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The role of excitatory amino acids in experimental models of Parkinson's disease

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Summary. The aim of this article was to review the recent literature on the role of excitatory amino acids in Parkinson's disease and in animal equivalents of parkinsonian symptoms. Effects of NMDA and AMPA antagonists on the reserpine-induced akinesia, catalepsy and rigidity, on the neuroleptic-induced catalepsy, on the turning behaviour of 6-OHDA-lesioned rats, as well as on the parkinsonian symptoms evoked by MPTP in monkeys were analysed. Moreover, the role of NMDA antagonists in Parkinson's disease was discussed. Data concerning the protective influence of these drugs on degenerative properties of methamphetamine, MPTP and 6-OHDOPA were also presented. On the basis of the above findings, the following conclusions may be drawn: (1) disturbances in the glutamatergic transmission in various brain structures seem to play a significant role in the development of symptoms of Parkinson's disease; (2) the NMDA-receptor blocking component may make a substantial contribution to the therapeutic effect of antiparkinsonian drugs; a similar contribution of AMPA-receptor blocking component has not been sufficiently documented, so far; (3) compounds blocking NMDA receptors may possibly prevent the development of Parkinson's disease; this presumption needs, however further studies; (4) side effects of NMDA receptor antagonists may be a limiting factor in the use of these compounds in humans.

Keywords: Parkinson's disease, animal models, NMDA antagonists, AMPA antagonists, therapy, neuroprotection.

Abbreviations and drugs

trans ACPD	trans-1-amino-cyclopentane-1, 3 dicarboxylic acid
αMT	α-methyl-p-tyrosine
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate
L-AP4	2-amino-4-phosphonobutyric acid
AP5	DL-2-amino-5-phosphonovaleric acid
AP7	2-amino-7-phosphonoheptamoic acid
budipine	1-t-butyl-4, 4-diphenylpiperidine

L-BMAA	β-N-methylamino-l-alanine
CGP 37849	(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid
CGP 39551	(E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid ethylester
CGS 19755	cis-4-phosphonomethyl-2-piperidine-carboxylic acid
CNQX	6-cyano-7-nitroquinozaline-2, 3-dione
CPP	3-(2-carboxy-piperazine-4-yl)-propyl-1-phosphonic acid
CPPene	(E)-4-(3-phosphonoprop-2-enyl)-piperazine-2-carboxylic acid
CY 208–243	(-)-4,6,6a,7,8,12b-hexahydro-7-methyl-indolo[4,3a-b]phenanthyxidine
DOPAC	3,4-dihydroxyphenylacetic acid
GDEE	L-glutamic acid diethylester
HVA	homovanillic acid
lamotrigine	3,5-diamino-6-[2,3-dichlorophenyl]-1,2,4-triazine
L-DOPA	3,4-dihydroxyphenyl-L-alanine
MAO	monoamine oxidase
MK-801	dizocilpine
$MPDP^+$	1-methyl-4-phenyldihydropyridinium
MPP^+	1-methyl-4-phenyl-pyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NBQX	6-nitro-7-sulfamobenzo(f)quinoxaline-2,3-dione
NMDA	N-methyl-D-aspartate
NPC 26126	2-amino-4,5-(1,2-cyclohexyl)-7-phosphonoheptanoic acid
6-OHDA	6-hydroxydopamine
6-OHDOPA	6-hydroxydopa – 2,4,5-trihydroxyphenylalanine
PCP	phencyclidine
(+)-PHNO	(+)-4-propyl-9-hydroxynaphthoxazine
SL 82.0715	(±) α-(4-chlorophenyl)-4-[(4-fluorophenyl) methyl]-1-piperidineethanol

Introduction

Despite the fact that Parkinson's disease was first described already ca. 180 years ago, no prophylactic agents have been found so far, which would alleviate all its symptoms and stop its development. Parkinson's disease is characterized by a triad of primary symptoms: akinesia, muscular rigidity and tremor. The primary symptoms are accompanied by a number of secondary signs, such as shuffling gait, flexed body posture, mask-like face and many others, all of them contributing to the characteristic appearance of parkinsonian patients.

Since the discovery of Ehringer and Hornykiewicz (1960) it has been accepted that the primary cause of Parkinson's disease is a lesion of dopaminergic neurons which are located in the substantia nigra pars compacta and which send out their axons to the striatum (nigrostriatal pathway). The lesion of these neurons leads to a decrease in the striatal dopamine level by ca. 80–98%, which is directly connected with the appearance of symptoms of this disease (mainly akinesia and muscular rigidity) (Hornykiewicz, 1989; Hornykiewicz et al., 1989; McGeer et al., 1989; Ellenbroek et al., 1985). The knowledge of pathomechanisms of Parkinson's disease permitted application of substitutive therapy, i.e. administration of levodopa (L-DOPA), a dopamine precursor which is transformed into dopamine in the brain, to patients; in this way, losses caused by lesions of dopaminergic neurons are being compensated for. L-DOPA counteracts akinesia and muscular rigidity;

at present, it is the most widely used antiparkinsonian drug (Birkmayer and Hornykiewicz, 1961; Barbeau, 1969; Bianchine, 1985). However, there has been aroused a controversy about its beneficial effect on parkinsonian tremor (Bianchine, 1985; Nutt, 1990). Moreover, L-DOPA does not prevent development of the disease and produces a number of undesirable, grave side effects, such as psychoses, dyskinesias and others (Bianchine, 1985; Nutt, 1990). Therefore the search has been continued for new methods of treatment of Parkinson's disease, as well as for compounds which, having a therapeutic effect, would at the same time be devoid of L-DOPA's side effects. In recent years it has become of interest to elucidate the role that compounds acting on receptors of excitatory amino acids may play in Parkinson's disease. Studies were carried out to find out whether: (1) the altered glutamatergic neurotransmission may play a role in symptoms of Parkinson's disease; (2) glutamic acid is likely to participate in the degeneration of dopaminergic neurons of the substantia nigra pars compacta; (3) compounds acting on receptors of excitatory amino acids could be used in the treatment of symptoms of Parkinson's disease or in preventing its development.

Receptors of excitatory amino acids

Glutamic acid, which is the main excitatory amino acid, acts on a number of receptors. They are NMDA and non-NMDA receptors. The NMDA receptor is a ionotropic receptor which is linked to an ion channel permeable for calcium (Ca^{2+}) ions (Honoré, 1989; Yoneda and Ogita, 1991; Gasic and Hollmann, 1992). Among the non-NMDA receptors, there can be distinguished ionotropic and metabotropic ones. The ionotropic non-NMDA receptors are represented by kainate (bound by kainic acid) and AMPA (bound by AMPA and quisqualic acid) ones. The metabotropic receptors are bound by quisqualic acid, trans-ACPD and L-AP4. The non-NMDA ionotropic receptors are connected with ion channels permeable for sodium (Na^+) and potassium (K^+) ions, and – in some cases – also for Ca^{2+} ions (Honoré, 1989, Gasic and Hollmann, 1992). Stimulation of the metabotropic receptors evokes – via G protein – hydrolysis of cyclic guanosine monophosphate (cGMP), or formation of diacyloglycerol in the neuron (Gasic and Hollmann, 1992).

The structure of NMDA receptor has been known best. Compounds acting on this receptor bind to a few sites within its complex. The site that recognizes the neurotransmitter – glutamic acid, is bound by NMDA and the following competitive antagonists: AP5, AP7, CPP, CPPene, NPC 126126, CGP 37849, CGP 39551 and CGS 19755. Stimulation of this site by a natural neurotransmitter or by NMDA leads to the opening of a channel and influx of Ca^{2+} into a neuron. Glycine or glycine antagonists bind to the so-called modulatory glycine site which is insensitive to strychnine. Polyamines and polyamine antagonists (ifenprodil and SL 820715) bind to be modulatory polyamine site. On the other hand, the calcium channel is labelled by non-competitive NMDA receptor antagonists, such as MK-801, phencyclidine, ketamine, amantadine and memantine (Yoneda and Ogita, 1991). Under

normal conditions, the calcium channel of the NMDA receptor complex is blocked by magnesium (Mg^{2+}) ions. Depolarization of the neuron removes the Mg^{2+} block and thus enhances the stimulatory effect of glutamic acid on this receptor (Headley and Grillner, 1990).

Clinical data favouring a role of excitatory amino acids in Parkinson's disease

It has recently been found that the well-known antiparkinsonian drugs amantadine and memantine – (Schwab et al., 1969; Schneider et al., 1984; Rabey et al., 1992) are non-competitive NMDA antagonists (Kornhuber et al., 1989; Bormann, 1989; Kornhuber et al., 1991; Greenamyre and O'Brien, 1991). It has been shown that these drugs block the calcium channel of the NMDA receptor complex already at therapeutic concentrations (Kornhuber et al., 1989, 1991). Memantine has been postulated to be a strong antagonist of NMDA receptor complex (Kornhuber et al., 1989, 1991). This finding suggests that the NMDA receptor blocking component may be important for the antiparkinsonian effect of these drugs. Moreover, Olney et al. (1987) pointed out that antagonists of central muscarinic receptors (trihexyphenidyl, ethopropazine, procyclidine and others), commonly used in Parkinson's disease are also non-competitive NMDA antagonists. However, they block the NMDA receptor complex at high concentrations only; therefore it has not been confirmed so far that this mechanism of action contributes substantially to their antiparkinsonian effect.

