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Metabotropic Glutamate Receptors

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1. INTRODUCTION

L-Glutamate, one of the main neurotransmitters in the central nervous system (CNS), acts on two groups of receptors: (a) a group of ionotropic receptors that includes *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), and kainate receptors, and *(2)* a group of metabotropic receptors (mGluRs). Ionotropic glutamate receptors, which are ligand-gated ion channels permeable for Ca^{2+}, Na^{+}, and K^{+}, are responsible for fast and relatively large changes in membrane conductance *(1,2)* and are covered in Chapter 4. In contrast, stimulation of mGluRs evokes a complex cascade of intracellular events that indirectly modulates neuronal excitability and produces delayed and slow synaptic currents *(1,2)*. Both groups of glutamate receptors are involved in several physiological and pathological functions including neuronal growth and plasticity, neurotoxicity, cognitive and motor behavior, depression, anxiety, drug abuse, epilepsy, and others. Some ligands of ionotropic receptors have already been introduced to clinical practice (e.g., amantadine, memantine, D-cycloserine), whereas mGluRs may be considered as an emerging target for the treatment of several diseases (e.g., Parkinson's disease, depression, epilepsy and others; *see also* Chapters 10, 19, 21, and 22).

2. MOLECULAR STRUCTURES

The metabotropic glutamate receptors were discovered in the mid-1980s, when Bardsley and Roberts *(3)*, Sladeczek et al. *(4)*, Nicoletti *(5–7)*, and others (for review, *see* ref. *2*) described glutamate-dependent phosphoinositide hydrolysis in the striatal and cerebellar cell cultures, as well as in brain slices, synaptosomes, and glial cells. Shortly thereafter, Sugiyama et al. *(8)* used for the first time the term "metabotropic" for receptors expressed in *Xenopus* oocytes transfected with rat brain mRNA. These receptors were preferentially activated by quisqualate, which triggered, via interaction with G protein, phosphoinositide hydrolysis leading to the formation of inositol 1,4,5-triphosphate (IP3) and mobilization of intracellular Ca^{2+} *(8)*.

Metabotropic glutamate receptors belong to a family 3 of heptahelix G protein-coupled receptors (GPCRs), which exhibits low-sequence homology (~12%) with classic rhodopsin-like family 1 *(9)*. Apart from mGluRs, the family 3 of GPCRs contains also

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parathyroid Ca^{2+}-sensing receptor, γ-aminobutyric acid $(GABA)_B$ receptor, and putative olfactory, pheromone and taste receptors *(9)*. Until now eight mGluRs, composed of 501–1199 amino acids, coded by eight genes, have been identified in rats, mice, and humans, and cloned (cf. ref. *2*). They have been classified into three groups according to their sequence homology, signal transduction, and pharmacological properties. Group I contains two receptors: mGluR1 (five isoforms: a, b, c, d, e) and mGluR5 (two isoforms: a, b). Group II includes two receptors: mGluR2 and mGluR3; and group III comprises four receptors: mGluR4 (two isoforms: a, b), mGluR6, mGluR7 (two isoforms; a, b), and mGluR8 (three isoforms: a, b, c) (cf. ref. *2*). These receptors are composed of an exceptionally long N-terminal extracellular domain of approx 560 amino acids, a seven-transmembrane (TM) domain, and a C-terminal intracellular domain, that is submitted to alternative splicing, which leads to formation of the above-mentioned isoforms *(9–11)*. MGluR1e is an exceptional splice variant (N-terminally truncated 578 amino acid protein) coded by a gene having an additional exon inserted before the seven-TM domain, which contains an in-frame stop codon *(11)*. N-terminal extracellular and seven-TM domains in other isoforms are separated by a cystein-rich region *(9,11)* (Fig. 1). Receptors belonging to one group exhibit 70% sequence homology, whereas homology between groups amounts to only 45%. *(11)*.

Glutamate, agonists, and competitive antagonists bind to the extracellular domain, which forms two globular domains separated by a cleft *(9,12,13)*. Such a flytrap configuration of this domain closes glutamate that leads to changes in conformation of the TM domain region and to alterations of intracellular signaling *(9)* (Fig. 1). In contrast, allosteric binding sites for positive modulators (allosteric enhancers) or noncompetitive antagonists are formed by the TM helices in mGluR1 *(14,15)*, mGluR5 *(14)*, mGluR2 *(16)*, and mGluR4a *(17)*. The second and the third intracellular loops and C-terminal tail are responsible for coupling with G proteins (Fig. 1). The least conservative second loop determines selectivity, whereas the third, highly conservative one is decisive for activation of G protein *(9)*. All mGluRs form homodimers, which is important for receptor activation *(9)*.

3. G PROTEINS AND SECOND MESSENGERS

3.1. Group I mGluRs

Receptors belonging to group I mGluRs (mGluR1 and mGluR5) couple to pertussis toxin (PTX)-insensitive G protein ($G_{q/11}$), which activates phospholipase Cβ (PLCβ) (cf. refs. *11,18*). This enzyme catalyzes phosphoinositide hydrolysis with a production of IP3 and diacylglycerol (DAG) (Fig. 2). Stimulation of PLC by mGluR1a activation is also partly dependent on the PTX-sensitive G_i/G_o protein (cf. ref. *11*). Moreover, agonist binding at mGluR1a in certain cell lines but not in neurons or astrocytes stimulates adenylate cyclase (cf. ref. *11*). Furthermore, some mGluR1 responses, e.g., activation of a nonreceptor tyrosine kinases belonging to Src family, may be independent of G proteins *(19)*.

Stimulation of the group I mGluRs increases an intracellular calcium ($[Ca^{2+}]_i$) concentration (Fig. 2). However, kinetics of this process differ depending on the activated receptor. Activation of mGluR5a induces oscillations of $[Ca^{2+}]_i$ *(20)*, whereas stimulation of mGluR1a produces a single peak followed by a plateau of $[Ca^{2+}]_i$ level *(9,21)*. Mobilization of intracellular $[Ca^{2+}]$ induced by stimulation of these receptors depends on at least three processes: (1) activation of PLCβ leading to a production of IP3. IP3 induces Ca^{2+} release from internal stores via activation of specific receptors (IP3Rs)

