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The NMDA receptor antagonist memantine as a symptomatological and neuroprotective treatment for Alzheimer's disease: preclinical evidence

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SUMMARY

There is increasing evidence for the involvement of glutamate-mediated neurotoxicity in the pathogenesis of Alzheimer's disease (AD). We suggest that glutamate receptors of the N-methyl-D-aspartate (NMDA) type are overactivated in a tonic rather than a phasic manner in this disorder. This continuous mild activation may lead to neuronal damage and impairment of synaptic plasticity (learning). It is likely that under such conditions Mg^{2+} ions, which block NMDA receptors under normal resting conditions, can no longer do so. We found that overactivation of NMDA receptors using a direct agonist or a decrease in Mg^{2+} concentration produced deficits in synaptic plasticity (*in vivo*: passive avoidance test and/or *in vitro*: LTP in the CA1 region). In both cases, memantine—an uncompetitive NMDA receptor antagonists with features of an 'improved' Mg^{2+} (voltage-dependency, kinetics, affinity)—attenuated this deficit. Synaptic plasticity was restored by therapeutically-relevant concentrations of memantine (1 μM). Moreover, doses leading to similar brain/serum levels provided neuroprotection in animal models relevant for neurodegeneration in AD such as neurotoxicity produced by inflammation in the NBM or β-amyloid injection to the hippocampus. As such, if overactivation of NMDA receptors is present in AD, memantine would be expected to improve both symptoms (cognition) and to slow down disease progression because it takes over the physiological function of magnesium. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — NMDA receptors; Alzheimer's dementia; memantine; neuroprotection; cognitive enhancement

INTRODUCTION

Glutamatergic neurons form the major excitatory system in the brain and play a pivotal role in many physiological functions. Glutamate activates several classes of metabotropic receptors and three major types of ionotropic receptor. These later receptors are ligand gated ionic channels permeable to the monovalent cations Na^+ and K^+ and, depending on the subtype, also to the divalent cation Ca^{2+}. α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are largely impermeable to Ca^{2+} and participate in most forms of fast synaptic transmission. In contrast, a subtype called N-methyl-D-aspartate (NMDA) (Figure 1) is only activated under certain conditions. This receptor has three cardinal features:

1. High permeability to Ca^{2+} ions
2. Voltage-dependent block by Mg^{2+} ions
3. Slow gating kinetics

These features, make NMDA receptors ideally suitable for mediating plastic changes in the brain, such as learning. An example of such plastic changes is long term potentiation (LTP, Figure 2) which is a phenomenon seen in brain slices and *in vivo* and believed to model basic mechanisms of memory formation. As presented in Figure 2, LTP can be described by the following sequence of events:

1. A high frequency signal (or convergence of several signals) arrives at the glutamatergic synapse leading to a massive glutamate release.
2. Glutamate binds to both NMDA and AMPA receptor, however only the later is activated initially

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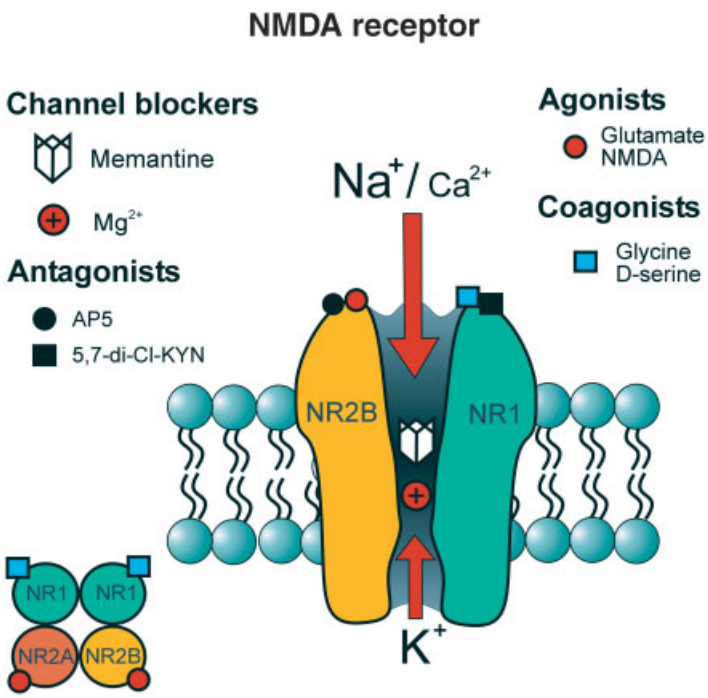

Figure 1. Scheme of the NMDA receptor. NB: permeability to Ca^{2+} and the channel blocking site for Mg^{2+} and memantine

since positively charged Mg^{2+} blocks the NMDA receptor channel. NB: this ion is attracted into the cell which has a negative resting membrane potential but gets trapped at a narrow region of the NMDA receptor channel.

