Ic	II	III	E55	IV	V	VI	VII	VIII	IX	X
human/mouse	58%	93%	63%	78%	88%	<30%	91%	87%	89%	90%	89%	95%	68%
human/rat	62%	95%	<30%	79%	89%	<30%	90%	88%	92%	90%	90%	96%	68%
mouse/rat	89%	97%	82%	93%	96%	80%	96%	93%	96%	95%	99%	95%	84%

FIG. 1. Genomic structure of *Grm1*. A, complete genomic structure of mouse, rat, and human mGlu1 genes. Transcribed regions are indicated by gray boxes. The size of exons is given in base pairs, whereas the size of introns (in italics) is given in kilobase pairs. B, table indicating the percentage of identity across mouse, rat, and human exons. The values shown in italics were calculated on the basis of in silico data and not from cloned sequences. C, putative polyadenylation signals present in exon X of several species. The position of each polyadenylation signal is indicated by a gray bar. The most 3′ polyadenylation signal is conserved across all species and is boxed. D, comparison of the genomic structure between *GRM1* and *GRM5*. Transcribed regions are indicated by gray boxes.

represent a transcriptional module, in which the interplay of at least these two transcription factors synergistically activates transcription (Crepaldi et al., 2007). It is not surprising that genes with a complex and highly restricted expression pattern, such as mGlu1, possess core promoters with almost unique features and different from more common core promoter modules, such as the TATA/initiator. However, preliminary experiments performed in embryonic day 18.5 embryos of thyroid transcription factor 1 KO mice (kindly provided by Dr. R. DiLauro and Dr. S. Kimura) indicate that expression of mGlu1 is preserved and suggest a more complex transcriptional regulation of this receptor (F. Ferraguti, personal communication).

Two silencing elements have a key role in restricting the expression of mGlu1 to neuronal cells, namely the neuronal restrictive silencing element, located between exons Ib and Ic, and the regulatory factor for X-box element found upstream from exon II (Crepaldi et al., 2007). Both silencing elements have a strong suppressive role in non-neuronal cells.

C. Alternative Splicing

Several splice variants of mGlu1 have been identified, and the first cloned isoform was originally named mGlu1α (Houamed et al., 1991; Masu et al., 1991). Either Greek or Latin characters have been used for subsequently identified mGlu1 alternatively spliced isoforms, which generated some ambiguity. Moreover, no clear evidence exists for some of the reported isoforms. We propose here a nomenclature that limits the use of Greek characters to the translated transcripts and uses arabic numbers that follow the Greek character for different mRNA forms encoding for the same protein (Fig. 2).

Among the known isoforms, mGlu1α is the longest isoform, composed of 1199 amino acids in rat (1194 amino acids in human), ~590 of which form the extracellular N-terminal domain and ~360 of which form the C-terminal intracellular domain, separated by a heptahelical transmembrane domain (7TMD) (Houamed et al., 1991; Masu et al., 1991).

The isoform mGlu1β (or mGlu1b) is characterized by a shorter C-terminal domain and derives from two differ-

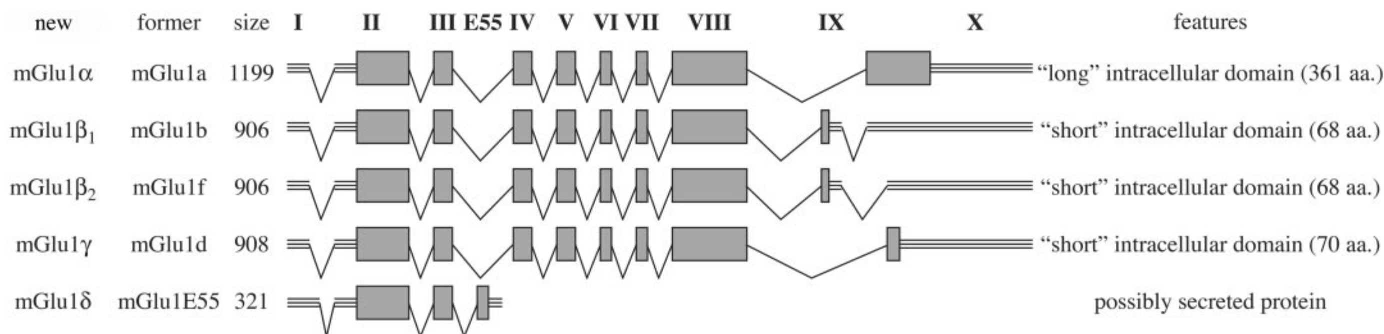


FIG. 2. Schematic drawing of mGlu1 receptor alternative splice variants giving rise to different translated isoforms and substantiated by their actual detection in tissue. The first column on the right provides the newly proposed classification of mGlu1 receptor splice variants; the second column provides the former name and the numbers on the right correspond to the length in amino acid (aa) residues. Gray boxes correspond to exonic translated sequences in each isoform.

ent transcripts, named here mGlu1β_1 and mGlu1β_2 (previously mGlu1f), generated by alternative splicing. In particular, mGlu1β_1 derives from the insertion of an 85-bp exon (exon IX) downstream from the 7TMD (Tanabe et al., 1992). This exon codes for an in-frame stop codon, thus generating a substitution of the last 318 amino acids of mGlu1α with 20 different residues. The resulting receptor protein is 906 amino acids long with a shorter intracellular domain. The isoform mGlu1β_2 (Soloviev et al., 1999) is produced by the insertion of the same 85-bp exon (exon IX) that generates mGlu1β_1, plus the usage of an alternative splice acceptor in exon X that is located 35 bp downstream from the 5′-end of the exon.

Additional mGlu1 isoforms characterized by a short C-terminal domain have been described. An isoform originally named mGlu1d (Laurie et al., 1996) and indicated here as mGlu1γ derives from the usage of the same alternative splice acceptor in exon X as in mGlu1β_2. The consequent frameshift inserts a stop codon 22 amino acids downstream from the splice site, resulting in a 908-amino acid receptor (Laurie et al., 1996). The expression of mGlu1γ mRNA has been demonstrated in both humans and rats (Laurie et al., 1996; Mary et al., 1997; Berthele et al., 1998).

The isoform mGlu1c was isolated from a rat cerebellum cDNA library (Pin et al., 1992) and would derive from an alternatively spliced exon inserted after the 7TMD, thus producing a further splice variant with a short C-terminal domain. However, the sequence of mGlu1c finds no match in the rat *Grm1* genomic locus, suggesting that it derives from a recombination event of the cDNA library used to isolate this isoform.

A further isoform named mGlu1g (Makoff et al., 1997) has been cloned from a human cerebellum cDNA library and would derive from skipping of the splice donor in the 7TMD coding exon (exon VIII); the resulting protein, because of an in-frame stop codon present 1 bp downstream from the skipped splice site, would be composed of 887 amino acids (Makoff et al., 1997). Despite the reported expression of this isoform in kidney, Makoff et al. did not rule out the possibility that the subcloned mGlu1g transcripts may derive from partially processed pre-mRNA.

A further splice variant, whose translation would encode a potentially secreted protein, has been identified in mouse and was originally named mGlu1E55 (Zhu et al., 1999) (here indicated as mGlu1δ). It derives from the insertion between exons III and IV of a 110-nucleotide-long exon (exon E55), which contains an in-frame stop codon. The transcript generates a truncated protein of 321 amino acids, containing only part of the extracellular domain (Zhu et al., 1999). We could confirm the existence of a region highly homologous to mouse exon E55 in rats but not in humans.

A novel rat mGlu1 splice variant has been identified in the papillae vallate (San Gabriel et al., 2005). The 5′-untranslated region of this isoform would comprise 170 bp in the intronic region upstream from exon IV, the entire exon IV, and 41 nt in exon V. The authors suggested Met^{410} as the translation start site (San Gabriel et al., 2005).

III. Structural Features of Metabotropic Glutamate 1 Receptors

mGlu receptors belong to class 3 of G-protein-coupled receptors (GPCRs), which also includes the Ca^{2+}-sensing receptor (CaR), class-B GABA ($GABA_B$) receptors, and taste and pheromone receptors (for review, see Pin et al., 2003). These receptor molecules are characterized by a large extracellular ligand-binding domain (LBD), similar to the Venus flytrap module (VFTM) of bacterial periplasmic amino acid-binding proteins, a highly hydrophobic heptahelical TM, in most cases separated by a cysteine-rich domain (CRD), and an intracellular C-terminal domain of different length depending on the receptor subtype (Bhave et al., 2003).

A. The Extracellular Domain and the Agonist Binding Site

A structural model of the extracellular N-terminal domain of mGlu1 was proposed on the basis of the weak,

but significant, sequence homology with bacterial leucine/isoleucine/valine-binding proteins (O'Hara et al., 1993; Costantino et al., 1999). This model predicts the folding of the N terminus into two lobules separated by a cleft, which forms the agonist binding pocket. Agonist binding critically involves Ser^{165}, Thr^{188}, and Arg^{78}, as demonstrated by mutation analysis (O'Hara et al., 1993; Jensen et al., 2000). The exclusive role of the extracellular domain in glutamate binding was confirmed by functional analysis of chimeric receptors (Takahashi et al., 1993) and of the soluble extracellular domain (Okamoto et al., 1998). Additional evidence indicated that mGlu1 receptors form homodimers (Romano et al., 1996; Okamoto et al., 1998; Robbins et al., 1999), with Cys^{140} forming a disulfide bridge that covalently binds two mGlu1 receptor monomers (Ray and Hauschild, 2000; Tsuji et al., 2000). However, mutation of Cys^{140} into Ala does not prevent dimer formation and ligand binding, suggesting that dimerization is also mediated by noncovalent interactions (Tsuji et al., 2000). The structure of the mGlu1 LBD has been determined by X-ray crystallography under different configurations [i.e., in a glutamate-bound form, a two-ligand free form (Kunishima et al., 2000), a glutamate- and Gd^{3+}-bound form, and an antagonist-bound form (Tsuchiya et al., 2002)]. This finding confirmed the model proposed by O'Hara and colleagues and also provided new insights into the mechanisms of receptor activation. The LBD (amino acids 33–522) displays an α/β topology and associates in homodimers, with two globular structures, designated LB1 and LB2, connected by three short loops, to form the clamshell-like structure known as the Venus flytrap module (Kunishima et al., 2000). The LB1 domain provides the dimer interface, characterized by a core of hydrophobic residues. Cys^{140}, which contributes to dimer formation is present within a disordered segment of LB1 (Kunishima et al., 2000). On the basis of the solved structure and mutagenesis, four residues (Thr^{188}, Asp^{208}, Tyr^{236}, and Asp^{318}) seem to be essential for agonist binding, whereas Tyr^{74}, Arg^{78}, and Gly^{293} are important for agonist selectivity because their substitution reduces the response to glutamate but not to quisqualate (Sato et al., 2003). Mutation of Ile^{120}, located at the dimer interface, abolishes the response to orthosteric agonists, suggesting that the dimer interface, which undergoes a substantial structural rearrangement upon glutamate binding, plays a crucial role in receptor activation (Sato et al., 2003).

As mentioned, homodimerization of mGlu1 receptors (and mGlu receptors in general) has been demonstrated by different approaches (Romano et al., 1996; Okamoto et al., 1998; Kunishima et al., 2000; Ray and Hauschild, 2000; Tsuji et al., 2000) and seems to take place within the endoplasmic reticulum (Robbins et al., 1999; Selkirk et al., 2002). The N-terminal domain of mGlu1 receptors seems sufficient to allow dimerization because the soluble extracellular domain can form homodimers in heterologous expression systems (Okamoto et al., 1998; Robbins et al., 1999; Selkirk et al., 2002).

It has been shown that extracellular cations, such as Ca^{2+} and Gd^{3+}, activate mGlu1 receptors (Kubokawa et al., 1996; Kubo et al., 1998; Saunders et al., 1998; Tateyama et al., 2004). Mutational analysis identified Ser^{166} as a key residue in the interaction with extracellular Ca^{2+} ions (Kubo et al., 1998).

Four consensus sequences [NX(T/S)] for *N*-glycosylation are present within the N-terminal domain (Asn^{98}, Asn^{223}, Asn^{397}, and Asn^{515}), and one (Asn^{747}) is present within the second extracellular loop (e2) of mGlu1 receptors (Masu et al., 1991). Of these asparagine residues, Asn^{98} and Asn^{223} were found to be glycosylated in the soluble LBD derived from Sf9 insect cells (Kunishima et al., 2000). However, all four *N*-glycosylation consensus sequences located within the extracellular domain of the mGlu1 receptors seem to be relevant for receptor function (Selkirk et al., 2002).

The presence of a signal peptide for membrane targeting was hypothesized after the uncovering of the primary structure of mGlu1 receptors. The first N-terminal 20 residues of the mGlu1 receptor show features typical of a signal peptide, such as hydrophobicity and the presence of consecutive leucine residues (Masu et al., 1991). The soluble extracellular domain of the mGlu1 receptor expressed in recombinant cells was shown to lack the first 32 residues, suggesting that this region indeed corresponds to the signal peptide (Tsuji et al., 2000; Selkirk et al., 2002).

B. The Cysteine-Rich Domain

A cluster of nine cysteine residues, conserved among all mGlu receptors, is located within the C-terminal region of the extracellular domain, similarly to the cysteine-rich regions characteristic of tyrosine kinase receptors (O'Hara et al., 1993). The soluble LBD of mGlu1 receptors lacking the CRD shows much lower expression and ligand binding than the full extracellular domain (Okamoto et al., 1998). The role of the CRD has been partially characterized in the CaR, which shares several structural features with mGlu receptors. Mutagenesis of any of the nine cysteines in the CaR causes loss of receptor function, because of a misfolding or incomplete processing of the receptor (Fan et al., 1998). Functional analysis of chimeric receptors suggests that the CRD is involved in the communication between the VFTM and the 7TMD (Hu et al., 2000).

C. The Heptahelical Transmembrane Domain

The heptahelical transmembrane domain and particularly its intracellular loops plays a major role in coupling mGlu1 receptors to G-proteins. For class 1 GPCRs, G-protein coupling is mediated by the third intracellular loop (i3), which in mGlu receptors is relatively short and highly conserved among different subtypes. In contrast, loop i2 is the longest and most variable and has there-

fore been implicated in G-protein coupling and selectivity (Pin et al., 1994). The use of mGlu1/mGlu3 chimeric receptors has confirmed the primary role of loop i2 in G-protein coupling, whereas loops i1 and i3 and the C-terminal tail are not required for but facilitate G-protein coupling (Pin et al., 1994; Gomeza et al., 1996). Several key residues in loops i2 and i3 seem to be important for G-protein coupling and selectivity (Francesconi and Duvoisin, 1998).

A binding site for noncompetitive antagonists has been identified within the 7TMD (Litschig et al., 1999; Carroll et al., 2001; Malherbe et al., 2003). Analysis of chimeric receptors and of amino acid point mutations identified Thr^{815} and Ala^{818}, located in TM7, as essential residues for the binding of the noncompetitive antagonist, 7-(hydroxyimino)-cyclopropan[*b*]chromen-1*a*-carboxylate ethyl ester (CPCCOEt) (Litschig et al., 1999), and TM7 as an essential domain for the action of the inverse agonist, BAY 36-7620 (Carroll et al., 2001). Mutational analysis has also shown that residues within the 7TMD of mGlu1 receptors are critical for the binding and the selectivity of positive allosteric modulators (Knoflach et al., 2001a). A recent model of the structure of rat mGlu1 7TMD proposes the existence of a binding pocket for the noncompetitive antagonist 1-ethyl-2-methyl-6-oxo-4-(1,2,4,5-tetrahydro-benzo[*d*]azepin-3-yl)-1,6-dihydro-pyrimidine-5-carbonitrile (EM-TBPC), (Malherbe et al., 2003). Several residues in TM3, TM5, TM6, TM7, and extracellular loop 2 have also been identified by mutagenesis as determinants for the binding of EM-TBPC (Malherbe et al., 2003).

D. Possible Mechanisms of Metabotropic Glutamate 1 Receptor Activation

The characterization of the unbound and agonist/antagonist-bound conformations of the mGlu1 receptor LBD (Kunishima et al., 2000; Tsuchiya et al., 2002), as well as of the binding sites for allosteric modulators and metal ions (Litschig et al., 1999; Kunishima et al., 2000; Carroll et al., 2001; Knoflach et al., 2001a; Tsuchiya et al., 2002; Sato et al., 2003), has allowed the development of models of receptor activation and has shed light on the mechanisms mediating the intramolecular transduction between the extra- and intracytoplasmic domains of mGlu1 receptors (Jensen et al., 2002; Jingami et al., 2003; Parmentier et al., 2002).

Several conformations of the dimeric LBD can be defined on the basis of two states of each monomer (open/closed) and of two states of the dimer, resting (R) and active (A). Open/closed states are defined by the relative position of LB1 and LB2 of the monomer, which can be brought in closer proximity through a rotation around an axis passing across the three connecting loops (Kunishima et al., 2000; Jingami et al., 2003). The R and A states are defined by the relative spatial orientation of the two LBDs within the dimer. The unbound form has been crystallized in both open/closed$A$ state (with only one of the two monomers in the close state) and open/open$R$ state (Kunishima et al., 2000). The glutamate-bound form is in the open/closed$A$ state, with two glutamate molecules bound to each monomer. This finding suggests that the A state corresponds to the active conformation of the receptor. Glutamate interacts only with LB1 in the open state and with both LB1 and LB2 in the closed state. The existence of a dynamic equilibrium between the open and the closed states, shifted by glutamate toward the closed state through the interaction with the residues of the binding pocket, has been hypothesized. The structural perturbation consequent to ligand binding could thus induce a coordinated relocation of the dimer interface, stabilizing the A state (Kunishima et al., 2000). Modeling of the open/open$A$ state that simulates an active unbound receptor suggests that this conformation is energetically unfavorable. A strong electrostatic repulsion is present at the interface of LB2 domains, which in this conformation are in close proximity (Tsuchiya et al., 2002). The LBD bound to the competitive antagonist α-methyl-4-carboxyphenylglycine (MCPG) has been shown to be in open/open$R$ state, supporting the view that the R structure corresponds to the resting state of the receptor (Tsuchiya et al., 2002). Both LB1 and LB2 interact with MCPG in the binding pocket, and the steric hindrance created by the antagonist is likely to stabilize the open state. The structure of the LBD complexed with glutamate and Gd^{3+} has revealed a closed/closed$A$ conformation (Tsuchiya et al., 2002). Molecular modeling suggested that this structure is energetically unfavorable, because of the electrostatic repulsion exerted by negatively charged residues, which come in close contact at the LB2 interface. This repulsion is relieved by the coordination with Gd^{3+} (Tsuchiya et al., 2002). Accordingly, it has been shown that Gd^{3+} can both activate mGlu1 receptors and increase the effect of glutamate on mGlu1 receptor activation (Abe et al., 2003b). Mutation of Glu^{238} suppresses the modulation of mGlu1 receptors by Gd^{3+} (Abe et al., 2003b).

The observation that glutamate is bound to the VFTM in open/closed$A$ and in closed/closed$A$ states raised the question of whether both conformations correspond to an active receptor. An answer to this question came from the work of Kniazeff et al. (2004), in which they elegantly showed that the closure of one VFTM per dimer is sufficient for a partial activation of the receptor, whereas full receptor activation requires the closure of both VFTMs. Accordingly, binding of glutamate to only one binding site within mGlu1α receptor dimers is not sufficient to achieve full receptor activation but requires binding to both subunits (Kammermeier and Yun, 2005). Interestingly, the dimeric LBD has been shown to display a strong negative cooperativity of glutamate binding between each subunit, which could have the functional effect of extending the concentration range at which the receptor can work or increasing the sensitivity to low ligand concentrations (Suzuki et al., 2004). Recent studies indicate that full activation of mGlu1 receptors

requires only the activation of one of the two 7TMDs of the dimeric receptor (Hlavackova et al., 2005).

Fluorescence resonance energy transfer analysis showed that agonist binding causes a spatial rearrangement of the mGlu1α receptor homodimer by modifying the relative orientation of the monomers (Tateyama et al., 2004). The spacing between intracellular loops i2 is reduced in response to agonist stimulation, and the noncompetitive antagonist CPCCOEt increases the loop spacing even in the absence of an agonist (Tateyama et al., 2004). A rearrangement, similar to that caused by glutamate binding, is detected also in response to di- and trivalent cations. This finding supports the controversial hypothesis that cations can independently activate mGlu1 receptors (Kubo et al., 1998; Nash et al., 2001; Tateyama et al., 2004). Finally, no intra- or intermolecular rearrangement has been demonstrated for the C-terminal tail, although this particular domain plays an important role in receptor signaling (Tateyama et al., 2004).

An interesting model describing the functioning of class 3 GPCRs has been proposed by Parmentier et al. (2002). According to this model, both the LBD and the 7TMD oscillate between an active and a resting state in a dynamic equilibrium. Agonist binding to the LBD shifts the equilibrium of the 7TMD toward the active state. However, in the particular case of the mGlu1 receptor, it has been suggested that the coupling of LBD and 7TMD is "loose"; i.e., activation of the two domains is relatively independent. This independence may contribute to explaining the constitutive activity observed for the mGlu1α receptor (Joly et al., 1995; Prézeau et al., 1996; Mary et al., 1997), which would reflect the activation of the 7TMD in the absence of an agonist (Parmentier et al., 2002). This model also explains why competitive antagonists, which bind to the extracellular domain, do not block the constitutive activity of mGlu1α receptors. Conversely, noncompetitive antagonists are supposed to act either by shifting the 7TMD toward the resting state or by decreasing the coupling efficiency between LBD and 7TMD (Parmentier et al., 2002). It would be of great interest to clarify the role of the CRD in the communication between LBD and 7TMD, bearing in mind that these two domains are "tightly" coupled in $GABA_B$ receptors, which lack the CRD (Parmentier et al., 2002).

E. The Carboxyl-Terminal Domain

Within the intracellular tail of mGlu1 receptors, the first helix downstream from the 7TMD shows an amphipathic profile, similar to that of the corresponding helix (H8) of class 1 GPCRs (Pin et al., 2003). These helices have been shown to facilitate G-protein coupling (Pin et al., 1994; Gomeza et al., 1996).

Analysis of a series of truncated and chimeric receptors allowed the identification of four amino acid residues in the C-terminal domain (RRKK) that are responsible for the lack of agonist-independent activity and lower responses to agonist stimulation characteristic of the short isoforms of the mGlu1 receptor (Mary et al., 1998; see also section VI.A). The RRKK signal is present in all mGlu1 splice variants, but the long tail of the mGlu1α receptor prevents the action of these four amino acids (Mary et al., 1998). Moreover, the RRKK stretch may also have a role in mGlu1 receptor trafficking by acting as a signal for retention in the endoplasmic reticulum (Chan et al., 2001). Residues 975 to 1088 of the intracellular tail of the mGlu1α receptors allow the effect of RRKK on receptor trafficking to be overcome (Chan et al., 2001). The RRKK signal would also determine the axonal/apical targeting of mGlu1 receptors in Madin-Darby canine kidney epithelial cells and in chick retina neurons (Francesconi and Duvoisin, 2002). Its effect is suppressed in the mGlu1α isoform, which is targeted to the dendritic/basolateral compartment by its "long" intracellular domain (Francesconi and Duvoisin, 2002).

The primary sequence of mGlu1α possesses several putative Ser/Thr phosphorylation sites within the C terminus (Masu et al., 1991). These sites, which include Thr^{695}, are phosphorylated by protein kinase C (PKC) and have a role in receptor desensitization (Alaluf et al., 1995; Francesconi and Duvoisin, 2000; see also section IV.D).

The C-terminal domain of mGlu1 receptors physically interacts with a variety of cytoskeletal, scaffolding, and signaling proteins, as well as with integral membrane receptors (see also section VI.C). The intracellular tail of the mGlu1α but not the mGlu1β and mGlu1γ receptors incorporates a PPSPFR stretch, which binds to Homer proteins (Tu et al., 1998). A second consensus sequence that binds to scaffolding proteins, namely a (PSD-95)/discs-large/ZO-1 (PDZ) domain binding sequence (residues SSSL) is present in the C terminus of the mGlu1α receptor (Tu et al., 1999). Two binding sites for calmodulin have been identified in the C terminus of mGlu1α receptors (Ishikawa et al., 1999). Several serine/threonine residues within these sites are targets for PKC phosphorylation, which could be then suppressed by the interaction with calmodulin (Minakami et al., 1997).

In silico analysis identified two sequences that may serve as a signal for proteolysis. These sequences are named PEST and overlap the PPSFR consensus sequence for Homer binding (Soloviev, 2000).

IV. Intracellular Coupling of Metabotropic Glutamate 1 receptors

Activation of mGlu1 receptors stimulates polyphosphoinositide (PI) hydrolysis (Fig. 3), as shown by measurements of inositol phosphate formation and/or intracellular Ca^{2+} release in heterologous expression systems (Houamed et al., 1991; Masu et al., 1991; Aramori and Nakanishi, 1992; Pin et al., 1992; Pickering et al., 1993;

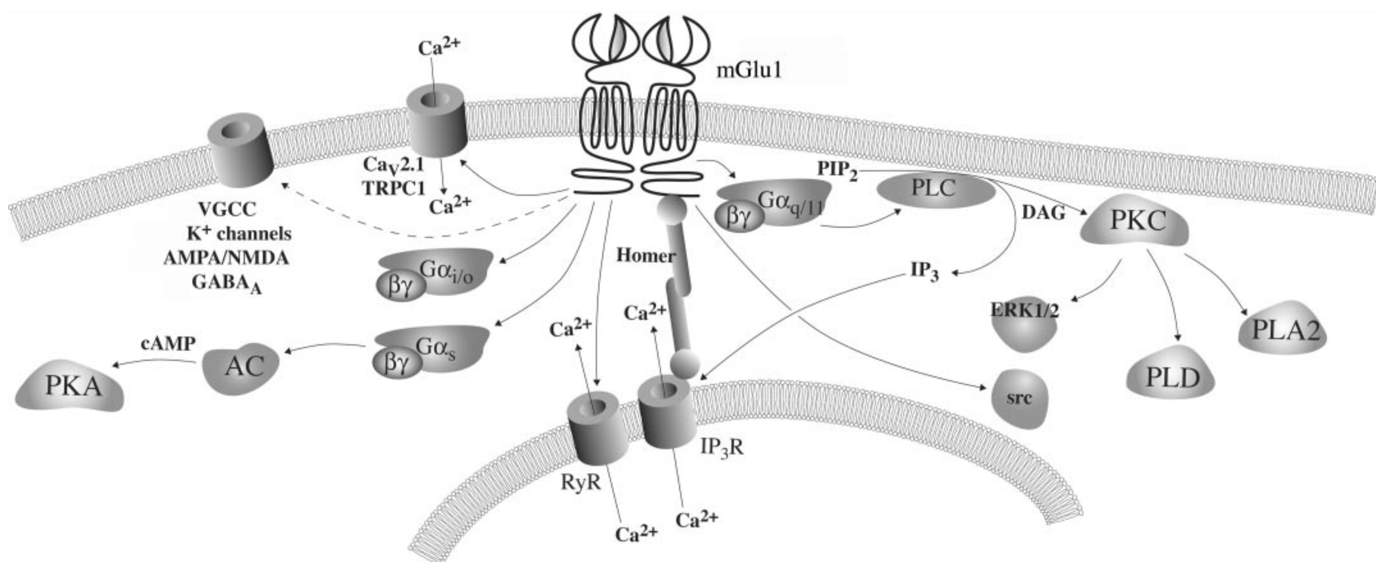


FIG. 3. Schematic diagram of the main transduction pathways activated by mGlu1 receptors. Upon stimulation by glutamate to the Venus flytrap module, mGlu1 receptors (which generally homodimerize) can couple to multiple signaling pathways through different G-proteins. The C-terminal domain of mGlu1 receptors interacts with Homer proteins, which mediate the association with IP_3 receptors in the endoplasmic reticulum. PIP_2, phosphatidylinositol bisphosphate; AC, adenylate cyclase.

Ferraguti et al., 1994; Hermans et al., 1998) or in cultured cerebellar granule cells (Nicoletti et al., 1986b, 1987).

A. G-Protein Coupling

mGlu1 receptors are primarily coupled to proteins of the G_q family, because receptor responses are insensitive or only partially sensitive to inhibition by pertussis toxin (PTX) (Houamed et al., 1991; Masu et al., 1991; Aramori and Nakanishi, 1992; Pin et al., 1992; Pickering et al., 1993; Thomsen et al., 1993; Thomsen, 1996; Hiltscher et al., 1998; Hartmann et al., 2004). Mice with genetic deletion of the $G\alpha_q$ protein showed a complete loss of LTD in cerebellar PCs, a particular form of synaptic plasticity that is mediated by the activation of mGlu1 receptors (Hartmann et al., 2004).

The role of G-proteins of the $G_{i/o}$ family in mGlu1 receptor signaling is unclear. In some systems, stimulation of PI hydrolysis mediated by mGlu1 receptors is partially sensitive to PTX and may therefore involve receptor coupling with a G_o (Offermanns, 2003). Coupling of mGlu1 receptors to G_i protein is unlikely because receptor activation does not inhibit adenylyl cyclase activity (Aramori and Nakanishi, 1992; Tanabe et al., 1992; Kasahara and Sugiyama, 1994; but see Akam et al., 1997). Pretreatment with PTX enhances PI hydrolysis in BHK cells expressing mGlu1α receptors, suggesting an inhibitory role of $G_{i/o}$ proteins on mGlu1-receptor stimulated phospholipase (PL) C activity (Carruthers et al., 1997; Hermans et al., 2000; Selkirk et al., 2001). The functional significance of this intriguing finding is unclear at present.

In several systems, activation of mGlu1 receptors enhanced cAMP formation, a finding that suggests a coupling of the receptor with G_s proteins (Aramori and Nakanishi, 1992; Pickering et al., 1993; Joly et al., 1995; Thomsen, 1996; but see Hiltscher et al., 1998). Although stimulation of cAMP formation might be secondary to other transduction pathways, the fact that there are residues within the i2 loop of mGlu1 receptors that are critical for receptor coupling to adenylate cyclase should be highlighted (Francesconi and Duvoisin, 1998).

Differences in the selectivity and/or efficiency of G-protein coupling have been reported for the splice variants of mGlu1 receptors. The "short" mGlu1β and mGlu1γ receptor isoforms are coupled to PI hydrolysis less efficiently than the mGlu1α receptor (Prézeau et al., 1996; Mary et al., 1997) and require higher concentration of agonist (Flor et al., 1996). However, this coupling applies to rat mGlu1 receptors, whereas human mGlu1α and -β receptors seem to be coupled to PI hydrolysis with equal efficacy (Stephan et al., 1996). The mGlu1α receptor but not the mGlu1β or mGlu1γ receptor is constitutively active in stimulating PI hydrolysis; i.e., it is active in the absence of an orthosteric agonist, in transfected LLC-PK1, HEK-293, or BHK cells (Joly et al., 1995; Prézeau et al., 1996; Carruthers et al., 1997; Mary et al., 1997; Hiltscher et al., 1998). This constitutive activity is not prevented by orthosteric mGlu1 receptor antagonists, which reduce the response to applied glutamate, but not the basal activity; hence, this activity is not triggered by endogenous glutamate present in the culture medium (Prézeau et al., 1996). In contrast, experiments performed in Chinese hamster ovary (CHO) cells suggest that the endogenous glutamate released by these cells is ultimately responsible for the "constitutive" activity of mGlu1α receptors (Hermans et al., 1998).

Stimulation of PI hydrolysis mediated by mGlu1β receptors in BHK cells is completely insensitive to PTX, indicating that receptor coupling to PLC is mediated by $G_{q/11}$ but not G_o proteins (Pickering et al., 1993). Activation of mGlu1β receptors does not stimulate cAMP formation in LLC-PK1 cells (Joly et al., 1995), whereas it can stimulate cAMP formation in BHK cells but less efficiently than the activation of mGlu1α receptors (Pickering et al., 1993). Thus, mGlu1β and mGlu1α receptors seem to be differentially coupled to G_s proteins.

Group I mGlu receptor signaling is regulated by at least two members of the regulators of G-protein signaling (RGS) family. Proteins of the RGS family accelerate the GTP turnover of Gα subunits, thereby reducing the interaction of Gα with effector proteins (for review, see Dohlman and Thorner, 1997). In transfected *X. laevis* oocytes, RGS4 inhibits the Ca^{2+}-dependent Cl^- currents mediated by mGlu1α or mGlu5a receptors (Saugstad et al., 1998). Signaling of mGlu1α receptors can also be regulated by RGS2 (see section IV.B) (Kammermeier and Ikeda, 1999). More recently, the existence of complexes comprising mGlu1α and RGS3 has been reported (Calò et al., 2005).

B. Signal Transduction Mechanisms

The role of PLCβ in mGlu1 receptor signaling has been firmly established. This enzyme cleaves phosphatidylinositol-4,5-bisphosphate into inositol-1,4,5-trisphosphate and diacylglycerol (DAG), which release Ca^{2+} from intracellular stores and activates PKC, respectively (Fig. 3). Analysis of PLCβ4 knockout mice revealed that this PLC isoform transduces the signal triggered by mGlu1 receptors in PCs (Miyata et al., 2001). LTD at parallel fiber-PC synapses, which is mediated by mGlu1 receptors (Aiba et al., 1994b; Ichise et al., 2000), is completely abolished in mice lacking PLCβ4 (Miyata et al., 2001). Expression of PLCβ4 and mGlu1 receptors is overlapping throughout the central nervous system, and PLCβ4 can be detected in complexes formed by mGlu1α and type-1 IP_3 receptors (Nakamura et al., 2004). In addition, a mGlu1 receptor-PLCβ4 cascade in the thalamus was shown to play a key role in the processing of inflammatory pain (Miyata et al., 2003).

Mobilization of intracellular Ca^{2+} in response to mGlu1 receptor activation occurs through both the IP_3 receptor and the ryanodine receptor present on the surface of the endoplasmic reticulum (del Río et al., 1999; Fagni et al., 2000). It should be highlighted that activation of mGlu1 receptors can also increase intracellular Ca^{2+} concentrations through the opening of voltage-sensitive calcium channels (VSCCs) and nonselective cation channels (see later in this section).

Activation of mGlu1 receptors also stimulates the release of arachidonic acid (Aramori and Nakanishi, 1992; Thomsen, 1996), which may originate either from membrane phospholipids or DAG (by the action of phospholipase A2 and DAG lipase, respectively). In CHO cells, arachidonic acid release mediated by mGlu1 receptors is inhibited by PTX and enhanced by PKC activation (Aramori and Nakanishi, 1992). mGlu1α receptors expressed in CHO cells are also coupled to PLD through a mechanism that involves extracellular Ca^{2+} influx, PKC, tyrosine kinase(s), and RhoA (Kanumilli et al., 2002).

Phosphorylation of the transcription factor cAMP response element-binding protein has recently been reported in response to quisqualate application in CHO cells expressing either mGlu1α or mGlu5a receptors (Warwick et al., 2005). This effect is secondary to PKC activation (Warwick et al., 2005).

We have shown that extracellular signal-regulated kinases (ERKs)/mitogen-activated protein kinases (MAPKs) are involved in the mGlu1 receptor signaling. Activation of mGlu1α receptors in CHO cells induces ERK2 phosphorylation through a mechanism that is sensitive to PTX and requires the activation of PKC (Ferraguti et al., 1999). In a subsequent study, the mGlu1α receptor-mediated ERK phosphorylation was shown to require the activation of src-family kinases and to be independent of Ca^{2+} and phosphatidylinositol 3-kinase (PI3K) activity (Thandi et al., 2002). In addition to preferential activation of ERK2, ERK1 can also be phosphorylated in response to mGlu1 receptor activation (Thandi et al., 2002). A number of reports highlight the importance of the ERK pathway in the functioning of native mGlu1 receptors. In the spinal cord, ERK1/2 activation mediated by mGlu1 (and mGlu5) receptors contributes to the process of nociceptive sensitization, which underlies some of the hallmark features of chronic pain (Karim et al., 2001). Hypoxia combined with glucose deprivation induces a particular form of long-term potentiation (LTP) in cultured striatal neurons. This “pathological” LTP requires the stimulation of NMDA and mGlu1 receptors and is mediated by the activation of PKC and ERK1/2 (Calabresi et al., 2001).

Tyrosine phosphorylation of focal adhesion kinase mediated by mGlu1 (and mGlu5) receptors has been shown both in recombinant cells and in hippocampal slices and seems to be mediated by PLC and Ca^{2+}/calmodulin signaling pathways (Siciliano et al., 1996; Shinohara et al., 2001). Focal adhesion kinase phosphorylation might mediate the effect of glutamate on cytoskeleton dynamics.

mGlu1 receptors can also evoke responses that are independent of G-proteins. In CA3 pyramidal cells, for example, the induction of excitatory postsynaptic currents (EPSCs) mediated by mGlu1 receptors is G-protein-independent and requires the activation of tyrosine kinases of the src family (Heuss et al., 1999). It is noteworthy that cytosolic tyrosine kinases, such as syk, c-src, and fyn, can interact directly with the C terminus of mGlu1α receptors (Okubo et al., 2004). Activation of the tyrosine kinase src by mGlu1 receptors has also been shown in cerebellar PCs, where, in turn, it modulates $GABA_A$ receptor function (Boxall, 2000).

Activation of mGlu receptors regulates the activity of a variety of ligand- and voltage-gated ion channels, such as Ca^{2+} channels, K^+ channels, and nonselective cation channels (for review, see Anwyl, 1999). Group I mGlu receptors negatively modulate VSCCs in several cellular systems (Sayer et al., 1992; Swartz and Bean, 1992; Hay and Kunze, 1994; Choi and Lovinger, 1996). Activation of mGlu1α receptors was shown to inhibit both N-type and P/Q-type VSCCs in HEK-293 cells (McCool et al., 1998) and N-type VSCCs in superior cervical ganglion neurons (Kammermeier and Ikeda, 1999). The molecular mechanism underlying the inhibition of P/Q-type Ca^{2+} currents by mGlu1 receptors was explored by Kitano et al.(2003a), who found that mGlu1α receptors and the α subunit of P/Q-type VSCCs colocalize at dendrites of cerebellar PCs and can form heteromeric complexes mediated by the intracellular domains of the two proteins. Activation of mGlu1 receptors can also activate L-type Ca^{2+} currents in cultured cerebellar granule cells (Chavis et al., 1995, 1996). The coupling of mGlu1 receptors to L-type Ca^{2+} channels is mediated by a PTX-sensitive G-protein and by ryanodine receptors (RyRs) (Chavis et al., 1996; Fagni et al., 2000). In particular, the activation of mGlu1 receptors triggers a functional coupling between RyRs and L-type Ca^{2+} channels, possibly through the interaction with Homer proteins that provide a physical link between mGlu1 receptors and RyRs (Fagni et al., 2000). It is noteworthy that activation of mGlu1 receptors can also enhance the activity of Ca^{2+}-dependent K^+ channels, an effect that also involves RyRs and L-type Ca^{2+} channels (Chavis et al., 1998).

In transfected SCG neurons, mGlu1α receptors negatively modulate M-type voltage-gated K^+ channels via a PTX-resistant pathway (Ikeda et al., 1995). Cotransfection with RGS2 strongly reduces this inhibitory action of mGlu1α on M-type K^+ currents (Kammermeier and Ikeda, 1999). The inwardly rectifying K^+ channels are also negatively modulated by mGlu1 receptors. However, the underlying mechanism is debatable. In RNA-injected *X. laevis* oocytes, inhibition of inwardly rectifying K^+ channels by mGlu1α receptors was found to be either insensitive (Sharon et al., 1997) or sensitive (Saugstad et al., 1996) to PTX. The different amounts of RNA injected into oocytes in the two studies may help to explain this discrepancy.

Tandem-pore K^+ channels are additional targets for group I mGlu receptors. The members of this family mainly expressed in neurons are TASK and TREK channels, which can be modulated by both mGlu1 and mGlu5 receptors. For example, activation of mGlu1 receptors inhibits TREK and/or TASK channels in cultured cerebellar granule cells and spinal motoneurons (Alvarez et al., 2000; Talley et al., 2000; Chemin et al., 2003). In transfected COS-7 cells, activation of mGlu1α receptors inhibits TREK and TASK currents as a result of PI hydrolysis. In particular, inhibition of TREK is mediated by DAG and phosphatidic acid (produced, respectively, by PLC and PLD), whereas inhibition of TASK involves IP_3 (Chemin et al., 2003).