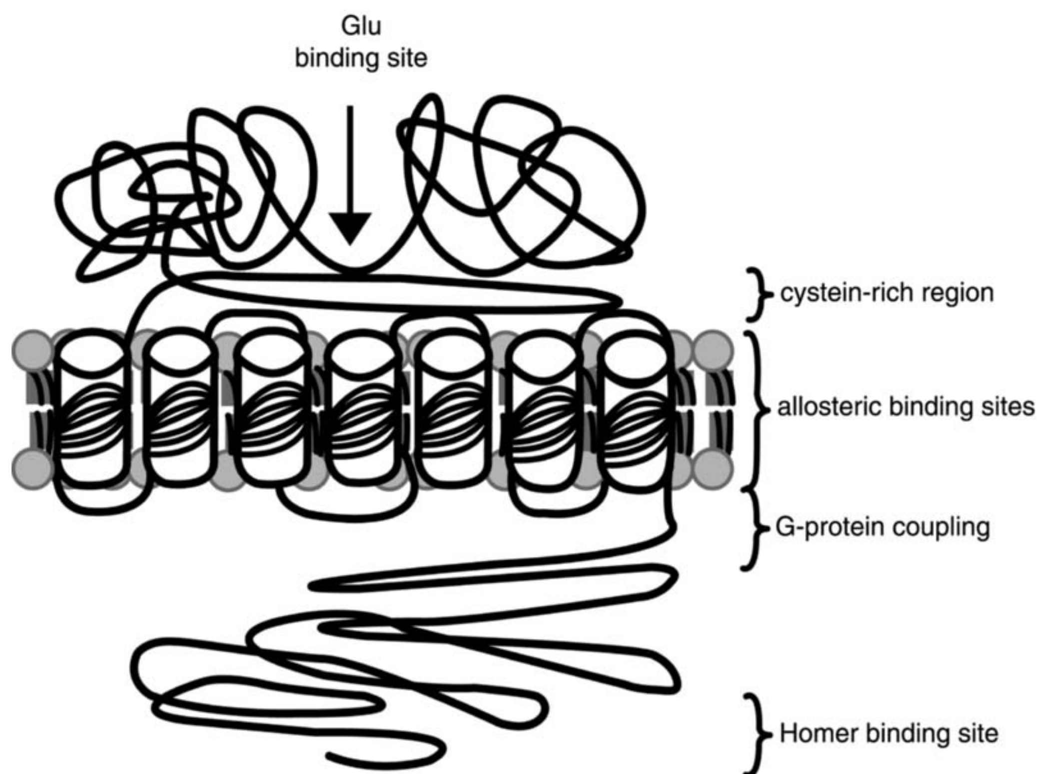
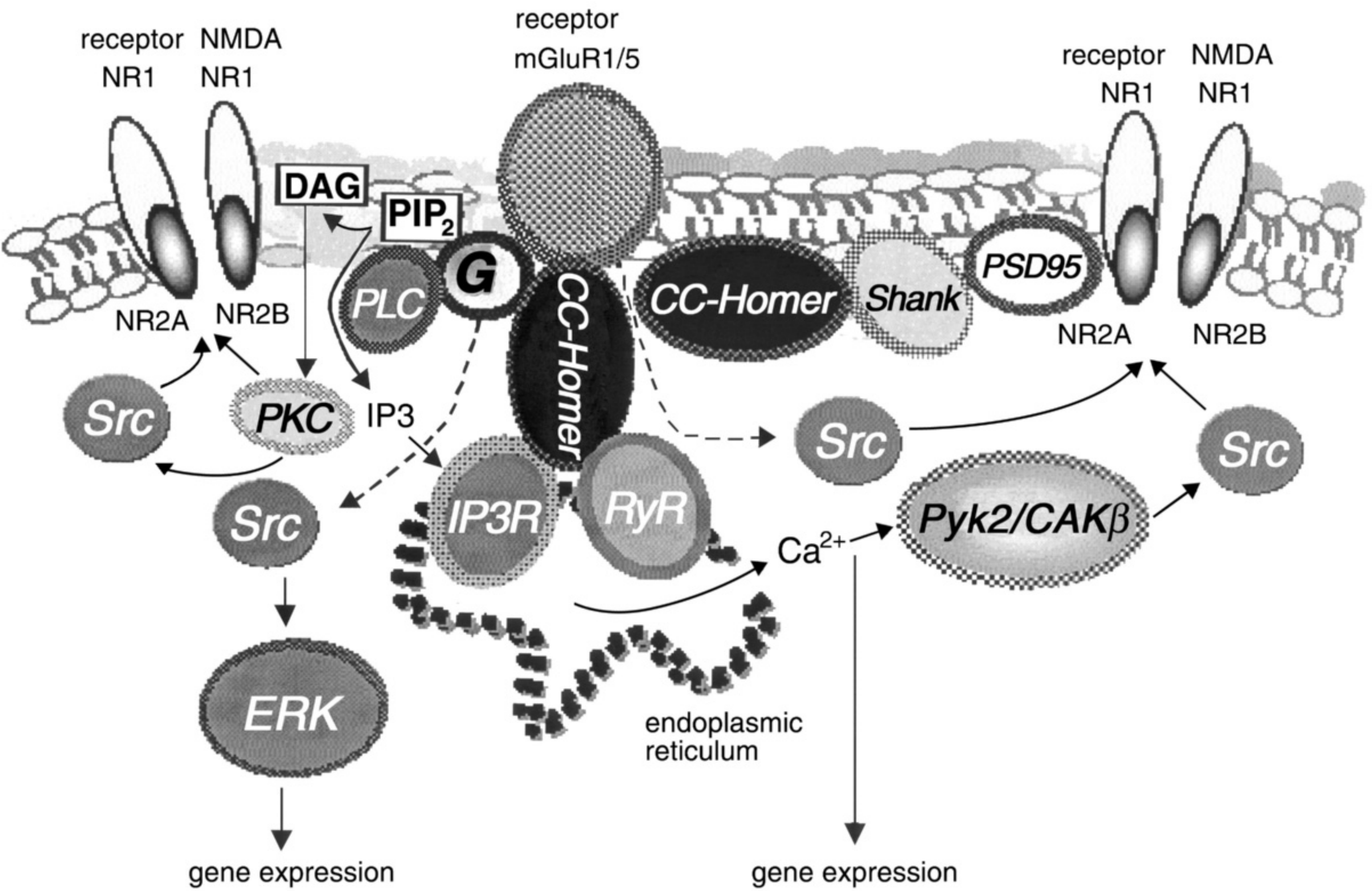


Fig. 1. A model of metabotropic glutamate receptor.

associated with endoplasmic reticulum *(10)* (Fig. 2); (2) mobilization of Ca^{2+} from internal stores via ryanodine-sensitive receptors (RyRs) (Fig. 2) *(10)*. These receptors colocalize with IP3Rs on endoplasmic reticulum, but it is not known whether RyRs-sensitive stores constitute the same calcium pool as those sensitive to IP3Rs; (3) Ca^{2+} influx through plasma-membrane voltage-dependent L-calcium channels. This process is also ryanodine-sensitive *(10)*.

Homer proteins may be involved in all the above-mentioned processes contributing to an increase in $[Ca^{2+}]_i$. These proteins constitute a physical link between mGluRs and Ca^{2+} internal stores (Fig. 2) *(10,22)*. Homer proteins form dimers (CC-Homers) by coiled-coil interaction of C-terminal regions that contain a leucine-zipper motif. Their N-terminals recognize, in turn, a proline sequence (PPXXFR) of the distal region of C-terminal domain of mGluR1a or mGluR5a/b, on one side, and the same sequence of IP3Rs or RyRs, on the other *(22)*. Immunochemical studies have indicated that Homer proteins 3, 1b/1c co-immunoprecipitate with mGluR1a and IP3Rs, which suggests that they form a complex with these receptors *(22)*. A family of Homer proteins includes also Homer 1a, which is a product of an immediate early gene (IEG), transiently induced by physiological synaptic stimuli. This protein is devoid of leucine-zipper sequence and does not form dimers. Therefore, in spite of the fact that Homer 1a binds either to mGluRs or to IP3Rs, it cannot crosslink mGluRs and internal Ca^{2+} stores. Contrariwise, a competition of Homer 1a with CC-Homers for common binding sites disrupts the link induced by the latter proteins and inhibits the mGluRs-evoked Ca^{2+} release *(22)*.



receptor NMDA
NR1 NR1
receptor
mGluR1/5
receptor NMDA
NR1 NR1
DAG
PIP2
G
PLC
CC-Homer
CC-Homer
Shank
PSD95
NR2A NR2B
NR2A NR2B
Src
PKC
IP3
Src
Src
Src
IP3R
RyR
Ca2+
Pyk2/CAKβ
ERK
endoplasmic
reticulum
gene expression
gene expression

Group I mGluRs (mGluR1 and mGluR5) couple also, independently of Ca^{2+}, to another intracellular signaling pathway, viz. the extracellular signal-regulated kinase (ERK) cascade (Fig. 2). ERKs are a subgroup of the family of the mitogen-activated protein kinases (MAPKs), which are key regulators of gene expression, cell proliferation, differentiation, and cell survival. It has been found that stimulation of either mGluR1a or mGluR5a phosphorylates ERKs, which leads to their activation *(23,24)*. This process is dependent on a G protein (Gi/Go for mGluR1a, Gq for mGluR5a) and nonreceptor tyrosine kinases (Src) (Fig. 2) *(24)*. Tyrosine receptor kinase seems to be also involved in activation of ERK cascade by mGluR1a *(24)*.

3.1.1. Regulation of Group I mGluR Function by Protein Kinases

Several recent studies indicate that the function of mGluRs may remain under positive or negative control of protein kinases. It has been found that an increase in $[Ca^{2+}]_i$ induced by mGluR1a is dependent on protein tyrosine kinases. It has been hypothesized that these kinases may phosphorylate tyrosine residues of either G protein, or the receptor itself, and in this way may activate IP3/Ca^{2+} signaling *(18,25)*. However, the most recent study has shown that phosphorylation of mGluR5 by protein tyrosine kinases does not influence phosphoinositide hydrolysis *(26)*.

In contrast, phosphorylation of serine and threonine residues of mGluR1 and mGluR5 by protein kinase C (PKC), which is an enzyme activated by DAG (Fig. 2), leads to desensitization of these receptors and a drop of IP3 production and $[Ca^{2+}]_i$ level *(9,20,23)*. In accordance with this view, the previously described mGluR5-induced oscillations of $[Ca^{2+}]_i$, result probably from a sequence of activations and PKC-dependent inactivations of this receptor *(20)*. On the other hand, PKC-induced phosphorylation of mGluR5 is inhibited by calmodulin, which binds to C-terminal domain of this receptor in a Ca^{2+}-dependent manner *(27)*.

