

Neuroprotective And Symptomatological Action Of Memantine Relevant For Alzheimer's Disease – An Unified Hypothesis On The Mechanism Of Action

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28.1. Abstract

The involvement of glutamate mediated neurotoxicity in the pathogenesis of Alzheimer's disease is finding increasingly more acceptance in the scientific community. Central to this hypothesis is the assumption that in particular glutamate receptors of the NMDA type are overactivated in a tonic rather than a phasic manner. Such continuous mild activation leads under chronic conditions to neuronal damage. Moreover, one should consider that impairment of plasticity (learning) may result not only from neuronal damage per se but also from continuous activation of NMDA receptors. To investigate this possibility we tested whether overactivation of NMDA receptors using either non-toxic doses/concentrations of a direct NMDA agonist or through an indirect approach - decrease in magnesium concentration - produces deficits in plasticity. In fact NMDA both *in vivo* (passive avoidance test) and *in vitro* (LTP in CA1 region) impaired learning and synaptic plasticity. Under these conditions memantine which is an uncompetitive NMDA receptor antagonists with features of "improved magnesium" (voltage dependence, affinity) attenuated the deficit. The more direct proof that memantine can act as a surrogate for magnesium was obtained in LTP experiments under low magnesium conditions. In this case as well, impaired LTP was restored in the presence of therapeutically relevant concentrations of memantine (1 μ M). *In vivo*, doses leading to similar brain/serum levels produce neuroprotection in animal models relevant for neurodegeneration in Alzheimer's disease such as neurotoxicity produced by inflammation in the NBM or β -amyloid injection to the hippocampus. Hence, we postulate that if in Alzheimer's disease overactivation of NMDA receptors occurs indeed, memantine would be expected to improve both symptoms (cognition) and slow down disease progression because it takes over the physiological function of magnesium.

28.2. Introduction to the role of glutamate in the CNS

It is now generally accepted that glutamate is the major fast excitatory neurotransmitter in the mammalian CNS. It activates three major types of ionotropic receptors, namely α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA),

kainate and N-methyl-D-aspartate (NMDA) and several types of metabotropic receptors. AMPA receptors (Figure 1) are probably involved in all forms of fast glutamatergic neurotransmission (Danysz *et al.*, 1995a; Parsons *et al.*, 1998). There are four known subunits GluR1 to GluR4 which form functional receptors as tetrameric subunit assemblies. All AMPA receptors are permeable to Na^+ and K^+ while complexes lacking GluR2 subunits are also permeable to Ca^{2+} . NMDA-sensitive ionotropic glutamate receptors are coupled to high conductance cationic channels permeable to Na^+ , K^+ , and Ca^{2+} . NMDA receptors are modulated positively by polyamines (spermine and spermidine) and the obligatory co-agonist glycine (glycine $_{\beta}$ site). The NMDA channel is blocked in a use- and voltage-dependent manner by Mg^{2+} and many exogenous agents. NMDA receptors are only activated following depolarisation of the postsynaptic membrane which physiologically follows AMPA receptor stimulation which relieves blockade by Mg^{2+} . This unique feature and the high Ca^{2+} permeability renders NMDA receptors inherently suitable as mediators of synaptic plasticity (*e.g.*, learning and memory). Similar to Mg^{2+} , uncompetitive NMDA receptor antagonists such as ketamine, dextromethorphan, memantine, phencyclidine and MK-801 block the NMDA channel in the open state, although the blocking kinetics and voltage-dependence of this effect vary considerably (see later). NMDA receptors are formed as tetrameric assemblies and two major subunit families named NMDAR1 and NMDAR2 have been cloned from the rat CNS. NMDA receptor channels are formed by combinations of NMDAR1 and various NMDAR2 subunits and differ in gating properties, magnesium sensitivity and pharmacological profile.

