

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

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Received July 7, 2001

Accepted August 6, 2001

Published online September 10, 2002; © Springer-Verlag 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 responsible for degeneration of dopaminergic cells. We found that the selective antagonist of the mGluR5 subtype MPEP in a dose of 5 mg/kg diminished basal and veratridine (100 μ M)-stimulated dopamine release in rat striatum in an *in vivo* model of microdialysis. In contrast, MPEP given intrastrially in a high concentration (500 μ M) enhanced the striatal extracellular concentration of dopamine. DCG-IV (100 μ M), a non-selective agonist of group II mGluRs, inhibited the veratridine-stimulated striatal dopamine release. In an animal model of neurotoxicity *in vivo*, methamphetamine (5 $\times$ 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 $\times$ 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 divided 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 suggests 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 cellu-

lar 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 μ M)-stimulated dopamine release in rat striatum. Intrastriatal perfusion of MPEP (100 μ M) did not affect the veratridine-stimulated dopamine release, but its high concentration (500 μ M) 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 μ M) 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 suppression 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 occurring 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 excitotoxic 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 (1S,3R)-ACPD (Kalda et al., 2000; Montoliu et al., 1997; Adamchik and Baskys, 2000; Colwell et al., 1996). On the other hand, the (1S,3R)-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 (1S,3R)-ACPD, which leads to neuroprotection, whereas enhancement of the neurotoxicity is likely to be mediated by activation of group I mGluRs. Interestingly, 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 sufficient 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 quinolinic 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 microglial cells (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 Parkinson's disease is unlikely to depend 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 processes

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 suppression 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.

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