Activation of mGlu1 receptors in cerebellar PCs induces a slow EPSC, which seems to be mediated by nonselective cation channels (Canepari et al., 2001). Induction of this current is G-protein-dependent, does not require PKC, protein kinase A, protein kinase G, or PLC, and is inhibited by tyrosine phosphorylation (Canepari and Ogden, 2003). Slow EPSCs have been proposed to be mediated, at least in part, by TRPC1, a member of the TRPC family of nonspecific cation channels (Kim et al., 2003). Immunoprecipitation experiments on rat brain extracts showed an association between mGlu1α receptors and TRPC1, possibly through Homer proteins, and the onset of slow EPSC can be reconstituted in CHO cells expressing both mGlu1α receptors and TRPC1 (Kim et al., 2003). TRP-dependent slow EPSCs mediated by mGlu1 and mGlu5 receptors have also been described in hippocampal CA3 pyramidal cells (Gee et al., 2003).

Group I mGlu receptors can also modulate the activity of ligand-gated ion channels, such as AMPA and NMDA receptors, thus contributing to the induction of activity-dependent forms of synaptic plasticity (Anwyl, 1999). Pharmacological activation of group I mGlu receptors facilitates both AMPA and NMDA responses in spinal motoneurons through a pathway that involves PKC (Ugolini et al., 1997). Because spinal motoneurons do not express mGlu5 receptors (Alvarez et al., 2000), potentiation of AMPA/NMDA currents is likely to be mediated by mGlu1 receptors. In *X. laevis* oocytes, activation of mGlu1 receptors enhances the trafficking of NMDA receptors to the outer membrane, a process that is mediated by exocytosis (Lan et al., 2001). The mechanisms underlying the potentiation of NMDA currents mediated by mGlu1 receptors include PI hydrolysis, activation of PKC, and changes in cytoskeleton dynamics (Skeberdis et al., 2001). More recently, a tyrosine kinase cascade, involving Pyk2 kinase and the src family kinases Src and Fyn, has been implicated in the potentiation of NMDA receptor activity mediated by mGlu1α receptors in cultured cortical neurons (Heidinger et al., 2002). Activation of both mGlu1 and mGlu5 receptors induces phosphorylation of the NR2B NMDA receptor subunit in the spinal cord under conditions of inflammatory hyperalgesia (Guo et al., 2004). This phosphorylation is mediated by PKC and requires the activation of IP_3 receptors (Guo et al., 2004).

There are also a few reports showing that activation of mGlu1 receptors modulates $GABA_A$ currents. This modulation has been shown in cerebellar PCs in response to the combined activation of mGlu1 and TrkB receptors (see section VI.B.6) and in retinal amacrine cells, in which stimulation of group I mGlu receptors inhibits $GABA_A$ currents through a mechanism that involves an increase in intracellular Ca^{2+}, which triggers a calmodulin/calcineurin cascade (Vigh and Lasater, 2003). How-

ever, it is not known whether the latter process is mediated by mGlu1 or mGlu5 receptors (Vigh and Lasater, 2003).

C. Metabotropic Glutamate 1 Receptor Function and Interacting Proteins

Homer proteins are a family of proteins characterized by an enabled/vasodilator-stimulated phosphoprotein homology-like domain, which binds specifically to a prolin-rich sequence present in several proteins, such as group I mGlu receptors, IP_3 receptors, ryanodine receptors, and Shank. So far, several members of the Homer family have been cloned: Homer1a, -1b, -1c, -2, and -3 (Brakeman et al., 1997; Kato et al., 1997, 1998; Sun et al., 1998; Tu et al., 1998). With the exception of Homer1a, they are characterized by a C-terminal coiled-coil domain, which allows multimerization (Kato et al., 1998; Tu et al., 1998). Homer proteins are constitutively expressed, with the exception of Homer1a that is an immediate early gene rapidly induced in response to neuronal activation (Brakeman et al., 1997; Tu et al., 1998).

All Homer proteins bind to a proline-rich domain (PPSPFR) within the C terminus of mGlu1α and -5 receptors (Brakeman et al., 1997; Tu et al., 1998). The colocalization of Homer proteins and group I mGlu receptors in discrete clusters has been reported in several systems (Brakeman et al., 1997; Ango et al., 2000; Kammermeier et al., 2000), although there are exceptions. For example, mGlu1 receptors and Homer1c colocalize in the molecular layer of the cerebellar cortex, but they are segregated in the hippocampus (Tadokoro et al., 1999). The expression of Homer1a, which lacks the multimerization domain, disrupts the interaction between group I mGlu receptors and the other Homer proteins (Tu et al., 1998). This finding suggests that Homer1a may have a role in regulating the association of mGlu/Homer complexes, possibly acting as a dominant-negative Homer (Tu et al., 1998).

Homer multimers, in particular Homer1b, -1c, and -3, can associate with mGlu1α and IP_3 receptors (Fig. 3), providing a structural link between two molecules that are functionally coupled (Tu et al., 1998). Homer can also associate with Shank, a scaffolding protein of the PSD that forms macromolecular complexes with other scaffolding proteins (e.g., PSD-95), ion channels (e.g., NMDA receptors), mGlu1/5 receptors, and signaling proteins (Tu et al., 1999; Sheng, 2001). Although group I mGlu receptors can associate with Shank indirectly, via interactions with Homer, they can also bind the PDZ domain of Shank directly through their C-terminal domain (Tu et al., 1999). Homer1 has been shown to mediate the association of mGlu1, PLCβ4, and IP_3 receptor in mouse cerebellum (Nakamura et al., 2004). More recently, the interaction between Homer1b and Shank2 has been implicated in the coupling of group I mGlu receptors to PLCβ3 (Hwang et al., 2005). All of these findings indicate that at glutamatergic synapses Homer proteins are involved in the organization of the postsynaptic signaling molecules in a functional unit, bridging group I mGlu receptors, IP_3, and ryanodine receptors to scaffolding molecules such as Shank, which in turn associates to several other effectors (Sheng, 2001). Group I mGlu receptors are coupled to PI3K via the interaction with Homer proteins and the PI3K enhancer, a recently identified GTPase that activates PI3K (Rong et al., 2003). In cultured hippocampal neurons, activation of mGlu receptors induces the association of a complex composed of mGlu1/5 receptors, Homer, and PI3K enhancer, which may contribute to the neuroprotective activity of group I mGlu receptors by preventing apoptotic death (Rong et al., 2003).

A role for Homer proteins in regulating the activity of mGlu1 receptors has been demonstrated in cultured cerebellar PCs transfected with Homer 1a, which show reduced Ca^{2+} responses mediated by mGlu1 receptors, compared with cells transfected with Homer1b or with nontransfected cells (Tu et al., 1998). The reduced activity of mGlu1 receptors can be explained by a dominant-negative effect of Homer1a toward other Homer proteins, which disrupts the physical and functional coupling between mGlu1α and IP_3 receptors.

Transfection of Homer2b, which contains the coiled-coil multimerization domain, reduces the inhibition of the N-type VSCCs mediated by mGlu1α receptors in SCG neurons (Kammermeier et al., 2000). This effect of Homer2b is reversed by coexpression of the nonmultimerizing Homer1a (Kammermeier et al., 2000). A similar pattern of modulation applies also to M-type potassium currents (Kammermeier et al., 2000).

As described in section IV.A, agonist-independent activity has been reported for mGlu1α receptors expressed in heterologous systems (Prézeau et al., 1996). The interaction of Homer3 with mGlu1α receptors in cultured cerebellar granule cells prevents the constitutive activity of mGlu1α receptors (Ango et al., 2001). Knock down of Homer3 or its coexpression with Homer1a leads to an increase in basal PI turnover and in the basal open probability of Ca^{2+}-dependent big K^{+} channels (Ango et al., 2001). Homer proteins, therefore, may have a pivotal role in the mechanisms of activation of group I mGlus, even in the absence of exogenous stimulation (Ango et al., 2001). Finally, Homer1c modulates intracellular Ca^{2+} transients induced by mGlu1α stimulation by metal cations (Ca^{2+} and Gd^{3+}) in cotransfected HEK-293 cells (Abe et al., 2003a).

Besides their effects on receptor signaling, Homer proteins can also regulate the trafficking of mGlu1 receptors. The expression of mGlu1α receptors on the cell surface of HEK-293 cells is increased when they are cotransfected with Homer1a (Ciruela et al., 1999b; Minami et al., 2003). However, such an increase was not observed in HeLa cells (Roche et al., 1999), but this inconsistency could be explained by a different endoge-

nous expression of long Homer proteins. Conversely, cell surface expression of mGlu1α receptors is reduced when they are cotransfected with Homer1b or -1c (Roche et al., 1999; but see Ciruela et al., 2000; Abe et al., 2003a; Kammermeier, 2006). This restraint on cell surface expression of mGlu1α receptors by Homer1b seems to depend on the retention of the receptor in the endoplasmic reticulum (Roche et al., 1999). In cultured neocortical neurons, Homer1c produces an increase in the dendritic trafficking of mGlu1α receptors, possibly because of a facilitation of receptor transport (Ciruela et al., 2000). Moreover, long Homer proteins induce mGlu1α receptor surface clustering both in non-neuronal cell lines and primary neurons in culture (Kammermeier, 2006). Studies carried out in cerebellar PCs in vitro show that depolarization induces the expression of Homer1a, which in turn suppresses internalization of mGlu1 receptors and increases their number on the cell plasma membrane, with both effects being mediated by the MAPK pathway (Minami et al., 2003). Homer1a may, therefore, exert a functional competition with the longer Homer isoforms for receptor binding, hence providing a mechanism for the regulation of mGlu1α receptor content at the plasma membrane and consequently also at synaptic sites. This mechanism might contribute to tune neuronal excitability and synaptic plasticity.

The recently identified PDZ domain-containing protein tamalin associates with cytohesin and with the C terminus of mGlu1α receptors, thereby regulating mGlu1α receptor trafficking (Kitano et al., 2002). Tamalin is characterized by several protein-binding domains that allow its interaction with signaling or scaffolding proteins (Kitano et al., 2003b). More recently, tamalin has been shown to possess an immunoreceptor tyrosine-based activation motif that upon phosphorylation allows the association with syk kinase (Hirose et al., 2004). The c-src and fyn kinases phosphorylate both immunoreceptor tyrosine-based activation motif and syk after their recruitment (Hirose et al., 2004). Coimmunoprecipitation experiments showed that in rat brain mGlu1α is present in complexes containing tamalin, c-src, fyn, syk, and the phosphatase SHP-2 (Hirose et al., 2004). However, the functional significance of these interactions is still unclear.

Activation of mGlu1α expressed in heterologous systems has been linked to a rearrangement of the cytoskeleton, which might result from a direct interaction of the receptor with cytoskeletal proteins. Activation of mGlu1α receptors in CHO cells causes a marked rearrangement of actin filaments and a modification of cell morphology from a square shape to a spindle/bar shape (Kubo et al., 1998; Mody et al., 1999; Shinohara et al., 2001). Increases in extracellular Ca^{2+} concentrations amplify these effects, suggesting a role for the Ca^{2+} sensing properties of mGlu1 receptors (Kubo et al., 1998). Activation of mGlu1α receptors in transfected HEK-293 cells induces cytoskeletal changes similar to those associated with an increased synthesis of membrane phospholipids (Hirai et al., 1999). Immunoprecipitation experiments performed on rat brain extracts revealed a direct interaction between mGlu1α receptors and tubulin, one of the main constituents of the cytoskeleton (Ciruela et al., 1999a). This association was confirmed in mGlu1α-transfected BHK cells, in which receptor activation induces the reorganization of tubulin and morphological changes (Ciruela and McIlhinney, 2001).

The mGlu1α receptor can also associate directly with 4.1G, a member of the 4.1 superfamily of cytoskeletal proteins, which play key roles in several cellular functions, such as protein sorting, mitosis, and intracellular signaling (Lu et al., 2004). It is noteworthy that immunoprecipitation experiments failed to show any interaction between mGlu1β receptors and 4.1G, suggesting that the C-terminal tail of mGlu1α receptors is critical for this interaction (Lu et al., 2004).

A further association of mGlu1α receptors with caveolin proteins has been reported (Burgueño et al., 2003, 2004). Caveolin networks form small membrane microdomains known as caveolae, which have a critical role in endocytosis, lipid transport, and signal transduction. The interaction with caveolins seems to have a role in mGlu1α receptor trafficking and signaling as cotransfection of mGlu1α receptors with caveolin-2β in HEK-293 cells modifies the subcellular localization of mGlu1α receptors, whereas cotransfection with caveolin-1 suppresses the constitutive activity of the receptor (Burgueño et al., 2004).

Coimmunoprecipitation experiments have shown an association between mGlu1α and adenosine A1 receptors in cerebellar synaptosomes and recombinant cells (Ciruela et al., 2001). This association involves the C-terminal domain of mGlu1α receptors and might be relevant for mechanisms of neurodegeneration/neuroprotection because activation of A1 receptors attenuates the amplification of NMDA toxicity produced by the mGlu1/5 receptor agonist, quisqualate, in cultured cortical neurons (Ciruela et al., 2001).

A specific interaction between the C-terminal tail of group I mGlu receptors and a member of the mammalian seven in absentia homologs (Siah) family, Siah-1A, has also been demonstrated (Ishikawa et al., 1999). Within the C terminus of mGlu1α, residues Lys^{905}–Pro^{932} interact directly with Siah-1A and with Ca^{2+}/calmodulin in a competitive manner (Ishikawa et al., 1999). Siah proteins contain a RING finger domain suggesting that they might participate in targeting specific proteins for degradation in the proteasome (Lorick et al., 1999). When coexpressed with mGlu1α receptors in SCG neurons, Siah-1A reduces the ability of the receptor to inhibit N-type Ca^{2+} currents (Kammermeier and Ikeda, 2001).

In cultured cerebellar PCs, a direct interaction between mGlu1 and $GABA_B$ receptors, in which both

$GABA_B$ receptors and extracellular Ca^{2+} regulate mGlu1 receptor signaling, has been found (Tabata et al., 2004). Whether this interaction is peculiar to PCs or can be extended to other neurons remains to be established.

The existence of a functional interaction between mGlu1 receptors and ephrin-B2 has been demonstrated recently (Calò et al., 2005). Immunoprecipitation experiments performed on rat brain extracts revealed the presence of macromolecular complexes composed of mGlu1α receptors, ephrin-B2, Homer1b/-1c, the NR1 subunit of NMDA receptors, and RGS3. In addition, activation of ephrin-B2 by means of a clustered Eph-B receptor/Fc chimera amplifies the stimulation of PI hydrolysis mediated by mGlu1 receptors in brain slices and cultured neurons. However, fluorescence resonance energy transfer analysis excludes a direct interaction between mGlu1 receptors and ephrin-B2, suggesting that coupling is mediated through scaffolding proteins (Calò et al., 2005).

D. Desensitization and Trafficking

Desensitization of GPCRs (i.e., the reduced response to prolonged agonist stimulation) involves several mechanisms, such as phosphorylation, uncoupling from G-proteins, internalization, and down-regulation. Desensitization/internalization of mGlu1 receptors may be induced by the activation of mGlu1 receptors themselves (homologous desensitization) and by the activation of different receptors (heterologous desensitization) (Desai et al., 1996; Mundell et al., 2002). Both PKC and G-protein coupled receptor kinases (GRKs) have been implicated in mGlu1 receptor desensitization.

A role for PKC was first demonstrated in cultured cerebellar granule cells, which express mGlu1 receptors. In these cultures, activation of PKC by phorbol esters reduces the stimulation of PI hydrolysis mediated by mGlu1 receptors, whereas PKC inhibitors reduce homologous desensitization of mGlu1 receptors (Catania et al., 1990). In recombinant cells, PKC activation by phorbol esters can also inhibit both the constitutive and agonist-stimulated activity of mGlu1 receptors, whereas PKC inhibitors enhance mGlu1 receptor signaling (Aramori and Nakanishi, 1992; Thomsen et al., 1993). The molecular bases of PKC-mediated desensitization have been partially clarified. It has been shown that activated mGlu1 receptors are transiently phosphorylated by PKC (Alaluf et al., 1995). PKC phosphorylates at least one threonine residue (Thr^{695}), which has a critical role in the onset of desensitization (Francesconi and Duvoisin, 2000). It should be here remembered that Thr^{695} is located within intracellular loop i2, a key domain for G-protein coupling (Gomeza et al., 1996). In addition, PKC desensitizes the stimulation of PI hydrolysis but not the activation of adenylyl cyclase activity mediated by mGlu1 receptors, suggesting that Thr^{695} phosphorylation specifically impairs coupling to G_q (Francesconi and Duvoisin, 2000). Besides Thr^{695}, most of the intracellular tail of the mGlu1α receptor (residues Ser^{894}–Leu^{1199}) is critical for PKC-dependent desensitization (Mundell et al., 2003). Internalization of both mGlu1α and -1β receptors in response to agonist or phorbol ester application has been reported in several heterologous expression systems, with a higher efficacy toward mGlu1β receptors (Ciruela and McIlhinney, 1997; Mundell et al., 2002). It is noteworthy that PKC is involved in the internalization of mGlu1α receptors, whereas internalization of mGlu1β receptors is PKC-independent (Mundell et al., 2002). In HEK-293 cells, stimulation of M_1 muscarinic receptors, which are coupled to $G_{q/11}$ and are endogenously expressed by these cells, induces mGlu1 receptor internalization through a mechanism that involves PKC and Ca^{2+}/calmodulin-dependent protein kinase II (Mundell et al., 2002).

A major mechanism of homologous desensitization of GPCRs involves GRKs and β-arrestins. Phosphorylation of GPCRs by GRKs promotes binding of β-arrestin proteins, which uncouple the receptor from the G-protein and target the receptor to clathrin-coated pits for internalization (Dale et al., 2002). A number of GRKs, namely GRK2, GRK4, and GRK5, were found to induce mGlu1α receptor phosphorylation and desensitization (Dale et al., 2000; Sallese et al., 2000). In HEK-293 cells, GRK2 contributes to the desensitization of both basal and agonist-stimulated mGlu1α activity (Dale et al., 2000). Whereas the role of GRK4 in mGlu1α receptor desensitization in HEK-293 cells remains controversial (Dale et al., 2000; Sallese et al., 2000), GRK4 seems to be involved in the homologous desensitization of native mGlu1 receptors in cultured cerebellar PCs, as shown by the use of GRK4 antisense oligonucleotides (Sallese et al., 2000). Immunoprecipitation experiments confirmed a direct interaction of mGlu1 with both GRK2 (Dale et al., 2000) and GRK4 (Sallese et al., 2000). The residues Ser^{869} to Val^{893} within the C terminus of mGlu1α receptors seem to be essential for GRK-dependent internalization (Mundell et al., 2003). Different mechanisms mediate the desensitization of mGlu1 receptors by GRK2 and GRK4 (Iacovelli et al., 2003; Dhami et al., 2004); whereas GRK4 acts by phosphorylating mGlu1 receptors (Iacovelli et al., 2003), GRK2 activity is largely independent of phosphorylation and might be mediated by a direct interaction of GRK2 with $G\alpha_q$ (Dale et al., 2000; Dhami et al., 2004). Agonist-induced internalization of mGlu1α and -β receptors also depends on β-arrestins and dynamin (Dale et al., 2001; Mundell et al., 2001, 2002). GRK-mediated desensitization and certain intracellular transduction mechanisms seem to be interdependent, as activation of the cAMP/protein kinase A pathway inhibits the interaction of GRK2 and β-arrestin with mGlu1 receptors (Pula et al., 2004), whereas β-arrestin may also act as a signaling protein mediating ERK1/2 activation by mGlu1 receptors (Iacovelli et al., 2003).

A constitutive internalization, independent of agonist stimulation, has been described for the mGlu1α receptor (Dale et al., 2001; Doherty et al., 1999b). When transfected in HEK-293 cells, mGlu1α receptors are constitutively internalized, whereas cell surface expression of mGlu1β receptors remains stable (Pula et al., 2004). Constitutive internalization of mGlu1α receptors requires β-arrestins and clathrin (Pula et al., 2004) and is mediated by the small GTP-binding protein Ral, its guanine nucleotide exchange factor RalGDS (Ral GDP dissociation stimulator), and phospholipase D2, which is found to be associated with mGlu1 receptors under resting conditions (Bhattacharya et al., 2004).

A marked alteration of mGlu1 receptor trafficking has been observed in a transgenic mouse model of spinocerebellar ataxia type 1 (SCA1) (Skinner et al., 2001). In SCA1 mice, cerebellar PCs are characterized by dendritic atrophy and by the presence of cytoplasmic vacuoles that contain several proteins such as AMPA, PKCγ, and mGlu1 receptors (Skinner et al., 2001).

V. Pharmacology

The ability of glutamate to bind to different types of receptors resides in its great conformational flexibility. Distinct domains of mGlu1 receptors are involved in agonist binding, G-protein coupling, and intermolecular interactions, indicating that multiple regions of the receptor can be targeted for pharmacological intervention.

The glutamate binding site in the mGlu1 receptor resides in the large N terminus extracellular domain, as established by crystallography and mutagenesis studies (Takahashi et al., 1993; Okamoto et al., 1998; Kunishima et al., 2000; see also section III.A for further details). These studies allowed resolution of the binding pocket for glutamate (Jingami et al., 2003) and construction of numerous models of receptor activation (Jensen et al., 2002; Parmentier et al., 2002; Jingami et al., 2003). However, no orthosteric agonists that activate selectively mGlu1 receptors without also recruiting mGlu5 receptors have been developed; this may simply reflect the similarity in the amino acid sequence of the LBD of mGlu1 and mGlu5 receptors. Conversely, the two receptors can be distinguished by the use of orthosteric antagonists or allosteric modulators, as highlighted in the following.

A. Agonist Pharmacology

The first orthosteric group I mGlu receptor agonists, quisqualate (Sladeczek et al., 1985; Nicoletti et al., 1986c) and ibotenic acid (Nicoletti et al., 1986a,b), were described before the cloning of the mGlu1 receptor. However, these two drugs are not selective and can also activate ionotropic glutamate receptors (Watkins et al., 1990; Schoepp et al., 1999). Quisqualate is frequently used as a reference mGlu1 receptor agonist in heterologous expression systems because of its high potency (Sugiyama et al., 1987; Houamed et al., 1991; Masu et al., 1991; Aramori and Nakanishi, 1992). A number of conformationally restricted glutamate analogs show agonist activity at mGlu1 receptors. These include *trans*-1-amino-cyclopentyl-1,3-dicarboxylic acid (ACPD) (Palmer et al., 1989) and two L-isomers of 2-carboxycyclopropylglycine, L-carboxycyclopropylglycine-I and L-carboxycyclopropylglycine-II (Hayashi et al., 1992). The activity of these molecules suggests that glutamate activates mGlu1 receptors (and other mGlu receptors) in its extended configuration. *Trans*-ACPD is historically important as the first mGlu receptor ligand that does not interact with ionotropic glutamate receptors. The activity of *trans*-ACPD resides exclusively in the 1*S*,3*R*-isomer (1*S*,3*R*-ACPD) (Irving et al., 1990; Schoepp et al., 1991; Schoepp and True, 1992; Cartmell et al., 1993). Although 1*S*,3*R*-ACPD has been used for several years for the study of group I mGlu receptors, it is not selective for mGlu1 or mGlu5 receptors but displays agonist activity at nearly all mGlu receptor subtypes (Schoepp et al., 1999).

The development of phenylglycine derivatives as mGlu receptor ligands led to the identification of 3,5-DHPG as the first selective agonist of group I mGlu receptors (Schoepp et al., 1994). The activity of 3,5-DHPG resides exclusively in the *S*-isomer (Baker et al., 1995). Isosteric replacement of the α-carboxylic acid of 3,5-DHPG by a phosphinic group results in 3,5-dihydroxyphenylmethylphosphinic acid, which behaves as a relatively potent agonist (EC_{50} = 28 μM) on PI-linked mGlu receptors in cortical slices (Boyd et al., 1996). The monophenolic analog of 3,5-DHPG, namely 3-hydroxyphenylglycine, retains the agonist activity, although it displays lower potency and efficacy (Birse et al., 1993; Thomsen et al., 1994a; Joly et al., 1995).

The rank order of potency of agonists at recombinant mGlu1 receptors is quisqualate > 3,5-DHPG = glutamate $\gg$ 1*S*,3*R*-ACPD > 3-hydroxyphenylglycine, with glutamate behaving as a full agonist and the other drugs as partial agonists (Aramori and Nakanishi, 1992; Thomsen et al., 1993; Ferraguti et al., 1994; Joly et al., 1995; Lin et al., 1997).

Comparable rank orders of agonist potencies have been obtained for rat and human mGlu1 receptors (Lin et al., 1997). Agonists show higher potency in activating rat mGlu1α than rat mGlu1β receptors (Pickering et al., 1993; Flor et al., 1996) but equal potency in activating human receptors (Stephan et al., 1996). However, it should be kept in mind that agonist potency correlates with the expression levels of mGlu1 receptors, as shown by data obtained in cultured cerebellar granule cells (Favaron et al., 1992) and by the use of an inducible expression system, which allows a timed control of mGlu1 receptor expression (Hermans et al., 1999).

Other molecules, which include β-*N*-methylamino-L-alanine (Copani et al., 1991; Thomsen et al., 1993) and several sulfur-containing amino acids (e.g., cysteic acid,

homocysteic acid, L-homocysteine sulfinic acid, and L-cysteine sulfinic acid) (Nicoletti et al., 1986b; Porter and Roberts, 1993; Thomsen et al., 1994b; Clark et al., 1998) can stimulate PI hydrolysis in brain slices and in cells expressing recombinant mGlu1 receptors. However, the activity of sulfur-containing amino acids might be due to the inhibition of glutamate uptake (Thomsen et al., 1994b).

B. Competitive Antagonists

The first important advance for the development of mGlu1 antagonists was the discovery that phenylglycine analogs [4-carboxyphenylglycine (4-CPG), 4-carboxy-3-hydroxyphenylglycine, and MCPG] were able to antagonize mGlu-mediated responses in rat spinal motoneurons and cortical slices with little or no effects on ionotropic glutamate receptors (Birse et al., 1993; Eaton et al., 1993). When tested on mGlu1 receptors expressed in recombinant systems, these phenylglycines were shown to be competitive antagonists (Ferraguti et al., 1994; Hayashi et al., 1994; Thomsen et al., 1994a; Kingston et al., 1995). However, these compounds also showed antagonist activity on mGlu5 receptors and either agonist or antagonist activity at group II and III mGlu receptors (Ferraguti et al., 1994; Hayashi et al., 1994; Thomsen et al., 1994a; Kingston et al., 1995; Roberts, 1995). Chiral separation or X-ray diffraction analysis indicated that the antagonistic properties reside in the S-isomers of phenylglycine (Birse et al., 1993; Wilson et al., 1997). Substitution at the α-position of *S*-4-CPG with *n*-pentyl or cyclopropyl substituents causes a shift in the selectivity from mGlu1 toward mGlu5 receptors (Doherty et al., 1999a).

The selectivity and potency of phenylglycines as mGlu1 receptor antagonists is increased with the addition of 2-methyl substituents (Clark et al., 1997). LY367385, a 2-methylphenylglycine, behaves as a relatively potent mGlu1 receptor antagonist with little or no activity on mGlu5 or group II mGlu receptors. This compound inhibits quisqualate-stimulated PI hydrolysis in AV-12 cells expressing mGlu1α receptors with an apparent IC_{50} value close to 10 μM (Clark et al., 1997; Kingston et al., 2002). The α-thioxanthyl-9-methyl analog of *S*-4-CPG (LY367366) is a more potent mGlu1 antagonist than LY367385 but shows similar potency on mGlu5, mGlu2, and mGlu4 receptors (Clark et al., 1998; Kingston et al., 2002). A conformationally restricted analog of MCPG named (*RS*)-1-aminoindan-1,5-dicarboxylic acid (AIDA), in which the α-substituent is tied to the 2-position of the phenyl ring, is a preferential mGlu1 receptor antagonist (Pellicciari et al., 1995; Moroni et al., 1997), although its pharmacological window is not sufficiently large to guarantee selective inhibition of mGlu1 versus mGlu5 receptors within a wide range of concentrations.

A derivative of aminothiophene dicarboxylic acid, 3-MATIDA, was shown to possess potent antagonist activity toward mGlu1 receptors (IC_{50} = 6.3 μM) and no affinity for mGlu5, mGlu2, and mGlu4 receptors (Moroni et al., 2002). The antagonistic activity of 3-MATIDA on mGlu1 receptors resides in the (+)-isomer (Costantino et al., 2004). However, at high concentrations 3-MATIDA also antagonizes AMPA and NMDA receptor responses (Moroni et al., 2002).

A number of additional compounds show mixed antagonist activity at multiple glutamate receptors, including mGlu1 receptors. For these compounds we refer the reader to a dedicated review (Schoepp et al., 1999).

C. Positive Allosteric Modulators

Several compounds acting as positive allosteric modulators at mGlu1 have been identified recently. These compounds are inactive on their own, but potentiate the action of orthosteric agonists. The theoretical advantage of these compounds from a therapeutic standpoint is that they recruit exclusively receptors that are endogenously activated. Agonist potency and efficacy at rat mGlu1α receptors are increased by 2-phenyl-1-benzenesulfonyl-pyrrolidine derivatives (including Ro 67-7476), diphenylacetyl- and (9*H*-xanthene-9-carbonyl)-carbamic acid esters (including Ro 01-6128), and the (9*H*-xanthene-9-carbonyl)-carbamic acid butyl ester (Ro 67-4853) (Knoflach et al., 2001a). However, only Ro 67-4853 enhances glutamate efficacy on human mGlu1α, whereas Ro 67-7476 and Ro 01-6128 are inactive (Knoflach et al., 2001a). Subsequently, a series of diphenylacetyl-, 9*H*-xanthene-, and 9*H*-thioxanthene-carbonyl carbamates were reported as positive allosteric modulators of rat mGlu1α (Wichmann et al., 2002).

D. Noncompetitive Antagonists

Early work suggested that 2-amino-3-phosphonopropionic acid (AP3) was capable of antagonizing glutamate-stimulated PI hydrolysis (Schoepp and Johnson, 1989a,b) and 1*S*,3*R*-ACPD-induced Ca^{2+} mobilization (Irving et al., 1990). Soon after, it was recognized that AP3 was basically inactive on both rat mGlu1α and mGlu5a receptors (Abe et al., 1992; Aramori and Nakanishi, 1992; Yuzaki and Mikoshiba, 1992; Thomsen et al., 1993), displaying only partial inhibition at doses $\geq$1 mM (Aramori and Nakanishi, 1992; Ito et al., 1992; Thomsen et al., 1993; Saugstad et al., 1995). This weak inhibition was noncompetitive because it could not be reversed by increasing the agonist concentration (Schoepp et al., 1990). However, the action of L-AP3 is confounded by its ability to prevent the incorporation of *myo*-[^{3}H]inositol into membrane phospholipids (Ikeda, 1993).

The identification in 1996 of CPCCOEt showed that compounds structurally unrelated to glutamate can selectively and potently inhibit mGlu1 receptor function (Annoura et al., 1996; Casabona et al., 1997) via allosteric sites distant from the glutamate-binding pocket (Okamoto et al., 1998; Litschig et al., 1999). This molecule was shown to interact with Thr^{815} and Ala^{818} lo-

cated at the extracellular surface of the TM helix 7 (Litschig et al., 1999) and its benzene ring to lie between TM7 and TM3 (Pagano et al., 2000). The optical isomer (−) is responsible for most of the antagonistic activity of CPCCOEt at mGlu1 receptors (Ott et al., 2000). Subsequently, several additional noncompetitive mGlu1 antagonists with a higher potency than that of CPCCOEt have been discovered. Compounds BAY 36-7620 and EM-TBPC were reported to interact within the 7TMD (Carroll et al., 2001; Malherbe et al., 2003). BAY 36-7620 displays high potency ($IC_{50} = 0.16 \pm 0.01\ \mu M$) in antagonizing responses mediated by rat mGlu1α receptors and also behaves as an inverse agonist, being able to inhibit the constitutive activity of mGlu1α receptors (Carroll et al., 2001). EM-TBPC is characterized by nanomolar concentration affinity for rat mGlu1α receptors but low affinity for human mGlu1 receptors (Malherbe et al., 2003).

NPS 2390, which belongs to a series of quinoline and quinoxaline amides, is a noncompetitive antagonist of group I mGlu receptors, with IC_{50} values of 5.2 and 82 nM for CaR/mGlu1 and CaR/mGlu5 chimeras, respectively (van Wagenen et al., 2000). In a further effort to identify more selective compounds based on these templates, a 2-quinoxaline carboxamide (NPS 2407) and a 2-quinoxaline ester (NPS 3018) were identified as selective mGlu1 inhibitors, with IC_{50} values of 17 and 52 nM, respectively, at the CaR/mGlu1 chimera and no or low activity (10 μM) at the CaR/mGlu5 chimera (Fairbanks et al., 2001).

2,4-Dicarboxypyrroles have been identified as a new class of highly selective noncompetitive mGlu1 antagonists (Micheli et al., 2003c). The most potent molecules of this class (e.g., GW398171X) are characterized by nanomolar concentration potency and are active both in vitro and in vivo (Micheli et al., 2003a,b,c, 2004a,b). These compounds interact with a region near the extracellular loops of the mGlu1 receptor, although the precise binding site has not been identified (Micheli et al., 2003c).

R214127 is a selective noncompetitive mGlu1 receptor antagonist that binds to the same site as CPCCOEt and BAY 36-7620 at human mGlu1α receptors with a K_d value of 0.9 nM (Lavreysen et al., 2003). The availability of radiolabeled [^{3}H]R214127 enabled the evaluation of the brain occupancy of BAY 36-7620 and NPS 2390 by ex vivo autoradiography (Lavreysen et al., 2004a). At doses of 10 mg/kg, NPS 2390 completely displaces specifically bound [^{3}H]R214127 in the cerebellum, whereas BAY 36-7620 inhibits [^{3}H]R214127 binding by only 36 and 32% in cerebellum and thalamus, respectively (Lavreysen et al., 2004a). A derivative of R214127, JNJ16259685, acts as a selective noncompetitive antagonist of rat and human mGlu1α receptors, with IC_{50} values of 3.24 and 1.21 nM, respectively (Lavreysen et al., 2004b). Ex vivo autoradiography experiments were used to evaluate the occupancy of mGlu1 receptors by JNJ16259685, which is maximal in the cerebellum at doses as low as 0.16 mg/kg (Lavreysen et al., 2004b). After subcutaneous injection of 63 mg/kg JNJ16259685, mGlu1 receptor occupancy is maximal after 10 min in thalamus and 30 min in cerebellum and lasts for 2 h. Maximal plasma concentrations (C_{max}) are 70.3 ng/ml (30 min postdose), whereas maximal brain concentrations are 62.9 ng/ml (1 h postdose) (Lavreysen et al., 2004b).

YM-202074 is a new negative allosteric modulator of mGlu1 receptors that displays nanomolar affinity and is systemically active, reaching maximal brain concentrations in a few minutes after intravenous injection (Kohara et al., 2008).

Antagonist pretreatment of cells expressing the recombinant human mGlu1α receptor causes a marked increase in both potency and efficacy of glutamate stimulation (Lavreysen et al.,2002). This particular form of "supersensitivity," which is induced by both noncompetitive and competitive mGlu1 receptor antagonists, cannot be simply described by the inhibition of receptor desensitization mediated by the endogenous glutamate (Lavreysen et al., 2002). Antagonist pretreatment increases cell surface expression of mGlu1α receptors, suggesting recruitment or stabilization of receptors at the plasma membrane (Lavreysen et al., 2002).

VI. Anatomy and Physiology

A. Cellular and Subcellular Distribution

mGlu1 has been extensively expressed in the central nervous system, being most intense in PCs of the cerebellar cortex and mitral/tufted cells of the olfactory bulb (Martin et al., 1992; Shigemoto et al., 1992; Baude et al., 1993). Strong expression was also detected in neurons of the lateral septum, globus pallidus, ventral pallidum, substantia nigra, hippocampus, and most of the thalamic nuclei but not in the reticular nucleus, epithalamus, and brainstem (Martin et al., 1992; Baude et al., 1993). Many other brain areas display moderate to low expression levels of mGlu1. A detailed description of the expression of mGlu1 receptor both at mRNA and protein level can be found in Shigemoto and Mizuno (2000).

In most neuronal populations, the subcellular localization of mGlu1 or of some of its splice variants has been consistently associated with the postsynaptic specialization of excitatory synapses (Martin et al., 1992; Baude et al., 1993; Gorcs et al., 1993; Petralia et al., 1996; Shigemoto et al., 1997; Mateos et al., 2000). Immunogold studies have suggested that mGlu1 receptors do not reside in the main body of asymmetric synapses but rather are concentrated in the perisynaptic area, an annulus of approximately 60 nm around the synaptic specialization (Baude et al., 1993; Nusser et al., 1994; Lujan et al., 1996; Mateos et al., 2000). Immunolabeling for mGlu1 was also found in extrasynaptic areas up to 600 nm from the synapse (Lujan et al., 1996; Mateos et al., 2000), although we often observed immunogold la-

beling for mGlu1 even further. An interesting finding was the detection of mGlu1α within the main body of symmetric and probably GABAergic synapses (Hanson and Smith, 1999; Hubert et al., 2001; Paquet and Smith, 2003; Kuwajima et al., 2004). However, the detection method used in these studies, namely the pre-embedding immunogold/silver labeling technique, does not provide unequivocal evidence for the localization of this receptor in the membrane specialization of GABAergic synapses. On the other hand, preliminary confirmation of these findings comes from the use of SDS-freeze-fracture replica labeling (Ferraguti et al., 2007).

A critical analysis of studies describing the distribution of mGlu1 receptors should take into account the specificity of the antibodies and of the conditions used. Rigorous analysis, including testing in mGlu1-null mice, has been performed for only a few antibodies (Ferraguti et al., 1998, 2004; Alvarez et al., 2000), which may explain the largely diverse pattern of immunostaining reported in different papers. For example, in our hands, all well characterized antibodies do not label glial cells. Conversely, with two commercial antibodies [rabbit polyclonal obtained from Chemicon International (Temecula, CA) and mouse monoclonal obtained from BD Pharmingen (San Diego, CA)], we could observe, respectively, neuropil immunolabeling, which was attributed to a partial cross-reactivity with mGlu5 receptors (Ferraguti et al., 1998; Alvarez et al., 2000), and cross-reactivity with unknown proteins, because the labeling persisted in mGlu1-null mice (F. Ferraguti, personal communication). Several functional studies have suggested a presynaptic localization of mGlu1 (Fotuhi et al., 1994; Mannaioni et al., 2001; Wittmann et al., 2001); this was corroborated by some ultrastructural immunocytochemical studies (Hubert et al., 2001; Paquet and Smith, 2003; Kuwajima et al., 2004). However, the evidence for such presynaptic localization remains, in our opinion, weak and requires independent confirmation by means of alternative approaches.

B. General Physiological Properties

Several different physiological responses to glutamate, including the modulation of interneuron and principal neuron excitability in numerous brain areas as well as of diverse forms of synaptic plasticity, have been linked to mGlu1 receptors. Many of these effects depend on the specific network in which mGlu1 receptors are expressed and are discussed in detail in the appropriate section. In the following sections, we provide a perspective on the role and implications of mGlu1 receptors in specific neuronal circuitries by integrating distribution and functional studies carried out for these receptors. Because of space limitations, only those systems for which a substantial body of anatomical and functional data is available will be analyzed.

1. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Olfactory System. The olfactory system is important for reproductive functions, neuroendocrine regulation, emotional responses, food selection, and recognition of conspecifics, predators, and preys (Shipley and Ennis, 1996). Odor molecules are transduced by olfactory receptor neurons located in the olfactory epithelium. These neurons then project their axons through the olfactory nerve to the olfactory bulb where they make synapses in the glomerular layer with the apical dendrites of mitral and tufted cells. The relay from the nose to the mitral and tufted neurons is regulated by local intrabulbar circuitries and by inputs from other brain areas. Mitral and tufted cells, the output neurons of the olfactory bulb, convey olfactory information to higher order olfactory structures, which include the anterior olfactory nucleus, piriform cortex, olfactory tubercle, entorhinal cortex, and some amygdaloid nuclei. From these primary olfactory cortical structures other connections are made to brain regions that integrate olfactory information with other neural functions (Shipley and Ennis, 1996).