The recently manufactured antiparkinsonian drug budipine (Byk-Gulden, Konstanz, Germany), which is at present in the III phase of clinical studies, has also turned out to be a non-competitive NMDA receptor antagonist which binds to the phencyclidine site (Klockgether et al., 1993). However, it is not clear whether the NMDA receptor blocking component of budipine is actually responsible for its antiparkinsonian effect. The budipine brain concentrations observed after single application of an effective dose were lower than those necessary to block the calcium channel of the NMDA receptor in vitro (Zech et al., 1985; Klockgether et al., 1993).

Lamotrigine (an antiepileptic drug), an unspecific inhibitor of the glutamic acid release which also inhibits in a weaker manner the release of GABA, acetylcholine, noradrenaline and dopamine, has been reported to have antiakinetic properties in Parkinson's disease (Zipp et al., 1993). However, so far this finding has not been confirmed in controlled studies.

Furthermore, studies of the binding of radioactive ligands have shown that the density of NMDA receptors is 22–46% higher in the striatum and nucleus accumbens septi of parkinsonian patients than in healthy people (Weihmuller et al., 1992).

A further premise that excitatory amino acids participate in the appearance of parkinsonian symptoms was a high incidence of a fatal disease, known as the Guam amyotropic lateral sclerosis-parkinsonism dementia – ALS-PD, on the isle of Guam of the Mariana Archipelago in the Pacific Ocean. The basis for this disease is the degeneration of anterior horns of the spinal cord, motor nuclei of the brain stem and motor cortex, and its characteristic clinical

picture resembles Parkinson's disease. It was found that the incidence of this disease was caused by consumption of flour made from Cycas circinalis seeds, of long tradition on that island. The flour in question contains an excitatory amino acid, l-BMAA. The above-mentioned amino acid has already been isolated; when given to monkeys, it evoked symptoms similar to those found in patients suffering from ALS, i.e. akinesia, hypokinesia, tremor, flexed body posture, shuffling gait, etc. (Spencer et al., 1987; Weiss and Choi, 1988). On the basis of this finding, Spencer et al. (1987) and Weiss and Choi (1988) proposed that the Guam ALS-PD symptoms resulted from the excitotoxic effect of l-BMAA. However, this concept has recently been questioned. Duncan et al. (1990, 1991) claimed that the estimated dose of l-BMAA resulting from the consumption of cycads was several orders of magnitude smaller than used to induce BMAA neurotoxicity. Moreover, Duncan et al. (1992) found that the soaking period of a cycad flour preparation increased the total zinc content; he also proposed that zinc was a neurotoxic compound responsible for the neuronal degeneration observed in ALS-PD. However, even if l-BMAA is not the cause of Guam ALS-PD, the discovery of that compound drew researchers' attention to the role of excitatory amino acids in the pathophysiology of parkinsonian symptoms.

Animal models of Parkinson's disease

The prevailing number of data pointing to a causal relationship between the action of excitatory amino acids and Parkinson's disease come from studies conducted on animal models of this disease.

Animal models of Parkinson's disease are obtained by administration of compounds which: (1) cause a permanent lesion of the dopaminergic nigrostriatal pathway, (2) impair reversibly (temporarily) the function of this pathway, or (3) block postsynaptic dopamine receptors in the striatum.

Compounds causing a lesion of the dopaminergic nigrostriatal pathway

MPTP

The best model compound hitherto discovered, which was used to cause a lesion of dopaminergic neurons of the substantia nigra, is MPTP. MPTP is a compound which also evokes parkinsonism in humans. MPTP in doses of 0.5–12 mg/kg given to monkeys evokes parkinsonian symptoms and a lesion of dopaminergic neurons, the latter being most often measured by dramatic decreases in the level of dopamine and its metabolites – DOPAC and HVA – in the striatum (Kinemuchi et al., 1987; Crossman et al., 1989; Mitchell et al., 1989; Bergman et al., 1990; Close et al., 1990; Klockgether et al., 1991; Löschmann et al., 1991; Zuddas et al., 1992; Greenamyre, 1993). The mechanism of the neurotoxic effect of MPTP on dopaminergic neurons has been partly known so far. It has been established that MPTP in astrocytes is transformed by MAO-B to ion $MPDP^+$ which, in turn, is oxidized – most probably non-enzymatically – to the active ion MPP^+. This active ion is then transported – via a dopamine neuronal uptake carrier to dopaminergic neurons

(Javitch and Snyder, 1985; Javitch et al., 1985; Kinemuchi et al., 1987; Sonsalla et al., 1992a). It has been postulated that striatal dopaminergic terminals are a primary site of entry of MPP^+ into dopamine neurons after systemic injection of MPTP to monkeys (Herkenham et al., 1991). After being accumulated by dopaminergic terminals, MPP^+ is afterwards transported – via a retrograde transport – to axons and cell bodies (Herkenham et al., 1991). Inside the dopaminergic neuron, MPP^+ is transported to mitochondria where it is accumulated and where it impairs respiratory complex I by inactivation of NADH dehydrogenase (Kinemuchi et al., 1987; Sonsalla et al., 1992a). Blockade of the processes of cellular respiration by MPP^+ leads to a decrease in the level of high-energy compounds such as ATP which, in turn, must result in a partial depolarization of neurons due to the impaired functioning of Na^+, K^+-ATPases (Storey et al., 1992). Further processes leading to the degeneration of dopaminergic neurons induced by MPTP are unknown and might involve a stimulation of NMDA receptors (Turski et al., 1991; Storey et al., 1992; Brouillet and Beal, 1993).

Also in mice, MPTP causes a lesion of dopaminergic neurons, yet to this end injection of much higher doses than in monkeys (20–80 mg/kg) is required (Sonsalla et al., 1989, 1992a, b; Fuller, 1992; Heikkila and Sonsalla, 1992).

MPTP administered peripherally has little effect in rats (Kinemuchi et al., 1987; Heikkila and Sonsalla, 1992), probably due to different penetration into the brain and diverse metabolism of this compound in this species (Kinemuchi et al., 1987). Therefore, in order to cause a lesion of dopaminergic neurons in the rat, the active metabolite of MPTP, MPP^+ is usually administered intracerebrally – directly in the vicinity of cell bodies of these neurons – into the substantia nigra pars compacta, or – in the vicinity of terminals – into the striatum (Bradbury et al., 1986; Sayre et al., 1986; Harik et al., 1987; Turski et al., 1991; Sonsalla et al., 1992b; Storey et al., 1992; Ter Horst et al., 1992). The dopamine uptake carrier was found to be present not only on dopaminergic terminals in the striatum, but also in membranes of dopaminergic cell bodies and/or dendrites in the substantia nigra pars compacta (Dawson et al., 1986; Leroux-Nicollet and Costentin, 1988; Richfield, 1991; Vaugeois et al., 1992). According to different authors, a nigral content of the dopamine uptake carrier equals 14–43% of the striatal content (Dawson et al., 1986; Leroux-Nicollet and Costentin, 1988; Richfield, 1991). Therefore it is likely that MPP^+ can also enter dopaminergic cell bodies directly from their vicinity in the substantia nigra pars compacta. According to the above concept, MPP^+ injected directly into this region in rats induces excessive degeneration of dopaminergic neurons, measured by a derease in their number or by losses in the dopamine and its metabolite levels in the striatum (Bradbury et al., 1986; Sayre et al., 1986; Harik et al., 1987; Turski et al., 1991; Sonsalla et al., 1992b). After intranigral injections, toxic doses of MPP^+ were found to be smaller than those necessary to induce a similar effect after injections into the striatum (Sayre et al., 1986; Harik et al., 1987; Turski et al., 1991; Sonsalla et al., 1992b; Storey et al., 1992). It has been found, however, that intracerebral administration of MPP^+ does not guarantee an absolutely selective lesion of

dopaminergic neurons. MPP^+ injected into the substantia nigra pars compacta or into the striatum also causes a lesion of non-dopaminergic neurons – serotoninergic, GABAergic, P-ergic and others (Harik et al., 1987; Storey et al., 1992; Ter Horst et al., 1992).

6-Hydroxydopamine

The most frequently used method of a fairly selective lesion of dopaminergic neurons in rats is administration of 6-hydroxydopamine (6-OHDA) in the vicinity of these neurons. Like MPP^+, 6-OHDA enters the dopaminergic neurons via a dopamine uptake carrier (if a noradrenaline uptake carrier is blocked by desmethylimipramine) when it is injected into the substantia nigra pars compacta or striatum (Zigmond et al., 1992). Afterwards, it readily undergoes autooxidation which leads to formation of toxic, free-oxygen radicals and quinones (Zigmond et al., 1992) and thus produces degeneration of the dopaminergic neurones. Such a lesion results in the appearance of akinesia and muscular rigidity (Duvoisin, 1976; Klockgether et al., 1987; Fuller, 1992). As a rule, 6-OHDA is administered unilaterally. A unilateral lesion of the dopaminergic nigrostriatal pathway results in the appearance of ipsilateral postural asymmetry which may constitute a model of unilateral Parkinson's disease (Duvoisin, 1976). Administration of potential antiparkinsonian drugs in this model evokes contralateral rotations (Ungerstedt, 1971; Heikkila and Sonsalla, 1992; Greenamyre, 1993).

