Memantine: An antiglutamatergic option for dementia

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Abstract

Alzheimer's disease (AD) is the most common form of dementia in occidental countries. Currently approved treatments for AD provide mainly symptomatic benefits without clear evidence of neuroprotection. N-methyl-D-aspartate (NMDA) receptor antagonists have therapeutic potential in several central nervous system disorders, including neuroprotective treatment in chronic neurodegenerative diseases, and symptomatic treatment in other neurologic diseases. Memantine, an NMDA antagonist, has been recently approved for the treatment of advanced AD. Due to its mechanism of action, memantine is considered a neuroprotective drug, whose utility has been demonstrated in preclinical studies. In addition, memantine is a useful symptomatic treatment for AD and vascular dementia. This paper reviews both aspects of memantine as well as some basic mechanisms mediating cognition and glutamatergic neurodegeneration.

Key words: memantine, Alzheimer's disease, dementia, NMDA, neuroprotective treatment

Introduction

The most common cause of dementia is likely the neurodegenerative disorder known as Alzheimer's disease (AD). Currently, it is estimated that more than 3 million people in Europe and 4.5 million people in the US suffer from dementia. In Europe, dementia affects 4 to 8 percent of the population over the age of 65.[1] More than 10 percent of individuals over 65 years, and more than 24 percent of those over 85 years suffer from dementia.[1,2] As life expectancy increases, the incidence of AD is increasing substantially as the population ages, and the number of sufferers is predicted to double for every six years of life expectancy. Approximately 800,000 new cases will be diagnosed every year in Europe.[2,3]

Early diagnosis of AD is important in order to develop and apply therapeutic strategies for preventing or slowing progression of the disease.[4] There is a great need to develop neuroprotective approaches, since a treatment that can slow progression of the disease over five years will reduce its cost by 50 percent.[5] Several cholinesterase inhibitors have been approved for mild to moderate AD, based on symptomatic improvement of cognitive function and a favorable global clinical impression.[6] However, until recently, there was no scientific evidence of an effective treatment for advanced AD, and there is still no clinical evidence of neuroprotective treatments.

Memantine is a low- to moderate-affinity, noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist.[7] It has been marketed in Germany since 1982, initially for the treatment of parkinsonism, cerebral and peripheral spasticity, and cognitive impairment.[8] Based on clinical benefits observed in patients with cognitive dysfunction, the focus of therapeutic interest shifted to dementia. Recently, memantine has been approved for the treatment of moderate to severe AD. The NMDA receptor antagonists have a wide range of potential therapeutic applications, from neuroprotection in acute and chronic neurodegeneration, demonstrated through in vitro studies, to symptomatic treatment of several neurological conditions such as epilepsy and Parkinson's disease.[9-11]

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As an antiglutamatergic agent, memantine offers potential neuroprotective properties, which have been demonstrated in preclinical studies. It addition, it is effective in the symptomatic treatment of AD and vascular dementia. This article will review both aspects of memantine along with the basic mechanisms that mediate glutamatergic neurodegeneration and the implication of glutamate in cognition.

Pharmacokinetic properties

Memantine is a noncompetitive, low to moderate affinity NMDA receptor antagonist. Memantine is absorbed completely from the gastrointestinal tract. Peak plasma concentration is achieved six to eight hours after oral intake. Time to maximum plasma concentration following single oral doses of 10 to 40 mg was between three and 7.7 hours, respectively. Following repeated doses, steady state levels are reached in approximately 21 days and are about three to four times the maximum plasma concentration after a single dose. Under therapeutic conditions in men, the serum levels of memantine with daily maintenance doses of 20 mg range from 0.5-1 mM.

Memantine is bound by plasma proteins to about 45 percent and is eliminated from plasma with a mean $T_{1/2}$ of 60 to 100 hours. Memantine is eliminated predominantly by the kidneys, 80 percent as an unchanged substance and the rest as hydroxylated metabolites and, to a smaller extent, by the liver to bile and feces. Because memantine clearance correlates with creatinine clearance, memantine plasma levels may increase in people with renal insufficiency, and the drug should not be administered to persons with severe renal insufficiency. Memantine crosses the blood-brain barrier, although cerebroespinal fluid (CSF) levels are 20 to 50 percent lower in respect to plasma levels due to albumin binding in serum.[12]

Pharmacological interactions

Because of its pharmacological effect and mechanisms of action, memantine may interact with other drugs. Due to its mode of action, concomitant treatment with L-dopa, dopaminergic agonists, and anticholinergics may enhance their pharmacological effects. By contrast, the effects of barbiturates and neuroleptics could be reduced. Because concomitant administration of memantine with antispasmodic agents, such as dantrolene or baclofen, may modify their clinical effect, adjustment of the dosage may be necessary.

