PERGAMON

Neuropharmacology 38 (1999) 735–767

NEURO PHARMACOLOGY

Review

Memantine is a clinically well tolerated *N*-methyl-D-aspartate (NMDA) receptor antagonist—a review of preclinical data

C.G. Parsons *, W. Danysz, G. Quack

Department of Pharmacological Research, Merz and Co., Eckenheimer Landstrasse 100-104, D-60318 Frankfurt am Main, Germany

Accepted 19 January 1999

Abstract

N-methyl-D-aspartate (NMDA) receptor antagonists have therapeutic potential in numerous CNS disorders ranging from acute neurodegeneration (e.g. stroke and trauma), chronic neurodegeneration (e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease, ALS) to symptomatic treatment (e.g. epilepsy, Parkinson's disease, drug dependence, depression, anxiety and chronic pain). However, many NMDA receptor antagonists also produce highly undesirable side effects at doses within their putative therapeutic range. This has unfortunately led to the conclusion that NMDA receptor antagonism is not a valid therapeutic approach. However, memantine is clearly an uncompetitive NMDA receptor antagonist at therapeutic concentrations achieved in the treatment of dementia and is essentially devoid of such side effects at doses within the therapeutic range. This has been attributed to memantine's moderate potency and associated rapid, strongly voltage-dependent blocking kinetics. The aim of this review is to summarise preclinical data on memantine supporting its mechanism of action and promising profile in animal models of chronic neurodegenerative diseases. The ultimate purpose is to provide evidence that it is indeed possible to develop clinically well tolerated NMDA receptor antagonists, a fact reflected in the recent interest of several pharmaceutical companies in developing compounds with similar properties to memantine.

Keywords: Memantine; NMDA receptor antagonist uncompetitive; Kinetics; Voltage-dependence; Learning; Neuroprotection; Dementia

Contents

* Corresponding author. Tel.: +49-69-1503-368; fax: +49-69-596-21-50.
E-mail address: chris.parsons@merz.de (C.G. Parsons)

1. Introduction

When a new therapeutic concept is proposed, this is usually followed by intensive screening in in vitro and in vivo studies, testing of selected agents in appropriate animal models and finally therapeutic verification with a few agents in clinical trials. This process may well take more than a decade to accomplish, and then discouraging clinical results with non-optimally selected agents might finally 'kill' the concept (see Muir and Lees, 1995). This is probably particularly true for NMDA receptor antagonists as clinical trials with newly developed agents failed to support good therapeutic utility due to numerous side effects (e.g. Dizocilpine ((+)MK-801); Cerestat (CNS-1102); Licostinel (ACEA 1021); Selfotel (CGS-19755) and D-CPP-ene) raising doubts about the possibility of developing NMDA receptor antagonists with a satisfactory side effect to benefit ratio (Leppik et al., 1988; Sveinbjornsdottir et al., 1993; SCRIP 2229/30, 1997, p. 21; Yenari et al., 1998).

NMDA receptor antagonists potentially have a wide range of therapeutic applications ranging from acute neurodegeneration (e.g. stroke and trauma), chronic neurodegeneration (e.g. Parkinson's disease, Alzheimer's disease, Huntington's disease, ALS) to symptomatic treatment (e.g. epilepsy, Parkinson's disease, drug dependence, depression, anxiety, chronic pain etc.—for reviews see: Meldrum, 1992; Danysz et al., 1995a; Müller et al., 1995; Parsons et al., 1998c). Functional modulation of NMDA receptors can be achieved through actions at different recognition sites such as: the primary transmitter site (competitive), the phencyclidine site located inside the cation channel (uncompetitive), the polyamine modulatory site and the strychnine-insensitive, coagonistic glycine site ($glycine_B$). However, NMDA receptors also play a crucial physiological role in various forms of synaptic plasticity such as those involved in learning and memory (see Collingridge and Singer, 1990; Danysz et al., 1995b). Neuroprotective agents which completely block NMDA receptors also impair normal synaptic transmission and thereby cause numerous side effects—a double sided sword. The challenge has therefore been to develop antagonists that prevent the pathological activation of NMDA receptors but allow their physiological activity. However, the potential for good clinical tolerability of NMDA receptor antagonism was in fact verified years before the concept was formulated. Memantine (1-amino-3,5-dimethyl-adamantane, Fig. 1) was already registered in Germany for a variety of CNS-indications in 1978 but its most likely therapeutic mechanism of action—uncompetitive NMDA receptor antagonism—was only discovered 10 years later (Bormann, 1989; Kornhuber et al., 1989, 1991; Parsons et al., 1993, 1995).