G protein-coupled receptor kinases (GRKs) may be additionally involved in the desensitization of mGluRs *(21)*. Such a GRK-induced process has been described for mGluR1a. In the presence of agonist, this receptor is phosphorylated by GRK4. Then, arrestin1a and dynamin, which act as adaptors between the phosphorylated receptors and components of endocytotic machinery, bind to mGluR1a. This results in the receptor uncoupling from G

Fig. 2. Complex intracellular processes triggered by stimulation of mGluR1/5 receptors, and their interactions with *N*-methyl-D-aspartate (NMDA) receptors. MGluR1/5 receptors couple with G protein and activate phospholipase C (PLC), which catalyzes hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2) with a production of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). DAG activates protein kinase C (PKC), whereas IP3 stimulates specific receptors (IP3R) localized on the endoplasmic reticulum, thereby leading to Ca^{2+} release from internal stores. MGluR1/5 receptors may also stimulate Ca^{2+} release via stimulation of ryanodine receptors (RyR). MGluR1/5 are physically linked with IP3R and RyR via CC-Homer proteins. Moreover, these receptors crosslink NMDA receptors via CC-Homers and/or postsynaptic density proteins, Shank, and PSD-95. Stimulation of group I mGluRs activates different tyrosine kinases belonging to Src family, in a manner dependent on or independent of G protein, which results, e.g., in activation of NMDA receptors (phosphorylation of NR2A/NR-2B subunits) or activation of extracellular signal-regulated kinase cascade (ERK). NMDA receptors may be phosphorylated and activated also by PKC or Ca^{2+}- and calmodulin-activated kinases. Sometimes activation of Src kinases may depend on PKC, or Ca^{2+} and Pyk2/Cell adhesion kinase (CBK)β. For further details, *see* text.

protein, internalization, and a decrease in phosphoinositide hydrolysis and Ca^{2+} level *(21,28)*. The previously mentioned data show that a prolonged stimulation of these receptors by specific agonists leads to their homologous desensitization via activation of PKC and GRKs *(9,21)*. However, the most recent study carried out on slices of rat globus pallidus has indicated that in some cases desensitization of mGluR1 may need coactivation of mGluR5 *(29)*. This is a heterologous desensitization that involves PKC *(29)*. ERK pathway becomes also desensitized as a result of continuous stimulation of mGluR5. However, the basic mechanism of this process is unknown because it does not involve PKC activation *(23)*.

3.2. *Group II and III mGluRs*

It is generally accepted that both groups II and III mGluRs couple to PTX-sensitive Gi/Go proteins (cf. ref. *30*). Stimulation of these receptors inhibits adenylate cyclase activity and decreases cyclic adenosine monophosphate (cAMP) level (cf. ref. *30*). However, this process does not seem to be the sole alteration in second messenger systems evoked by activation of these receptors. Stimulation of recombinant mGluR2 in CHO (Chinese hamster ovary) cells has been reported to activate PLC and phosphoinositide hydrolysis via $G_{\alpha 15}$ subunit, a member of the G_q protein family *(31)*. However, in hippocampal slices selective agonists of group II mGluRs: (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate (LY 354740) and (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate (2R,4R-APDC) increase phosphoinositide hydrolysis only indirectly via enhancing the effect of group I mGluRs *(32,33)*. Similarly, activation of mGluR7 via G_o in cultured cerebellar granule cells or via $G_{\alpha 15}$ in cell lines has been found to stimulate PLC/IP3/$[Ca^{2+}]_i$ cascade *(34,35)*.

Quite a different signal transduction pathway is stimulated by mGluR6 in depolarizing bipolar cells of retina, which are activated by cyclic guanosine monophosphate (cGMP) *(36)*. In these neurons, mGluR6 activates cGMP phosphodiesterase which, in turn, hydrolyses cGMP to 5′-GMP and in this way inhibits membrane conductance *(36)*.

3.2.1. *Regulation of Group II and III mGluRs Function by Protein Kinases*

The function of receptors belonging to group II and III is modulated by protein kinases: PKC and/or cAMP-dependent protein kinase (PKA). PKC has been found to phosphorylate mGluR2 *(37)* which leads to uncoupling of this receptor from G protein and reversal of its effects on cAMP and neuronal activity *(38–40)*. Regarding group III mGluRs, a direct phosphorylation of mGluR7 by PKC, which inhibits its functioning, has also been reported *(39,41,42)*. This PKC-induced phosphorylation of mGluR7 is diminished by binding of calmodulin to C-terminal domain of this receptor *(42)*.

PKA phosphorylates serine residue (Ser^{843}) of the intracellular C-terminus of mGluR2, and uncouples this receptor from $G_{\alpha 15}$. The latter process results in a decrease in phosphoinositide hydrolysis and in reversal of presynaptic inhibition induced by this receptor stimulation *(31,38)*. PKA does not phosphorylate mGluR7 *(42)*.

4. LOCALIZATION

4.1. *Group I mGluRs*

MGluRs belonging to group I are widely distributed in the CNS. The highest concentration of mGluR1 is present in Purkinje cells and molecular layer of the cerebellum, in glomeruli of olfactory bulb, and in CA1 region of the hippocampus *(43)*. Moderate levels

of these receptors have been found in the basal ganglia (globus pallidus, islands of Calleya, caudate-putamen and nucleus accumbens, subthalamic nucleus), midbrain (substantia nigra, superior colliculus, ventral tegmental area), other regions of cerebellum (stellate cells, basket cells, etc.), pyriform and cingulate cortex, amygdala, CA3 region, and dentate gyrus of the hippocampus *(43)*.

In spite of the fact that regional distribution of mGluR5 mostly overlaps that of mGluR1, their densities in distinct brain structures differ markedly. The highest concentration of mGluR5 has been detected in the basal ganglia (caudate–putamen, nucleus accumbens, olfactory tubercle) and CA1, CA3, and dentate gyrus of the hippocampus whereas their moderate and low levels occur in the globus pallidus and the substantia nigra, respectively (cf. ref. *44*). In all these structures the density of mGluR5 is considerably higher than that of mGluR1. In contrast, Purkinje cell layer of the cerebellum, which is enriched of mGluR1, is devoid of mGluR5 (cf. ref. *44*). Moreover, mGluR1 and mGluR5 may be differentially distributed on neuronal subpopulations, e.g., in the cerebral cortex. In this structure, somatostatin neurons exhibit almost four times higher immunoreactivity of mGluR1 than mGluR5, whereas the opposite relationship is characteristic of neurons stained for glutamic acid decarboxylase 67 (GAD67) or parvalbumin *(45)*.

MGluR1a and mGluR5 are mainly postsynaptic receptors. Their highest density is observed in perisynaptic annulus, located at the edge of both axo-spineous and axo-dendritic synaptic junctions, which surrounds the postsynaptic density of so-called type 1 synapses. Smaller numbers of these receptors are localized extrasynaptically on dendrites and somatic membranes *(43,46–48)*. These receptors have never been found in the main body of the postsynaptic density *(43,47)*. Immunohistochemical methods discovered also presynaptic mGluR1 and mGluR5 on axon terminals in the cerebral cortex, striatum, CA1 region of the hippocampus, or substantia nigra pars reticulata *(46,49,50)*. MGluR5 has also been found on astrocytes *(51)*.

4.2. Group II and III mGluRs

Immunohistochemical as well as binding studies using a selective antagonist—[^{3}H]-(2S)-2-amino-2-[(1S,2S)-2-carboxycyclopropan-1-yl]-3-(xanth-9-yl) propionic acid ([^{3}H]LY 341495)—or agonist—[^{3}H]LY 354740 of group II mGluRs—revealed that densities of these receptors varied throughout the brain *(52–55)*. Their highest density was identified in the forebrain: cerebral cortex, hippocampus, caudate-putamen, nucleus accumbens, olfactory bulb. Medium levels were found in hypothalamus, cerebellum, amygdala, thalamus, superior colliculus, whereas their densities in the globus pallidus, pons, and medulla were low *(52–55)*.

Group II (mGluR2/3) mGluRs are localized mainly in the terminal zone of axons. MGluR2 and mGluR3 are present in preterminal axonal region, and in extrasynaptic membrane of axon terminals and only rarely in presynaptic membrane *(53,56)*. They are not associated with the presynaptic junction sites. Glial processes have also been reported to be immunopositive for mGluR3 *(56)*.

Distribution of individual members of group III mGluRs in the brain also varies considerably. Intense mGluR7 immunoreactivity was seen in olfactory bulbs, anterior olfactory nucleus, islands of Calleya, olfactory tubercle, piriform and entorhinal cortices, amygdala and hippocampus, layer I of the neocortical regions, globus pallidus, superior colliculus, locus coeruleus, medulla, and spinal cord *(57)*. MGluR4 are most prominently

expressed in the cerebellum, basal ganglia, the sensory relay nuclei of the thalamus, and some hippocampal regions *(58)*. MGluR6 receptors show a unique distribution. They are present only in depolarizing bipolar cells of retina (cf. ref. *11*). In contrast to other receptors, the highest expression of mGluR8 is localized in the pontine nuclei and reticulotegmental nucleus followed by reticular thalamic nucleus, olfactory bulb, basal amygdaloid nucleus, and cerebral cortex *(34)*. Low expression of this receptor has been found in molecular layer of the cerebellum *(59)* and hippocampus *(56)*.

In contrast to mGluR2/3 receptors, mGluR4, mGluR7, and mGluR8 are abundant in the active zone of the presynaptic membrane of both asymmetric (glutamatergic) and symmetric (GABAergic) synapses *(56–58,60)*. Therefore, they may act as glutamatergic autoreceptors, and heteroreceptors that influence GABA release.

MGluR2, 3, 4, and 7 receptors have also been found postsynaptically on dendritic shafts and somatic membrane *(48,52,53,61,62)*.