Concomitant use of memantine with other chemically related NMDA antagonists, such as amantadine, ketamine, budipine, and dextromethorphan, should be avoided due to the risk of pharmacopsychosis. Memantine plasma levels may increase when using drugs that share the same renal cationic transport system, such as cimetidine, ranitidine, procainamide, quinidine, quinine, and nicotine.

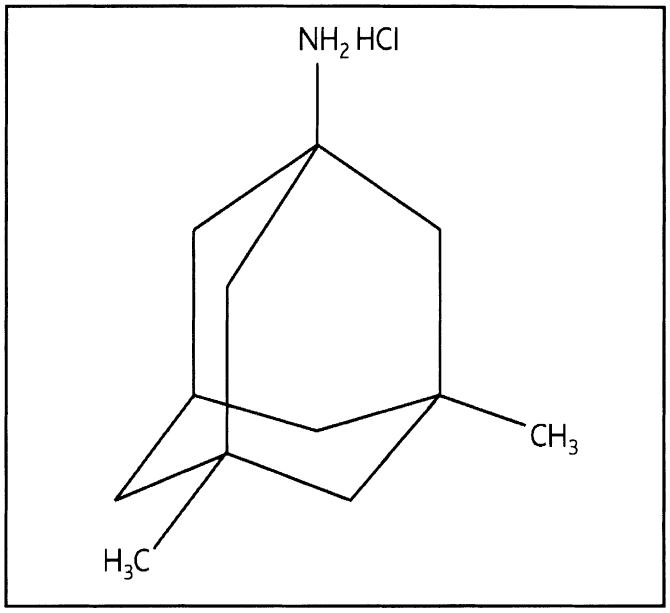

Figure 1. The chemical structure of memantine ($C_{12}H_{21}N$) is 1-amino-3,5-dimethyl-adamantane.

Adverse events

Clinical trials have shown that most adverse events were of mild to moderate severity, presenting similar incidence in the memantine-treated group and the placebo group. The symptoms presenting most frequently in the memantine-treated group were hallucinations, dizziness, agitation, headache, and fatigue. Less frequent symptoms included anxiety, vomiting, urinary tract infection, and increased sweating. Memantine may also cause adverse events in healthy volunteers, such as fatigue, headache, vertigo, somnolence, dry mouth, agitation, and nausea.

Pharmacodynamic properties

The role of glutamate in AD

Over the past decade, research has focused on enhancing cholinergic transmission because AD patients experience a loss of cholinergic neurons, synapses, and activity. However, the involvement of glutamate in the pathogenesis of AD is finding increasingly more acceptance in the scientific community.

Glutamatergic neurons form the major excitatory system in the brain and glutamate plays a pivotal role in