In situ hybridization showed that neurons present in almost all brain structures involved in the olfactory circuitry express relatively high levels of mGlu1 receptors (Shigemoto et al., 1992). Mitral cells in the main and accessory olfactory bulb are among the neurons with the highest expression level of mGlu1 receptors in the brain (Shigemoto et al., 1992). Tufted cells in the external plexiform and glomerular layer also have high transcript levels for mGlu1 receptors, whereas granule cells display only weak labeling (Shigemoto et al., 1992). Of the different mGlu1 receptor splice variants, mGlu1α is most abundantly expressed by mitral and tufted cells both in terms of transcripts and protein (Martin et al., 1992; Baude et al., 1993; Hampson et al., 1994; van den Pol, 1995; Berthele et al., 1998; Ferraguti et al., 1998). Intense mGlu1α immunoreactivity is found in the glomeruli and in the external plexiform layer where the apical and lateral dendrites of mitral cells extend, respectively (Martin et al., 1992; van den Pol, 1995; Ferraguti et al., 1998; Sahara et al., 2001). Somata and dendritic arbors of tufted cells are also seen as immunolabeled (van den Pol, 1995). At the ultrastructural level, mGlu1α receptor immunoreactivity in the glomerular layer is associated with the postsynaptic junctions of apical mitral dendrites forming asymmetrical synapses with olfactory nerve terminals (van den Pol, 1995). It is noteworthy that the immunolabeling in the external plexiform layer is particularly strong in the presynaptic region of the reciprocal synapse between the excitatory mitral cell dendrite and the inhibitory granule cell dendrite (van den Pol, 1995).

Mitral and tufted neurons display, in addition to mGlu1α, abundant mRNA expression of the mGlu1γ receptor (Berthele et al., 1998); however, no immunolocalization data for this splice variant are available, because no selective immunological tools have as yet been developed. Transcripts for the mGlu1β receptor isoform

are weakly expressed in the olfactory bulb (Hampson et al., 1994), where they are present in granule cells and to a small extent in periglomerular neurons (Berthele et al., 1998). However, this evidence cannot be easily reconciled with a lack of labeling in periglomerular cells using a pan-mGlu1 probe (Shigemoto and Mizuno, 2000). Moreover, despite the apparent presence of mGlu1β mRNA in the main olfactory bulb, we failed to detect immunoreactivity for this isoform (Ferraguti et al., 1998). The use of antibodies against the N terminus of mGlu1, common to all splice variants (pan-mGlu1), confirmed the general distribution observed with specific mGlu1α antibodies (Fotuhi et al., 1993; Ferraguti et al., 1998), which suggests a distribution of the short isoforms, namely mGlu1β and/or mGlu1γ, similar to mGlu1α. In the granule cell layer, few large neurons are intensely immunolabeled for mGlu1 and mGlu1α, whereas the small granule cells do not show detectable immunoreactivity (van den Pol, 1995; Ferraguti et al., 1998). The largest of these cells might have been displaced mitral cells, whereas those with smaller somata had the appearance of short axon cells (van den Pol, 1995; Ferraguti et al., 1998).

The expression pattern of mGlu1 receptors in the olfactory bulb indicates that these receptors contribute to mitral and tufted cell responses to glutamatergic inputs from the olfactory nerve and can function as autoreceptors to sense the glutamate released from lateral dendrites of mitral cells. Studies in cultured neurons, dissociated from the main olfactory bulb, show that mGlu1 receptor activation enhances intracellular Ca^{2+} concentrations in mitral cells and interneurons (Geiling and Schild, 1996; Carlson et al., 1997) and increases the frequency of miniature EPSCs in mitral cells (Schoppa and Westbrook, 1997; Heinbockel et al., 2004). Activation of mGlu1 receptors increases the firing rate of mitral cells, producing a voltage-dependent inward current sensitive to K^+ and Ca^{2+} channel blockers (Heinbockel et al., 2004). Antagonists of mGlu1 receptors significantly reduce mitral cell spontaneous firing and olfactory nerve-evoked discharges via modulation of membrane bistability (Heinbockel et al., 2004), an intrinsic property of mitral cells that determines the responses to olfactory nerve inputs (Heyward et al., 2001). These results led Heinbockel et al. (2004) to suggest that mGlu1 receptors exert a tonic modulation of basal and sensory-evoked mitral cell discharges. Responses evoked by the activation of mGlu1 receptors in mitral cells would be facilitated by repetitive inhalations of an odor and influence the temporal firing pattern, including oscillations and synchronous activity. In line with this hypothesis, MCPG was shown to reduce rhythmic oscillations in mitral cells evoked by olfactory nerve stimulation (Schoppa and Westbrook, 2001). Activation of mGlu1 receptors in the lateral dendrites of mitral cells, presynaptic to granule cell dendrites, may produce a local depolarization through a mechanism of autoexcitation (van den Pol, 1995), which would counteract the reciprocal inhibition from granule cells. Such an effect would be specific for strongly activated mitral cells and would increase lateral inhibition, hence increasing the signal/noise ratio.

Glutamatergic deafferentation of the olfactory bulb, by intranasal irrigation of $ZnSO_4$, causes a biphasic change (strong up-regulation at 2 days and down-regulation at 16 days) in the expression of mGlu1α mRNA without affecting the transcript levels of mGlu1β (Ferraris et al., 1997). Conversely, mGlu1α receptor protein levels are found to be elevated at both 2 and 16 days after olfactory deafferentation (Casabona et al., 1998). It can be hypothesized that these two mGlu1 variants either have a different cellular distribution or undergo a different transcriptional regulation in the olfactory bulb. In addition, altered trafficking of the mGlu1α receptor protein might also account for these changes.

In the olfactory tubercle and piriform cortex, the neuropil of all layers showed immunoreactivity for pan-mGlu1, whereas no significant mGlu1α labeling is detected (Wada et al., 1998). Likewise, marked immunostaining was reported in the periamygdaloid cortex for pan-mGlu1 but not for mGlu1α (Wada et al., 1998).

Optical imaging studies have recently shown that a late component in the signal propagation of excitatory transmission from association fibers to pyramidal cells of the piriform cortex in guinea pig is mediated by postsynaptic mGlu1 receptors (Sugitani et al., 2002, 2004). These findings confirm and extend previous pharmacological data, showing that group I mGlu receptors are involved in postsynaptic transmission in pyramidal cells of the guinea pig piriform cortex (Libri et al., 1997). This late propagation component seems to be important for the maintenance of the reverberating positive feedback composed of association fibers in an active state (Sugitani et al., 2004).

2. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Hypothalamus. The hypothalamus is responsible for integrating the myriad of endocrine, autonomic, and behavioral responses that guarantee homeostasis and reproduction. Consistent with the complexity of the responses it regulates, the hypothalamus is composed of numerous and heterogeneous nuclei. In the rat hypothalamus, mGlu1 mRNA levels range from low to high, depending on the nucleus (Shigemoto et al., 1992), with most of the nuclei displaying labeled neurons. Immunolabeling for mGlu1α reveals labeling mainly in the lateral and anterior hypothalamus, preoptic area, and tuberomammillary, mammillary, suprachiasmatic, and dorsomedial nuclei (Van den Pol, 1994; Kiss et al., 1996). On the other hand, the neuroendocrine regions of the hypothalamus show weak or no mGlu1α immunoreactivity (Van den Pol, 1994; but see Kiss et al., 1996) but intense mGlu1β immunoreactivity (Mateos et al., 1998), suggesting a major role for the latter receptor isoform in neuroendocrine regulation.

From a functional standpoint, hypothalamic mGlu1 receptors have multiple implications. Increases in serum corticosterone levels have been found after intracerebroventricular injection of group I mGlu receptor agonists and of the selective mGlu1 receptor antagonist, LY367285 (Johnson et al., 2001). These ambiguous results have been explained by illustrating a model in which neurons of the hypothalamic paraventricular nucleus that secrete corticotropin-releasing hormone are tonically inhibited by GABAergic neurons, which, in turn, are tonically stimulated by glutamate acting at both ionotropic and mGlu1 receptors. On the other hand, corticotropin-releasing hormone-secreting neurons also express mGlu1 receptors and can therefore be directly stimulated by group I mGlu receptor agonists (Johnson et al., 2001). In the arcuate nucleus, all neurons containing growth-hormone releasing hormone and β-endorphin express mGlu1α receptors (Kiss et al., 1997). However, the effect of mGlu1 receptor ligands on growth hormone secretion has not been investigated as yet. Recent evidence suggests a role for hypothalamic mGlu1α receptors in modulating female sexual receptivity. In rats, estradiol activation induces a μ-opioid receptor internalization in the medial preoptic nucleus, leading to full expression of sexual receptivity. Within this system, the membrane-associated estrogen receptor-α and the mGlu1α receptor directly interact in mediating the action of estradiol on μ-opioid receptors and, therefore, on female sexual behavior (Dewing et al., 2007).

Given the intense expression of mGlu1 receptors in the hypothalamic suprachiasmatic nucleus and the importance of glutamate as a transmitter inducing phase changes in circadian rhythms (Mick et al., 1995; Ebling, 1996), mGlu1 receptors may play an important role in long-term changes in circadian clock function modulating the activity of suprachiasmatic neurons receiving retinal glutamatergic inputs. Indeed, translation of clock rhythmicity into neural firing in the suprachiasmatic nucleus was shown to require mGlu1-PLCβ4 signaling (Park et al., 2003).

A recent report highlights the role of mGlu1 and mGlu5 receptors in modulating the activity of hypothalamic neurons containing melanin-concentrating hormone, which are involved in the regulation of food intake and energy metabolism. In hypothalamic slices, the combined activation of mGlu1 and mGlu5 receptors by 3,5-DHPG increases the activity of melanin-concentrating hormone neurons by multiple pre- and postsynaptic mechanisms (Huang and van den Pol, 2007), which involve long-lasting enhancement of NMDA responses and the activation of the Na^+/Ca^{2+} exchanger. Therefore, mGlu1 (or mGlu5) receptor antagonists may have a potential role in the treatment of obesity.

3. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Thalamus. The thalamus plays an important role in the processing of sensory information to the cerebral cortex. In particular, the ventrobasal complex is critically involved in both nociception and pain.

Thalamic relay nuclei express high levels of mGlu1 receptor mRNA and protein (Martin et al., 1992; Shigemoto et al., 1992; Petralia et al., 1997), mostly represented by mGlu1α or mGlu1γ receptor variants (Berthele et al., 1998). mGlu1α receptors seem to be localized predominantly postsynaptically to corticothalamic fibers (Godwin et al., 1996; Vidnyanszky et al., 1996). Activation of mGlu1 receptors in thalamic relay nuclei causes a slow depolarizing response associated with an increase in membrane resistance, probably mediated by potassium channels (McCormick and von Krosigk, 1992; Turner and Salt, 2000) and may initiate a slow oscillation of thalamic neurons (Hughes et al., 2002). The generation of such oscillations depends on cortical activity and would regulate sleep patterns in vivo (Hughes et al., 2002).

Thalamic responses to sensory stimuli are dependent on mGlu1 receptor activation as mGlu1 antagonists reduce these responses (Salt and Turner, 1998; Rivadulla et al., 2002). In the ventrobasal complex, stimulation of mGlu1 receptors potentiate both AMPA and NMDA responses (Salt and Binns, 2000); hence, when the activation of mGlu1 receptors in the perisynaptic area of ventrobasal neurons is achieved by sustained activity of corticothalamic inputs, it would be able to exert a profound influence on ionotropic receptor-mediated responses (Salt, 2002). Intrathalamic injection of group I agonists enhances inflammatory pain behavior, whereas mGlu1 antagonists or gene targeting deletion of its primary intracellular effector PLCβ4 attenuates nociceptive behavior in the second phase of inflammatory pain induced by formalin injection (Miyata et al., 2003). These findings, therefore, indicate an important role for mGlu1 receptors for inflammatory pain processing at the supraspinal level.

4. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Basal Ganglia. Behavioral studies combined with functional neuroanatomical mapping, such as 2-deoxyglucose uptake or cFos immunohistochemistry, have shown that activation of group I mGlus in the basal ganglia induces a selective activation of the "indirect" pathway and thereby increases overall activity at the output nuclei (Kaatz and Albin, 1995; Kearney et al., 1997).

In the basal ganglia, mGlu1 receptors are expressed in all four principal nuclei, namely the caudate/putamen or striatum, globus pallidus, subthalamic nucleus, and substantia nigra (Shigemoto et al., 1992; Testa et al., 1994). These nuclei are highly interconnected and form a circuit that integrates motor signals originating from the cerebral cortex with postural inputs originating from the periphery. The neostriatum is the major input station of the basal ganglia and receives inter alia glutamatergic inputs from the cerebral cortex and thalamus and dopaminergic inputs from the pars compacta of the

substantia nigra. There are at least four major types of neurons in the caudate/putamen: medium spiny GABAergic projection neurons, fast-spiking parvalbumin-containing GABAergic interneurons, burst spiking NADPH-diaphorase/somatostatin-positive GABAergic interneurons, and large aspiny cholinergic interneurons. Medium spiny neurons can be subdivided into two main subclasses based on their projections and expression of dopamine receptors or neuropeptides: 1) neurons expressing D2 dopamine receptors and enkephalin, which project to the globus pallidus; and 2) neurons expressing D1 dopamine receptors and substance P, which project to the internal globus pallidus and pars reticulata of the substantia nigra (reviewed in Conn et al., 2005).

Low to moderate expression of mGlu1 mRNA is found in almost all neurons (Shigemoto et al., 1992; Testa et al., 1994). This expression is confirmed by detection of the mGlu1-βGal fusion protein in mGlu1-expressing cells of mice with gene-targeted mutation of the mGlu1 receptor (Conquet et al., 1994; Ferraguti et al., 1998). In situ hybridization with oligonucleotide probes specific for the different mGlu1 isoforms showed that striatal neurons express mainly the transcripts for mGlu1β and mGlu1γ receptor variants (Berthele et al., 1998; Kosinski et al., 1998). Neurons containing substance P express significantly higher levels of mGlu1 mRNA (detected with a pan-mGlu1 probe) than those of other striatal neurons (Kerner et al., 1997). Immunohistochemical analysis with antibodies raised against the N-terminal domain of mGlu1 receptors shows predominant labeling not only of the neuropil but also of scattered neuronal somata that may represent striatal interneurons (Fotuhi et al., 1994; Ferraguti et al., 1998; Kosinski et al., 1998).

At the ultrastructural level, only mGlu1α immunolabeling has been analyzed in detail. Immunoreactivity was found primarily in striatal postsynaptic elements, such as somata, dendrites, and spines of both projection cells and interneurons and also in axon terminals (Paquet and Smith, 2003). Most of mGlu1α labeling is perisynaptic to asymmetric corticostriatal and thalamostriatal axospinous synapses, although labeling is also observed in the main body of some axodendritic symmetric synapses (Paquet and Smith, 2003). Immunometal particles corresponding to mGlu1α receptors were additionally reported at extrasynaptic locations either on the plasma membrane or associated with intracellular organelles, such as the endoplasmic reticulum, Golgi apparatus, and spine apparatus (Paquet and Smith, 2003). Axon terminals labeled for mGlu1α were reported to form mostly asymmetric synapses and to be present in approximately 50% of thalamostriatal terminals, although a small population of cortical and nigral boutons also seemed to possess presynaptic mGlu1α receptors (Paquet and Smith, 2003). A possible caveat for this presynaptic labeling is, however, the location of the immunometal particles, always depicted inside the terminals instead of being associated with the plasma membrane of the bouton, as would be expected for an integral membrane receptor protein. Glial processes immunolabeled for mGlu1α receptor were also reported (Paquet and Smith, 2003).

Several studies have shown that group I mGlu receptors influence the efficacy of synaptic transmission in the striatum (for review, see Gubellini et al., 2004). In particular, mGlu1 receptors are involved in the induction of LTD at corticostriatal synapses (Gubellini et al., 2001; Sung et al., 2001) through a mechanism that involves the regulation of intracellular Ca^{2+} levels (Calabresi et al., 1994) and the activation of PLC, IP_3/DAG, and VSCCs (Fagni et al., 2000). At the same synapses, mGlu1 cooperates with mGlu5 for the induction but not for the maintenance of LTP (Gubellini et al., 2003). Long-term changes in synaptic efficacy (such as LTP and LTD) in the striatum underlie motor learning and "habit memory," and the flexibility of these changes allows motor habits to cope with environmental changes. Disruption of these mechanisms contributes to the onset of involuntary movements in Huntington's disease and other disorders (Conn et al., 2005).

Among striatal interneurons, virtually all parvalbumin-expressing cells were reported to coexpress mGlu1α (Kerner et al., 1997; Tallaksen-Greene et al., 1998). Likewise, a high percentage of the large aspiny cholinergic interneurons contained mGlu1α immunoreactivity (Kerner et al., 1997; Tallaksen-Greene et al., 1998), although in a different study in which single-cell reverse transcriptase-polymerase chain reaction was used, only ~25% were found to be positive (Bell et al., 2002). Approximately half of the somatostatin-positive interneurons also display mGlu1α receptor immunoreactivity (Tallaksen-Greene et al., 1998; Nakamura et al., 2004). Data on the coexpression of mGlu5 with mGlu1 receptors in striatal interneurons are contradictory (Testa et al., 1995; Kerner et al., 1997; Tallaksen-Greene et al., 1998; Bell et al., 2002).

Several studies have investigated the function of group I mGlus in striatal cholinergic interneurons. Application of 3,5-DHPG produces a reversible membrane depolarization mediated by K^+ conductances and enhances the release of acetylcholine (Takeshita et al., 1996; Calabresi et al., 1999; Pisani et al., 2000; Marti et al., 2001; Pisani et al., 2001). Striatal cholinergic interneurons fire tonically at a frequency of 2 to 10 Hz in response to glutamatergic inputs, which arise from the nucleus parafascicularis of the thalamus and to a lesser extent from the cortex. These interneurons give rise to the main cholinergic innervation of the striatum and exert powerful modulatory control over projection neurons. The increased excitability of the cholinergic interneurons may, therefore, contribute to the overall effect of mGlu1 receptors in the basal ganglia motor circuits (see section VII.B).

Activation of group I mGlu receptors has also been shown to mediate presynaptic effects on both GABA and dopamine release in the striatum (Verma and Moghaddam, 1998; Bruton et al., 1999; Battaglia et al., 2001; Zhang and Sulzer, 2003). Zhang and Sulzer (2003) have shown that activation of mGlu1 receptors by glutamate spilled over from corticostriatal synapses after high-frequency stimulation inhibits DA release from nigrostriatal terminals (Zhang and Sulzer, 2003). This regulation of neurotransmitter release reproposes the controversial issue of presynaptic mGlu1 receptors in striatum. In our opinion, there is no compelling evidence for a presynaptic localization of mGlu1α receptors despite several reports. However, the fact that the regulation of neurotransmitter release is mediated by one of the short mGlu1 isoforms (e.g., mGlu1β or -1γ) targeted to presynaptic terminals cannot be excluded.

Projection GABAergic neurons of the neostriatum send signals to the output nuclei of the basal ganglia (i.e., the internal globus pallidus and the pars reticulata of the substantia nigra) through "direct" and "indirect" pathways. The direct pathway exerts a powerful inhibition on the output nuclei and is activated by striatal D1 receptors. The indirect pathway includes the external globus pallidus and the subthalamic nucleus and stimulates the output nuclei. Activation of D2 receptors by nigrostriatal dopamine inhibits the indirect pathway.

The external globus pallidus is composed of GABAergic neurons that receive a dense inhibitory input from the striatum and project to the subthalamic nucleus. In the rodent globus pallidus, approximately 50% of neurons express moderate to high levels of mGlu1 receptor mRNA (Testa et al., 1994). These neurons express primarily the mGlu1α isoform (Berthele et al., 1998; Testa et al., 1998) and have been identified on the basis of functional and morphological criteria as type II neurons (Poisik et al., 2003). Dendrites of pallidal neurons are innervated predominantly by striatal GABAergic terminals, forming symmetric synapses intermingled with a few glutamatergic boutons arising from the subthalamic nucleus. At the electron microscopic level, localization of mGlu1α receptors in both rat and monkey is detected exclusively in postsynaptic elements (Hanson and Smith, 1999). The subsynaptic distribution of mGlu1α receptors reveals a predominant perisynaptic location, which is associated with asymmetric as well as symmetric synapses formed by striatal terminals (Hanson and Smith, 1999). However, in the symmetric synapses, immunometal particles visualizing mGlu1α receptors are also found in the main body of the postsynaptic specialization (Hanson and Smith, 1999). The presence of mGlu1α in symmetric GABAergic synapses raises the question of the source of glutamate. A widely accepted view is that mGlu1 receptors at these synapses are activated by glutamate spilled over from the cleft of neighboring glutamatergic synapses. However, given the relative low number of glutamatergic synapses present on pallidal dendrites, other possibilities, which include nonsynaptic release of glutamate from astrocytes (Araque et al., 1999) or dendrites (Duguid et al., 2007; Shin et al., 2008) and corelease of GABA and glutamate from the same terminal, should be considered.

Activation of group I mGlu receptors in pallidal neurons produces inhibition of N- and P-type Ca^{2+} conductances (Stefani et al., 1998) and a direct membrane depolarization, which is selectively mediated by the activation of a nonspecific cationic conductance (Poisik et al., 2003). Pharmacological blockade of mGlu5 receptors amplifies the depolarization mediated by mGlu1 receptors by limiting a cross-desensitization between mGlu1 and mGlu5 receptors (Poisik et al., 2003).

The subthalamic nucleus receives major afferents from the external globus pallidus, the motor cortex, and the pedunculopontine nucleus and sends glutamatergic projections to the globus pallidus and substantia nigra. Hyperactivity of glutamatergic neurons of the subthalamic nucleus produces bradykinesia, one of the hallmark features of Parkinson's disease. Moderate levels of mGlu1 mRNA (Testa et al., 1998) and protein (Fotuhi et al., 1994) have been observed in the rat subthalamic nucleus. The major mGlu1 isoform in this nucleus seems to be mGlu1α (Martin et al., 1992; Testa et al., 1998). At the electron microscopic level mGlu1α immunoreactivity in the rat and monkey subthalamic nucleus is mainly associated with dendritic processes, although immunolabeled axons and glial processes are also reported (Awad et al., 2000; Wang et al., 2000b; Kuwajima et al., 2004). Kuwajima et al. (2004) reported that immunogold labeling for mGlu1α receptor in the monkey subthalamic nucleus is two-thirds intracellular and one-third apposed to the plasma membrane. The membrane-bound immunoparticles are mostly associated with postsynaptic specializations in which they are found perisynaptically at both symmetric and asymmetric synapses (Kuwajima et al., 2004). Similar to that in the striatum and globus pallidus, the localization of mGlu1α receptors in symmetric synapses of subthalamic neurons renews the problem of the source of glutamate at these GABAergic synapses. In this respect, it is noteworthy that terminals from the external globus pallidus contain significantly more immunoreactivity for glutamate than do striatopallidal terminals (Shink and Smith, 1995). Although there is no direct evidence for a corelease of glutamate and GABA from pallidal terminals in the subthalamic nucleus, this remains a plausible possibility.

The selective group I mGlu receptor agonist 3,5-DHPG induces a robust depolarization of subthalamic neurons that depends on the inhibition of a leak K^+ current and is mediated by mGlu5 receptors (Awad et al., 2000). On the other hand, activation of mGlu1 receptors in subthalamic neurons inhibits glutamatergic transmission through a presynaptic mechanism (Awad-Granko and Conn, 2001). Although there is evidence for presynaptic mGlu1α receptor labeling in the subtha-

lamic nucleus (Awad et al., 2000; Kuwajima et al., 2004), inhibition of glutamate release may follow the activation of postsynaptic mGlu1 receptors with an ensuing formation of endocannabinoids, which, acting as retrograde messengers, would activate presynaptic type 1 cannabinoid (CB1) receptors (Maejima et al., 2001; Varma et al., 2001).

The substantia nigra is composed of two structurally and functionally different subdivisions, the pars reticulata (SNr) and pars compacta (SNc), and gives rise to the major output projections from the basal ganglia. Expression of mGlu1 mRNA is high in both SNr and SNc neurons (Shigemoto et al., 1992; Testa et al., 1994; Kosinski et al., 1998) and consists mainly of the mGlu1α and/or mGlu1γ isoforms (Berthele et al., 1998; Kosinski et al., 1998). In the SNc, expression of mGlu1 receptors largely predominates over the expression of mGlu5 receptors (Shigemoto and Mizuno, 2000). In situ hybridization analysis suggests that in the SNc the predominant form is mGlu1γ (Berthele et al., 1998; Kosinski et al., 1998), although this suggestion remains to be confirmed at the protein level.

Neurons of the SNr receive glutamatergic projections from the subthalamic nucleus as well as inhibitory GABAergic projections from the globus pallidus and striatum. These neurons possess high mGlu1 and mGlu1α immunoreactivity mainly in their dendrites (Martin et al., 1992; Fotuhi et al., 1994; Kosinski et al., 1998; Yung, 1998). In the SNc, DAergic neurons are intensely immunoreactive for mGlu1 in their somatodendritic domain, but they do not display immunolabeling for mGlu1α (Fotuhi et al., 1994; Kosinski et al., 1998; Testa et al., 1998; Yung, 1998). Conversely, in monkeys, DAergic neurons in the ventral component of SNc express mGlu1α (Hubert et al., 2001; Kaneda et al., 2003). The lack of mGlu1α immunostaining in rat DAergic neurons of the SNc is quite puzzling, given the relatively high abundance of mGlu1α mRNA (Berthele et al., 1998; Kosinski et al., 1998). There are at present no explanations for these contrasting results.

The subsynaptic distribution of mGlu1α receptors in both the SNr and SNc seems to be highly similar to that of the other components of the basal ganglia with a predominantly perisynaptic location in asymmetric synapses and intrasynaptic location in symmetric synapses established by GABAergic striatal terminals (Hubert et al., 2001; Marino et al., 2001). Activation of mGlu1 receptors in SNr GABAergic neurons produces a direct robust postsynaptic depolarization accompanied by a decrease in a leak membrane K^+ conductance sensitive to tetraethylammonium (Marino et al., 2001). Because the subthalamic nucleus gives rise to the main glutamatergic input to SNr GABAergic neurons, it is likely that the primary source of glutamate acting on mGlu1 is released from subthalamic afferents. In addition to well established postsynaptic localization of mGlu1 receptors in neurons of the SNr, substantial anatomical and functional evidence suggests the presence of mGlu1α within axon terminals (Hubert et al., 2001; Marino et al., 2001; Wittmann et al., 2001). According to Hubert et al. (2001), mGlu1α-containing presynaptic terminals are found exclusively in symmetric synapses, whereas Wittmann et al. (2001) described mGlu1α immunoreactivity in small unmyelinated axon and terminals forming asymmetric synapses. Moreover, activation of mGlu1 receptors in SNr GABAergic neurons is shown to reduce either EPSCs (Wittmann et al., 2001), or, in combination with mGlu5, inhibitory postsynaptic currents (IPSCs) (Marino et al., 2001) through presynaptic mechanisms. Once again, it is possible that some functional effects are mediated by postsynaptic mGlu1 receptors through the formation of endocannabinoids (see section VI.B.5).

In DAergic neurons of the SNc, glutamate induces biphasic responses characterized by an initial hyperpolarization followed by a slow depolarization, which are mimicked by group I mGlu agonists (Mercuri et al., 1993; Meltzer et al., 1997; Shen and Johnson, 1997; Fiorillo and Williams, 1998; Guatteo et al., 1999; Katayama et al., 2003). The glutamate-induced hyperpolarization and depolarization were accompanied by an inhibition and a robust increase of spontaneous firing, respectively (Katayama et al., 2003). The depolarization seemed to require a higher frequency of stimulation than the hyperpolarization (Fiorillo and Williams, 1998). The hyperpolarization is, at least partially, mediated by mGlu1 and dependent on a Ca^{2+}-activated K^+ conductance that Fiorillo and Williams (1998) reported as being apamin-sensitive, whereas Katayama et al. (2003) found it insensitive to both apamin and iberiotoxin (Katayama et al., 2003). The hyperpolarization generated by the activation of mGlu1 receptors induces a transient pause in the spontaneous firing of DA neurons (Morikawa et al., 2003). Serotonin depresses mGlu1-mediated IPSCs through the stimulation of 5-HT_{2A} and 5-HT_4 receptors, which decreases the intracellular Ca^{2+} mobilization triggered by mGlu1 receptors (Paolucci et al., 2003). The depression of mGlu1-mediated IPSCs by serotonin would exert a facilitatory control on the activity of DA neurons in response to short, high-frequency trains of stimulation of glutamatergic afferents. The slow depolarization mediated by mGlu1 receptors in DAergic neurons is independent from Ca^{2+} mobilization and requires tyrosine phosphorylation (Guatteo et al., 1999; Tozzi et al., 2001) and activation of a TRP channel (Tozzi et al., 2003).

Given the wide distribution and multiple functions of mGlu1 receptors in the basal ganglia, it is difficult to predict the net effect of mGlu1 receptor ligands on the basal ganglia motor circuit. It has been suggested that mGlu1 receptor antagonists may have antiparkinsonian effects, particularly when combined with mGlu5 receptor antagonists (Conn et al., 2005).

5. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Hippocampus. In the hippocampal for-

mation, mGlu1 receptors have been implicated in a variety of physiological responses to glutamate, which include modulation of synaptic transmission and plasticity as well as neuronal excitability and synchronization (for review, see Anwyl, 1999; Bortolotto and Collingridge, 1999). However, for some of these functions the precise role of mGlu1 receptors has been a matter of intense controversial debate. For instance, the inhibition of LTP in the CA1 Schaffer collateral-commissural pathway by the antagonist MCPG (Bashir et al., 1993) has been debated for years with several authors confirming this finding (Bortolotto et al., 1994; Brown et al., 1994; Izumi and Zorumski, 1994; Richter-Levin et al., 1994; Little et al., 1995) and others failing to confirm it (Chinestra et al., 1993; Izumi and Zorumski, 1994; Manzoni et al., 1994; Selig et al., 1995; Thomas and O'Dell, 1995; Martin and Morris, 1997). A clue to resolving this controversy was that the activation of group I mGlu receptors before LTP could set an input-specific "molecular switch" (Bortolotto et al., 1994), which would negate the need for further activation of mGlu receptors for the induction of LTP (Bortolotto and Collingridge, 1999). Once again, several groups failed to find experimental evidence for this molecular switch hypothesis (Selig et al., 1995; Thomas and O'Dell, 1995; Martin and Morris, 1997). Later, the effect of MCPG on LTP was ascribed to a novel unidentified mGlu receptor (Bortolotto and Collingridge, 1999). Similar discrepancies were also observed for the blocking of LTP induction by other phenylglycine antagonists (Manahan-Vaughan and Reymann, 1997; Breakwell et al., 1998; Fitzjohn et al., 1998; Manahan-Vaughan et al., 1998; McCaffery et al., 1998). LTP induction in CA1 was also controversial in mice lacking mGlu1, as several studies found it to be unaffected (Conquet et al., 1994; McCaffery et al., 1998), whereas a separate study using a different mGlu1 KO strain reported a 50% reduction in LTP (Aiba et al., 1994a). This marked reduction of LTP in CA1, however, has been difficult to reconcile with the available anatomical data on mGlu1 receptors, as no specific labeling was ever detected at Schaffer collateral-commissural excitatory synapses.

The role of mGlu1 in the induction of LTP at mossy fiber synapses, a distinct form of plasticity fully independent of NMDA receptors, is also characterized by contradictory views. MCPG was shown to block the induction of mossy fiber LTP but not of post-tetanic potentiation (Bashir et al., 1993; Fitzjohn et al., 1998; but see Hsia et al., 1995). A small deficit in mossy fiber LTP was also reported in mice lacking mGlu1 (Conquet et al., 1994), but this was not confirmed in a subsequent study (Hsia et al., 1995).

There is also compelling evidence that mGlu1 is involved in hippocampal LTD, although again this issue has not been without controversy. Two forms of LTD seem to be present in the hippocampus, one that is NMDA-dependent and mGlu-independent and one that can be blocked by group I mGlu receptor antagonists and is NMDA-independent (Oliet et al., 1997). Neyman and Manahan-Vaughan (2008) have shown in rat hippocampal slices that antagonism of mGlu1 receptors impairs both the induction and late phases of LTD in CA1. However, these effects occurred only when receptor antagonism took place before stimulation.

The long-lasting disputes concerning the role of mGlu1 receptor in synaptic plasticity in hippocampus may have been biased by the limited selectivity of the compounds used in these studies or the specific experimental protocols (Wilsch et al., 1998; Neyman and Manahan-Vaughan, 2008). The recent availability of subtype-specific and potent drugs may soon clarify these controversial issues.

In the hippocampus, transcripts for mGlu1 receptors are prominently expressed in dentate granule cells, CA2–CA3 pyramidal neurons, and CA1–CA3 interneurons of stratum oriens/alveus (Shigemoto et al., 1992). In addition, moderate to weak labeling is found in scattered interneurons in all laminae of CA1–CA3 and in CA1 pyramidal cells (Shigemoto et al., 1992). A clear differential distribution of the mRNA for mGlu1 receptor splice variants occurs in the hippocampus (Berthele et al., 1998) with mGlu1α transcripts that are restricted to interneurons, whereas mGlu1β and mGlu1γ receptors are expressed in both interneurons and principal cells, in particular of the CA3 region and dentate gyrus (Berthele et al., 1998). Weak mRNA expression of both mGlu1β and mGlu1γ receptors is also detected in CA1 pyramidal cells (Berthele et al., 1998). Immunolabeling obtained with pan-mGlu1- or receptor splice variant-specific antibodies is in good agreement with in situ hybridization data, suggesting a largely postsynaptic localization of the receptors (Martin et al., 1992; Baude et al., 1993; Shigemoto et al., 1997; Ferraguti et al., 1998). Also at the protein level, mGlu1α receptors are only expressed by nonprincipal cells (Ferraguti et al., 2004), whereas mGlu1β receptors are enriched in both pyramidal cells and interneurons of the CA3 area but are undetectable in the CA1 area (Ferraguti et al., 1998).

Anatomical and physiological data have indicated the presence of mGlu1 in several distinct classes of hippocampal interneurons. In the hippocampus proper, the mGlu1α receptor is particularly enriched in somatostatin-containing interneurons of the CA1 stratum oriens-alveus (Baude et al., 1993; Hampson et al., 1994; Kerner et al., 1997; Yanovsky et al., 1997; Ferraguti et al., 2004). Scattered interneurons immunopositive for mGlu1α can also be observed in all strata of both CA1 and CA3, as well as in the hilus (Martin et al., 1992; Baude et al., 1993; Lujan et al., 1996; Shigemoto et al., 1997). At least two populations of somatostatin-immunopositive interneurons, namely oriens-lacunosum moleculare (O-LM) and oriens-bistratified (O-Bi) cells, which have a distinct laminar axonal pattern (McBain et al., 1994; Losonczy et al., 2002) are present in the CA1

hippocampal region. Interneurons intensely labeled for mGlu1α belong primarily to the O-LM interneuron class (Ferraguti et al., 2004), which selectively innervates the most distal part of the pyramidal cell dendritic tree in conjunction with entorhinal and thalamic afferents (Baude et al., 1993; McBain et al., 1994). A subpopulation of O-Bi interneurons also expresses mGlu1α receptors, often in combination with the calcium-binding protein calbindin (van Hooft et al., 2000; Ferraguti et al., 2004). Four additional mGlu1α-immunopositive types of hippocampal interneuron have been identified, which project to distinct laminae and cell types; these include the cholecystokinin-positive Schaffer collateral-associated cells and the interneuron-selective (IS) interneurons (Ferraguti et al., 2004; Boscia et al., 2008). This latter class of interneurons selectively targets the soma and/or dendrites of other interneurons and is composed of three distinct groups differing in their connectivity and expression of the vasoactive intestinal polypeptide and/or calretinin (Acsády et al., 1996). All three reported classes of IS interneurons express mGlu1α (Ferraguti et al., 2004).

At present, little is known about the differences in the glutamatergic activation of specific types of hippocampal interneuron and, in particular, which physiologically relevant conditions produce activation of mGlu1α-positive neurons. Several types of interneuron are differentially affected by the in vitro activation of group I mGlu receptors (McBain et al., 1994; Woodhall et al., 1999; van Hooft et al., 2000), which may thus influence hippocampal function in multiple interneuron-specific ways. Because of its peri- and extrasynaptic location (Baude et al., 1993; Nusser et al., 1994; Lujan et al., 1996), mGlu1α is expected to be strongly activated during population bursts of pyramidal cells, when glutamate increases in the extracellular space. The most prominent population burst occurs during sharp waves, a phenomenon that represents synchronization across the hippocampal-cortical loop (Csicsvari et al., 2000). Hippocampal interneurons also participate in both γ and θ frequency rhythmic activity (Cobb et al., 1995; Buzsáki, 2002). Such rhythmic activity may arise through several different mechanisms, each probably involving distinct subtypes of interneurons. Agonists of group I mGlu receptors can evoke slow oscillatory inward currents and rises in intracellular Ca^{2+} in subsets of CA1 interneurons (McBain et al., 1994; Carmant et al., 1997; Woodhall et al., 1999; van Hooft et al., 2000). The mGlu-induced inward currents are large in O-LM cells and small in calbindin-positive interneurons as well as in interneurons near stratum lacunosum-moleculare (McBain et al., 1994; Woodhall et al., 1999; van Hooft et al., 2000). In O-LM cells, dendritic Ca^{2+} signals seem to be highly heterogeneous and dependent on specific microdomains of a given cell, suggesting differential involvement of synaptic and extrasynaptic mGlu1 receptors (Topolnik et al., 2005). EPSCs mediated by mGlu1 in oriens-alveus interneurons may result from activation of nonselective cation channels (Topolnik et al., 2005), although the involvement of VSCCs has also been proposed (Huang et al., 2004). Rhythmic action potential firing is found only in O-LM cells and in a fraction of calbindin-immunopositive interneurons (van Hooft et al., 2000; but see McBain et al., 1994), and it seems to be mediated almost exclusively by mGlu1 receptors (van Hooft et al., 2000). Thus, it is possible that mGlu1α receptors promote oscillatory activity also at physiologically relevant frequencies in vivo.

Synchronization may enhance cooperativity in neuronal networks and may generate synaptic potentiation or depression (Singer, 1993). Perez et al. (2001) elicited LTP by θ burst stimulation associated with postsynaptic depolarization in oriens-alveus interneurons but not in interneurons in strata radiatum or lacunosum-moleculare. Evoking LTP in oriens-alveus interneurons, in those with axonal projections to both stratum lacunosum-moleculare (O-LM cells) and strata oriens and radiatum (O-Bi cells), requires the activation of mGlu1 and is NMDA receptor-independent (Perez et al., 2001; Lapointe et al., 2004). The effectiveness of θ burst stimulation suggests that during hippocampal θ activity the inputs from rhythmically active pyramidal cells, such as place cells, are potentiated and the activated O-LM interneurons may sustain rhythmic hyperpolarization of the distal pyramidal dendrites assisting in the maintenance of the efficacy of the entorhinal input (Losonczy et al., 2002). Furthermore, mGlu1 receptors on oriens alveus interneurons produce a long-lasting increase in polysynaptic IPSC amplitude in pyramidal cells, suggesting that mGlu1-dependent LTP at excitatory synapses on these interneurons may regulate pyramidal cell inhibition (Lapointe et al., 2004).

The GABAergic innervation provided by IS cells to other hippocampal interneurons gives rise to a complex interaction among GABAergic neurons. Group I mGlu agonists are effective on some interneurons in the strata radiatum and lacunosum-moleculare, probably by means of mGlu1 receptors (Ouardouz and Lacaille, 1995; Woodhall et al., 1999; Perez et al., 2001). Although IS interneurons express a much lower concentration of mGlu1α than O-LM cells, their highly specific relationship to other interneurons could amplify the effect of mGlu1 receptor activation as each IS GABAergic neuron innervates thousands of pyramidal cells.