3. Continued activation of AMPA receptors leads to a significant influx of Na^{+} ions into the cell which, in turn, leads to a decrease in membrane potential (partial depolarization).
4. This depolarization removes blockade by Mg^{2+} since the relative charge of the neuronal membrane is now much less negative (due to the influx of positively charged Na^{+} ions).
5. At this stage, Ca^{2+} ions can freely enter the cell via the NMDA receptor channel and initiate a number of enzymatic processes that are involved in the fixation of increased synaptic strength (neuronal memory formation). This post synaptic change is manifested as an enhancement of AMPA receptor sensitivity and number.

One should emphasize the crucial role of Mg^{2+} ions which function as a switch keeping NMDA receptors blocked under 'normal' conditions but allowing ion flux when the activation has features characteristic for learning processes, i.e. temporal and spatial convergence (co-operativity). In fact, experimental evidence clearly support this statement demonstrating that lowering the concentration of Mg^{2+} impairs synaptic plasticity (see Memantine Restores Impaired Neuronal Plasticity and Improves Learning).

Unfortunately, apart from the physiological role of glutamate, excessive activation of its receptors can also evoke neuronal dysfunction and even damage/death. This cell death ascribed to an excessive activation of glutamate receptors has been termed 'excitotoxicity' and seems to occur in acute insults such as stroke and trauma, but also in chronic neurodegenerative diseases such as AD.

The present review, is an attempt to elucidate the rational for the use of memantine (3,5-dimethylaminoadamantane) in AD. Memantine, is an NMDA receptor antagonist that has been recently approved in EU for this indication (moderate-to-severe AD). The NMDA receptor blocking property of this agent had been recognized by the end of 1980s (Kornhuber *et al.*, 1989), however only recently it's precise mode of action such as voltage and use dependency have

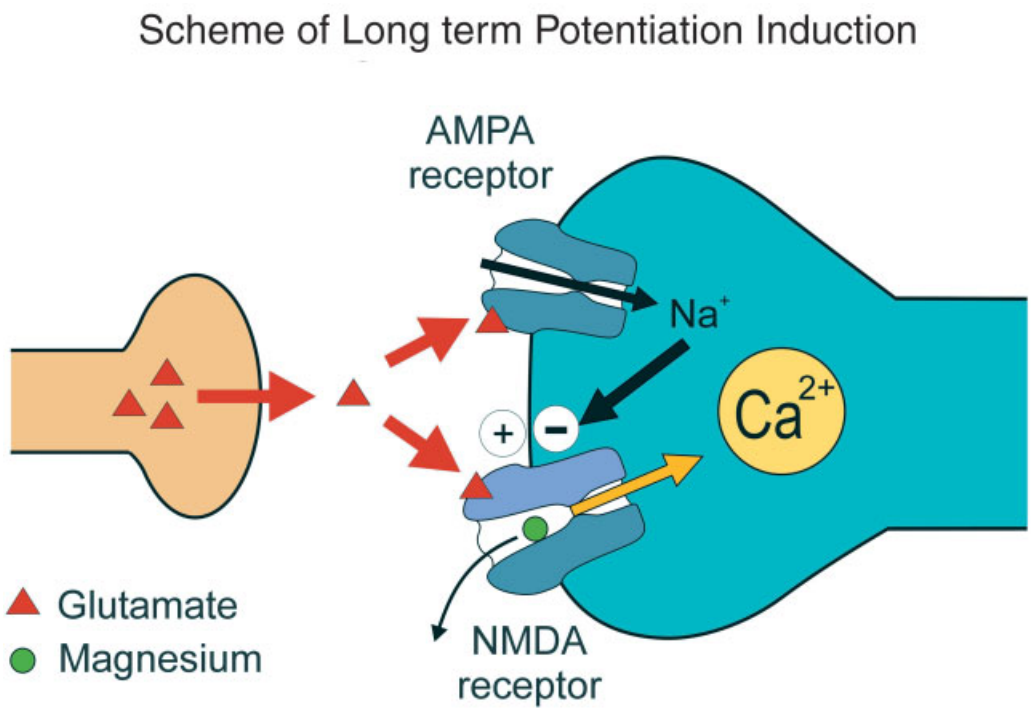

Figure 2. NMDA receptors are involved in Long Term Potentiation (LTP)—a neuronal model of memory formation. See text for description. Modified with permission from (Danysz *et al.*, 2000). Copyrights belong to Taylor & Francis Limited