Amphetamines

Methamphetamine and amphetamine administered peripherally in very high doses (16–100 mg/kg) are other tools to produce a selective lesion of dopaminergic neurons in mice and rats (Sonsalla et al., 1989, 1991, 1992a; Fuller, 1992; O'Dell et al., 1992). The primary site of action of these compounds are striatal dopaminergic terminals (Sonsalla et al., 1989, 1991, 1992a; Fuller, 1992; O'Dell et al., 1992; Marshall et al., 1993). Animals exposed to neurotoxic effects of methamphetamine or amphetamine display falls in the activity of tyrosine hydroxylase, in the level of dopamine and its metabolites, in the density of binding sites of the dopamine uptake carrier and in the number of dopaminergic terminals and axons in the striatum (Sonsalla et al., 1989, 1991, 1992a; Fuller, 1992).

The mechanism of the neurotoxic effect of methamphetamine and amphetamine remains unclear. It is assumed to be connected with an excessive, carrier-mediated release of dopamine from presynaptic terminals by these compounds (Parker and Cubeddu, 1986a,b; Sonsalla et al., 1989, 1991, 1992a; Fuller, 1992; O'Dell et al., 1992; Marshall et al., 1993). It was found that the toxic effect of methamphetamine depends on dopamine synthesis (it is inhibited by αMT); moreover, it is decreased by the neuroleptic-induced blockade of dopamine receptors. According to some authors, excessive amounts of the released dopamine might be subjected to an oxidative stress and, due to the action of MAO and to autooxidation, there are formed toxic, free-oxygen radicals and quinones (Sonsalla et al., 1989, 1992a; O'Dell et al.,

1992). According to an unconfirmed concept of Seiden and Vosmer (1984), formation of the neurotoxin 6-hydroxydopamine (6-OHDA) might be an intermediate phase of the pathological metabolism of dopamine released by methamphetamine.

Compounds impairing the function of the dopaminergic nigrostriatal pathway

The most frequently used model compound which temporarily impairs the function of dopaminergic neurons is reserpine. It depletes dopamine from the storage vesicles of dopaminergic varicosities. This drug is also used in combination with the dopamine synthesis inhibitor α-methyl-paratyrosine (α-MT) (Carlsson and Carlsson, 1989a,b; Klockgether and Turski, 1990; Klockgether et al., 1991; Kannari and Markstein, 1991; Maj et al., 1993b). Reserpine is a not selective compound for central dopaminergic neurons: besides dopamine, it also depletes – both centrally and peripherally – other monoamines. Reserpine given to rats or mice evokes, among other symptoms, akinesia and muscular rigidity (Carlsson and Carlsson, 1989a,b; Klockgether and Turski, 1990; Klockgether et al., 1991; Kannari and Markstein, 1991).

Compounds blocking postsynaptic dopamine receptors in the striatum

In order to block striatal postsynaptic dopamine receptors, above all neuroleptics, such as haloperidol, fluphenazine and others are used. These drugs block mainly dopamine D_2 receptors, but also – to a considerably lesser extent, though – D1 receptors (Seeman and Grigoriadis, 1987). After peripheral or direct intrastriatal injections, the compounds in question evoke a characteristic syndrome: akinesia, catalepsy (inability to change an imposed, uncomfortable position) and muscular rigidity. These signs are regarded as animal equivalents of symptoms appearing in the so-called drug-induced parkinsonism in humans (Ellenbroek et al., 1985; Ossowska et al., 1990a,b; Schmidt et al., 1992). Apart from classic neuroleptics, also the selective D_2 receptor antagonists sulpiride and raclopride, or the D_1 receptor antagonist SCH 23390 are administered. Like classic neuroleptics, raclopride and SCH 23390 induce catalepsy after peripheral injections (Morelli and Di Chiara, 1985; Tamminga and Gerlach, 1987; Papa et al., 1993). Contrariwise, peripheral administration of sulpiride induces neither catalepsy in rats, nor parkinsonism in humans (Honda et al., 1977; Jenner and Marsden, 1983; Wambebe, 1987). However, a direct injection of the latter drug (which blocks dopamine D_2 receptors) to the rat striatum evokes catalepsy (Ossowska et al., 1990a,b).

The effect of NMDA receptor antagonists in animal models of Parkinson's disease

The effect of NMDA receptor antagonists on the neuroleptic- or reserpine-induced catalepsy

Catalepsy is a state of akinesia, which is characterized by the inability of an animal to change an uncomfortable position which was imposed by the experi-

menter. Catalepsy is usually measured by means of various tests, in which the degree of the imposed uncomfortable position and the time of its maintenance are quantified.

Table 1 shows the effect of single injections of competitive and non-competitive NMDA receptor antagonists on the catalepsy evoked by:

1. systemic administration of the following neuroleptics: haloperidol (0.1–2.0 mg/kg), fluphenazine (0.03–0.4 mg/kg), perphenazine (5 mg/kg), spiperone (0.3–0.4 mg/kg) and raclopride (2.5 mg/kg);
2. peripheral administration of the dopamine D_1 receptor antagonist SCH 23390 (0.5–1 mg/kg);
3. systemic administration of reserpine (5 mg/kg) jointly with αMT (250 mg/kg);
4. intrastriatal administration of fluphenzine (0.03–0.3 μg) and sulpiride (1 μg).

The greatest number of studies were devoted to the non-competitive NMDA receptor antagonist dizocilpine (MK-801). That compound turned out to be the most potent of all the drugs studied; when used in doses ranging from 0.04 to 0.5 mg/kg, it attenuated in a dose-dependent manner the catalepsy induced by neuroleptics and by SCH 23390 (Elliot et al., 1990; Mehta and Ticku, 1990; Schmidt et al., 1991, 1992; Kretschmer et al., 1992; Verma and Kulkarni, 1992; Maj et al., 1993b; Papa et al., 1993). However, MK-801 used in a dose of 0.2 mg/kg did not affect the catalepsy evoked by joint administration of reserpine and αMT (Maj et al., 1993b). Of other non-competitive antagonists, phencyclidine (PCP) in doses of 0.3–3 mg/kg, amantadine in doses of 20–80 mg/kg and memantine in doses of 5–10 mg/kg antagonized the neuroleptic-induced catalepsy (Maj et al., 1972; Elliot et al., 1990; Schmidt et al., 1991).

Competitive NMDA receptor antagonists (CGP 37849 – 2–4 mg/kg; CGP 39551 – 2.5–10 mg/kg; CPPene – 5 mg/kg) also inhibited the neuroleptic-induced catalepsy (Schmidt et al., 1991, 1992; Kretschmer et al., 1992; Maj et al., 1993b). No such effect was shown only by CPP on the fluphenazine-induced catalepsy (Elliot et al., 1990), or by CGP 37849 – on the SCH 23390-induced catalepsy (Schmidt et al., 1991).

The effect of NMDA receptor antagonists on the neuroleptic- and reserpine-induced akinesia

The term "akinesia" has been diversely defined by different authors. Most frequently, akinesia is defined as inhibition of the locomotor activity, which may be measured – among others – in photoresistor actometers. This method of assessing akinesia has been used by numerous authors (Carlsson and Carlsson, 1989a,b; Klockgether and Turski, 1990; Klockgether et al., 1991; Kannari and Markstein, 1991; Maj et al., 1993b). On the other hand, according to Hauber and Schmidt (1990), Schmidt et al. (1991, 1992) and Kretschmer et al. (1992), akinesia of the parkinsonian type consists of a delayed initiation of a movement. In this connection, in studies of the above-mentioned authors,

Table 1. The effect of single injections of NMDA receptor antagonists on the neuroleptic-induced catalepsy

Neuroleptic	NMDA Antagonists (doses in mg/kg sc or ip)								
	Competitive				Non-competitive				Authors
	CGP 37849	CGP 39551	CPPene	CPP	MK 801	Memantine	PCP	Amantadine	
Haloperidol ip	↓ 2–4	↓ 5–10	↓ 5		↓ 0.04–0.5	↓ 5–10			Mehta and Ticku (1990) Schmidt et al. (1991, 1992) Kretschmer et al. (1992) Verma and Kulkarni (1992)
Spiperone ip	↓ 2–4	↓ 2.5–10			↓ 0.2			↓ 20–80	Maj et al. (1972, 1993b)
Fluphenazine sc or ip	↓ 2–4	↓ 2.5–10		no effect 3–100	↓ 0.03		↓ 0.3–1		Elliot et al. (1990) Maj et al. (1993b)
into the CP					↓ 0.03				Elliot et al. (1990)
Perphenazine ip					↓ 0.025–0.5				Verma and Kulkarni (1992)
Raclopride ip					↓ 0.1				Papa et al. (1993)
SCH 23390 ip	no effect 4		↓ 5		↓ 0.025–0.5	↓ 10			Schmidt et al. (1991) Verma and Kulkarni (1992) Papa et al. (1993)
Sulpiride into the CP					↓ 0.067–0.2		↓ 1–3		Elliot et al. (1990)
Reserpine + αMT ip	↓ 2–4				no effect 0.2				Maj et al. (1993b)

↓ a decrease in catalepsy, *CP* caudate-putamen

akinesia was regarded as an increased time lapse between the action of a conditioned stimulus and the locomotor reaction of an animal.