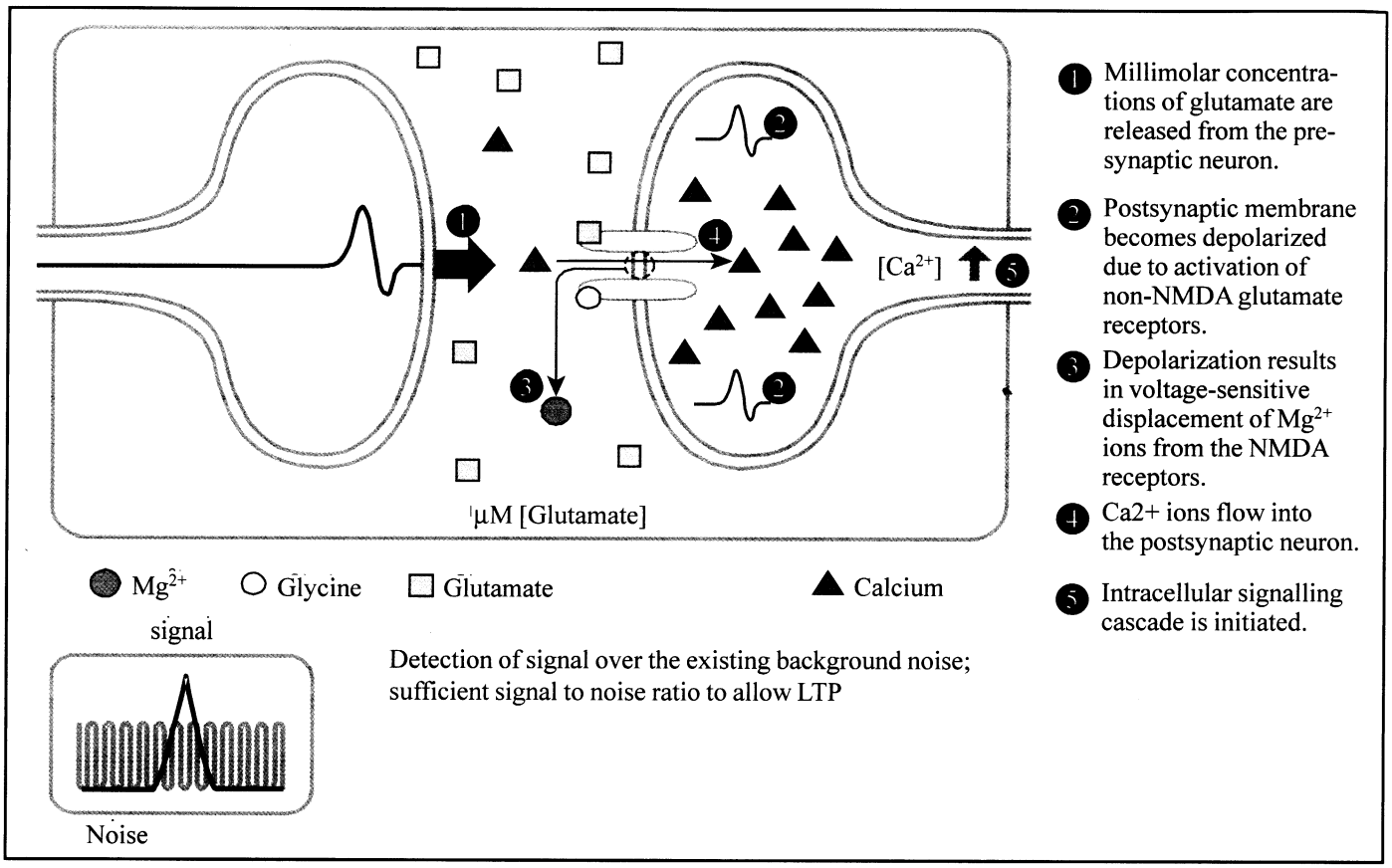

Figure 2. Synaptic activation under normal glutamatergic transmission.

many neurophysiological functions. In this sense, glutamate is a key neurotransmitter in primary perception and cognition.[13] The excitatory effect of glutamate is exerted through the activation of several classes of metabotropic receptors linked to G-protein[14] and three major types of ionotropic receptors: NMDA, kainic acid, and AMPA. These ionotropic receptors are ligand-gated ionic channels permeable to different cations.[15] The NMDA receptor has several features: high permeability to Ca^{+2} ions, voltage-dependent block by Mg^{+2} ions, and slow-gating kinetics. These characteristics are essential in generating long-term potentiation and synaptic plasticity, and to understanding the mechanism of action of memantine (Figures 2-5). Unfortunately, apart from the physiological role of glutamate, excessive activation of glutamate receptors can result in neuronal dysfunction and death, a process called excitotoxicity.

Recent studies performed on animal models give direct evidence that the hippocampus is the main anatomical structure participating in declarative episodic memory.[16] In terms of mechanisms of memory storage in the hippocampal system, the process of long-term potentiation (LTP) is widely favored.[17,18] In this sense, high frequency or appropriately patterned stimulation of axons induce long lasting monosynaptic increases in synaptic transmission in all major subfields of the hippocampus.[19] In addition, considerable indirect evidence supports the view that a process like LTP may underlie processes of memory storage in the hippocampus,[20] and that glutamate NMDA receptors play a critical role in its induction.[17]

It is also generally accepted that NMDA antagonists with high affinity to the receptor (such as MK-801) inhibit learning and LTP, and that noncompetitive antagonists similar to memantine, with lower receptor affinity and fast voltage-dependent channel unblocking kinetics, appear to act differently.