It is noteworthy that CA1 pyramidal neurons show a variety of mGlu1 receptor-mediated responses such as depolarization, an increase in the frequency of spontaneous IPSPs, and a depression of the slow hyperpolarization (Mannaioni et al., 2001; Ireland and Abraham, 2002; Ireland et al., 2004; Rae and Irving, 2004), despite the fact that no immunohistochemical study has revealed expression of mGlu1 receptors in these cells (Lujan et al., 1996; Shigemoto et al., 1997; Ferraguti et al., 1998). However, it should be remembered that accumu-

lation of the mGlu1-βGal fusion protein in the somata of CA1 pyramidal neurons was detected in mGlu1 KO mice, suggesting the expression of at least one receptor variant by these cells (Ferraguti et al., 1998). A possible explanation that could settle the discrepancies between functional and anatomical studies is the formation of heterodimers between a short form of mGlu1 receptors (perhaps mGlu1γ) with either mGlu5 or other GPCRs. The generation in CA1 neurons of enhanced Ca^{2+} signals and depolarization by mGlu1 stimulation may represent a means of coincident detection that could play a role in synaptic plasticity.

In addition to the reported postsynaptic effects in both interneurons and pyramidal cells, mGlu1 receptors influence presynaptic functions, producing a reversible suppression of both excitatory (termed depolarization-induced suppression of excitation) and inhibitory (depolarization-induced suppression of inhibition) synaptic transmission. For years, this type of synaptic modulation could not be reconciled with the restricted localization of mGlu1 receptors to the postsynaptic membrane. It is now well established that the presynaptic inhibition mediated by mGlu1 involves retrograde signaling from the postsynaptic membrane. Upon activation of mGlu1 receptors an endogenous endocannabinoid, 2-arachidonoyl glycerol is produced from diacylglycerol by diacylglycerol lipase and released in the extracellular space from where it reaches CB1 receptors, which in turn cause presynaptic inhibition of transmitter release (Maejima et al., 2001; Varma et al., 2001). This synaptic modulation mediated by mGlu1 receptors through a retrograde messenger is also expected to associate with presynaptic regulation of Ca^{2+} channels mediated by presynaptic group III mGlu receptors (Millán et al., 2002).

In the perforant path, LTP induction possesses the same basic properties as those at Schaffer collateral fibers; therefore, the role(s) of mGlu1 in synaptic plasticity should be substantially similar. In slices of the dentate gyrus from mGlu1 receptor KO mice, LTP is unaltered in both the medial and lateral perforant paths (Conquet et al., 1994); conversely, a significant reduction is observed in vivo (Bordi, 1996). Likewise, the use of mGlu1 antagonists in vivo dose dependently impairs LTP expression, but not LTP induction (Riedel and Reymann, 1993; Naie and Manahan-Vaughan, 2005). The reduction of LTP in the perforant path of anesthetized mGlu1 KO mice (Bordi, 1996) is explained as being dependent on a decreased level of feedback inhibition operated by interneurons (Bordi et al., 1997; but see Naie and Manahan-Vaughan, 2005), a view that could also explain the negative results observed in vitro. In fact, the inhibitory circuits involving mGlu1 in vivo are probably lost in the slice preparation.

Several studies have established the involvement of mGlu1 receptors in spatial and associative learning (Aiba et al., 1994a; Conquet et al., 1994; Nielsen et al., 1997; Steckler et al., 2005; Gravius et al., 2006). A critical role of mGlu1 receptors has been demonstrated for the acquisition of hippocampally dependent trace conditioning and for the enhancement of synaptic strength in hippocampal circuits across conditioning sessions (Gil-Sanz et al., 2008). These findings strongly support a definitive role for mGlu1 receptors in activity-dependent synaptic activity and plasticity underlying associative learning (Gil-Sanz et al., 2008). Nevertheless, definitive elucidation of how mGlu1 receptors contribute to the neural mechanisms of associative learning is still missing. However, these effects of mGlu1 receptors may tentatively be ascribed to a modulation of GABAergic transmission involving hippocampal interneurons (Speed and Dobrunz, 2008).

6. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Cerebellum. In the cerebellar cortex, PCs abundantly express mGlu1 receptors in their dendritic arbors, such that immunoreactivity in the molecular layer is much stronger than that in any other brain area (Fig. 4) (Martin et al., 1992; Baude et al., 1993; Fotuhi et al., 1993). Besides PCs, almost all basket and stellate interneurons in the molecular layer were found to express mGlu1 receptor mRNA (Shigemoto et al., 1992) and to be immunoreactive for mGlu1α (Baude et al., 1993; Gorcs et al., 1993; Grandes et al., 1994). Gran-

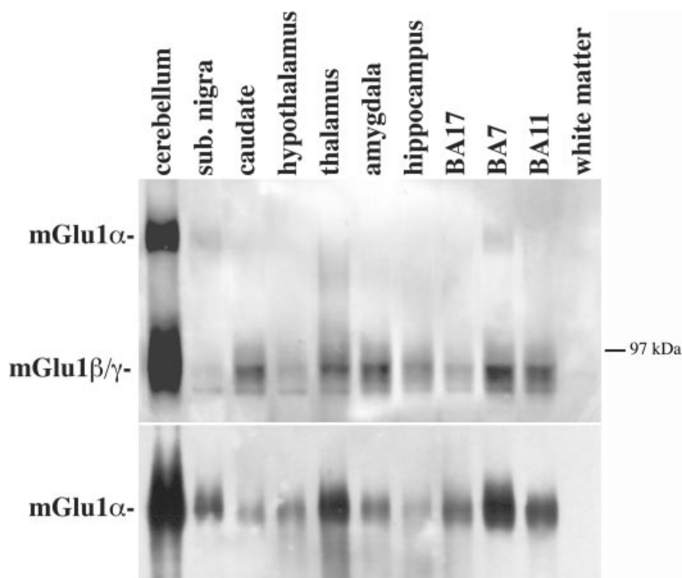


FIG. 4. Expression of mGlu1 receptors in human brain. Top, expression of mGlu1 receptors in several human brain areas is analyzed by using a polyclonal antibody directed to the N-terminal domain of mGlu1 receptors, common to all splice variants (Ferraguti et al., 1998). Post mortem brain membrane extracts (40 μg) obtained from a subject with no neurological or psychiatric illnesses were subjected to SDS-polyacrylamide gel electrophoresis; proteins were then transferred onto a polyvinylidene difluoride membrane. The upper band corresponds to mGlu1α receptors and the lower band to the shorter mGlu1β and/or mGlu1γ receptors. The highest expression level of mGlu1 receptors is observed in membranes obtained from the cerebellum, followed by the ventrobasal thalamus and neocortical areas. Bottom, because of its better efficacy, a rabbit polyclonal antibody raised against the C-terminal domain of mGlu1α receptors (DiaSorin, Stillwater, MN), is probed to confirm the mGlu1α expression profile detected with the NH_2-terminal antibody.

ule cell bodies were reported to exhibit a low but detectable amount of mGlu1 mRNA (Shigemoto et al., 1992; Berthele et al., 1998, 1999), whereas mGlu1 receptor immunoreactivity is not found in these cells (Martin et al., 1992; Grandes et al., 1994; Jaarsma et al., 1998). In the granular layer, many Lugaro cells, unipolar brush cells (UBCs), and some Golgi cells display mGlu1α immunoreactivity (Martin et al., 1992; Baude et al., 1993; Grandes et al., 1994; Wright et al., 1996); labeling was also reported in glomeruli (Baude et al., 1993).

A similar expression profile for the mRNAs of all main mGlu1 splice variants has been described in the cerebellum, with high levels of mGlu1α, mGlu1β, and mGlu1γ in PCs, moderate levels in stellate and basket neurons, and weak levels in granule cells (Berthele et al., 1998). Immunolabeling with an mGlu1β antibody confirms the expression of the receptor protein in PCs, basket neurons, and glomeruli (Grandes et al., 1994). The mRNA expression pattern of mGlu1 receptor isoforms in human cerebellum is similar to that seen in rat cerebellum (Lin et al., 1997; Berthele et al., 1998, 1999).

High-resolution immunohistochemical studies have shown that mGlu1 receptors, including mGlu1α and mGlu1β, are selectively localized postsynaptically at the perijunctional site of both types of excitatory inputs received by PCs (Martin et al., 1992; Baude et al., 1993; Nusser et al., 1994; Shigemoto et al., 1994; Petralia et al., 1998; Mateos et al., 2000): the climbing fibers (CFs), which originate in the inferior olive, and the parallel fibers (PFs), which are the ascending axons of granule cells. The PF-PC synapse is one of the most extensively studied glutamatergic synapses and is characterized by the lack of postsynaptic NMDA receptors. However, synaptic transmission at this synapse undergoes a variety of activity-dependent changes, including short-term plasticity, LTP, and LTD, that are considered important for the role of cerebellum in motor coordination and learning (Levenes et al., 1998).

Activation of mGlu1 receptors in PCs by repetitive PF stimulation was shown to produce an initial slow excitation (or inward current) (Ito and Karachot, 1990; Crepel et al., 1991; Glaum et al., 1992; Staub et al., 1992; Batchelor and Garthwaite, 1993; Batchelor et al., 1994, 1997; Linden et al., 1994; Tempia et al., 1998., 2001). This current is independent of the stimulation of PI hydrolysis (Hirono et al., 1998; Tempia et al., 1998; Canepari et al., 2001), is produced by the activation of a nonselective cation channel (Canepari et al., 2001), requires G-protein activation (Tempia et al., 1998; Canepari and Ogden, 2003), and is inhibited by tyrosine phosphorylation (Canepari and Ogden, 2003). An additional effect mediated by mGlu1 receptors in PCs is a small hyperpolarization that follows the initial excitation and depends on the activation of an inhibitory K^+ current (Batchelor and Garthwaite, 1993; East and Garthwaite, 1992; Finch and Augustine, 1998; Ito and Karachot, 1990; Khodakhah and Ogden, 1995; Staub et al., 1992; Vranesic et al., 1993). This follows the receptor-mediated activation of PLCβ4 with an ensuing formation of IP_3 and Ca^{2+} release from intracellular stores (Yuzaki and Mikoshiba, 1992; Finch and Augustine, 1998; Takechi et al., 1998; Hartmann et al., 2004). It is noteworthy that Okubo et al. (2004) have shown a cooperative action between mGlu1 and AMPA receptors in PF-induced production of IP_3. Complementary recordings from PCs in vivo confirm the multiphasic response observed upon mGlu1 receptor activation in vitro (Lingenhöhl et al., 1993).

Repetitive PF stimulation evokes a complex Ca^{2+} signal confined to the dendritic PC target region of the activated PF. The synaptic Ca^{2+} response consists of two distinct components, an early response with a fast rising phase mediated by AMPA receptors, and a delayed component mediated by mGlu1 receptors (Gruol et al., 1996; Finch and Augustine, 1998; Takechi et al., 1998; Hartmann et al., 2004). The delayed component has been ascribed to the release of Ca^{2+} from intracellular stores (Takechi et al., 1998), although the influx of extracellular Ca^{2+} through VSCCs might also have a role (Daniel et al., 1996). The group of Nakanishi has demonstrated that in PC dendrites mGlu1α receptors form a heteromeric assembly with $Ca_v2.1$, a pore-forming subunit of P/Q-type VSCCs (Kitano et al., 2003a). Activation of mGlu1α receptors modulates $Ca_v2.1$ in a time-dependent fashion (Kitano et al., 2003a). Preactivation of mGlu1α receptors inhibits $Ca_v2.1$ Ca^{2+} channels in both ligand-dependent and -independent manners, which were mediated by coupling through PTX-sensitive G-proteins (probably G_o) and by physical coupling between the two receptors, respectively (Kitano et al., 2003a). In contrast, a coincident stimulation of mGlu1α receptors and $Ca_v2.1$ amplifies intracellular Ca^{2+} increase (Daniel et al., 1996; Wang et al., 2000a; Kitano et al., 2003a). This different modulation of $Ca_v2.1$ channel activity by mGlu1α receptors could provide a temporal window for the regulation of intracellular Ca^{2+} concentration and integration of synaptic inputs onto PCs (Berridge, 1998; Ito, 2002; Kitano et al., 2003a).

The initial slow EPSCs observed upon activation of mGlu1 receptors in PCs seems to be mediated by TRPC1 cation channels (Kim et al., 2003). This interaction between mGlu1 receptors and TRPC1 might be direct (Kim et al., 2003) or mediated by Homer proteins (Brakeman et al., 1997; Yuan et al., 2003). However, these channels may not be the unique generator of slow EPSCs as certain properties of this current cannot be accounted for by TRPC (Canepari et al., 2004).

At present, the functional significance of mGlu1-evoked slow EPSCs remains to be established, although several hypotheses have been formulated: 1) the Ca^{2+} influx associated with this current could serve to replenish internal stores depleted by IP_3; or 2) the Ca^{2+} and/or Na^+ influx mediated by TRPC channels may engage alternative transduction pathways, which could be in-

volved in the release of endocannabinoids (Kim et al., 2003).

Marked increases in mGlu1-mediated currents are found by the concomitant application of GABA or the $GABA_B$ receptor agonist baclofen (Hirono et al., 2001). This amplification is specific because baclofen does not affect AMPA-induced currents. Baclofen enhances not only the inward currents but also the Ca^{2+} transients mediated by mGlu1 receptors in both proximal and distal PC dendrites.

PFs also form excitatory connections with interneurons, hence eliciting GABA release at interneuron-PC synapses. Therefore, endogenous GABA released synaptically from cerebellar interneurons after PF stimulation can elicit on PCs, through the activation of postsynaptic $GABA_B$ receptors, a profound enhancement of mGlu1-induced slow EPSCs and a rise in Ca^{2+} (Hirono et al., 2001). The amplifying action of $GABA_B$ receptors on mGlu1-mediated responses seems to be a unique property of $GABA_B$ receptors as other G-protein-coupled receptors including serotonin, adenosine, and muscarinic receptors are devoid of such action in PCs (Hirono et al., 2001). $GABA_B$ receptors have also been shown to promote and to broaden the dynamic range of mGlu1-mediated responses in PCs (Tabata et al., 2002, 2004) independently of GABA, by means of their interaction with extracellular Ca^{2+} and possibly through complexing with mGlu1 receptors (Tabata et al., 2004). Therefore, $GABA_B$ receptors can function as a Ca^{2+}-dependent cofactor that constitutively enhances mGlu1-signaling in PCs. This novel mechanism of mGlu1 sensitization may constitute an important factor for understanding the physiological basis of the unsaturated properties of mGlu1 EPSCs (Batchelor et al., 1997; Tempia et al., 1998).

Long-lasting enhancement of mGlu1-mediated responses has also been shown in PCs in culture after a conditioning depolarization with 50 mM KCl (Minami et al., 2003). Depolarization inhibits the internalization of mGlu1 receptors by means of an increased expression of Homer1a (Minami et al., 2003). All of these changes are prevented by inhibitors of the MAPK pathway (Minami et al., 2003).

As previously discussed for the hippocampal formation, activation of mGlu1 receptors influences presynaptic functions through the release of diffusible endogenous endocannabinoids, which in turn act on CB1 receptors on presynaptic terminals (Maejima et al., 2001), thus producing a reversible suppression of both excitatory and inhibitory synaptic transmission (Conquet et al., 1994; Levenes et al., 2001; Brown et al., 2003; Galante and Diana, 2004). The physiological role that these forms of synaptic depression elicited postsynaptically may have on the overall processing of synaptic information conveyed to the cerebellar cortex is unclear; however, a role in synaptic refinement during development has been postulated (Maejima et al., 2001).

Conjunctive stimulation of CF and PF inputs onto PCs has been shown to result in LTD at PF-PC synapses (Ito and Kano, 1982). The molecular and cellular mechanisms of this form of synaptic plasticity require the activation of a signaling cascade initiated by mGlu1 and involving PKC (Hansel et al., 2001; Gao et al., 2003). Because the involvement of mGlu1 in LTD generation has been reviewed recently (Kano et al., 2008), we refer the reader to this review for a more comprehensive coverage of the topic.

An mGlu1-dependent form of long-lasting synaptic depression has been shown recently to be expressed at PC-CF synapses (Hansel and Linden, 2000). Like PF-PC LTD, CF-PC LTD requires, beside activation of mGlu1, postsynaptic Ca^{2+} elevation and PKC activation (Hansel and Linden, 2000). Dzubay and Otis (2002) have shown that mGlu1 receptors perisynaptic at CF-PC synapses are activated in response to CF stimulation and, similarly to those at PF-PC synapses, generate divergent signaling cascades: one of these is characterized by slow EPSCs independent from release of Ca^{2+} from intracellular stores and a second is linked to mobilization of intracellular Ca^{2+}. The similarities in mGlu1-mediated responses between PF-PC and CF-PC synapses suggest that in PCs, mGlu1 initiates the same intracellular transduction program independently from its location or presynaptic input.

An additional mechanism of regulation that seems to operate on the activation of mGlu1 receptors involves glutamate transporters. Inhibition of glial and neuronal glutamate transporters enhances mGlu1-mediated EPSCs in PCs at both PF-PC and CF-PC synapses, thereby facilitating the induction of LTD (Brasnjo and Otis, 2001; Dzubay and Otis, 2002; Reichelt and Knöpfel, 2002; Otis et al., 2004). An interplay between neuronal glutamate transporters and mGlu1 receptors is further suggested by their overlapping subcellular distribution (Baude et al., 1993; Dehnes et al., 1998; Brasnjo and Otis, 2001). As perisynaptic mGlu1 receptors are activated by the glutamate that escapes the clearing mechanisms and diffuses to the extracellular space, the activity of glutamate transporters is critically set to provide a threshold for the recruitment of mGlu1 receptors in response to synaptic activation.

Cerebellar LTD has been hypothesized to underlie vestibulo-ocular reflex adaptation, eye-blink classic conditioning, and acquisition of motor skills (Lisberger, 1998; Mauk et al., 1998). However, how activity-dependent plasticity in the cerebellar cortex actually modifies behavior remains to be ascertained as does the role played by mGlu1 receptors. Gene-targeted deletion of the mGlu1 receptor impairs LTD at PF-PC synapses and results in motor impairment and severe ataxia (Aiba et al., 1994b; Conquet et al., 1994). However, the lack of mGlu1 receptors in brain areas other than the cerebellum complicates the interpretation of behavioral data. In an elegant study, Ichise et al. (2000) demonstrated

that reintroduction of mGlu1α under the control of the L7 promoter, which selectively allows the expression of the transgene only in PCs of mGlu1-null mice, completely rescues the disruption of cerebellar LTD and the motor impairment. Using these rescued mice, Kishimoto et al. (2002) examined the role of mGlu1 within and outside PCs for the association of temporally contiguous and discontiguous stimuli in paradigms of classic conditioning. Their results show that mGlu1 receptors in PCs are essential for normal delay eye-blink conditioning (Kishimoto et al., 2002). Conversely, mGlu1 receptors present in other cell types contribute to the association of discontiguous stimuli and long-term memory formation of nonspatial hippocampus-dependent learning (Kishimoto et al., 2002).

Compared with mGlu1 in PCs, the role of mGlu1 receptors in cerebellar interneurons has not been investigated in great detail. Basket and stellate interneurons in the molecular layer express mGlu1 receptors postsynaptically in conjunction with PF terminals, and their activation leads to a robust depolarization of these neurons (Karakossian and Otis, 2004). This depolarization triggers bursts of IPSCs in PCs (Karakossian and Otis, 2004) and may provide a phasic long-lasting inhibition of these cells.

The granular layer of the mammalian vestibulocerebellum is highly enriched in the glutamatergic UBC interneurons. The branchlets forming the brush-like tip of their unique dendrite establish an elaborate synaptic junction with a single mossy fiber rosette, which evokes upon stimulation a prolonged excitation of the UBC (Rossi et al., 1995). UBCs receive input from the vestibular ganglion and vestibular nuclei and project their axons in the granular layer where they form a system of intrinsic excitatory mossy fiber-like synapses with granule cells and other UBCs. These cells have been proposed to exert a feed-forward excitation within the granular layer, which may amplify vestibular signals and synchronize activity in clusters of functionally related granule cells projecting to patches of PCs (Diño et al., 2000; Nunzi et al., 2001). Two distinct classes of UBC have been identified, one expressing calretinin and the two vesicular glutamate transporters VGlut1 and -2, whereas the other contains mGlu1 receptors (including mGlu1α) in the somatodendritic compartment and only VGlut1 (Jaarsma et al., 1998; Takács et al., 1999; Nunzi et al., 2002). The localization of mGlu1α is primarily associated with the thin appendages of UBCs and is absent from the large postsynaptic density of giant mossy fiber-UBC synapses (Jaarsma et al., 1998). The two subsets of UBCs seem to have a different distribution within the mouse nodulus and to support two largely independent microcircuits (Nunzi et al., 2002, 2003), which associate with different subsets of primary and secondary vestibular afferents. The precise role of mGlu1 receptors in UBC is not known. However, mGlu1 receptors may take part in the dynamic process of intracellular Ca^{2+} increase that follows mossy fiber activation (Nunzi et al., 2002).

In addition to UBCs, two other interneurons, namely Golgi and Lugaro cells in the granular layer, display weak mGlu1 immunoreactivity (Baude et al., 1993; Víg et al., 2003). Lugaro cells are GABAergic interneurons located just underneath the PC layer and exhibit a fusiform cell body and thick dendrites horizontally oriented with respect to the laminar organization of the cerebellar cortex. They receive predominantly inhibitory afferents from PC recurrent collaterals and project their axons to the molecular layer where they contact basket cells (Lainé and Axelrad, 1996). It has been suggested that Lugaro cells are disinhibitory feedback interneurons modulating the cerebellar output.

Among Golgi cells, only a small subpopulation expresses postsynaptic mGlu1 at synapses with PF terminals (Hámori et al., 1996). Application of 3,5-DHPG to freshly dissociated Golgi cells inhibits VSCCs (Knoflach et al., 2001b). However, this effect may be mediated by either mGlu1 and/or mGlu5 receptors, because both receptors are found in Golgi cells (Neki et al., 1996).

The reported expression of mGlu1 receptor mRNA in cerebellar granule cells but the lack of detectable immunoreactivity in these cells remains an unresolved issue. Vetter et al. (1999) have shown functional responses to 3,5-DHPG in granule cells of rat cerebellar slices that are probably mediated by mGlu1 receptors. We have found a small accumulation of mGlu1-βGal fusion protein in granule cells of mGlu1-null mice, which favors the hypothesis that mGlu1 mRNA undergoes translation in cerebellar granule cells.

A synthesis of the role(s) of mGlu1 receptors in cerebellar function is at present unattainable, given its presence in many cerebellar neurons as well as at many different synapses. Important indications have been obtained regarding mGlu1 at PC-PF and PC-CF synapses and the requirement of at least mGlu1α in LTD and motor coordination. However, participation of the short mGlu1 isoform in mGlu1-mediated responses remains entirely to be elucidated. Indeed, it would be of great interest to know whether mGlu1β or mGlu1γ is able to rescue the cerebellar phenotype exhibited by mGlu1-null mice entirely or partially.

7. Distribution and Role of Metabotropic Glutamate 1 Receptors in the Spinal Cord. The importance of mGlu1 receptors in the processing of sensory transmission in the spinal cord has been extensively studied, particularly in view of their role in nociception.

In situ hybridization experiments performed in rat spinal cord show diffuse labeling throughout its rostrocaudal extent, whereas most intensely labeled neurons are found in the ventral horn and central gray (Shigemoto et al., 1992). The substantia gelatinosa contains many weakly labeled neurons as do the sensory trigeminal nuclei (Shigemoto et al., 1992). Within the dorsal horn, mGlu1 mRNA is distributed over laminae I

through III and labeled cells are mainly observed in the deeper laminae (IV–VII) and in the intermediate gray matter (Berthele et al., 1999). Two populations of motoneurons can be discriminated by either the expression or lack of expression of mGlu1 mRNA. Motoneurons expressing mGlu1 contain the mGlu1α receptor variant predominantly (Berthele et al., 1999).

Expression of mGlu1α and -1β receptor proteins has been analyzed in the rat spinal cord in several studies (Fotuhi et al., 1993; Petralia et al., 1997; Tang and Sim, 1999; Alvarez et al., 2000). mGlu1 receptor immunostaining is detected rostrocaudally throughout the spinal cord (Alvarez et al., 2000). Intense mGlu1α immunolabeling is found in dendritic and somatic membranes of neurons of the deep dorsal horn (lamina III–IV) and ventral horn (lamina VI–IX). Deeper laminae (III–VI) of the dorsal horn also contain several mGlu1α-positive neurons and dendrites. Large lamina I neurons and dendrites show occasional immunostaining for mGlu1α receptors, whereas lamina II interneurons express low levels of mGlu1α immunoreactivity (Petralia et al., 1997; but see Tang and Sim, 1999; Alvarez et al., 2000).

Somata and dendrites of motoneurons display variable mGlu1α immunoreactivity, with small to medium-sized motoneurons showing higher levels of immunostaining (Alvarez et al., 2000). Some motoneuron pools possess particularly strong immunoreactivity, such as phrenic and pudendal motoneurons, Onuf's ventrolateral motoneurons, and motoneurons in the central cervical nucleus and Clarke's column (Alvarez et al., 2000). Within the dorsolateral funiculus, several neurons of the lateral spinal nucleus also display mGlu1α immunoreactivity (Alvarez et al., 2000). In the human spinal cord, the expression pattern of mGlu1α seems similar to what was reported in rodents (Aronica et al., 2001). Neurons immunoreactive for mGlu1β receptors are found throughout the dorsal horn, although only a group of neurons in lamina X show strong mGlu1β expression (Alvarez et al., 2000).

The physiological role of mGlu1 receptors in fast and slow excitatory synaptic transmission in the spinal cord is still largely uncertain. Activation of group I mGlu receptors in motoneurons and dorsal horn neurons induces transient membrane depolarizations and modulates excitation meditated by ionotropic glutamate receptors (Bleakman et al., 1992; Cerne and Randic, 1992; Jones and Headley, 1995; Ugolini et al., 1997, 1999; Zhong et al., 2000; Neugebauer, 2002), alters spike frequency accommodation, and decreases the firing threshold of these neurons and/or the amplitude and duration of afterhyperpolarizations (Cao et al., 1995; King and Liu, 1996; Morisset and Nagy, 1996; Russo et al., 1997). Group I mGlu receptor activation also induces rhythmic oscillations of the membrane potential and long-term changes in the excitability of sympathetic neurons (Spanswick et al., 1995; Nolan and Logan, 1998). In the dorsal horn, these mechanisms produce hyperexcitability to sensory stimuli that can result in allodynia, hyperalgesia, and sustained nociceptive transmission (Meller et al., 1993; Neugebauer et al., 1994, 1999; Young et al., 1994, 1995, 1997, 1998; Boxall et al., 1996; Fisher and Coderre, 1996, 1998; Meller et al., 1996; Budai and Larson, 1998; Stanfa and Dickenson, 1998).

Slow EPSPs evoked by group I mGlu receptors or by a stimulus train at dorsal horn sensory neuron synapses occur through a cooperative action of both mGlu1 and mGlu5 receptors (Galik et al., 2008). This cooperativity may arise from interaction between downstream intracellular signaling pathways coupled to mGlu1 and mGlu5 receptors, which are activated by the coincident stimulation of multiple synaptic inputs onto a given neuron (Mori and Gerber, 2002).

VII. Implication in Diseases

As described earlier, mGlu1 receptors are involved in the regulation of neuronal excitability, synaptic plasticity, synapse selection, and neurotransmitter release, which are important for brain development and mechanisms of learning and neuroprotection. Therefore, it is not surprising that mGlu1 receptors have been implicated also in the pathophysiology of several neurological and psychiatric disorders. The repertoire of selective compounds at these receptors has recently expanded; thus, novel chances are offered for the development of new therapeutically effective drugs for neuropsychiatric diseases. In this section, we review the potential clinical and therapeutic implications of mGlu1 receptors in some representative disorders.

A. Cerebellar Ataxia

Gene-targeted deletion of the mGlu1 gene in mice results in severe cerebellar motor discoordination (ataxia) and impaired LTD (Aiba et al., 1994b; Conquet et al., 1994). An important feature observed in mGlu1-null mice is also a persistent multiple CF innervation of PCs without an apparent defect in PF-PC synaptogenesis (Kano et al., 1997; Levenes et al., 1997). During cerebellar development, both CF and PF synapses are formed supernumerarily and are then dynamically modified with the resulting elimination of redundant synapses. Elimination of the supernumerary CFs proceeds in parallel with other developmental events in the cerebellum, including granule cell migration, PC dendritic growth, and PF-PC synaptogenesis (Mariani et al., 1977; Crepel et al., 1980). In the adult cerebellum, each PC is eventually innervated by a single CF. This one-to-one relationship is reached by the end of the third postnatal week and is maintained throughout life. CF-PC synapses can be observed on PC somatic processes from postnatal day 2, whereas PF-PC synapses begin forming at postnatal days 7 to 10. The supernumerary CFs in the cerebellum of mGlu1-null mice formed typical synapses onto PC proximal dendrites and gave rise to EPSCs with

fast rise times similar to CFs in wild-type animals (Hashimoto and Kano, 2003).

The persistence of multiple CF innervation of PCs, impaired LTD, and lack of motor coordination has been observed in a number of mice deficient in signal transduction elements downstream of mGlu1, including $G\alpha_q$ (Offermanns et al., 1997), PLCβ4 (Kano et al., 1998), and PKCγ (Kano et al., 1995). Reinsertion in mGlu1-null mice of mGlu1α in PCs only reverses the disruption of synaptic plasticity (LTD) and the motor impairment and induces normal regression of multiple CF innervation (Ichise et al., 2000). Taken together, these results clearly demonstrate that activation of mGlu1 and of its downstream intracellular signaling cascade to PKCγ plays a critical role in the maturation of the cerebellar cortex.

Although good parallelism between cerebellar motor discoordination, multiple CF innervation of PCs, and impaired LTD has been observed, it still remains unclear whether the two latter phenomena contribute to generate the ataxia. Cerebellar motor coordination deficits also occur in mice deficient in the GluRδ2 subunit (Kashiwabuchi et al., 1995), which is highly enriched at the junctional site of PF-PC synapses but not at the site of CF-PC synapses. These animals, as for mGlu1-null mice, show impaired LTD and persistent multiple CF innervation, which is paralleled, however, by a nearly 50% reduction in the number of PF-PC synapses compared with that in wild-type animals (Kurihara et al., 1997). In GluRδ2-null mice, CFs were shown to innervate both the proximal and the distal dendrites of PCs (Hashimoto et al., 2001). Kano and coworkers concluded that GluRδ2 is required primarily for consolidating PF-PC synapses and restricting CFs to the proximal dendrites, whereas the mGlu1-signaling pathway is involved during cerebellar maturation in eliminating surplus of CFs at the proximal dendrites (Kurihara et al., 1997; Hashimoto et al., 2001).

The persistent innervation of PCs by multiple CFs has been proposed to be the main causal link to the impairment of motor coordination. However, autoantibodies to the extracellular domain of mGlu1 can generate paraneoplastic cerebellar ataxia in adult patients with Hodgkin's disease who had normal maturation of the cerebellar cortex (Sillevis Smitt et al., 2000; Coesmans et al., 2003), and when injected into the subarachnoid space of normal mice produce a severe and reversible ataxia (Sillevis Smitt et al., 2000). Hence, inhibition of mGlu1 after complete maturation of the cerebellar cortex is still able to produce ataxia, which may result either from interference with the excitability and firing rate of PCs or by prevention of the formation and maintenance of LTD (Coesmans et al., 2003). Nonetheless, persistence of multiple CF innervation may still remain an important developmental defect contributing to the motor impairment. Disruption of LTD is more likely to be the cause of the learning deficits associated with mGlu1 loss of function, such as in eye-blink conditioning (Aiba et al., 1994b; Kishimoto et al., 2002) and adaptation of saccadic eye movements (Coesmans et al., 2003).

The pathophysiological mechanisms by which mGlu1 autoantibodies evoked motor coordination deficits in patients with Hodgkin's disease remain to be demonstrated, as these antibodies, besides affecting synaptic transmission and plasticity, might also induce chronic neurodegeneration with consequent PC loss and/or changes in their dendritic arbor morphology (Coesmans et al., 2003). Evidence for a role of mGlu1 in PC survival and differentiation has been obtained by its pharmacological inhibition in vitro in mixed cerebellar cultures (Mount et al., 1993, 1998; Catania et al., 2001). However, deletion of mGlu1 in mice does not produce degeneration of PCs, nor does it affect the formation of their dendritic arbors (Aiba et al., 1994b; Conquet et al., 1994; Kano et al., 1997). It is possible, of course, that the lack of mGlu1 throughout development may have elicited some compensatory changes.

The molecular mechanisms by which mGlu1 induces elimination of supernumerary CTs remain to be identified as does the more general role that mGlu1 (and the individual alternatively spliced isoforms) plays in the critical period of maturation of the cerebellar cortex. Studies in which mGlu1 receptors are reinserted in cell-specific populations, such as PCs, under inducible promoters will help to elucidate answers to some of these questions.

B. Extrapyramidal Motor Dysfunctions

The recent advances in our understanding of the involvement of mGlu1 receptors in the basal ganglia motor circuit have direct implications for the elucidation of the pathophysiological role of these receptors in basal ganglia disorders such as Parkinson's disease. Parkinson's disease is a debilitating motor disorder characterized by akinesia, bradykinesia, and tremor. Modulation of DA/acetylcholine equilibrium in the striatum is still the mainstream pharmacological rational for treating the symptoms of this disease. However, anticholinergic and dopamine precursors or receptor agonists are not devoid of serious side effects, such as dyskinesias. Alternative strategies that can help to modulate striatal DA/acetylcholine transmission are therefore of great interest and potential clinical application. mGlu1 receptors are widely distributed in all the main nuclei of the basal ganglia and their activation contributes to potentiate excitatory transmission between the subthalamic nucleus and the globus pallidus (see section VI.B.4), hence opposing the effects of dopamine and facilitating the activity of the indirect pathway. However, no selective antagonist of mGlu1 receptors has so far been rigorously tested in animal models of Parkinson's disease. In parkinsonian animals, both mGlu1 and mGlu5 receptors significantly increase the excitation of subthalamic and SNr neurons (Marino et al., 2002). Although these findings imply that the two receptor subtypes might have

redundant roles in the basal ganglia of these animals, it remains to be established whether blockade of mGlu1 receptor alone is sufficient to produce anti-parkinsonian activity. If not, simultaneous blockade of both mGlu1 and mGlu5 receptors might be required for maximal therapeutic activity. It is noteworthy that intrastriatal administration of AIDA reverses haloperidol-induced parkinsonian-like muscle rigidity and catalepsy and normalizes the increased enkephalin mRNA expression induced by haloperidol (Ossowska et al., 2002, 2003). In the model of DA nerve cell degeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice, the mGlu1 antagonist AIDA effectively protects DAergic cells (Aguirre et al., 2001). 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys show a marked decrease in mGlu1α expression in the surviving neurons of the SNc ventral component and in the SNr (Kaneda et al., 2003), further implicating this receptor in the susceptibility of DAergic neurons to parkinsonian insults.

A growing body of evidence suggests that mGlu1 receptor antagonists might protect striatal medium spiny neurons against excitotoxic damage (for review, see Conn et al., 2005). Selective loss of this neuronal population occurs in Huntington's disease, a progressive and fatal disorder that is characterized by choreiform movements and is caused by an expansion of a trinucleotide CAG repeat in the gene that encodes the protein huntingtin. Antagonists of mGlu1 receptors protect striatal neurons against toxicity induced by NMDA or quinolinic acid, an endogenous NMDA receptor agonist (Bruno et al., 1999; Battaglia et al., 2001). A permissive role for mGlu1 and/or mGlu5 receptors in NMDA toxicity could explain why the integrity of the corticostriatal glutamatergic pathways is required for the induction of striatal neuronal damage by quinolinic acid (Orlando et al., 2001). mGlu1 receptor antagonists, but not mGlu5 receptor antagonists, protect striatal neurons by enhancing GABA release (Battaglia et al., 2001). One of the features of Huntington's disease is an impairment of complex II of the mitochondrial respiratory chain (succinate dehydrogenase), which can be reproduced experimentally using the mitochondrial toxins 3-NP or malonic acid (Greene and Greenamyre, 1996). A link between mitochondrial dysfunction and the excitotoxic hypothesis of Huntington's disease is supported by the finding that 3-NP and methylmalonic acid induce a pathological form of corticostriatal LTP, which is expressed as selective potentiation of synaptic responses mediated by NMDA receptors. This pathological form of synaptic potentiation might underlie long-term disruption of motor programs as well as the excitotoxic death of medium spiny neurons (Gubellini et al., 2004). As opposed to induction of physiological LTP, induction of 3-NP-LTP requires the selective activation of mGlu1 receptors, which might act synergistically with D2 receptors to trigger events that include activation of the MAPK pathway (Gubellini et al., 2004). These findings suggest mGlu1 receptor antagonists as potential candidates for the treatment of Huntington's disease.

C. Fear and Anxiety

Antagonists of mGlu1 receptors have been proposed to exhibit potential therapeutic effect in anxiety and stress disorders. Intrahippocampal injection in rats of 4-carboxy-3-hydroxyphenylglycine, 4-CPG, CPCCOEt, AIDA, and LY456236 evokes anxiolytic-like effects in the conflict drinking Vogel test (Chojnacka-Wójcik et al., 1997; Tatarczynska et al., 2001; Kłodzińska et al., 2004; Varty et al., 2006). Furthermore, in rats AIDA increases the entries and time spent in open arms in the elevated plus-maze test, a widely used model based on the rodent's natural aversion to height and open space, but fails to exert anxiolytic-like activity in mice in the four-plate test (Kłodzińska et al., 2004). The novel, selective, brain-permeable, and potent mGlu1 antagonist JNJ16259685 confirmed the anxiolytic effect of mGlu1 inhibition in the Vogel test (Steckler et al., 2005). A compound structurally related to JNJ16259685, namely 3-ethyl-2-methyl-quinolin-6-yl)-(4-methoxy-cyclohexyl)-methanone methanesulfonate, although showing no activity in the elevated plus-maze test in rats, significantly inhibits fear-potentiated startle and attenuates freezing responses in the contextual fear conditioning test (Pietraszek et al., 2005; Gravius et al., 2006). In line with these findings, mGlu1-deficient mice have impairments in contextual fear conditioning (Aiba et al., 1994a).

These findings suggest that the anxiolytic activity obtained by blocking mGlu1 receptors is task-specific. Antagonism at mGlu1 seems efficacious, in terms of anxiolytic activity, in tests involving a conflict component, but not spontaneous exploration (Chojnacka-Wójcik et al., 1997; Tatarczynska et al., 2001; Kłodzińska et al., 2004; but see Pietraszek et al., 2005; Steckler et al., 2005). The mechanisms through which mGlu1 antagonists exert anxiolytic activity are not known, but it can be postulated that they involve the GABAergic system in the limbic system. Blockade of mGlu1 receptors may, therefore, have important therapeutic potential in the treatment of anxiety disorders.

D. Mood Disorders

In a recent study, Brody et al. (2003a) have investigated the role of mGlu1 receptors in sensorimotor gating, measured by prepulse inhibition (PPI) of the startle response. Sensorimotor gating is a fundamental form of information processing that is deficient in patients with schizophrenia and bipolar disorder (Braff et al., 1992; Perry et al., 2001). Deficits in PPI have been observed in a number of animal models of schizophrenia and mania in both nonhuman primates and rodents (Dulawa and Geyer, 1996; Linn and Javitt, 2001; Brody et al., 2003b, 2004). Mice with gene-targeted deletion of mGlu1 exhibit a significant deficit of PPI, which is evident as early as 6 weeks postnatally, and PPI remains impaired

till adulthood (Brody et al., 2003a). Treatment with the mood-stabilizing drug lamotrigine partially reverses the PPI deficit in mGlu1 KO mice, whereas typical antipsychotic drugs are ineffective (Brody et al., 2003a). This study suggests that the modulation of sensorimotor gating by mGlu1 is consistent with a role of this receptor in the treatment and/or etiology of bipolar disorders.