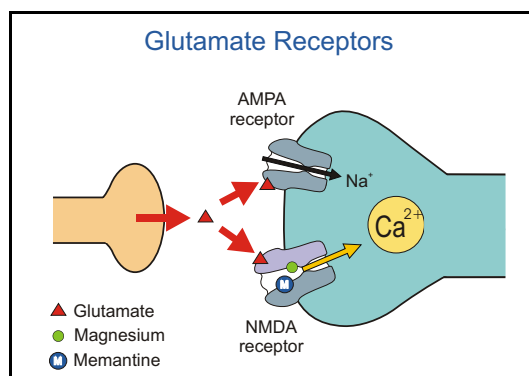


Figure 1. Schematic presentation of the glutamatergic synapse and major ionotropic glutamate receptors – AMPA and NMDA.

Glutamate is probably involved to some degree in virtually all CNS functions from primary sensory perception to cognition. The hippocampus is the structure most often connected with memory formation. All fast excitatory projection pathways to, within and from the hippocampus utilise glutamate as a transmitter. This brain region, due to its highly organised structure, is ideally suited for studies on long term potentiation (LTP) which is believed to represent an elementary feature of memory formation at the neuronal level. LTP refers to a persistent increase in synaptic sensitivity following high frequency stimulation of input neurones (Figure 2). NMDA receptors are involved in mediating the postsynaptic components of LTP in the hippocampus *e.g.*, in the Schaffer collateral projection from CA3 to CA1 (Danysz *et al.*, 1995b; Parsons *et al.*, 1998).

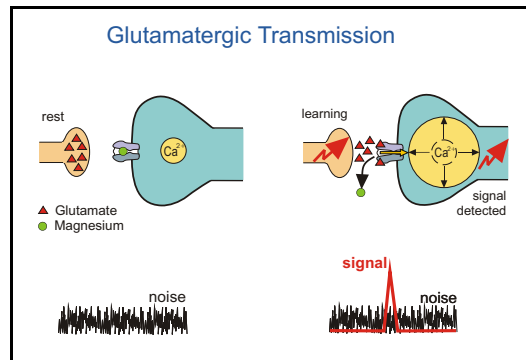


Figure 2. The principle of synaptic plasticity in the CNS is detection of the relevant signal over the existing background noise. Such a signal, once detected, may lead to a long lasting alteration in synaptic strength. NMDA receptors plays a central role in such alterations and an endogenous “noise suppressant” is magnesium. Physiological mechanisms are fully capable of keeping very low glutamate levels in the synaptic cleft under normal conditions.

Although glutamate is a crucial mediator of physiological communication between neuronal cells, under certain conditions activation of glutamate receptors kills neurones - a term called “excitotoxicity” (Rothman and Olney, 1987). It has been implied that excitotoxicity is involved in many types of acute and chronic CNS neurodegenerative disorders and is connected with Ca^{2+} overload (Choi, 1995). Disturbance of glutamate homeostasis probably plays a pivotal role in neuropathology triggered by other factors that facilitate the neurotoxic potential of endogenous glutamate such as: energy deficits, free radicals formation etc. (Danysz *et al.*, 1995a; Parsons *et al.*, 1998).

28.3. An alternative view on the role of glutamate in the pathomechanism and/or symptomatology of dementia

It was already suggested almost two decades ago that glutamate might be involved in the pathomechanism of neurodegenerative diseases, like Alzheimer's disease (Greenamyre *et al.*, 1984). Surprisingly, this hypothesis is still neglected by most supporters of the cholinergic hypothesis, although it should be stressed that the two hypotheses are by no means mutually exclusive (Palmer and Gershon, 1990). In contrast, the combination of them would probably give a more complete picture of pathological alterations within neurotransmitter systems in the brain of Alzheimer's patients. Glutamate would be an executor of neurodegenerative processes, and cholinergic neurones would be one of the victims. Recent findings provided several lines of support for the glutamatergic hypothesis.

There are indications that in Alzheimer's disease there is an increase in either glutamate (decrease of uptake and/or increase of release) or other endogenous glutamate receptors agonists in the vicinity of neurones

1. In post-mortem samples from brains of Alzheimer's patients there is a decrease in astroglial glutamate carrier EAA2 in the frontal cortex (Li *et al.*, 1997).