The non-competitive NMDA receptor antagonists MK-801 (0.08–0.16 mg/kg) and memantine (10 mg/kg) diminished the delay in initiation of a movement, evoked by haloperidol (0.1–0.5 mg/kg). The competitive antagonist of this receptor, CGP 37849 (4 mg/kg), also showed antagonism towards the akinesia induced by lower (0.1–0.3 mg/kg), but not higher, doses of haloperidol (Hauber and Schmidt, 1990; Schmidt et al., 1991, 1992; Kretschmer et al., 1992).

MK-801 given to mice (1–4 mg/kg) or rats (0.39–1.56 mg/kg) also counteracted the akinesia (measured as a decrease in the locomotor activity) evoked by joint administration of reserpine (5 or 10 mg/kg) and αMT (250 mg/kg) (Carlsson and Carlsson, 1989a,b; Klockgether and Turski, 1990; see Greenamyre, 1993). However, in that model in rats, no effect was produced by the following competitive antagonists: CPP – tested in a wide range of doses (0.39–25 mg/kg) (Klockgether and Turski, 1990), CGP 39551 – in doses of 10–40 mg/kg and CGP 37849 – in doses of 10–40 mg/kg (Maj et al., 1993b). In contrast, Kannari and Markstein (1991) reported attenuation of the reserpine+αMT-induced akinesia in mice, by the competitive NMDA receptor antagonists CPPene (5–10 mg/kg) and CGP 37849 (7.5–10 mg/kg).

The effect of NMDA receptor antagonists on the reserpine-induced rigidity

Klockgether and Turski (1990) also studied the effect of the competitive antagonist CPP and the non-competitive one MK-801 on the muscular rigidity evoked by joint administration of reserpine (5 mg/kg) and αMT (250 mg/kg). According to these authors, the reserpine+αMT-induced muscular rigidity was indicated by the appearance of a tonic electromyographic activity in the gastrocnemius muscle at rest. MK-801 (0.39–1.56 mg/kg) and CPP (0.39–25 mg/kg) attenuated in a dose-dependent manner – until complete abolition – the reserpine+αMT-induced rigidity. A similar effect was obtained by Ossowska et al. (1994), who used a mechanomyographic method of measuring the muscular rigidity. By this method one can measure the resistance of the rat's hind limb in response to an imposed bending and straightening in the ankle joint (Kolasiewicz et al., 1987). This resistance is accepted as muscular rigidity. MK-801 in doses of 0.32–1.28 mg/kg diminished the reserpine (10 mg/kg) – or reserpine (10 mg/kg) + αMT (250 mg/kg)-induced muscular rigidity, measured in that model (Ossowska et al., 1994)

The effect of joint administration of NMDA receptor antagonists and L-DOPA on "parkinsonian symptoms" in various animal models of Parkinson's disease

As it has already been mentioned above, L-DOPA evokes a number of side effects in humans. One may also expect side effects to appear after NMDA receptor antagonists. Therefore, the effect of joint administration of low doses of the above compounds on "parkinsonian symptoms" was studied in animal models, in the hope that such a mode of treatment in

humans might prevent side effects evoked by high doses of either of these drugs, or minimize them.

The non-competitive antagonist MK-801 (0.00156–0.00625 mg/kg) (Klockgether and Turski, 1990), as well as the competitive antagonists CPP (0.025–0.1 mg/kg) (Klockgether and Turski, 1990) and CGP 37849 (1–3 mg/kg) (Maj et al., 1993b) showed a synergistic effect with L-DOPA (50 mg/kg) + benserazide in a model of akinesia (Klockgether and Turski, 1990; Maj et al., 1993b) and in a model of the muscular rigidity (Klockgether and Turski, 1990) induced by reserpine and αMT. Unlike the above compounds, CGP 39551 (0.1–3 mg/kg) did not enhance the effect of L-DOPA in the model of the reserpine-induced akinesia (Maj et al., 1993b).

Mk-801 (0.1 mg/kg) or CPP (0.025–6.25 mg/kg) also increased contralateral rotations after L-DOPA (25 mg/kg) + benserazide, given to rats with an unilateral lesion of the nigrostriatal pathway, caused by 6-OHDA (Morelli and Di Chiara, 1990; Löschmann et al., 1991).

The data presented above indicate that both non-competitive and competitive NMDA receptor antagonists inhibit the majority of disorders in models of Parkinson's disease in rodents; besides, they also enhance the effect of L-DOPA, a widely accepted antiparkinsonian drug.

The role of various brain structures in the "antiparkinsonian effect" of NMDA receptor antagonists

The effect of administration of competitive NMDA receptor antagonists to various brain structures on disorders in models of parkinsonism was studied in rats. According to Klockgether and Turski (1990), CPP antagonized the reserpine + αMT-induced akinesia and muscular rigidity after injections to the nucleus subthalamicus, substantia nigra pars reticulata or nucleus entopeduncularis (an equivalent of the internal segment of the globus pallidus in monkeys). Besides, another competitive NMDA receptor antagonist – AP5, injected into the substantia nigra pars compacta, antagonized the haloperidol-induced catalepsy (Schuster and Schmidt, 1988; Schuster, 1990). In contrast, Klockgether and Turski (1990) did not succeed in weakening post-reserpine disorders by injecting CPP into the striatum. On the grounds of the latter result, the above-mentioned authors negated the role of striatal NMDA receptors in the "antiparkinsonian" effect of drugs (Klockgether and Turski, 1990). However, other authors (Yoshida et al., 1991) came to an opposite conclusion regarding the role of the striatum in the action of NMDA receptor antagonists. They found that AP5, injected into the striatum, attenuated the catalepsy evoked by peripheral administration of haloperidol. Furthermore, also other findings indicated a role of striatal NMDA receptors in "parkinsonian disorders". It is well known that the main source of glutamic acid in the striatum is a glutamatergic pathway from the frontal cortex (Fonnum, 1984). It has been ascertained that a lesion of the frontal cortex produced the same effect as did administration of the NMDA receptor antagonist AP5 to the striatum, i.e. it attenuated the haloperidol-induced catalepsy (Yoshida et al., 1991). On the other hand, catalepsy was restored by

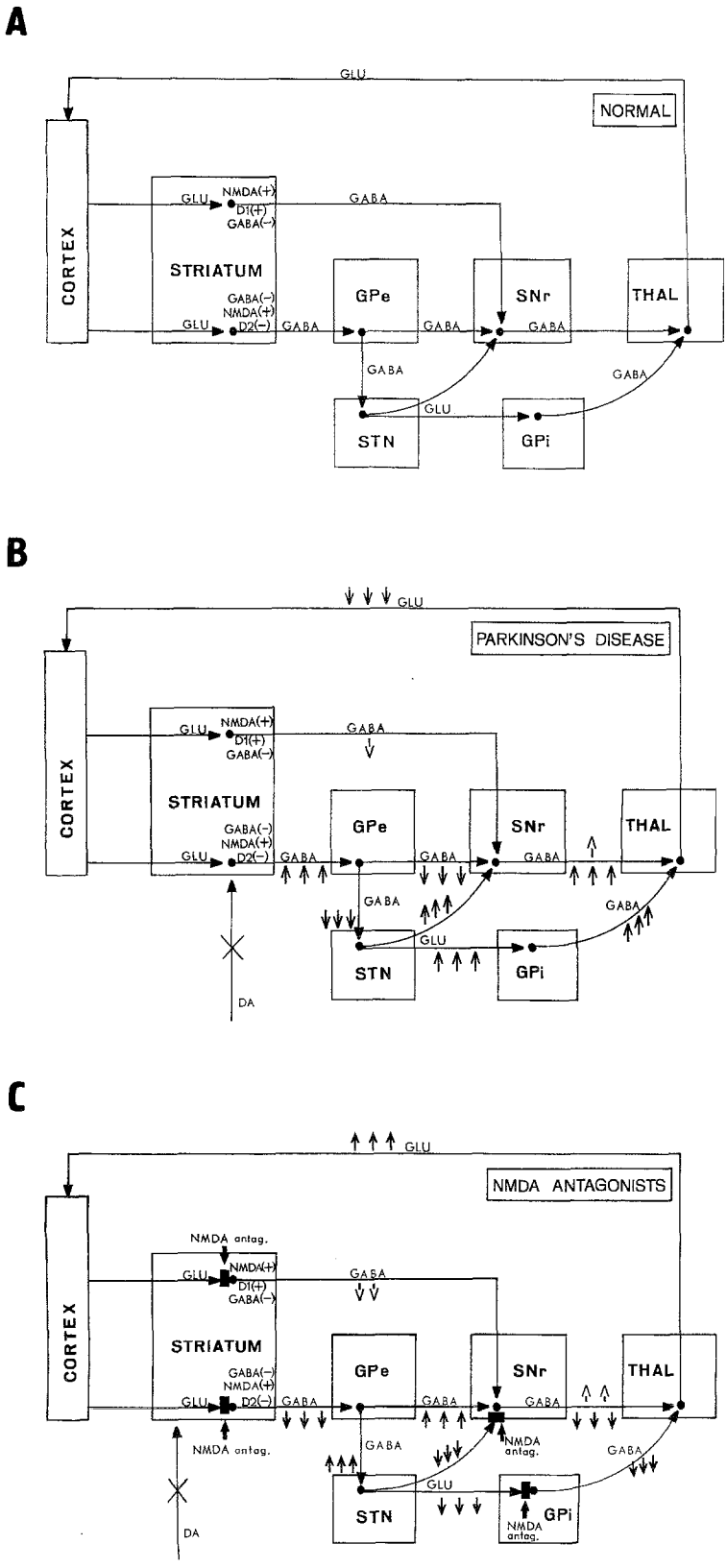
a subsequent injection of NMDA to the striatum (Yoshida et al., 1991). Administration of NMDA alone into the striatum evoked akinesia (Schmidt and Bury, 1988), whereas injections of the antagonists AP5 and AP7 alone – increased the locomotor activity (Scheel-Krüger and Vrijmoed-de Vries, 1986; Schmidt and Bury, 1988). On the basis of the above results it may be hypothesized that parkinsonian symptoms result from the enhanced glutamatergic transmission in numerous brain structures, such as the striatum, nucleus subthalamicus, pars compacta and pars reticulata of the substantia nigra, and internal segment of the globus pallidus. All these structures have a glutamatergic innervation and NMDA receptors which may constitute a target for potential antiparkinsonian drugs (Albin et al., 1992; Tallaksen-Greene et al., 1992).

