

Aminoadamantanes as NMDA Receptor Antagonists and Antiparkinsonian Agents — Preclinical Studies

W. DANYSZ^{a,*}, C. G. PARSONS^a, J. KORNHUBER^b, W. J. SCHMIDT^c
AND G. QUACK^a

^a*Dept of Pharmacology, Merz + Co. Frankfurt/Main, Germany*

^b*Dept of Psychiatry, University of Göttingen, Göttingen, Germany*

^c*Zoological Institute, Dept of Neuropharmacology, University of Tübingen, Tübingen, Germany*

DANYSZ, W., C.G. PARSONS, J. KORNHUBER, W. J. SCHMIDT, AND G. QUACK. *Aminoadamantanes as NMDA receptor antagonists and antiparkinsonian agents — preclinical studies.* NEUROSCI BIOBEHAV REV 21(4) 455–468, 1997.—Aminoadamantanes such as 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) are N-methyl-D-aspartate (NMDA) receptor antagonists which show antiparkinsonian-like activity in animal models and in Parkinson's patients. The issue of whether NMDA antagonism plays a role in the symptomatological antiparkinsonian activity of amantadine and memantine is addressed by comparing: behaviourally effective doses, serum/brain levels, and their potency as NMDA receptor antagonists. In the case of memantine, blockade of NMDA receptors is probably the only mechanism responsible for antiparkinsonian activity, whereas for amantadine the situation is clearly far more complex. There are a number of differences between memantine and amantadine both in vitro and in vivo, and although NMDA receptor antagonism certainly participates in the antiparkinsonian activity of amantadine, other effects, some of which are elusive, also play a role. Moreover, it has been suggested that the pathomechanism of Parkinson's disease involves excitotoxic processes and that treatment with NMDA receptor antagonists might also slow the progression of neurodegeneration. If this claim is true, such an effect could be achieved with amantadine and memantine which show neuroprotective activity in animals at therapeutically relevant doses. © 1997 Elsevier Science Ltd.

memantine amantadine NMDA receptors Parkinson's disease animal models neuroprotection mechanism of action
serum levels brain levels review

1. AMINOADAMANTANES AS ANTIPARKINSONIAN AGENTS — HISTORICAL BACKGROUND¹

The discovery that degeneration of dopaminergic pathways in the basal ganglia is the main deficiency in Parkinson's disease provided the rationale for substitution therapy with dopamine agonists (32). The use of the dopamine precursor L-DOPA has proven to be the most successful approach in this respect (8), although several alternative therapies have also been proposed. These include among others, aminoadamantanes such as 1-aminoadamantane (amantadine) and 1-amino-3,5-dimethyladamantane (memantine) (11,101,114,115) [for reviews see: (7,64,70,87,130,149)]. Although direct dopaminomimetic activity of therapeutically-relevant concentrations of amantadine or memantine has never been shown, it is assumed on the basis of indirect in vivo evidence. Thus, amantadine and memantine produce some effects in animal models which are indicative of dopaminomimetic activity, e.g. stereotypy,

increase in locomotion in reserpinized animals, or rotation in rodents with unilateral lesion of the nigrostriatal dopaminergic system (7,24,70). Therefore, in the 1970s, dopaminomimetic activity of amantadine and memantine found wide acceptance in the scientific community as the primary mechanism of action—partly because of a lack of alternatives at that time. This assumption was the expression of a general tendency in neuropharmacology in the 1960s and 1970s to propose a precise mechanism of action at the neuronal/receptor level on the basis of results from behavioural studies. This trend obviously neglected the complexity of neuronal networks and interactions between neuronal systems. The idea that dopaminomimetic activity was the principal mechanism of action of amantadine persisted until the late 1980s. However, several studies at this time provided the impetus for the re-evaluation of such one-sided concepts and gave precedence for a new therapeutical approach, i.e. N-methyl-D-aspartate (NMDA) receptor antagonism.

*Dept of Pharmacology, Merz + Co., Eckenheimer Landstrasse 100–104, 60318 Frankfurt/Main, Germany. Tel.: (+49)-69-15-03-564; Fax: (+49)-69-59-62-150; e-mail: 0691503-0003@t-online.de

¹In the present text, reference to an author's name followed by 'unpublished' refers to unpublished data obtained by a given author as a result of cooperation with Merz + Co. More details are available upon request.

Following the establishment of the role of glutamate as a major neurotransmitter (139) glutamate receptors attracted substantial attention as possible targets for drug development (25,33,75). In this respect, ionotropic glutamatergic receptors of the NMDA type have been studied the most. This was because of the early availability of several selective antagonists and the discovery of a wide range of

possible therapeutic applications including: neuroprotection, anxiolytic activity, antidepressive activity, antiepileptic properties and antiparkinsonian actions. Specifically in the case of antiparkinsonian activity, Schmidt et al. (110) showed that the competitive NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP-5) increased activity when injected directly into the striatum; and then Schmidt

TABLE 1
COMPILATION OF IN VITRO ACTIONS OF AMANTADINE

Studied effect	Assay	Potency μM	Ref.
NMDA channel	[³ H]-(+)-MK-801 (human cortex)	10.0 (K _i)	(58)
NMDA channel	[³ H]-(+)-MK-801 (rat cortex)	56.0 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat cortex)	215 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus CA1/CA3)	56.1 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus CA1)	256 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus dentate gyrus)	90.1 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus dentate gyrus)	228 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat striatum)	76.3 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat striatum)	183 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (cerebellum)	92 (IC ₅₀)	(98)
NMDA channel	Patch clamp (hippocampus, - 100 mV)	18.6 (IC ₅₀)	(96)
NMDA channel	Patch clamp (striatum, - 100 mV)	12.4 (IC ₅₀)	(96)
NMDA channel	Patch clamp (superior colliculus, - 70 mV)	71 (IC ₅₀)	(97)
NMDA channel	NMDA-induced [³ H]-ACh release in striatal slices	30 (IC ₅₀)	(68)
NMDA channel	NMDA-induced [³ H]-ACh release in striatal slices	20 (IC ₅₀)	(124)
NMDA channel	NMDA-induced [³ H]-NA release	29 (IC ₅₀)	Behl, unpub.
NMDA channel	NMDA toxicity in cultured retinal ganglion cells	50 (IC ₅₀)	(19)
NMDA channel	NMDA toxicity in cultured cortical cells	30 (IC ₅₀)	(69)
NMDA channel	Glutamate toxicity in cultured cortical neurones	< 100	(141)
NMDA channel	Glutamate toxicity in cultured cerebellar neurones	< 100	(141)
NMDA channel	Glutamate toxicity in cultured dopaminergic striatal neurones	> 100	(141)
Ach (1A nicotinic)	Patch clamp hippocampal neurones	6.5 (IC ₅₀)	(74)
Ach (nicotinic)	[³ H]-HTX	40 (K _i)	(5)
Ach (nicotinic)	Rat phrenic nerve-diaphragm	20 (IC ₅₀)	Grossmann, unpub.
Ach (muscarinic)	[³ H]-QNB	40 (K _i)	(5)
Sigma	[³ H]-(+)-pentazocine	20.3 (K _i)	(63)
5-HT	[³ H]-5HT	> 100	(149)
5-HT release	Synaptosomal 5-HT release	> 100 (stim)	(149)
5-HT uptake	Synaptosomal high affinity 5-HT uptake	57 (IC ₅₀)	(146)
5-HT uptake	[³ H]-5HT uptake in rat whole brain slices	100 (c.a. IC ₅₀)	(44)
5-HT uptake	5-HT uptake in human platelets	200 (IC ₅₀)	Demisch, unpub.
Adenylate cyclase	Basal cAMP levels in striatal slices (stimulation)	10 (c.a. EC ₅₀)	(48,49)
Adenylate cyclase	Basal cAMP levels in striatal slices	> 10	(52)
Adenylate cyclase	Basal cAMP levels in striatal slices	> 100	Riederer, unpub.
AMPA	Patch clamp (hippocampus, superior colliculus)	> 300	(96,97)
AMPA	[³ H]-AMPA binding	> 100	(18)
DA release	[³ H]-DA release in striatal slices (stimulation)	50-100	(47)
DA release	[³ H]-DA release from striatal synaptosomes	> 100	(13)
DA ₁	DA-stimulated cAMP	> 10	Riederer, unpub.
DA ₁	DA-stimulated cAMP	> 100	(52)
Dopamine uptake	[³ H]-dopamine uptake in rat whole brain slices	100 (c.a. IC ₅₀)	(44)
Dopamine uptake	[³ H]-dopamine uptake in rat cortical slices	50 (IC ₅₀)	(44)
Dopamine uptake	[³ H]-dopamine uptake in rat striatal slices	1000 (c.a. IC ₅₀)	(44)
Dopamine uptake	[³ H]-dopamine uptake in striatal homogenates	220 (IC ₅₀)	(30)
Dopamine uptake	[³ H]-NPA	1000 (c.a. IC ₅₀)	(30)
GABA	Patch clamp (hippocampus)	> 100	(96)
Glycine _A	[³ H]-Strychnine	> 10	Larue, unpub.
Glycine _A	Patch clamp - cultured spinal cord neurones	> 100	(65)
MAO _A	[¹⁴ C]-5-HT metabolism in vitro	> 100	(147)
MAO _A	[¹⁴ C]-5-HT metabolism in vitro	> 1000	Demisch, unpub.
MAO _B	[¹⁴ C]-benzylamine metabolism in vitro	> 1000	Demisch, unpub.
VAKC (ATP-sens)	Patch clamp in HIT-T15 cell line	120 (K _i)	(6)

c.a. — refers to approximate concentration that produces 50% inhibition or stimulation. Abbreviations used: 5-HT, 5-hydroxytryptamine (serotonin); Ach, Acetylcholine; AMPA, (S)- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ATP, Adenosine triphosphate; cAMP, Cyclic adenosine-monophosphate; cGMP, Cyclic guanosine-monophosphate; CCK, Cholecystokinin; CYP, Cyanopindolol; DA, Dopamine; DADLE, D-al⁵-leu enkephalin; DAGO, D-al²-N-methyl-phe⁴glyol⁵ enkephalin; EKC, ethylketocyclazocine; fEPSP, Field excitatory postsynaptic potentials; GABA, γ -aminobutyric acid; Glycine_A Inhibitory glycine receptor; Glycine_B Glycine recognition site at NMDA receptor complex; HTX, perhydrohistrionicotoxin; MAO, Monoamine oxidase; NA, Noradrenaline; NBTI, Nitrobenzylthioinosine; NMDA, N-methyl-D-aspartate; NPA, N-propylnorapomorphine; 8-OHDPAT, 8-Hydroxy-dipropylaminotetralin; PGE, Prostaglandin esterase; PIA, N⁶-phenylisopropyladenosine; QNB, Quinuclidinyl benzilate; TBPS, *t*-butylbicyclophosphorothionate; VACC, Voltage-activated calcium channel; VAKC, Voltage-activated potassium channel; VASC, Voltage-activated sodium channel

and Bubser (111) reported that the same treatment also antagonised haloperidol-induced catalepsy. Carlsson and Carlsson (17) found that the uncompetitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate [(+)-MK-801] attenuates hypokinesia in mice depleted of monoamines. Moreover it was demonstrated that both phencyclidine (PCP) and (+)-MK-801 produced ipsilateral rotation in rats with unilateral lesion of the SNc (substantia nigra pars compacta), (85,118). An important step forward was the discovery that some existing antiparkinsonian agents were also able to inhibit NMDA receptors. The most important of these was probably the revelation of Kornhuber and colleagues (58,59), and Bormann (10) that memantine and amantadine, both of which have been used in the treatment of Parkinson's disease, inhibit NMDA receptors at therapeutically relevant concentrations.