2. *In vitro* β -amyloid enhances depolarisation stimulated glutamate release - more in aged animals (Arias *et al.*, 1995) and inhibits its glial uptake (Harris *et al.*, 1996).
3. Glutamate and oxygen free radical production by macrophages is enhanced by A β 1-40 but not reverse A β 40-1 or the A β 25-35 subfragment (Klegeris and McGeer, 1997). In the case of glutamate a reversal of glutamate transporter is implied (Noda *et al.*, 1999).
4. There is a strong negative correlation between the distribution of the immunoreactivity of glutamate transporter and neuronal pathology in Alzheimer's brains (Masliah *et al.*, 1998).
5. *In vitro* constituents of senile plaques stimulate microglia to produce an unknown neurotoxin having agonistic properties at NMDA receptors (Giulian *et al.*, 1995).

β -amyloid peptide either activates NMDA receptors or enhances their sensitivity

6. Somewhat compatible is the finding that β -amyloid (1-40) stimulates NO production by microglia (Goodwin *et al.*, 1995) - NO is known to enhance glutamate release and to inhibit uptake (Lees, 1993).
7. *In vitro* β -amyloid peptide enhances the toxicity of glutamate (Mattson *et al.*, 1992) (Brorson *et al.*, 1995) and augments NMDA receptor mediated transmission (Wu *et al.*, 1995).
8. β -amyloid (25-35) displaces [3 H]glycine binding and stimulates functional [3 H]MK-801 binding which implies that this β -amyloid fragment might enhance NMDA receptor function acting as a glycine $_B$ agonist or partial agonist (Cowburn *et al.*, 1997).
9. *In vivo* injection of β -amyloid i.c.v. produces long lasting depression of EPSPs in the hippocampus - an expression of ongoing mild excitotoxicity - that is prevented by the NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) (Cullen *et al.*, 1996) – see signal to noise hypothesis.

Activation of NMDA receptors may enhance production of elements implied in the pathology of Alzheimer's disease such as β -amyloid or tau protein

10. Acute or chronic NMDA-induced excitotoxicity in neuronal cultures is associated with an augmented immune-labelling of phosphorylated tau proteins at serine 202 (AT8 antibody) as observed in paired helical neuro-filaments (Couratier *et al.*, 1995; Couratier *et al.*, 1996a). NMDA-induced cell death and elevated AT8 tau immunoreactivity is blocked significantly by NMDA receptor antagonists (Couratier *et al.*, 1996b). It is noteworthy that *in vitro* glutamate toxicity is blocked by antisense of tau mRNA (Pizzi *et al.*, 1995).
11. *In vivo* excitotoxicity increases APP production in glia (Topper *et al.*, 1995).

Post mortem or epidemiological studies suggest an association between glutamate dysfunction and Alzheimer's disease

12. Some authors observed co-localisation of glutamatergic neurones and pathological alterations (neurofibrillary tangles and senile plaques) in post-mortem analysis of the brains of Alzheimer's patients (Braak *et al.*, 1993; Francis *et al.*, 1993).

13. Head trauma (associated with glutamatergic dysfunction) has been suggested to be an important risk factor for Alzheimer's disease by some (Mortimer *et al.*, 1991) but not by other studies (Mendez *et al.*, 1992).

The above presented evidence - by no means complete - is probably convincing enough to consider glutamate, and NMDA receptors in particular, as contributing factors to the pathomechanism of Alzheimer's disease. In turn, for over a decade intensive research has been dedicated to search for NMDA receptor antagonists as a potential neuroprotective treatment for both acute (*e.g.*, stroke) and chronic neurodegenerative diseases. Although only very few such agents reached late stages of clinical development because of side-effects, it was discovered that several compounds currently in clinical use such as memantine, amantadine, dextromethorphan and others have NMDA blocking properties which likely play a role in their therapeutic efficacy. The present papers overviews the preclinical data on memantine supporting its current use for the treatment of Alzheimer's disease.