The dopaminergic-glutamatergic imbalance in Parkinson's disease and hypotheses about the antiparkinsonian effect of NMDA receptor antagonists

The finding that an enhancement of glutamatergic neurotransmission could be responsible for parkinsonian symptoms has led to a hypothesis that, apart from the already known dopaminergic-cholinergic imbalance, in Parkinson's disease there also occur disturbances in the dopaminergic-glutamatergic balance (Riederer et al., 1991b, 1992). This imbalance appears in the basal ganglia and related brain structures. Administration of dopaminominetics (L-DOPA), as well as of NMDA receptor antagonists, restores the balance (Riederer et al., 1991b, 1992).

Figure 1 presents a hypothesis concerning alterations in the neuronal chain, which might constitute a basis for Parkinson's disease, and about the role of the glutamatergic neurotransmission in these changes (Klockgether and Turski, 1989; Carlsson and Carlsson, 1990; Schmidt et al., 1990, 1992; Greenamyre, 1993).

It has been established that in the striatum dopamine acts on D_1 and D_2 receptors. Data obtained by an in situ hybridization method showed that D_1 receptors are located mainly on neurons of the strionigral GABAergic pathway which leaves the striatum for the substantia nigra pars reticulata (SNr), whereas D_2 receptors are situated mainly on neurons of the striopallidal GABAergic pathway which leads to the external segment of the globus pallidus (GPe) (Beckstead, 1988; Gerfen et al., 1990; Gerfen, 1992). Acting via D_1 receptors dopamine stimulates the strionigral, while acting via D_2 ones it inhibits the striopallidal pathway (Gerfen, 1992). Glutamic acid, released from terminals of the corticostriatal pathway in the striatum, stimulates both output pathways to the substantia nigra pars reticulata (SNr) and globus pallidus (GPe) (Brown and Arbuthnott, 1983; Smith and Bolam, 1990; Schmidt et al., 1992; Tallaksen-Greene et al., 1992) (Fig. 1A). A lesion of the nigrostriatal pathway (from the substantia nigra pars compacta (SNc) to the striatum) or blockade of the dopamine receptors in the striatum – which takes place in Parkinson's disease and its animal equivalents – leads to a glutamatergic-dopaminergic imbalance in the striatum and excessive activation (lack of the inhibitory effect of dopamine) of the striopallidal pathway,


A
GLU
NORMAL
CORTEX
GLU
NMDA(+)
D1(+)
GABA(−)
GABA
STRIATUM
GABA(−)
NMDA(+)
GLU
D2(−)
GABA
GPe
GABA
SNr
GABA
THAL
GABA
GABA
GLU
STN
GPi
B
GLU
PARKINSON'S DISEASE
CORTEX
GLU
NMDA(+)
D1(+)
GABA(−)
GABA
STRIATUM
GABA(−)
NMDA(+)
GLU
D2(−)
GABA
GPe
GABA
SNr
GABA
THAL
GABA
GABA
GLU
STN
GPi
DA
C
GLU
NMDA ANTAGONISTS
NMDA antag.
CORTEX
GLU
NMDA(+)
D1(+)
GABA(−)
GABA
STRIATUM
GABA(−)
NMDA(+)
GLU
D2(−)
GABA
GPe
GABA
SNr
GABA
THAL
NMDA antag.
GABA
NMDA antag.
GABA
GLU
STN
NMDA antag.
GPi
DA

as well as to inhibition (lack of the stimulating effect of dopamine) of the strionigral pathway. As a result of these processes, there take place an increased GABA release in the external segment of the globus pallidus (GPe), inhibition of the GABAergic pathway which leaves this structure for the nucleus subthalamicus (STN) and, eventually, disinhibition of glutamatergic pathways leaving the latter structure for the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) (Fig. 1B). A growing body of experimental data – behavioural, biochemical and metabolic – confirm the genuineness of such a sequence of neurotransmitter changes (Mitchell et al., 1989; Gerfen, 1992; see Schmidt et al., 1992; Ossowska et al., 1993; see Greenamyre, 1993). Among others, experiments conducted on monkeys treated with MPTP showed that a lesion of the nucleus subthalamicus (STN) results in attenuation of parkinsonian symptoms (Bergman et al., 1990). An excessive release of glutamic acid in the substantia nigra pars reticulata and in the internal segment of the globus pallidus (GPi), with a simultaneous decrease in the GABA release from the inhibited strionigral pathway lead to a shift of balance towards glutamic acid, and to stimulation of GABAergic pathways leaving the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GPi) for the thalamus (THAL). This, in turn, causes inhibition of glutamatergic pathways leading from the thalamus to the motor cortex (CORTEX), and stimulation of glutamatergic pathways leading from the cortex back to the striatum and substantia nigra pars compacta (SNc) (Fig. 1B).

According to the above concept, the target for NMDA receptor antagonists would be receptors situated on neurons of a pathway leading from the striatum to the external segment of the globus pallidus, as well as of pathways leading from the substantia nigra pars reticulata (SNr) and the internal segment of the globus pallidus (GPi) to the thalamus (THAL). These antagonists would block the stimulating effect of glutamic acid on the above-mentioned pathways; hence this effect might be resposible for their antiparkinsonian effect (Fig. 1C). On the other hand, the action of NMDA receptor antagonists directly on the strionigral pathway would produce (according to the above hypothesis) an opposite effect, i.e. potentiation of parkinsonian symptoms (Fig. 1C). The latter assumption is corroborated by the results obtained by Ossowska and Wolfarth (1993a), who reported the occurrence of ipsilateral

Fig. 1. Schematic drawing of the neuronal circuitry which is engaged in Parkinson's disease. **A** Normal **B** Parkinson's disease *arrows up* increased activity of the pathway vs normal, *arrows down* decreased activity of the pathway vs normal **C** Effect of NMDA antagonists in Parkinson's disease; *arrows up* increased activity of the pathway vs Parkinson's disease, *arrows down* decreased activity of the pathway vs Parkinson's disease. *GPe* globus pallidus external segment, *GPi* globus pallidus internal segment, *SNr* substantia nigra pars reticulata, *STN* subthalamic nucleus, *THAL* motor nuclei of the thalamus; *DA* dopaminergic pathway, *GABA* GABAergic pathway, *GLU* glutamatergic pathway, **D1(+)** stimulatory dopamine D1 receptor, **D2(–)** inhibitory dopamine D2 receptor, **GABA(–)** inhibitory GABAergic receptor, **NMDA(+)** stimulatory NMDA receptor, *NMDA antag.* NMDA antagonists. For further explanations see text

rotations and head turns after administration of AP5 to the intermediate-posterior part of the striatum, i.e. to the region from which there emerges a GABAergic projection leading to the substantia nigra pars reticulata (Araki et al., 1985). When injected into the same region, NMDA produced an opposite effect: contralateral rotations and head turns (Ossowska and Wolfarth, 1993a,b; Wolfarth and Ossowska, 1993; 1994). Both these effects – after AP5 and NMDA – were weak, probably because the strionigral pathway is under normal conditions powerfully inhibited by GABA released mainly from its reccurrent collaterals (Park et al., 1980). This assumption was supported by the fact that the GABA antagonist picrotoxin injected into the same striatal region enhanced contralateral rotations induced by NMDA (Ossowska and Wolfarth, 1993a,b). The weak responsiveness of the strionigral pathway to drug influence could explain the prevalence of the "antiparkinsonian effect" over the stimulating effect on "parkinsonian symptoms" of NMDA receptor antagonists after their peripheral administration.