E. Excitotoxicity

Substantial evidence has accumulated to show that mGlu1 receptors contribute somehow to the neurotoxic effects of glutamate, also known as "excitotoxicity," and are implicated in the mechanisms that lead to neurodegeneration in models of cerebral ischemia. Activation of mGlu1 receptors may exacerbate postischemic neuronal injury through multiple noxious mechanisms, including an increase in intracellular free Ca^{2+} or the potentiation of NMDA receptor responses. However, their actual role in excitotoxicity remains controversial and seems to depend on the particular experimental paradigm investigated. Several new viewpoints on the neuroprotective mechanisms of mGlu1 receptor antagonists have been put forward. However, because of the very large and complex body of literature on the topic and space limits, we refer the reader to another dedicated review (Pellegrini-Giampietro, 2003). Only a topical study will be discussed here because of its great impact on the field. Baudry and coworkers found that activation of NMDA receptors results in calpain-mediated truncation of the C-terminal domain of the mGlu1α receptor at Ser^{936} (Xu et al., 2007). The truncated mGlu1α receptor is no longer able to activate the neuroprotective PI_3-Akt signaling pathway; hence, it facilitates the exacerbation of excitotoxicity (Xu et al., 2007). Despite the obvious interest that these findings generate, it is perhaps premature to surmise that this positive feedback loop for excitotoxicity is operating in neurodegenerative conditions in vivo.

F. Epilepsy and Seizures

Altered glutamatergic transmission is recognized as one of the primary metabolic and pathological mechanisms behind the etiology of several types of epilepsy (Chapman et al., 1996). The role of ionotropic glutamate receptor activation in the generation of epileptic discharges has been extensively studied (Prince, 1999), whereas the importance of the different classes of mGlu receptors in the patterning of epileptiform activities is only beginning to be recognized (for review, see Moldrich et al., 2003; Wong et al., 2002).

Early reports have consistently shown antiepileptiform effects by nonselective mGlu receptor antagonists (Thomsen et al., 1994c; Arvanov et al., 1995; Burke and Hablitz, 1995; Merlin et al., 1995). On the other hand, application of group I mGlu agonists in vitro elicits synchronized oscillations and population bursting, resembling interictal spikes in vivo, in hippocampal slices (Merlin et al., 1995; Taylor et al., 1995). Moreover, if epileptiform discharges were initiated by inhibition of $GABA_A$ receptor-mediated inhibitory transmission, activation of group I mGlu receptors can further increase the duration and the frequency of the bursts (Merlin et al., 1995, 1998; Merlin and Wong, 1997; Rutecki and Yang, 1997) independently of NMDA receptors (Galoyan and Merlin, 2000). The potentiated bursts are shown to persist for hours after washout of the agonist (Merlin and Wong, 1997) and are reversibly shortened by application of group I mGlu receptor antagonists (Merlin, 1999, 2002; Thuault et al., 2002). It is noteworthy that Stoop et al. (2003) have shown, using both mGlu1- and mGlu5-null mice and selective antagonists at these receptors, that the absence or block of either mGlu1 or mGlu5 receptors is sufficient to lead to a total absence of increase in bursting frequency in the hippocampal CA3 field caused by 3,5-DHPG. This total loss of sensitivity to 3,5-DHPG, resulting from the independent blockade of either receptor, suggests the need for their simultaneous activation (Stoop et al., 2003). Although in earlier reports cooperation of mGlu1 and mGlu5 receptors in promoting seizure-like activities had been anticipated, in these preparations the effects of 3,5-DHPG were different and only partially blocked by antagonists at mGlu1 or mGlu5 receptors (Merlin, 2002; Thuault et al., 2002; Smolders et al., 2004). These studies also postulate different roles for the two group I mGlu receptors, in particular, that mGlu1 receptors would mainly sustain the duration of prolonged synchronized discharges (Merlin, 2002; Thuault et al., 2002). Support for this hypothesis comes from Wong and coworkers (Chuang et al., 2000, 2001, 2002), who have demonstrated using mGlu1-null mice that in CA3 pyramidal cells mGlu1 distinctively activates a PLCβ1-dependent voltage-gated inward current, which contributes significantly to sustaining the prolonged rhythmic bursts (Chuang et al., 2001, 2002). Moreover, synaptically activated mGlu1 receptors seem to involve additional unidentified, but PLCβ1-independent, mechanisms to promote the lengthening of the synchronized discharges (Lee et al., 2002).

Consistent with these findings in vitro, administration in vivo of group I mGlu receptor agonists has been repeatedly found to be proconvulsant, independent of whether they were injected focally in different brain areas or in the cerebral ventricles (Tizzano et al., 1995; Camón et al., 1998; Thomsen and Dalby, 1998). The proconvulsant activity of group I mGlu receptors is likely to result from a direct excitatory action dependent on the opening of VSCCs (Schumacher et al., 2000) and blockade of Ca^{2+}-dependent and/or independent K^+ channels. A requirement for tyrosine phosphorylation and ERK1/2 activation for group I mGlu receptor-mediated epileptiform discharges has also been reported (Zhao et al., 2004).

Antagonism at mGlu1 receptors by means of AIDA or LY367385 has anticonvulsant activity in the absence of both epilepsy and generalized motor seizures (Chapman

et al., 1999; Smolders et al., 2004). Experiments using other competitive phenylglycine-like antagonists demonstrate the potent anticonvulsant activity of these compounds in models of 3,5-DHPG-induced limbic seizures (Kingston et al., 2002). Likewise, a series of aminopyridine derivatives with high selectivity for mGlu1 were shown to be anticonvulsant in a number of mouse and rat epilepsy models, including sound-induced seizures in DBA/2 mice, mouse focal seizures, and amygdala kindling (Shannon and Peters, 2002).

Intraperitoneal injections of kainic acid (KA) in young rats lead to a prolonged seizure followed by chronic recurrent seizures and long-term hippocampal dysfunction. Coadministration of AIDA with KA does not change acute seizure-onset latency, seizure duration, or severity (Renaud et al., 2002). However, AIDA prevents the occurrence of spontaneous recurrent seizures and loss of CA1 oriens/alveus interneurons (Renaud et al., 2002). Moreover, blockade of group I mGlu receptors limits the loss of hippocampal function as a result of KA treatment, as tested by the Morris water maze (Renaud et al., 2002). With the amygdala kindling model, significant suppression of the rate of seizure progression, but with no effect on afterdischarge duration, was obtained by intrahippocampal injection of mGlu1 antisense oligonucleotides (Greenwood et al., 2000).

Activation of group I mGlu receptors, besides producing direct excitatory actions, also induces up-regulation of both mRNA and protein of neuropeptide Y and of its Y2 receptors in rat dentate granule cells (Smiałowska and Bajkowska, 1997; Schwarzer and Sperk, 1998; Schwarzer et al., 1998). Given the important role played by neuropeptide Y in modulating glutamate release in the hippocampus, regulation of the transcriptional activity for this neuropeptide and for one of its receptors mediated by group I mGlu receptors may serve as a long-term feedback mechanism to control hippocampal excitability.

In animal models of acquired epilepsy, several changes in expression and function of group I mGlu receptors and more specifically of mGlu1 receptors have been described. However, the data seem highly controversial, as different reports have described opposite regulation of mGlu1 receptor expression, sometimes using the same animal model. Electrical kindling of the amygdala was shown to produce, after the last seizure, a transient up-regulation (24–48 h) of mGlu1 transcripts and mGlu1α protein in the rat hippocampus (Akbar et al., 1996; Blümcke et al., 2000), whereas a more prolonged increase lasting at least 1 month was observed in the neocortex and supraoptic nucleus (Al-Ghoul et al., 1998). In the rat KA model of temporal lobe epilepsy, up-regulation of mGlu1 receptor mRNA expression in the dentate gyrus was detected 30 days after KA injection (Blümcke et al., 2000). Increased immunoreactivity for mGlu1α receptors in the dentate molecular layer was also reported by the same group in kindled and KA-treated rats as well as in surgical specimens from patients with temporal lobe epilepsy (Blümcke et al., 2000). However, the pattern of immunolabeling described in this article (intense immunoreactivity in the CA1 neuropil) was largely inconsistent with the known distribution of mGlu1α receptors in the hippocampus; hence raising some doubts about the specificity of the immunostaining. Ong et al. (1998) observed a reduction in mGlu1α receptor immunoreactivity in the CA1 field lasting from 1 to 5 days postinjection in KA-treated rats. In the rat pilocarpine model, mGlu1 receptors were also found to be markedly down-regulated in the hippocampus between 3 and 31 days after pilocarpine-induced status epilepticus (Tang et al., 2001). In the same pilocarpine model, although performed in mice, reduced expression of mGlu1 receptors was similarly detected in the dentate gyrus of animals in the chronic recurrent seizure stage (Chen et al., 2005).

High expression of mGlu1α receptors has been observed in dysplastic neurons in the cortex of patients with a pediatric form of intractable epilepsy known as focal cortical dysplasia (Aronica et al., 2003). The intense expression of this receptor in the dysplastic neurons may result either from a constitutive or an induced event associated with chronic seizure activity. These findings raise questions about the contribution of the high levels of mGlu1 receptors found in dysplastic neurons to the intrinsic and high epileptogenicity of dysplastic cortical regions. The lack of correlation between mGlu1α receptor immunoreactivity in the dysplastic tissue and duration of epilepsy, as well as the largely similar expression of mGlu1α receptors in normal cortex adjacent to dysplastic regions and control tissue from patients with no history of epilepsy (Aronica et al., 2003), speaks against a critical role of this receptor in the dysplastic neurons for the generation of focal epileptic discharges.

Despite a lack of conclusive evidence on the implications of mGlu1 transcriptional regulation in epileptogenesis, a large body of data clearly identifies a critical role for mGlu1 receptors in the transition of interictal bursting into ictal activity and maintenance of the prolonged synchronized discharges. Therefore, antagonists at mGlu1 receptors may represent a new therapeutic promise for the future treatment of epilepsy syndromes.

G. Pain

The involvement of group I mGlu receptors in nociception has been an area of intense investigation. Intrathecal administration of 3,5-DHPG induces spontaneous nociceptive behaviors, prolonged mechanical allodynia, and hyperalgesia in rodents (Fisher and Coderre, 1996, 1998). Also in sheep, intrathecal administration of low doses of 3,5-DHPG increases the responsiveness to noxious mechanical stimulation (mechanical hyperalgesia), an effect that is reversed by the coadministration of AIDA (Dolan and Nolan, 2000). The induction of spon-

taneous nociceptive behaviors by 3,5-DHPG seems to depend on glutamate release from primary afferent C-fibers (Lefebvre et al., 2000; Lorrain et al., 2002). In monkeys, capsaicin injection or 3,5-DHPG administration by microdialysis produces central sensitization of spinothalamic tract cells and enhances responses to both innocuous and noxious stimuli (Neugebauer et al., 1999).

A critical step in establishing the important role of mGlu1 receptors in pain has been obtained by antisense knockdown, which by decreasing mGlu1 receptor expression inhibits spinal nociceptive transmission and neuropathic hyperalgesia (Young et al., 1998; Fundytus et al., 2001, 2002; Noda et al., 2003). It is noteworthy that the use of mGlu1 antisense oligonucleotides also revealed a role for mGlu1 in the development of tolerance to morphine, as the analgesic response to morphine is conserved in antisense-treated neuropathic animals (Fundytus et al., 2001; Sharif et al., 2002).

Intrathecal administration of selective antibodies against mGlu1 receptors also effectively attenuates persistent pain, chemical pain (formalin test), and neuropathic pain (Fundytus et al., 1998). Likewise, antagonists of mGlu1 receptors significantly reduced chronic hyperalgesia and allodynia in a number of experimental models and species, corroborating the finding obtained with antisense oligonucleotides and receptor-selective antibodies. For example, in the model of chronic inflammation produced by the application of complete Freund's adjuvant, intrathecal pretreatment with mGlu1 receptor antagonists, such as CPCCOEt or A-841720, significantly reduces heat hyperalgesia and mechanical allodynia (Guo et al., 2004; Morè et al., 2007). Pretreatment with different classes of mGlu1 antagonists reduces nociceptive responses in the formalin test, in the carrageenan test, and in the chronic constriction injury model of inflammatory pain (Bhave et al., 2001; Zhang et al., 2002; Micheli et al., 2003c; Varty et al., 2005; Sevostianova and Danysz, 2006). However, when applied after the induction of inflammation, only LY367385 and AIDA seem to be slightly effective in reducing hyperalgesia (Zhang et al., 2002). In the capsaicin-induced central sensitization of spinothalamic tract neurons, pretreatment with AIDA or CPCCOEt decreases thermal and/or mechanical hypersensitivity in rats and primates (Neugebauer et al., 1999; Soliman et al., 2005). Therefore, mGlu1 receptor antagonists seem to produce anti-allodynic and antihyperalgesic effects only in states of hypersensitivity.

Activation of group I mGlu receptors enhances excitability of spinal neurons and induces a long-lasting potentiation of C-fiber-evoked potentials (Park et al., 2004), which are mediated by a cooperative action of mGlu1 and mGlu5 receptors (Park et al., 2004). Group I mGlu receptor agonist-evoked responses are enhanced in the spinal cord of hyperalgesic animals and are reversed by the administration of NMDA receptor antagonists (Boxall and Lancaster, 1998). NMDA currents in dorsal horn neurons are potentiated by the activation of group I mGlu receptors (Bleakman et al., 1992; Cerne and Randic, 1992; Bond and Lodge, 1995). The ionotropic function of NMDA receptor in vivo is subject to phosphorylation, which is initiated by mGlu/G-protein-linked mechanisms during injury-induced spinal dorsal horn plasticity (Guo et al., 2004). Inflammation and mGlu agonists both increase NR2B phosphorylation through similar mechanisms that require PKC, Ca^{2+} release, and Src activation (Guo et al., 2004). The likely postsynaptic mGlu-NMDA receptor coupling seems to occur mainly in the initiation phase of dorsal horn hyperexcitability, because post-treatment with CPCCOEt does not attenuate hyperalgesia-allodynia (Guo et al., 2004). A functional consequence of mGlu1 receptor activation after inflammation may be to prime NMDA receptors to further enhance hyperexcitability. This mechanism may be a critical initiator for central nociceptive sensitization. A partially unresolved issue is whether the facilitatory effect of mGlu1 receptors is entirely due to their functional interaction with ionotropic receptors (Boxall et al., 1996; Fisher and Coderre, 1996; Budai and Larson, 1998) or involves other mechanisms to increase neuronal excitability (Jones and Headley, 1995). Inflammation leads to a long-lasting enhancement of behavioral responses induced by the activation of group I mGlu receptors [e.g., intrathecal injection of 3,5-DHPG (Adwanikar et al., 2004)], which in turn induces ERK1/2 phosphorylation in dorsal horn neurons (Karim et al., 2001; Adwanikar et al., 2004). Blockade of either mGlu1 or mGlu5 receptors reduces ERK1/2 activation and nociceptive responses (Karim et al., 2001; Adwanikar et al., 2004), suggesting that the ERK1/2 signaling pathway is a potential mediator of mGlu1-dependent enhancement of nociception (Karim et al., 2001).

It can be concluded that strong anatomical, functional, and behavioral evidence indicate a promising therapeutic use of mGlu1 receptor antagonists and/or allosteric modulators for the relief of neuropathic pain.

H. Role of Metabotropic Glutamate 1 Receptors in Melanoma Development

mGlu1 signaling has been implicated in melanocytic neoplasia (Pollock et al., 2003; Marín and Chen, 2004). The mouse mutant line TG3, in which multiple tandem insertions are present in the *Grm1* locus with the concomitant deletion of 70 kb of intronic sequence, is highly predisposed to develop melanoma. Strong mGlu1α receptor expression is also detected in melanomas deriving from these mice, as well as in several human melanoma biopsy samples and in melanoma cell lines, but not in normal human or mouse melanocytes (Pollock et al., 2003; Marín and Chen, 2004). Moreover, in a line of transgenic mice with mGlu1α receptor expression targeted to melanocytes, significant development of melanoma was observed (Pollock et al., 2003; Marín and

Chen, 2004). These findings strongly suggest an involvement of mGlu1 receptor signaling in the pathogenesis of melanocytic neoplasia, including activation of ERK1/2 and PKCε, which have been implicated in melanoma onset (Marín and Chen, 2004; Marín et al., 2006). Recent findings further implicate mGlu1 receptors and glutamate signaling in melanoma onset (Namkoong et al., 2007). Human melanoma cells release high levels of glutamate, which in turn induce mGlu1 receptor activation in an autocrine fashion (Namkoong et al., 2007). Treatment of mGlu1-expressing melanoma cells with specific antagonists, such as LY367385 and BAY36-7620, or with the glutamate release inhibitor riluzole reduces both extracellular glutamate levels and cell proliferation (Namkoong et al., 2007). The involvement of mGlu1 receptors in the development of melanoma provides a clear rational for targeting these receptors as good candidates for melanoma therapy.

VIII. Perspectives and Directions for Future Studies

The widespread but discrete distribution of mGlu1 receptors, their coupling to diverse intracellular signaling pathways, and their important role in synaptic modulation underscore their potential relevance in the pathophysiology of a wide range of neurological and psychiatric disorders. However, almost 25 years from their discovery and 15 years from the cloning of mGlu1 receptors, as yet no selective drugs for these receptors are in clinical trials. Moreover, the current view on the potential therapeutic role of mGlu1 receptors relies solely on preclinical evidence. However, the recent development of drugs that act as highly selective allosteric modulators will probably foster their use in clinical studies and exploit their potential as therapeutic targets. These compounds have great advantages over orthosteric ligands, as they do not require amino acid moieties for their binding. In fact, most of these allosteric modulators are neutral, lipophilic molecules with good brain permeability.

mGlu1 receptor antagonists have clear analgesic, antiepileptic, and anxiolytic potential; however, possible impairments of learning and memory may reduce their therapeutical promise for diseases of the central nervous system. Even so, the recent implication of mGlu1 receptor antagonists in the treatment of melanoma and perhaps of irritable bowel syndrome warrant further efforts for the development of bioavailable and safe drugs for these receptors.

REFERENCES

Abe H, Misaka T, Tateyama M, and Kubo Y (2003a) Effects of coexpression with Homer isoforms on the function of metabotropic glutamate receptor 1α. *Mol Cell Neurosci* **23:**157–168.

Abe H, Tateyama M, and Kubo Y (2003b) Functional identification of Gd^{3+} binding site of metabotropic glutamate receptor 1α. *FEBS Lett* **545:**233–238.

Abe T, Sugihara H, Nawa H, Shigemoto R, Mizuno N, and Nakanishi S (1992) Molecular characterization of a novel metabotropic glutamate receptor mGluR5 coupled to inositol phosphate/Ca^{2+} signal transduction. *J Biol Chem* **267:**13361–13368.

Acsády L, Görcs TJ, and Freund TF (1996) Different populations of vasoactive intestinal polypeptide-immunoreactive interneurons are specialized to control pyramidal cells or interneurons in the hippocampus. *Neuroscience* **73:**317–334.

Adwanikar H, Karim F, and Gereau RW 4th (2004) Inflammation persistently enhances nocifensive behaviors mediated by spinal group I mGluRs through sustained ERK activation. *Pain* **111:**125–135.

Aguirre JA, Andbjer B, González-Barón S, Hansson A, Strömberg I, Agnati LF, and Fuxe K (2001) Group I mGluR antagonist AIDA protects nigral DA cells from MPTP-induced injury. *Neuroreport* **12:**2615–2617.

Aiba A, Chen C, Herrup K, Rosenmund C, Stevens CF, and Tonegawa S (1994a) Reduced hippocampal long-term potentiation and context-specific deficit in associative learning in mGluR1 mutant mice. *Cell* **79:**365–375.

Aiba A, Kano M, Chen C, Stanton ME, Fox GD, Herrup K, Zwingman TA, and Tonegawa S (1994b) Deficient cerebellar long-term depression and impaired motor learning in mGluR1 mutant mice. *Cell* **79:**377–388.

Akam EC, Carruthers AM, Nahorski SR, and Challiss RA (1997) Pharmacological characterisation of type 1α metabotropic glutamate receptor-stimulated [^{35}S]GTPγS binding. *Br J Pharmacol* **121:**1203–1209.

Akbar MT, Rattray M, Powell JF, and Meldrum BS (1996) Altered expression of group I metabotropic glutamate receptors in the hippocampus of amygdala-kindled rats. *Brain Res Mol Brain Res* **43:**105–116.

Akiyama K, Yamada N, and Sato M (1987) Increase in ibotenate-stimulated phosphatidylinositol hydrolysis in slices of the amygdala/pyriform cortex and hippocampus of rat by amygdala kindling. *Exp Neurol* **98:**499–508.

Al-Ghoul WM, Meeker RB, and Greenwood RS (1998) Kindled seizures increase metabotropic glutamate receptor expression and function in the rat supraoptic nucleus. *J Neurosci Res* **54:**412–423.

Alaluf S, Mulvihill ER, and McIlhinney RA (1995) Palmitoylation of metabotropic glutamate receptor subtype 4 but not 1α expressed in permanently transfected BHK cells. *Biochem Soc Trans* **23:**87S.

Alvarez FJ, Villalba RM, Carr PA, Grandes P, and Somohano PM (2000) Differential distribution of metabotropic glutamate receptors 1a, 1b, and 5 in the rat spinal cord. *J Comp Neurol* **422:**464–487.

Ango F, Pin JP, Tu JC, Xiao B, Worley PF, Bockaert J, and Fagni L (2000) Dendritic and axonal targeting of type 5 metabotropic glutamate receptor is regulated by homer1 proteins and neuronal excitation. *J Neurosci* **20:**8710–8716.

Ango F, Prézeau L, Muller T, Tu JC, Xiao B, Worley PF, Pin JP, Bockaert J, and Fagni L (2001) Agonist-independent activation of metabotropic glutamate receptors by the intracellular protein Homer. *Nature* **411:**962–965.

Annoura H, Fukunaga A, Uesugi M, Tatsuoka T, and Horikawa Y (1996) A novel class of antagonists for metabotropic glutamate receptors, 7-(hydroxyimino)cyclopropa[*b*]chromen-1*a*-carboxylates. *Bioorg Med Chem Lett* **6:**763–766.

Anwyl R (1999) Metabotropic glutamate receptors: electrophysiological properties and role in plasticity. *Brain Res Brain Res Rev* **29:**83–120.

Aramori I and Nakanishi S (1992) Signal transduction and pharmacological characteristics of a metabotropic glutamate receptor, mGluR1, in transfected CHO cells. *Neuron* **8:**757–765.

Araque A, Sanzgiri RP, Parpura V, and Haydon PG (1999) Astrocyte-induced modulation of synaptic transmission. *Can J Physiol Pharmacol* **77:**699–706.

Aronica E, Catania MV, Geurts J, Yankaya B, and Troost D (2001) Immunohistochemical localization of group I and II metabotropic glutamate receptors in control and amyotrophic lateral sclerosis human spinal cord: upregulation in reactive astrocytes. *Neuroscience* **105:**509–520.

Aronica E, Gorter JA, Jansen GH, van Veelen CW, van Rijen PC, Ramkema M, and Troost D (2003) Expression and cell distribution of group I and group II metabotropic glutamate receptor subtypes in Taylor-type focal cortical dysplasia. *Epilepsia* **44:**785–795.

Arvanov VL, Holmes KH, Keele NB, and Shinnick-Gallagher P (1995) The functional role of metabotropic glutamate receptors in epileptiform activity induced by 4-aminopyridine in the rat amygdala slice. *Brain Res* **669:**140–144.

Awad H, Hubert GW, Smith Y, Levey AI, and Conn PJ (2000) Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. *J Neurosci* **20:**7871–7879.

Awad-Granko H and Conn PJ (2001) Activation of groups I or III metabotropic glutamate receptors inhibits excitatory transmission in the rat subthalamic nucleus. *Neuropharmacology* **41:**32–41.

Baker SR, Goldsworthy J, Harden RC, Salhoff CR, and Schoepp DD (1995) Enzymatic resolution and pharmacological activity of the enantiomers of 3,5-dihydrooxyphenylglycine, a metabotropic glutamate receptor agonist. *Bioorg Med Chem Lett* **5:**223–228.

Bashir ZI, Bortolotto ZA, Davies CH, Berretta N, Irving AJ, Seal AJ, Henley JM, Jane DE, Watkins JC, and Collingridge GL (1993) Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors. *Nature* **363:**347–350.

Batchelor AM and Garthwaite J (1993) Novel synaptic potentials in cerebellar Purkinje cells: probable mediation by metabotropic glutamate receptors. *Neuropharmacology* **32:**11–20.

Batchelor AM, Knöpfel T, Gasparini F, and Garthwaite J (1997) Pharmacological characterization of synaptic transmission through mGluRs in rat cerebellar slices. *Neuropharmacology* **36:**401–403.

Batchelor AM, Madge DJ, and Garthwaite J (1994) Synaptic activation of metabotropic glutamate receptors in the parallel fibre-Purkinje cell pathway in rat cerebellar slices. *Neuroscience* **63:**911–915.

Battaglia G, Bruno V, Pisani A, Centonze D, Catania MV, Calabresi P, and Nicoletti F (2001) Selective blockade of type-1 metabotropic glutamate receptors induces neuroprotection by enhancing gabaergic transmission. *Mol Cell Neurosci* **17:**1071–1083.

Baude A, Nusser Z, Roberts JD, Mulvihill E, McIlhinney RA, and Somogyi P (1993) The metabotropic glutamate receptor (mGluR1α) is concentrated at perisynaptic

membrane of neuronal subpopulations as detected by immunogold reaction. *Neuron* **11:**771–787.
Bell MI, Richardson PJ, and Lee K (2002) Functional and molecular characterization of metabotropic glutamate receptors expressed in rat striatal cholinergic interneurones. *J Neurochem* **81:**142–149.
Berridge MJ (1998) Neuronal calcium signaling. *Neuron* **21:**13–26.
Berthele A, Boxall SJ, Urban A, Anneser JM, Zieglgänsberger W, Urban L, and Tölle TR (1999) Distribution and developmental changes in metabotropic glutamate receptor messenger RNA expression in the rat lumbar spinal cord. *Brain Res Dev Brain Res* **112:**39–53.
Berthele A, Laurie DJ, Platzer S, Zieglgänsberger W, Tölle TR, and Sommer B (1998) Differential expression of rat and human type I metabotropic glutamate receptor splice variant messenger RNAs. *Neuroscience* **85:**733–749.
Bhattacharya M, Babwah AV, Godin C, Anborgh PH, Dale LB, Poulter MO, and Ferguson SS (2004) Ral and phospholipase D2-dependent pathway for constitutive metabotropic glutamate receptor endocytosis. *J Neurosci* **24:**8752–8761.
Bhave G, Karim F, Carlton SM, and Gereau RW 4th (2001) Peripheral group I metabotropic glutamate receptors modulate nociception in mice. *Nat Neurosci* **4:**417–423.
Bhave G, Nadin BM, Brasier DJ, Glauner KS, Shah RD, Heinemann SF, Karim F, and Gereau RW 4th (2003) Membrane topology of a metabotropic glutamate receptor. *J Biol Chem* **278:**30294–30301.
Birse EF, Eaton SA, Jane DE, Jones PL, Porter RH, Pook PC, Sunter DC, Udvarhelyi PM, Wharton B, and Roberts PJ (1993) Phenylglycine derivatives as new pharmacological tools for investigating the role of metabotropic glutamate receptors in the central nervous system. *Neuroscience* **52:**481–488.
Bleakman D, Rusin KI, Chard PS, Glaum SR, and Miller RJ (1992) Metabotropic glutamate receptors potentiate ionotropic glutamate responses in the rat dorsal horn. *Mol Pharmacol* **42:**192–196.
Blümcke I, Becker AJ, Klein C, Scheiwe C, Lie AA, Beck H, Waha A, Friedl MG, Kuhn R, Emson P, et al. (2000) Temporal lobe epilepsy associated up-regulation of metabotropic glutamate receptors: correlated changes in mGluR1 mRNA and protein expression in experimental animals and human patients. *J Neuropathol Exp Neurol* **59:**1–10.
Bond A and Lodge D (1995) Pharmacology of metabotropic glutamate receptor-mediated enhancement of responses to excitatory and inhibitory amino acids on rat spinal neurones in vivo. *Neuropharmacology* **34:**1015–1023.
Bordi F (1996) Reduced long-term potentiation in the dentate gyrus of mGlu1 receptor-mutant mice in vivo. *Eur J Pharmacol* **301:**R15–R16.
Bordi F, Reggiani A, and Conquet F (1997) Regulation of synaptic plasticity by mGluR1 studied in vivo in mGluR1 mutant mice. *Brain Res* **761:**121–126.
Bortolotto ZA, Bashir ZI, Davies CH, and Collingridge GL (1994) A molecular switch activated by metabotropic glutamate receptors regulates induction of long-term potentiation. *Nature* **368:**740–743.
Bortolotto ZA and Collingridge GL (1999) Evidence that a novel metabotropic glutamate receptor mediates the induction of long-term potentiation at CA1 synapses in the hippocampus. *Biochem Soc Trans* **27:**170–174.
Boscia F, Ferraguti F, Moroni F, Annunziato L, and Pellegrini-Giampietro DE (2008) mGlu1α receptors are co-expressed with CB1 receptors in a subset of interneurons in the CA1 region of organotypic hippocampal slice cultures and adult rat brain. *Neuropharmacology* **55:**428–439.
Boxall AR (2000) GABAergic mIPSCs in rat cerebellar Purkinje cells are modulated by TrkB and mGluR1-mediated stimulation of Src. *J Physiol* **524:**677–684.
Boxall AR and Lancaster B (1998) Tyrosine kinases and synaptic transmission. *Eur J Neurosci* **10:**2–7.
Boxall SJ, Thompson SW, Dray A, Dickenson AH, and Urban L (1996) Metabotropic glutamate receptor activation contributes to nociceptive reflex activity in the rat spinal cord in vitro. *Neuroscience* **74:**13–20.
Boyd EA, Alexander SPH, Kendall DA, and Loh VJ (1996) DHPMP: a novel group I specific metabotropic glutamate receptor agonist. *Bioorg Med Chem Lett* **6:**2137–2140.
Braff DL, Grillon C, and Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. *Arch Gen Psychiatry* **49:**206–215.
Brakeman PR, Lanahan AA, O'Brien R, Roche K, Barnes CA, Huganir RL, and Worley PF (1997) Homer: a protein that selectively binds metabotropic glutamate receptors. *Nature* **386:**284–288.
Brasnjo G and Otis TS (2001) Neuronal glutamate transporters control activation of postsynaptic metabotropic glutamate receptors and influence cerebellar long-term depression. *Neuron* **31:**607–616.
Breakwell NA, Rowan MJ, and Anwyl R (1998) (+)-MCPG blocks induction of LTP in CA1 of rat hippocampus via agonist action at an mGluR group II receptor. *J Neurophysiol* **79:**1270–1276.
Brody SA, Conquet F, and Geyer MA (2003a) Disruption of prepulse inhibition in mice lacking mGluR1. *Eur J Neurosci* **18:**3361–3366.
Brody SA, Dulawa SC, Conquet F, and Geyer MA (2004) Assessment of a prepulse inhibition deficit in a mutant mouse lacking mGlu5 receptors. *Mol Psychiatry* **9:**35–41.
Brody SA, Geyer MA, and Large CH (2003b) Lamotrigine prevents ketamine but not amphetamine-induced deficits in prepulse inhibition in mice. *Psychopharmacology (Berl)* **169:**240–246.
Brown RE, Rabe H, and Reymann KG (1994) (RS)-α-methyl-4-carboxyphenylglycine (MCPG) does not block theta burst-induced long-term potentiation in area CA1 of rat hippocampal slices. *Neurosci Lett* **170:**17–21.
Brown SP, Brenowitz SD, and Regehr WG (2003) Brief presynaptic bursts evoke synapse-specific retrograde inhibition mediated by endogenous cannabinoids. *Nat Neurosci* **6:**1048–1057.
Bruno V, Battaglia G, Kingston A, O'Neill MJ, Catania MV, Di Grezia R, and Nicoletti F (1999) Neuroprotective activity of the potent and selective mGlu1a metabotropic glutamate receptor antagonist, (+)-2-methyl-4 carboxyphenylglycine (LY367385): comparison with LY357366, a broader spectrum antagonist with equal affinity for mGlu1a and mGlu5 receptors. *Neuropharmacology* **38:**199–207.
Bruton RK, Ge J, and Barnes NM (1999) Group I mGlu receptor modulation of dopamine release in the rat striatum in vivo. *Eur J Pharmacol* **369:**175–181.
Budai D and Larson AA (1998) The involvement of metabotropic glutamate receptors in sensory transmission in dorsal horn of the rat spinal cord. *Neuroscience* **83:**571–580.
Burgueño J, Canela EI, Mallol J, Lluis C, Franco R, and Ciruela F (2004) Mutual regulation between metabotropic glutamate type 1α receptor and caveolin proteins: from traffick to constitutive activity. *Exp Cell Res* **300:**23–34.
Burgueño J, Enrich C, Canela EI, Mallol J, Lluis C, Franco R, and Ciruela F (2003) Metabotropic glutamate type 1α receptor localizes in low-density caveolin-rich plasma membrane fractions. *J Neurochem* **86:**785–791.
Burke JP and Hablitz JJ (1995) Modulation of epileptiform activity by metabotropic glutamate receptors in immature rat neocortex. *J Neurophysiol* **73:**205–217.
Burset M, Seledtsov IA, and Solovyev VV (2000) Analysis of canonical and non-canonical splice sites in mammalian genomes. *Nucleic Acids Res* **28:**4364–4375.
Buzsáki G (2002) Theta oscillations in the hippocampus. *Neuron* **33:**325–340.
Calabresi P, Centonze D, Pisani A, and Bernardi G (1999) Metabotropic glutamate receptors and cell-type-specific vulnerability in the striatum: implication for ischemia and Huntington's disease. *Exp Neurol* **158:**97–108.
Calabresi P, Pisani A, Mercuri NB, and Bernardi G (1994) Post-receptor mechanisms underlying striatal long-term depression. *J Neurosci* **14:**4871–4881.
Calabresi P, Saulle E, Marfia GA, Centonze D, Mulloy R, Picconi B, Hipskind RA, Conquet F, and Bernardi G (2001) Activation of metabotropic glutamate receptor subtype 1/protein kinase C/mitogen-activated protein kinase pathway is required for postischemic long-term potentiation in the striatum. *Mol Pharmacol* **60:**808–815.
Calò L, Bruno V, Spinsanti P, Molinari G, Korkhov V, Esposito Z, Patanè M, Melchiorri D, Freissmuth M, and Nicoletti F (2005) Interactions between ephrin-B and metabotropic glutamate 1 receptors in brain tissue and cultured neurons. *J Neurosci* **25:**2245–2254.
Camón L, Vives P, de Vera N, and Martínez E (1998) Seizures and neuronal damage induced in the rat by activation of group I metabotropic glutamate receptors with their selective agonist 3,5-dihydroxyphenylglycine. *J Neurosci Res* **51:**339–348.
Canepari M, Auger C, and Ogden D (2004) Ca^{2+} ion permeability and single-channel properties of the metabotropic slow EPSC of rat Purkinje neurons. *J Neurosci* **24:**3563–3573.
Canepari M and Ogden D (2003) Evidence for protein tyrosine phosphatase, tyrosine kinase, and G-protein regulation of the parallel fiber metabotropic slow EPSC of rat cerebellar Purkinje neurons. *J Neurosci* **23:**4066–4071.
Canepari M, Papageorgiou G, Corrie JE, Watkins C, and Ogden D (2001) The conductance underlying the parallel fibre slow EPSP in rat cerebellar Purkinje neurones studied with photolytic release of L-glutamate. *J Physiol* **533:**765–772.
Cao CQ, Evans RH, Headley PM, and Udvarhelyi PM (1995) A comparison of the effects of selective metabotropic glutamate receptor agonists on synaptically evoked whole cell currents of rat spinal ventral horn neurones in vitro. *Br J Pharmacol* **115:**1469–1474.
Carlson GC, Slawecki ML, Lancaster E, and Keller A (1997) Distribution and activation of intracellular Ca^{2+} stores in cultured olfactory bulb neurons. *J Neurophysiol* **78:**2176–2185.
Carmant L, Woodhall G, Ouardouz M, Robitaille R, and Lacaille JC (1997) Interneuron-specific Ca^{2+} responses linked to metabotropic and ionotropic glutamate receptors in rat hippocampal slices. *Eur J Neurosci* **9:**1625–1635.
Carroll FY, Stolle A, Beart PM, Voerste A, Brabet I, Mauler F, Joly C, Antonicek H, Bockaert J, Müller T, et al. (2001) BAY36–7620: a potent non-competitive mGlu1 receptor antagonist with inverse agonist activity. *Mol Pharmacol* **59:**965–973.
Carruthers AM, Challiss RA, Mistry R, Saunders R, Thomsen C, and Nahorski SR (1997) Enhanced type 1α metabotropic glutamate receptor-stimulated phosphoinositide signaling after pertussis toxin treatment. *Mol Pharmacol* **52:**406–414.
Cartmell J, Curtis AR, Kemp JA, Kendall DA, and Alexander SP (1993) Subtypes of metabotropic excitatory amino acid receptor distinguished by stereoisomers of the rigid glutamate analogue, 1-aminocyclopentane-1,3-dicarboxylate. *Neurosci Lett* **153:**107–110.
Casabona G, Catania MV, Storto M, Ferraris N, Perroteau I, Fasolo A, Nicoletti F, and Bovolin P (1998) Deafferentation up-regulates the expression of the mGlu1a metabotropic glutamate receptor protein in the olfactory bulb. *Eur J Neurosci* **10:**771–776.
Casabona G, Knöpfel T, Kuhn R, Gasparini F, Baumann P, Sortino MA, Copani A, and Nicoletti F (1997) Expression and coupling to polyphosphoinositide hydrolysis of group I metabotropic glutamate receptors in early postnatal and adult rat brain. *Eur J Neurosci* **9:**12–17.
Catania MV, Aronica E, Sortino MA, Canonico PL, and Nicoletti F (1990) Homologous desensitization of metabolotropic glutamate receptors in neuronal cultures. *Pharmacol Res* **22 (Suppl 1):**79–80.
Catania MV, Bellomo M, Di Giorgi-Gerevini V, Seminara G, Giuffrida R, Romeo R, De Blasi A, and Nicoletti F (2001) Endogenous activation of group-I metabotropic glutamate receptors is required for differentiation and survival of cerebellar Purkinje cells. *J Neurosci* **21:**7664–7673.
Cerne R and Randic M (1992) Modulation of AMPA and NMDA responses in rat spinal dorsal horn neurons by trans-1-aminocyclopentane-1,3-dicarboxylic acid. *Neurosci Lett* **144:**180–184.
Chan WY, Soloviev MM, Ciruela F, and McIlhinney RA (2001) Molecular determinants of metabotropic glutamate receptor 1B trafficking. *Mol Cell Neurosci* **17:**577–588.
Chapman AG, Elwes RD, Millan MH, Polkey CE, and Meldrum BS (1996) Role of glutamate and aspartate in epileptogenesis; contribution of microdialysis studies in animal and man. *Epilepsy Res Suppl* **12:**239–246.
Chapman AG, Yip PK, Yap JS, Quinn LP, Tang E, Harris JR, and Meldrum BS (1999) Anticonvulsant actions of LY 367385 ((+)-2-methyl-4-carboxyphenylglycine) and AIDA ((*RS*)-1-aminoindan-1,5-dicarboxylic acid). *Eur J Pharmacol* **368:**17–24.
Chavis P, Ango F, Michel JM, Bockaert J, and Fagni L (1998) Modulation of big K^+

