Amino Acids (2002) 23: 199–205
DOI 10.1007/s00726-001-0129-z

Amino
Acids
Printed in Austria

The role of striatal metabotropic glutamate receptors in degeneration of dopamine neurons: Review article

K. Gołembiowska, J. Konieczny, K. Ossowska, and **S. Wolfarth**

Department of Pharmacology and Department of Neuro-Psychopharmacology, Institute of Pharmacology, Polish Academy of Sciences, Kraków, Poland

Received July 7, 2001
Accepted August 6, 2001
Published online September 10, 2002;

Summary. Degeneration of dopaminergic nigrostriatal neurons is a primary cause of Parkinson's disease. Oxidative stress, excitotoxicity and mitochondrial failure are thought to be key mechanisms resposible for degeneration of dopaminergic cells. We found that the selective antagonist of the mGluR5 subtype MPEP in a dose of 5 mg/kg diminshed basal and veratridine (100 μM)-stimulated dopamine release in rat striatum in an *in vivo* model of microdialysis. In contrast, MPEP given intrastriatally in a high concentration (500 μM) enhanced the striatal extracellular concentration of dopamine. DCG-IV (100 μM), a non-selective agonist of group II mGluRs, inhibited the veratridine-stimulated striatal dopamine release. In an animal model of neuroxicity *in vivo*, methamphetamine (5×10 mg/kg, injected at 2 h intervals) produced deficits in the striatal content of dopamine and its metabolites DOPAC and HVA 72 h after the treatment. MPEP (5×5 mg/kg) given before each methamphetamine injection reversed the decrease in the striatal content of dopamine and diminished the methamphetamine-induced dopamine outflow from nigrostriatal terminals. It is concluded that the MPEP-produced blockade of mGluR5 situated on dopaminergic cells, or the suppression of glutamate release in the subthalamic nucleus or substantia nigra pars reticulata may directly and indirectly cause a decrease in striatal dopamine release. However, inhibitory effect of DCG-IV on dopamine release can be induced by attenuation of excitatory input from corticostriatal terminals by activation of mGluR2/3. Regulation of dopamine carriers by MPEP, an antagonist of group I mGluRs may be responsible for the reversal of toxicity induced by methamphetamine.

Keywords: Metabotropic glutamate receptors – Dopamine release – Neurotoxicity – Striatum

Introduction

Glutamate is a primary neurotransmitter in excitatory synaptic pathways of the central nervous system. Glutamate-mediated neurotransmission takes part in numerous neuronal functions, and an excess of glutamatergic stimulation may be involved in the etiology of stroke, epilepsy, and neurodegenerative disorders. On the basis of their signal transduction pathways, glutamate receptors can be assigned to two distinct groups: ionotropic glutamate receptors, which are directly coupled to cationic channels, and metabotropic glutamate receptors (mGluRs), which are G-protein-coupled receptors. On the grounds of amino acid sequences, the coupling to second-messenger systems and agonist selectivity, the subtypes of mGluRs can be dividied into three groups, yet the diversity of the mGluR family is further increased by the existence of variants with regard to the C-terminal amino acid sequence. Group I comprises mGluR1 and mGlu5 receptors which activate phospholipase C; group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7 and mGluR8) receptors can inhibit the activity of adenylyl cyclase (Conn and Pin, 1997). All these receptors are localized either pre- or postsynaptically at the majority of glutamatergic synapses, and at some GABAergic synapses (Hanson and Smith, 1999; Neki et al., 1996; Petralia et al., 1996).

Recent studies using *in situ* hybridization indicate regional heterogeneity in the distribution of mGluR subtypes. All the mGluRs are expressed in the striatum (Testa et al., 1994). MGluR1 is abundantly co-expressed with the mGluR5 subtype on striatal cholinergic and GABAergic interneurons (Pisani et al., 2001; Tallaksen-Greene et al., 1998); mGluR1, mGluR5 and mGluR4 have been found in GABAergic striatopallidal and striatonigral neurons (Bradley et al., 1999; Hanson and Smith, 1999; Testa