2. COMPILATION OF IN VITRO AND IN VIVO ACTIONS OF MEMANTINE AND AMANTADINE

2.1. *In vitro*

In electrophysiological experiments (patch clamp) memantine inhibits NMDA receptors at low micromolar concentrations (1–3 μM , see Table 2) whilst amantadine is some 4–40-fold less potent depending on the neuronal type (Table 1). In binding experiments the potency of both agents is somewhat higher, i.e. K_i s of 0.5–2 and 20–80 μM respectively (Table 1 Table 2). Both memantine and amantadine inhibit NMDA-stimulated Ach release in the rat/rabbit striatum with IC_{50} s of approximately 2–5 and 20–30 μM respectively (68,88,124). This indirect anticholinergic activity probably plays a pivotal role in mediating the antiparkinsonian effects of NMDA receptor antagonists *in vivo* as suggested by Di Chiara and co-workers (26).

Therapeutic serum concentrations of amantadine range from 5 to 14 μM [Table 3, (61)] whereas those of memantine range from 0.4 to 1.0 μM (Table 4; Quack, unpublished data). On the basis of cerebrospinal fluid (CSF) sampling in animals and humans it can be concluded that the effective free brain concentrations of both agents are slightly higher than free serum levels, but lower than total serum levels (ca. 50% albumin binding is seen). This seems true, in spite of the fact that the content of brain homogenates is much higher (10–30 \times), probably due to lysosomal accumulation [(46,62), Tables 3 and 4]. For memantine, only effects seen *in vitro* with EC_{50} s below 2–3 μM seem relevant for therapeutic effects while for amantadine the upper limit of therapeutic relevance is probably around 20–30 μM . In this respect it should be noted that *in vivo* concentrations would not necessarily have to reach these subjective 50% values to be of therapeutic relevance, but should certainly not be more than 2–3 fold lower. As such, the fact that enhancement of DA (dopamine) release or inhibition of DA uptake is not seen until concentrations of 100–300 μM are reached (47,64,68,124,141) excludes this as the primary mechanism of action of the aminoadamantanes *in vivo*. Bearing this in mind, it seems clear from Table 2 that NMDA receptor antagonism is the primary (if not only) therapeutically relevant mechanism of memantine action — at least at our present stage of knowledge. However, for amantadine,

additional effects such as at sigma-1 receptors with a $K_i = 20 \mu\text{M}$ [(63), Table 1] interactions with neuronal and non-neuronal nicotinic receptors [(5,73,74,129,132), Table 1] or enhancement of noradrenergic transmission (35,70,86) must also be taken into account.

2.2. *Biochemical studies on the in vivo effects of aminoadamantanes*

2.2.1. *Pharmacokinetic aspects*

The serum/CSF concentrations achieved at given doses of memantine or amantadine determine the relevance of the observed biochemical effects of these agents to their therapeutic efficacy — or in other words, actions observed above a given dose or concentration are irrelevant. Here these aspects are discussed on the basis of experiments in rats and on the assumption that effective extracellular levels in the brain are slightly lower than total serum levels [see also refs (24,60–62) for further discussion]. When acute *i.p.* administration of amantadine (hydrochloride) is employed, injection of 25 mg kg^{-1} leads to serum levels of 6 μM (60–90 min) while this is doubled after 46 mg kg^{-1} [Danysz et al., unpublished, (100), Table 3]. A level of 50 mg kg^{-1} can be considered to be the upper limit of therapeutically relevant effects after acute administration. For memantine, acute administration of 5 or 10 mg kg^{-1} leads to serum levels of 1.0 and 2.3 μM respectively [(24) Table 4]; thus, the maximal acute dose that can be considered to be of therapeutic relevance would seem to be around 5 mg kg^{-1} . Memantine and amantadine inhibit NMDA-induced convulsions with ED_{50} s of 4.6 and 116 mg kg^{-1} respectively, indicating that relatively high doses of amantadine are required to assure clear NMDA receptor antagonism in this model, possibly due to the stronger voltage dependence of amantadine than memantine (97). Of course, it cannot be excluded that lower doses are sufficient to affect populations of NMDA receptors other than those involved in seizure propagation via for example differential effects on NMDA receptor subtypes.

2.2.2. *Studies ex vivo*

According to Scatton et al. (109) amantadine at 40 mg kg^{-1} increases *ex vivo* synthesis and release of DA in slices prelabelled with 3,5- ^3H -L-tyrosine. Most other studies, however, failed to show a clear-cut direct effect on DA release/uptake. Amantadine even at high doses (150 mg kg^{-1}) does not affect DA levels in the whole brain but seems to decrease noradrenaline (NA) and serotonin (5-HT) turnover (126). Similarly, no consistent change in DA turnover was found by Brown and Redfern (13), and therefore the dopaminomimetic effect was questioned by these authors. Maj et al. (70) reported that amantadine up to 80 mg kg^{-1} does not change DA concentration in the striatum.

Memantine 10–40 mg kg^{-1} has also been reported to cause small (< 50%), but highly variable, changes in the levels of 5-HT, DA and/or their metabolites in various structures such as the prefrontal cortex and nucleus accumbens. Thus, the small magnitude of these changes and the highly inconsistent results for DA in the striatum indicate that such effects are not relevant for memantine's

TABLE 2
 COMPILATION OF IN VITRO ACTIONS OF MEMANTINE

Studied effect	Assay	Potency μM	Ref.
NMDA channel	[³ H]-(+)-MK-801 (human cortex)	0.54 (K _i)	(58,59)
NMDA channel	[³ H]-(+)-MK-801 (rat cortex)	1.7 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat cortex)	6.7 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus CA1/CA3)	1.4 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus CA1)	7.6 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus dentate gyrus)	2.4 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat hippocampus dentate gyrus)	5.4 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (rat striatum)	1.8 (K _i)	(12)
NMDA channel	[³ H]-(+)-MK-801 (rat striatum)	5.6 (IC ₅₀)	(98)
NMDA channel	[³ H]-(+)-MK-801 (cerebellum)	1.4 (IC ₅₀)	(98)
NMDA channel (subtype?)	NMDA-induced Ca ²⁺ influx in cultured cerebellar neurones (FURA2)	0.2 (IC ₅₀)	Müller, unpub.
NMDA channel	NMDA-induced Ca ²⁺ influx in cultured retinal ganglion cells (FURA2)	5.0 (IC ₅₀)	(19)
NMDA channel (subtypes)	Patch clamp in <i>Xenopus</i> oocytes (NMDAR1A or B with NMDAR2C)	0.1 (IC ₅₀)	(99)
NMDA channel	Patch clamp (hippocampus, -100 mV)	1.0 (IC ₅₀)	(96)
NMDA channel	Patch clamp (retinal ganglion cells, -60 mV)	2.0 (K _d)	(19)
NMDA channel	Patch clamp (spinal cord, -70 mV)	2.2 (IC ₅₀)	(10), Parsons, unpub.
NMDA channel	Patch clamp (superior colliculus, -70 mV)	2.3 (IC ₅₀)	(95)
NMDA channel	Patch clamp (striatum, -100 mV)	2.9 (IC ₅₀)	(96)
NMDA channel	Glutamate-induced toxicity in cultured cortical neurones	1.5 (IC ₅₀)	Netzer, unpub.
NMDA channel	Glutamate-induced toxicity in cultured cortical neurones	< 10	(141)
NMDA channel	Glutamate-induced toxicity in cultured cerebellar neurones	< 30	(141)
NMDA channel	Glutamate-induced toxicity in cultured dopaminergic striatal neurones	> 100	(141)
NMDA channel	NMDA-induced toxicity in cultured cortical neurones	15 (IC ₅₀)	(34)
NMDA channel	NMDA-induced toxicity in cultured retinal ganglion cells	3 (IC ₅₀)	(19)
NMDA channel	NMDA-induced depolarisations: grease gap - cortical wedge	12.9 (IC ₅₀)	(95)
NMDA channel	Zero Mg ²⁺ -induced epileptic activity in hippocampal slices	16.6 (IC ₅₀)	(4)
NMDA channel	NMDA-receptor mediated LTP and EPSCs in hippocampal slices	11.6 (IC ₅₀)	(37)
NMDA channel	NMDA-induced [³ H]-ACh release in striatal slices	5.0 (IC ₅₀)	(68)
NMDA channel (subtype?)	NMDA-induced [¹⁴ C]ACh release in striatal slices	1.8 (IC ₅₀)	(88)
NMDA channel (subtype?)	NMDA-induced [³ H]spermidine release in striatal slices	38 (IC ₅₀)	(88)
NMDA channel	NMDA-induced [³ H]-NA release in hippocampal slices	6 (IC ₅₀)	Behl, unpub.
NMDA channel	NMDA-induced cGMP in cerebellum	10 (IC ₅₀)	Scatton, unpub.
NMDA channel	NMDA-induced IP ₃ turnover	24 (IC ₅₀)	(80)
5-HT release	Synaptosomal 5-HT release	> 100 (stim.)	(149)
5-HT uptake	[³ H]-Imipramine	> 10	Larue, unpub.
5-HT uptake	Synaptosomal high affinity 5-HT uptake	50 (IC ₅₀)	Demisch, unpub.
5-HT uptake	Synaptosomal high affinity 5-HT uptake	97 (IC ₅₀)	(146)
5-HT	[³ H]-5HT	> 100	(149)
5-HT _{1A}	[³ H]-8-OH-DPAT	> 10	Millan, unpub.
5HT ₂	5-HT stimulated IP ₃ in polyploid glioma cells	> 100	(103)
5HT ₃	5-HT stimulated cGMP and Ca ²⁺ influx	50 (IC ₅₀)	(104)
Ach (muscarinic)	Carbachol-induced IP ₃	> 100	(80)
Ach (nicotinic)	[³ H]-Nicotine	> 10	Larue, unpub.
Ach (nicotinic)	Frog nerve muscle preparation	18 (K _d)	(73)
Ach (nicotinic)	Mouse phrenic nerve-diaphragm.	20 (IC ₅₀)	Maeno, unpub.
Ach (nicotinic)	Rat phrenic nerve-diaphragm.	10 (IC ₅₀)	Grossmann, unpub.
Ach (nicotinic)	Mouse phrenic nerve-diaphragm.	120 (IC ₅₀)	(132)
Adenosine uptake	[³ H]-Adenosine (synaptosomes)	> 100	Kupferberg, unpub.
Adenylate cyclase	Basal cAMP levels in striatal slices (stimulation)	10 (c.a.EC ₅₀)	(48,49)
Adenylate cyclase	Basal and Forskolin - stimulated cAMP levels	> 10	Lemmer, unpub.
Adenylate cyclase	Basal cAMP levels in striatal slices	> 10	Riederer, unpub.
Adenylate cyclase	Basal cAMP levels in striatal slices	> 100	(52)
Adrenergic (a1)	[³ H]-PIA	> 100	Lohse, unpub.
Adrenergic (a2)	NA (+ phentolamine) - stimulated cAMP levels	> 50	Bayer, unpub.
Adrenergic (a2)	NECA - stimulated cAMP levels	> 1000	Lohse, unpub.
Adrenergic (β)	Isoproterenol - stimulated cAMP levels	> 50	Bayer, unpub.
Adrenergic (β)	[¹²⁵ I]-CYP	> 100	Lohse, unpub.
AMPA	Patch clamp (retinal ganglion cells)	> 12	(19)
AMPA	Patch clamp (hippocampus, superior colliculus)	> 30	(95,97)
AMPA	AMPA-induced depolarisations: grease gap - cortical wedge	> 100	(95)
AMPA	AMPA-receptor mediated fEPSPs in hippocampal slices	> 100	(37)
AMPA	[³ H]-AMPA binding	> 10 000	Bresink, unpub.
AMPA	AMPA-induced toxicity in cultured neurones	> 100	(34)
Aspartate	[³ H]-D-aspartate	> 10	Larue, unpub.
Barbiturate	[³ H]-TBPS	> 10	Larue, unpub.
Benzodiazepine	[³ H]-Flunitrazepam	> 100	Kupferberg, unpub.
Bradykinin	Bradykinin-stimulated IP ₃	> 100	(103)