28.4. Memantine at therapeutically relevant doses provides neuroprotection in animal models of chronic neurodegenerative diseases

To allow extrapolation of animal data to the clinical situation therapeutically relevant doses should be used in animal experiments. A "therapeutically relevant" dose in animals is the one that leads to plasma levels close to the therapeutic range in humans treated with therapeutic doses of Memantine. Patients treated with 10-30 mg Memantine per day, have plasma levels of *c.a.* 0.2-1.0 μM supporting NMDA antagonism as the mechanism of clinical action. Brain microdialysis experiments with *in vivo* recovery indicate that the free brain interstitial concentration is only 20-30 % lower than in plasma (Kornhuber and Quack, 1995; Danysz *et al.*, 1997; Hesselink *et al.*, 1999). Similarly, 1 μM plasma concentrations are achieved in rats after acute injection of 2.5-5.0 mg/kg (*i.p.*) or *s.c.* infusion of 20 mg/kg/day using Alzet minipumps and these should be regarded as maximal clinically-relevant doses in rats (Danysz *et al.*, 1997).

To mimic some aspects of neurodegeneration occurring in Alzheimer's disease which is chronic in nature, the endogenous NMDA receptor agonist quinolinic acid was infused chronically directly to the brain (*i.c.v.*) via an ALZET osmotic minipump while a second pump delivered either saline or Memantine *s.c.* - all for 2 weeks (Miształ *et al.*, 1996). The Memantine concentration was adjusted to assure that steady-state plasma levels were similar to those seen in man (around 1 M). After two weeks, all pumps were removed and a few days later behavioural testing was initiated. Under these conditions, animals previously infused with quinolinic acid alone showed clear learning deficits in the T-maze while those infused in parallel *s.c.* with Memantine were able to acquire the task normally (Miształ *et al.*, 1996). Similarly, a decrease in choline uptake sites (an indicator of the density of ACh terminals) was seen in the cortex of animals treated with quinolinic acid but not in those receiving additional treatment with Memantine (*ibid*).

Of particular relevance to the clinical use of Memantine are preclinical studies on neurodegeneration in structures known to be important for learning and affected in Alzheimer's disease such as the cholinergic nucleus basalis of Meynert (NBM-nucleus basalis magnocellularis in rats). Wenk and colleagues (Wenk *et al.*, 1994, 1995) studied the effects of lesions of cholinergic neurones in the NBM in rats by directly injecting NMDA. This treatment caused a considerable decrease in levels of the acetylcholine synthesising

enzyme, choline acetyltransferase in target cortical areas. Memantine given i.p. before NMDA microinjection produced a clear cut protection with an ED₅₀ of 2.8 mg/kg (Wenk *et al.*, 1995). This dose produces quite low peak plasma levels < 1µM demonstrating good neuroprotective potential of Memantine even at such low, therapeutically relevant doses. The protective effect of Memantine was also expressed in functional tests such as spatial alternation learning in a "T"-maze (Wenk *et al.*, 1994) where memantine pre-treatment completely antagonised the learning deficits induced by microinjection of NMDA.

There are most probably many interacting factors contributing to the neuronal damage in neurodegenerative disorders, one of them is possibly secondary mitochondrial dysfunction. Wenk and co-workers (Wenk *et al.*, 1996) found that lesions of the NBM produced by a direct injection of mitochondrial toxin 3-nitropropionic acid (3-NP) is inhibited by Memantine. This indicates that NMDA receptors might be a likely link between different factors contributing to the neuronal insult. Memantine also significantly attenuates striatal lesions induced by the mitochondrial toxin malonate, again implicating utility in chronic neurodegenerative diseases associated with deficits in mitochondrial function (Schulz *et al.*, 1996).

It has been also suggested that also inflammation might play a major role in neurodegeneration in Alzheimer's disease (McGeer and McGeer, 1995). Recently, Wenk and colleagues (Wenk *et al.*, 1998) using a ChAT assay observed that Memantine infused s.c. by Alzet minipumps prevented the loss of cholinergic neurones in the NBM produced by chronic inflammation through i.c.v. infusion of lipopolysaccharide (bacterial wall component, LPS). The neuroprotective effect observed was not related to a change in ChAT activity per se but resulted from saving of neurones since the decrease in the number of cells immunoreactive for ChAT was also prevented by memantine (Wenk *et al.*, 1998). It is note worthy that, as expected, the inflammation process itself was not affected (measured by OX-6 microglial immunostaining).