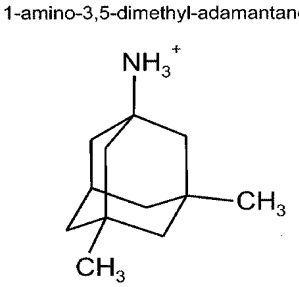

Fig. 1. Chemical structure of memantine.

Memantine was first synthesised by researchers at Eli Lilly in order to prepare a *N*-arylsulfonyl-*N'*-3,5-dimethyladamantylurea derivative as an agent to lower elevated blood sugar levels (Gerzon et al., 1963) but it was completely devoid of such activity. In 1972 Merz and Co. applied for a German patent demonstrating that this compound (code D 145) has central nervous system (CNS) activity indicating potential for the treatment of Parkinson's disease, spasticity and cerebral disorders like coma, cerebrovascular and geronto-psychiatric disturbances (see Grossmann and Schutz, 1982; Miltner, 1982a,b; Schneider et al., 1984; Mundinger and Milios, 1985). In 1975 and 1978, patents were granted in Germany and the USA, respectively. At that time, three major groups were engaged in the biochemical, pharmacological and pharmacokinetic evaluation of D 145 which had been given the INN memantine. In 1983, these groups published a joint synopsis on memantine in an attempt to summarise experimental evidence to explain clinical observations (Wesemann et al., 1983). They postulated direct and indirect dopaminomimetic activity as well as effects on serotonergic and noradrenergic

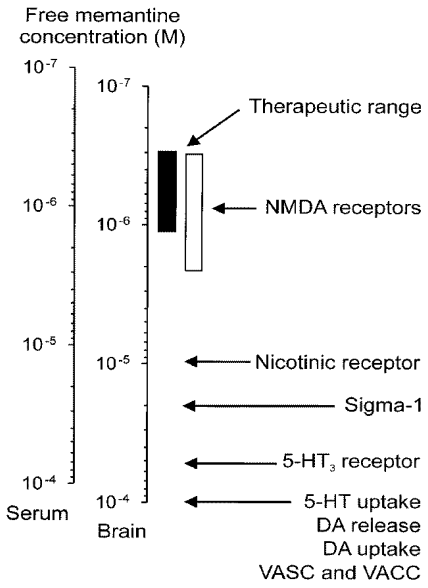

Fig. 2. Graphic presentation of in vitro effects of memantine in relation to its serum levels. The scale for brain levels is also shown on the basis of CSF sampling in man and brain microdialysis experiments in rats. NB: logarithmic scales.

systems. However, most in vitro data were obtained at concentrations 100 fold higher than those achieved therapeutically, a fact that was not recognised at the time. Since then, extensive preclinical research has revealed the most likely therapeutic mechanism of action of memantine to be via antagonism of NMDA receptors (Bormann, 1989; Kornhuber et al., 1989; Chen and Lipton, 1991; Kornhuber et al., 1991; Parsons and Pantev, 1991; Chen et al., 1992; Parsons et al., 1993). Based on these results, Merz filed an international application in 1989 claiming the treatment of cerebral ischæmia and Alzheimer's dementia. Since then, clinical research has focused on the treatment of dementia (Ditzler, 1991; Görtelmeyer et al., 1993; Pantev et al., 1993; Schulz et al., 1996a).

The present review discusses the mechanism of action of memantine as a clinically used and well tolerated NMDA receptor antagonist. It is an attempt to summarise the prerequisite features of memantine that determine its clinical safety in the treatment of dementia and possible utility in other CNS disorders. The aim is to demonstrate that NMDA receptor antagonism is indeed a valid therapeutic approach and that it is possible to develop compounds that show the desired separation between pathological and physiological activation of NMDA receptors. For other reviews on memantine which came to the same conclusion the reader is referred to the following (Rogawski, 1993; Müller et al., 1995; Kornhuber and Weller, 1997).