TABLE 2 CONTINUED

Studied effect	Assay	Potency μM	Ref.
Cholecystokinin	[³ H]-CCK ₈	> 10	(136)
Cocaine	[³ H]-Cocaine	> 10	Larue, unpub.
DA release	[³ H]-DA release in striatal slices	50–100	(47)
DA uptake	[³ H]-GBR 12935	> 10	Larue, unpub.
DA uptake	[³ H]-DA uptake in striatal homogenates	210 (IC ₅₀)	(30)
DA uptake	[³ H]-NPA	520 (IC ₅₀)	(30)
DA ₁	DA-stimulated cAMP	> 10	Riederer, unpub.
DA ₁	DA-stimulated cAMP	> 100	(52)
GABA _A	Patch clamp (hippocampus, sup. colliculus)	> 10	(95,96)
GABA _A	[³ H]-GABA	> 10	Kupferberg, unpub.
GABA _B	[³ H]-(-)Baclofen	> 10	Larue, unpub.
Glutamate (NMDA competit)	[³ H]-Glutamate	> 10	Larue, unpub.
Glycine _A	Patch clamp - cultured spinal cord neurones	1–100	(65) ¹
Glycine _A	[³ H]-Strychnine	> 10	Betz, unpub.
Glycine _A	[³ H]-Glycine _A	> 10	Larue, unpub.
Guanylate cyclase	GTP - stimulated cAMP levels	> 10	Lemma, unpub.
Histamine 1	[³ H]-Mepyramine	> 10	Larue, unpub.
Histamine 2	[³ H]-Tiotidine	> 10	Larue, unpub.
Kainate	Patch clamp (hippocampus)	> 8	(95)
Kainate	Patch clamp (retinal ganglion cells)	> 12	(19)
Kainate	Kainate-induced toxicity in cultured cortical neurones	> 100	(34)
MAO _A	[¹⁴ C]-5-HT metabolism in vitro	100 (IC ₅₀)	(147)
MAO _A	[¹⁴ C]-5-HT metabolism in vitro	500 (IC ₅₀)	Demisch, unpub.
MAO _B	[¹⁴ C]-benzylamine metabolism in vitro	> 1000	Demisch, unpub.
mGluR1 and 5	t-ACPD stimulated PI hydrolysis	> 100	Pilc, unpub. Wroblewski, unpub.
Opioid (μ)	[³ H]-DAGO	> 10	Larue, unpub.
Opioid (d)	[³ H]-DADLE	> 10	Larue, unpub.
Opioid (k)	[³ H]-EKC	> 10	Larue, unpub.
PGE ₁	PGE ₁ -stimulated cAMP levels	> 50	Bayer, unpub.
Phenytoin	[³ H]-Phenytoin	> 10	Larue, unpub.
Phospholipase C?	Basal IP ₃ levels in retinal neuronal cultures	4.0 (EC ₅₀)	(91) ²
Somatostatin	[¹²⁵ I]-Somatostatin	> 10	Larue, unpub.
Substance P	Substance P stimulated IP ₃	> 100	(103)
Sigma1	[³ H]-(+)pentazocine	20.0 (K _i)	(63)
VACC (L-type)	KCl-induced Ca ²⁺ influx in cultured cerebellar neurones (FURA2)	62 (IC ₅₀)	Müller, unpub.
VACC type II	[³ H]-Desmethoxyverapamil	> 10	Larue, unpub.
VACC (HV)	Voltage-clamp in hippocampal slices	> 100	tenBruggencate, unpub.
VACC (LV)	Voltage-clamp in hippocampal slices	> 100	tenBruggencate, unpub.
VAKC	Sucrose gap rat primary afferents	100 (inhib.)	(41)
VAKC	Current clamp cultured spinal cord neurones	> 100	(89)
VAKC (A type)	Voltage-clamp in hippocampal slices	> 100	tenBruggencate, unpub.
VAKC (M type)	Voltage-clamp in hippocampal slices	> 100	tenBruggencate, unpub.
VASC	Current clamp cultured spinal cord neurones	10–50 (inhib.)	(89)
VASC	Sucrose gap rat primary afferents	100 (inhib.)	(41)
VASC	Current clamp Aplysia neurones	100 (inhib.)	(55)
VASC	VASC induced ¹⁴ C-guanidium influx	> 100	(103)

¹ Potentiation of glycine currents was observed at +ve potentials and inhibition at -ve potentials. This effect could not be reproduced in our own laboratory

² For discussion of the effect on Pi hydrolysis see Mistry et al. (1995)

therapeutic effects [(1,14,30,102), Baran et al., unpublished; Ito et al., unpublished].

2.2.3. Studies in vivo

In cats perfused i.c.v. with amantadine (500 μM) a significant increase in preloaded [³H]DA was observed that was attenuated by lesion of the of SNc system (137). It is difficult to draw any conclusions on the relevance of this effect as the concentration of amantadine in the striatum could not be determined. Using brain microdialysis, Mizoguchi et al. (80) found that amantadine (1 mM infused through the probe) increases DA concentrations in the striatum by around 50–70%. However, there are two caveats to this study:

1. It can be assumed that at the flow rate used in that study, 10% of amantadine leaves the probe (Hesselink, unpublished data). Hence, the local concentration would have been 100 μM , i.e. approx 10 times higher than normal therapeutic CSF concentrations (60,64). Indeed Mizoguchi et al. (82) mention that 10-fold lower concentrations failed to change DA levels. Thus, the increase in striatal DA observed by these authors is unlikely to be of major relevance for the effects of amantadine in Parkinson's disease.
2. Moreover, the fact that the site of 'antiparkinsonian' action of NMDA receptor antagonists could also lie outside of the striatum, e.g. in the SN reticulata (125) further weakens the therapeutic relevance of any direct effects seen with high concentrations of amantadine in the striatum.

TABLE 3
CONCENTRATIONS OF AMANTADINE IN HUMANS AND LABORATORY ANIMALS (PEAK OR STEADY STATE)

Species	Dose	Use	Body fluids μM	Brain — CSF/IS μM	Brain homog. μM	Ref.
Humans daily dose mg (for 70 kg body weight)	200 (p.o. > 8 days)	Antiparkinsonian	5.0 (s)	4.0 (CSF)	159	(61) ¹
	300 (p.o.)		13.5 (s)	9.5 (CSF)	281	
	300 (p.o. 3 weeks)	Antidepressive	3.6–5.4 (p)			(105)
	200 (i.v.)	Antiparkinsonian	3–5 (s)	1.3 \times s ²		(11)
	600 (p.o. 1–24 weeks)		8–11 (s)	(CSF)		
	200 (p.o. 2 weeks)	Antagonism of drug induced Parkinsonism	2.1–4.5 (p)			(93)
	c.a. 280–350 (p.o.)	Pharmacokinetics	2.7–3.2 (b)			(9)
	50 (p.o.) 15 days	Influenza A	0.59 (p)			(2,3)
200 (p.o.)		1.62 (p)				
steady state 300 (p.o.)		3.06 (p)				
Rat mg kg ⁻¹	25 (p.o.)	Anticatalytic	4.5 (s)		—90.0—	(24)
	50 (p.o.)		10.5 (s)			
	100 (p.o.)		21.0 (s)			
	23 (i.p.)	Anticatalytic,		7.7 (IS)		(61,100) ³
	46 (i.p.)	pharmacokinetics —		11.9 (IS)		
	92 (i.p.)	microdialysis		23.1 (IS)		
	100 (per day — infusion for 14 days)	Neuroprotection study	8.77 (s)		107.5	(144)
Mouse mg kg ⁻¹	25 (p.o.)		42.7 (b)			(9)

s — serum; p — plasma; b — blood, CSF — cerebrospinal fluid; IS — interstitial fluid; homog. — homogenates

¹ The values given for brain homogenates are not derived from the same group of patients as serum, CSF levels

² CSF levels specified as 1.3 times higher than serum

³ Microdialysis sample analysis based on in vitro recovery

TABLE 4
THERAPEUTIC CONCENTRATIONS OF MEMANTINE

Species	Dose	Use	Body fluids μM	Brain—CSF/IS μM	Brain homog μM	Ref.
Humans	20 (p.o. 53 days)	Parkinson's	0.32 (b)		1.3	(150)
	Daily dose mg					
	20 (p.o., > 11 days)	Dementia	0.37 (s)	0.2 (CSF)		(60)
	30 (p.o.)		0.53 (s)	0.3 (CSF)		
Rats mg kg ⁻¹	5 (i.p.)	Anticatalytic	1.0 (s)			(24)
	10 (i.p.)		2.3 (s)			
	20 (i.p.)		5.3 (s)			
	21 (i.p.)	Pharmacokinetics	8.0 (b)		25	(148)
	54 (i.p.)		17.0 (b)		130	
	10 (i.p.)	Pharmacokinetics—microdialysis		1.2 (IS)		(100,120)
	20 (i.p.)			2.6 (IS)		
	20 (s.c. per day infusion for 7 days)	Neuroprotection	1.1 (s)		40	(81)
	30 (i.p.)	Neuroprotection	11.6 (s)			(142)
	60 (s.c. per day infusion for 14 days)	Chronic pain	4.5 (s)			Eisenberg, unpub.
	90 (as above)		8.1 (s)			
	20 (per day, infusion for 14 days)	Neuroprotection	0.7–0.9 (s)		19–35	(144)
	30 (p.o. acute in food)	Pharmacokinetics	2.7 (s)		90	Danzysz, unpub.
	70 (as above)		4.4 (s)		130	
	30 (p.o. per day in food for 2 weeks)	Pharmacokinetics	5.0 (s)		200	Danzysz, unpub.
70 (as above)		13.0 (s)		500		

See Table 3 for description

TABLE 5
EFFECTS OF AMANTADINE IN ANIMAL MODELS OF PARKINSONISM

Model	Species	Dose mg/kg	Effect	Ref.
Movement initiation task impairment by haloperidol	R	20		Fig. 1
Bradykinesia			No effect	
Reaction time			Moderate effect	
Force slope			No effect	
α -MPT-induced catalepsy	R	50-100	Attenuates	(94)
Neuroleptic-induced catalepsy	R	20	Attenuates	(71)
	M	80	Attenuates	(151)
	R	25	Attenuates	(24)
		50		
		100		
Sedation after α -MPT	R	50-100	Attenuates	(94)
	R	50	Attenuates	(66)
	R	40	Attenuates	(71)
Sedation after reserpine	M	100	Increases	(79)
Sedation after α -MPT + reserpine	M	37	Attenuates	(45)
	R	100	Attenuates (very modest)	(24)
	R	20-40	Attenuates (modest)	(117)
	R	20	Potentiates L-DOPA action	(117)
Sedation after reserpine and Ro4-4602	R	5	Potentiates L-DOPA effect	(35)
	R	25	Attenuates	(35)
SNC system lesion	R	50	Ipsilateral rotation	(35)
	R	50-150	Ipsilateral rotation	(126)
	M	37	Ipsilateral rotation (modest)	(45)
	R	100	Ipsilateral rotation (very modest)	(24)

R — rat; M — mouse

Usually only minimal effective dose rather than the range of doses is given

In our own experience (100) only modest and highly variable increases in DA content were observed after systemic administration of amantadine (46 and 92 mg kg⁻¹). Likewise, memantine only produced a similar effect at 20 mg kg⁻¹ (120). The same dose increases DOPAC formation in the striatum as indicated by in vivo voltametry studies by Weseman et al. (145). However, this dose of memantine results in serum concentrations of around 5.3 μ M [(24) Table 4] and is more likely to be selective for NMDA receptors in vivo. In both cases it is plausible that the observed increase in striatal DA levels is indirect, i.e. via NMDA receptor blockade, and is not relevant to the antiparkinsonian-like activity of these

aminoadamantanes in the haloperidol-induced catalepsy test, since the threshold doses were 25 and 10 mg kg⁻¹ for amantadine and memantine respectively (compare Tables 3 and 4 with Tables 5 and 6).