Many studies *in vitro* suggest that glutamate receptors, and in particular NMDA receptors, contribute to the neuronal toxicity produced by β-amyloid peptide, a hallmark of Alzheimer's disease. Recently, Miguel-Hidalgo and colleagues (1998) found that memantine (15 mg/kg/day) infused s.c. by ALZET minipumps prevented pathological changes in the hippocampus produced by direct injection of β-amyloid. This included attenuation of damage, GFAP staining, ED1 labelled βAP deposits, and the number of picnotic/fragmented nuclei in the hippocampus (*ibid*). The latter indicates a decrease in apoptotic cell death.

These studies indicate that memantine is able to provide neuroprotection through blockade of NMDA receptors at doses apparently devoid of side effects.

28.5. Continuous overactivation of NMDA receptors might trigger memory impairment in dementia – signal to noise hypothesis

As mentioned above NMDA receptors are involved in various forms of synaptic plasticity including learning (Collingridge and Singer, 1990; Danysz *et al.*, 1995b). It should be mentioned that physiologically, NMDA receptors are transiently activated by mM concentrations of glutamate (Clements *et al.*, 1992) following depolarisation of the postsynaptic membrane which rapidly relieves their voltage-dependent blockade by Mg²⁺ (Nowak *et al.*, 1984) whereas during pathological activation, NMDA receptors are activated by lower concentrations of glutamate but for much longer periods of time (Globus *et al.*, 1988). The fact that neurodegenerative processes involve enhanced activation of NMDA

receptors might lead to the over simplistic assumption that an improvement of cognitive functions should be observed, at least at early stages of the disease. This however, is clearly not the case. The reason is that the crucial role of NMDA receptors in mediating synaptic plasticity depends on their ability to act as a coincidence detector. Only those synapses that show temporally and spatially discrete activation of NMDA receptors undergo plastic changes secondary to Ca^{2+} influx (Figure 2). In contrast, temporally uncoordinated, continuous stimulation of NMDA receptors due to energy deficits, prolonged membrane depolarization and enhanced glutamate levels, just produces enhanced noise decreasing the probability of detecting the relevant signal once it arrives (Figure 3). Hence, according to our hypothesis the following scenario might take place during the progression of Alzheimer's disease.

1. Increasing degree of continuous overactivation of NMDA receptors produces a progressive deficit in cognitive functions (Figure 3).
2. This over activation of glutamate receptors ultimately leads to damage of neurones not able to cope with the situation and further deterioration of cognitive functions (Figure 3)

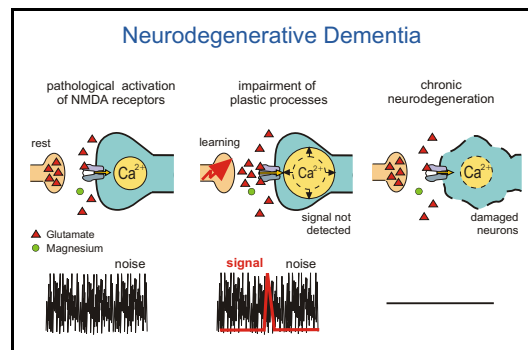


Figure 3. In neurodegenerative diseases such as Alzheimer's diseases contributing factors (e.g., malfunctioning uptake into astroglia) lead to sustained enhanced concentrations of glutamate in the synaptic cleft and resulting partial depolarisation. Under such conditions magnesium is not capable of suppressing the "noise" anymore. This leads to malfunctioning of signal detection (cognitive functions) and with time to damage of vulnerable neurones.

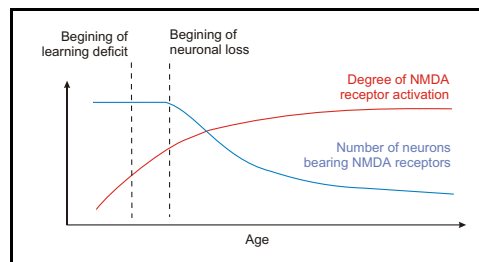


Figure 4. Graphic presentation of the hypothesis of Alzheimer's pathology proposed by John Olney (1998) implying early over stimulation of NMDA receptors leading to death of neurones bearing these receptors and in turn to a decrease in NMDA receptor number (NMDA receptor hypofunction).