channel activity by ryanodine receptors and L-type Ca^{2+} channels in neurons. *Eur J Neurosci* **10:**2322–2327.
Chavis P, Fagni L, Bockaert J, and Lansman JB (1995) Modulation of calcium channels by metabotropic glutamate receptors in cerebellar granule cells. *Neuropharmacology* **34:**929–937.
Chavis P, Fagni L, Lansman JB, and Bockaert J (1996) Functional coupling between ryanodine receptors and L-type calcium channels in neurons. *Nature* **382:**719–722.
Chemin J, Girard C, Duprat F, Lesage F, Romey G, and Lazdunski M (2003) Mechanisms underlying excitatory effects of group I metabotropic glutamate receptors via inhibition of 2P domain K^+ channels. *EMBO J* **22:**5403–5411.
Chen J, Larionov S, Pitsch J, Hoerold N, Ullmann C, Elger CE, Schramm J, and Becker AJ (2005) Expression analysis of metabotropic glutamate receptors I and III in mouse strains with different susceptibility to experimental temporal lobe epilepsy. *Neurosci Lett* **375:**192–197.
Chinestra P, Aniksztejn L, Diabira D, and Ben-Ari Y (1993) (RS)-α-methyl-4-carboxyphenylglycine neither prevents induction of LTP nor antagonizes metabotropic glutamate receptors in CA1 hippocampal neurons. *J Neurophysiol* **70:**2684–2689.
Choi S and Lovinger DM (1996) Metabotropic glutamate receptor modulation of voltage-gated Ca^{2+} channels involves multiple receptor subtypes in cortical neurons. *J Neurosci* **16:**36–45.
Chojnacka-Wójcik E, Tatarczyńska E, and Pilc A (1997) The anxiolytic-like effect of metabotropic glutamate receptor antagonists after intrahippocampal injection in rats. *Eur J Pharmacol* **319:**153–156.
Chuang SC, Bianchi R, Kim D, Shin HS, and Wong RK (2001) Group I metabotropic glutamate receptors elicit epileptiform discharges in the hippocampus through PLCβ1 signaling. *J Neurosci* **21:**6387–6394.
Chuang SC, Bianchi R, and Wong RK (2000) Group I mGluR activation turns on a voltage-gated inward current in hippocampal pyramidal cells. *J Neurophysiol* **83:**2844–2853.
Chuang SC, Zhao W, Young SR, Conquet F, Bianchi R, and Wong RK (2002) Activation of group I mGluRs elicits different responses in murine CA1 and CA3 pyramidal cells. *J Physiol* **541:**113–121.
Ciruela F, Escriche M, Burgueno J, Angulo E, Casado V, Soloviev MM, Canela EI, Mallol J, Chan WY, Lluis C, et al. (2001) Metabotropic glutamate 1α and adenosine A1 receptors assemble into functionally interacting complexes. *J Biol Chem* **276:** 18345–18351.
Ciruela F and McIlhinney RA (1997) Differential internalisation of mGluR1 splice variants in response to agonist and phorbol esters in permanently transfected BHK cells. *FEBS Lett* **418:**83–86.
Ciruela F and McIlhinney RA (2001) Metabotropic glutamate receptor type 1α and tubulin assemble into dynamic interacting complexes. *J Neurochem* **76:**750–757.
Ciruela F, Robbins MJ, Willis AC, and McIlhinney RA (1999a) Interactions of the C terminus of metabotropic glutamate receptor type 1α with rat brain proteins: evidence for a direct interaction with tubulin. *J Neurochem* **72:**346–354.
Ciruela F, Soloviev MM, Chan WY, and McIlhinney RA (2000) Homer-1c/Vesl-1L modulates the cell surface targeting of metabotropic glutamate receptor type 1α: evidence for an anchoring function. *Mol Cell Neurosci* **15:**36–50.
Ciruela F, Soloviev MM, and McIlhinney RA (1999b) Co-expression of metabotropic glutamate receptor type 1α with homer-1a/Vesl-1S increases the cell surface expression of the receptor. *Biochem J* **341:**795–803.
Clark BP, Baker RS, Goldsworthy J, Harris JR, and Kingston AE (1997) 2-Methyl-4-carboxyphenylglycine(LY367385) selectively antagonises metabotropic glutamate mGluR1 receptors. *Bioorg Med Chem Lett* **7:**2777–2780.
Clark BP, Harris JR, Kingston AE, and McManus, D (1998) α-Substituted phenylglycines as group I metabotropic glutamate receptor antagonists (Abstract), in *Proceedings of the 15th European International Symposium on Medicinal Chemistry*; 1998 Sept 6–10; Edinburgh, Scotland. Royal Society of Chemistry, Cambridge, UK.
Cobb SR, Buhl EH, Halasy K, Paulsen O, and Somogyi P (1995) Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons. *Nature* **378:**75–78.
Coesmans M, Smitt PA, Linden DJ, Shigemoto R, Hirano T, Yamakawa Y, van Alphen AM, Luo C, van der Geest JN, Kros JM, et al. (2003) Mechanisms underlying cerebellar motor deficits due to mGluR1-autoantibodies. *Ann Neurol* **53:**325–336.
Conn PJ, Battaglia G, Marino MJ, and Nicoletti F (2005) Metabotropic glutamate receptors in the basal ganglia motor circuit. *Nat Rev Neurosci* **6:**787–798.
Conquet F, Bashir ZI, Davies CH, Daniel H, Ferraguti F, Bordi F, Franz-Bacon K, Reggiani A, Matarese V, and Condé F (1994) Motor deficit and impairment of synaptic plasticity in mice lacking mGluR1. *Nature* **372:**237–243.
Copani A, Canonico PL, Catania MV, Aronica E, Bruno V, Ratti E, van Amsterdam FT, Gaviraghi G, and Nicoletti F (1991) Interaction between β-*N*-methylamino-L-alanine and excitatory amino acid receptors in brain slices and neuronal cultures. *Brain Res* **558:**79–86.
Costantino G, Macchiarulo A, and Pellicciari R (1999) Modeling of amino-terminal domains of group I metabotropic glutamate receptors: structural motifs affecting ligand selectivity. *J Med Chem* **42:**5390–5401.
Costantino G, Marinozzi M, Camaioni E, Natalini B, Sarichelou I, Micheli F, Cavanni P, Faedo S, Noe C, Moroni F, et al. (2004) Stereoselective synthesis and preliminary evaluation of (+)- and (−)-3-methyl-5-carboxy-thien-2-yl-glycine (3-MATIDA): identification of (+)-3-MATIDA as a novel mGluR1 competitive antagonist. *Farmaco* **59:**93–99.
Crepaldi L, Lackner C, Corti C, and Ferraguti F (2007) Transcriptional activators and repressors for the neuron-specific expression of a metabotropic glutamate receptor. *J Biol Chem* **282:**17877–17889.
Crepel F, Daniel H, Hemart N, and Jaillard D (1991) Effects of ACPD and AP3 on parallel-fibre-mediated EPSPs of Purkinje cells in cerebellar slices in vitro. *Exp Brain Res* **86:**402–406.
Crepel F, Delhaye-Bouchaud N, Guastavino JM, and Sampaio I (1980) Multiple innervation of cerebellar Purkinje cells by climbing fibres in staggerer mutant mouse. *Nature* **283:**483–484.
Csicsvari J, Hirase H, Mamiya A, and Buzsáki G (2000) Ensemble patterns of hippocampal CA3-CA1 neurons during sharp wave-associated population events. *Neuron* **28:**585–594.
Dale LB, Babwah AV, and Ferguson SS (2002) Mechanisms of metabotropic glutamate receptor desensitization: role in the patterning of effector enzyme activation. *Neurochem Int* **41:**319–326.
Dale LB, Bhattacharya M, Anborgh PH, Murdoch B, Bhatia M, Nakanishi S, and Ferguson SS (2000) G protein-coupled receptor kinase-mediated desensitization of metabotropic glutamate receptor 1A protects against cell death. *J Biol Chem* **275:**38213–38220.
Dale LB, Bhattacharya M, Seachrist JL, Anborgh PH, and Ferguson SS (2001) Agonist-stimulated and tonic internalization of metabotropic glutamate receptor 1a in human embryonic kidney 293 cells: agonist-stimulated endocytosis is beta-arrestin1 isoform-specific. *Mol Pharmacol* **60:**1243–1253.
Daniel H, Levenes C, Conquet F, and Crépel F (1996) mGluR1 mutant mice as a tool to study calcium signalling and multiple innervation in the cerebellum. *J Physiol Paris* **90:**171–172.
Dehnes Y, Chaudhry FA, Ullensvang K, Lehre KP, Storm-Mathisen J, and Danbolt NC (1998) The glutamate transporter EAAT4 in rat cerebellar Purkinje cells: a glutamate-gated chloride channel concentrated near the synapse in parts of the dendritic membrane facing astroglia. *J Neurosci* **18:**3606–3619.
del Río E, McLaughlin M, Downes CP, and Nicholls DG (1999) Differential coupling of G-protein-linked receptors to Ca^{2+} mobilization through inositol(1,4,5)trisphosphate or ryanodine receptors in cerebellar granule cells in primary culture. *Eur J Neurosci* **11:**3015–3022.
Desai MA, Burnett JP, Mayne NG, and Schoepp DD (1996) Pharmacological characterization of desensitization in a human mGlu1α-expressing non-neuronal cell line co-transfected with a glutamate transporter. *Br J Pharmacol* **118:**1558–1564.
Dewing P, Boulware MI, Sinchak K, Christensen A, Mermelstein PG, and Micevych P (2007) Membrane estrogen receptor-α interactions with metabotropic glutamate receptor 1a modulate female sexual receptivity in rats. *J Neurosci* **27:**9294–9300.
Dhami GK, Dale LB, Anborgh PH, O'Connor-Halligan KE, Sterne-Marr R, and Ferguson SS (2004) G protein-coupled receptor kinase 2 regulator of G protein signaling homology domain binds to both metabotropic glutamate receptor 1a and $G\alpha_q$ to attenuate signaling. *J Biol Chem* **279:**16614–16620.
Diño MR, Schuerger RJ, Liu Y, Slater NT, and Mugnaini E (2000) Unipolar brush cell: a potential feedforward excitatory interneuron of the cerebellum. *Neuroscience* **98:**625–636.
Doherty AJ, Collingridge GL, and Jane DE (1999a) Antagonist activity of α-substituted 4-carboxyphenylglycine analogues at group I metabotropic glutamate receptors expressed in CHO cells. *Br J Pharmacol* **126:**205–210.
Doherty AJ, Coutinho V, Collingridge GL, and Henley JM (1999b) Rapid internalization and surface expression of a functional, fluorescently tagged G-protein-coupled glutamate receptor. *Biochem J* **341:**415–422.
Dohlman HG and Thorner J (1997) RGS proteins and signaling by heterotrimeric G proteins. *J Biol Chem* **272:**3871–3874.
Dolan S and Nolan AM (2000) Behavioural evidence supporting a differential role for group I and II metabotropic glutamate receptors in spinal nociceptive transmission. *Neuropharmacology* **39:**1132–1138.
Duguid IC, Pankratov Y, Moss GW, and Smart TG (2007) Somatodendritic release of glutamate regulates synaptic inhibition in cerebellar Purkinje cells via autocrine mGluR1 activation. *J Neurosci* **27:**12464–12474.
Dulawa SC and Geyer MA (1996) Psychopharmacology of prepulse inhibition in mice. *Chin J Physiol* **39:**139–146.
Duvoisin RM, Zhang C, and Ramonell K (1995) A novel metabotropic glutamate receptor expressed in the retina and olfactory bulb. *J Neurosci* **15:**3075–3083.
Dzubay JA and Otis TS (2002) Climbing fiber activation of metabotropic glutamate receptors on cerebellar Purkinje neurons. *Neuron* **36:**1159–1167.
East SJ and Garthwaite J (1992) Actions of a metabotropic glutamate receptor agonist in immature and adult rat cerebellum. *Eur J Pharmacol* **219:**395–400.
Eaton SA, Jane DE, Jones PL, Porter RH, Pook PC, Sunter DC, Udvarhelyi PM, Roberts PJ, Salt TE, and Watkins JC (1993) Competitive antagonism at metabotropic glutamate receptors by (*S*)-4-carboxyphenylglycine and (*RS*)-α-methyl-4-carboxyphenylglycine. *Eur J Pharmacol* **244:**195–197.
Ebling FJ (1996) The role of glutamate in the photic regulation of the suprachiasmatic nucleus. *Prog Neurobiol* **50:**109–132.
Fagni L, Chavis P, Ango F, and Bockaert J (2000) Complex interactions between mGluRs, intracellular Ca^{2+} stores and ion channels in neurons. *Trends Neurosci* **23:**80–88.
Fairbanks DM, Stormann TM, Artman LD, Hammerland LG, Heaton WL, Krapcho KJ, Levinthal C, Moe ST, Mueller AM, Sheehan SK, et al. (2001) Structure-activity relationship studies of NPS 2407 and NPS 3018: potent and selective metabotropic glutamate receptor 1 antagonists. *Soc Neurosci Abstr* **27:**705.4.
Fan GF, Ray K, Zhao XM, Goldsmith PK, and Spiegel AM (1998) Mutational analysis of the cysteines in the extracellular domain of the human Ca^{2+} receptor: effects on cell surface expression, dimerization and signal transduction. *FEBS Lett* **436:**353–356.
Favaron M, Rimland JM, and Manev H (1992) Depolarization- and agonist-regulated expression of neuronal metabotropic glutamate receptor 1 (mGluR1). *Life Sci* **50:**PL189–PL194.
Ferraguti F, Baldani-Guerra B, Corsi M, Nakanishi S, and Corti C (1999) Activation of the extracellular signal-regulated kinase 2 by metabotropic glutamate receptors. *Eur J Neurosci* **11:**2073–2082.
Ferraguti F, Cavanni P, Eistetter H, Salvagno C, Ratti E, and Trist DG (1994) Competitive antagonism by phenylglycine derivatives at type I metabotropic glutamate receptors. *Mol Cell Neurosci* **5:**269–276.
Ferraguti F, Cobden P, Pollard M, Cope D, Shigemoto R, Watanabe M, and Somogyi P (2004) Immunolocalization of metabotropic glutamate receptor 1α (mGluR1α) in

distinct classes of interneuron in the CA1 region of the rat hippocampus. *Hippocampus* **14:**193–215.
Ferraguti F, Conquet F, Corti C, Grandes P, Kuhn R, and Knopfel T (1998) Immunohistochemical localization of the mGluR1β metabotropic glutamate receptor in the adult rodent forebrain: evidence for a differential distribution of mGluR1 splice variants. *J Comp Neurol* **400:**391–407.
Ferraguti F, Fukazawa Y, Watanabe M, and Shigemoto R (2007) Intrasynaptic enrichment of mGlu1 receptors in GABAergic synapses as revealed by SDS-digested freeze-fracture replica labelling. *Soc Neurosci Abstr* **33:**679.9/F38.
Ferraris N, Perroteau I, De Marchis S, Fasolo A, and Bovolin P (1997) Glutamatergic deafferentation of olfactory bulb modulates the expression of mGluR1a mRNA. *Neuroreport* **8:**1949–1953.
Finch EA and Augustine GJ (1998) Local calcium signalling by inositol-1,4,5-trisphosphate in Purkinje cell dendrites. *Nature* **396:**753–756.
Fiorillo CD and Williams JT (1998) Glutamate mediates an inhibitory postsynaptic potential in dopamine neurons. *Nature* **394:**78–82.
Fisher K and Coderre TJ (1996) The contribution of metabotropic glutamate receptors (mGluRs) to formalin-induced nociception. *Pain* **68:**255–263.
Fisher K and Coderre TJ (1998) Hyperalgesia and allodynia induced by intrathecal (RS)-dihydroxyphenylglycine in rats. *Neuroreport* **9:**1169–1172.
Fitzjohn SM, Bortolotto ZA, Palmer MJ, Doherty AJ, Ornstein PL, Schoepp DD, Kingston AE, Lodge D, and Collingridge GL (1998) The potent mGlu receptor antagonist LY341495 identifies roles for both cloned and novel mGlu receptors in hippocampal synaptic plasticity. *Neuropharmacology* **37:**1445–1458.
Flor PJ, Gomeza J, Tones MA, Kuhn R, Pin JP, and Knöpfel T (1996) The C-terminal domain of the mGluR1 metabotropic glutamate receptor affects sensitivity to agonists. *J Neurochem* **67:**58–63.
Fotuhi M, Sharp AH, Glatt CE, Hwang PM, von Krosigk M, Snyder SH, and Dawson TM (1993) Differential localization of phosphoinositide-linked metabotropic glutamate receptor (mGluR1) and the inositol 1,4,5-trisphosphate receptor in rat brain. *J Neurosci* **13:**2001–2012.
Fotuhi M, Standaert DG, Testa CM, Penney JB Jr, and Young AB (1994) Differential expression of metabotropic glutamate receptors in the hippocampus and entorhinal cortex of the rat. *Brain Res Mol Brain Res* **21:**283–292.
Francesconi A and Duvoisin RM (1998) Role of the second and third intracellular loops of metabotropic glutamate receptors in mediating dual signal transduction activation. *J Biol Chem* **273:**5615–5624.
Francesconi A and Duvoisin RM (2000) Opposing effects of protein kinase C and protein kinase A on metabotropic glutamate receptor signaling: selective desensitization of the inositol trisphosphate/Ca^{2+} pathway by phosphorylation of the receptor-G protein-coupling domain. *Proc Natl Acad Sci U S A* **97:**6185–6190.
Francesconi A and Duvoisin RM (2002) Alternative splicing unmasks dendritic and axonal targeting signals in metabotropic glutamate receptor 1. *J Neurosci* **22:** 2196–2205.
Fundytus ME, Fisher K, Dray A, Henry JL, and Coderre TJ (1998) In vivo antinociceptive activity of anti-rat mGluR1 and mGluR5 antibodies in rats. *Neuroreport* **9:**731–735.
Fundytus ME, Osborne MG, Henry JL, Coderre TJ, and Dray A (2002) Antisense oligonucleotide knockdown of mGluR1 alleviates hyperalgesia and allodynia associated with chronic inflammation. *Pharmacol Biochem Behav* **73:**401–410.
Fundytus ME, Yashpal K, Chabot JG, Osborne MG, Lefebvre CD, Dray A, Henry JL, and Coderre TJ (2001) Knockdown of spinal metabotropic glutamate receptor 1 ($mGluR_1$) alleviates pain and restores opioid efficacy after nerve injury in rats. *Br J Pharmacol* **132:**354–367.
Galante M and Diana MA (2004) Group I metabotropic glutamate receptors inhibit GABA release at interneuron-Purkinje cell synapses through endocannabinoid production. *J Neurosci* **24:**4865–4874.
Galik J, Youn DH, Kolaj M, and Randić M (2008) Involvement of group I metabotropic glutamate receptors and glutamate transporters in the slow excitatory synaptic transmission in the spinal cord dorsal horn. *Neuroscience* **154:**1372–1387.
Galoyan SM and Merlin LR (2000) Long-lasting potentiation of epileptiform bursts by group I mGluRs is NMDA receptor independent. *J Neurophysiol* **83:**2463–2467.
Ganesh S, Amano K, and Yamakawa K (2000) Assignment of the gene GRM1 coding for metabotropic glutamate receptor 1 to human chromosome band 6q24 by in situ hybridization. *Cytogenet Cell Genet* **88:**314–315.
Gao W, Dunbar RL, Chen G, Reinert KC, Oberdick J, and Ebner TJ (2003) Optical imaging of long-term depression in the mouse cerebellar cortex in vivo. *J Neurosci* **23:**1859–1866.
Gee CE, Benquet P, and Gerber U (2003) Group I metabotropic glutamate receptors activate a calcium-sensitive transient receptor potential-like conductance in rat hippocampus. *J Physiol* **546:**655–664.
Geiling H and Schild D (1996) Glutamate-mediated release of Ca^{2+} in mitral cells of the olfactory bulb. *J Neurophysiol* **76:**563–570.
Gil-Sanz C, Delgado-García JM, Fairén A, and Gruart A (2008) Involvement of the mGluR1 receptor in hippocampal synaptic plasticity and associative learning in behaving mice. *Cereb Cortex* **18:**1653–1663.
Glaum SR, Slater NT, Rossi DJ, and Miller RJ (1992) Role of metabotropic glutamate (ACPD) receptors at the parallel fiber-Purkinje cell synapse. *J Neurophysiol* **68:** 1453–1462.
Godwin DW, Van Horn SC, Eriir A, Sesma M, Romano C, and Sherman SM (1996) Ultrastructural localization suggests that retinal and cortical inputs access different metabotropic glutamate receptors in the lateral geniculate nucleus. *J Neurosci* **16:**8181–8192.
Gomeza J, Joly C, Kuhn R, Knöpfel T, Bockaert J, and Pin JP (1996) The second intracellular receptor 1 cooperates with the other intracellular domains to control coupling to G-proteins. *J Biol Chem* **271:**2199–2205.
Gorcs TJ, Penke B, Boti Z, Katarova Z, and Hámori J (1993) Immunohistochemical visualization of a metabotropic glutamate receptor. *Neuroreport* **4:**283–286.
Grandes P, Mateos JM, Rüegg D, Kuhn R, and Knöpfel T (1994) Differential cellular localization of three splice variants of the mGluR1 metabotropic glutamate receptor in rat cerebellum. *Neuroreport* **5:**2249–2252.
Gravius A, Barberi C, Schäfer D, Schmidt WJ, and Danysz W (2006) The role of group I metabotropic glutamate receptors in acquisition and expression of contextual and auditory fear conditioning in rats—a comparison. *Neuropharmacology* **51:**1146–1155.
Greene JG and Greenamyre JT (1996) Bioenergetics and glutamate excitotoxicity. *Prog Neurobiol* **48:**613–634.
Greenwood RS, Fan Z, McHugh R, and Meeker R (2000) Inhibition of hippocampal kindling by metabotropic glutamate receptor antisense oligonucleotides. *Mol Cell Neurosci* **16:**233–243.
Gruol DL, Netzeband JG, and Parsons KL (1996) Ca^{2+} signaling pathways linked to glutamate receptor activation in the somatic and dendritic regions of cultured cerebellar Purkinje neurons. *J Neurophysiol* **76:**3325–3340.
Guatteo E, Mercuri NB, Bernardi G, and Knöpfel T (1999) Group I metabotropic glutamate receptors mediate an inward current in rat substantia nigra dopamine neurons that is independent from calcium mobilization. *J Neurophysiol* **82:**1974–1981.
Gubellini P, Pisani A, Centonze D, Bernardi G, and Calabresi P (2004) Metabotropic glutamate receptors and striatal synaptic plasticity: implications for neurological diseases. *Prog Neurobiol* **74:**271–300.
Gubellini P, Saulle E, Centonze D, Bonsi P, Pisani A, Bernardi G, Conquet F, and Calabresi P (2001) Selective involvement of mGlu1 receptors in corticostriatal LTD. *Neuropharmacology* **40:**839–846.
Gubellini P, Saulle E, Centonze D, Costa C, Tropepi D, Bernardi G, Conquet F, and Calabresi P (2003) Corticostriatal LTP requires combined mGluR1 and mGluR5 activation. *Neuropharmacology* **44:**8–16.
Guo W, Wei F, Zou S, Robbins MT, Sugiyo S, Ikeda T, Tu JC, Worley PF, Dubner R, and Ren K (2004) Group I metabotropic glutamate receptor NMDA receptor coupling and signaling cascade mediate spinal dorsal horn NMDA receptor 2B tyrosine phosphorylation associated with inflammatory hyperalgesia. *J Neurosci* **24:**9161–9173.
Hámori J, Takács J, and Görcs TJ (1996) Immunocytochemical localization of mGluR1a metabotropic glutamate receptor in inhibitory interneurons of the cerebellar cortex. *Acta Biol Hung* **47:**181–194.
Hampson DR, Theriault E, Huang XP, Kristensen P, Pickering DS, Franck JE, and Mulvihill ER (1994) Characterization of two alternatively spliced forms of a metabotropic glutamate receptor in the central nervous system of the rat. *Neuroscience* **60:**325–336.
Hansel C and Linden DJ (2000) Long-term depression of the cerebellar climbing fiber-Purkinje neuron synapse. *Neuron* **26:**473–482.
Hansel C, Linden DJ, and D'Angelo E (2001) Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. *Nat Neurosci* **4:**467–475.
Hanson JE and Smith Y (1999) Group I metabotropic glutamate receptors at GABAergic synapses in monkeys. *J Neurosci* **19:**6488–6496.
Hartmann J, Blum R, Kovalchuk Y, Adelsberger H, Kuner R, Durand GM, Miyata M, Kano M, Offermanns S, and Konnerth A (2004) Distinct roles of $G\alpha_q$ and $G\alpha_{11}$ for Purkinje cell signaling and motor behavior. *J Neurosci* **24:**5119–5130.
Hashimoto K, Ichikawa R, Takechi H, Inoue Y, Aiba A, Sakimura K, Mishina M, Hashikawa T, Konnerth A, Watanabe M, et al. (2001) Roles of glutamate receptor delta 2 subunit (GluRδ2) and metabotropic glutamate receptor subtype 1 (mGluR1) in climbing fiber synapse elimination during postnatal cerebellar development. *J Neurosci* **21:**9701–9712.
Hashimoto K and Kano M (2003) Functional differentiation of multiple climbing fiber inputs during synapse elimination in the developing cerebellum. *Neuron* **38:**785–796.
Hay M and Kunze DL (1994) Glutamate metabotropic receptor inhibition of voltage-gated calcium currents in visceral sensory neurons. *J Neurophysiol* **72:**421–430.
Hayashi Y, Sekiyama N, Nakanishi S, Jane DE, Sunter DC, Birse EF, Udvarhelyi PM, and Watkins JC (1994) Analysis of agonist and antagonist activities of phenylglycine derivatives for different cloned metabotropic glutamate receptor subtypes. *J Neurosci* **14:**3370–3377.
Hayashi Y, Tanabe Y, Aramori I, Masu M, Shimamoto K, Ohfune Y, and Nakanishi S (1992) Agonist analysis of 2-(carboxycyclopropyl)glycine isomers for cloned metabotropic glutamate receptor subtypes expressed in Chinese hamster ovary cells. *Br J Pharmacol* **107:**539–543.
Heidinger V, Manzerra P, Wang XQ, Strasser U, Yu SP, Choi DW, and Behrens MM (2002) Metabotropic glutamate receptor 1-induced upregulation of NMDA receptor current: mediation through the Pyk2/Src-family kinase pathway in cortical neurons. *J Neurosci* **22:**5452–5461.
Heinbockel T, Heyward P, Conquet F, and Ennis M (2004) Regulation of main olfactory bulb mitral cell excitability by metabotropic glutamate receptor mGluR1. *J Neurophysiol* **92:**3085–3096.
Hermans E, Challiss RA, and Nahorski SR (1999) Effects of varying the expression level of recombinant human mGlu1α receptors on the pharmacological properties of agonists and antagonists. *Br J Pharmacol* **126:**873–882.
Hermans E, Saunders R, Selkirk JV, Mistry R, Nahorski SR, and Challiss RA (2000) Complex involvement of pertussis toxin-sensitive G proteins in the regulation of type 1α metabotropic glutamate receptor signaling in baby hamster kidney cells. *Mol Pharmacol* **58:**352–360.
Hermans E, Young KW, Challiss RA, and Nahorski SR (1998) Effects of human type 1α metabotropic glutamate receptor expression level on phosphoinositide and Ca^{2+} signalling in an inducible cell expression system. *J Neurochem* **70:**1772–1775.
Heuss C, Scanziani M, Gähwiler BH, and Gerber U (1999) G-protein-independent signaling mediated by metabotropic glutamate receptors. *Nat Neurosci* **2:**1070–1077.
Heyward P, Ennis M, Keller A, and Shipley MT (2001) Membrane bistability in olfactory bulb mitral cells. *J Neurosci* **21:**5311–5320.
Hiltscher R, Seuwen K, Boddeke HW, Sommer B, and Laurie DJ (1998) Functional coupling of human metabotropic glutamate receptor hmGlu1d: comparison to splice variants hmGlu1a and -1b. *Neuropharmacology* **37:**827–837.
Hirai H, Yoshioka K, and Yamada K (1999) Regulation of phosphatidylcholine

biosynthesis by mGluR1α expressed in human embryonic kidney 293 cells—a ^{31}P-NMR study. *Mol Cell Neurosci* **14:**444–454.

Hirono M, Konishi S, and Yoshioka T (1998) Phospholipase C-independent group I metabotropic glutamate receptor-mediated inward current in mouse Purkinje cells. *Biochem Biophys Res Commun* **251:**753–758.

Hirono M, Yoshioka T, and Konishi S (2001) $GABA_B$ receptor activation enhances mGluR-mediated responses at cerebellar excitatory synapses. *Nat Neurosci* **4:**1207–1216.

Hirose M, Kitano J, Nakajima Y, Moriyoshi K, Yanagi S, Yamamura H, Muto T, Jingami H, and Nakanishi S (2004) Phosphorylation and recruitment of Syk by immunoreceptor tyrosine-based activation motif-based phosphorylation of tamalin. *J Biol Chem* **279:**32308–32315.

Hlavackova V, Goudet C, Kniazeff J, Zikova A, Maurel D, Vol C, Trojanova J, Prézeau L, Pin JP, and Blahos J (2005) Evidence for a single heptahelical domain being turned on upon activation of a dimeric GPCR. *EMBO J* **24:**499–509.

Houamed KM, Kuijper JL, Gilbert TL, Haldeman BA, O'Hara PJ, Mulvihill ER, Almers W, and Hagen FS (1991) Cloning, expression, and gene structure of a G protein-coupled glutamate receptor from rat brain. *Science* **252:**1318–1321.

Hsia AY, Salin PA, Castillo PE, Aiba A, Abeliovich A, Tonegawa S, and Nicoll RA (1995) Evidence against a role for metabotropic glutamate receptors in mossy fiber LTP: the use of mutant mice and pharmacological antagonists. *Neuropharmacology* **34:**1567–1572.

Hu J, Hauache O, and Spiegel AM (2000) Human Ca^{2+} receptor cysteine-rich domain: analysis of function of mutant and chimeric receptors. *J Biol Chem* **275:**16382–16389.

Huang CC, You JL, Wu MY, and Hsu KS (2004) Rap1-induced p38 mitogen-activated protein kinase activation facilitates AMPA receptor trafficking via the GDI. Rab5 complex: potential role in (*S*)-3,5-dihydroxyphenylglycene-induced long term depression. *J Biol Chem* **279:**12286–12292.

Huang H and van den Pol AN (2007) Rapid direct excitation and long-lasting enhancement of NMDA response by group I metabotropic glutamate receptor activation of hypothalamic melanin-concentrating hormone neurons. *J Neurosci* **27:**11560–11572.

Hubert GW, Paquet M, and Smith Y (2001) Differential subcellular localization of mGluR1a and mGluR5 in the rat and monkey substantia nigra. *J Neurosci* **21:** 1838–1847.

Hughes SW, Cope DW, Blethyn KL, and Crunelli V (2002) Cellular mechanisms of the slow (<1 Hz) oscillation in thalamocortical neurons in vitro. *Neuron* **33:**947–958.

Hwang JI, Kim HS, Lee JR, Kim E, Ryu SH, and Suh PG (2005) The interaction of phospholipase C-β3 with shank2 regulates mGluR-mediated calcium signal. *J Biol Chem* **280:**12467–12473.

Iacovelli L, Salvatore L, Capobianco L, Picascia A, Barletta E, Storto M, Mariggiò S, Sallese M, Porcellini A, Nicoletti F, et al. (2003) Role of G protein-coupled receptor kinase 4 and β-arrestin 1 in agonist-stimulated metabotropic glutamate receptor 1 internalization and activation of mitogen-activated protein kinases. *J Biol Chem* **278:**12433–12442.

Ichise T, Kano M, Hashimoto K, Yanagihara D, Nakao K, Shigemoto R, Katsuki M, and Aiba A (2000) mGluR1 in cerebellar Purkinje cells essential for long-term depression, synapse elimination, and motor coordination. *Science* **288:**1832–1835.

Ikeda M (1993) Reduction of phosphoinositide hydrolysis by L-amino-3-phosphonopropionate may be caused by the inhibition of synthesis of phosphatidylinositols. *Neurosci Lett* **157:**87–90.

Ikeda SR, Lovinger DM, McCool BA, and Lewis DL (1995) Heterologous expression of metabotropic glutamate receptors in adult rat sympathetic neurons: subtype-specific coupling to ion channels. *Neuron* **14:**1029–1038.

Ireland DR and Abraham WC (2002) Group I mGluRs increase excitability of hippocampal CA1 pyramidal neurons by a PLC-independent mechanism. *J Neurophysiol* **88:**107–116.

Ireland DR, Guevremont D, Williams JM, and Abraham WC (2004) Metabotropic glutamate receptor-mediated depression of the slow afterhyperpolarization is gated by tyrosine phosphatases in hippocampal CA1 pyramidal neurons. *J Neurophysiol* **92:**2811–2819.

Irving AJ, Schofield JG, Watkins JC, Sunter DC, and Collingridge GL (1990) 1S,3R-ACPD stimulates and L-AP3 blocks Ca^{2+} mobilization in rat cerebellar neurons. *Eur J Pharmacol* **186:**363–365.

Ishikawa K, Nash SR, Nishimune A, Neki A, Kaneko S, and Nakanishi S (1999) Competitive interaction of seven in absentia homolog-1A and Ca^{2+}/calmodulin with the cytoplasmic tail of group 1 metabotropic glutamate receptors. *Genes Cells* **4:**381–390.

Ito I, Kohda A, Tanabe S, Hirose E, Hayashi M, Mitsunaga S, and Sugiyama H (1992) 3,5-Dihydroxyphenyl-glycine: a potent agonist of metabotropic glutamate receptors. *Neuroreport* **3:**1013–1016.

Ito M (2002) The molecular organization of cerebellar long-term depression. *Nat Rev Neurosci* **3:**896–902.

Ito M and Kano M (1982) Long-lasting depression of parallel fiber-Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex. *Neurosci Lett* **33:**253–258.

Ito M and Karachot L (1990) Receptor subtypes involved in, and time course of, the long-term desensitization of glutamate receptors in cerebellar Purkinje cells. *Neurosci Res* **8:**303–307.

Izumi Y and Zorumski CF (1994) Developmental changes in the effects of metabotropic glutamate receptor antagonists on CA1 long-term potentiation in rat hippocampal slices. *Neurosci Lett* **176:**89–92.

Jaarsma D, Diño MR, Ohishi H, Shigemoto R, and Mugnaini E (1998) Metabotropic glutamate receptors are associated with non-synaptic appendages of unipolar brush cells in rat cerebellar cortex and cochlear nuclear complex. *J Neurocytol* **27:**303–327.

Jensen AA, Greenwood JR, and Bräuner-Osborne H (2002) The dance of the clams: twists and turns in the family C GPCR homodimer. *Trends Pharmacol Sci* **23:** 491–493.

Jensen AA, Sheppard PO, O'Hara PJ, Krogsgaard-Larsen P, and Bräuner-Osborne H (2000) The role of Arg^{78} in the metabotropic glutamate receptor $mGlu_1$ for agonist binding and selectivity. *Eur J Pharmacol* **397:**247–253.

Jingami H, Nakanishi S, and Morikawa K (2003) Structure of the metabotropic glutamate receptor. *Curr Opin Neurobiol* **13:**271–278.

Johnson MP, Kelly G, and Chamberlain M (2001) Changes in rat serum corticosterone after treatment with metabotropic glutamate receptor agonists or antagonists. *J Neuroendocrinol* **13:**670–677.

Joly C, Gomeza J, Brabet I, Curry K, Bockaert J, and Pin JP (1995) Molecular, functional, and pharmacological characterization of the metabotropic glutamate receptor type 5 splice variants: comparison with mGluR1. *J Neurosci* **15:**3970–3981.

Jones MW and Headley PM (1995) Interactions between metabotropic and ionotropic glutamate receptor agonists in the rat spinal cord in vivo. *Neuropharmacology* **34:**1025–1031.

Joost P and Methner A (2002) Phylogenetic analysis of 277 human G-protein-coupled receptors as a tool for the prediction of orphan receptor ligands. *Genome Biol* 3:RESEARCH0063.

Kaatz KW and Albin RL (1995) Intrastriatal and intrasubthalamic stimulation of metabotropic glutamate receptors: a behavioral and Fos immunohistochemical study. *Neuroscience* **66:**55–65.

Kammermeier PJ (2006) Surface clustering of metabotropic glutamate receptor I induced by long Homer proteins. *BMC Neuroscience* **7:**1.

Kammermeier PJ and Ikeda SR (1999) Expression of RGS2 alters the coupling of metabotropic glutamate receptor 1a to M-type K^+ and N-type Ca^{2+} channels. *Neuron* **22:**819–829.

Kammermeier PJ and Ikeda SR (2001) A role for Seven in Absentia Homolog (Siah1a) in metabotropic glutamate receptor signaling. *BMC Neurosci* **2:**15.

Kammermeier PJ, Xiao B, Tu JC, Worley PF, and Ikeda SR (2000) Homer proteins regulate coupling of group I metabotropic glutamate receptors to N-type calcium and M-type potassium channels. *J Neurosci* **20:**7238–7245.

Kammermeier PJ and Yun J (2005) Activation of metabotropic glutamate receptor 1 dimers requires glutamate binding in both subunits. *J Pharmacol Exp Ther* **312:**502–508.

Kaneda K, Imanishi M, Nambu A, Shigemoto R, and Takada M (2003) Differential expression patterns of mGluR1α in monkey nigral dopamine neurons. *Neuroreport* **14:**947–950.

Kano M, Hashimoto K, Chen C, Abeliovich A, Aiba A, Kurihara H, Watanabe M, Inoue Y, and Tonegawa S (1995) Impaired synapse elimination during cerebellar development in PKCγ mutant mice. *Cell* **83:**1223–1231.

Kano M, Hashimoto K, Kurihara H, Watanabe M, Inoue Y, Aiba A, and Tonegawa S (1997) Persistent multiple climbing fiber innervation of cerebellar Purkinje cells in mice lacking mGluR1. *Neuron* **18:**71–79.

Kano M, Hashimoto K, and Tabata T (2008) Type-1 metabotropic glutamate receptor in cerebellar Purkinje cells: a key molecule responsible for long-term depression, endocannabinoid signalling and synapse elimination. *Philos Trans R Soc Lond B Biol Sci* **363:**2173–2186.

Kano M, Hashimoto K, Watanabe M, Kurihara H, Offermanns S, Jiang H, Wu Y, Jun K, Shin HS, Inoue Y, et al. (1998) Phospholipase Cβ4 is specifically involved in climbing fiber synapse elimination in the developing cerebellum. *Proc Natl Acad Sci U S A* **95:**15724–15729.

Kano M and Kato M (1987) Quisqualate receptors are specifically involved in cerebellar synaptic plasticity. *Nature* **325:**276–279.

Kanumilli S, Toms NJ, Venkateswarlu K, Mellor H, and Roberts PJ (2002) Functional coupling of rat metabotropic glutamate 1a receptors to phospholipase D in CHO cells: involvement of extracellular Ca^{2+}, protein kinase C, tyrosine kinase and Rho-A. *Neuropharmacology* **42:**1–8.

Karakossian MH and Otis TS (2004) Excitation of cerebellar interneurons by group I metabotropic glutamate receptors. *J Neurophysiol* **92:**1558–1565.

Karim F, Wang CC, and Gereau RW 4th (2001) Metabotropic glutamate receptor subtypes 1 and 5 are activators of extracellular signal-regulated kinase signaling required for inflammatory pain in mice. *J Neurosci* **21:**3771–3779.

Kasahara J and Sugiyama H (1994) Inositol phospholipid metabolism in *Xenopus* oocytes mediated by endogenous G_o and G_i proteins. *FEBS Lett* **355:**41–44.

Kashiwabuchi N, Ikeda K, Araki K, Hirano T, Shibuki K, Takayama C, Inoue Y, Kutsuwada T, Yagi T, and Kang Y (1995) Impairment of motor coordination, Purkinje cell synapse formation, and cerebellar long-term depression in GluRδ2 mutant mice. *Cell* **81:**245–252.

Katayama J, Akaike N, and Nabekura J (2003) Characterization of pre- and postsynaptic metabotropic glutamate receptor-mediated inhibitory responses in substantia nigra dopamine neurons. *Neurosci Res* **45:**101–115.

Kato A, Ozawa F, Saitoh Y, Fukazawa Y, Sugiyama H, and Inokuchi K (1998) Novel members of the Vesl/Homer family of PDZ proteins that bind metabotropic glutamate receptors. *J Biol Chem* **273:**23969–23975.

Kato A, Ozawa F, Saitoh Y, Hirai K, and Inokuchi K (1997) *vesl*, a gene encoding VASP/Ena family related protein, is upregulated during seizure, long-term potentiation and synaptogenesis. *FEBS Lett* **412:**183–189.

Kearney JA, Frey KA, and Albin RL (1997) Metabotropic glutamate agonist-induced rotation: a pharmacological, FOS immunohistochemical, and [^{14}C]-2-deoxyglucose autoradiographic study. *J Neurosci* **17:**4415–4425.

Kerner JA, Standaert DG, Penney JB Jr, Young AB, and Landwehrmeyer GB (1997) Expression of group one metabotropic glutamate receptor subunit mRNAs in neurochemically identified neurons in the rat neostriatum, neocortex, and hippocampus. *Brain Res Mol Brain Res* **48:**259–269.