5. THE ROLE OF mGluRs IN SYNAPTIC TRANSMISSION

5.1. Postsynaptic and Presynaptic Effects of Group I mGluRs

Postsynaptic mGluRs belonging to group I are mainly excitatory receptors. They are activated by glutamate at submicromolar and low micromolar concentrations *(1)*. Activation of these receptors by repetitive electrical stimulation or selective agonists increases neuronal excitability (depolarization, slow excitatory synaptic current, inward current) in slices of various brain regions and cell cultures *(61,63–68)*. Depending on the brain structure or neuronal subpopulation, these effects result from stimulation of either mGluR1 (e.g., substantia nigra pars compacta) or mGluR5 (e.g., subthalamic nucleus) or both receptors (e.g., cholinergic striatal interneurons) *(25,67,69)*. Sometimes, however, stimulation of these receptors does not induce any synaptic currents but enhances that produced by stimulation of NMDA receptors (e.g., mGluR5 localized on striatal medium spiny neurons) *(70)*. The excitatory effects induced by group I mGluRs have been suggested to result from inhibition of K^+ channels (cf. refs. *11* and *29*), increased permeability of nonselective cationic channels for Na^+, K^+, and Cs^+ (cf. refs. *29, 63,* and *71*), or Cl^- efflux through Ca^{2+}-activated Cl^- channels *(66)*. The contribution of specific signal transduction pathways to these effects is unclear. Some studies have shown that they are dependent on G protein *(25,63,72)* and Ca^{2+} level *(63,66)*. However, other data have not confirmed any involvement of G protein *(71)*, PLC/IP3/Ca^{2+} pathway, or PKC in these processes *(25,64,71,72)*, but postulated a significant contribution of non-Src protein kinases *(25)*.

Stimulation of mGluR1 on the dopaminergic neurons of the substantia nigra or ventral tegmental area produces a more complex effect: first hyperpolarization (outward current) mediated by activation of Ca^{2+}-dependent K^+-channels, which is followed by depolarization (inward current) *(65)*. It has been speculated that the first inhibitory effect of mGluR activation becomes quickly desensitized and replaced by excitatory response *(73)*.

Presynaptic mGluRs belonging to group I may also regulate glutamatergic transmission. Both mGluR1 and mGluR5 receptors have been found to facilitate glutamate release from presynaptic terminals *(74–76)*. However, the contribution of each receptor to that effect may depend on an examined region; e.g., glutamate release in forebrain or cerebral cortex has been found to be stimulated by mGluR5 but not mGluR1 receptors *(75,76)*. These data suggest that presynaptic mGluR1 and mGluR5 may not colocalize on the same terminals or they act differently. Moreover, Grillner and Mercuri *(77)* and

Katayama et al. *(65)* have reported an opposite effect of stimulation of presynaptic group I mGluRs in the substantia nigra pars compacta. They have found that depolarization of dopaminergic neurons induced by electrical stimulation is diminished by an agonist of group I mGluRs—(S)-3,5-dihydroxyphenylglycine (S)-3,5-DHPG)—which may suggest a decrease in glutamate release as a result of stimulation of these receptors *(65,77)*. Similar effect has been postulated for mGluR1 in the substantia nigra pars reticulata *(78)* and subthalamic nucleus *(79)*. The previously mentioned opposite effects of presynaptic receptors of group I observed in different structures may be explained by desensitization of these receptors, which results in functional switch from facilitation to inhibition of glutamate release *(80)*. In fact, such a sequence of effects has been found in cerebrocortical nerve terminals *(80)*.

5.2. Presynaptic Effects of Group II and III mGluRs

Stimulation of group II and III by their selective agonists does not induce any postsynaptic current in different brain regions *(29,61,65,70,71)*. In contrast, activation of both these groups of receptors has been reported to inhibit excitatory postsynaptic currents induced by electrical stimulation, which suggests their depressive influence on presynaptic terminals *(39,41,61,65,77,81–83)*. This suggestion has been supported by a number of studies that indicate that activation of group II and III inhibits glutamate release from presynaptic terminals *(41,84–86)*. That process seems to result from inhibition of L- and N-type voltage-dependent Ca^{2+} channels (group II mGluRs), or P/Q-type of Ca^{2+} channels (group III mGluRs) (cf. refs. *11*, *35*, and *87*). The facilitating effect of group II and III mGluRs on K^+ channels *(88–90)*, or a direct modulation of release machinery has also been postulated *(81)*. Inhibition of adenylate cyclase induced by these receptors does not seem to contribute to the previously mentioned presynaptic inhibition and neurotransmitter release *(31,41)*. In contrast, this process seems to involve Ca^{2+}-dependent calmodulin binding to C-terminal domain of mGluR7 *(91)*.

Glutamate concentration in the synaptic cleft appears to be in a milimolar range (cf. ref. *30*). This neurotransmitter binds to mGluR7 with low affinity (at almost milimolar concentrations) (cf. ref. *30*). In comparison, group II mGluRs are much more sensitive and activated by low micromolar concentrations of this amino acid (cf. ref. *30*). It has been hypothesized that because mGluR7 is present in the active zone of the presynaptic membrane, it is stimulated by glutamate released during normal physiological synaptic activity and mediates feedback inhibition. In contrast, group II mGluRs, which are localized peri- or extrasynaptically, can be activated only when the terminal is overstimulated and synaptic level of glutamate is excessively elevated *(84,85,92)*. This is also the reason why receptors of group II are particularly sensitive to glutamate whose concentration drops with an increasing distance *(30)*. Therefore, receptors belonging to group II seem to inhibit excessive glutamatergic transmission, which may lead to pathological disturbances.

5.3. Interactions Between Group I mGluRs and NMDA Receptors

Metabotropic glutamate receptors belonging to group I may also influence synaptic transmission by complex and multifarious interactions with NMDA receptors. A number of studies have shown that stimulation of both mGluR1 and mGluR5 enhances the NMDA-induced excitatory (depolarization, inward currents) responses in brain slices,

neuronal cultures or cell lines *(70,93–99)*. Several mechanisms have been postulated to be involved in this process. Group I mGluRs are localized in a proximity of NMDA receptors and may couple to these receptors via CC-Homers and postsynaptic density proteins: Shank and PSD-95 (Fig. 2) *(100)*. Moreover, because CC-Homers bind also to IP3Rs and RyRs, they may constitute a physical link between mGluRs, NMDA receptors, and intracellular Ca^{2+} stores *(100)*.

Facilitation of NMDA-induced responses by stimulation of mGluRs has also been suggested to depend on phosphorylation of protein subunits of NMDA receptor, which leads to (1) removal of Mg^{2+} block and opening of the NMDA-gated channel (cf. ref. *10*), or (2) delivery of new NMDA channels to the plasma membrane by regulated exocytosis *(66)*. NR2A and NR2B subunits of NMDA receptors may be phosphorylated by PKC, Ca^{2+}- and calmodulin-activated kinases, and tyrosine Src kinases *(99,101–104)* (Fig. 2). A role of PKC in mGluR1/5-induced activation of NMDA receptors has been postulated by some authors *(93,98,99,102–104),* but not by others *(97,105)*. Moreover, a cascade of processes relaying signals from mGluRs to NMDA receptor, which finally leads to its phosphorylation by Src-kinases, has been defined for mGluR1a in *Xenopus* oocytes, frog spinal motoneurons, or cortical neurons. This chain of reactions includes: (1) coupling to G protein, (2) activation of PLC, (3) mobilization of intracellular Ca^{2+}, (4) activation of calmodulin, (5) activation of proline-rich cell adhesion kinase 2 (Pyk2/CAKβ), (6) activation of Src kinases, and (7) phosphorylation of tyrosine residues of NR2A and NR2B subunits of NMDA receptor (Fig. 2) *(99,101,106)*. Similarly, stimulation of mGluR5 in CA3 region of the hippocampus enhances NMDA-induced current in a way dependent on both G protein and Src kinases *(95)*. Some studies, however, which also pointed to the significant role of Src kinases in potentiation of mGluR1-evoked NMDA receptor responses in CA3 region, have shown that this process is independent from G protein *(95)*. Moreover, facilitative influence of group I mGluRs on NMDA-induced responses independent of phosphoinositide hydrolysis and intracellular Ca^{2+} level has also been reported by others *(66,94)*.

Interaction between mGluRs and NMDA receptors is not limited to facilitation of responses of the latter receptors. Thus, stimulation of group I mGluRs has been reported to inhibit NMDA-induced currents in cultures of hippocampal, striatal, cortical, and cerebellar neurons *(107–109)*. This effect, which may result from internalization of NMDA receptors *(108)*, has been reported to be G protein-dependent but independent of Ca^{2+} homeostasis and PKC activation *(109)*. In addition, the NR2C subunit of the NMDA receptor may be involved in this process, at least in the cerebellum *(107)*.