et al., 1995, 1998), whereas mGluR2/3 are present on corticostriatal glutamatergic terminals (Testa et al., 1998). Outside the striatum, mGluR1, mGluR5 and mGluR3 are expressed in the substantia nigra pars reticulata, whereas dopaminergic cells in the substantia nigra pars compacta contain mGluR1 and sparse mGluR5 isoforms (Testa et al., 1994, 1998; Kosinski et al., 1998; Hubert et al., 2001). Considerable amounts of mGluR4 and mGluR7 mRNA were found in thalamic nuclei (Bradley et al., 1999; Neto et al., 2000). The subthalamic nucleus, whose activity is altered in Parkinson's disease exhibited mGluR2 located presynaptically and postsynaptic mGluR5 (Testa et al., 1994; Awad et al., 2000; Bradley et al., 2000). Evidence of the presence of group II and III mGluRs on descending glutamatergic inputs to midbrain dopamine neurons has also been presented (Wigmore and Lacey, 1998). Hence the location of mGluRs subtypes on dopaminergic, glutamatergic and GABAergic neurons may play a regulatory role in the complex function of the basal ganglia.

Modulation of dopamine release by agonists and antagonists of mGluRs

A number of data show that the brain dopamine system is under regulatory glutamatergic influence. By activation of ionotropic receptors, glutamate exerts excitatory or inhibitory actions on DA release (Keefe et al., 1992; Westerink et al., 1992; Wu et al., 2000). The abundance of mGluRs in the basal ganglia sugggests that they may play a role in the modulation of dopamine function in the brain. It was found that local application of the group I and II mGluR agonist 1S,3R-1-aminocyclopentane-trans-1,3-dicarboxylic acid ((*1S*,*3R*)-ACPD) to dopamine terminals in the striatum increased dose-dependently dopamine release (Verma and Moghaddam, 1998). That increase was in part TTX-insensitive, which indicates a direct presynaptic mechanism of the later effect. On the other hand, (*1S*,*3R*)-ACPD attenuated the depolarization-induced stimulated striatal dopamine release (Verma and Moghaddam, 1998), suggesting that under activation conditions mGluRs reduce excessive dopamine release. The group I mGluR agonist DHPG (3,5-dihydroxyphenylglycine) also enhanced dopamine release, which was then antagonized by the non-selective mGluRs antagonist alpha-methyl-4-carboxyphenylglycine ((+)-MCPG) (Bruton et al., 1999). Distinct subtypes of mGluRs with diverse cellular localization may be involved in the modulation of dopamine release. Indeed, evidence is available that the mGluR5 subtype may be located on striatal dopamine terminals (Yu et al., 2001), and that its direct activation with DHPG induces dopamine release. On the other hand, expression of mGluR1 and mGluR5 subtypes on striatal cholinergic interneurons has been documented (Pisani et al., 2001). It was shown that activation of those receptors with DHPG or the selective mGluR5 agonist 2-chloro-5-hydroxyphenylglycine (CHPG) resulted in excitation of cholinergic interneurons and, – as an intermediate response –, in activation of dopaminergic terminals (Pisani et al., 2001).

The aim of our study was to further characterize the role of mGluR subtypes in the modulation of dopamine release. Systemic administration of the selective, non-competitive mGluR5 antagonist MPEP in a dose of 5 mg/kg resulted in a decrease in basal and veratridine (100 μM)-stimulated dopamine release in rat striatum. Intrastriatal perfusion of MPEP (100 μM) did not affect the veratridine-stimulated dopamine release, but its high concentration (500 μM) increased basal dopamine levels. Intrastriatal perfusion with a low concentration of the less specific group II mGluR agonist 2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV, 100 μM) inhibited the veratridine-stimulated dopamine release in rat striatum. It is likely that the MPEP-induced alteration of the activity of dopamine neurons depends on the route of administration of the mGluR5 antagonist. Attenuation of basal or stimulated dopamine release may be an indirect effect due to the blockade of excitatory transmission in the substantia nigra pars reticulata, or in the subthalamic nucleus mediated by the mGluR5 subtype. Instead, the blockade of mGluR5 on striatal GABAergic interneurons by freeing striatal neuronal terminals from the inhibitory GABAergic tone may be responsible for the enhancement of extracellular dopamine levels after local administration of a higher concentration of MPEP. Our preliminary experiments with the non-selective mGluR2/3 agonist DCG-IV indicate that the supression of cortical glutamatergic input to the striatum by DCG-IV (Wigmore and Lacey, 1998) may presynaptically regulate dopamine release. The effect of group II mGluR agonists on the stimulation-induced increases in DA release precludes a tonic role of glutamate in maintaining basal dopamine release. The reduction in extracellular dopamine, elicited only by a low concentration of DCG-IV, may be

due to the fact that DCG-IV has low selectivity as an agonist of group II mGluR (Ishida et al., 1993). Thus stimulation of NMDA receptors by higher concentrations of DCG-IV possibly masks the reduction of extracellular dopamine, produced by selective stimulation of group II mGluRs.