Recently, it has been shown that there is an excess of glutamate and glutamatergic activity in AD.[21,22] In AD, glutamate does not exert its physiological role, since NMDA glutamate receptors are overactivated in a tonic rather than a phasic manner. Such continuous activation of NMDA receptors leads to an excessive influx of Ca^{+2} and an increase in synaptic "noise," which impairs both the LTP process and neuronal plasticity (learning),[14] and under chronic conditions produces neuronal damage.

Additional research documents a role for glutamate in the neurodegenerative process of dementia.[14] It is unlikely that a disturbance in glutamate homeostasis is

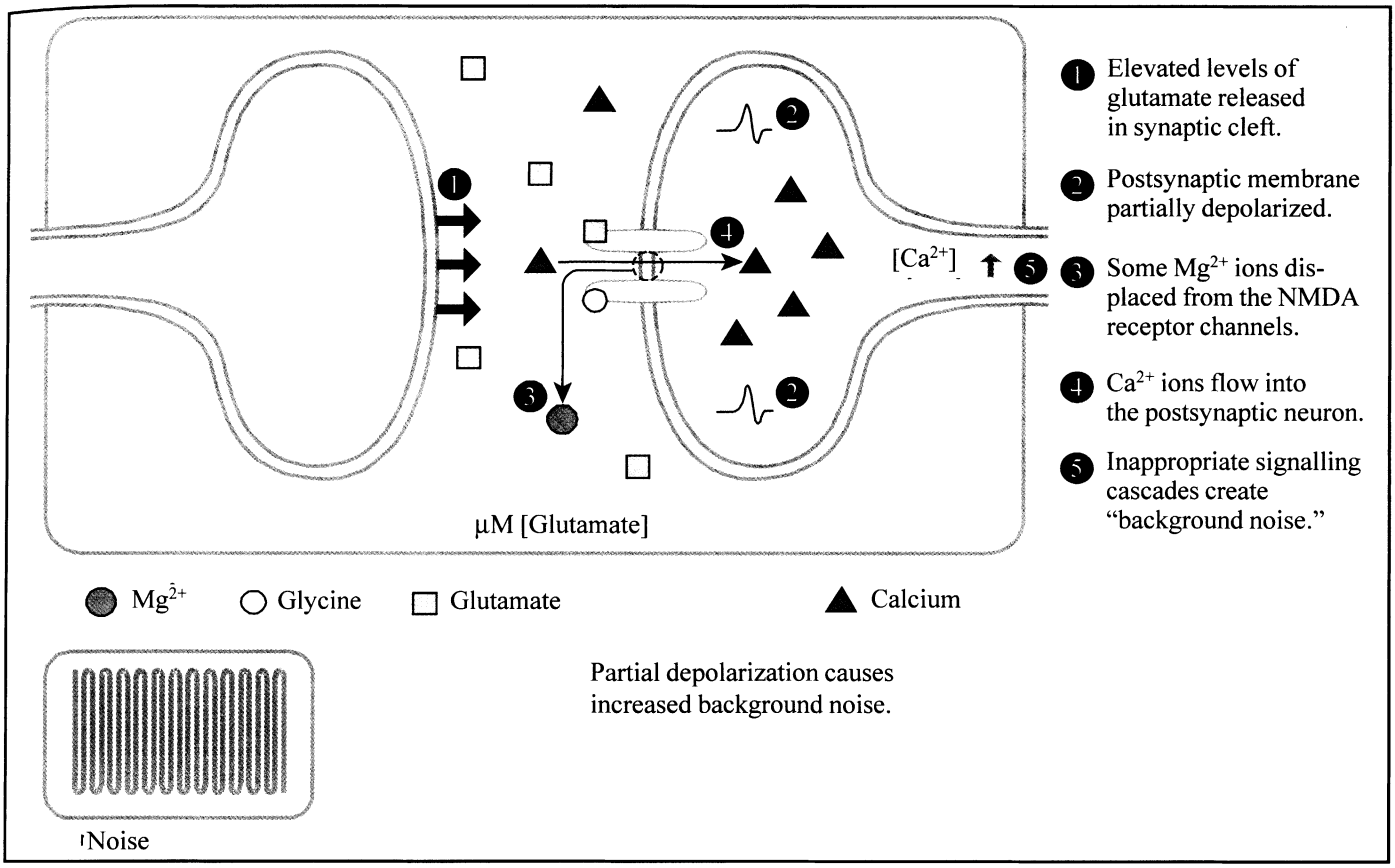

Figure 3. Tonic pathological activation of the NMDA receptor.

the sole initiator of AD, but it probably plays a pivotal role, which could be triggered by energy deficits, free radical formation, or other factors. Recent findings provide several lines of support for the glutamatergic hypothesis in AD (for revision, see Danysz and Parsons.)[15] In this sense, scientific evidence documents an increase in either glutamate or other endogenous glutamate agonists in AD. It has also been suggested that there is a reciprocal influence and relationship between β-amyloid production and NMDA activation: β-amyloid peptide either activates NMDA receptors or enhances their sensitivity, while activation of NMDA receptors enhances β-amyloid and τ-protein production.[23-25] Postmortem or epidemiological studies have also suggested an association between glutamatergic dysfunction and AD.