NMDA receptors may also reciprocally influence group I mGluRs in a complex manner. It has been shown that lower concentrations of NMDA enhance, whereas higher ones inhibit responses of mGluRs *(110–113)*. The former phenomenon has been suggested to result from the NMDA-induced dephosphorylation of those sites of mGluR5, which are normally phosphorylated by PKC. Activation of phosphatases (phosphatase 2B or calcineurin) is involved in this process *(114)*. Because PKC-induced phosphorylation of group I mGluRs leads to their desensitization, NMDA seems to reverse that process *(114)*. On the other hand, a precise mechanism of inhibition of mGluR5 by high concentration of NMDA is not known. Phosphorylation of tyrosine residues of mGluR5 by stimulation of NMDA receptors has been reported; however, no functional significance of that process has been discovered so far *(26)*.

6. THE ROLE OF mGluRs IN BRAIN PATHOLOGY

6.1. The Role of mGluRs in Neurodegeneration

Apart from its role of a neurotransmitter, glutamate may also exert neurotoxic effects in some pathological states. When the extracellular level of this amino acid is excessively elevated as a result of an increased release or impaired reuptake, glutamatergic receptors are overactivated, which may lead to the so-called excitotoxicity and neuronal death by apoptosis and/or necrosis. Sensitivity of glutamate receptors, activity of ion channels, and intracellular mechanisms triggered by glutamate (e.g., activation of Ca^{2+}-dependent enzymatic pathways, increased generation of intracellular free radicals, and glutathione depletion) have been suggested to be involved in excitotoxic effects of glutamate. Stimulation of ionotropic glutamate receptors (NMDA, AMPA/kainate) plays a crucial role in this process (cf. ref. *115*). Several recent in vitro and in vivo studies have indicated that mGluRs may also make a substantial contribution to the glutamate-induced neurotoxicity.

MGluRs belonging to group I are the first candidate supposed to be involved in neurotoxicity since they are mainly excitatory receptors that cooperate with NMDA complex, and increase $[Ca^{2+}]_i$ level. In accordance with this view, stimulation of these receptors by a nonselective (1S,3R)-1-aminocyclopentane-1,3-dicarboxylic acid [(1S,3R)-ACPD] or selective (S)-3,5-DHPG and (R,S)-2-chloro-5-hydroxyphenylglycine [(R,S)CHPG] agonists (Table 1) have been found to produce neuronal degeneration and increase neurotoxic effect of NMDA in different in vitro and in vivo models *(116)*, (for review, *see* ref. *117*). However, a number of studies have shown an opposite, i.e., neuroprotective, effect of stimulation of group I receptors in in vitro models (hippocampal slices and neuronal culture, cerebellar granule cells, spinal motor neurons) exposed to NMDA, kainate, hypoxia, or hypoglycemia *(107,118–122)*, as well as in in vivo studies of focal cerebral ischemia *(123)*.

Several hypotheses have been presented to explain the above-mentioned discrepancies. Opposite effects of stimulation of group I mGluRs may result from: (1) different state of mGluRs activity, (2) different subunit composition of NMDA receptors present in the examined tissue, and (3) the presence or the lack of astrocytes. It has been found that first (S)-3,5-DHPG administration to cortical cultures increases NMDA-induced toxicity, whereas the second treatment affords neuroprotection. These effects parallel an enhancement and diminution of the NMDA-induced glutamate release, respectively *(118)*. Therefore, it has been hypothesized that, at least in cortical neurons, group I mGluRs switch from the state of facilitation to inhibition of both glutamate release and neurotoxicity *(118)*. On the other hand, group I mGluRs localized on other neurons, where their stimulation induces only protective effect, may be endogenously switched on attaining a "neuroprotective mode" *(118)*.

According to the second concept, the presence of the NR-2C subunit in the NMDA receptor complex may be crucial for the group I mGluR-induced inhibition of glutamate excitotoxicity in cerebellar granule cells *(107)*. When this subunit is depleted, the depressing effect of group I agonists is reversed and these compounds show a tendency to potentiate glutamate toxicity *(107)*. In some pathological conditions, for example, during experimental ischemia, the expression of NR-2C is increased in the hippocampus or cerebral cortex *(124)*. In such a situation, the neuroprotective action of group I mGluRs agonists may be of special importance.

Table 1
Selected Ligands of Metabotropic Glutamate Receptors According (If Not Stated Otherwise) to Schoepp et al. *(2)*

<table>
<tr><th colspan="2">Subtype</th><th colspan="4">AGONISTS</th><th>ALLOSTERIC ENHANCERS</th><th colspan="2">COMPETITIVE ANTAGONISTS</th><th>NON-COMPETITIVE ANTAGONISTS</th></tr>
<tr><td rowspan="2">Group I</td><td>mGluR1</td><td rowspan="8">1S,3R-ACPD</td><td rowspan="4"></td><td rowspan="2">(S)-3,5-DHPG
t-ADA</td><td></td><td>Ro 67-7476 (15)
Ro 01-6128 (15)
Ro 67-4853 (15)
Xanthene and thioxantene derivatives (227)</td><td rowspan="4">(S)-MCPG</td><td>AIDA
LY 367385</td><td>CPCCOEt
PHCCC
BAY 36-7620*
(226)
Substituted pyrroles (230)</td></tr>
<tr><td>mGluR5</td><td>CHPG</td><td></td><td></td><td>MPEP*# (132)
SIB-1757
SIB 1893*# (132)</td></tr>
<tr><td rowspan="2">Group II</td><td>mGluR2</td><td colspan="2" rowspan="2">DCG-IV[a]
L-CCG-I
2R,4R-APDC
LY 354740*
LY 389795*
LY 379268*
LY 404040* (221)</td><td>substituted sulfonamides (228,229)</td><td rowspan="2">LY 341495*</td><td rowspan="2"></td></tr>
<tr><td>mGluR3</td><td></td></tr>
<tr><td rowspan="4">Group III</td><td>mGluR4</td><td rowspan="4">L-AP4
L-SOP
(RS)-PPG
(212)</td><td colspan="2">ACPT-1 (222)</td><td>PHCCC
(17)</td><td colspan="3" rowspan="4">MSOP
DCG-IV+
(189)
MAP4</td></tr>
<tr><td>mGluR6</td><td colspan="2">L-CCG-I (189)</td><td rowspan="3"></td></tr>
<tr><td>mGluR7</td><td colspan="2"></td></tr>
<tr><td>mGluR8</td><td colspan="2">(R,S)-3,4-DCPG*[a]
(224)
(S)-3,4-DCPG (224)
L-CCG-I (189)</td></tr>
</table>

[a](R)-isomer-antagonist of AMPA receptors.
*Active in vivo after systemic administration; + at higher concentrations, an agonist of NMDA receptors.
#at concentrations higher than 20 μ*M*, an antagonist of NMDA receptors.
t-ADA, *trans*-Azetidine-2,4-dicarboxylic acid; BAY 36-7620, (3aS,6aS)-6a-naphtalen-2-ylmethyl-5-methyliden-hexahydro-cyclopenta[c]furan-1-on; MAP4, (S)-2-amino-2-methyl-4-phosphonobutanoic acid; (S)-MCPG, (S)-α-methyl-4-carboxyphenylglycine; MSOP, (RS)-α-methylserine-*O*-phosphate; PHCCC, *N*-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide; Ro 67-7476, (S)-2-(4-fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine; Ro 01-6128, diphenylacetyl-carbamic acid ethyl ester; Ro 67-4853, (9H-xanthene-9-carbonyl)-carbamic acid butyl-ester.

As mentioned earlier, astrocytes express mGluR5 *(51)*. Their role in excitotoxic effect of group I mGluRs has been supported by the finding that their supplement to cultured granule cells switches the neuroprotective effect of (S)-3,5-DHPG to exacerbation of excitotoxicity *(117)*.

In contrast to agonists, antagonists of both mGluR1 and mGluR5 exhibit uniformly neuroprotective effects in several models. Selective antagonists of mGluR1—(RS)-1-aminoindan-1,5-dicarboxylic acid (AIDA), (S)-(+)-α-amino-4-carboxy-2-methylbenzeneacetic acid (LY 367385), and 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylate ethyl ester (CPCCOEt) (Table 1)—have been found to diminish neuronal degeneration induced by NMDA, hypoxia, glucose deprivation, mechanical injury in cortical culture, or hippocampal slices *(125–128)*, and injury caused in vivo by transient global ischemia, trauma *(127–130)*, or intrastriatal NMDA application *(125,126)*. Selective antagonists of mGluR5—2-methyl-6-(phenylethynyl)pyridine (MPEP), 6-methyl-2-(phenylazo)-3-pyridinol (SIB-1757), and 2-methyl-6-(2-phenylethenyl)pyridine (SIB-1893) (Table 1)—are neuroprotective against toxicity induced by NMDA or by β-amyloid peptide in cortical cultures in vitro, and against focal cerebral ischemia or NMDA/quinolinic acid-induced injury in vivo *(117,123,125,131)*. MPEP and SIB-1893 administered systemically selectively block mGluR5 *(2)*. However, when applied in vitro at concentrations higher than 20 μ*M*, they act as NMDA receptor antagonists, which may make some contribution to their neuroprotective effects observed in the above models *(132)*. The mechanism of neuroprotection afforded by mGluR1 (but not mGluR5) antagonists has been suggested to involve also an enhancement of GABAergic transmission *(125,128)*.