The role of mGluRs in the neurotoxicity of dopaminergic neurons

Three main mechanisms of neuronal cell death: a metabolic compromise, excitotoxicity and oxidative stress, which work separately or jointly, cause neurodegeneration that occuring in acute or chronic disorders in the central nervous system, such as stroke, hypoglycemia, epilepsy, Parkinson's disease, Alzheimer's and Huntington's diseases (for review see: Alexi et al., 2000). An overactivation of the excitatory synaptic neurotransmission mediated by amino acids, and an excessive activation of ionotropic glutamate receptors resulting in large increases in the concentration of neuronal cytosolic Ca^{2+} produce neuronal death during a pathological process defined as excitotoxicity (Olney, 1971).

Glutamate plays an integrative role in the functioning of the basal ganglia, yet the balance between glutamate and dopamine is disturbed when dopaminergic nigrostriatal neurons degenerate in the course of Parkinson's disease (Starr, 1995). Nigral dopaminergic neurons possess glutamate receptors (Chatha et al., 2000; Testa et al., 1994) and they degenerate when are exposed to an excitiotoxic impact of glutamate (Alexi et al., 2000; Tapia et al., 1999). The antagonizing of excitotoxicity has been regarded as a potential therapy in Parkinson's disease. Antagonists of ionotropic glutamate receptors, especially antagonists of the NMDA receptor and its modulatory glycine site, improve parkinsonian symptoms (for review see Ossowska, 1994), but severe side-effects associated with their use during chronic therapy limit their efficacy as potential drugs. Recent evidence has shown that mGluRs may play an important role in excitotoxicity. Some members of group II and III mGluRs are likely to function as autoreceptors and may inhibit glutamate release, whereas activation of group I mGluRs increases the excitability and release of glutamate (Glaum and Miller, 1994). Activation of group II and III mGluRs is generally thought to protect cells against glutamate toxicity. Although antagonists of group I mGluRs are neuroprotective, agonists of these receptors have been found to be either neuroprotective or neurotoxic.

Several studies showed that the selective agonists of group II mGluRs, (+)-2-aminobicyclo[3.1.0] hexane-2,6-dicarboxylate (LY354740), LY379268 and the less selective DCG-IV, slowed down death in some models of glutamate toxicity in cortical cells in vitro, or attenuated cerebral ischemia in rat hippocampus in vivo (Allen et al., 1999; Bond et al., 1999, 2000; Kingston et al., 1999). Similarly, activation of group III mGluRs with (R,S)-4-phosphonophenylglycine ((R,S)-PPG) or L-2-amino-4-phosphonobutyrate (L-AP4) was protective against hypoxic/hypoglycemic injury in rat hippocampus or against the NMDA-mediated excitotoxicity in cultured mouse cerebellar granule neurons (Sabelhaus et al., 2000; Lafon-Cazal et al., 1999). The slowed down neuronal cell death, induced by glutamate and quinolic acid, as well as the oxygen-glucose deprivation in cerebellar neurons and hippocampal slices or rat striatum, were observed upon administration of the non-selective mGluRs agonist (1*S*,3*R*)-ACPD (Kalda et al., 2000; Montoliu et al., 1997; Adamchik and Baskys, 2000; Colwell et al., 1996). On the other hand, the (1*S*,3*R*)-ACPD – enhanced hippocampal damage was observed in the model of global ischemia in gerbils (Henrich-Noack and Reyman, 1999). These contradictory results can be explained by activation of group II or III mGluRs by (1*S*,3*R*)-ACPD, which leads to neuroprotection, whereas enhancement of the neurotoxicity is likely to be mediated by activation of group I mGluRs. Interstingly, some data showed a neuroprotective effect of the selective agonist of group I mGluR DHPG against hypoxic/hypoglycemic injury in rat hippocampus, and against glutamate toxicity or oxygen-glucose deprivation toxicity in cultures of cerebellar neurons (Schroder et al., 1999; Montoliu et al., 1997; Kalda et al., 2000). It is thus speculated that the neuroprotection achieved using the selective group I mGluR agonist is caused by its antiapoptotic action which – in turn – is mediated by protein kinase C activation (Kalda et al., 2000). The results obtained with mGluR antagonists are more consistent. Thus, the group I mGluR antagonists 1-aminoindan-1,5-dicarboxylic acid (AIDA) and (S)-(+)-2-(3′-carboxybicyclo[1.1.1]pentyl)-glycine (CBPG), with a preferential activity towards the mGluR1 subtype, showed neuroprotection in an oxygen-glucose deprivation rat model and in a model of global ischemia in gerbil hippocampus (Pellegrini-Giampietro et al., 1999). The blockade of mGluR1 with (+)-2-methyl-