3. MEMANTINE AND AMANTADINE ARE LOW AFFINITY UNCOMPETITIVE NMDA RECEPTOR ANTAGONISTS

Memantine and amantadine both antagonize NMDA-induced currents in neurones from various regions in a use- and strongly voltage-dependent manner, indicating that they block the open NMDA receptor channel (19,95-97). Memantine is about three-fold less potent against

TABLE 6
EFFECTS OF MEMANTINE IN ANIMAL MODELS OF PARKINSONISM

Model	Species	Dose mg kg ⁻¹	Effect	Ref.
Movement initiation impairment by haloperidol	R	10		Fig. 1
Bradykinesia			No effect	
Reaction time			Moderate	
Force slope			No effect	
Neuroleptic-induced catalepsy	R	10	Attenuates (partially)	(24)
		5 and 20	No effect	
	R	5 and 10	Attenuates	(113)
	R	10	Attenuates	(72)
Sedation after α -MPT + reserpine	R	20	Attenuates (moderate).	(24)
	R	10-20	Attenuates	(72)
	R	10	Attenuates (strong)	(117)
	R	5	Potentiates action of L-DOPA	(117)
Sedation after reserpine	M	21.5	Attenuates	(45)
SNC system lesion	R	20	Ipsilateral rotation (moderate)	(24)
	R	20-30	Ipsilateral rotation	(21,22)
	R	25	Ipsilateral rotation	(127)
	M	10.8	Ipsilateral rotation (strong)	(45)

R — rat; M — mouse

NMDA-induced currents in freshly dissociated striatal neurones than in hippocampal neurones whereas amantadine is relatively more potent on striatal neurones (96). As a result, amantadine was about 18 times less potent than memantine in the hippocampus but only four times less potent in the striatum. This relative difference in the potencies of amantadine and memantine in freshly dissociated striatal neurones agrees well with the effects of these two compounds in blocking NMDA-induced acetylcholine release and NMDA receptor-mediated EPSPs in striatal slices (68,106,124). Similarly, in binding studies ($[^3\text{H}]\text{MK-801}$) on human brain homogenates the difference in potency between both agents was found to be somewhat smaller in the striatum than in the hippocampus (Kornhuber et al., unpublished). Taken together, these data suggest that therapeutically relevant concentrations of amantadine may be somewhat more active in the striatum whereas memantine is likely to be more active in non-striatal structures (24,64,120). This could offer an explanation for the better clinical profile of amantadine than memantine in Parkinson's disease. Thus, the expression of NMDA receptors is increased in the striatum of Parkinson's patients (135,140) and NMDA receptor antagonists have been proposed to mediate their positive effects in Parkinson's disease within the striatum as well as in other basal ganglion structures (16,40,57,112). As a result, the relatively higher doses of memantine required in animal models of Parkinson's disease might be expected to cause more side effects associated with higher activity in structures other than basal ganglia (24).

Both amantadine and memantine show *in vivo* actions indicative of NMDA receptor antagonism. They inhibit NMDA-mediated convulsions ($\text{ED}_{50} = 116$ and 4.6 mg kg^{-1} respectively) (97) and attenuate NMDA-induced lesions to the nuclei basalis magnocellularis ($\text{ED}_{50} = 46$ and 2.7 mg kg^{-1} respectively) (143). Additionally, memantine blocks neuronal excitation evoked by microiontophoretic application of NMDA to spinal cord neurones with an approx. ED_{50} of 2.0 mg kg^{-1} (90). Moreover low doses of amantadine ($6\text{--}12 \text{ mg kg}^{-1}$; Dimpfel, unpublished) and memantine ($1\text{--}4.5 \text{ mg kg}^{-1}$), (29) produce a similar pattern of EEG changes in the striatum (20–50 min after injection). It is characterised by: a moderate decrease (20%) of delta, theta and beta-2 (18.75–35.00 Hz) waves and stronger decrease (20–40%) of alpha-2 (9.75–12.5 Hz) and beta-1 (12.75–18.50 Hz) waves. In general, a similar pattern of striatal EEG changes was seen with MK-801 at low doses ($0.05\text{--}0.1 \text{ mg kg}^{-1}$), additionally a decrease in the alpha-1 (7.0–9.5 Hz) range was observed (28). It is noteworthy that up to now no other clear-cut *in vivo* effects have been observed at such low doses of either aminoadamantane (6 and 1 mg kg^{-1} for amantadine and memantine respectively).

It is still not clear as to why low affinity open channel blockers such as amantadine and memantine should be able to reduce NMDA receptor-mediated synaptic transmission in the striatum as high concentrations of memantine are required to block NMDA receptor-dependent long term potentiation in the hippocampus (27,37,123). This relatively weak effect on the synaptic activation of hippocampal NMDA receptors has been attributed to the strong voltage-dependency and fast unblocking kinetics of memantine (95,97). Thus, low affinity open channel blockers

such as amantadine and memantine might be able to antagonise the neurotoxic effects of sustained, but relatively small, increases in extracellular glutamate concentration occurring under several pathological conditions (38) but, like Mg^{2+} , leave the NMDA channel following transient physiological activation due to the pronounced depolarisation of the postsynaptic membrane induced by high concentrations of synaptically-released glutamate (20). The somewhat reduced voltage-dependency of memantine on NMDA responses of striatal neurones reported by Parsons et al. (95) may indicate that a subclass of NMDA receptors showing altered relative voltage-dependency of channel blockade is expressed in the striatum. This assumption is supported by the finding that memantine- and amantadine-sensitive NMDA receptor-mediated EPSPs can be recorded in the striatum in the presence of Mg^{2+} even at potentials as negative as -90 mV (50,106). Indeed, there are already some indications that memantine and amantadine show NMDA receptor subtype selectivity. Thus, memantine blocks NMDAR1A or B / NMDAR2C heteromeric receptors in *Xenopus* oocytes in a voltage-independent manner with higher potency ($\text{IC}_{50} 0.1 \mu\text{M}$) (99). The highest levels of NMDAR2C receptors are expressed in the cerebellum, an area where both memantine and amantadine have been reported to have relatively higher affinities (98). Although NMDAR2C subunits also show a reduced sensitivity to Mg^{2+} it is unlikely that this subunit is responsible for the observed effects as it is not expressed in the striatum (84). However, point mutations in NMDAR1 subunits have been shown to have pronounced effects on the voltage-dependent blockade by Mg^{2+} and TCP (15,53). The possibility that preferential expression of a NMDAR1 splice variant in the striatum may be responsible for the effects observed in this structure remains to be addressed.

4. EFFICACY OF AMANTADINE AND MEMANTINE IN ANIMAL MODELS OF PARKINSON'S DISEASE IN RELATION TO SERUM LEVELS AND NMDA RECEPTOR ANTAGONISM

It is now widely accepted that NMDA receptor antagonists manifest their antiparkinsonian effects by attenuating the imbalance between dopaminergic and glutamatergic pathways within the basal ganglia network as reviewed by Schmidt in this same issue [see also refs (57,92,112,121)]. These actions could involve interactions with NMDA receptors in the striatum, subthalamic nucleus, SNr or SNc. NMDA receptor antagonists show activity in a number of animal models/tests used for studying behavioural parameters relevant for antiparkinsonian-like activity. These models will be listed focusing on the effects of amantadine and memantine.

4.1. Locomotion in naïve animals

In general, many uncompetitive NMDA receptor antagonists increase locomotion in naïve animals (23) while competitive antagonist are ineffective, at least at moderate doses (23,67). In this respect memantine behaves like other uncompetitive NMDA receptor antagonists in contrast to amantadine which shows no locomotor stimulation and even some inhibition during initial recording periods (23,79,122,127). In those studies where enhancement of locomotion after amantadine was observed, the doses were

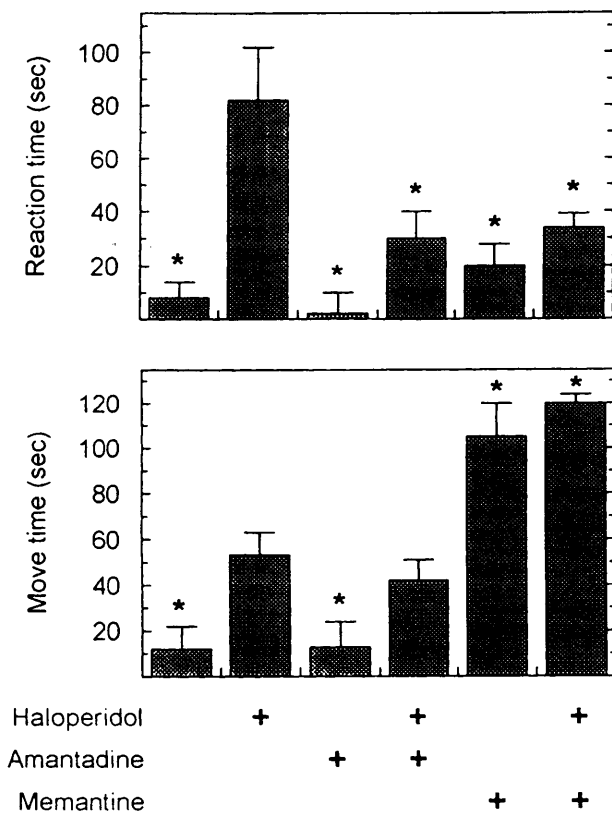


FIG. 1. Effect of amantadine (20 mg kg⁻¹) and memantine (10 mg kg⁻¹) on haloperidol- (0.15 mg kg⁻¹) induced movement initiation deficit. Results are expressed as mean \pm SE reaction time (upper panel) or movement time (lower panel) obtained from N = 8–10 rats. Experiment were performed as described by Hauber and Schmidt (43).

generally quite high and the registration periods very long allowing for lower levels of control activity [e.g. refs (66,126)].

4.2. DA antagonists-induced catalepsy

Both uncompetitive and competitive NMDA receptor antagonists antagonise catalepsy induced by DA receptor antagonists (92,112). The anticataleptic effect of amantadine is robust, and clearly dose-dependent starting at 25 mg kg⁻¹ (Table 5). A modest effect is also observed after memantine, although it shows a bell-shaped dose-response relationship. The ineffectiveness of memantine at higher doses (20 mg kg⁻¹) does not indicate that anticataleptic activity is lost but rather that strong myorelaxant effects dominate and mask the expression of the antiakinetic action [see also ref. (113)].