been shown (Parsons *et al.*, 1993). For more extensive description of this agent see review by Parsons *et al.* (1999).

INDICATIONS FOR ENHANCED ACTIVITY OF THE GLUTAMATERGIC SYSTEM IN ALZHEIMER'S DISEASE

Over a decade ago it was suggested by Greenamyre that glutamate might be involved in the pathomechanism of neurodegenerative diseases, like AD (Greenamyre, 1986). An important aspect of this concept is the fact that an increase in glutamate levels *per se* is not necessarily required, because changes in receptors sensitivity and their overactivation by resting levels of glutamate could also contribute to neuronal death (Albin and Greenamyre, 1992). Since that time, a very large amount of supportive evidence for this hypothesis has accumulated and selected findings are listed briefly below.

POST MORTEM STUDIES

It is most likely that glutamatergic neurons are both executors and victims of excitotoxic processes. Thus, individual synapses may show overactivity which may lead to death of postsynaptic neurons and result in a secondary hypofunction of the whole system (Francis *et al.*, 1993).

1. Some authors have observed co-localisation of glutamatergic neurones and neurofibrillary tangles or senile plaques in the brains of AD patients (Pearson *et al.*, 1985; Rogers and Morrison, 1985; Braak *et al.*, 1993; Francis *et al.*, 1993).
2. There is a decrease in the astroglial glutamate transporter EAA2 in the frontal cortex (Li *et al.*, 1997) and some authors reported a correlation between a decrease in the immunoreactivity of glutamate transporter and neuronal pathology in AD patients (Masliah *et al.*, 1996; Masliah *et al.*, 1998). However, there is no consensus on that matter and according to some researchers there is no change in glutamate transporters in AD.
3. High affinity platelet glutamate uptake is decreased by 40% in AD as compared to controls (Ferrarese *et al.*, 2000).
4. In severe AD cases the intensity of NR1a (subunit of NMDA receptors) immunolabelling within the

hippocampal CA3 field is increased and in the dentate gyrus there are a number of NR1-labeled plaques (Ikonomovic *et al.*, 1999).

IN VITRO

1. Cultured macrophages exposed to Aβ1-40 produce higher concentrations of glutamate and oxygen free radical and β-amyloid peptide enhances glutamate release from primary cultured rat microglia via the Na^+-dependent glutamate transporter (Klegeris and McGeer, 1997; Noda *et al.*, 1999).
2. In glial cultures, β-amyloid (25–35) inhibits glutamate uptake, probably connected with increased production of free radicals (Harris *et al.*, 1995; Harris *et al.*, 1996; Hensley *et al.*, 1997).
3. Constituents of senile plaques stimulate microglia to produce an unknown neurotoxin (not glutamate!) with agonistic properties at NMDA receptors (Giulian *et al.*, 1995).
4. β-amyloid peptide enhances the toxicity of glutamate (Koh *et al.*, 1990; Mattson *et al.*, 1992; Brorson *et al.*, 1995).
5. Hippocampal neurons prepared from PS1 mutant knock-in mice show increased vulnerability to glutamate-induced excitotoxicity (Guo *et al.*, 1999; Grilli *et al.*, 2000).

IN VIVO

1. Injection of β-amyloid i.c.v. produces NMDA receptor dependent, long lasting depression of EPSPs in the hippocampus which seems to be an expression of ongoing mild excitotoxicity (Cullen *et al.*, 1996).
2. Mice, carrying mutant human preseniline-1 (PS-1) show an enhanced excitotoxic reaction to kainate (Schneider *et al.*, 2001). Neurons isolated from these mice also show an enhanced increase in $[Ca^{2+}]_I$ levels in response to glutamate (ibid.).
3. PS-1 mutant mice show enhanced sensitivity to damage induced by transient focal ischaemia (MCA occlusions) (Mattson *et al.*, 2000).
4. Transgenic mice with an APP mutation in the *a*-secretase site show enhanced sensitivity to glutamatergic agonists such as kainic acid and NMDA (Moechars *et al.*, 1996). Similar observations were seen in mutants bearing the Swedish or London mutations of APP (Moechars *et al.*, 1999).