Stimulation of group II and III mGluRs has been expected to be neuroprotective because these receptors reduce glutamate release and inhibit voltage-dependent Ca^{2+} channels (cf. refs. *11, 41,* and *84–87*). Moreover, mGluR3 receptors are localized on astrocytes and stimulate synthesis and release of a putative neuroprotective factor (transforming growth factor β = TGF-β) *(117,133)*. In accordance with this view, selective agonists of group II—(2R,4R)-APDC, LY 354740, (1R,4R,5S,6R)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate (LY379268) and (1R,4R,5S,6R)-2-(thia-4-aminobicyclo[3.1.0hexane-4,6-dicarboxylate (LY 389795) (Table 1)—have been evidenced to afford neuroprotection against neuronal degeneration induced by NMDA/kainic acid in vitro and in vivo *(129,134,135)*. Moreover, LY 354740 and LY 389795 administered systemically protected the brain against transient global but not focal ischemia (129,135,136). In contrast to the previously cited data, Behrens et al. *(137)* did not find any neuroprotective effect of LY 354740 against NMDA-induced toxicity or ischemia in vitro and in vivo.

Group III mGluRs agonists do not penetrate across the blood–brain barrier and therefore, the only available information about their neuroprotective effects derives from in vitro studies or in vivo experiments after intracerebral administration. These compounds—(RS)-4-phosphonophenylglycine ((R,S)-PPG), L-(+)-2-amino-4-phosphonobutyric acid (L-AP-4), and L-(+)-2-amino-4-phosphonobutyric acid (L-SOP) (Table 1)—provided protection against toxic pulse of NMDA and mechanical injury in cortical or cerebellar cultures *(138–142)*, or quinolinic acid-induced striatal lesions *(141)*. Moreover, L-AP-4 and L-SOP exhibit antiapoptotic activity against neurotoxicity induced by β-amyloid peptide *(143)*. In contrast, (R,S)-PPG administered icv was ineffective in

focal cerebral ischemia in mice and global cerebral ischemia in gerbils or rats *(144)*. The above-mentioned compounds do not differentiate subtypes of group III mGluRs. However, these compounds have been found to be ineffective in mGluR4-deficient mice, which suggests a contribution of this receptor to neuroprotection *(138)*.

6.2. The Role of mGluRs in Parkinson's Disease

6.2.1. Neuronal Mechanisms Involved in Pathophysiology of Parkinson's Disease

Parkinson's disease (PD) is a relatively common chronic neurodegenerative disease that is characterized by the following primary symptoms: akinesia (bradykinesia), muscle rigidity, and tremor. It is generally accepted that parkinsonian symptoms result from degeneration of dopaminergic neurons of the nigrostriatal pathway whose cell bodies are localized in the substantia nigra pars compacta and axon terminals in the striatum. That lesion leads to dramatic losses of dopamine in the latter structure *(145)*. Although the role of dopaminergic deficiency in PD has been known for years, neither pathological factor that induces this disease nor its appropriate therapy has been discovered so far.

Degeneration of nigrostriatal pathway results in a number of secondary functional alterations affecting interconnections of the basal ganglia. First of all, the lack of striatal dopamine leads to activation of striatal cholinergic interneurons, which is involved in the well-known disturbance in the dopaminergic–cholinergic equilibrium *(146)*. Furthermore, an imbalance between the two main GABAergic striatal efferents—the striopallidal ("indirect"—leading to the lateral part of the globus pallidus) and strionigral ("direct"—leading to the substantia nigra pars reticulata) pathways—has been suggested to occur in PD *(147)*. These pathways exert an opposite influence on the GABAergic neurons of the substantia nigra pars reticulata, which project to the thalamus. The strionigral pathway "directly" inhibits nigrothalamic neurons, whereas the striopallidal one activates them "indirectly" via a sequence of pallido-subthalamo-nigral projections. It has been hypothetized that in the course of PD the balance is shifted toward activation of the striopallidal pathway. In normal individuals, this pathway is inhibited by dopamine via D2 receptors, and stimulated, via NMDA and AMPA receptors, by glutamic acid released from the cortico-thalamo-striatal terminals *(147,148)*. Therefore, the lack of striatal dopamine in PD results in activation of this pathway and a release of GABA in the lateral globus pallidus, which inhibits the next link—the GABAergic pallidosubthalamic pathway. This effect leads, in turn, to disinhibition of glutamatergic subthalamonigral neurons and to an increase in glutamatergic input, via NMDA and AMPA receptors, to nigral efferent neurons *(149)*. Because in PD the "direct" strionigral GABAergic pathway (normally activated by dopamine via D1 receptors) is inhibited, the excitatory influence predominates in the substantia nigra pars reticulata, which results in overactivation of the GABAergic nigrothalamic output pathway. GABA released from nigrothalamic terminals inhibits, in turn, glutamatergic thalamocortical neurons, which indirectly leads to activation of the glutamatergic corticostriatal pathway closing the previously mentioned neuronal circuit *(147)* (Fig. 3).

Several lines of evidence support the view that glutamate-induced excitation of neurons in the striatum, subthalamic nucleus, and substantia nigra pars reticulata plays a significant role in development of parkinsonian symptoms (cf. ref. *150*). First of all, the blockade of NMDA receptors by antagonists and the inhibition of subthalamic neurons by high-frequency stimulation have been found to exert therapeutic effects in parkinsonian patients and in animal models of PD (cf. refs. *150* and *151*). Recent studies have

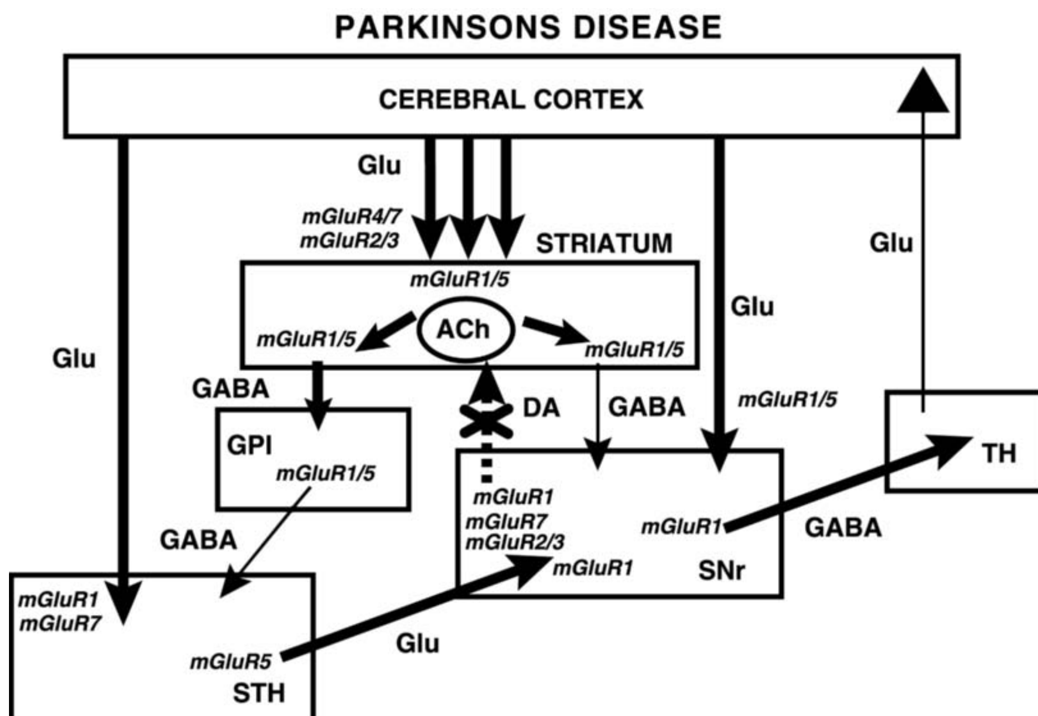


Fig. 3. Neuronal pathways engaged in development of Parkinson's disease symptoms. The activated pathways are drawn as thick arrows, whereas the inhibited ones are marked by thin arrows. Lesioned dopaminergic pathway is marked by broken line. ACh, cholinergic interneuron, GABA, (γ-amino-butyric acid)-ergic pathway; Glu, glutamatergic pathway, GPl, globus pallidus, lateral part, mGluR1,2,3,4,5 and 7, subtypes of metabotropic glutamate receptors localized either postsynaptically (bigger letters) or presynaptically (smaller letters); SNr, substantia nigra pars reticulata; STH, subthalamic nucleus; TH, thalamus.

indicated that mGluRs seem to be also involved in generation of parkinsonian symptoms and may constitute a target for potential antiparkinsonian therapy.