4.3. Haloperidol-induced movement initiation deficit

In a food reinforced runway test, the effects of haloperidol on various parameters of motor responses can be studied [see refs (43,113)]. The task demands stimulus-triggered rapid initiation of locomotion to get a food reward. Haloperidol at a low dose (0.15 mg kg⁻¹) causes: (1) delayed movement initiation as indicated by an increase in reaction time, and (2) impaired movement execution seen as a decrease in the rate of development and amplitude of

the accelerated force component. NMDA receptor antagonists such as (+)-MK-801 (43) or DL-(E)-2-amino-4-methyl-5-phosphono-3-pentanoic acid (CGP-37849) (113) attenuate these impairments induced by haloperidol. Similar effects are seen after amantadine (113) and to a lesser extent after memantine, possibly due to the stronger myorelaxant effects of this agent (see Fig. 1).

4.4. Hypokinesia in monoamine-depleted rodents

A pronounced hypokinesia is observed in rodents depleted of monoamines, e.g. by using α -methyl-*p*-tyrosine (α -MPT), or reserpine, or both. This hypokinesia is often attenuated by a number of NMDA receptor antagonists (16,17,39). Similar anti-hypokinetic effects have been observed for memantine and amantadine by some authors (Tables 5 and 6) but it should be stressed that the effect of amantadine is very modest, observed only after high doses (Table 5) and has not been observed at all in some studies (122). This inconsistency could result from some methodological differences such as the species employed or the type of monoamine depletion used, which in turn determines the basal levels of locomotor activity.

In monoamine-depleted rodents memantine and amantadine were found to enhance the effect of L-DOPA in a clearly synergistic manner (117). Comparable results have also been obtained by combination of L-DOPA with (+)-MK-801 (56). Moreover, a similar synergism between L-DOPA and amantadine or memantine has also been observed in Parkinson's patients (36,101).

However, recently Starr and Starr (120) reported a lack of enhancement of the effects of the D-1 partial agonist (SKF-37849) by amantadine, which contrasts to positive findings obtained previously with (+)-MK-801. This seems to differentiate amantadine from other NMDA receptor antagonists (121,122).

It has been reported that the combination of NMDA receptor antagonists with D-2 agonists (Bromocriptine, RU 24213, Quinpirole) actually leads to antagonism rather than to an overadditive effect (122,128). In our studies slight potentiation (but not synergism) by (+)-MK-801, amantadine and memantine was obtained if the dose of bromocriptine was low, i.e. leading to a modest increase of activity by itself (117).

4.5. Rotation in rodents with unilateral lesion to SNc system

In rodents with unilateral lesions of the SNc, systemic administration NMDA receptor antagonists produce ipsilateral rotations—an effect implying an indirect presynaptic locus of action (85,118,138). Memantine and amantadine also produce similar effects although the absolute magnitude of rotations is moderate in the case of memantine and minor in amantadine-treated animals as compared to, for example (+)-MK-801. Also, relatively high doses (37–100 mg kg⁻¹) of amantadine are required, which contrasts to the haloperidol-induced catalepsy test (Table 5).

5. THE DIFFERENCES BETWEEN AMANTADINE AND MEMANTINE

Although both memantine and amantadine show some similarities, a number of important differences that might determine their different therapeutic profile should be noted,

i.e. amantadine is a better antiparkinsonian agent than memantine (Pantev, personal communication).

- Amantadine, but not memantine, binds to the sigma-1 site at therapeutically-relevant concentrations [(63) Tables 1 and 2]. Moreover, very recent data indicate that neuronal nicotinic receptors (ACh1A) are blocked by amantadine with an IC_{50} of $6.5 \mu M$ (74). Similar data are not available for memantine.
- The effects of amantadine and memantine on peripheral nicotinic receptors also appear to be different. Thus, both non-use-dependent block and stimulation have been reported for relatively low concentrations of amantadine [(5,129), Grossmann, unpublished], whereas relatively high concentrations of memantine consistently block nicotinic receptors in a use-dependent manner (73,132).
- Amantadine but not memantine increases noradrenaline release (35).
- It has recently been reported that low doses of amantadine (20 mg kg^{-1}) increased c-fos immunoreactivity in the rat striatum (in this case an indicator of neuronal activation), whilst high doses of (+)-MK-801 were without effect (131). This effect of amantadine was blocked by a D-1 receptor antagonist and (+)-MK-801 but not by a D-2 receptor antagonist (131). It is worth noting that the (+)-MK-801 dose used (1 mg kg^{-1}) was very high— 0.1 – 0.2 mg kg^{-1} is usually sufficient to block NMDA receptors in vivo. It may also reflect an action of amantadine that has nothing to do with NMDA receptor antagonism, or differential effects at NMDA receptor subtypes. This observation is in line with the results of a brain microdialysis study by Mizoguchi et al. (80) who reported that (+)-MK-801 reversed the effects of amantadine in increasing striatal DA levels. The mechanism of action for the effects of amantadine on c-fos induction remains to be established.
- There is a difference in affinity of memantine and amantadine in various brain structures as discussed above ('Memantine and amantadine are low affinity uncompetitive NMDA receptor antagonists').
- In contrast to memantine, amantadine (5 – 10 mg kg^{-1}) has no effect on decerebrate rigidity seen in spinally-intact rats and cats, and actually increases the amplitude of spinal reflexes in spinalized rats [Ito, unpublished]. This effect was proposed to reflect activation of α -1 receptors by amantadine, and also to underlie the opposing effects of memantine and amantadine on blood pressure (70,72)—see, however, the caveats discussed above.
- Memantine produces much stronger effects in the rotation model and in monoamine-depleted rats than amantadine (Tables 5 and 6).
- Amantadine produces clear antagonism of haloperidol-induced catalepsy and movement initiation deficits at low doses whilst memantine is weaker due to inherent myorelaxant activity at higher doses (24,116).
- EMG measured in normal rats indicates that memantine (25 mg kg^{-1}) decreases muscle tone whereas amantadine (40 mg kg^{-1}) increases it (Holtwick, unpublished).
- Amantadine, but not memantine, antagonises reserpine-induced hypothermia (86).
- Amantadine shows no generalisation to PCP in rats and monkeys, whereas memantine does, although this effect occurs at doses that decrease respinding rate, in contrasts

to some other NMDA antagonists, e.g. MK-801 [Balster, presented during EBPS workshop, Marseilles, 1995, see also ref. (108)].

- Memantine enhances locomotion in naïve animals while amantadine decreases it (23) and even reverses the stimulatory effects of memantine (76–78)

6. POSSIBLE EFFECT ON PARKINSON'S PATHOGENESIS — NEUROPROTECTION

Antagonists of NMDA receptors have been shown to inhibit neurodegeneration of the DA substantia nigra (SNc) system induced by MPP⁺ and methamphetamine (40,119,133). Similar direct evidence for protection of the SNc by either memantine or amantadine is not available [but see ref. (107)]. However, in vitro both adamantanes show clear antagonism of NMDA receptor-mediated excitotoxicity in cultured neurones at concentrations corresponding to their potency at this receptor type, and their therapeutic serum range [(64,141); Netzer et al., unpublished; Tables 1 and 2]. Repetitive oral treatment with memantine attenuates hippocampal cell loss produced by direct injection of quinolinic acid (54) and striatal damage resulting from long-term haloperidol treatment (model of tardive dyskinesia) (51). In an acute dose–response study memantine and amantadine were shown to inhibit neurodegeneration produced by a direct NMDA injection in the NBM as assessed by ChAT activity in the frontal cortex (143). The respective ED_{50} s were 2.7 and 46 mg kg^{-1} respectively, thus being within their therapeutically-relevant ranges (5 and 50 mg kg^{-1} respectively).

NMDA receptor antagonists in general, and aminoadamantanes in particular, have been suggested as potential neuroprotective therapies in Parkinson's disease (64,83). In fact, it has recently been reported that amantadine increases life expectancy in Parkinson's patients—an effect attributed to neuroprotective activity of this agent (134). In turn, on the basis of above listed arguments and assuming the relevance of NMDA receptor-mediated excitotoxicity as a factor underlying neurodegeneration in Parkinson's disease (40), neuroprotective effects of both amantadine and memantine might be predicted.

There are indications of beneficial effects of amantadine in traumatic brain injury, that are not related to neuroprotective action *per se*, but possibly rather to trophic activity increasing plastic adaptive changes [(31) see also ref. (42) for review]. In a case study by Edby et al. (29) treatment started 2 years after injury and an improvement of communication, mood, muscle tension, speech abilities and reaction time were observed, and some of these effects were sustained even after termination of the treatment. In animal studies, post-NBM lesion infusion of amantadine for 2 weeks ($100 \text{ mg kg}^{-1}/\text{day}$ —serum $8.8 \mu M$ achieved approx. 20 h after the lesion; Table 3) still lead to significant improvement of ACh parameters in the projection areas (144). In the same experimental design a beneficial effect was also observed after post-lesion infusion of memantine ($20 \text{ mg kg}^{-1}/\text{day}$) also leading to steady-state serum levels within the therapeutic range (0.7 – $1 \mu M$, Table 4). Interestingly, the treatment with memantine (also $20 \text{ mg kg}^{-1}/\text{day}$) also prevented 3-NP- (mitochondrial toxic) and neostigmine-induced damage (144).

7. CONCLUSIONS

- Considering their potency at NMDA receptors in vitro, and effective CNS concentrations in vivo (preclinical, therapeutic) NMDA receptor antagonism almost certainly plays an important role in mediating the antiparkinsonian activity of both memantine and amantadine. However, there are many reasons to believe that this is not the only mechanism of action of amantadine.
- The anticataleptic action of amantadine in rodents and therapeutic antiparkinsonian effects in humans are stronger than those of memantine, possibly due to myorelaxant actions of the latter agent.
- There are clear differences between memantine and amantadine effects in laboratory animals — including models used for detecting antiparkinsonian-like activity.

- These effects could result from additional effects of amantadine reported in vitro such as: actions at the sigma site, modulation of nicotinic receptors, enhancement of noradrenergic transmission, due to different effects of both agents on various subtypes of NMDA receptor, or related to as yet unknown effects.
- The combination of aminoadamantanes with L-DOPA, but not with direct DA agonists, results in synergistic enhancement of antiparkinsonian-like activity in animal models and probably also in clinical practice.
- There are reasons to believe that both memantine and amantadine used at relatively low doses (5 and 50 mg kg⁻¹ respectively) are neuroprotective against overstimulation of NMDA receptors, e.g. in NBM nuclei (143). However, evidence for neuroprotection directly relevant for Parkinson's pathology is not yet available — e.g. against MPTP toxicity [but see (107)].