2. Clinical tolerability of memantine

As indicated above memantine has been applied clinically for over 15 years showing good tolerability and the number of treated patients exceeds 200 000. Although memantine has been reported to produce psychotomimetic effects in man (Riederer et al., 1991), as shown before for several other uncompetitive NMDA receptor antagonists, such reports should be put into context. Psychotomimetic effects only appear if the recommended titration of dosing from 5 to 20 mg over 3–4 weeks is skipped or when memantine is combined with dopaminomimetic therapies. In this respect it is noteworthy that in spite of the 15 year clinical history, side effects are sporadic and memantine is widely accepted as a very well tolerated medication (Grossmann and Schutz, 1982; Miltner, 1982a,b; Schneider et al., 1984; Mundinger and Milios, 1985; Ditzler, 1991; Görtelmeyer et al., 1993; Pantev et al., 1993; Schulz et al., 1996a).

The clinical observations indeed indicate the therapeutic utility of memantine. But to defend the concept of the validity of NMDA receptor antagonism it must first be proven that memantine is a NMDA receptor antagonist with sufficient affinity to block CNS NMDA receptors at therapeutic doses.

3. Memantine is a NMDA receptor antagonist

3.1. Receptor binding

Memantine displaces the binding of [^{3}H](+)MK-801 in human cortex, rat cortex and the CA1 region of hippocampus with Kis of around 1 μM (Kornhuber et al., 1989, 1991, 1994; Bresink et al., 1995a,b; Porter and Greenamyre, 1995). Due to the uncompetitive nature of such binding, inhibition could theoretically be indirect via antagonism at other sites of the NMDA receptor complex. This is unlikely, as our own previously unpublished binding date indicate no antagonistic interactions with the glutamate, glycine and sigma sites at therapeutically-relevant concentrations: memantine (10–100 μM) doesn't displace the binding of [^{3}H]aspartate, [^{3}H]glutamate, [^{3}H]glycine or [^{3}H]MDL-105,519 and high concentrations are required to displace [^{3}H](+)pentazocine binding from sigma-1 sites (K_i 20 μM, Kornhuber et al., 1993). Despite its relatively moderate affinity, memantine seems to be selective for the (+)MK-801 site and doesn't influence the binding of ligands for numerous other CNS receptors at 10–100 μM (e.g. Wesemann et al., 1979, 1981, 1983; Wesemann and Von Pusch, 1979, 1981; Osborne et al., 1982; Wesemann and Ekenna, 1982; Reiser et al., 1988; Verspohl et al., 1988; Reiser and Koch, 1989; Kornhuber et al., 1993; see Danysz et al., 1997 for review of previously unpublished data; see also Fig. 2). A radiolabelled memantine derivative (1-amino-3-[^{18}F]fluoro-methyl-5-methyl-adamantane) has been developed recently and should provide further insights into the nature and distribution of binding sites for memantine in the CNS (Samnick et al., 1997, 1998). The distribution of binding sites for 1-amino-3-[^{18}F]fluoro-methyl-5-methyl-adamantane in the murine CNS was similar to that of [^{3}H](+)MK-801 except for higher levels in the cerebellum, as expected for compounds binding with higher affinity to NR2C receptors (Bresink et al., 1995a,b; Porter and Greenamyre, 1995).

3.2. Electrophysiology

Whole cell patch clamp data from cultured and freshly dissociated neurones, retinal ganglion cells and NMDA receptors expressed in HEK-293 or CHO cells provide more conclusive evidence for open channel blockade of NMDA receptors by memantine, i.e. uncompetitive antagonism (Bormann, 1989; Chen et al., 1992; Parsons et al., 1993, 1995, 1996; Bresink et al., 1996; Frankiewicz et al., 1996; Blanpied et al., 1997; Chen and Lipton, 1997; Sobolevsky and Koshelev, 1998; Sobolevsky et al., 1998). In all studies, memantine antagonised NMDA receptor-mediated inward currents in a use and strongly voltage-dependent manner with IC_{50}s of 1–3 μM at −100 to −70 mV. For example, memantine blocked NMDA-induced currents in freshly dissociated hippocampal neurones with an IC_{50} of 1.04 μM at −100 mV (Parsons et al., 1996).