CONSEQUENCES OF ENHANCED ACTIVITY OF THE GLUTAMATERGIC SYSTEM—SIGNAL-TO-NOISE HYPOTHESIS

It is known that physiologically, NMDA receptors are transiently activated by mM concentrations of glutamate (Clements *et al.*, 1992) (Figure 3A), whereas during pathological activation such as that occurring in AD, NMDA receptors are likely activated by lower concentrations of glutamate but more or less continuously. Under such conditions, temporally uncoordinated, continuous stimulation of NMDA receptors produces enhanced noise, decreasing the probability of detecting the relevant signal once it arrives (here referring to increased intracellular Ca^{2+} levels). This produces a progressive deficit in cognitive functions (Figure 3B). Thus Mg^{2+} which normally acts as a filter or switch is too weak to serve this role and the NMDA receptor can no longer function as a coincidence detector. This overactivation of glutamate receptors and continuous Ca^{2+} influx ultimately leads to damage of neurones not able to compensate and further decline of cognitive functions (Figure 3B). Thus, the same mechanism (overactive glutamatergic synapses) may be responsible for both cognitive deficits and neuronal loss in neurodegenerative dementia (Figure 3B).

SEARCH FOR A BETTER MAGNESIUM

As indicated above, and clearly evident from Figure 3B, a more effective surrogate for Mg^{2+} ions would be required to counteract this deficit. Mg^{2+}, the endogenous antagonist of NMDA receptors, is necessary for normal function, and obviously 'well tolerated' in contrast to high affinity antagonists such dizocilpine ((+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)MK-801) which produce numerous side effects. What makes these antagonists so different even though both act at the same channel site of the NMDA receptor? The answer came from electrophysiological experiments which showed that factors such as affinity, kinetics (Figure 4A) and voltage-dependency (Figure 4B) are crucial determinants of tolerability. Mg^{2+} shows strong voltage-dependency and very low affinity which is associated with fast blocking kinetics. In contrast, dizocilpine shows very high affinity which is associated with very slow kinetics and weak voltage-dependency. Electrophysiological studies also revealed that the moderate potency of memantine is associated with kinetics and voltage-dependency between those of Mg^{2+} and dizocilpine (Figure 4).