REFERENCES

1. Allman, S. A.; Campbell, W.; Needham, P. L., Evidence that D145 is limbic specific. *British Journal of Pharmacology*, **75**, 103 1982.
2. Aoki, F. Y.; Sitar, D. S., Clinical pharmacokinetics of amantadine hydrochloride. *Clinical Pharmacokinetics*, **14**, 35–51 1988.
3. Aoki, F. Y.; Sitar, D. S.; Ogilvie, R. I., Amantadine kinetics in healthy young subjects after long-term dosing. *Clinical Pharmacokinetics and Therapeutics*, **26**, 729–736 1979.
4. Aplan, J. P.; Cann, F. J., Anticonvulsant effects of memantine and MK-801 in guinea pig hippocampal slices. *Brain Research Bulletin*, **37**, 311–316 1995.
5. Aronstam, R. S.; Eldefrawi, A. T.; Eldefrawi, M. E., Similarities in the binding sites of the muscarinic receptor and the ionic channel of the nicotinic receptor. *Biochemical Pharmacology*, **29**, 1311–1314 1980.
6. Ashroft, F. M.; Kerr, A. J.; Gibson, J. S.; Williams, B. A., Amantadine and sparteine inhibit ATP-regulated K-currents in the insulin-secreting beta-cell line. *British Journal of Pharmacology*, **104**, 574–584 1991.
7. Bailey, E. V.; Stone, T. W., The mechanism of amantadine in Parkinsonism: a review. *Archives of International Pharmacodynamics*, **216**, 246–262 1975.
8. Birkmayer, W.; Hornykiewicz, O., Der 3,4-dioxyphenylalanin (= L-dopa) - Effekt bei der Parkinson akinesie. *Wien Klinik Wochenschrift*, **73**, 787–788 1961.
9. Bleidner, W. E.; Harmon, J. B.; Hewes, W. E.; Lynes, T. E.; Hermann, E. C., Absorption, distribution and excretion of amantadine hydrochloride. *Journal of Pharmacology and Experimental Therapeutics*, **150**, 484–490 1965.
10. Bormann, J., Memantine is a potent blocker of N-methyl-D-aspartate (NMDA) receptor channels. *European Journal of Pharmacology*, **166**, 591–592 1989.
11. Brenner, M.; Haass, A.; Jacobi, P.; Schimrigk, K., Amantadine sulphate in treating Parkinson's disease: Clinical effects, psychometric tests and serum concentrations. *Journal of Neurology*, **236**, 153–156 1989.
12. Bresink, I.; Danysz, W.; Parsons, C. G.; Mutschler, E., Different binding affinities of NMDA receptor channel blockers in various brain regions—indication of NMDA receptor heterogeneity. *Neuropharmacology*, **34**, 533–540 1995.
13. Brown, F.; Redfern, P. H., Studies on the mechanism of action of amantadine. *British Journal of Pharmacology*, **58**, 561–567 1976.
14. Bubser, M.; Keseberg, U.; Notz, P. K.; Schmidt, W. J., Differential behavioural and neurochemical effects of competitive and non-competitive NMDA receptor antagonists in rats. *European Journal of Pharmacology*, **229**, 75–82 1992.
15. Burnashev, N.; Schoepfer, R.; Monyer, H.; Ruppersberg, J. P.; Gunther, W.; Seeburg, P. H.; Sakmann, B., Control by asparagine residues of calcium permeability and magnesium blockade in the NMDA receptor. *Science*, **257**, 1415–1419 1992.
16. Carlsson, M.; Carlsson, A., Interaction between glutamatergic and monoaminergic systems within the basal ganglia—implications for schizophrenia and Parkinson's disease. *Trends in Neuroscience*, **13**, 272–276 1990.
17. Carlsson, M.; Carlsson, A., The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. *Journal of Neural Transmission*, **75**, 221–226 1989.
18. Cha, J. H. J.; Dure, L. S.; Sakurai, S. Y.; Penney, J. B.; Young, A. B., 2,4,5-Trihydroxyphenylalanine (6-hydroxy-DOPA) displaces [³H]AMPA binding in rat striatum. *Neuroscience Letters*, **132**, 55–58 1991.
19. Chen, H. S. V.; Pellegrini, J. W.; Aggarwal, S. K.; Lei, S. Z.; Warach, S.; Jensen, F. E.; Lipton, S. A., Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine—therapeutic advantage against NMDA receptor-mediated neurotoxicity. *Journal of Neuroscience*, **12**, 4427–4436 1992.
20. Clements, J. D.; Lester, R. A. J.; Tong, G.; Jahr, C. E.; Westbrook, G. L., The time course of glutamate in the synaptic cleft. *Science*, **258**, 1498–1501 1992.
21. Costall, B.; Naylor, R. J., Neuropharmacological studies on D145 (1,3-dimethyl-5-aminoadamantan). *Psychopharmacology*, **43**, 53–61 1975.
22. Costall, B.; Naylor, R. J.; Pycoc, C., The 6-hydroxydopamine rotational model for the detection of dopamine agonist activity: reliability of effect from different locations of 6-hydroxydopamine. *Journal of Pharmacy and Pharmacology*, **279**, 943–946 1975.
23. Danysz, W.; Essmann, U.; Bresink, I.; Wilke, R., Glutamate antagonists have different effects on spontaneous locomotor activity in rats. *Pharmacology and Biochemistry of Behavior*, **48**, 111–118 1994.
24. Danysz, W.; Gossel, M.; Zajackowski, W.; Dill, D.; Quack, G., Are NMDA antagonistic properties relevant for antiparkinsonian-like activity in rats? Case of amantadine and memantine. *Journal of Neural Transmission [Parkinson's Disease Section]*, **7**, 155–166 1994.
25. Danysz, W.; Parsons, C. G.; Bresink, I.; Quack, G., Glutamate in CNS disorders - a revived target for drug development. *Drugs News Perspectives*, **8**, 261–277 1995.
26. Di Chiara, G.; Morelli, M.; Consolo, S., Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions. *Trends in Neuroscience*, **17**, 228–233 1994.
27. Dimpfel, W., Effects of memantine on synaptic transmission in the hippocampus in vitro. *Arzneimittelforschung*, **45-1**, 1–5 1995.
28. Dimpfel, W.; Spüler, M.; Dizocilpine (MK-801), ketamine and phencyclidine: low doses affect brain field potentials in the freely moving rats in the same way as activation of dopaminergic transmission. *Psychopharmacology*, **101**, 317–323 1990.
29. Dimpfel, W.; Spüler, M.; Koch, R.; Schatton, W., Radioelectroencephalographic comparison of memantine with receptor-specific drugs acting on dopaminergic transmission in freely moving rats. *Neuropsychobiology*, **18**, 212–218 1987.

30. Dunn, J. P.; Henkel, J. G.; Gianutsos, G., Pharmacological activity of amantadine: Effect of N-alkyl substitution. *Journal of Pharmacy and Pharmacology*, **38**, 353–356 1986.
31. Eddy, K.; Larsson, J.; Eek, M.; von Wendt, L.; Östergard, B., Amantadine treatment of patient with anoxic brain injury. *Child's Nervous Systems*, **11**, 607–609 1995.
32. Ehringer, H.; Hornykiewicz, O., Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klinische Wochenschrift*, **38**, 1236–1239 1960.
33. Engelsen, B., Neurotransmitter glutamate: its clinical importance. *Acta Neurologica Scandinavica*, **74**, 337–355 1986.
34. Erdo, S. J.; Schafer, M., Memantine is highly potent in protecting cortical cultures against excitotoxic cell death evoked by glutamate and N-methyl-D-aspartate. *European Journal of Pharmacology*, **198**, 215–217 1991.
35. Farnedo, L.-O.; Fuxe, K.; Goldstein, M.; Hamberger, B.; Ungerstedt, U., Dopamine and noradrenaline releasing action of amantadine in the central and peripheral nervous system: a possible mode of action in Parkinson's disease. *European Journal of Pharmacology*, **16**, 27–38 1971.
36. Feiling, C., The effect of adding amantadine to optimum L-DOPA dosage in Parkinson's syndrome. *Acta Neurologica Scandinavica*, **49**, 245–251 1973.
37. Frankiewicz, T.; Potier, B.; Bashir, Z. I.; Collingridge, G. L.; Parsons, C. G., Comparison of the effects of memantine and MK-801 on NMDA-induced current responses in cultured neurons and on synaptic transmission and LTP in area CA1 of the rat hippocampus in vitro. *British Journal of Pharmacology*, **117**, 689–697 1996.
38. Globus, M. Y. T.; Busto, R.; Martinez, E.; Valdes, I.; Dietrich, W. D.; Ginsberg, M. D., Comparative effect of transient global ischemia on extracellular levels of glutamate, glycine, and gamma-aminobutyric acid in vulnerable and nonvulnerable brain regions in the rat. *Journal of Neurochemistry*, **57**, 470–478 1991.
39. Goodwin, P.; Starr, B. S.; Starr, M. S., Motor responses do dopamine-D1 and dopamine-D2 agonists in the reserpine-treated mouse are affected differentially by the NMDA receptor antagonist MK-801. *Journal of Neural Transmission [Parkinson's Disease Section]*, **4**, 15–26 1992.
40. Greenamyre, J. T.; O'Brien, C. F., N-methyl-D-aspartate antagonists in the treatment of Parkinson's disease. *Archives in Neurology*, **48**, 977–981 1991.
41. Grossmann, A.; Grossmann, W.; Jurna, I., The effect of dimethylaminoadamantane on neuronal membranes. *European Journal of Pharmacology*, **35**, 379–388 1976.
42. Gualtieri, T.; Chandler, M.; Coons, T. B.; Brown, L. T., Amantadine: a new clinical profile for traumatic brain injury. *Clinical Neuropharmacology*, **12**, 258–270 1989.
43. Hauber, W.; Schmidt, W. J., The NMDA antagonist dizocipiline (MK-801) reverses haloperidol-induced movement initiation deficits. *Behavioral Brain Research*, **41**, 161–166 1990.
44. Heikkilä, R. E.; Cohen, G., Evaluation of amantadine as a releasing agent or uptake blocker for [³H]dopamine in rat brain slices. *European Journal of Pharmacology*, **20**, 156–160 1972.
45. Henkel, J. G.; Hane, J. T.; Gianutsos, G., Structure antiParkinson activity relationships in the aminoadamantanes. Influence of bridge-head substitution. *Journal of Medical Chemistry*, **25**, 51–56 1982.
46. Honegger, U. E.; Quack, G.; Wiesmann, U. N., Evidence for lysosomotropism of memantine in cultured human cells—cellular kinetics and effects of memantine on phospholipid content and composition, membrane fluidity and beta-adrenergic transmission. *Pharmacology and Toxicology*, **73**, 202–208 1993.
47. Jackisch, R.; Link, T.; Neufang, B.; Koch, R., Studies on the mechanism of action of the antiparkinsonian drugs memantine and amantadine—no evidence for direct dopaminomimetic or antimuscarinic properties. *Archives of International Pharmacodynamics and Therapeutics*, **320**, 21–42 1992.
48. Janiec, W.; Piekarska, T.; Paletko, Z.; Pytlik, M., The effect of drugs stimulating central dopaminergic system on transformation of exogenous adenine into c-AMP. *Polish Journal of Pharmacology and Pharmacy*, **30**, 529–535 1978.
49. Janiec, W.; Piekarska, T.; Szczypior, M.; Misterkiewicz, E., The effect of apomorphine, amantadine and dimethylaminoadamantane on the level of cyclic AMP in the rat striatum. *Polish Journal of Pharmacology and Pharmacy*, **29**, 93–99 1977.
50. Jiang, Z. G.; North, R. A., Membrane properties and synaptic responses of rat striatal neurones in vitro. *Journal of Physiology (London)*, **443**, 533–553 1991.
51. Jorgensen, H. A.; Andreassen, O. A., Memantine inhibits the development of haloperidol-induced persistent oral movements in rats. *Society of Neuroscience Abstracts*, **21**, 470 1995.
52. Karobath, M. E., Amantadine and D-145, an amantadine derivative, do not effect dopamine sensitive adenylate cyclase from the caudate-putamen of the rat brain. *European Journal of Pharmacology*, **28**, 376–378 1974.
53. Kawajiri, S.; Dingledine, R., Multiple structural determinants of voltage-dependent magnesium block in recombinant NMDA receptors. *Neuropharmacology*, **32**, 1203–1211 1993.
54. Keilhoff, G.; Wolf, G., Memantine prevents quinolinic acid-induced hippocampal damage. *European Journal of Pharmacology*, **219**, 451–454 1992.
55. Klee, M. R., The effect of memantine on membrane properties and postsynaptic potentials in neurons of *Aplysia californica*. *Arzneimittelforschung*, **32**, 1259–1267 1982.
56. Klockgether, T.; Turski, L., NMDA antagonists potentiate antiparkinsonian action of L-DOPA in monoamine-depleted rats. *Annals of Neurology*, **28**, 539–546 1990.
57. Klockgether, T.; Turski, L., Toward an understanding of the role of glutamate in experimental parkinsonism—agonist-sensitive sites in the basal ganglia. *Annals of Neurology*, **34**, 585–593 1993.
58. Kornhuber, J.; Bormann, J.; Hubers, M.; Rusche, K.; Riederer, P., Effects of the 1-amino-adamantanes at the MK-801-binding site of the NMDA-receptor-gated ion channel—a human postmortem brain study. *European Journal of Pharmacology*, **206**, 297–300 1991.
59. Kornhuber, J.; Bormann, J.; Retz, W.; Hubers, M.; Riederer, P., Memantine displaces [³H]MK-801 at therapeutic concentrations in postmortem human frontal cortex. *European Journal of Pharmacology*, **166**, 589–590 1989.
60. Kornhuber, J.; Quack, G., Cerebrospinal fluid and serum concentrations of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine in man. *Neuroscience Letters*, **195**, 137–139 1995.
61. Kornhuber, J.; Quack, G.; Danyasz, W.; Jellinger, K.; Danielczyk, W.; Gsell, W.; Riederer, P., Therapeutic brain concentration of the NMDA receptor antagonist amantadine. *Neuropharmacology*, **34**, 713–721 1995.
62. Kornhuber, J.; Retz, W.; Riederer, P., Slow accumulation of psychotropic substances in the human brain. Relationship to therapeutic latency of neuroleptic and antidepressant drugs? *Journal of Neural Transmission*, **46** (Suppl.), 311–319 1995.
63. Kornhuber, J.; Schoppmeyer, K.; Riederer, P., Affinity of 1-aminoadamantanes for the sigma binding site in post-mortem human frontal cortex. *Neuroscience Letters*, **163**, 129–131 1993.
64. Kornhuber, J.; Weller, M.; Schoppmeyer, K.; Riederer, P., Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties. *Journal of Neural Transmission* **91**–104; 1994.
65. Lampe, H.; Bigalke, H., Modulation of glycine activated membrane current by adamantane derivatives. *NeuroReport*, **2**, 373–376 1991.
66. Lassen, J., The effect of amantadine and (+)-amphetamine on motility in rats after inhibition of monoamine synthesis and storage. *Psychopharmacologia*, **29**, 55–64 1973.
67. Löscher, W.; Annies, R.; Honack, D., Comparison of competitive and uncompetitive NMDA receptor antagonists with regard to monoaminergic neuronal activity and behavioural effects in rats. *European Journal of Pharmacology*, **242**, 263–274 1993.
68. Lupp, A.; Lucking, C. H.; Koch, R.; Jackisch, R.; Feuerstein, T. J., Inhibitory effects of the antiparkinsonian drugs memantine and amantadine on N-methyl-D-aspartate-evoked acetylcholine release in the rabbit caudate nucleus in vitro. *Journal of Pharmacology and Experimental Therapeutics*, **263**, 717–724 1992.
69. Lustig, H. S.; Ahern, K. V.; Greenberg, D. A., Antiparkinsonian drugs and in vitro excitotoxicity. *Brain Research*, **597**, 148–150 1992.
70. Maj, J., Effect of memantine on central neurotransmitter systems. Review of the results. *Arzneimittelforschung*, **32**, 1256–1259 1982.
71. Maj, J.; Sowinska, H.; Baran, L., The effect of amantadine on motor activity and catalepsy in rats. *Psychopharmacology*, **24**, 296–307 1972.
72. Maj, J.; Sowinska, H.; Baran, L.; Sarnek, J., Pharmacological effects of 1,3-dimethyl-5-aminoadamantane, a new adamantane derivative. *European Journal of Pharmacology*, **26**, 9–14 1974.