The antagonistic effects of memantine at −70 mV were not influenced by increasing concentrations of glycine (Parsons et al., 1993). Thus, antagonism via interactions at the glycine$_B$ site is unlikely. However, it is possible that memantine increases the affinity of glycine at NMDA receptors as reflected in a potentiation of NMDA currents at positive potentials by low concentrations of memantine (Wang et al., 1994; Wang and MacDonald, 1995; Parsons et al., 1998a). Although Berger et al. (1996) have proposed that part of the inhibition by memantine is due to interactions with the polyamine site, our own patch clamp data with cultured neurones indicate that the potency of memantine is identical in the absence and presence of spermine (with spermine 100 μM at −70 mV IC_{50} of 2.1 ± 0.1 μM, without spermine IC_{50} of 2.3 ± 0.3 μM; Parsons et al. unpublished). It seems more likely that any changes in the displacement of [^{3}H](+)MK-801 binding in the presence of polyamine antagonists or agonists is secondary to effects on the apparent affinity of [^{3}H](+)MK-801 itself. Much higher concentrations of memantine also gain access to the channel in the absence of agonist but the 100 fold lower affinity negates the therapeutic significance of such interactions (Blanpied et al., 1997; Sobolevsky et al., 1998).

Memantine and Mg^{2+} seem to block at the same or similar channel site as they are mutually exclusive—as evidenced by the kinetics of unblock in the presence of both (Chen et al., 1992; Sobolevsky et al., 1998). Memantine blocked human NR1/NR2A receptors expressed in *Xenopus* oocytes in a strongly voltage-dependent manner (IC_{50} at −80 mV = 0.3 μM, $\delta = 0.77$; Ferrer-Montiel et al., 1998). The potency of memantine was reduced 20 fold by mutations at the *N*-site of the M2 membrane inserted segment in NR1 subunits (N598Q) and 30–100 fold by double mutations (W593L/N598Q) within the channel forming domain. Double mutations at the equivalent L- (L577W) and Q/R-sites (Q582T) in GluR1 receptors permitted open channel blockade of AMPA receptors by memantine (IC_{50} at −70 mV = 1.3 μM, $\delta = 0.75$) (Ferrer-Montiel et al., 1998).

Memantine is two to three times more potent against NMDA receptors expressed in *Xenopus* oocytes than against NMDA-induced currents in cultured hippocampal neurones at the same membrane potential, i.e. −70 mV. The difference between these two electrophysiological assays is probably related to the following factors. Firstly, the NR1 splice variants expressed in cultured hippocampal neurones are not known but are very likely to influence the potencies of NMDA receptor channel blockers at heteromeric receptor complexes containing NR2A or NR2B subunits (Sakurada et al., 1993; Rodriguez Paz et al., 1995). Secondly, in order to

minimise artefacts mediated via voltage-activated K^+ channels at positive potentials, Cs^+ ions are often used as the major intracellular cation in most patch clamp experiments. Cs^+ ions have recently been reported to lower the affinity of memantine as a NMDA receptor antagonist in cultured retinal ganglion cells by increasing voltage-dependency (see Chen and Lipton, 1997). The fact that the influence of 'ionic pressure gradients' on Mg^{2+} block are different for various cations (Ruppersberg et al., 1994) prompted us to test the potency of memantine with intracellular K^+. We observed a 2.6 fold increase in the potency of memantine when K^+ was used as the major intracellular cation ($IC_{50} = 1.1$ μM at −70 mV, Parsons et al., 1999). Finally, memantine is also more potent at NMDA receptor subtypes expressed in HEK-293 and CHO cells (Bresink et al., 1996; Blanpied et al., 1997) and native NMDA receptors in freshly dissociated hippocampal neurones (Parsons et al., 1996; Sobolevsky and Koshelev, 1998; Sobolevsky et al., 1998) all of which lack the large dendritic arborization of cultured hippocampal pyramidal neurones. As such, the strong voltage-dependency of memantine might weaken its antagonistic effects at NMDA receptors on inadequately clamped distal dendrites in large cultured hippocampal pyramidal neurones.