The influence of NMDA receptor antagonists on the dopaminergic neurotransmission

Another hypothesis which has been advanced to elucidate the antiparkinsonian action of NMDA receptor antagonists postulates that they exert a direct or indirect effect on dopaminergic neurons. It arose from biochemical studies that single injections of non-competitive NMDA receptor antagonists (MK-801, ketamine, memantine and phencyclidine) enhance the synthesis, release and metabolism of dopamine in various brain structures (Deutch et al., 1987; Imperato et al., 1990; Rao et al., 1990; Tanii et al., 1990; Irufune et al., 1991; Löscher et al., 1991; Liljequist et al., 1991; Svensson et al., 1991; Bubser et al., 1992). However, the data on the effect of these compounds on nigrostriatal dopaminergic neurons are controversial. Some authors reported an increase in the dopamine metabolism and dopamine release in the striatum after MK-801 (Imperato et al., 1990; Löscher et al., 1991; Svensson et al., 1991). However, Deutch et al. (1987), Rao et al. (1990), Bubser et al. (1992) and Gandolfi et al. (1992) did not find any increase in the striatal dopamine metabolism after MK-801 or other non-competitive NMDA antagonists. Bubser et al. (1992) observed only a small increase in the dopamine metabolism after memantine in the posterior, but not anterior, part of the striatum. Moreover, Liljequist et al. (1991) reported that MK-801 did not increase the DOPAC level in the striatum, though it accelerated the rate of dopamine disappearance and the rate of tyrosine hydroxylation.

The findings concerning the effect of single or repeated peripheral injections of competitive NMDA receptor antagonists (CPP, CGS 19755, CGP 39551, CPPene, CGP 37849) do not point to stimulation of nigrostriatal dopaminergic neurons by them, either (Rao et al., 1990, 1991; Svensson et al., 1991; Bubser et al., 1992; Maj et al., 1993a). In contrast to the latter findings are the results obtained by a microdialysis method, which show an increased release of dopamine in the striatum after administration of CGP 37849 or CPP to that structure with a microdialysis cannula (Imperato et al.,

1990; Wędzony et al., 1991). Furthermore, an increase in the density of D_1 receptors in the striatum after CGP 37849 administered repeatedly (10 mg/kg p.o., twice daily for 14 days) was found by a radioactive ligand binding (Maj et al., 1993a).

Single injections of non-competitive NMDA antagonists (MK-801, phencyclidine, memantine and others) were found to increase the dopamine metabolism in limbic structures (the nucleus accumbens, olfactory tubercle, olfactory bulb, hippocampus) and in cortical areas (the frontal and prefrontal cortex, pyriform cortex, cingulate cortex) (Deutch et al., 1987; Rao et al., 1990; Tanii et al., 1990; Löscher et al., 1991; Svensson et al., 1991; Irufune et al., 1991; Bubser et al., 1992). There has been, however, some disagreement about the influence of competitive antagonists on the dopamine metabolism in the above-mentioned limbic structures. According to some authors, CPP, CGS 19755 and CGP39551 do not increase the dopamine metabolism in the prefrontal and pyriform cortices or in the nucleus accumbens after single injections (Rao et al., 1990, 1991; Bubser et al., 1992). In contrast, Svensson et al. (1991) found an increase in the DOPAC level after single injections of CPPene in the limbic forebrain, and Maj et al. (1993a) reported a similar effect after repeated administration of CGP 37849 (10 mg/kg p.o., twice daily for 14 days) in the nucleus accumbens.

It has been widely accepted that the striatum is responsible for the antiparkinsonian effect of dopaminomimetics. However, the role of striatal dopaminergic mechanisms in the antiparkinsonian effect of competitive NMDA receptor antagonists has been unclear, so far. After peripheral administration, these compounds do not seem to stimulate dopaminergic neurons in this structure, yet at least one of them (CGP 37849) might compensate for the loss of dopaminergic transmission by increasing the density of postsynaptic D_1 receptors (Maj et al., 1993a). It is likely that a dopaminergic mechanism in the striatum plays a role in the action of non-competitive antagonists only. If this is the case, these compounds may affect dopaminergic neurons indirectly, i.e. via blockade of the NMDA receptors localized on neurons of the GABAergic pathway which leads from the striatum to the substantia nigra pars compacta. Abolition of the stimulating effect of glutamic acid on these neurons may cause their inhibition, a decrease in the GABA release in the substantia nigra pars compacta and, in consequence, disinhibition of dopaminergic neurons of the nigrostriatal pathway (Carlsson and Carlsson, 1989 a, b, 1990).

One can suggest, however, that the antiparkinsonian effect of NMDA receptor antagonists develops via their action on other structures which have the dopaminergic innervation, such as the prefrontal cortex or nucleus accumbens septi. It has been found that in Parkinson's disease there also occurs loss of dopaminergic innervation in the nucleus accumbens and many cortical areas (Hornykiewicz and Kish, 1987). Moreover, it has been shown that blockade of dopamine receptors in both these structures evokes catalepsy (Klockgether et al., 1988; Ossowska et al., 1990a), while administration of apomorphine to the nucleus accumbens septi abolishes the reserpine-induced akinesia (Andén and Johnels, 1977). However, according to the general opinion, the loss of dopaminergic innervation in the cerebral cortex and limbic

structures is connected with the dementia and depression observed in certain parkinsonian patients rather than with primary symptoms of this disease (Deutch, 1993). Moreover, on the basis of experiments in which the c-fos expression was used as a marker of metabolically activated neurons, it has been proposed that the nucleus accumbens is engaged in the antipsychotic, but not the extrapyramidal, effects of neuroleptics (Deutch, 1993). Therefore it may be concluded that stimulation of the dopaminergic neurotransmission in this structure by NMDA antagonists can be related to their adverse psychotomimetic effects rather than presumable therapeutic ones.

The effect of NMDA receptor antagonists on parkinsonian symptoms after MPTP in monkeys

In animal studies with new compounds which may become efficient drugs in humans, there always emerges a problem of the adequacy of an animal model in relation to symptoms of a disease. Therefore in studies into the role of NMDA receptor antagonists in symptoms of Parkinson's disease, the experiments conducted on monkeys treated with MPTP turned out to be the most important. Because of the phylogenetic relationship between monkeys and man, this model seems to be the most closely related to Parkinson's disease, though it does not fully represent, either, changes occurring in this disease (Hornykiewicz et al., 1989; Greenamyre, 1993). Experiments concerning the effect of the non-competitive antagonist MK-801 on parkinsonian symptoms in monkeys yielded poor results. MK-801 in doses of 0.01–0.1 mg/kg did not attenuate bradykinesia (Close et al., 1990), augmented parkinsonism (mainly akinesia) (Crossman et al., 1989; Rupniak et al., 1992), diminished the therapeutic effect of l-DOPA (Crossman et al., 1989); when given jointly with l-DOPA, it evoked dystonia and the loss of balance (Rupniak et al., 1992). Only the competitive NMDA receptor antagonist CPP (0.1–1.56 mg/kg) enhanced the therapeutic effect of L-DOPA (Löschmann et al., 1991).

Side effects of NMDA receptor antagonists

Non-competitive NMDA receptor antagonists (phencyclidine, ketamine, amantadine, memantine and MK-801) evoke a number of undesirable symptoms. Psychotomimetic effects of these drugs have been reported by several authors (Chen et al., 1966; DiMascio et al., 1976; Hausner, 1980; Flaherty and Bellur, 1981; Wilcox, 1985; Nestelbaum et al., 1986; Balster, 1987; Hermesh et al., 1989; Porter, 1989; Johnson and Jones, 1990; Wilcox and Tsuang, 1990; Javitt and Zukin, 1991; Riederer et al., 1991a,b; Kornhuber and Weller, 1993). However, the potency of various non-competitive antagonists in inducing these effects was reported to be different. Phencyclidine, (PCP) which was developed as an anaesthetic agent, is a widely abused psychotomimetic drug which induces a state which closely resembles schizophrenia. The PCP-induced psychosis includes both positive (e.g. hallucinations, paranoia) and negative (e.g. emotional withdrawal, motor retardation) schizofrenic symptoms. The PCP-induced psychosis also uniquely incorporates a formal thought disorder and a neuropsychological deficit associated with schizophrenia (Javitt and Zukin, 1991). Moreover, further evidence also implicates

that PCP abuse may lead to later schizofrenic episodes, which suggests that PCP may actually precipitate latent psychosis (Johnson and Jones, 1990).

Ketamine is still used for anaesthesia in humans, despite the fact that awakening is frequently accompanied with disagreable dreams, excitement and halucinations (Marshall and Wollman, 1985).