4carboxyphenylglycine (LY367385) was sufficent to achieve neuroprotection against global ischemia in gerbils, or against the NMDA-induced toxicity in rat hippocampus and striatum, respectively (Bruno et al., 1999). In turn, the selective mGluR5 antagonist MPEP was effective in protecting cortical cells against NMDA toxicity and mechanical injury *in vitro* (Bruno et al., 2000; O'Leary et al., 2000; Movsesyan et al., 2001), against ischemia in gerbil hippocampus *in vivo* (Rao et al., 2000) or the neuronal damage induced by NMDA and quinolic acid in rat striatum (Bruno et al., 2000).

In order to carry on with our studies into the role of mGluR antagonists in the neuroprotection of dopamine neurons, we performed experiments with the selective antagonist of mGluR5 MPEP in the rat neurotoxicity model using methamphetamine. Methamphetamine acts as a potent dopamine neurotoxin in rodents, non-human primates and humans. Multiple administration of methamphetamine causes a rapid, partially reversible decrease in dopamine transporter activity in rat striatum (Sandoval et al., 2000). Dopamine, which is released in large quantities by methamphetamine, is the source of reactive oxygen species (ROS) (Giovanni et al., 1995; Hirata et al., 1996). In a cascade of neurodegenerative events, the increased concentration of ROS and dopamine-derived quinones (Cadet and Brannock, 1998) causes a disruption of mitochondrial functions (Burrows et al., 2000), depletion of the antioxidant glutathione (Moszczynska et al., 1998; Harold et al., 2000), induction of microglisis (Escubedo et al., 1998) and lipid peroxidation (Acikgoz et al., 1998). Exposure to high doses of methamphetamine eventually results in depletion of striatal dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), as well as in a decrease in the activity of tyrosine hydroxylase, dopamine transporter (DAT) and vesicular monoamine transporter (Fleckenstein et al., 2000; Ricaurte et al., 1982). Glutamatergic excitotoxicity has also been implicated in diverse mechanisms of methamphetamine toxicity (Sonsalla et al., 1989, 1991). In our study, methamphetamine (5×10 mg/kg sc in 2 h intervals) induced significant hyperthermia and depletion of dopamine, DOPAC and HVA in the striatum 72 h after the treatment. MPEP in a dose of 5 mg/kg, which was effective in reversing the haloperidol-induced rigidity in rats (Ossowska et al., in press), given before every methamphetamine injection, attenuated dopamine deficit in rat striatum. In our additional experiments, MPEP (5 mg/kg) was able to diminish the methamphetamine (10 mg/kg)-induced dopamine outflow in rat striatum in a microdialysis *in vivo* model. Thus the data discussed above, together with our findings revealing an inhibitory effect of MPEP on basal dopamine release after peripheral administration, as well as anatomical data showing brain distribution of mGluRs incline us to link the effect of an mGluR5 antagonist with attenuation of the excitatory input to dopaminergic cells through mGluR5 blockade in the subthalamic nucleus and/or substantia nigra. Methamphetamine produces an increase in extracellular dopamine and glutamate, hence both these neurotransmitters are involved in its neurotoxic mechanism (Cadet and Brannock, 1998; Nash and Yamamoto., 1992; Stephans and Yamamoto, 1994; Abekava et al., 1994). However, some recent data gathered by Wallace et al. (2001) indicate that the mechanism of the methamphetamine-induced depletion of dopamine may not depend on a delayed increase in the extracellular concentration of glutamate. Thus a decrease in the excitotoxic impact of glutamate, caused by mGluR5 blockade, may be irrelevant to the protection against methamphetamine neurotoxicity. It is assumed that the primary action of methamphetamine is a reversal of dopamine transporter function, which leads to rapid inhibition of dopamine uptake (Fleckenstein et al., 2000). The decrease in DAT function is due to modification of the transporter protein *per se*, or to a change of factors that regulate DAT functioning. Interestingly, it has recently been found that MPEP prevents the inhibition of dopamine uptake, produced by activation of mGluR5 receptors, in the striatum (Page et al., 2001). Hence the decrease in dopamine deficit observed in our study, or the dopamine outflow induced by methamphetamine may be related to the restored functioning of DAT by MPEP, previously disrupted by that neurotoxin. This finding seems to be of great importance and provides a valuable therapeutic approach to neuroprotection, especially as regards disorders involving the dopamine carrier protein.