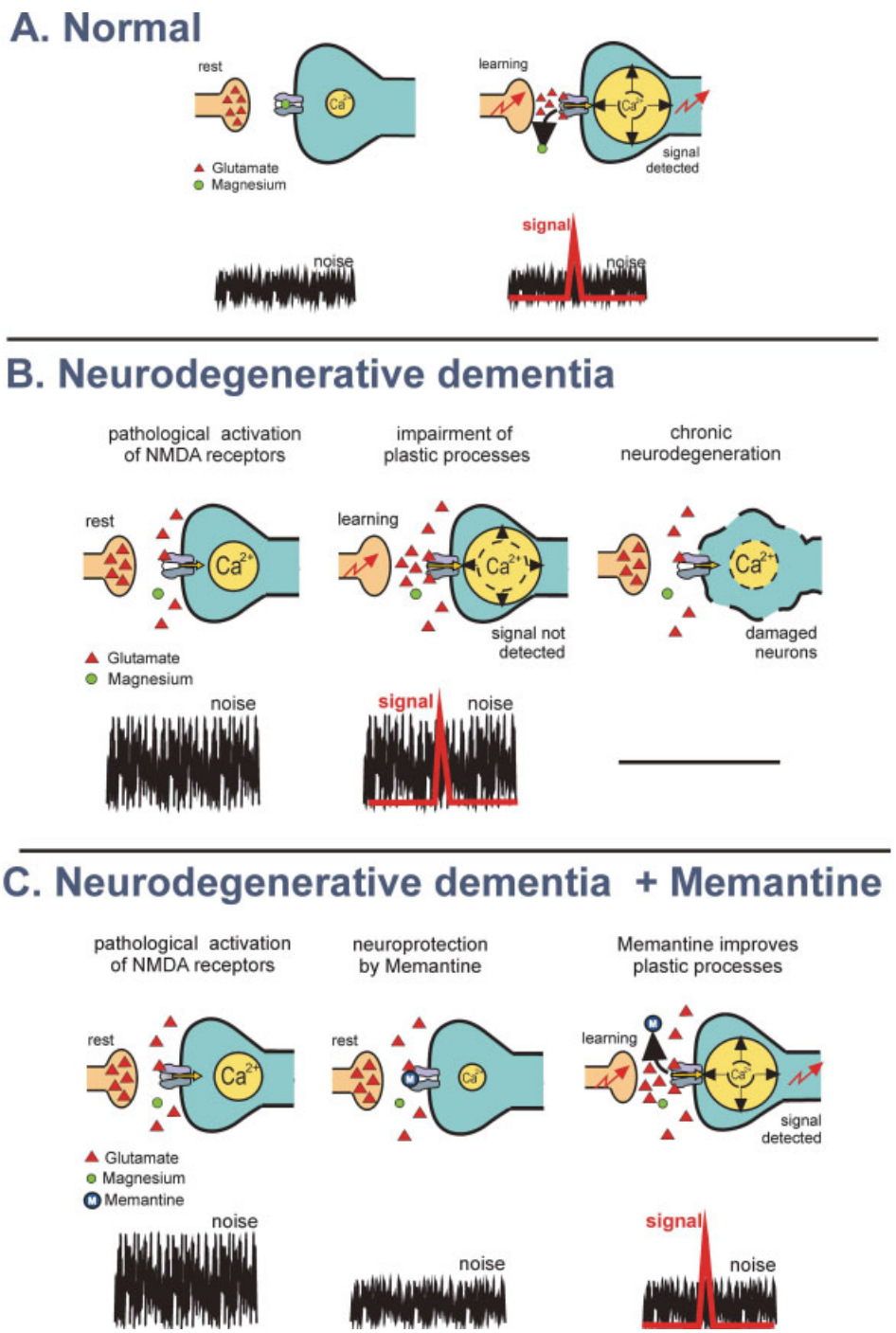

Figure 3. A. Under normal conditions, learning is based on detection of a relevant (sufficiently strong) signal over baseline activity (here referring to Ca^{2+} fluctuations), i.e. sufficient signal-to-noise ratio. B. Our signal-to-noise ratio hypothesis assumes that in Alzheimer's disease, due to overactive glutamatergic system, Mg^{2+} is not effective enough to play its 'filtering' function. In turn, synaptic noise rises, impairing detection of the relevant signal such as in learning. C. Scheme explaining memantine's action in Alzheimer's disease based on the signal-to-noise hypothesis. Memantine is able to serve as a filter blocking 'synaptic noise' and thereby allowing detection of the relevant signal i.e. synaptic plasticity is restored. Modified with permission from (Danysz *et al.*, 2000). Copyrights belong to Taylor & Francis Limited