73. Masuo, K.; Enomoto, K.; Maeno, T., Effects of memantine on the frog neuromuscular junction. *European Journal of Pharmacology*, **130**, 187–195 1986.
74. Matsubayashi, H.; Albuquerque, E. X., Inhibitory effects of the antiviral agent amantadine on nicotinic acetylcholine responses in rat hippocampal cultured neurons. *Society of Neuroscience Abstracts*, **21**, 18–34 1995.
75. Meldrum, B., Possible therapeutic applications of antagonists of excitatory amino acid neurotransmitters. *Clinical Science*, **68**, 113–122 1985.
76. Menon, M. K.; Clark, W. G., GABA-ergic drugs block the locomotor stimulant effects of 1,3-dimethyl-5-aminoadamantane (D-145). *Neuropharmacology*, **18**, 223–225 1979.
77. Menon, M. K.; Clark, W. G., Pharmacological evidence for the involvement of GABA-ergic system in the locomotor stimulation produced in mice by 1,3-dimethyl-5-aminoadamantane (D-145). *Neuropharmacology*, **17**, 1049–1052 1978.
78. Menon, M. K.; Vivonia, C. A.; Haddox, V. G., Evidence for presynaptic antagonism by amantadine of indirectly acting central stimulants. *Psychopharmacology*, **82**, 89–92 1984.
79. Messiha, F. S., Effect of amantadine on chlorpromazine and reserpine-induced behavioral depression in the mouse. *Neuroscience and Biobehavioral Reviews*, **12**, 219–222 1988.
80. Mistry, R.; Wilke, R.; Challiss, R. A. J., Modulation of NMDA effects on agonist-stimulated phosphoinositide turnover by memantine in neonatal rat cerebral cortex. *British Journal of Pharmacology*, **114**, 797–804 1995.
81. Misztal, M.; Frankiewicz, T.; Parsons, C. G.; Danysz, W., Learning deficit induced by chronic intraventricular infusion of quinolinic acid—protection by MK-801 and memantine. *European Journal of Pharmacology*, **296**, 1–8 1996.
82. Mizoguchi, K.; Yokoo, H.; Yoshida, M.; Tanaka, T.; Tanaka, M., Amantadine increases the extracellular dopamine levels in the striatum by re-uptake inhibition and by N-methyl-D-aspartate antagonism. *Brain Research*, **662**, 255–258 1994.
83. Mizuno, Y.; Mori, H.; Kondo, T., Potential of neuroprotective therapy in Parkinsons disease. *CNS Drugs*, **1**, 45–56 1994.
84. Monyer, H.; Sprengel, R.; Schoepfer, R.; Herb, A.; Higuchi, M.; Lomeli, H.; Burnashev, N.; Sakmann, B.; Seeburg, P. H., Heteromeric NMDA receptors—molecular and functional distinction of subtypes. *Science*, **256**, 1217–1221 1992.
85. Morelli, M.; Fenu, S.; Pinna, A.; Dichiaro, G., Opposite effects of NMDA receptor blockade on dopaminergic D1-mediated and D2-mediated behavior in the 6-hydroxydopamine model of turning - relationship with c-fos expression. *Journal of Pharmacology and Experimental Therapeutics*, **260**, 402–408 1992.
86. Moryl, E.; Danysz, W.; Quack, G., Potential antidepressive properties of amantadine, memantine and bifemelane. *Pharmacology and Toxicology*, **72**, 394–397 1993.
87. Müller, W. E.; Mutschler, E.; Riederer, P., Noncompetitive NMDA receptor antagonists with fast open-channel blocking kinetics and strong voltage-dependency as potential therapeutic agents for Alzheimer's dementia. *Pharmacopsychiatry*, **28**, 113–124 1995.
88. Nankai, M.; Fage, D.; Carter, C., NMDA receptor subtype selectivity: eliprodil, polyamine spider toxins, dextromethorphan, and desipramine selectively block NMDA-evoked striatal acetylcholine but not spermidine release. *Journal of Neurochemistry*, **64**, 2043–2048 1995.
89. Netzer, R.; Binscheck, T.; Koch, R.; Bigalke, H. Memantine: suppression of high frequency action potentials is caused by prolongation of the refractory period of the sodium current. Berlin, Heidelberg: Springer Verlag; 217–221;1991.
90. Neugebauer, V.; Kornhuber, J.; Lucke, T.; Schaible, H. G., The clinically available NMDA receptor antagonist memantine is antinociceptive on rat spinal neurones. *NeuroReport*, **4**, 1259–1262 1993.
91. Osborne, N. N.; Quack, G., Memantine stimulates inositol phosphates production in neurones and nullifies N-methyl-D-aspartate-induced destruction of retinal neurones. *Neurochemistry International*, **21**, 329–336 1992.
92. Ossowska, K., The role of excitatory amino acids in experimental models of parkinson's disease. *Journal of Neural Transmission [Parkinson's Disease Section]*, **8**, 39–71 1994.
93. Pacifici, G. M.; Nardini, M.; Ferrari, P.; Latini, R.; Fieschi, C.; Morselli, P. L., Effect of amantadine on drug-induced parkinsonism: relationship between plasma levels and effects. *British Journal of Clinical Pharmacology*, **3**, 883–889 1976.
94. Papeschi, R., Amantadine may stimulate dopamine and noradrenaline receptors. *Neuropharmacology*, **13**, 77–83 1974.
95. Parsons, C. G.; Gruner, R.; Rozental, J.; Millar, J.; Lodge, D., Patch clamp studies on the kinetics and selectivity of N-methyl-D-aspartate receptor antagonism by memantine (1-amino-3,5-dimethyladamantan). *Neuropharmacology*, **32**, 1337–1350 1993.
96. Parsons, C. G.; Panchenko, V. A.; Pinchenko, V. O.; Tsyndrenko, A. Y.; Krishtal, O. A., Comparative patch clamp studies with freshly dissociated rat hippocampal and striatal neurones on the NMDA receptor antagonistic effects of amantadine and memantine. *European Journal of Neuroscience*, **8**, 446–454 1996.
97. Parsons, C. G.; Quack, G.; Bresink, I.; Baran, L.; Przegalinski, E.; Kostowski, W.; Krzascik, P.; Hartmann, S.; Danysz, W., Comparison of the potency, kinetics and voltage-dependency of open channel blockade for a series of uncompetitive NMDA antagonists in vitro with anticonvulsive and motor impairment activity in vivo. *Neuropharmacology*, **34**, 1239–1258 1995.
98. Porter, R. H. P.; Greenamyre, J. T., Regional variations in the pharmacology of NMDA receptor channel blockers: implications for therapeutic potential. *Journal of Neurochemistry*, **64**, 614–623 1995.
99. Prado de Carvalho, L.; Bochet, P.; Rossier, J., NMDA receptors expressed in oocytes: effects of ligands related to HIV infection. *Society of Neuroscience Abstracts*, **19.16**, 730 1993.
100. Quack, G.; Hesselink, M.; Danysz, W.; Spanagel, R., Microdialysis studies with amantadine and memantine on pharmacokinetics and effects on dopamine turnover. *Journal of Neural Transmission*, **46 (Suppl.)**, 95–102 1995.
101. Rabej, J. M.; Nissipeanu, P.; Korczyn, A. D., Efficacy of memantine, and NMDA receptor antagonist, in the treatment of Parkinson's disease. *Journal of Neural Transmission [Parkinson's Disease Section]*, **4**, 277–282 1992.
102. Randrup, A.; Mogilnicka, E., Pharmacology of monoaminergic mechanisms. *Polish Journal of Pharmacology and Pharmacy*, **28**, 551–556 1976.
103. Reiser, G.; Binmoller, F.; Koch, R., Memantine (1-amino-3,5-dimethyladamantane) blocks the serotonin-induced depolarization response in a neuronal cell line. *Brain Research*, **443**, 338–344 1988.
104. Reiser, G.; Koch, R., Memantine inhibits serotonin-induced rise of cytosolic Ca²⁺ activity and of cyclic GMP level in a neuronal cell line. *European Journal of Pharmacology [Molecular Pharmacology]*, **172**, 199–203 1989.
105. Rizzo, M.; Biandrate, P.; Tognoni, G.; Morselli, P. L., Amantadine in depression: relationship between behavioural effects and plasma levels. *European Journal of Clinical Pharmacology*, **5**, 226–228 1973.
106. Rohrbacher, J.; Bijak, M.; Misgeld, U., Suppression by memantine and amantadine of synaptic excitation intrastrially evoked in rat neostriatal slices. *Neuroscience Letters*, **182**, 95–98 1994.
107. Rojas, P.; Altagracia, M.; Kravzov, J.; Rios, C., Amantadine increases striatal dopamine turnover in MPTP-treated mice. *Drug Development Research*, **29**, 222–226 1993.
108. Sanger, D. J.; Terry, P.; Katz, J. L., Memantine has phencyclidine-like but not cocaine-like discriminative stimulus effects in rats. *Behavioral Pharmacology*, **3**, 265–268 1992.
109. Scatton, B.; Cheramy, A.; Besson, M. J.; Glowinski, J., Increased synthesis and release of dopamine in the striatum of the rat after amantadine treatment. *European Journal of Pharmacology*, **13**, 131–133 1970.
110. Schmidt, W. J., Intrastriatal injection of DL-2-amino-5-phosphonovaleric acid (AP-5) induces sniffing stereotypy that is antagonised by haloperidol and clozapine. *Psychopharmacology*, **90**, 123–130 1986.
111. Schmidt, W. J.; Bubser, M., Anticatalytic effects of the N-methyl-D-aspartate antagonist MK-801 in rats. *Pharmacology and Biochemistry of Behavior*, **32**, 621–623 1989.
112. Schmidt, W. J.; Bubser, M.; Hauber, W., Behavioural pharmacology of glutamate in the basal ganglia. *Journal of Neural Transmission [General Section, Suppl.]*, **38**, 65–89 1992.
113. Schmidt, W. J.; Zadow, B.; Kretschmer, B. D.; Hauber, W., Anticatalytic potencies of glutamate-antagonists. *Amino Acids*, **1**, 225–237 1991.
114. Schneider, E.; Fischer, P. A.; Clemens, R.; Balzereit, F.; Funfgeld, E. W.; Haase, H. J., Effects of oral memantine administration on Parkinson's symptoms. Results of placebo-controlled multicenter study. *Deutsch Medizin Wochenschrift*, **109**, 987–990 1984.
115. Schwab, R. S.; England, A. C.; Poskranzer, D. C.; Young, R. R.,