A selective loss of dopaminergic nigrostriatal cells in Parkonson's disease is unlikely to dependent exclusively on the overactivity of glutamatergic pathways in the basal ganglia. Excitotoxicity may possibly be a secondary factor in neurodegeneration. Nevertheless, depression of the excitatory synaptic activity with mGluRs ligands may be a target in the therapy of neurodegenerative diseases. Other cellular processess

mediated by mGluRs, such as regulation of the generation of free radicals which promotes oxidative stress, regulation of glutathione metabolism (Cambonie et al., 2000; Sagara and Schubert, 1998), BDNF expression (Matarredona et al., 2001), voltage-gated calcium channels (Colwell and Levin, 1999), or preservation of DNA integrity by inhibiting the activity of caspase and other proteins in the cellular mechanism of apoptosis (Maiese et al., 2000) may account for the neuroprotection provided by mGluRs.

Although elucidation of the entire neuroprotective mechanism mediated by mGluRs is far from being resolved, the data discussed above open up a possibility that mGluRs are promising candidates for the therapy of degenerative disorders.

Conclusions

In summary, the data presented above indicate that mGluRs are involved in the regulation of dopaminergic transmission. Group I mGluRs stimulate, whereas group II/III ones have an inhibitory effect on dopamine release. These effects are mediated directly by receptors on dopaminergic cells, or indirectly via supression of glutamate release from neuronal terminals in the subthalamic nucleus or substantia nigra pars reticulata, and from corticostriatal terminals. The selective mGluR5 antagonist MPEP seems to be a neuroprotective agent in an animal model of neurotoxicity after multiple administration of methamphetamine. Reversal of the methamphetamine–induced depletion of striatal dopamine by MPEP may be due to its regulatory effect on the dopamine transporter.

Acknowledgements

This study was supported by the KBN (State Committee for Scientific Research) 4 P05A 123 19 grant.

References

Abekawa T, Ohmori T, Koyama T (1994) Effect of repeated administration of a high dose of methamphetamine on dopamine and glutamate release in rat striatum and nucleus accumbens. Brain Res 643: 276–281

Acikgoz O, Gonenc S, Kayatekin BM, Uysal N, Pekcetin C, Semin I, Gure A (1998) Methamphetamine causes lioid peroxidation and an increase in superoxide dismutase activity in the rat striatum. Brain Res 813: 200–202

Adamchik Y, Baskys A (2000) Glutamate-mediated neuroprotection against *N*-methyl-D-aspartate toxicity: a role for metabotropic glutamate receptors. Neuroscience 99: 731–736

Alexi T, Borlongan CV, Faull LM, Williams CE, Clark RG, Gluckman PD, Hughes PE (2000) Neuroprotective strategies for basal ganglia degeneration: Parkinson's and Huntington's diseases. Prog Neurobiol 60: 409–470

Allen JW, Ivanova SA, Fan L, Espey MG, Basile AS, Faden AI (1999) Group II metabotropic glutamate receptor activation attenuates traumatic neuronal injury and improves neurological recovery after traumatic brain injury. J Pharmacol Exp Ther 290: 112–120

Awad H, Hubert GW, Smith Y, Levey AI, 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

Bond A, Ragumoorthy N, Monn JA, Hicks CA, Ward MA, Lodge D, O'Neill MJ (1999) LY379268, a potent and selective group II metabotropic glutamate receptor agonist, is neuroprotective in gerbil global, but not focal, cerebral ischaemia. Neurosci Lett 273: 191–194

Bond A, Jones NM, Hicks CA, Whiffin GM, Ward MA, O'Neill MF, Kingston AE, Monn JA, Ornstein PL, Schoepp DD, Lodge D, O'Neill MJ (2000) Neuroprotective effects of LY379268, a selective mGlu2/3 receptor agonist: investigations into possible mechanism of action in vivo. J Pharmacol Exp Ther 294: 800–809

Bradley SR, Standaert DG, Rhodes KJ, Rees HD, Testa CM, Levey AI, Conn PJ (1999) Immunohistochemical localization of subtype 4a metabotropic glutamate receptors in the rat and mouse basal ganglia. J Comp Neurol 407: 33–46