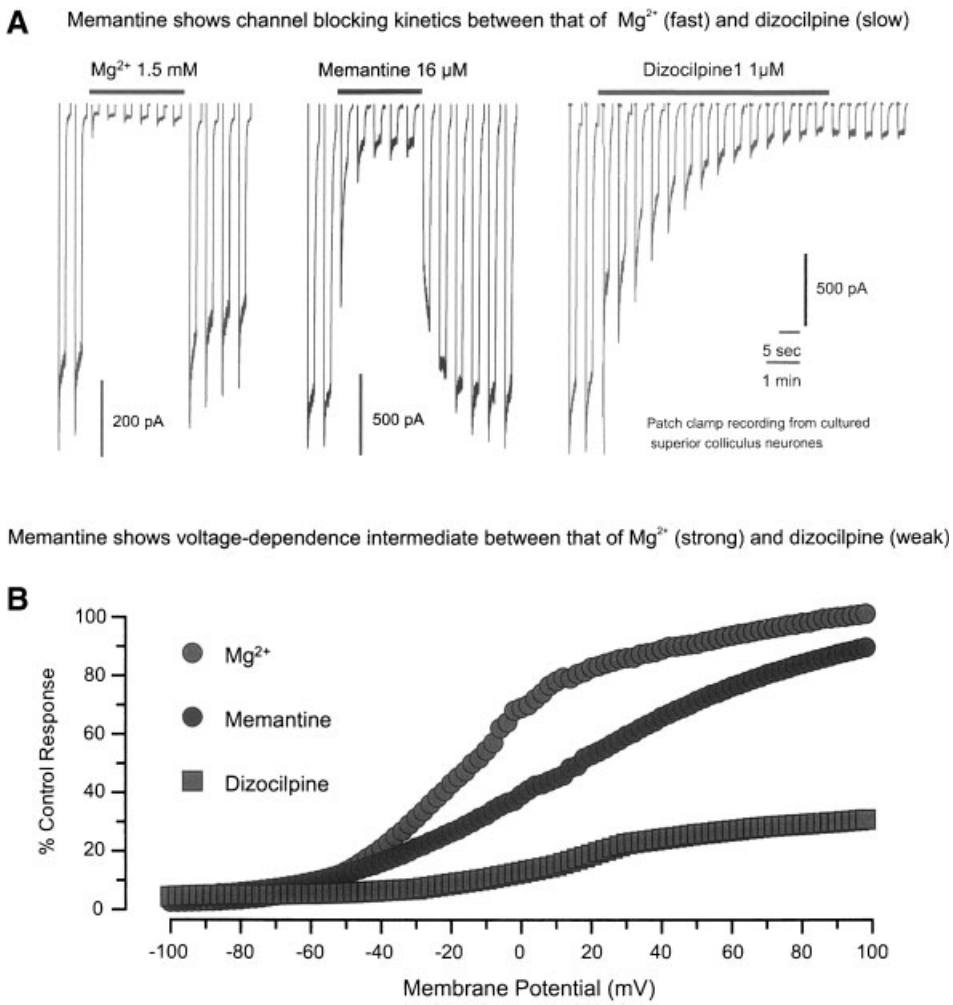

Figure 4. Graph showing electrophysiological recordings performed with the patch clamp technique. A. Note the difference in the speed of block and unblock by Mg^{2+}, memantine and the high affinity antagonist dizocilpine ((+)MK-801). Modified from (Parsons *et al.*, 1993). B. Graph showing pooled data from electrophysiological recordings performed with the patch clamp technique at different holding potentials. Such conditions mimic different synaptic status: resting conditions (negative potentials), pathological activation (moderate but prolonged synaptic activity at slightly depolarized potentials) and physiological synaptic transmission (strong but short lasting synaptic activity at strongly depolarized potentials)

As a result of its somewhat less pronounced voltage-dependency, memantine is more effective than Mg^{2+} in blocking tonic pathological activation of NMDA receptors at moderately depolarized membrane potentials (Figure 3C). However, following strong synaptic activation, memantine like Mg^{2+}, can leave the NMDA receptor channel due to its voltage-dependency and fast unblocking kinetics. As such, memantine suppresses synaptic noise but allows the relevant physiological synaptic signal to be detected (Figure 3C). This provides both neuroprotection and symptomatic restoration of synaptic plasticity by one and the same mechanism. In contrast, dizocilpine is too potent and shows such slow unblocking kinetics and weak voltage-dependency that it essentially acts as an irreversible plug of the NMDA receptor channel and blocks both pathological and physiological function.

MEMANTINE RESTORES IMPAIRED NEURONAL PLASTICITY AND IMPROVES LEARNING

In order to test the signal-to-noise hypothesis, an appropriate model should be selected that mimics