MGluRs belonging to group I (mGluR1 and mGluR5) contribute to stimulation of neuronal pathways involved in expression of parkinsonian symptoms: the striopallidal, subthalamonigral, and nigrothalamic ones. Stimulation of mGluR5 potentiates the NMDA-induced membrane depolarization and inward current in striatal efferent neurons *(70)*, and increases striatal proenkephalin mRNA level *(152)*. Because expression of enkephalin, which selectively colocalizes with GABA in striopallidal neurons, parallels their activity, it seems that mGluR5 may actually stimulate the striopallidal pathway. Furthermore, this pathway is also activated by striatal cholinergic interneurons *(146)* (Fig. 3). Although expression of mGluR1 and mGluR5 on these neurons is low, they are activated by both these receptors (Fig. 3), which leads to acetylcholine release *(61,67,153)*. In this way, mGluR1 and mGluR5 may indirectly activate the striopallidal pathway via their influence on cholinergic interneurons.

Electrophysiological studies have indicated that subthalamonigral and nigro-thalamic neurons are also activated by mGluR5 and mGluR1, respectively *(69,154)*. Moreover, presynaptic receptors, mGluR1 and mGluR5, localized on GABAergic terminals in the

substantia nigra pars reticulata (Fig. 3) may decrease GABA release and in this way cooperate with postsynaptic receptors in activation of the nigrothalamic pathway *(154)*. However, stimulation of some mGluR1 receptors may also induce an opposite effect; i.e., they may counteract the glutamate-induced stimulation of the above-mentioned subthalamonigral and nigro-thalamic pathways. Such an effect has been described for presynaptic mGluR1 localized on glutamatergic terminals in both the substantia nigra pars reticulata and subthalamic nucleus *(78,79)* (Fig. 3). Moreover, mGluR1 localized postsynaptically in the globus pallidus (Fig. 3) activates neurons of this structure *(29)*. Because at least some of them are GABAergic neurons projecting to the subthalamic nucleus, their stimulation by glutamate may indirectly inhibit a subsequent glutamatergic subthalamonigral pathway.

As mentioned above, group II and III mGluRs of the basal ganglia act predominantly as presynaptic receptors (Fig. 3), which inhibit glutamate-induced neuronal excitation. They have been found to inhibit glutamate release in the striatum *(84–86)* and diminish excitatory postsynaptic currents/potentials induced by stimulation of afferents in this structure *(82,83)*, as well as in the subthalamic nucleus (only group III mGluRs) *(79)* and substantia nigra pars reticulata *(155,156)*. Presynaptic group III mGluRs diminish additionally inhibitory GABAergic transmission in the lateral globus pallidus and substantia nigra pars reticulata *(156,157)*. The role of individual receptor subtypes in all the above-mentioned structures is difficult to establish, because of a poor selectivity of agonists of group II [L-(+)-2-amino-4-phosphonobutyric acid (DCG-IV), 2R,4R-APDC, LY 354740] or III (L-AP-4 (Table 1) used in these studies. However, the level of effective concentration of L-AP-4 seems to suggest that presynaptic effect of this compound in the subthalamic nucleus or substantia nigra pars reticulata results from stimulation of mGluR7 *(156,157)* (Fig. 3).

6.2.2. Symptomatological Effects of mGluRs Ligands

The previously described effects of mGluRs in the basal ganglia have advanced the conclusion that antagonists of group I, or agonists of group II or III, which predominantly inhibit glutamate-induced excitation of striatal, subthalamic, or nigral neurons, may alleviate parkinsonian symptoms. Unfortunately, only a few selective compounds that penetrate well through the blood–brain barrier are available so far (Table 1).

It has been found that systemic (LY 354740) or intraventricular (DCG-IV) administration of selective group II agonists inhibits parkinsonian-like muscle rigidity and catalepsy induced by haloperidol *(155,158,159)* or akinesia induced by reserpine in rats *(160)*. These effects seem to be owing to stimulation of nigral but not striatal receptors since DCG-IV administered directly into the substantia nigra produces similar effects *(160)*, whereas intrastriatal injections of other group II agonists [2R,4R-APDC or (2S,1′S,2′S)-2-(carboxycyclopropyl)glycine = L-CCG-I] (Table 1) do not reverse the haloperidol-induced deficits *(161–163)*.

Several studies have also supported the role of group I mGluR blockade in antiparkinsonian effects. Systemic treatment of rats with a single dose of MPEP, a noncompetitive antagonist of mGluR5, has been reported to reduce the haloperidol-induced catalepsy, hypolocomotion, and muscle rigidity *(163,164)*. Moreover, Breysse and coworkers *(165)* have reported that akinesia induced by a lesion of dopaminergic neurons is reversed by chronic but not acute treatment with this compound. However, according to the latter authors MPEP does not inhibit the haloperidol-induced catalepsy *(165)*.

Selective antagonists of mGluR1 available so far cross the blood–brain barrier poorly. However, a representative of these compounds, AIDA, administered directly into the striatum has been shown to inhibit parkinsonian-like muscle rigidity *(162,163)* and catalepsy induced by haloperidol *(166)*. Antiparkinsonian-like effects of both AIDA and MPEP may be attributed, at least partly, to inhibition of the striopallidal pathway since these compounds reverse the haloperidol-induced increase in striatal proenkephalin mRNA expression *(166,167)*. AIDA is a low-potency antagonist of mGluR1 whose selectivity is limited *(2)*. However, other more potent and selective antagonists of this receptor—LY 367385 and CPCCOEt *(2)* (Table 1)—administered intrastriatally induce even stronger inhibitory effect on the haloperidol-increased proenkephalin expression *(167)*.

The scarcest information is available on the potential role of agonists of group III mGluRs. None of these compounds crosses the blood–brain barrier; however, the most recent study of Marino and coworkers *(157)* has shown that L-AP4 administered intraventricularly decreases both the reserpine-induced akinesia and haloperidol-induced catalepsy.

6.2.3. Neuroprotective Effects of mGluRs Ligands

MGluRs may also be involved in producing lesions of dopaminergic nigrostriatal neurons in PD (*see also* Chapters 19, 21, and 22). Although a pathogenic factor that triggers this degeneration has not been discovered yet, experimental studies with the use of dopaminergic toxins—1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and methamphetamine—suggest that excitotoxic effect of glutamate may contribute to this process (cf. ref. *150*). Dopaminergic nigrostriatal neurons are activated via NMDA and AMPA receptors by glutamatergic projections originating from the subthalamic nucleus and cerebral cortex *(65,77)*. In addition, dopaminergic neurons express considerable numbers of mGluR1 and low amounts of mGluR5 *(62)*. The mGluR1 has been found to contribute to activation of these neurons *(65,168)*, inducing their hyperpolarization, which is rapidly desensitized and followed by depolarization *(65)*. Potential role of mGluR1 in degeneration of these neurons has been proven by a protective action of AIDA administered intraventicularly against MPTP-induced toxicity *(169)*. MGluR5 seems also be involved in this process since its selective blockade by MPEP or SIB 1893 administered systemically reduces toxic effect of methamphetamine (170–172). Moreover, a reduction of excitatory, glutamatergic input to the striatum by stimulation of group II mGluRs by DCG-IV *(82)* has also been found to protect striatal dopaminergic terminals against 1-methyl-4-phenyl-pyridinium (MPP^+)-induced neurotoxicity *(173)*.

6.3. The Role of mGluRs in Antidepressant Action

Neuronal mechanisms underlying depressive symptoms, as well as those responsible for antidepressant drug action, are largely unknown. They seem to involve alterations in noradrenergic, serotonergic, and dopaminergic neurotransmission. Recently some role of reduced tone of glutamatergic transmission in antidepressant action has been postulated (*see also* Chapter 10). First of all, chronic treatment with clinically effective antidepressants induces an adaptive subsensitivity of NMDA receptor complex. Moreover, antagonists which bind to recognition, phencyclidine, and allosteric glycine sites of this receptor are effective in animal screening tests for antidepressant activity (for review, *see* ref. *174*).

Animal studies seem to indicate that antidepressant therapy may also produce adaptive changes in group I mGluRs, and that these receptors may constitute a target for new potential antidepressant drugs. Chronic treatment of rats with a classic antidepressant, imipramine, or electroconvulsive shocks reduces excitatory influence of group I mGluRs (increase in population spike amplitude, depolarization, inhibition of after-hypolarization) on hippocampal neurons of CA1 region *(175–177)*, which may suggest functional subsensitivity of these receptors. Several reports have been published that corroborated the contribution of the previously mentioned effect to antidepressant action. It has been found that the blockade of mGluR5 by an acute or chronic (14 d) treatment with their noncompetitive antagonist, MPEP (Table 1), induces antidepressant-like effects in tail-suspension test in mice *(178)*, or in bulbectomized rats *(179)*. On the other hand, chronic administration of imipramine or electroconvulsive shocks increases expression of mGluR1 and mGluR5 in CA1 and CA3 regions of the hippocampus *(180–182)*. Such elevated synthesis of both these receptors may be a compensatory response to their functional inhibition induced by antidepressant treatment.

In contrast to the above-mentioned antagonist of mGluR5, which inhibits glutamatergic transmission at the level of postsynaptic mGluRs, stimulation of group II mGluRs by their selective agonist, LY 354740, has not been found to produce any antidepressant-like effect in tail-suspension test or behavioral despair test *(183)*. However, the latter observation does not conclusively exclude the role of this group of mGluRs in antidepressant drug action since chronic imipramine treatment has been found to upregulate mGluR2/3 expression and their signal transduction in rats *(181)*.