Khodakhah K and Ogden D (1995) Fast activation and inactivation of inositol trisphosphate-evoked Ca^{2+} release in rat cerebellar Purkinje neurones. *J Physiol* **487:**343–358.

Kim SJ, Kim YS, Yuan JP, Petralia RS, Worley PF, and Linden DJ (2003) Activation of the TRPC1 cation channel by metabotropic glutamate receptor mGluR1. *Nature* **426:**285–291.

King AE and Liu XH (1996) Dual action of metabotropic glutamate receptor agonists

on neuronal excitability and synaptic transmission in spinal ventral horn neurons in vitro. *Neuropharmacology* **35:**1673–1680.

Kingston AE, Burnett JP, Mayne NG, and Lodge D (1995) Pharmacological analysis of 4-carboxyphenylglycine derivatives: comparison of effects on mGluR1α and mGluR5a subtypes. *Neuropharmacology* **34:**887–894.

Kingston AE, Griffey K, Johnson MP, Chamberlain MJ, Kelly G, Tomlinson R, Wright RA, Johnson BG, Schoepp DD, Harris JR, et al. (2002) Inhibition of group I metabotropic glutamate receptor responses in vivo in rats by a new generation of carboxyphenylglycine-like amino acid antagonists. *Neurosci Lett* **330:**127–130.

Kishimoto Y, Fujimichi R, Araishi K, Kawahara S, Kano M, Aiba A, and Kirino Y (2002) mGluR1 in cerebellar Purkinje cells is required for normal association of temporally contiguous stimuli in classical conditioning. *Eur J Neurosci* **16:**2416–2424.

Kiss J, Görcs TJ, Kuhn R, Knöpfel T, Csáky A, and Halász B (1996) Distribution of metabotropic glutamate receptor 1a in the rat hypothalamus: an immunocytochemical study using monoclonal and polyclonal antibody. *Acta Biol Hung* **47:**221–237.

Kiss J, Kocsis K, Csáki A, Görcs TJ, and Halász B (1997) Metabotropic glutamate receptor in GHRH and β-endorphin neurones of the hypothalamic arcuate nucleus. *Neuroreport* **8:**3703–3707.

Kitano J, Kimura K, Yamazaki Y, Soda T, Shigemoto R, Nakajima Y, and Nakanishi S (2002) Tamalin, a PDZ domain-containing protein, links a protein complex formation of group 1 metabotropic glutamate receptors and the guanine nucleotide exchange factor cytohesins. *J Neurosci* **22:**1280–1289.

Kitano J, Nishida M, Itsukaichi Y, Minami I, Ogawa M, Hirano T, Mori Y, and Nakanishi S (2003a) Direct interaction and functional coupling between metabotropic glutamate receptor subtype 1 and voltage-sensitive Cav2.1 Ca^{2+} channel. *J Biol Chem* **278:**25101–25108.

Kitano J, Yamazaki Y, Kimura K, Masukado T, Nakajima Y, and Nakanishi S (2003b) Tamalin is a scaffold protein that interacts with multiple neuronal proteins in distinct modes of protein-protein association. *J Biol Chem* **278:**14762–14768.

Kłodzińska A, Tatarczyńska E, Stachowicz K, and Chojnacka-Wójcik E (2004) The anxiolytic-like activity of AIDA (1-aminoindan-1,5-dicarboxylic acid), an mGlu 1 receptor antagonist. *J Physiol Pharmacol* **55:**113–126.

Kniazeff J, Bessis AS, Maurel D, Ansanay H, Prézeau L, and Pin JP (2004) Closed state of both binding domains of homodimeric mGlu receptors is required for full activity. *Nat Struct Mol Biol* **11:**706–713.

Knoflach F, Mutel V, Jolidon S, Kew JN, Malherbe P, Vieira E, Wichmann J, and Kemp JA (2001a) Positive allosteric modulators of metabotropic glutamate 1 receptor: characterization, mechanism of action, and binding site. *Proc Natl Acad Sci U S A* **98:**13402–13407.

Knoflach F, Woltering T, Adam G, Mutel V, and Kemp JA (2001b) Pharmacological properties of native metabotropic glutamate receptors in freshly dissociated Golgi cells of the rat cerebellum. *Neuropharmacology* **40:**163–169.

Kohara A, Takahashi M, Yatsugi S, Tamura S, Shitaka Y, Hayashibe S, Kawabata S, and Okada M (2008) Neuroprotective effects of the selective type 1 metabotropic glutamate receptor antagonist YM-202074 in rat stroke models. *Brain Res* **1191:**168–179.

Kosinski CM, Standaert DG, Testa CM, Penney JB Jr, and Young AB (1998) Expression of metabotropic glutamate receptor 1 isoforms in the substantia nigra pars compacta of the rat. *Neuroscience* **86:**783–798.

Kubo Y, Miyashita T, and Murata Y (1998) Structural basis for a Ca^{2+}-sensing function of the metabotropic glutamate receptors. *Science* **279:**1722–1725.

Kubokawa K, Miyashita T, Nagasawa H, and Kubo Y (1996) Cloning and characterization of a bifunctional metabotropic receptor activated by both extracellular calcium and glutamate. *FEBS Lett* **392:**71–76.

Kunishima N, Shimada Y, Tsuji Y, Sato T, Yamamoto M, Kumasaka T, Nakanishi S, Jingami H, and Morikawa K (2000) Structural basis of glutamate recognition by a dimeric metabotropic glutamate receptor. *Nature* **407:**971–977.

Kuramoto T, Maihara T, Masu M, Nakanishi S, and Serikawa T (1994) Gene mapping of NMDA receptors and metabotropic glutamate receptors in the rat (*Rattus norvegicus*). *Genomics* **19:**358–361.

Kurihara H, Hashimoto K, Kano M, Takayama C, Sakimura K, Mishina M, Inoue Y, and Watanabe M (1997) Impaired parallel fiber→Purkinje cell synapse stabilization during cerebellar development of mutant mice lacking the glutamate receptor δ2 subunit. *J Neurosci* **17:**9613–9623.

Kuwajima M, Hall RA, Aiba A, and Smith Y (2004) Subcellular and subsynaptic localization of group I metabotropic glutamate receptors in the monkey subthalamic nucleus. *J Comp Neurol* **474:**589–602.

Lainé J and Axelrad H (1996) Morphology of the Golgi-impregnated Lugaro cell in the rat cerebellar cortex: a reappraisal with a description of its axon. *J Comp Neurol* **375:**618–640.

Lan JY, Skeberdis VA, Jover T, Zheng X, Bennett MV, and Zukin RS (2001) Activation of metabotropic glutamate receptor 1 accelerates NMDA receptor trafficking. *J Neurosci* **21:**6058–6068.

Lapointe V, Morin F, Ratté S, Croce A, Conquet F, and Lacaille JC (2004) Synapse-specific mGluR1-dependent long-term potentiation in interneurones regulates mouse hippocampal inhibition. *J Physiol* **555:**125–135.

Laurie DJ, Boddeke HW, Hiltscher R, and Sommer B (1996) HmGlu1d, a novel splice variant of the human type I metabotropic glutamate receptor. *Eur J Pharmacol* **296:**R1–R3.

Lavreysen H, Janssen C, Bischoff F, Langlois X, Leysen JE, and Lesage AS (2003) [^{3}H]R214127: a novel high-affinity radioligand for the mGlu1 receptor reveals a common binding site shared by multiple allosteric antagonists. *Mol Pharmacol* **63:**1082–1093.

Lavreysen H, Le Poul E, Van Gompel P, Dillen L, Leysen JE, and Lesage AS (2002) Supersensitivity of human metabotropic glutamate 1a receptor signaling in L929sA cells. *Mol Pharmacol* **61:**1244–1254.

Lavreysen H, Pereira SN, Leysen JE, Langlois X, and Lesage AS (2004a) Metabotropic glutamate 1 receptor distribution and occupancy in the rat brain: a quantitative autoradiographic study using [^{3}H]R214127. *Neuropharmacology* **46:**609–619.

Lavreysen H, Wouters R, Bischoff F, Nóbrega Pereira S, Langlois X, Blokland S, Somers M, Dillen L, and Lesage AS (2004b) JNJ16259685, a highly potent, selective and systemically active mGlu1 receptor antagonist. *Neuropharmacology* **47:**961–972.

Lee AC, Wong RK, Chuang SC, Shin HS, and Bianchi R (2002) Role of synaptic metabotropic glutamate receptors in epileptiform discharges in hippocampal slices. *J Neurophysiol* **88:**1625–1633.

Lefebvre C, Fisher K, Cahill CM, and Coderre TJ (2000) Evidence that DHPG-induced nociception depends on glutamate release from primary afferent C-fibres. *Neuroreport* **11:**1631–1635.

Levenes C, Daniel H, and Crépel F (1998) Long-term depression of synaptic transmission in the cerebellum: cellular and molecular mechanisms revisited. *Prog Neurobiol* **55:**79–91.

Levenes C, Daniel H, and Crépel F (2001) Retrograde modulation of transmitter release by postsynaptic subtype 1 metabotropic glutamate receptors in the rat cerebellum. *J Physiol* **537:**125–140.

Levenes C, Daniel H, Jaillard D, Conquet F, and Crépel F (1997) Incomplete regression of multiple climbing fibre innervation of cerebellar Purkinje cells in mGLuR1 mutant mice. *Neuroreport* **8:**571–574.

Libri V, Constanti A, Zibetti M, and Postlethwaite M (1997) Metabotropic glutamate receptor subtypes mediating slow inward tail current (IADP) induction and inhibition of synaptic transmission in olfactory cortical neurones. *Br J Pharmacol* **120:**1083–1095.

Lin FF, Varney M, Sacaan AI, Jachec C, Daggett LP, Rao S, Flor P, Kuhn R, Kerner JA, Standaert D, et al. (1997) Cloning and stable expression of the mGluR1b subtype of human metabotropic receptors and pharmacological comparison with the mGluR5a subtype. *Neuropharmacology* **36:**917–931.

Linden DJ, Smeyne M, and Connor JA (1994) Trans-ACPD, a metabotropic receptor agonist, produces calcium mobilization and an inward current in cultured cerebellar Purkinje neurons. *J Neurophysiol* **71:**1992–1998.

Lingenhöhl K, Knöpfel T, and Olpe HR (1993) Multiphasic responses of cerebellar Purkinje cells to 1S,3R-ACPD: an in vivo study. *Neurosci Res* **18:**223–228.

Linn GS and Javitt DC (2001) Phencyclidine (PCP)-induced deficits of prepulse inhibition in monkeys. *Neuroreport* **12:**117–120.

Lisberger SG (1998) Cerebellar LTD: a molecular mechanism of behavioral learning? *Cell* **92:**701–704.

Litschig S, Gasparini F, Rueegg D, Stoehr N, Flor PJ, Vranesic I, Prézeau L, Pin JP, Thomsen C, and Kuhn R (1999) CPCCOEt, a noncompetitive metabotropic glutamate receptor 1 antagonist, inhibits receptor signaling without affecting glutamate binding. *Mol Pharmacol* **55:**453–461.

Little Z, Grover LM, and Teyler TJ (1995) Metabotropic glutamate receptor antagonist, (*R,S*)-α-methyl-4-carboxyphenyglycine, blocks two distinct forms of long-term potentiation in area CA1 of rat hippocampus. *Neurosci Lett* **201:**73–76.

Lorick KL, Jensen JP, Fang S, Ong AM, Hatakeyama S, and Weissman AM (1999) RING fingers mediate ubiquitin-conjugating enzyme (E2)-dependent ubiquitination. *Proc Natl Acad Sci U S A* **96:**11364–11369.

Lorrain DS, Correa L, Anderson J, and Varney M (2002) Activation of spinal group I metabotropic glutamate receptors in rats evokes local glutamate release and spontaneous nociceptive behaviors: effects of 2-methyl-6-(phenylethynyl)-pyridine pretreatment. *Neurosci Lett* **327:**198–202.

Losonczy A, Zhang L, Shigemoto R, Somogyi P, and Nusser Z (2002) Cell type dependence and variability in the short-term plasticity of EPSCs in identified mouse hippocampal interneurones. *J Physiol* **542:**193–210.

Lu D, Yan H, Othman T, and Rivkees SA (2004) Cytoskeletal protein 4.1G is a binding partner of the metabotropic glutamate receptor subtype 1α. *J Neurosci Res* **78:**49–55.

Lujan R, Nusser Z, Roberts JD, Shigemoto R, and Somogyi P (1996) Perisynaptic location of metabotropic glutamate receptors mGluR1 and mGluR5 on dendrites and dendritic spines in the rat hippocampus. *Eur J Neurosci* **8:**1488–1500.

Maejima T, Hashimoto K, Yoshida T, Aiba A, and Kano M (2001) Presynaptic inhibition caused by retrograde signal from metabotropic glutamate to cannabinoid receptors. *Neuron* **31:**463–475.

Makoff AJ, Phillips T, Pilling C, and Emson P (1997) Expression of a novel splice variant of human mGluR1 in the cerebellum. *Neuroreport* **8:**2943–2947.

Malherbe P, Kratochwil N, Knoflach F, Zenner MT, Kew JN, Kratzeisen C, Maerki HP, Adam G, and Mutel V (2003) Mutational analysis and molecular modeling of the allosteric binding site of a novel, selective, noncompetitive antagonist of the metabotropic glutamate 1 receptor. *J Biol Chem* **278:**8340–8347.

Manahan-Vaughan D, Braunewell KH, and Reymann KG (1998) Subtype-specific involvement of metabotropic glutamate receptors in two forms of long-term potentiation in the dentate gyrus of freely moving rats. *Neuroscience* **86:**709–721.

Manahan-Vaughan D and Reymann KG (1997) Group 1 metabotropic glutamate receptors contribute to slow-onset potentiation in the rat CA1 region in vivo. *Neuropharmacology* **36:**1533–1538.

Mannaioni G, Marino MJ, Valenti O, Traynelis SF, and Conn PJ (2001) Metabotropic glutamate receptors 1 and 5 differentially regulate CA1 pyramidal cell function. *J Neurosci* **21:**5925–5934.

Manzoni OJ, Weisskopf MG, and Nicoll RA (1994) MCPG antagonizes metabotropic glutamate receptors but not long-term potentiation in the hippocampus. *Eur J Neurosci* **6:**1050–1054.

Mariani J, Crepel F, Mikoshiba K, Changeux JP, and Sotelo C (1977) Anatomical, physiological and biochemical studies of the cerebellum from Reeler mutant mouse. *Philos Trans R Soc Lond B Biol Sci* **281:**1–28.

Marín YE and Chen S (2004) Involvement of metabotropic glutamate receptor 1, a G protein coupled receptor, in melanoma development. *J Mol Med* **82:**735–749.

Marín YE, Namkoong J, Cohen-Solal K, Shin SS, Martino JJ, Oka M, and Chen S (2006) Stimulation of oncogenic metabotropic glutamate receptor 1 in melanoma cells activates ERK1/2 via PKCε. *Cell Signal* **18:**1279–1286.

Marino MJ, Awad-Granko H, Ciombor KJ, and Conn PJ (2002) Haloperidol-induced

alteration in the physiological actions of group I mGlus in the subthalamic nucleus and the substantia nigra pars reticulata. *Neuropharmacology* **43:**147–159.

Marino MJ, Wittmann M, Bradley SR, Hubert GW, Smith Y, and Conn PJ (2001) Activation of group I metabotropic glutamate receptors produces a direct excitation and disinhibition of GABAergic projection neurons in the substantia nigra pars reticulata. *J Neurosci* **21:**7001–7012.

Marti M, Paganini F, Stocchi S, Bianchi C, Beani L, and Morari M (2001) Presynaptic group I and II metabotropic glutamate receptors oppositely modulate striatal acetylcholine release. *Eur J Neurosci* **14:**1181–1184.

Martin LJ, Blackstone CD, Huganir RL, and Price DL (1992) Cellular localization of a metabotropic glutamate receptor in rat brain. *Neuron* **9:**259–270.

Martin SJ and Morris RG (1997) (*R,S*)-α-methyl-4-carboxyphenylglycine (MCPG) fails to block long-term potentiation under urethane anaesthesia *in vivo*. *Neuropharmacology* **36:**1339–1354.

Mary S, Gomeza J, Prézeau L, Bockaert J, and Pin JP (1998) A cluster of basic residues in the carboxyl-terminal tail of the short metabotropic glutamate receptor 1 variants impairs their coupling to phospholipase C. *J Biol Chem* **273:**425–432.

Mary S, Stephan D, Gomeza J, Bockaert J, Pruss RM, and Pin JP (1997) The rat mGlu1d receptor splice variant shares functional properties with the other short isoforms of mGlu1 receptor. *Eur J Pharmacol* **335:**65–72.

Masu M, Tanabe Y, Tsuchida K, Shigemoto R, and Nakanishi S (1991) Sequence and expression of a metabotropic glutamate receptor. *Nature* **349:**760–765.

Mateos JM, Azkue J, Benítez R, Sarría R, Losada J, Conquet F, Ferraguti F, Kuhn R, Knöpfel T, and Grandes P (1998) Immunocytochemical localization of the mGluR1b metabotropic glutamate receptor in the rat hypothalamus. *J Comp Neurol* **390:**225–233.

Mateos JM, Benítez R, Elezgarai I, Azkue JJ, Lázaro E, Osorio A, Bilbao A, Doñate F, Sarría R, Conquet F, et al. (2000) Immunolocalization of the mGluR1b splice variant of the metabotropic glutamate receptor 1 at parallel fiber-Purkinje cell synapses in the rat cerebellar cortex. *J Neurochem* **74:**1301–1309.

Mauk MD, Garcia KS, Medina JF, and Steele PM (1998) Does cerebellar LTD mediate motor learning? Toward a resolution without a smoking gun. *Neuron* **20:**359–362.

McBain CJ, DiChiara TJ, and Kauer JA (1994) Activation of metabotropic glutamate receptors differentially affects two classes of hippocampal interneurons and potentiates excitatory synaptic transmission. *J Neurosci* **14:**4433–4445.

McCaffery B, Bashir ZI, Collett VJ, Gasparini F, Flor PJ, Jane D, Conquet F, and Collingridge GL (1998) Effects of metabotropic glutamate receptor mGluR1 antagonists on long term potentiation in area CA1 of the hippocampus, in *Metabotropic Glutamate Receptors and Brain Function: Proceedings of the 2nd International Meeting on Metabotropic Glutamate Receptors* (Moroni F, Nicoletti F, Pellegrini-Giampietro DE eds) pp 139–145, Portland Press Ltd, London.

McCool BA, Pin JP, Harpold MM, Brust PF, Stauderman KA, and Lovinger DM (1998) Rat group I metabotropic glutamate receptors inhibit neuronal Ca^{2+} channels via multiple signal transduction pathways in HEK 293 cells. *J Neurophysiol* **79:**379–391.

McCormick DA and von Krosigk M (1992) Corticothalamic activation modulates thalamic firing through glutamate "metabotropic" receptors. *Proc Natl Acad Sci U S A* **89:**2774–2778.

Meller ST, Dykstra CL, and Gebhart GF (1993) Acute mechanical hyperalgesia is produced by coactivation of AMPA and metabotropic glutamate receptors. *Neuroreport* **4:**879–882.

Meller ST, Dykstra C, and Gebhart GF (1996) Acute mechanical hyperalgesia in the rat can be produced by coactivation of spinal ionotropic AMPA and metabotropic glutamate receptors, activation of phospholipase A2 and generation of cyclooxygenase products. *Prog Brain Res* **110:**177–192.

Meltzer LT, Serpa KA, and Christoffersen CL (1997) Metabotropic glutamate receptor-mediated inhibition and excitation of substantia nigra dopamine neurons. *Synapse* **26:**184–193.

Mercuri NB, Stratta F, Calabresi P, Bonci A, and Bernardi G (1993) Activation of metabotropic glutamate receptors induces an inward current in rat dopamine mesencephalic neurons. *Neuroscience* **56:**399–407.

Merlin LR (1999) Group I mGluR-mediated silent induction of long-lasting epileptiform discharges. *J Neurophysiol* **82:**1078–1081.

Merlin LR (2002) Differential roles for mGluR1 and mGluR5 in the persistent prolongation of epileptiform bursts. *J Neurophysiol* **87:**621–625.

Merlin LR, Bergold PJ, and Wong RK (1998) Requirement of protein synthesis for group I mGluR-mediated induction of epileptiform discharges. *J Neurophysiol* **80:**989–993.

Merlin LR, Taylor GW, and Wong RK (1995) Role of metabotropic glutamate receptor subtypes in the patterning of epileptiform activities in vitro. *J Neurophysiol* **74:**896–900.

Merlin LR and Wong RK (1997) Role of group I metabotropic glutamate receptors in the patterning of epileptiform activities in vitro. *J Neurophysiol* **78:**539–544.

Micheli F, Di Fabio R, Benedetti R, Capelli AM, Cavallini P, Cavanni P, Davalli S, Donati D, Feriani A, Gehanne S, et al. (2004a) 3-Methyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester: an exploration of the C-2 position. Part I. *Farmaco* **59:**175–183.

Micheli F, Di Fabio R, Bordi F, Cavallini P, Cavanni P, Donati D, Faedo S, Maffeis M, Sabbatini FM, Tarzia G, et al. (2003a) 2,4-Dicarboxy-pyrroles as selective non-competitive mGluR1 antagonists: further characterization of 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester and structure-activity relationships. *Bioorg Med Chem Lett* **13:**2113–2118.

Micheli F, Di Fabio R, Cavallini P, Cavanni P, Donati D, Hamdan M, Maria Sabbatini F, and Messeri T (2004b) 3-Methyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-trimethyl-propyl) ester: an exploration of the C-2 position. Part II, a solid-phase approach. *Farmaco* **59:**119–123.

Micheli F, Di Fabio R, Cavanni P, Donati D, Faedo S, Gehanne S, Maffeis M, Marchioro C, Sabbatini FM, Tarzia G, et al. (2003b) 2,4-Dicarboxy-pyrroles as selective non-competitive mGluR1 antagonists: an exploration of the role of the pyrrolic scaffold. *Farmaco* **58:**1005–1009.

Micheli F, Fabio RD, Cavanni P, Rimland JM, Capelli AM, Chiamulera C, Corsi M, Corti C, Donati D, Feriani A, et al. (2003c) Synthesis and pharmacological characterisation of 2,4-dicarboxy-pyrroles as selective non-competitive mGluR1 antagonists. *Bioorg Med Chem* **11:**171–183.

Mick G, Yoshimura R, Ohno K, Kiyama H, and Tohyama M (1995) The messenger RNAs encoding metabotropic glutamate receptor subtypes are expressed in different neuronal subpopulations of the rat suprachiasmatic nucleus. *Neuroscience* **66:**161–173.

Millán C, Luján R, Shigemoto R, and Sánchez-Prieto J (2002) Subtype-specific expression of group III metabotropic glutamate receptors and Ca^{2+} channels in single nerve terminals. *J Biol Chem* **277:**47796–47803.

Minakami R, Jinnai N, and Sugiyama H (1997) Phosphorylation and calmodulin binding of the metabotropic glutamate receptor subtype 5 (mGluR5) are antagonistic in vitro. *J Biol Chem* **272:**20291–20298.

Minami I, Kengaku M, Smitt PS, Shigemoto R, and Hirano T (2003) Long-term potentiation of mGluR1 activity by depolarization-induced Homer1a in mouse cerebellar Purkinje neurons. *Eur J Neurosci* **17:**1023–1032.

Miyata M, Kashiwadani H, Fukaya M, Hayashi T, Wu D, Suzuki T, Watanabe M, and Kawakami Y (2003) Role of thalamic phospholipase Cβ4 mediated by metabotropic glutamate receptor type 1 in inflammatory pain. *J Neurosci* **23:**8098–8108.

Miyata M, Kim HT, Hashimoto K, Lee TK, Cho SY, Jiang H, Wu Y, Jun K, Wu D, Kano M, et al. (2001) Deficient long-term synaptic depression in the rostral cerebellum correlated with impaired motor learning in phospholipase Cβ4 mutant mice. *Eur J Neurosci* **13:**1945–1954.

Mody N, Hermans E, Nahorski SR, and Challiss RA (1999) Inhibition of N-linked glycosylation of the human type 1α metabotropic glutamate receptor by tunicamycin: effects on cell-surface receptor expression and function. *Neuropharmacology* **38:**1485–1492.

Moldrich RX, Chapman AG, De Sarro G, and Meldrum BS (2003) Glutamate metabotropic receptors as targets for drug therapy in epilepsy. *Eur J Pharmacol* **476:**3–16.

Morè L, Gravius A, Pietraszek M, Belozertseva I, Malyshkin A, Shekunova E, Barberi C, Schaefer D, Schmidt WJ, and Danysz W (2007) Comparison of the mGluR1 antagonist A-841720 in rat models of pain and cognition. *Behav Pharmacol* **18:**273–281.

Mori M and Gerber U (2002) Slow feedback inhibition in the CA3 area of the rat hippocampus by synergistic synaptic activation of mGluR1 and mGluR5. *J Physiol* **544:**793–799.

Morikawa H, Khodakhah K, and Williams JT (2003) Two intracellular pathways mediate metabotropic glutamate receptor-induced Ca^{2+} mobilization in dopamine neurons. *J Neurosci* **23:**149–157.

Morisset V and Nagy F (1996) Modulation of regenerative membrane properties by stimulation of metabotropic glutamate receptors in rat deep dorsal horn neurons. *J Neurophysiol* **76:**2794–2798.

Moroni F, Attucci S, Cozzi A, Meli E, Picca R, Scheideler MA, Pellicciari R, Noe C, Sarichelou I, and Pellegrini-Giampietro DE (2002) The novel and systemically active metabotropic glutamate 1 (mGlu1) receptor antagonist 3-MATIDA reduces post-ischemic neuronal death. *Neuropharmacology* **42:**741–751.

Moroni F, Lombardi G, Thomsen C, Leonardi P, Attucci S, Peruginelli F, Torregrossa SA, Pellegrini-Giampietro DE, Luneia R, and Pellicciari R (1997) Pharmacological characterization of 1-aminoindan-1,5-dicarboxylic acid, a potent mGluR1 antagonist. *J Pharmacol Exp Ther* **281:**721–729.

Mount HT, Dreyfus CF, and Black IB (1993) Purkinje cell survival is differentially regulated by metabotropic and ionotropic excitatory amino acid receptors. *J Neurosci* **13:**3173–3179.

Mount HT, Elkabes S, Dreyfus CF, and Black IB (1998) Differential involvement of metabotropic and p75 neurotrophin receptors in effects of nerve growth factor and neurotrophin-3 on cultured Purkinje cell survival. *J Neurochem* **70:**1045–1053.

Mundell SJ, Matharu AL, Pula G, Holman D, Roberts PJ, and Kelly E (2002) Metabotropic glutamate receptor 1 internalization induced by muscarinic acetylcholine receptor activation: differential dependency of internalization of splice variants on nonvisual arrestins. *Mol Pharmacol* **61:**1114–1123.

Mundell SJ, Matharu AL, Pula G, Roberts PJ, and Kelly E (2001) Agonist-induced internalization of the metabotropic glutamate receptor 1a is arrestin- and dynamin-dependent. *J Neurochem* **78:**546–551.

Mundell SJ, Pula G, Carswell K, Roberts PJ, and Kelly E (2003) Agonist-induced internalization of metabotropic glutamate receptor 1A: structural determinants for protein kinase C- and G protein-coupled receptor kinase-mediated internalization. *J Neurochem* **84:**294–304.

Naie K and Manahan-Vaughan D (2005) Pharmacological antagonism of metabotropic glutamate receptor 1 regulates long-term potentiation and spatial reference memory in the dentate gyrus of freely moving rats via *N*-methyl-D-aspartate and metabotropic glutamate receptor-dependent mechanisms. *Eur J Neurosci* **21:**411–421.

Nakajima Y, Iwakabe H, Akazawa C, Nawa H, Shigemoto R, Mizuno N, and Nakanishi S (1993) Molecular characterization of a novel retinal metabotropic glutamate receptor mGluR6 with a high agonist selectivity for L-2-amino-4-phosphonobutyrate. *J Biol Chem* **268:**11868–11873.

Nakamura M, Sato K, Fukaya M, Araishi K, Aiba A, Kano M, and Watanabe M (2004) Signaling complex formation of phospholipase Cβ4 with metabotropic glutamate receptor type 1α and 1,4,5-trisphosphate receptor at the perisynapse and endoplasmic reticulum in the mouse brain. *Eur J Neurosci* **20:**2929–2944.

Nakanishi S (1992) Molecular diversity of glutamate receptors and implications for brain function. *Science* **258:**597–603.

Namkoong J, Shin SS, Lee HJ, Marín YE, Wall BA, Goydos JS, and Chen S (2007) Metabotropic glutamate receptor 1 and glutamate signaling in human melanoma. *Cancer Res* **67:**2298–2305.

Nash MS, Saunders R, Young KW, Challiss RA, and Nahorski SR (2001) Reassessment of the Ca^{2+} sensing property of a type I metabotropic glutamate receptor by simultaneous measurement of inositol 1,4,5-trisphosphate and Ca^{2+} in single cells. *J Biol Chem* **276:**19286–19293.

Neki A, Ohishi H, Kaneko T, Shigemoto R, Nakanishi S, and Mizuno N (1996) Metabotropic glutamate receptors mGluR2 and mGluR5 are expressed in two non-overlapping populations of Golgi cells in the rat cerebellum. *Neuroscience* **75:**815–826.

Neugebauer V (2002) Metabotropic glutamate receptors—important modulators of nociception and pain behavior. *Pain* **98:**1–8.

Neugebauer V, Chen PS, and Willis WD (1999) Role of metabotropic glutamate receptor subtype mGluR1 in brief nociception and central sensitization of primate STT cells. *J Neurophysiol* **82:**272–282.

Neugebauer V, Lücke T, and Schaible HG (1994) Requirement of metabotropic glutamate receptors for the generation of inflammation-evoked hyperexcitability in rat spinal cord neurons. *Eur J Neurosci* **6:**1179–1186.

Neyman S and Manahan-Vaughan D (2008) Metabotropic glutamate receptor 1 (mGluR1) and 5 (mGluR5) regulate late phases of LTP and LTD in the hippocampal CA1 region in vitro. *Eur J Neurosci* **27:**1345–1352.

Nicoletti F, Iadarola MJ, Wroblewski JT, and Costa E (1986a) Excitatory amino acid recognition sites coupled with inositol phospholipid metabolism: developmental changes and interaction with α_1-adrenoceptors. *Proc Natl Acad Sci U S A* **83:**1931–1935.

Nicoletti F, Meek JL, Iadarola MJ, Chuang DM, Roth BL, and Costa E (1986b) Coupling of inositol phospholipid metabolism with excitatory amino acid recognition sites in rat hippocampus. *J Neurochem* **46:**40–46.

Nicoletti F, Wroblewski JT, Alho H, Eva C, Fadda E, and Costa E (1987) Lesions of putative glutamatergic pathways potentiate the increase of inositol phospholipid hydrolysis elicited by excitatory amino acids. *Brain Res* **436:**103–112.

Nicoletti F, Wroblewski JT, Novelli A, Alho H, Guidotti A, and Costa E (1986c) The activation of inositol phospholipid metabolism as a signal-transducing system for excitatory amino acids in primary cultures of cerebellar granule cells. *J Neurosci* **6:**1905–1911.

Nielsen KS, Macphail EM, and Riedel G (1997) Class I mGlu receptor antagonist 1-aminoindan-1,5-dicarboxylic acid blocks contextual but not cue conditioning in rats. *Eur J Pharmacol* **326:**105–108.

Noda K, Anzai T, Ogata M, Akita H, Ogura T, and Saji M (2003) Antisense knockdown of spinal-mGluR1 reduces the sustained phase of formalin-induced nociceptive responses. *Brain Res* **987:**194–200.

Nolan MF and Logan SD (1998) Metabotropic glutamate receptor-mediated excitation and inhibition of sympathetic preganglionic neurones. *Neuropharmacology* **37:**13–24.

Nunzi MG, Birnstiel S, Bhattacharyya BJ, Slater NT, and Mugnaini E (2001) Unipolar brush cells form a glutamatergic projection system within the mouse cerebellar cortex. *J Comp Neurol* **434:**329–341.

Nunzi MG, Russo M, and Mugnaini E (2003) Vesicular glutamate transporters VGLUT1 and VGLUT2 define two subsets of unipolar brush cells in organotypic cultures of mouse vestibulocerebellum. *Neuroscience* **122:**359–371.

Nunzi MG, Shigemoto R, and Mugnaini E (2002) Differential expression of calretinin and metabotropic glutamate receptor mGluR1α defines subsets of unipolar brush cells in mouse cerebellum. *J Comp Neurol* **451:**189–199.

Nusser Z, Mulvihill E, Streit P, and Somogyi P (1994) Subsynaptic segregation of metabotropic and ionotropic glutamate receptors as revealed by immunogold localization. *Neuroscience* **61:**421–427.

O'Hara PJ, Sheppard PO, Thøgersen H, Venezia D, Haldeman BA, McGrane V, Houamed KM, Thomsen C, Gilbert TL, and Mulvihill ER (1993) The ligand-binding domain in metabotropic glutamate receptors is related to bacterial periplasmic binding proteins. *Neuron* **11:**41–52.

Offermanns S (2003) G-proteins as transducers in transmembrane signalling. *Prog Biophys Mol Biol* **83:**101–130.

Offermanns S, Hashimoto K, Watanabe M, Sun W, Kurihara H, Thompson RF, Inoue Y, Kano M, and Simon MI (1997) Impaired motor coordination and persistent multiple climbing fiber innervation of cerebellar Purkinje cells in mice lacking Gα_q. *Proc Natl Acad Sci U S A* **94:**14089–14094.

Okamoto N, Hori S, Akazawa C, Hayashi Y, Shigemoto R, Mizuno N, and Nakanishi S (1994) Molecular characterization of a new metabotropic glutamate receptor mGluR7 coupled to inhibitory cyclic AMP signal transduction. *J Biol Chem* **269:**1231–1236.

Okamoto T, Sekiyama N, Otsu M, Shimada Y, Sato A, Nakanishi S, and Jingami H (1998) Expression and purification of the extracellular ligand binding region of metabotropic glutamate receptor subtype 1. *J Biol Chem* **273:**13089–13096.

Okubo Y, Kakizawa S, Hirose K, and Iino M (2004) Cross talk between metabotropic and ionotropic glutamate receptor-mediated signaling in parallel fiber-induced inositol 1,4,5-trisphosphate production in cerebellar Purkinje cells. *J Neurosci* **24:**9513–9520.

Oliet SH, Malenka RC, and Nicoll RA (1997) Two distinct forms of long-term depression coexist in CA1 hippocampal pyramidal cells. *Neuron* **18:**969–982.

Ong WY, Lim TM, and Garey LJ (1998) A light and electron microscopic study of the metabotropic glutamate receptor mGluR1a in the normal and kainate-lesioned rat hippocampus. *Mol Chem Neuropathol* **35:**173–186.

Orlando LR, Alsdorf SA, Penney JB Jr, and Young AB (2001) The role of group I and group II metabotropic glutamate receptors in modulation of striatal NMDA and quinolinic acid toxicity. *Exp Neurol* **167:**196–204.

Ossowska K, Konieczny J, Pilc A, and Wolfarth S (2002) The striatum as a target for anti-rigor effects of an antagonist of mGluR1, but not an agonist of group II metabotropic glutamate receptors. *Brain Res* **950:**88–94.

Ossowska K, Wardas J, Pietraszek M, Konieczny J, and Wolfarth S (2003) The striopallidal pathway is involved in antiparkinsonian-like effects of the blockade of group I metabotropic glutamate receptors in rats. *Neurosci Lett* **342:**21–24.

Otis TS, Brasnjo G, Dzubay JA, and Pratap M (2004) Interactions between glutamate transporters and metabotropic glutamate receptors at excitatory synapses in the cerebellar cortex. *Neurochem Int* **45:**537–544.

Ott D, Floersheim P, Inderbitzin W, Stoehr N, Francotte E, Lecis G, Richert P, Rihs G, Flor PJ, Kuhn R, et al. (2000) Chiral resolution, pharmacological characterization, and receptor docking of the noncompetitive mGlu1 receptor antagonist (±)-2-hydroxyimino-1*a*,2-dihydro-1*H*-7-oxacyclopropa[*b*]naphthalene-7*a*-carboxylic acid ethyl ester. *J Med Chem* **43:**4428–4436.

Ouardouz M and Lacaille JC (1995) Mechanisms of selective long-term potentiation of excitatory synapses in stratum oriens/alveus interneurons of rat hippocampal slices. *J Neurophysiol* **73:**810–819.

Pagano A, Ruegg D, Litschig S, Stoehr N, Stierlin C, Heinrich M, Floersheim P, Prezèau L, Carroll F, Pin JP, et al. (2000) The non-competitive antagonists 2-methyl-6-(phenylethynyl)pyridine and 7-hydroxyiminocyclopropan[*b*]chromen-1*a*-carboxylic acid ethyl ester interact with overlapping binding pockets in the transmembrane region of group I metabotropic glutamate receptors. *J Biol Chem* **275:**33750–33758.

Palmer E, Monaghan DT, and Cotman CW (1989) Trans-ACPD, a selective agonist of the phosphoinositide-coupled excitatory amino acid receptor. *Eur J Pharmacol* **166:**585–587.

Paolucci E, Berretta N, Tozzi A, Bernardi G, and Mercuri NB (2003) Depression of mGluR-mediated IPSCs by 5-HT in dopamine neurons of the rat substantia nigra pars compacta. *Eur J Neurosci* **18:**2743–2750.

Paquet M and Smith Y (2003) Group I metabotropic glutamate receptors in the monkey striatum: subsynaptic association with glutamatergic and dopaminergic afferents. *J Neurosci* **23:**7659–7669.

Park D, Lee S, Jun K, Hong YM, Kim DY, Kim YI, and Shin HS (2003) Translation of clock rhythmicity into neural firing in suprachiasmatic nucleus requires mGluR-PLCβ4 signaling. *Nat Neurosci* **6:**337–338.

Park YK, Galik J, Ryu PD, and Randic M (2004) Activation of presynaptic group I metabotropic glutamate receptors enhances glutamate release in the rat spinal cord substantia gelatinosa. *Neurosci Lett* **361:**220–224.

Parmentier ML, Prézeau L, Bockaert J, and Pin JP (2002) A model for the functioning of family 3 GPCRs. *Trends Pharmacol Sci* **23:**268–274.

Pellegrini-Giampietro DE (2003) The distinct role of mGlu1 receptors in post-ischemic neuronal death. *Trends Pharmacol Sci* **24:**461–470.

Pellicciari R, Luneia R, Costantino G, Marinozzi M, Natalini B, Jakobsen P, Kanstrup A, Lombardi G, Moroni F, and Thomsen C (1995) 1-Aminoindan-1,5-dicarboxylic acid: a novel antagonist at phospholipase C-linked metabotropic glutamate receptors. *J Med Chem* **38:**3717–3719.

Perez Y, Morin F, and Lacaille JC (2001) A hebbian form of long-term potentiation dependent on mGluR1a in hippocampal inhibitory interneurons. *Proc Natl Acad Sci U S A* **98:**9401–9406.

Perry W, Minassian A, Feifel D, and Braff DL (2001) Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. *Biol Psychiatry* **50:**418–424.

Petralia RS, Wang YX, Singh S, Wu C, Shi L, Wei J, and Wenthold RJ (1997) A monoclonal antibody shows discrete cellular and subcellular localizations of mGluR1α metabotropic glutamate receptors. *J Chem Neuroanat* **13:**77–93.

Petralia RS, Wang YX, Zhao HM, and Wenthold RJ (1996) Ionotropic and metabotropic glutamate receptors show unique postsynaptic, presynaptic, and glial localizations in the dorsal cochlear nucleus. *J Comp Neurol* **372:**356–383.

Petralia RS, Zhao HM, Wang YX, and Wenthold RJ (1998) Variations in the tangential distribution of postsynaptic glutamate receptors in Purkinje cell parallel and climbing fiber synapses during development. *Neuropharmacology* **37:**1321–1334.

Pickering DS, Thomsen C, Suzdak PD, Fletcher EJ, Robitaille R, Salter MW, MacDonald JF, Huang XP, and Hampson DR (1993) A comparison of two alternatively spliced forms of a metabotropic glutamate receptor coupled to phosphoinositide turnover. *J Neurochem* **61:**85–92.