- Amantadine in the treatment of Parkinson's disease. *Journal of the American Medical Association*, **208**, 1168–1170 1969.
116. Schwarz, M.; Block, F.; Sontag, K. H., Normal N-methyl-D-aspartate (NMDA)-mediated muscle relaxant action of memantine in rats. *Neuroscience Letters*, **143**, 105–109 1992.
 117. Skuza, G.; Rogoz, Z.; Quack, G.; Danysz, W., Memantine, amantadine, and L-deprenyl potentiate the action of L-DOPA in monoamine-depleted rats. *Journal of Neural Transmission [General Section]*, **98**, 57–67 1994.
 118. Snell, L. D.; Johnson, K. M., Antagonism of N-methyl-D-aspartate-induced transmitter release in the rat striatum by phencyclidine-like drugs and its relationship to turning behavior. *Journal of Pharmacology and Experimental Therapeutics*, **235**, 50–57 1985.
 119. Sonsalla, P. K.; Nicklas, W. J.; Heikkila, R. E., Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. *Science*, **243**, 398–400 1989.
 120. Spanagel, R.; Eilbacher, B.; Wilke, R., Memantine-induced dopamine release in the prefrontal cortex and striatum of the rat - a pharmacokinetic microdialysis study. *European Journal of Pharmacology*, **262**, 21–26 1994.
 121. Starr, M. S., Glutamate/dopamine d-1/d-2 balance in the basal ganglia and its relevance to Parkinson's disease. *Synapse*, **19**, 264–293 1995.
 122. Starr, M. S.; Starr, B. S., Locomotor effects of amantadine in the mouse are not those of a typical glutamate antagonist. *Journal of Neural Transmission [Parkinson's Disease Section]*, **9**, 31–43 1995.
 123. Stieg, P. E.; Sathi, S.; Alvarado, S. P.; Jackson, P. S.; Pelligrini, J. W.; Chen, H. V.; Lipton, S. A.; Jensen, F. E., Post-stroke neuroprotection by memantine mimally affects behavior and does not block LTP. *Society of Neuroscience Abstracts*, **19**, 1502 1993.
 124. Stoof, J. C.; Booij, J.; Drukarch, B.; Wolters, E. C., The anti-parkinsonian drug amantadine inhibits the N-methyl-D-aspartic acid-evoked release of acetylcholine from rat neostriatum in a non-competitive way. *European Journal of Pharmacology*, **213**, 439–443 1992.
 125. Stipierre, J. A.; Bedard, P. J., Intrastriatal but not intrastriatal microinjection of the NMDA antagonist MK-801 induces contralateral circling in the 6-OHDA rat model. *Brain Research*, **660**, 255–260 1994.
 126. Strömberg, U.; Svensson, T. H., Further studies on the mode of action of amantadine. *Acta Pharmacologica et Toxicologica*, **30**, 161–171 1971.
 127. Svensson, T. H., Dopamine release and direct dopamine receptor activation in the central nervous system by D-145, an amantadine derivative. *European Journal of Pharmacology*, **23**, 232–238 1973.
 128. Svensson, A.; Carlsson, A.; Carlsson, M. L., Differential locomotor interactions between dopamine-d1/d2 receptor agonists and the NMDA antagonist dizocilpine in monoamine-depleted mice. *Journal of Neural Transmission [General Section]*, **90**, 199–217 1992.
 129. Tano, T.; Heluy-Dantas, M. C.; Marchiro, M.; Cintra, W. M.; Aracava, Y.; Albuquerque, E. X.; Schrattenholz, A.; Maelicke, A., The novel agonist site on nicotinic receptor (nAChR): activation by pyrazoles, amantadine and polyamines. *Society of Neuroscience Abstracts*, **19**, 1537 1993.
 130. Tilley, J. W.; Kramer, M. J. Amantadine derivatives. In: Ellis, G. P.; West, G. B., eds. *Progress in medicinal chemistry*, vol. 18. Amsterdam: Elsevier; 1981:1–44.
 131. Tomitaka, S.; Hashimoto, K.; Narita, N.; Minabe, Y.; Tamura, A., Amantadine induces c-fos in rat striatum: reversal with dopamine D1 and NMDA receptor antagonists. *European Journal of Pharmacology*, **285**, 207–211 1995.
 132. Tsai, M. C.; Chen, M. L.; Lo, S. C.; Tsai, G. C., Effects of memantine on the twitch tension of mouse diaphragm. *European Journal of Pharmacology*, **160**, 133–140 1989.
 133. Turski, L.; Bressler, K.; Rettig, K. J.; Loschmann, P. A.; Wachtel, H., Protection of substantia nigra from MPP + neurotoxicity by N-methyl-D-aspartate antagonists. *Nature*, **349**, 414–417 1991.
 134. Uitti, R. J.; Rajput, A. H.; Ahlskog, J. E.; Offord, K. P.; Schroeder, D. R.; Ho, M. M.; Prasad, M.; Rajput, A.; Basran, P., Amantadine treatment is an independent predictor of improved survival in Parkinson's disease. *Neurology*, **46**, 1551–1556 1996.
 135. Ulas, J.; Weihmuller, F. B.; Brunner, L. C.; Joyce, J. N.; Marshall, J. F.; Colman, C. W., Selective increase of NMDA-sensitive glutamate binding in the striatum of Parkinson's disease, Alzheimer's disease, and mixed Parkinson's disease/ Alzheimer's disease patients: an autoradiographic study. *Journal of Neuroscience*, **14**, 6317–6324 1994.
 136. Verspohl, E. J.; Koch, R.; Schatton, W., Interaction of memantine with cholecystokinin receptors in mouse brain. *Journal of Pharmacy and Pharmacology*, **40**, 111–115 1988.
 137. von Voigtlander, P. F.; Moore, K. E., Involvement of nigro-striatal neurons in the in vivo release of dopamine by amphetamine, amantadine and tyramine. *Journal of Pharmacology and Experimental Therapeutics*, **184**, 542–552 1973.
 138. Wachtel, H.; Kunow, M.; Loschmann, P. A., NBQX (6-nitro-sulfamoyl-benzo-quinoline-dione) and CPP (3-carboxy-piperazine-propyl phosphonic acid) potentiate dopamine agonist induced rotations in substantia-nigra lesioned rats. *Neuroscience Letters*, **142**, 179–182 1992.
 139. Watkins, J. C.; Evans, R. H., Excitatory amino acid transmitters. *Annual Review of Pharmacology and Toxicology*, **21**, 165–204 1981.
 140. Weihmuller, F. B.; Ulas, J.; Nguyen, L.; Cotman, C. W.; Marshall, J. F., Elevated NMDA receptors in parkinsonian striatum. *NeuroReport*, **3**, 977–980 1992.
 141. Weller, M.; Finielsmarlier, F.; Paul, S. M., NMDA receptor-mediated glutamate toxicity of cultured cerebellar, cortical and mesencephalic neurons - neuroprotective properties of amantadine and memantine. *Brain Research*, **613**, 143–148 1993.
 142. Wenk, G. L.; Danysz, W.; Mobley, S. L., Investigations of neurotoxicity and neuroprotection within the nucleus basalis of the rat. *Brain Research*, **655**, 7–11 1994.
 143. Wenk, G. L.; Danysz, W.; Mobley, S. L., MK-801, memantine and amantadine show neuroprotective activity in the nucleus basalis magnocellularis. *European Journal of Pharmacology*, **293**, 267–270 1995.
 144. Wenk, G. L.; Danysz, W.; Roice, D. D., NMDA receptor antagonist memantine blocks toxicity mediated by mitochondrial failure and cholinesterase inhibitor within the nucleus basalis magnocellularis. *NeuroReport*, **7**, 1453–1456 1996.
 145. Wesemann, W., Therapy of Morbus Parkinson and radical induced neurotoxicity in the rat. In vivo voltammetric studies. *Journal of Neural Transmission [Parkinson's Disease Section]*, **45**, 53, 1992.
 146. Wesemann, W.; Dette-Wildenhahn, G.; Fellehner, H., In vitro studies on the possible effects of 1-aminoadamantanes on the serotonergic system in M Parkinson. *Journal of Neural Transmission [General Section]*, **44**, 263–285 1979.
 147. Wesemann, W.; Ekenna, O., Effect of 1-aminoadamantanes on the MAO activity in brain, liver, and kidney of the rat. *Arzneimittelforschung*, **32**, 1241–1243 1982.
 148. Wesemann, W.; Schollmeyer, J. D.; Sturm, G., Distribution of memantine in brain, liver, and blood of the rat. *Arzneimittelforschung*, **32**, 1243–1245 1982.
 149. Wesemann, W.; Sontag, K. H.; Maj, J., On the pharmacodynamics and pharmacokinetics of memantine. *Arzneimittelforschung*, **33**, 1122–1134 1983.
 150. Wesemann, W.; Sturm, G.; Fünfgeld, E. W., Distribution and metabolism of the potential anti-parkinson drug memantine in the human. *Journal of Neural Transmission*, **16 (Suppl)** 1980.
 151. Zetler, G. Anticatalytic actions of amantadine hydrochloride. *Archiv für Experimentelle Pathologie und Pharmakologie* **266**: 1970; 276–278.