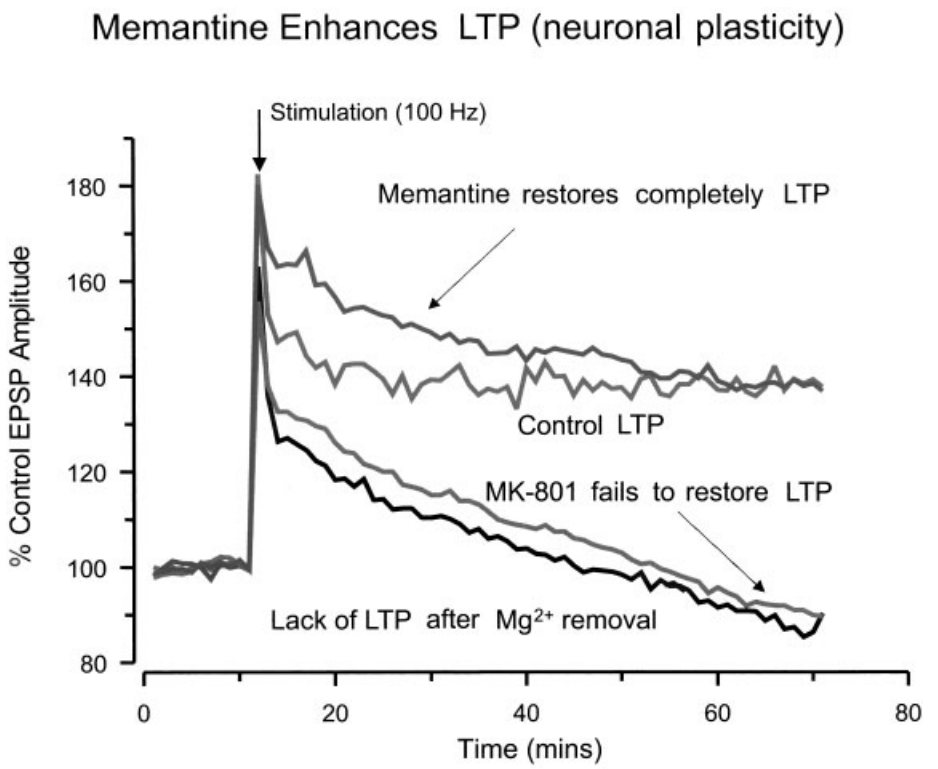

Figure 5. Normalized traces showing LTP induced by 100 Hz stimulation under different treatment condition. Under control conditions this stimulation produced long lasting (here shown till 60 min post induction) enhancement of synaptic efficacy. Note lack of LTP upon reduction of Mg^{2+} concentration and the failure of dizocilpine ((+)MK-801) to restore this deficit. In contrast memantine at 1 μM (therapeutically relevant concentration) completely restored LTP to control levels. Modified from Frankiewicz and Parsons (1999)

several aspects of a hyperactive glutamatergic system and is associated with pathological activity and impaired synaptic plasticity. In fact, it turned out that if NMDA receptors in hippocampal slices are over stimulated due to Mg^{2+} reduction or application of exogenous NMDA, synaptic plasticity such as LTP—the neuronal model of memory formation—is indeed impaired (Zajaczkowski *et al.*, 1997; Frankiewicz and Parsons, 1999). In these LTP experiments, synaptic plasticity impaired by glutamatergic hyperactivity—either in the presence of NMDA or lowered Mg^{2+} concentrations—was restored by memantine at concentrations equivalent to those known to improve cognition in AD patients (Figure 5, ibid.). Interestingly, no improvement was seen with the high affinity antagonist dizocilpine, indicating again fundamental differences in its mode of action. Some of these experiments were confirmed *in vivo* since memantine attenuated impairment of passive avoidance learning produced by NMDA (Figure 6) (Zajaczkowski *et al.*, 1997).

Memantine also improved learning in rats with entorhinal cortex lesions which has some relevance to AD since this structure is affected in early stages of this disease (Braak *et al.*, 1993). A few days after lesioning, minipumps containing memantine (20 mg/kg per day) were implanted subcutaneously and then rats were tested in a typical spatial learning task—the radial maze. Initially all lesioned groups showed a clear learning impairment, however after 9 days of testing (and parallel infusion) memantine-treated animals started to learn better reaching levels identical to non-lesioned animals (Zajaczkowski *et al.*, 1996).

Similarly, in moderately-aged rats memantine prolonged the duration of LTP *in vivo* and also showed a trend to improve memory retention in the Morris maze learning task (Barnes *et al.*, 1996).

Memantine also reversed learning impairment in the Morris water maze produced by a lesion (AF64A selective toxin) of the central cholinergic system (Bachurin *et al.*, 2001). In the same test, in rats withdrawn from chronic ingestion of alcohol,