Mechanism of action of memantine

Electrophysiological studies support the hypothesis that memantine modulates glutamatergic neurotransmission, allowing the physiologic activation of NMDA receptors during memory formation while blocking their pathological activation in AD. There is an excessive influx of Ca^{+2} in AD neurons, which may lead to the impairment of LTP and neuronal plasticity, as well as contribute to neurodegeneration. An ideal antiglutamatergic drug for the treatment of AD should therefore be able to block the massive entrance of Ca^{+2}, allowing a physiological activation of the receptor.

As shown by in vitro studies, memantine and Mg^{+2} seem to block the same NMDA channel site, behaving as mutually exclusive ligands.[26] However, because the blocking kinetics and voltage dependency of memantine are between those of Mg^{+2} and classical glutamate channel blockers, memantine does not leave the channel under pathological activation. In fact, therapeutically relevant concentrations of memantine in animal models have been shown to provide neuroprotection against the pathological, excitotoxic activation of glutamate receptors. Therefore, memantine as a noncompetitive, moderate affinity NMDA receptor antagonist generates a double action. Apart from blocking the tonic pathological activation of NMDA receptors by μM concentrations of glutamate and mild membrane depolarization in chronic neurodegenerative diseases, memantine rapidly leaves the receptor following synaptic release of mM concentrations of glutamate allowing its physiological activation. This