Bradley SR, Marino MJ, Wittman M, Rouse ST, Awad H, Levey AI, Conn PJ (2000) Activation of group II metabotropic glutamate receptors inhibits synaptic excitation of the substantia nigra pars reticulata. J Neurosci 20: 3085–3094

Bruno V, Battaglia G, Kingston A, O'Neil MJ, Catania MV, Di Grezia R, Nicoletti F (1999) Neuroprotective activity of the potent and selective mGlu1a metabotropic glutamate receptor antagonist, (+)-2-methyl-4-carboxyphenylglycine (LY 367385): comparison with LY 357366, a broader spectrum antagonist with equal affinity for mGlu1a and mGlu5 receptors. Neuropharmacology 38: 199–201

Bruno V, Ksiazek I, Battaglia G, Lukic S, Leonhardt T, Sauer D, Gasparini F, Kuhn R, Nicoletti F, Flor PJ (2000) Selective blockade of metabotropic glutamate receptor subtype 5 in neuroprotective. Neuropharmacology 39: 2223–2230

Bruton RK, Ge J, Barnes NM (1999) Group I mGlu receptor modulation of dopamine release in the rat striatum in vivo. Eur J Pharmacol 369: 175–181

Burrows KB, Gudelsky G, Yamamoto BK (2000) Rapid and transient inhibition of mitochondrial function following methamphetamine or 3,4-methylenedioxymethamphetamine administration. Eur J Pharmacol 398: 11–18

Cadet JL, Brannock C (1998) Free radicals and the pathobiology of brain dopamine systems. Neurochem Int 32: 117–131

Cambonie G, Laplanche L, Kamenka J-M, Barbanel G (2000) N-Methyl-D-Aspartate but not glutamate induces the release of hydroxyl radicals in the neonatal rat: modulation by group I metabotropic glutamate receptors. J Neurosci Res 62: 84–90

Chatha BT, Bernard V, Streit P, Bolam JP (2000) Synaptic localization of ionotropic glutamate receptors in the rat substantia nigra. Neuroscience 101: 1037–1051

Colwell CS, Levine M (1999) Metabotropic glutamate receptor modulation of excitotoxicity in the neostriatum: role of calcium channels. Brain Res 833: 234–241

Colwell CS, Altemus KL, Levine MS (1996) Metabotropic glutamate receptor activation selectively limits excitotoxic damage in the intact neostriatum. Brain Res 726: 223–226

Conn P, Pin J-O (1997) Pharmacology and functions of metabotropic glutamate receptors. Ann Rev Pharmacol Toxicol 37: 205–237

Escubedo E, Guitart L, Sureda FX, Jimenez A, Pubill D, Pallas M, Camins A, Camarasa J (1998) Microgliosis and down-regulation of adenosine transporter induced by methamphetamine in rats. Brain Res 814: 120–126

Fleckenstein AE, Gibb JW, Hanson GR (2000) Differential effects od stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol 406: 1–13

Giovanni A, Liang LP, Hastings TG, Zigmond MJ (1995) Estimating hydroxyl radical content in rat brain using systemic and intraventricular salicylate: impact of methamphetamine. J Neurochem 64: 1819–1825

Glaum SR, Miller RJ (1994) Acute regulation of synaptic transmission by metabotropic glutamate receptors. In: Patel J, Conn PJ (eds) The metabotropic glutamate receptors. Humana Press, Totowa, New Jersey, pp 147–172

Hanson JE, Smith Y (1999) Group I metabotropic glutamate receptors at GABAergic synapses in monkeys. J Neuroscience 19: 6488–6496

Harold C, Wallace T, Friedman R, Gudelsky G, Yamamoto B (2000) Methamphetamine selectivity alters brain glutathione. Eur J Pharmacol 400: 99–102

Henrich-Noack P, Reyman KG (1999) (1*S*,3*R*)-ACPD, a metabotropic glutamate receptor agonist, enhances damage after global ischemia. Eur J Pharmacol 365: 55–58

Hirata H, Ladenheim B, Carlson E, Epstein C, Cadet JL (1996) Autoradiographic evidence for methamphetamine-induced striatal dopaminergic loss in mouse brain: attenuation in CuZn – superoxide dismutase transgenic mice. Brain Res 714: 95–103

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

Ishida M, Saitoh T, Shimamoto K, Ohfune Y, Shinozaki H (1993) A novel metabotropic glutamate receptor agonist: marked depression of monosynaptic excitation in the newborn rat isolated spinal cord. Br J Pharmacol 109: 1169–1177