6.4. The Role of mGluRs in Anxiety

Stimulation of GABAergic transmission via benzodiazepine receptors is the main mechanism responsible for therapeutic effects of anxiolytic drugs. However, other neurotransmitter systems (e.g., serotonergic or noradrenergic) are also involved in this process. A number of experimental studies show that anxiolytic-like effect in animal models of anxiety may be achieved by a decrease in glutamatergic transmission induced by the blockade of NMDA receptors (for review, *see* refs. *174* and *184* and Chapter 12). Moreover, the most recent studies indicate that ligands of mGluRs, which inhibit glutamate-induced neuronal excitation at the level of pre- (group II and III) or postsynaptic (group I) receptors, may also be useful for anxiolytic therapy.

The first study that reported anxiolytic action of mGluRs ligands was published in 1997 *(185)*. This study has shown that (S)-4-carboxy-3-hydroxyphenyl-glycine (S-4-C3HPG)—which is an antagonist of group I and agonist of group II mGluRs—administered into CA1 region of the hippocampus exhibits anxiolytic-like effects in the Vogel conflict test in rats *(185)*. Shortly afterward, it appeared that both these mechanisms, that is, the blockade of group I and stimulation of group II mGluRs, may be involved in that effect. This conclusion has been supported by the fact that LY 354740, an agonist of group II, administered systemically or intrahippocampally induced anxiolytic-like effects in a number of the so-called conditioned (fear-potentiated startle response, Vogel conflict test, four-plate test) and unconditioned (elevated plus maze) tests *(183,186–188)*. A similar, but approx 100 times stronger effect in the fear-potentiated startle assay has also been reported after a systemic administration of a newly synthetized agonist of these receptors—a rigid version of LY 354740—(2S,1′S,2′S,3′R)-2-(2′-carboxy-3′-methyl-cyclopropyl)glycine *(189)*. Moreover, a blockade of mGluR5 by an acute, or chronic

systemic administration of a noncompetitive antagonist of these receptors, MPEP was effective in conditioned responses (Vogel test, four-plate paradigm, Geller–Seifter test) and unconditioned tests (elevated plus maze task, social exploration, stress-induced hyperthermia, marble burying) in rats and mice *(178,179,190)*. The blockade of mGluR1 by a selective noncompetitive antagonist, CPCCOEt, administered directly into CA1 region of the hippocampus has also induced anticonflict effect in the Vogel test *(188)*.

Only a few data are available on the contribution of group III mGluRs to anxiety and anxiolytic effects. L-SOP, an agonist of these receptors, administered into the hippocampus induced anticonflict effect in rats *(188)*. Although L-SOP is not selective for specific subtype of receptors belonging to group III, its anxiolytic effect may involve at least mGluR8. This suggestion is based on the fact that mGluR8-deficient mice exhibit higher anxiety level than wildtype mice in the elevated plus maze test *(191)*.

6.5. The Role of mGluRs in Antipsychotic Action

It is generally supposed that overactivity of subcortical dopaminergic and cortical serotonergic transmissions is involved in psychotic symptoms but some contribution of glutamatergic system dysfunction to these symptoms has also been suggested *(192)*. The latter view is based mainly on the finding that phencyclidine (PCP), which is an uncompetitive NMDA receptor antagonist, induces both positive and negative psychotic symptoms in humans *(193)*. On the other hand, PCP and ketamine induce an increase in glutamate release in the prefrontal cortex, as a compensatory effect to the blockade of NMDA receptors *(194)*. PCP is suggested to be the best model compound to study neuronal mechanisms underlying psychotic symptoms and to screen putative antipsychotic compounds in animals.

Data regarding the role of mGluRs in schizophrenia and in antipsychotic drug action are rather scarce and inconclusive. This may be because of a complexity of psychotic symptoms and a lack of their appropriate animal equivalents, which may be a reason for diverse effects of mGluR ligands in different models. Stimulation of group II mGluRs has been postulated to exert antipsychotic effects by a reversal of glutamate release induced by stimulation of 5-HT2A receptors, or by a blockade of NMDA receptors. In accordance with this view, LY 354740 and LY 379268 inhibit excitatory postsynaptic currents (EPSCs) induced by stimulation of 5-HT2A receptors in slices of medial prefrontal cortex *(195,196)*, as well as glutamate release induced by PCP or ketamine in this structure in vivo *(194,197)*.

Some studies seem to support the aforementioned view. First, an atypical neuroleptic, clozapine, also inhibits glutamate release in the frontal cortex in vivo *(198)*. Moreover, chronic treatment with clozapine or another atypical neuroleptic, olanzapine, increases the expression of mGluR2 and mGluR3 mRNA in this structure *(199)*. Furthermore, according to some studies, LY 354740, LY 379268, and L-CCG-I decrease the PCP- or (5S,10R)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyprohepten-5,10-imine maleate (MK-801)-induced locomotion and stereotypy *(194,200–203)*, as well as working memory deficits (estimated in delayed alternation task) *(194)*, in a manner dependent on the presence of mGluR2 *(202)* and similar to clozapine *(203)*. However, other authors did not find any influence of LY 354740 or its racemic form, LY 314582, on (1) the PCP-induced deficit in sensorimotor gating *(204,205)*, (2) the PCP-increased locomotor activity *(206)*, (3) an impairment of working memory induced by MK-801, a selective antagonist of NMDA receptors *(204)*, or (4) discriminating effects of PCP *(205)*. Moreover, no

association has been found between schizophrenia and mGluR2 *(207)* or mGluR3 gene polymorphisms *(208)*.

MGluR5 receptors have also been suggested to play a role in schizophrenia. In contrast to mGluR2/3, however, an association of allele frequency of gene coding for mGluR5 with this disease has been found *(209)*. Moreover, mGluR5-deficient mice exhibit sensorimotor gating deficit *(210)*, and MPEP administered in rats enhances the deficit induced by PCP, as well as PCP-increased locomotor activity *(206)*. The above results seem to suggest that agonists of mGluR5, rather than antagonists, may be therapeutic in psychoses. Unfortunately no such compounds that cross the blood–brain barrier have been discovered yet.

6.6. The Role of mGluRs in Drug Addiction

Ligands of mGluRs have also been reported to have a beneficial impact in the treatment of drug addiction (*see also* Part VIII). Agonists of group II mGluRs, DCG-IV, injected icv, or LY 354740 administered systemically, inhibit nicotine- or morphine-withdrawal symptoms in rats *(183,211–214)*. Similarly, a knockout of mGluR5 receptors in mice and their blockade by MPEP in rats inhibit acquisition and expression of addiction, measured by inhibition of the morphine-induced conditioned place preference or cocaine self-administration *(215,216)*. Moreover, chronic administration of cocaine has been found to induce subsensitivity of group II and III mGluRs in nucleus accumbens and amygdala *(217,218)*.

6.7. Antiepileptic Effects of mGluRs Ligands

Antiepileptic drugs may be searched for among ligands of all groups of mGluRs. In general, agonists of group II and III, or antagonists of group I may be therapeutic. Systemically active agonists of group II (LY 354740, LY 379268, LY 389795) have been shown to be anticonvulsive when administered alone, or to increase anticonvulsant activity of conventional antiepileptic drugs in different models *(219,220)*, (for review, *see* ref. *221*). Similar effects have been reported for agonists of mGluR4 [(1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid = ACPT-1] *(222)* (Table 1) and mGluR8 [PPG, (RS)-3,4-dicarboxyphenylglycine = (R,S)-3,4-DCPG] *(223,224)* (Table 1) or antagonists of both mGluR5 (for review, *see* ref. *44*) and mGluR1 *(225,226)*.

7. CONCLUSIONS

The review of a current knowledge about the role of mGluRs in brain functions indicates that these receptors are involved in various physiological and pathological processes. Ligands of these receptors may be useful as neuroprotective agents in Parkinson's disease, Alzheimer's disease, ischemia, hypoxia, or hypoglycemia. Moreover, they may possess anxiolytic, antidepressive, antipsychotic, antiepileptic, antiparkinsonian, and other therapeutic properties. Unfortunately only a few such compounds that cross the blood–brain barrier are available so far. They are agonists of group II (LY354740; LY389795; LY379268; (+)-4-amino-2-thiabicyclo[3,1,0]hexane-4,6-dicarboxylic acid 2-oxide = LY 404040), and III [(R,S)-3,4-DCPG, an agonist of mGluR8, whose R isomer is an antagonist of AMPA receptors], and antagonists of mGluR5 (SIB-1893, MPEP). Animal studies seem to indicate that these compounds, administered in therapeutic doses, may be devoid of serious side effects such as ataxia or memory dysfunctions

(179,186). At present one of them, namely LY 354740, is in phase II clinical trials for the treatment of panic disorder and/or anxiety *(221)*.

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