The potency of memantine and other uncompetitive NMDA receptor antagonists is often apparently much lower in in vitro slice preparations used for electrophysiological recordings (Parsons et al., 1993; Rohrbacher et al., 1994; Apland and Cann, 1995) than against NMDA-induced currents in isolated neurones or finely chopped tissue used for biochemical experiments (e.g. Lupp et al., 1992; Nankai et al., 1995a,b, 1996, 1998). This is likely to reflect slow penetration of lipophyllic substances into relatively thick slices and the use-dependent nature of the blockade (Frankiewicz et al., 1996). Such factors should always be considered when comparing potencies in different preparations. For example, the fact that memantine (6 μM) was claimed to be completely without effects on the induction of LTP in hippocampal slices (Stieg et al., 1993; Chen et al., 1998) has to be regarded with some degree of caution. In our hands high concentrations of memantine were able to block the induction of LTP with an IC_{50} of 11.6 μM in the same preparation when slices were pre-incubated for several hours with memantine (Frankiewicz et al., 1996) although full inhibition was not observed with the highest concentration tested (30 μM). In the same study we saw no effect on the induction of LTP following short 30 min incubations of memantine at 100 μM. The technical problems of this approach are further highlighted by the fact that Chen et al. (1998) required huge concentrations of (+)MK-801 (6–10 μM) to block LTP in the same preparation (Chen et al., 1998) whereas long pre-incubations with (+)MK-801 are in fact able to block the induction of LTP with an IC_{50} of 0.13 μM (Frankiewicz et al., 1996).

3.3. Other effects of memantine in vitro

Antagonism of neuronal nicotinic receptor channels is probably of therapeutic relevance for the in vivo effects of amantadine (Parsons et al., 1995, 1996; Blanpied et al., 1997; Matsubayashi et al., 1997; Buisson and Bertrand, 1998; Parsons et al., unpublished: IC_{50} of 3–6 μM compared to IC_{50}s against NMDA of 20–70 μM). Memantine also blocks neuronal nicotinic receptor channels but its relative potency in this regard is probably too weak to be of therapeutic significance (IC_{50} at −70 mV = 12.3 μM; Parsons et al., 1998b; see also Grossmann et al., 1976; Masuo et al., 1986; Tsai et al., 1989). Similarly, the fact that high concentrations of memantine (100 μM) block repetitive action potential firing in cultures by decreasing the activation of voltage-activated Na^+ channels (Grossmann et al., 1976; Grossmann and Jurna, 1977; Klee, 1982; Netzer et al., 1986; McLean, 1987; Netzer and Bigalke, 1990) is unlikely to be of therapeutic relevance. Recent patch clamp data indicate that memantine only blocks TTX-sensitive and TTX-resistant voltage-activated Na^+ channels in freshly dissociated dorsal root ganglion neurones with IC_{50}s > 100 μM (Krishtal, unpublished).

Memantine was also much less potent as an L-type Ca^{2+} channel antagonist with an IC_{50} of 62 μM against Ca^{2+} influx in response to 30 mM KCl assessed with FURA2 measurements in cultured cerebellar granule cells (Müller et al., unpublished). In patch clamp experiments, memantine only blocks L- and *N*-type voltage-activated Ca^{2+} channels in freshly dissociated hippocampal neurones and P-type voltage-activated Ca^{2+} channel in freshly dissociated cerebellar Purkinje neurones with IC_{50}s > 180 μM (Krishtal, unpublished).

Although memantine (10–100 μM) had no effect on whole cell inward currents to GABA, AMPA, kainate or quisqualate (Chen et al., 1992; Parsons et al., 1993, 1996) we have observed a moderate potentiation (10–20%) of AMPA-induced currents by high concentrations of memantine (30 μM) using perforated patch recordings from cultured superior colliculus neurones (Parsons et al., 1994). This acute effect was somewhat more pronounced (20–30%) following subchronic pre-treatment of cultures for 2 weeks with memantine (10 μM). These effects were similar to those observed on AMPA responses in the cortical wedge preparation (Parsons et al., 1993). However, the relevance of these observations is unclear. Firstly, the concentrations of memantine were high and the effects were only moderate. Secondly, we have not observed similar effects on AMPA receptor-mediated fEPSPs in hippocampal slices (Frankiewicz et al., 1996). Thirdly, the potentiation seen with perforated patch recordings often developed slowly and was not reversible. This indicates that it may have been an artefact due to changes in cell access resistance, a common problem with this difficult recording technique.

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