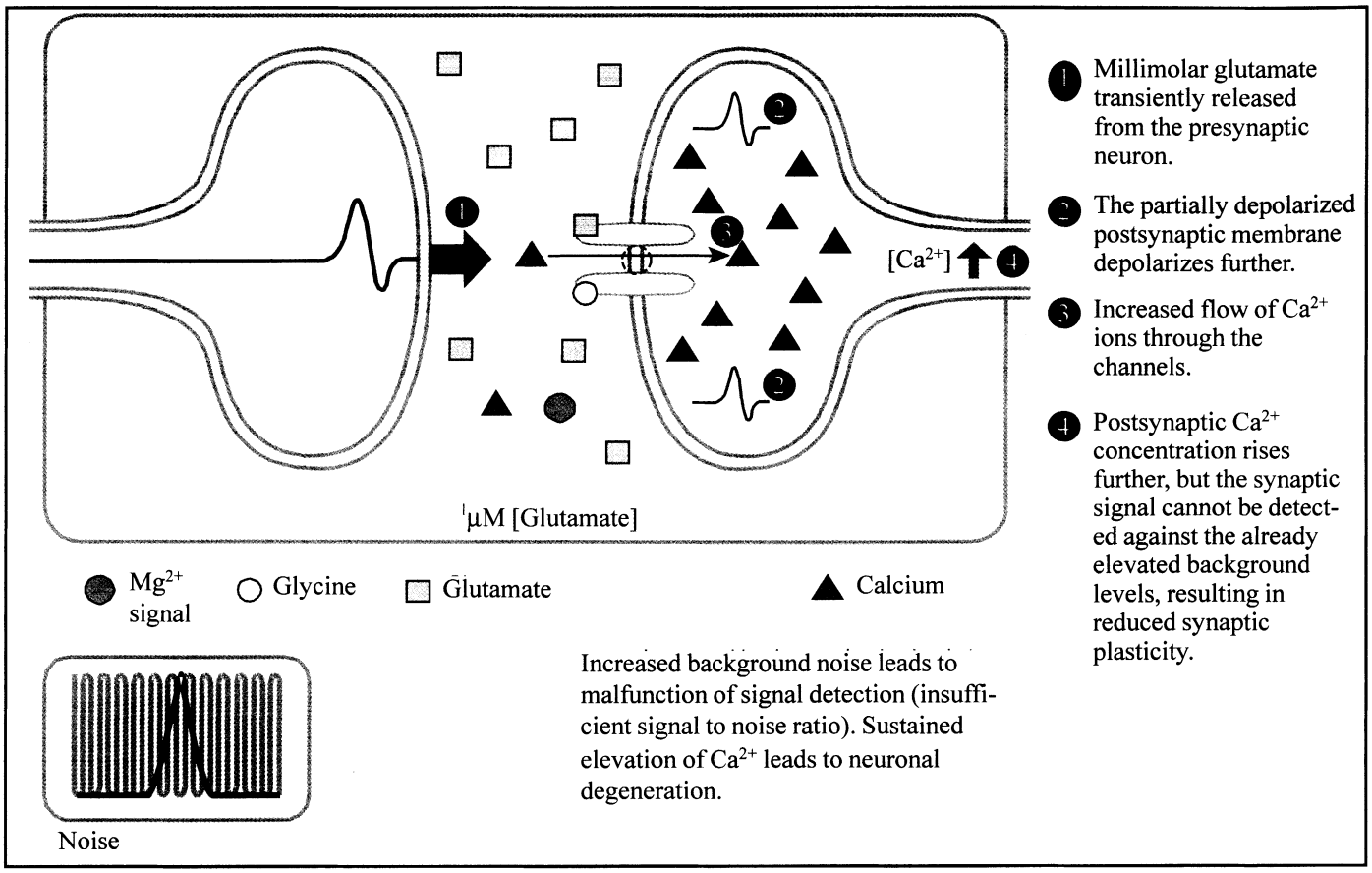

Figure 4. Failure to detect the synaptic signal due to tonic activation of the NMDA receptor.

causes a transient pronounced membrane depolarization, favoring the LTP and synaptic plasticity.[27]

In summary, in AD patients suffering from a tonic activation of the NMDA receptor, memantine may be able to re-establish the physiological activation of the receptor, allowing the LTP process and synaptic plasticity to occur. Indeed, the noncompetitive blockade of the NMDA channel diminishes Ca^{+2} influx and could exert a neuroprotective role.

Preclinical studies

In vitro studies

In AD, one of the likely consequences of the molecular alterations at the neuronal level, like β-amyloid accumulation, is a decrease of the Mg^{+2} blockade of the NMDA receptor, which enhances its activation. In vitro studies have shown how memantine is able to reverse this defect. In a quantitative autoradiographic study in human post-mortem hippocampus, Berger et al.[28] demonstrated that memantine was able to inhibit the binding of a noncompetitive NMDA antagonist MK-801. This supports the premise that, within the therapeutic concentration range of memantine, antagonism of endogenous glutamate at limbic NMDA receptors may be a molecular mechanism by which memantine is beneficial in dementia syndromes. Studies on rat hippocampal slices provide evidence that reduction of Mg^{+2} concentration induces severe functional perturbations, including complete impairment of neuronal plasticity and LTP, and that therapeutically relevant concentrations of memantine reversed these deficits.[29] These data indicate that memantine could produce symptomatic improvement in learning under conditions of tonic NMDA receptor activation, such as those occurring in chronic neurodegenerative diseases.