This scenario, if true, probably takes place in different brain areas in a non synchronised way so that at a given time there are neuronal populations at each of the stages mentioned above (Figure 4).

28.6. Memantine is able to replace magnesium during continuous activation of NMDA receptors

A central aspect of this hypothesis is the assumption that, the voltage-dependency of Mg^{2+} is so pronounced that it also leaves the NMDA channel upon moderate depolarisation under pathological conditions. In other words, the double charge renders Mg^{2+} over sensitive to small changes in membrane potential. On the other hand, the voltage-dependency of high affinity uncompetitive NMDA receptor antagonists such as (+)-5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)-MK-801, dizocilpine) is too low and they show very slow unblocking kinetics. Thus, although dizocilpine provides clear neuroprotection, it also inhibits plastic processes involving NMDA receptors such as learning (Figure 5).

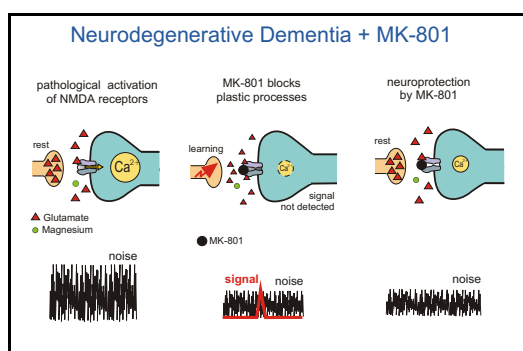


Figure 5. Although MK-801 would be expected to provide neuroprotection in the chronic neurodegenerative diseases but serious side effects are to be expected. The most serious would be inhibition of plastic processes like learning. Hence, MK-801 would not be expected to be able to “replace” magnesium due to its high affinity and low voltage dependence of the blockade.

It is becoming increasingly clear that uncompetitive NMDA receptor antagonists with fast unblocking kinetics and voltage-dependency between those of Mg^{2+} and MK-801 would be optimal. Such agents should be able to antagonise the pathological effects of the sustained, but relatively small increases in extracellular glutamate concentration but, like Mg^{2+} , leave the channel following physiological activation (Parsons *et al.*, 1993, 1995, 1996; Frankiewicz and Parsons, 1999) (Figure 6). Thus, uncompetitive NMDA receptor antagonists with moderate, rather than high affinity may be desirable. Memantine binds inside the NMDA receptor channel with a K_i of 0.5 μM (binding) and antagonises NMDA receptor-mediated inward currents *in vitro* with an IC_{50} of 1-3 μM (Kornhuber *et al.*, 1994; Parsons *et al.*, 1993, 1999).

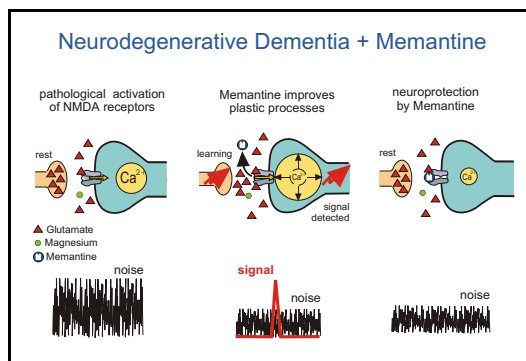


Figure 6. In contrast to MK-801 Memantine, thanks to its moderate affinity and high voltage dependency can replace endogenous magnesium leading to a decrease in background noise and restoration of synaptic plasticity. Such an action is accompanied by a neuroprotective effect. A high affinity NMDA receptor antagonist, although it can provide neuroprotection, can't act as a surrogate of magnesium and restore synaptic plasticity.