Pietraszek M, Sukhanov I, Maciejak P, Szyndler J, Gravius A, Wisłowska A, Płaźnik A, Bespalov AY, and Danysz W (2005) Anxiolytic-like effects of mGlu1 and mGlu5 receptor antagonists in rats. *Eur J Pharmacol* **514:**25–34.

Pin JP, Galvez T, and Prézeau L (2003) Evolution, structure, and activation mechanism of family 3/C G-protein-coupled receptors. *Pharmacol Ther* **98:**325–354.

Pin JP, Joly C, Heinemann SF, and Bockaert J (1994) Domains involved in the specificity of G protein activation in phospholipase C-coupled metabotropic glutamate receptors. *EMBO J* **13:**342–348.

Pin JP, Waeber C, Prezeau L, Bockaert J, and Heinemann SF (1992) Alternative splicing generates metabotropic glutamate receptors inducing different patterns of calcium release in *Xenopus* oocytes. *Proc Natl Acad Sci U S A* **89:**10331–10335.

Pisani A, Bernardi G, Bonsi P, Centonze D, Giacomini P, and Calabresi P (2000) Cell-type specificity of mGluR activation in striatal neuronal subtypes. *Amino Acids* **19:**119–129.

Pisani A, Bonsi P, Centonze D, Bernardi G, and Calabresi P (2001) Functional coexpression of excitatory mGluR1 and mGluR5 on striatal cholinergic interneurons. *Neuropharmacology* **40:**460–463.

Poisik OV, Mannaioni G, Traynelis S, Smith Y, and Conn PJ (2003) Distinct functional roles of the metabotropic glutamate receptors 1 and 5 in the rat globus pallidus. *J Neurosci* **23:**122–130.

Pollock PM, Cohen-Solal K, Sood R, Namkoong J, Martino JJ, Koganti A, Zhu H, Robbins C, Makalowska I, Shin SS, et al. (2003) Melanoma mouse model implicates metabotropic glutamate signaling in melanocytic neoplasia. *Nat Genet* **34:**108–112.

Porter RH and Roberts PJ (1993) Glutamate metabotropic receptor activation in neonatal rat cerebral cortex by sulphur-containing excitatory amino acids. *Neurosci Lett* **154:**78–80.

Prézeau L, Gomeza J, Ahern S, Mary S, Galvez T, Bockaert J, and Pin JP (1996) Changes in the carboxyl-terminal domain of metabotropic glutamate receptor 1 by alternative splicing generate receptors with differing agonist-independent activity. *Mol Pharmacol* **49:**422–429.

Prince DA (1999) Epileptogenic neurons and circuits. *Adv Neurol* **79:**665–684.

Pula G, Mundell SJ, Roberts PJ, and Kelly E (2004) Agonist-independent internalization of metabotropic glutamate receptor 1a is arrestin- and clathrin-dependent and is suppressed by receptor inverse agonists. *J Neurochem* **89:**1009–1020.

Rae MG and Irving AJ (2004) Both mGluR1 and mGluR5 mediate Ca^{2+} release and inward currents in hippocampal CA1 pyramidal neurons. *Neuropharmacology* **46:**1057–1069.

Ray K and Hauschild BC (2000) Cys-140 is critical for metabotropic glutamate receptor-1 dimerization. *J Biol Chem* **275:**34245–34251.

Reichelt W and Knöpfel T (2002) Glutamate uptake controls expression of a slow postsynaptic current mediated by mGluRs in cerebellar Purkinje cells. *J Neurophysiol* **87:**1974–1980.

Renaud J, Emond M, Meilleur S, Psarropoulou C, and Carmant L (2002) AIDA, a class I metabotropic glutamate-receptor antagonist limits kainate-induced hippocampal dysfunction. *Epilepsia* **43:**1306–1317.

Richter-Levin G, Errington ML, Maegawa H, and Bliss TV (1994) Activation of metabotropic glutamate receptors is necessary for long-term potentiation in the dentate gyrus and for spatial learning. *Neuropharmacology* **33:**853–857.

Riedel G and Reymann K (1993) An antagonist of the metabotropic glutamate receptor prevents LTP in the dentate gyrus of freely moving rats. *Neuropharmacology* **32:**929–931.

Rivadulla C, Martínez LM, Varela C, and Cudeiro J (2002) Completing the corticofugal loop: a visual role for the corticogeniculate type 1 metabotropic glutamate receptor. *J Neurosci* **22:**2956–2962.

Robbins MJ, Ciruela F, Rhodes A, and McIlhinney RA (1999) Characterization of the dimerization of metabotropic glutamate receptors using an N-terminal truncation of mGluR1α. *J Neurochem* **72:**2539–2547.

Roberts PJ (1995) Pharmacological tools for the investigation of metabotropic glutamate receptors (mGluRs): phenylglycine derivatives and other selective antagonists—an update. *Neuropharmacology* **34:**813–819.

Roche KW, Tu JC, Petralia RS, Xiao B, Wenthold RJ, and Worley PF (1999) Homer 1b regulates the trafficking of group I metabotropic glutamate receptors. *J Biol Chem* **274:**25953–25957.

Romano C, Yang WL, and O'Malley KL (1996) Metabotropic glutamate receptor 5 is a disulfide-linked dimer. *J Biol Chem* **271:**28612–28616.

Rong R, Ahn JY, Huang H, Nagata E, Kalman D, Kapp JA, Tu J, Worley PF, Snyder SH, and Ye K (2003) PI3 kinase enhancer-Homer complex couples mGluRI to PI3 kinase, preventing neuronal apoptosis. *Nat Neurosci* **6:**1153–1161.

Rossi DJ, Alford S, Mugnaini E, and Slater NT (1995) Properties of transmission at a giant glutamatergic synapse in cerebellum: the mossy fiber-unipolar brush cell synapse. *J Neurophysiol* **74:**24–42.

Russo RE, Nagy F, and Hounsgaard J (1997) Modulation of plateau properties in dorsal horn neurones in a slice preparation of the turtle spinal cord. *J Physiol* **499:**459–474.

Rutecki PA and Yang Y (1997) Metabotropic glutamate receptor activation modulates epileptiform activity in the hippocampus. *Neuroscience* **81:**927–935.

Sahara Y, Kubota T, and Ichikawa M (2001) Cellular localization of metabotropic glutamate receptors mGluR1, 2/3, 5 and 7 in the main and accessory olfactory bulb of the rat. *Neurosci Lett* **312:**59–62.

Sallese M, Salvatore L, D'Urbano E, Sala G, Storto M, Launey T, Nicoletti F, Knöpfel T, and De Blasi A (2000) The G-protein-coupled receptor kinase GRK4 mediates homologous desensitization of metabotropic glutamate receptor 1. *FASEB J* **14:**2569–2580.

Salt TE (2002) Glutamate receptor functions in sensory relay in the thalamus. *Philos Trans R Soc Lond B Biol Sci* **357:**1759–1766.

Salt TE and Binns KE (2000) Contributions of mGlu1 and mGlu5 receptors to interactions with *N*-methyl-D-aspartate receptor-mediated responses and nociceptive sensory responses of rat thalamic neurons. *Neuroscience* **100:**375–380.

Salt TE and Turner JP (1998) Reduction of sensory and metabotropic glutamate receptor responses in the thalamus by the novel metabotropic glutamate receptor-1-selective antagonist S-2-methyl-4-carboxy-phenylglycine. *Neuroscience* **85:**655–658.

San Gabriel A, Uneyama H, Yoshie S, and Torii K (2005) Cloning and characterization of a novel mGluR1 variant from vallate papillae that functions as a receptor for L-glutamate stimuli. *Chem Senses* **30 (Suppl 1):**i25–i26.

Sato T, Shimada Y, Nagasawa N, Nakanishi S, and Jingami H (2003) Amino acid mutagenesis of the ligand binding site and the dimer interface of the metabotropic glutamate receptor 1. Identification of crucial residues for setting the activated state. *J Biol Chem* **278:**4314–4321.

Saugstad JA, Kinzie JM, Mulvihill ER, Segerson TP, and Westbrook GL (1994) Cloning and expression of a new member of the L-2-amino-4-phosphonobutyric acid-sensitive class of metabotropic glutamate receptors. *Mol Pharmacol* **45:**367–372.

Saugstad JA, Marino MJ, Folk JA, Hepler JR, and Conn PJ (1998) RGS4 inhibits signaling by group I metabotropic glutamate receptors. *J Neurosci* **18:**905–913.

Saugstad JA, Segerson TP, and Westbrook GL (1995) L-2-Amino-3-phosphonopropionic acid competitively antagonizes metabotropic glutamate receptors 1α and 5 in *Xenopus* oocytes. *Eur J Pharmacol* **289:**395–397.

Saugstad JA, Segerson TP, and Westbrook GL (1996) Metabotropic glutamate receptors activate G-protein-coupled inwardly rectifying potassium channels in *Xenopus* oocytes. *J Neurosci* **16:**5979–5985.

Saunders R, Nahorski SR, and Challiss RA (1998) A modulatory effect of extracellular Ca^{2+} on type 1α metabotropic glutamate receptor-mediated signalling. *Neuropharmacology* **37:**273–276.

Sayer RJ, Schwindt PC, and Crill WE (1992) Metabotropic glutamate receptor-mediated suppression of L-type calcium current in acutely isolated neocortical neurons. *J Neurophysiol* **68:**833–842.

Schoepp DD, Goldsworthy J, Johnson BG, Salhoff CR, and Baker SR (1994) 3,5-Dihydroxyphenylglycine is a highly selective agonist for phosphoinositide-linked metabotropic glutamate receptors in the rat hippocampus. *J Neurochem* **63:**769–772.

Schoepp DD, Jane DE, and Monn JA (1999) Pharmacological agents acting at subtypes of metabotropic glutamate receptors. *Neuropharmacology* **38:**1431–1476.

Schoepp DD and Johnson BG (1989a) Comparison of excitatory amino acid-stimulated phosphoinositide hydrolysis and *N*-[^{3}H]acetylaspartylglutamate binding in rat brain: selective inhibition of phosphoinositide hydrolysis by 2-amino-3-phosphonopropionate. *J Neurochem* **53:**273–278.

Schoepp DD and Johnson BG (1989b) Inhibition of excitatory amino acid-stimulated phosphoinositide hydrolysis in the neonatal rat hippocampus by 2-amino-3-phosphonopropionate. *J Neurochem* **53:**1865–1870.

Schoepp DD, Johnson BG, Smith EC, and McQuaid LA (1990) Stereoselectivity and mode of inhibition of phosphoinositide-coupled excitatory amino acid receptors by 2-amino-3-phosphonopropionic acid. *Mol Pharmacol* **38:**222–228.

Schoepp DD, Johnson BG, True RA, and Monn JA (1991) Comparison of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*R*-ACPD)- and 1*R*,3*S*-ACPD-stimulated brain phosphoinositide hydrolysis. *Eur J Pharmacol* **207:**351–353.

Schoepp DD and True RA (1992) 1*S*,3*R*-ACPD-sensitive (metabotropic) [^{3}H]glutamate receptor binding in membranes. *Neurosci Lett* **145:**100–104.

Schoppa NE and Westbrook GL (1997) Modulation of mEPSCs in olfactory bulb mitral cells by metabotropic glutamate receptors. *J Neurophysiol* **78:**1468–1475.

Schoppa NE and Westbrook GL (2001) Glomerulus-specific synchronization of mitral cells in the olfactory bulb. *Neuron* **31:**639–651.

Schumacher TB, Beck H, Steffens R, Blümcke I, Schramm J, Elger CE, and Steinhäuser C (2000) Modulation of calcium channels by group I and group II metabotropic glutamate receptors in dentate gyrus neurons from patients with temporal lobe epilepsy. *Epilepsia* **41:**1249–1258.

Schwarzer C, Kirchmair E, and Sperk G (1998) Metabotropic glutamate receptors mediate activation of NPY-Y2 receptor expression in the rat dentate gyrus. *Neuroreport* **9:**2347–2351.

Schwarzer C and Sperk G (1998) Glutamate-stimulated neuropeptide Y mRNA expression in the rat dentate gyrus: a prominent role of metabotropic glutamate receptors. *Hippocampus* **8:**274–288.

Selig DK, Lee HK, Bear MF, and Malenka RC (1995) Reexamination of the effects of MCPG on hippocampal LTP, LTD, and depotentiation. *J Neurophysiol* **74:**1075–1082.

Selkirk JV, Challiss RA, Rhodes A, and McIlhinney RA (2002) Characterization of an N-terminal secreted domain of the type-1 human metabotropic glutamate receptor produced by a mammalian cell line. *J Neurochem* **80:**346–353.

Selkirk JV, Price GW, Nahorski SR, and Challiss RA (2001) Cell type-specific differences in the coupling of recombinant mGlu1α receptors to endogenous G protein sub-populations. *Neuropharmacology* **40:**645–656.

Sevostianova N and Danysz W (2006) Analgesic effects of mGlu1 and mGlu5 receptor antagonists in the rat formalin test. *Neuropharmacology* **51:**623–630.

Shannon HE and Peters SC (2002) Anticonvulsant effects of the selective mGlu1 receptor antagonist LY456236 in mice and rats (Abstract). *Neuropharmacology* **43:**308.

Sharif RN, Osborne M, Coderre TJ, and Fundytus ME (2002) Attenuation of morphine tolerance after antisense oligonucleotide knock-down of spinal mGluR1. *Br J Pharmacol* **136:**865–872.

Sharon D, Vorobiov D, and Dascal N (1997) Positive and negative coupling of the metabotropic glutamate receptors to a G protein-activated K^+ channel, GIRK, in *Xenopus* oocytes. *J Gen Physiol* **109:**477–490.

Shen KZ and Johnson SW (1997) A slow excitatory postsynaptic current mediated by G-protein-coupled metabotropic glutamate receptors in rat ventral tegmental dopamine neurons. *Eur J Neurosci* **9:**48–54.

Sheng M (2001) The postsynaptic NMDA-receptor—PSD-95 signaling complex in excitatory synapses of the brain. *J Cell Sci* **114:**1251.

Shigemoto R, Abe T, Nomura S, Nakanishi S, and Hirano T (1994) Antibodies inactivating mGluR1 metabotropic glutamate receptor block long-term depression in cultured Purkinje cells. *Neuron* **12:**1245–1255.

Shigemoto R, Kinoshita A, Wada E, Nomura S, Ohishi H, Takada M, Flor PJ, Neki A, Abe T, Nakanishi S, et al. (1997) Differential presynaptic localization of metabotropic glutamate receptor subtypes in the rat hippocampus. *J Neurosci* **17:**7503–7522.

Shigemoto R and Mizuno N (2000) Metabotropic glutamate receptors—immunocytochemical and in situ hybridization analyses, in *Handbook of Chemical Neuroanatomy*, *Vol 18, Glutamate* (Ottersen OP and Storm-Mathisen J eds) pp 63–98, Elsevier Science, New York.

Shigemoto R, Nakanishi S, and Mizuno N (1992) Distribution of the mRNA for a metabotropic glutamate receptor (mGluR1) in the central nervous system: an in situ hybridization study in adult and developing rat. *J Comp Neurol* **322:**121–135.

Shin JH, Kim YS, and Linden DJ (2008) Dendritic glutamate release produces autocrine activation of mGluR1 in cerebellar Purkinje cells. *Proc Natl Acad Sci U S A* **105:**746–750.

Shink E and Smith Y (1995) Differential synaptic innervation of neurons in the internal and external segments of the globus pallidus by the GABA- and glutamate-containing terminals in the squirrel monkey. *J Comp Neurol* **358:**119–141.

Shinohara Y, Nakajima Y, and Nakanishi S (2001) Glutamate induces focal adhesion kinase tyrosine phosphorylation and actin rearrangement in heterologous mGluR1-expressing CHO cells via calcium/calmodulin signaling. *J Neurochem* **78:**365–373.

Shipley MT and Ennis M (1996) Functional organization of olfactory system. *J Neurobiol* **30:**123–176.

Siciliano JC, Toutant M, Derkinderen P, Sasaki T, and Girault JA (1996) Differential regulation of proline-rich tyrosine kinase 2/cell adhesion kinase β (PYK2/CAKβ) and pp125(FAK) by glutamate and depolarization in rat hippocampus. *J Biol Chem* **271:**28942–28946.

Sillevis Smitt P, Kinoshita A, De Leeuw B, Moll W, Coesmans M, Jaarsma D, Henzen-Logmans S, Vecht C, De Zeeuw C, Sekiyama N, et al. (2000) Paraneoplastic cerebellar ataxia due to autoantibodies against a glutamate receptor. *N Engl J Med* **342:**21–27.

Singer W (1993) Neuronal representations, assemblies and temporal coherence. *Prog Brain Res* **95:**461–474.

Skeberdis VA, Lan J, Opitz T, Zheng X, Bennett MV, and Zukin RS (2001) mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C. *Neuropharmacology* **40:**856–865.

Skinner PJ, Vierra-Green CA, Clark HB, Zoghbi HY, and Orr HT (2001) Altered trafficking of membrane proteins in Purkinje cells of SCA1 transgenic mice. *Am J Pathol* **159:**905–913.

Sladeczek F, Pin JP, Récasens M, Bockaert J, and Weiss S (1985) Glutamate stimulates inositol phosphate formation in striatal neurones. *Nature* 317:717–719, 1985.

Sladeczek F, Récasens M, and Bockaert J (1988) A new mechanism for glutamate receptor action: phosphoinositide hydrolysis. *Trends Neurosci* **11:**545–549.

Smiałowska M and Bajkowska M (1997) Activation of metabotropic glutamate receptors increases neuropeptide Y expression in the rat hippocampus: immunohistochemical studies. *Pol J Pharmacol* **49:**357–362.

Smolders I, Lindekens H, Clinckers R, Meurs A, O'Neill MJ, Lodge D, Ebinger G, and Michotte Y (2004) In vivo modulation of extracellular hippocampal glutamate and GABA levels and limbic seizures by group I and II metabotropic glutamate receptor ligands. *J Neurochem* **88:**1068–1077.

Soliman AC, Yu JS, and Coderre TJ (2005) mGlu and NMDA receptor contributions to capsaicin-induced thermal and mechanical hypersensitivity. *Neuropharmacology* **48:**325–332.

Soloviev MM (2000) Detection of a surface-exposed PEST like sequence in the metabotropic glutamate receptor mGluR1α. *Bioinformatics* **16:**837–838.

Soloviev MM, Ciruela F, Chan WY, and McIlhinney RA (1999) Identification, cloning and analysis of expression of a new alternatively spliced form of the metabotropic glutamate receptor mGluR1 mRNA1. *Biochim Biophys Acta* **1446:**161–166.

Spanswick D, Pickering AE, Gibson IC, and Logan SD (1995) Excitation of sympathetic preganglionic neurons via metabotropic excitatory amino acid receptors. *Neuroscience* **68:**1247–1261.

Speed HE and Dobrunz LE (2008) Developmental decrease in short-term facilitation at Schaffer collateral synapses in hippocampus is mGluR1 sensitive. *J Neurophysiol* **99:**799–813.

Stanfa LC and Dickenson AH (1998) Inflammation alters the effects of mGlu receptor agonists on spinal nociceptive neurones. *Eur J Pharmacol* **347:**165–172.

Staub C, Vranesic I, and Knöpfel T (1992) Responses to metabotropic glutamate receptor activation in cerebellar Purkinje cells: induction of an inward current. *Eur J Neurosci* **4:**832–839.

Steckler T, Oliveira AF, Van Dyck C, Van Craenendonck H, Mateus AM, Langlois X, Lesage AS, and Prickaerts J (2005) Metabotropic glutamate receptor 1 blockade impairs acquisition and retention in a spatial Water maze task. *Behav Brain Res* **164:**52–60.

Stefani A, Spadoni F, and Bernardi G (1998) Group I mGluRs modulate calcium currents in rat GP: functional implications. *Synapse* **30:**424–432.

Stephan D, Bon C, Holzwarth JA, Galvan M, and Pruss RM (1996) Human metabotropic glutamate receptor 1: mRNA distribution, chromosome localization and functional expression of two splice variants. *Neuropharmacology* **35:**1649–1660.

Stoop R, Conquet F, and Pralong E (2003) Determination of group I metabotropic glutamate receptor subtypes involved in the frequency of epileptiform activity in vitro using mGluR1 and mGluR5 mutant mice. *Neuropharmacology* **44:**157–162.

Sugitani M, Sugai T, and Onoda N (2002) Postsynaptic activity of metabotropic glutamate receptors in the piriform cortex. *Neuroreport* **13:**1473–1476.

Sugitani M, Sugai T, and Onoda N (2004) Postsynaptic metabotropic glutamate receptor mGluR1 mediates the late component of signal propagation in the guinea pig piriform cortex: optical imaging study. *Neurosci Lett* **356:**29–32.

Sugiyama H, Ito I, and Hirono C (1987) A new type of glutamate receptor linked to inositol phospholipid metabolism. *Nature* **325:**531–533.

Sun J, Tadokoro S, Imanaka T, Murakami SD, Nakamura M, Kashiwada K, Ko J, Nishida W, and Sobue K (1998) Isolation of PSD-Zip45, a novel Homer/vesl family protein containing leucine zipper motifs, from rat brain. *FEBS Lett* **437:**304–308.

Sung KW, Choi S, and Lovinger DM (2001) Activation of group I mGluRs is necessary for induction of long-term depression at striatal synapses. *J Neurophysiol* **86:** 2405–2412.

Suzuki Y, Moriyoshi E, Tsuchiya D, and Jingami H (2004) Negative cooperativity of glutamate binding in the dimeric metabotropic glutamate receptor subtype 1. *J Biol Chem* **279:**35526–35534.

Swartz KJ and Bean BP (1992) Inhibition of calcium channels in rat CA3 pyramidal neurons by a metabotropic glutamate receptor. *J Neurosci* **12:**4358–4371.

Tabata T, Aiba A, and Kano M (2002) Extracellular calcium controls the dynamic range of neuronal metabotropic glutamate receptor responses. *Mol Cell Neurosci* **20:**56–68.

Tabata T, Araishi K, Hashimoto K, Hashimotodani Y, van der Putten H, Bettler B, and Kano M (2004) Ca^{2+} activity at $GABA_B$ receptors constitutively promotes metabotropic glutamate signaling in the absence of GABA. *Proc Natl Acad Sci U S A* **101:**16952–16957.

Tadokoro S, Tachibana T, Imanaka T, Nishida W, and Sobue K (1999) Involvement of unique leucine-zipper motif of PSD-Zip45 (Homer 1c/vesl-1L) in group 1 metabotropic glutamate receptor clustering. *Proc Natl Acad Sci U S A* **96:**13801–13806.

Takács J, Markova L, Borostyánköi Z, Görcs TJ, and Hámori J (1999) Metabotrop glutamate receptor type 1a expressing unipolar brush cells in the cerebellar cortex of different species: a comparative quantitative study. *J Neurosci Res* **55:**733–748.

Takahashi K, Tsuchida K, Tanabe Y, Masu M, and Nakanishi S (1993) Role of the large extracellular domain of metabotropic glutamate receptors in agonist selectivity determination. *J Biol Chem* **268:**19341–19345.

Takechi H, Eilers J, and Konnerth A (1998) A new class of synaptic response involving calcium release in dendritic spines. *Nature* **396:**757–760.

Takeshita Y, Harata N, and Akaike N (1996) Suppression of K^+ conductance by metabotropic glutamate receptor in acutely dissociated large cholinergic neurons of rat caudate putamen. *J Neurophysiol* **76:**1545–1558.

Tallaksen-Greene SJ, Kaatz KW, Romano C, and Albin RL (1998) Localization of mGluR1a-like immunoreactivity and mGluR5-like immunoreactivity in identified populations of striatal neurons. *Brain Res* **780:**210–217.

Talley EM, Lei Q, Sirois JE, and Bayliss DA (2000) TASK-1, a two-pore domain K^+ channel, is modulated by multiple neurotransmitters in motoneurons. *Neuron* **25:**399–410.

Tanabe Y, Masu M, Ishii T, Shigemoto R, and Nakanishi S (1992) A family of metabotropic glutamate receptors. *Neuron* **8:**169–179.

Tang FR, Lee WL, Yang J, Sim MK, and Ling EA (2001) Expression of metabotropic glutamate receptor 1α in the hippocampus of rat pilocarpine model of status epilepticus. *Epilepsy Res* **46:**179–189.

Tang FR and Sim MK (1999) Pre- and/or post-synaptic localisation of metabotropic glutamate receptor 1α (mGluR1α) and 2/3 (mGluR2/3) in the rat spinal cord. *Neurosci Res* **34:**73–78.

Tatarczynska E, Kłodzińska A, Kroczka B, Chojnacka-Wójcik E, and Pilc A (2001) The antianxiety-like effects of antagonists of group I and agonists of group II and III metabotropic glutamate receptors after intrahippocampal administration. *Psychopharmacology (Berl)* **158:**94–99.

Tateyama M, Abe H, Nakata H, Saito O, and Kubo Y (2004) Ligand-induced rearrangement of the dimeric metabotropic glutamate receptor 1α. *Nat Struct Mol Biol* **11:**637–642.

Taylor GW, Merlin LR, and Wong RK (1995) Synchronized oscillations in hippocampal CA3 neurons induced by metabotropic glutamate receptor activation. *J Neurosci* **15:**8039–8052.

Tempia F, Alojado ME, Strata P, and Knöpfel T (2001) Characterization of the $mGluR_1$-mediated electrical and calcium signaling in Purkinje cells of mouse cerebellar slices. *J Neurophysiol* **86:**1389–1397.

Tempia F, Miniaci MC, Anchisi D, and Strata P (1998) Postsynaptic current mediated by metabotropic glutamate receptors in cerebellar Purkinje cells. *J Neurophysiol* **80:**520–528.

Testa CM, Friberg IK, Weiss SW, and Standaert DG (1998) Immunohistochemical localization of metabotropic glutamate receptors mGluR1a and mGluR2/3 in the rat basal ganglia. *J Comp Neurol* **390:**5–19.

Testa CM, Standaert DG, Landwehrmeyer GB, Penney JB Jr, and Young AB (1995) Differential expression of mGluR5 metabotropic glutamate receptor mRNA by rat striatal neurons. *J Comp Neurol* **354:**241–252.

Testa CM, Standaert DG, Young AB, and Penney JB Jr (1994) Metabotropic glutamate receptor mRNA expression in the basal ganglia of the rat. *J Neurosci* **14:**3005–3018.

Thandi S, Blank JL, and Challiss RA (2002) Group-I metabotropic glutamate receptors, mGlu1a and mGlu5a, couple to extracellular signal-regulated kinase (ERK) activation via distinct, but overlapping, signalling pathways. *J Neurochem* **83:** 1139–1153.

Thomas MJ and O'Dell TJ (1995) The molecular switch hypothesis fails to explain the inconsistent effects of the metabotropic glutamate receptor antagonist MCPG on long-term potentiation. *Brain Res* **695:**45–52.

Thomsen C (1996) Metabotropic glutamate receptor subtype 1A activates adenylate cyclase when expressed in baby hamster kidney cells. *Prog Neuropsychopharmacol Biol Psychiatry* **20:**709–726.

Thomsen C, Boel E, and Suzdak PD (1994a) Actions of phenylglycine analogs at subtypes of the metabotropic glutamate receptor family. *Eur J Pharmacol* **267:** 77–84.

Thomsen C and Dalby NO (1998) Roles of metabotropic glutamate receptor subtypes in modulation of pentylenetetrazole-induced seizure activity in mice. *Neuropharmacology* **37:**1465–1473.

Thomsen C, Hansen L, and Suzdak PD (1994b) L-Glutamate uptake inhibitors may stimulate phosphoinositide hydrolysis in baby hamster kidney cells expressing mGluR1a via heteroexchange with L-glutamate without direct activation of mGluR1a. *J Neurochem* **63:**2038–2047.

Thomsen C, Klitgaard H, Sheardown M, Jackson HC, Eskesen K, Jacobsen P, Treppendahl S, and Suzdak PD (1994c) (*S*)-4-Carboxy-3-hydroxyphenylglycine, an antagonist of metabotropic glutamate receptor (mGluR) 1a and an agonist of mGluR2, protects against audiogenic seizures in DBA/2 mice. *J Neurochem* **62:** 2492–2495.

Thomsen C, Mulvihill ER, Haldeman B, Pickering DS, Hampson DR, and Suzdak PD (1993) A pharmacological characterization of the mGluR1α subtype of the metabotropic glutamate receptor expressed in a cloned baby hamster kidney cell line. *Brain Res* **619:**22–28.

Thuault SJ, Davies CH, Randall AD, and Collingridge GL (2002) Group I mGluRs modulate the pattern of non-synaptic epileptiform activity in the hippocampus. *Neuropharmacology* **43:**141–146.

Tizzano JP, Griffey KI, and Schoepp DD (1995) Induction or protection of limbic seizures in mice by mGluR subtype selective agonists. *Neuropharmacology* **34:** 1063–1067.

Topolnik L, Congar P, and Lacaille JC (2005) Differential regulation of metabotropic glutamate receptor- and AMPA receptor-mediated dendritic Ca^{2+} signals by presynaptic and postsynaptic activity in hippocampal interneurons. *J Neurosci* **25:** 990–1001.

Tozzi A, Bengtson CP, Longone P, Carignani C, Fusco FR, Bernardi G, and Mercuri NB (2003) Involvement of transient receptor potential-like channels in responses to mGluR-I activation in midbrain dopamine neurons. *Eur J Neurosci* **18:**2133–2145.

Tozzi A, Guatteo E, Caputi L, Bernardi G, and Mercuri NB (2001) Group I mGluRs coupled to G proteins are regulated by tyrosine kinase in dopamine neurons of the rat midbrain. *J Neurophysiol* **85:**2490–2497.

Tsuchiya D, Kunishima N, Kamiya N, Jingami H, and Morikawa K (2002) Structural views of the ligand-binding cores of a metabotropic glutamate receptor complexed with an antagonist and both glutamate and $Gd3^+$. *Proc Natl Acad Sci U S A* **99:**2660–2665.

Tsuji Y, Shimada Y, Takeshita T, Kajimura N, Nomura S, Sekiyama N, Otomo J, Usukura J, Nakanishi S, and Jingami H (2000) Cryptic dimer interface and domain organization of the extracellular region of metabotropic glutamate receptor subtype 1. *J Biol Chem* **275:**28144–28151.

Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M, et al. (1999) Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* **23:**583–592.

Tu JC, Xiao B, Yuan JP, Lanahan AA, Leoffert K, Li M, Linden DJ, and Worley PF (1998) Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP3 receptors. *Neuron* **21:**717–726.

Turner JP and Salt TE (2000) Synaptic activation of the group I metabotropic glutamate receptor mGlu1 on the thalamocortical neurons of the rat dorsal lateral geniculate nucleus in vitro. *Neuroscience* **100:**493–505.

Ugolini A, Corsi M, and Bordi F (1997) Potentiation of NMDA and AMPA responses by group I mGluR in spinal cord motoneurons. *Neuropharmacology* **36:**1047–1055.

Ugolini A, Corsi M, and Bordi F (1999) Potentiation of NMDA and AMPA responses by the specific mGluR5 agonist CHPG in spinal cord motoneurons. *Neuropharmacology* **38:**1569–1576.

Van den Pol AN (1994) Metabotropic glutamate receptor mGluR1 distribution and ultrastructural localization in hypothalamus. *J Comp Neurol* **349:**615–632.

van den Pol AN (1995) Presynaptic metabotropic glutamate receptors in adult and developing neurons: autoexcitation in the olfactory bulb. *J Comp Neurol* **359:**253–271.

van Hooft JA, Giuffrida R, Blatow M, and Monyer H (2000) Differential expression of group I metabotropic glutamate receptors in functionally distinct hippocampal interneurons. *J Neurosci* **20:**3544–3551.

van Wagenen BC, Smith DL, Artman LD, Hammerland LG, Heaton WL, Hung BP, Krapcho KJ, Levinthal C, Logan MA, Mueller AM, et al. (2000) Structure-activity relationship studies of NPS 2390: a potent and selective group I metabotropic glutamate receptor antagonist. *Soc Neurosci Abstr* **26:**618.3.

Varma N, Carlson GC, Ledent C, and Alger BE (2001) Metabotropic glutamate receptors drive the endocannabinoid system in hippocampus. *J Neurosci* **21:** RC188.

Varty GB, Grilli M, Forlani A, Fredduzzi S, Grzelak ME, Guthrie DH, Hodgson RA, Lu SX, Nicolussi E, Pond AJ, et al. (2005) The antinociceptive and anxiolytic-like effects of the metabotropic glutamate receptor 5 (mGluR5) antagonists, MPEP and MTEP, and the mGluR1 antagonist, LY456236, in rodents: a comparison of efficacy and side-effect profiles. *Psychopharmacology (Berl)* **179:**207–217.

Varty GB, Powell SB, Lehmann-Masten V, Buell MR, and Geyer MA (2006) Isolation rearing of mice induces deficits in prepulse inhibition of the startle response. *Behav Brain Res* **169:**162–167.

Verma A and Moghaddam B (1998) Regulation of striatal dopamine release by metabotropic glutamate receptors. *Synapse* **28:**220–226.

Vetter P, Garthwaite J, and Batchelor AM (1999) Regulation of synaptic transmission in the mossy fibre-granule cell pathway of rat cerebellum by metabotropic glutamate receptors. *Neuropharmacology* **38:**805–815.

Vidnyanszky Z, Gorcs TJ, Negyessy L, Borostyankio Z, Knopfel T, and Hámori J (1996) Immunocytochemical visualization of the mGluR1a metabotropic glutamate receptor at synapses of corticothalamic terminals originating from area 17 of the rat. *Eur J Neurosci* **8:**1061–1071.

Víg J, Takács J, Vastagh C, Baldauf Z, Veisenberger E, and Hámori J (2003) Distribution of mGluR1α and SMI 311 immunoreactive Lugaro cells in the kitten cerebellum. *J Neurocytol* **32:**217–227.

Vigh J and Lasater EM (2003) Intracellular calcium release resulting from mGluR1 receptor activation modulates GABAA currents in wide-field retinal amacrine cells: a study with caffeine. *Eur J Neurosci* **17:**2237–2248.

Vranesic I, Staub C, and Knöpfel T (1993) Activation of metabotropic glutamate receptors induces an outward current which is potentiated by methylxanthines in rat cerebellar Purkinje cells. *Neurosci Res* **16:**209–215.

Wada E, Shigemoto R, Kinoshita A, Ohishi H, and Mizuno N (1998) Metabotropic glutamate receptor subtypes in axon terminals of projection fibers from the main and accessory olfactory bulbs: a light and electron microscopic immunohistochemical study in the rat. *J Comp Neurol* **393:**493–504.

Wang SS, Denk W, and Haüsser M (2000a) Coincidence detection in single dendritic spines mediated by calcium release. *Nat Neurosci* **3:**1266–1273.

Wang XS, Ong WY, Lee HK, and Huganir RL (2000b) A light and electron microscopic study of glutamate receptors in the monkey subthalamic nucleus. *J Neurocytol* **29:**743–754.

Warwick HK, Nahorski SR, and Challiss RA (2005) Group I metabotropic glutamate receptors, mGlu1a and mGlu5a, couple to cyclic AMP response element binding protein (CREB) through a common Ca^{2+}- and protein kinase C-dependent pathway. *J Neurochem* **93:**232–245.

Watkins JC, Krogsgaard-Larsen P, and Honoré T (1990) Structure-activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonists. *Trends Pharmacol Sci* **11:**25–33.

Wichmann J, Bleicher K, Vieira E, Woltering T, Knoflach F, and Mutel V (2002) Alkyl diphenylacetyl, 9*H*-xanthene- and 9*H*-thioxanthene-carbonyl carbamates as positive allosteric modulators of mGlu1 receptors. *Farmaco* **57:**989–992.

Wilsch VW, Behnisch T, Jäger T, Reymann KG, and Balschun D (1998) When are class I metabotropic glutamate receptors necessary for long-term potentiation? *J Neurosci* **18:**6071–6080.

Wilson C, Howard JA, Jane DE, Sunter DC, and Watkins JC (1997) Absolute configuration of (+)-α-methyl-4-carboxyphenylglycine (MCPG), a metabotropic glutamate receptor antagonist. *Acta Crystallogr C* **53:**909–911.

Wittmann M, Hubert GW, Smith Y, and Conn PJ (2001) Activation of metabotropic glutamate receptor 1 inhibits glutamatergic transmission in the substantia nigra pars reticulata. *Neuroscience* **105:**881–889.

Wong RK, Chuang SC, and Bianchi R (2002) Metabotropic glutamate receptors and epileptogenesis. *Epilepsy Curr* **2:**81–85.

Woodhall G, Gee CE, Robitaille R, and Lacaille JC (1999) Membrane potential and intracellular Ca^{2+} oscillations activated by mGluRs in hippocampal stratum oriens/alveus interneurons. *J Neurophysiol* **81:**371–382.

Wright DD, Blackstone CD, Huganir RL, and Ryugo DK (1996) Immunocytochemical localization of the mGluR1α metabotropic glutamate receptor in the dorsal cochlear nucleus. *J Comp Neurol* **364:**729–745.

Xu W, Wong TP, Chery N, Gaertner T, Wang YT, and Baudry M (2007) Calpain-mediated mGluR1α truncation: a key step in excitotoxicity. *Neuron* **53:**399–412.

Yanovsky Y, Sergeeva OA, Freund TF, and Haas HL (1997) Activation of interneurons at the stratum oriens/alveus border suppresses excitatory transmission to apical dendrites in the CA1 area of the mouse hippocampus. *Neuroscience* **77:**87–96.

Young MR, Blackburn-Munro G, Dickinson T, Johnson MJ, Anderson H, Nakalembe I, and Fleetwood-Walker SM (1998) Antisense ablation of type I metabotropic glutamate receptor mGluR1 inhibits spinal nociceptive transmission. *J Neurosci* **18:**10180–10188.

Young MR, Fleetwood-Walker SM, Dickinson T, Blackburn-Munro G, Sparrow H, Birch PJ, and Bountra C (1997) Behavioural and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. *Brain Res* **777:**161–169.

Young MR, Fleetwood-Walker SM, Mitchell R, and Dickinson T (1995) The involvement of metabotropic glutamate receptors and their intracellular signalling pathways in sustained nociceptive transmission in rat dorsal horn neurons. *Neuropharmacology* **34:**1033–1041.

Young MR, Fleetwood-Walker SM, Mitchell R, and Munro FE (1994) Evidence for a role of metabotropic glutamate receptors in sustained nociceptive inputs to rat dorsal horn neurons. *Neuropharmacology* **33:**141–144.

Yuan JP, Kiselyov K, Shin DM, Chen J, Shcheynikov N, Kang SH, Dehoff MH, Schwarz MK, Seeburg PH, Muallem S, et al. (2003) Homer binds TRPC family channels and is required for gating of TRPC1 by IP3 receptors. *Cell* **114:**777–789.

Yung KK (1998) Localization of ionotropic and metabotropic glutamate receptors in distinct neuronal elements of the rat substantia nigra. *Neurochem Int* **33:**313–326.

Yuzaki M and Mikoshiba K (1992) Pharmacological and immunocytochemical characterization of metabotropic glutamate receptors in cultured Purkinje cells. *J Neurosci* **12:**4253–4263.

Zhang H and Sulzer D (2003) Glutamate spillover in the striatum depresses dopaminergic transmission by activating group I metabotropic glutamate receptors. *J Neurosci* **23:**10585–10592.

Zhang L, Lu Y, Chen Y, and Westlund KN (2002) Group I metabotropic glutamate receptor antagonists block secondary thermal hyperalgesia in rats with knee joint inflammation. *J Pharmacol Exp Ther* **300:**149–156.

Zhao W, Bianchi R, Wang M, and Wong RK (2004) Extracellular signal-regulated kinase 1/2 is required for the induction of group I metabotropic glutamate receptor-mediated epileptiform discharges. *J Neurosci* **24:**76–84.

Zhong J, Gerber G, Kojić L, and Randić M (2000) Dual modulation of excitatory synaptic transmission by agonists at group I metabotropic glutamate receptors in the rat spinal dorsal horn. *Brain Res* **887:**359–377.

Zhu H, Ryan K, and Chen S (1999) Cloning of novel splice variants of mouse mGluR1. *Brain Res Mol Brain Res* **73:**93–103.