In contrast to PCP, 1-amino-adamantanes (amantadine and memantine) were considered to be better tolerated and non-addictive (Kornhuber and Weller, 1993). It was reported that amantadine provoked psychotic symptoms only in a small minority of parkinsonian patients or in healthy persons (Flaherty and Bellur, 1981; Riederer et al., 1991a). However, when used in schizofrenic patients in order to control the neuroleptic-induced side-effects, the latter drug causes worsening of psychotic symptoms or even reccurence of psychosis (DiMascio et al., 1976; Hausner, 1980; Wilcox, 1985; Nestelbaum et al., 1986; Wilcox and Tsuang, 1990; Hermesh et al., 1989; Kornhuber and Weller, 1993).

MK-801 – which has been used for a short time in epileptic patients – has been reported to produce only minimal, if any, psychotomimetic effects at concentrations sufficient to reduce seizures (Troupin et al., 1986; Porter, 1989).

Moreover, it was found by a light and an electron microscopies that these compounds (MK-801, phencyclidine, ketamine) evoked pathomorphological changes, e.g. vacuolization in neuronal cells in rats (Olney et al., 1989). Those changes were transient after low doses of the drugs in question, but prolonged (over 48h) after high ones.

Studies into side-effects of competitive NMDA receptor antagonists have not been completed, as yet, though it seems that at least some of these compounds have a proamnesic effect in animals and humans (Morris et al., 1986; Sveinbjornsdottir et al., 1993). Nonetheless, the first publication on the use of CPPene in epileptic humans does not report any psychotomimetic side-effects of this drug (Sveinbjornsdottir et al., 1993).

The role of the AMPA receptor antagonist in animal models of Parkinson's disease

Up to the present, very few studies into the role of compounds acting on other than NMDA receptor of excitatory amino acids have been carried out. Such a situation has been caused mainly by the lack of selective antagonists which penetrate the blood-brain barrier. The only, relatively selective AMPA receptor antagonist that penetrates into the brain is the compound NBQX. This compound binds to AMPA receptors with a 30-fold stronger affinity than to kainic ones; furthermore, it shows no affinity for 10 other brain receptors, including the NMDA one (Sheardown et al., 1989).

NBQX administered in doses of 5–30 mg/kg did not antagonize akinesia in rats with monoamines depleted by reserpine given jointly with αMT (Klockgether et al., 1991). Similarly, NBQX (12.5 mg/kg) diminished neither the catalepsy induced by the selective dopamine D2 receptor antagonist raclopride, nor that induced by the selective dopamine D1 receptor antagonist

SCH 23390 (Papa et al., 1993). However, according to Klockgether et al. (1991), when given jointly with an ineffective dose of L-DOPA (50 mg/kg) + benserazide (100 mg/kg), NBQX potently increased the locomotor activity in reserpine and α-MT-treated rats.

The latter authors also postulated that NBQX (5–30 mg/kg) reduced the reserpine + αMT-induced muscular rigidity in rats, measured by a tonic electromyographic activity in the gastrocnemius muscle. When used in a dose of 5 mg/kg, together with an ineffective dose of L-DOPA, NBQX showed synergistic effect (Klockgether et al., 1991).

According to Löschmann et al. (1991), NBQX (0.1–12.5 mg/kg) alone did not evoke contralateral rotations in rats with an unilateral lesion of the nigrostriatal pathway, but enhanced the contralateral rotations induced by a low dose of L-DOPA (25 mg/kg) + benserazide (100 mg/kg).

According to Klockgether et al. (1991) NBQX antagonized the reserpine + αMT-induced akinesia and muscular rigidity after injection to the nucleus subthalamicus, substantia nigra pars reticulata and nucleus entopeduncularis (an equivalent of the internal segment of the globus pallidus). On the other hand, no effect of intrastriatal administration of this drug on akinesia or muscular rigidity was observed. Similarly, when administered to the striatum, the non-selective AMPA receptor antagonist GDEE did not affect the haloperidol-induced catalepsy (Yoshida et al., 1991).

According to Klockgether et al. (1991), when administered to parkinsonian monkeys pretreated with MPTP, NBQX (0.25–10 mg/kg), attenuated tremor and bradykinesia, improved the body posture and gait, and enhanced the therapeutic effect of L-DOPA; at the same time, no distinct side-effects such as dyskinesias, vomiting or psychotic disorders were observed. In contrast to Klockgether et al. (1991), Löschmann et al. (1991) did not show any therapeutic effect of NBQX (6.25 mg/kg) alone in parkinsonian monkeys, yet they demonstrated enhancement of the therapeutic effect of L-DOPA in that model.

The finding of Klockgether et al. (1991) was not confirmed by Luquin et al. (1993), who did not find any beneficial effects of NBQX (1–4 mg/kg) given alone or in combination with the specific dopamine D_2 receptor agonist (+)-PHNO, or the partial dopamine D_1 receptor agonist CY 208–243.

Summing up, the antiparkinsonian effect of AMPA antagonists has not been sufficiently documented, so far, and effects described by Klockgether et al. (1991) and Löschmann et al. (1991) require further confirmation. Moreover, little is known about their putative side-effects. Therefore these compounds need to be further studied in detail.

The role of excitatory amino acid receptors in degeneration of dopaminergic neurons in models of Parkinson's disease

The cause of Parkinson's disease in unknown, and so are pathological factors which evoke selective degeneration of dopaminergic neurons in it. It has been conclusively established that glutamic acid – apart from its physiological role

as a neurotransmitter – may also cause damage to neurons under certain conditions. Its degenerative effect plays some role in hypoglycemia, cerebral hypoxia and, possibly, also in Alzheimer's disease and in processes of ageing of the nervous system. It has been found that the neurodegenerative effect of glutamic acid may take place via NMDA-, AMPA- and kainate receptors (for ref. see Ossowska, 1993).

The role of glutamic acid in degeneration of dopaminergic neurons of the substantia nigra is unclear. Glutamic acid is one of the most widespread neurotransmitters in the brain; hence it is unlikely that it is the only factor that causes a selective damage to dopaminergic neurons, which is the case in Parkinson's disease. On the other hand, it may be assumed that the compound in question could be the substance supporting the action of neurotoxins which are directed towards a selective degeneration of these neurons. It is well known that the substantia nigra pars compacta receives a glutamatergic projection from the cerebral cortex (Fonnum, 1984), and that dopaminergic neurons of the substantia nigra pars compacta have NMDA receptors on their surface and are stimulated – via these receptors – by glutamic acid (Overton and Clark, 1992). Moreover, the striatum, where dopaminegic nigrostriatal neurons terminate, also receives glutamatergic innervation from the cortex and shows a high density of NMDA, AMPA and kainate receptors (Fonnum, 1984; Albin et al., 1992; Tallaksen-Greene et al., 1992). It was also found that stimulation of NMDA receptors increases the excitability of nigrostriatal dopamine terminals (Overton and Clark, 1991). Hence it seems that glutamic acid influences the nigrostriatal dopaminergic neurons at the level of both their cell bodies and terminals.

Therefore the influence of antagonists of excitatory amino acid receptors on the effects of the two toxins selectively damaging dopaminergic neurons, methamphetamine and MPTP, was intensively studied.

The effect of antagonists of excitatory amino acid receptors on the methamphetamine neurotoxicity

Sonsalla et al. (1989, 1991, 1992a) examined the effect of NMDA receptor antagonists on the methamphetamine neurotoxicity in mice. In their experiments, degeneration of dopaminergic neurons was assessed by means of a decreased level of dopamine and its metabolites DOPAC and HVA, as well as by a diminished activity of tyrosine hydroxylase. The above authors found that both non-competitive NMDA receptor antagonists (MK-801, phencyclidine, ketamine) as well as ifenprodil and SL 82.0715 and competitive NMDA receptor antagonists (CGS 19755, NPC 126126) showed a protective effect against the lesion of dopaminergic neurons by methamphetamine. By comparing doses (in millimole/kg) of the respective compounds, the authors observed that the most potently acting compound was (+)MK-801 (0.02 mmol/kg), and then – in descending order – (−)MK801 (0.09 mmol/kg), phencyclidine (0.33 mmol/kg), ifenprodill (0.33 mmol/kg), SL 82.0715 (0.58 mmol/kg), CGS 19755 (0.90 mmol/kg), ketamine (1.68 mmol/kg) and NPC 126126 (3.07 mmol/kg) (Sonsalla et al., 1992a). The results obtained

by Sonsalla et al. (1992a) concerning the protective effect of MK-801 were confirmed by O'Dell et al. (1992) and Marshall et al. (1993).

The enhanced neurotoxicity of metamphetamine, caused by unilateral administration of NMDA to the striatum, confirmed the role of NMDA receptors in its action (Sonsalla et al., 1992a).

In contrast to the NMDA receptor whose stimulation by glutamic acid seems to be involved in the degenerative effect of methamphetamine on dopaminergic neurons, no such role has been found for the AMPA receptor, so far. According to Sonsalla et al. (1992a), neither NBQX administered peripherally in a dose of 30 mg/kg, nor another agonist of AMPA receptors – quisqualic acid injected directly into the striatum affected the methamphetamine neurotoxicity.