If our hypothesis were true, the invention of a “superior” magnesium should result in both slowing down the disease progression and in symptomatological benefit. The first aspect was discussed above, however to pursue the second issue we tested whether memantine attenuates deficits in plasticity produced by continuous activation of NMDA receptors both *in vivo* and *in vitro*. Zajaczkowski *et al.* (1997) using a two-choice passive avoidance task found that dark avoidance learning was impaired by systemic administration of NMDA (starting at 25 mg/kg) that was neither related to toxic effects nor state-dependent learning. Such NMDA-induced amnesia was antagonized by memantine at low doses of 2.5 and 5 mg/kg, but not higher. In the same study LTP in the of CA1 of hippocampal slices was reduced by the presence of non-toxic concentrations of NMDA - similar results were obtained previously by Zorumski and co-workers (Izumi *et al.*, 1992). The reduction of LTP seen in our experiments was antagonized by low concentrations of memantine (1 μ M), (Zajaczkowski *et al.*, 1997). Thus, under conditions of tonic activation of NMDA receptors, memantine can reverse deficits in synaptic plasticity, both at the neuronal (LTP) and behavioural (learning) level.

Recently, in our lab an attempt was undertaken to induce continuous activation of NMDA receptors by an endogenous agonist (glutamate) rather than by direct activation by an exogenous agonist. Such an approach might be more relevant for Alzheimer's disease. We selected removal of magnesium since it has been shown previously by Collingridge's group to impair LTP in the same preparation (Coan *et al.*, 1989). In fact we were able to confirm such dysfunction of plasticity following a decrease in magnesium concentration in the medium, and to show that memantine (1 μ M) was able to restore the induction of LTP (low Mg^{2+} 88.6 \pm 0.6% control; low Mg^{2+} plus memantine 1 μ M, 137.8 \pm 0.3% control), (Frankiewicz and Parsons, 1999). MK-801, was not able to improve LTP at any concentration tested (see Figure 5).

28.7. A unifying hypothesis of memantine action in Alzheimer's dementia

NMDA receptors are present on many types of neurones in the brain, among them also inhibitory GABAergic neurones. Hence, physiological activation of NMDA receptors

can result in inhibition (by this activation of inhibitory neurones) and to the contrary, blockade of NMDA receptors may result in activation of neuronal circuits. Bearing that in mind, in the hypothesis put forth by John Olney and co-workers (Olney *et al.*, 1998) they divided the course of structural degeneration in Alzheimer's disease into two phases: first, when over-activation of NMDA receptors leads to damage of neurones bearing this receptor subtype – in particular GABAergic neurones (Figure 7 – Advanced Alzheimer's); second, when a secondary hypofunctional state of NMDA receptors is resulting (their number decreases due to cell loss, Figure 4). Such loss of inhibitory GABAergic neurones in the brain leads to further neurotoxicity due to disinhibition (Figure 7 – Late Stage of Alzheimer's). There are two points that need clarification. According to Olney and co-workers (Olney *et al.*, 1998), the pathology observed after administration of high doses of some high affinity NMDA receptor antagonists produce neurodegeneration that histologically resembles some aspects of Alzheimer's disease. However, one should keep in mind that according to this concept treatment with NMDA receptor antagonists does not actually kill the neurones at which they act directly (bearing NMDA receptors - here GABAergic, Figure 7), but neurones postsynaptic to these inhibitory interneurones. In contrast, in Alzheimer's disease - according to this hypothesis - obviously also the population of GABAergic neurones sensitive to NMDA should degenerate resulting in a loss of NMDA receptors (Figure 7). Hence, these two situations by principle should create quite a different histological profile of damage. Moreover, PET studies in humans indicate a decrease in brain metabolism, in Alzheimer's disease while treatment with NMDA receptor antagonists is connected to increased metabolism in the brain.