Kalda A, Kaasik A, Vassiljev V, Pokk P, Zharkovsky A (2000) Neuroprotective action of group I metabotropic glutamate receptor agonists against oxygen-glucose deprivation-induced neuronal death. Brain Res 853: 370–373

Keefe KA, Zigmond MJ, Abercrombie ED (1992) Extracellular dopamine in striatum: influence of nerve pulse activity in median forebrain bundle and local glutamatergic input. Neuroscience 47: 325–332

Kingston AE, O'Neill MJ, Lam A, Bales KR, Monn JA, Schoepp DD (1999) Neuroprotection by metabotropic glutamate agonists: LY354740, LY379268 and LY389795. Eur J Pharmacol 377: 155–165

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

Lafon-Cazal M, Fagni L, Guiraud M-J, Mary S, Lerner-Natoli M, Pin J-P, Shigemoto R, Bockaert J (1999) mGluR7-like metabotropic glutamate receptors inhibit NMDA-mediated excitotoxicity in cultured mouse cerebellar granule neurons. Eur J Neurosci 11: 663–672

Maiese K, Vincent A, Lin S-H, Shaw T (2000) Group I and group III metabotropic glutamate receptor subtypes provide enhanced neuroprotection. J Neurosci Res 62: 257–272

Matarredona ER, Santiago M, Venero JL, Cano J, Machado A (2001) Group II metabotropic glutamate receptor activation protects striatal dopaminergic nerve terminals against MPP^+-induced neurotoxicity along with brain-derived neurotrophic factor. J Neurochem 76: 351–360

Montoliu C, Llansola M, Cucarella C, Grisolia S, Felipo V (1997) Activation of the metabotropic glutamate receptor mGluR5 prevents glutamate toxicity in primary cultures of cerebellar neurons. J Pharmacol Exp Ther 281: 643–647

Moszczynska A, Turenne S, Kish SJ (1998) Rat striatal levels of the antioxidant glutathione are decreased following binge administration of methamphetamine. Neurosci Lett 255: 49–52

Movsesyan VA, O'Leary DM, Fan L, Bao W, Mullins PGM, Knoblach SM, Faden AI (2001) mGluR5 antagonists 2-methyl-6-(phenylethynyl)-pyridine and (*E*)-2-methyl-6-(2-phenylethenyl)-pyridine reduce traumatic neuronal injury in vitro and in vivo by antagonizing N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 296: 41–47

Nash JF, Yamamoto BK (1992) Methamphetamine neurotoxicity and striatal glutamate release: comparison to 3,4-methylenedioxymethamphetamine. Brain Res 581: 237–243

Neki A, Ohishi H, Kaneko T, Shigemoto R, Nakanishi S, Mizuno N (1996) Pre- and postsynaptic localization of a metabotropic glutamate receptor, $mGluR_2$, in the rat brain: an immunohistochemical study with a monoclonal antibody. Neurosci Lett 202: 197–200

Neto FL, Schadrack J, Berthele A, Zieglgansberger W, Tolle TR, Castro-Lopes JM (2000) Differential distribution of metabotropic glutamate receptor subtype mRNAs in the thalamus of the rat. Brain Res 854: 93–105

O'Leary DM, Movsesyan V, Vicini S, Faden AI (2000) Selective mGluR5 antagonists MPEP and SIB-1893 decrease NMDA or glutamate-mediated neuronal toxicity through actions that reflect NMDA receptor antagonism. Br J Pharmacol 131: 1429–1437

Olney JW (1971) Glutamate induced neuronal necrosis in the infant mouse hypothalamus. J Neuropathol Exp Neurol 30: 75–90

Ossowska K (1994) The role of excitatory amino acids in experimental models of Parkinson's disease. J Neural Transm [P-D Sect] 8: 39–71

Ossowska K, Konieczny J, Wolfarth S, Wieroñska J, Pilc A (2001) Blockade of the metabotropic glutamate receptor subtype 5 (mGluR5) produces antiparkinsonian-like effects in rats. Neuropharmacology (in press)

Page G, Peeters M, Najimi M, Maloteaux J-M, Hermans E (2001) Modulation of the neuronal dopamnie transporter activity by the metabotropic glutamate receptor mGluR5 in rat striatal symaptosomes through phosphorylation mediated processes. J Neurochem 76: 1282–1290