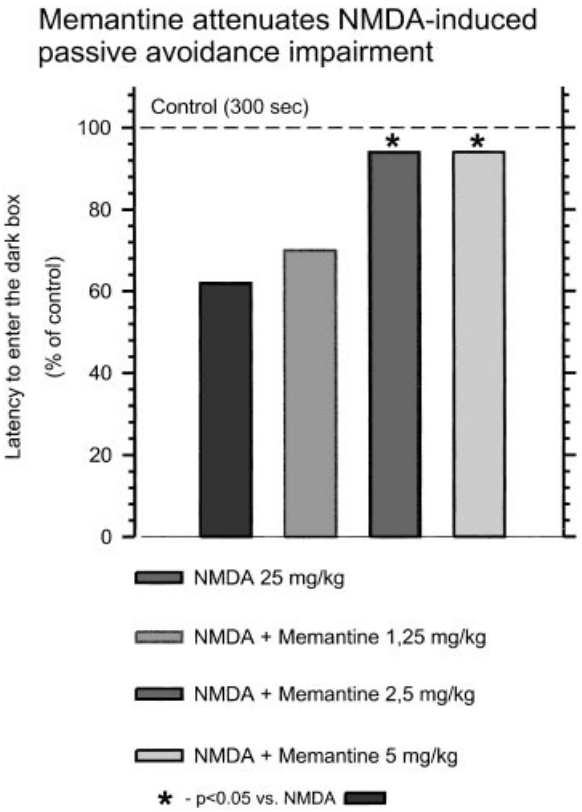

Figure 6. NMDA injected to rats produced amnesia (latency to enter the dark box is shorter) which was dose-dependently attenuated by memantine. In this test rats were trained to avoid a dark compartment connected with a footshock during training. When tested 24 h later, control animals, but not NMDA injected (during training) animals avoided this compartment. Memantine dose-dependently attenuated the deficit produced by NMDA. Modified from (Zajaczkowski *et al.*, 1997)

memantine similarly ameliorated learning deficits (Lukoyanov and Paula-Barbosa, 2001).

The experimental studies described above are in full agreement with clinical experience and controlled clinical studies showing positive effects of memantine on cognition in AD patients (Winblad and Poritis, 1999; Reisberg, 2003).

MEMANTINE PREVENTS NEURONAL DAMAGE

As mentioned above, long term overactivation of NMDA receptors would be expected to lead to neuronal death. Thus, it seems clear that under such conditions antagonism of NMDA receptors should provide neuroprotection. In fact, this seems to hold true for various conditions such as global and focal ischaemia, traumatic brain injury and also more chronic types of insult (Lees, 1993; Lipton and Rosenberg, 1994). Memantine has been tested against insults believed to contribute to the pathomechanism of AD. Thus, memantine at therapeutically relevant doses (leading to plasma levels c.a. 1 μM) provided *in vivo* protection from a variety of toxic conditions such as β-amyloid, inflammation, inhibition of mitochondrial function, and decrease in blood flow to the brain (Table 1). All of these factors have been implicated in the pathomechanism of AD. Thus, because the pathomechanism of AD involves multiple contributing factors, a drug like memantine should be a particularly effective disease modifying agent. This feature clearly distinguishes memantine from cholinesterase inhibitors which are not expected to inhibit disease progression. Clinical studies in AD aimed to demonstrate neuroprotective activity and inhibition of diseases progression by memantine are planned.

Table 1. Examples of neuroprotective effects of memantine in various conditions that may be relevant for the pathomechanism of Alzheimer's disease

Cause of insult	Type of insult	Effect of memantine	Reference
Injection of ß-amyloid into the hippocampus	Excitotoxicity?, others ?	Prevented neuronal damage and learning impairment	(Miguel-Hidalgo *et al.*, 2002)
Injection of antigen, LPS into NBM	Inflammation	Prevented neuronal damage in NBM	(Willard *et al.*, 2000)
Intraventricular infusion of NMDA agonist quinolinic acid	Excitotoxicity	Prevented neuronal damage in the hippocampus and learning impairment	(Misztal *et al.*, 1996)
Injection of NMDA into NBM	Excitotoxicity	Prevented neuronal damage in NBM and learning impairment	(Wenk *et al.*, 1994; Wenk *et al.*, 1995)
Injection of 3-NP into NBM	Metabolic compromise	Prevented neuronal damage in NBM	(Wenk *et al.*, 1996)
Focal ischaemia	Hypoxia, hypoglycaemia	Prevented structural and functional deficit	(Stieg *et al.*, 1999)

3-NP = 3-nitropropionic acid (mitochondrial toxin); LPS = lipopolysaccharide—an element of wall of Gram negative bacteria.

CONCLUSIONS

In contrast to cholinesterase inhibitors, memantine is likely to show neuroprotective effects at therapeutic concentrations used in the treatment of AD and to slow down disease progression. Clinically-relevant doses of memantine produce improvements in synaptic plasticity and learning under conditions of tonic NMDA receptor activation suggested to occur in AD.

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