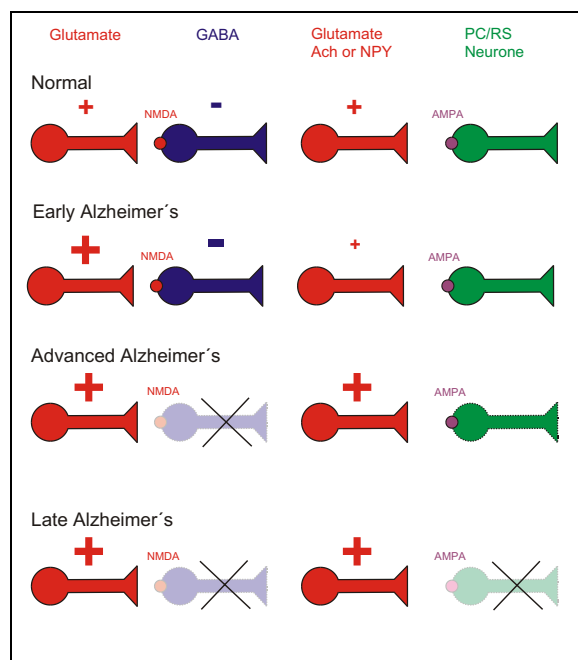


Figure 7. The hypothesis by Olney (1998) suggest that overactivation of NMDA receptors leads to damage of GABA neurones, and secondary damage produced by disinhibited neurones (e.g., glutamate, Ach, NPY).

The combination of data from the studies discussed above and the hypothesis of Olney and co-workers (Olney *et al.*, 1998) prompted us to propose the following scenario for Alzheimer's disease progression in relation to the beneficial effects of memantine seen in this disease.

1. Initial stages are characterized by continuous low level over stimulation of NMDA receptors. This leads first to dysfunction in synaptic plasticity - due to a decrease in signal-to-noise ratio – and ultimately, if no preventive therapy is in place, to death of vulnerable neurones (Figures 3 and 4). NMDA receptor antagonists like memantine which preserve physiological transmission but decrease the consequences of pathological activation may provide therefore a double benefit: decrease in disease progression and symptomatological improvement (Figure 6).
2. At later stages, when NMDA receptor mediated neurotoxicity is advanced, a functional deficit in glutamatergic transmission occurs due to loss of neurones bearing NMDA receptors (Figures 4 and 5). Since many of these are located on GABAergic neurones, this can lead to secondary neurodegeneration due to disinhibition (Figures 5 and 7). In contrast to (+)MK-801, Memantine does not worsen this secondary damage as physiological activation of NMDA receptors on neurones which are still functional is fully preserved in the presence of this moderate affinity antagonist. Thus, memantine is still able to exert its neuroprotective and positive symptomatological effects at intact glutamatergic synapses even at late stages of the disease.
3. Hence, this is a classical situation where both too much or too little is detrimental. In such case a stabilisation of neuronal activity at NMDA receptor bearing synapses is an optimal therapeutic approach. Such stabilisation, in our opinion, can be achieved by memantine which possesses a magnesium-like mode of action but not by agents like MK.801 (Figures 5 and 7).

Obviously, this hypothesis must be ultimately be verified in clinical trails in Alzheimer's disease. In fact clinical data clearly indicate that memantine might be a valuable treatment for Alzheimer's disease, producing significant positive symptomatological effects such as improvements in cognitive processes, activities of daily living and self care (Ditzler, 1991; Gortelmeyer and Erbler, 1992; Winblad and Poritis, 1999). It should be stressed that there are also other examples for of the use of glutamate antagonists for the treatment of Alzheimer's dementia. For example, ASTRA-ZENECA is developing a moderate affinity uncompetitive NMDA receptor antagonist Remacemide for this indication (Parsons *et al.*, 1998). Similarly, a recent study showed that the glutamate release inhibitor Lamotrigine improves word recognition, naming and mood in Alzheimer's patients (Tekin *et al.*, 1998).

28.8. Conclusions

In the light of recent findings the role of glutamate in the pathomechanism (neurodegeneration) of Alzheimer's disease seems very likely. The present review highlights the possibility that the same phenomenon (over activation of NMDA receptors) may paradoxically participate in the symptomatological deficit as well. The underlying

mechanism is supposedly a decrease of signal-to-noise ratio due to continuous, sustained activation of NMDA receptors.

Agents such as memantine which mimic some of the features of the endogenous antagonist magnesium may be an optimal treatment combining both neuroprotective activity with symptomatological improvement. The latter can be explained on the basis of a decrease in the noise level and restoration of a sufficient "signal-to-noise" ratio.

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