Pellegrini-Giampietro DE, Peruginelli F, Meli E, Cozzi A, Albani-Torregrossa S, Pellicciari R, Moroni F (1999) Protection with metabotropic glutamate I receptor antagonists in models of ischemic neuronal death: time-course and mechanisms. Neuropharmacology 38: 1607–1619

Petralia RS, Wang Y-X, Niedzielski AS, Wenthold RJ (1996) The metabotropic glutamate receptors, MGLUR2 and MGLUR3, show unique postsynaptic, presynaptic and glial localizations. Neuroscience 71: 949–976

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

Rao AM, Hatcher JF, Dempsey RJ (2000) Neuroprotection by group I metabotropic glutamate receptor antagonists in forebrain ischemia of gerbil. Neurosci Lett 293: 1–4

Ricaurte GA, Guillery RW, Seiden LS, Schuster CR, Moore RY (1982) Dopaminergic nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. Brain Res 235: 93–103

Sabelhaus CF, Schroder UH, Breder J, Henrich-Noack P, Reymann KG (2000) Neuroprotection against hypoxic/hypoglycaemic injury after the insult by the group III metabotropic glutamate receptor agonist (R,S)-4-phosphonophenylglycine. Br J Pharmacol 131: 655–658

Sagara Y, Schubert D (1998) The activation of metabotropic glutamate receptors protects nerve cells from oxidative stress. J Neurosci 18: 6662–6671

Sandoval V, Hanson GR, Fleckenstein AE (2000) Methamphetamine decreases mouse striatal dopamine transportes activity: roles of hyperthermia and dopamine. Eur J Pharmacol 409: 265–271

Schroder UH, Opitz T, Jager T, Sabelhaus CF, Breder J, Reymann KG (1999) Protective effect of group I metabotropic glutamate receptor activation against hypoxic/hypoglycemic injury in rat hippocampal slices: timing and involvement of protein kinase C. Neuropharmacology 38: 209–216

Sonsalla PK, Nicklas WJ, Heikkila RE (1989) Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. Science 243: 398–400

Sonsalla PK, Riordan DE, Heikkila RE (1991) Competetive and noncompetitive antagonists at N-methyl-D-aspartate receptors protect against methamphetamine-induced dopaminergic damage in mice. J Pharmacol Exp Ther 256: 506–512

Starr MS (1995) Glutamate/dopamine D1/D2 balance in the basal ganglia and its relevance to Parkinson's disease. Synapse 19: 264–293

Stephans SE, Yamamoto BK (1994) Methamphetamine-induced neurotoxicity: roles for glutamate and dopamine efflux. Synapse 17: 203–209

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

Tapia R, Medina-Ceja L, Pena F (1999) On the relationship between extracellular glutamate, hyperexcitation and neurodegeneration, in vivo. Neurochemistry Int 14: 23–31

Testa CM, Catania MV, Young AB (1994) Anatomical distribution of metabotropic glutamate receptors in mammalian brain. In: Conn PJ, Patel PJ (eds) The metabotropic glutamate receptors. Humana Press, Totowa, New Jersey, pp 99–123

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

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

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

Wallace TL, Vorhees CV, Gudelsky GA (2001) Effects of lubeluzole on the methamphetamine-induced increase in extracellular glutamate and the long-term depletion of striatal dopamine. Synapse 40: 95–101

Westerink BHC, Santiago M, de Vries JB (1992) The release of dopamine from nerve terminals and dendrites of nigrostriatal neurons induced by excitatory amino acids in the rat. Naunyn Schmiedebergs Arch Pharmacol 345: 523–529

Wigmore MA, Lacey MG (1998) Metabotropic glutamate receptors depress glutamate-mediated synaptic input to rat midbrain dopamine neurones in vitro. Br J Pharmacol 123: 667–674

Wu Y, Pearl SM, Zigmond MJ, Michael AC (2000) Inhibitory glutamatergic regulation of evoked dopamine release in striatum. Neuroscience 96: 65–72

Yu T-S, Wang S-D, Liu J-C, Yin H-S (2001) Changes in the gene expression of $GABA_A$ receptor α_1 and α_2 subunits and metabotropic glutamate receptor 5 in the basal ganglia of the rats with unilateral 6-hydroxydopamine lesion and embryonic mesencephalic grafts. Exp Neurol 168: 231–241

Authors' address: Dr. Krystyna Gołembiowska, Department of Pharmacology, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, PL-31-343 Kraków, Poland,
Fax: +48-1033-12-637 4500, E-mail: nfgolemb@cyf-kr.edu.pl