The effect of NMDA receptor antagonists on MPTP neurotoxicity

Data concerning the influcence of NMDA receptor antagonists on the MPTP-induced neurotoxicity in rodents are controversial.

A study by Turski et al. (1991) presents some evidence for the concept of participation of NMDA receptors in the MPTP neurotoxicity in rats. These autors administered the active MPTP metabolite MPP^+ directly to the substantia nigra pars compacta, which resulted in a dramatic fall in the number of dopaminergic neurons. That effect was counteracted by simultaneous administration of the competitive NMDA receptor antagonist AP7 to that structure. Besides, MK-801 injected peripherally in doses of 1.68–3.37 mg/kg at 0.5 h before MPP^+ showed protection against the neurotoxic effect of that compound, assessed by the number of degenerated dopaminergic neurons only at 4 h, but not at 24 or 72 h, after its administration. A similar protective effect was also shown by the competitive antagonist CPP (12.6–25.2 mg/kg). However, when MK-801 (3.37 mg/kg) or CPP (25.2 mg/kg) were given chronically – 6–18 times (!), every 4 hours – the protection given by those compounds was *permanent*, since the number of dopaminergic neurons did not decline within 7 days after MPP^+ administration.

However, according to Sonsalla et al. (1992a) MK-801 showed no protection against the lesion of dopaminergic neurons caused by MPTP administered to mice. In their studies MPTP was administered four times at 2-hour intervals. Sonsalla et al. (1992a) found that MK-801 administered in a dose of 2.5 mg/kg (twice, at 15 min before and 3 h after the first injection of MPTP) did not prevent the MPTP-induced decrease in striatal dopamine level and in activity of tyrosine hydroxylase, measured 3 days after the first injection of MPTP.

Turski et al. (1991) asserted that the effect of twofold MK-801 administration (a procedure used by Sonsalla et al., 1992a) was too transient to be sufficient for the protection against the long-lasting neurodegenerative effect of a neurotoxin such as MPTP. According to the latter authors, chronic administration seems to be necessary for the therapeutic effect of the drug in question. This concept is in line with the results of Storey et al. (1992), who showed that MPP^+ administered intrastriatally to rats had a long–lasting

effect on the energetic metabolism of neurons. These authors demonstrated that MPP^+ causes a 3-4-fold decrease in the ATP level, which persists for over 48 h. However, the same authors found that MK-801 (5 mg/kg), administered 6 times every 4 hours, protected dopaminergic neurons from the neurotoxic effect of MPP^+ (measured by losses of dopamine and DOPAC levels) within 24 h only. When animals were killed 7 days after MPP^+, Storey et al. (1992) did not observe any protective effects of MK-801.

Sonsalla et al. (1992b) repeated Turski's experiment in rats. They injected MPP^+ to the substantia nigra pars compacta. MK-801 was injected in doses of 2.2 mg/kg 6 (but not 18) times at 4 hour intervals. When the animals were killed after 7–11 days, no protective effect of MK-801 was found. No such effect was observed, either, when MK-801 (6×2.5 mg/kg) was injected likewise to MPTP-treated mice which were also killed after 7–11 days.

Recently, Brouillet and Beal (1993) who used the same schedule of MPTP injections as Sonsalla et al. (1992a) found that MK-801 (4 mg/kg) and CGP 39551 (35 mg/kg), administered 6 times, partially but significantly attenuated the striatal dopamine depletions induced by that neurotoxin in mice after both 24h and 1 week.

Moreover, MK-801 (0.010 mg/kg) administered to monkeys (Macaca fascicularis) 7 times daily for 5 days, jointly with MPTP given once daily, prevented degeneration of dopaminergic neurons (measured as decreases in the level of dopamine and its metabolites DOPAC and HVA, as well as by the number of dopamine perikarya in the substantia nigra pars compacta) 7 days after the last dose of MPTP (Zuddas et al., 1992). Moreover, these authors found that, apart from preventing degeneration of dopaminergic neurons, MK-801 prevented also the appearance of parkinsonian symptoms after MPTP, though – as has been mentioned earlier – it did not inhibit the already developed parkinsonian symptoms (Crossman et al., 1989; Close et al., 1990; Rupniak et al., 1992).

The cause of the discrepancies between all the above-mentioned studies (Turski et al., 1991; Storey et al., 1992; Sonsalla et al., 1992a,b; Zuddas et al., 1992; Brouillet and Beal, 1993) has not been found, as yet. Differences between species (mice, rats, monkeys) and rat strains (Sprague-Dawley: Sonsalla et al., 1992b and Storey et al., 1992, versus Wistar: Turski et al., 1991) may play a certain role in their sensitivity to MPTP, MPP^+ or MK-801; also different localization of MPP^+ injections or other minor methodological differences may be of importance here.

Summing up, it seems that no definite conclusion can be drawn from the experiment carried out on small experimental animals on a possible role of the NMDA receptor in MPTP neurotoxicity. Moreover, it seems that the conclusions emerging from the experiments with intrastructural injections of MPP^+ are of a minor value, because of a marked non-specificity of this neurotoxin. It is noteworthy to mention that the doses of MK-801 used in the study in question were very high, hence the non-selective effects of this drug cannot be excluded. Experiments carried out on monkeys seem to be more promising, but they must be confirmed by further studies. Moreover, it still remains an open question how far the neurodegenerative

action of amphetamines and MPTP reflects the pathological changes that occur in Parkinson's disease. Nevertheless, the search for the protective effects of NMDA antagonists in animal models of this disease promises to be successful.

The role of receptors of excitatory amino acids in the neurotoxic effect of L-DOPA and 6-OHDOPA

Studies conducted on isolated spinal motoneurons of frogs, as well as on cultured hippocampal neurons of rats indicate that L-DOPA, a natural precursor of dopamine and a commonly used antiparkinsonian drug, evokes weak excitatory responses (Biscoe et al., 1976; Olney et al., 1990). Moreover, its ortho-hydroxylated derivative 6-hydroxydopa (6-OHDOPA) has been reported to be a powerful neuronal excitant in the isolated chicken retina, frog spinal motoneurons and cultured rat hippocampal and cortical neurons (Biscoe et al., 1976; Aizenman et al., 1990; Olney et al., 1990; Rosenberg et al., 1991; Aizenman et al., 1992). The excitatory responses evoked by both those compounds were antagonized by the non-NMDA receptor antagonist CNQX, but not by AP5, a competitive NMDA receptor antagonist (Aizenman et al., 1990; Olney et al., 1990; Rosenberg et al., 1991).

It was also found that both L-DOPA and 6-OHDOPA are neurotoxic compounds. Olney et al. (1990) reported that L-DOPA at a high concentration of 1 – 2 mM caused degeneration of embryonal retinal neurons in chickens. 6-OHDOPA was suggested to be a powerful neurotoxin, since already at a concentration of 150 μM it caused neuronal degeneration in the same model (Olney et al., 1990). 6-OHDOPA also showed a neurotoxic effect when it was administered into the substantia nigra, striatum and frontal cortex of rats and to the rat's cortical cultures (Olney et al., 1990; Rosenberg et al., 1991; Aizenman et al., 1992). The neurotoxic effects of L-DOPA and 6-OHDOPA were counteracted by the non-NMDA receptor antagonist CNQX, but not by the non-competitive NMDA receptor antagonist MK-801 (Olney et al., 1990). The above-mentioned studies indicated that both those substances (L-DOPA and 6-OHDOPA) could perform excitotoxic action directly, or indirectly via non-NMDA receptors. This conclusion was supported by biochemical studies which showed that 6-OHDOPA (100 μM) displaced 80% of [^{3}H]AMPA, and levodopa (100 μM) 9% of it from striatal binding sites (Cha et al., 1991). Moreover, 6-OHDOPA and L-DOPA, used at the above concentrations, displaced 20% of [^{3}H]kainate from striatal binding sites (Cha et al., 1991). These results support the concept that at least 6-OHDOPA is a potent agonist of non-NMDA receptors (mainly AMPA receptors). Aizenman et al. (1990, 1992) and Rosenberg et al. (1991) postulated that not 6-OHDOPA itself, but its oxidation product 6-OHDOPA quinone is an excitotoxic, non-NMDA receptor agonist.

Irrespective of the fact that L-DOPA seems to be a very weak excitotoxin only, it cannot be excluded that in pathological states this substance (endo- or exogenic) may be transformed into 6-OHDOPA by way of abnormal hydroxylation. If such a possibility turns out to be true, 6-OHDOPA could contribute

to the pathophysiology of neurodegenerative diseases such as Parkinson's disease.

Conclusions

On the basis of the review presented above, the following conclusions may be drawn:

1. disturbances in the glutamatergic transmission in various brain structures seem to play a significant role in the development of symptoms of Parkinson's disease;
2. the NMDA-receptor blocking component may give a substantial therapeutic effect in antiparkinsonian drugs; a similar contribution of AMPA-receptor blocking component of the drugs has not been sufficiently documented, so far;
3. compounds blocking NMDA receptors may possibly prevent the development of Parkinson's disease; this presumption needs, however further studies;
4. side effects of NMDA receptor antagonists may be a limiting factor in the use of these compounds in humans.

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