Several other studies have shown that memantine can protect against the toxic effects of NMDA receptor agonists in cultured neurons, supporting its potential neuroprotective role. Pellegrini and Lipton[30] demonstrated that 12 μM memantine prevented the death of neonatal rat retinal ganglion cells in primary cell culture when administered up to four hours after the initiation of NMDA receptor-mediated neurotoxicity. Two studies presented at the 16th Congress of the European College of Neuropsychopharmacology have shown that memantine may also influence the accumulation of β-amyloid

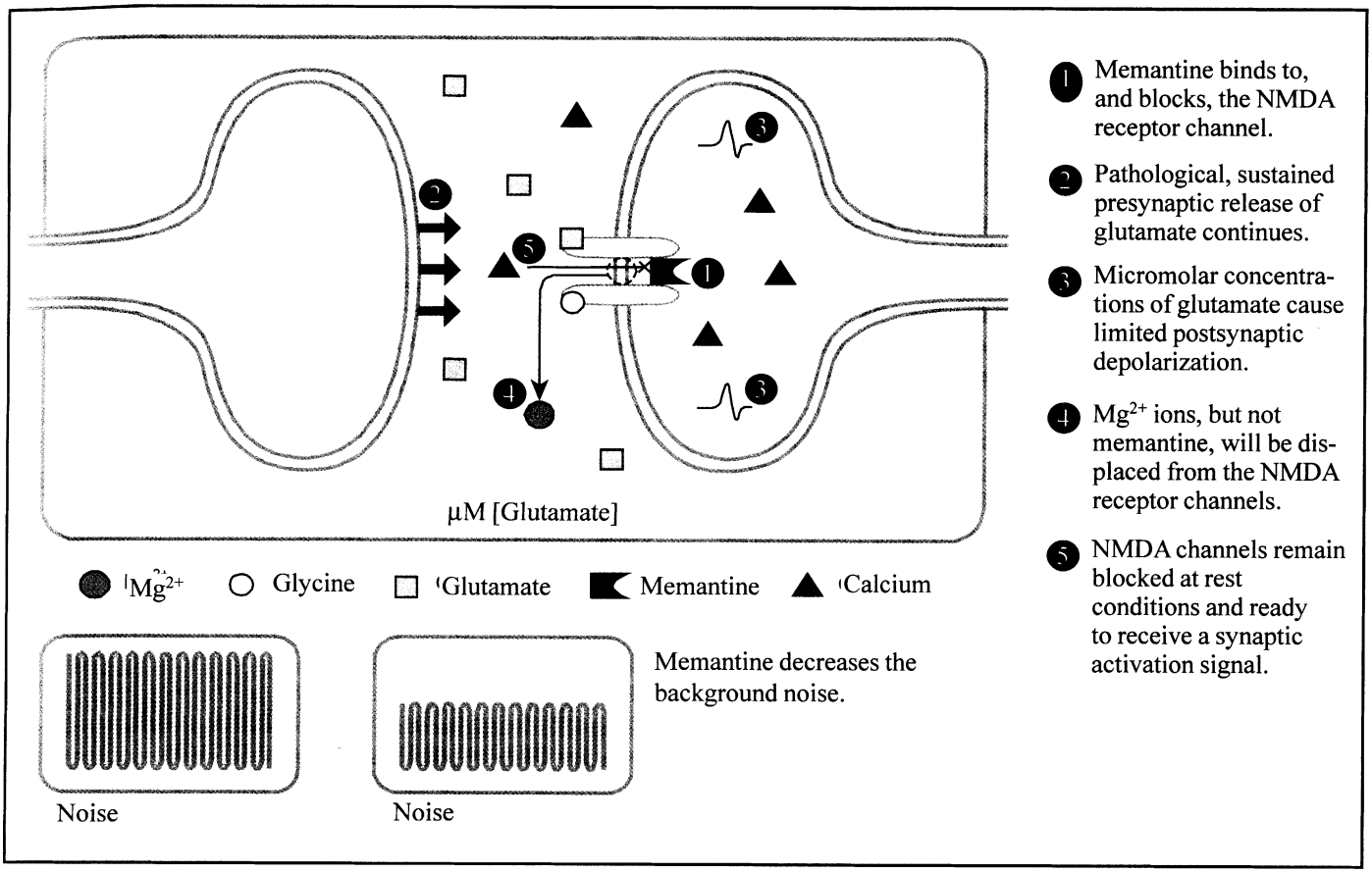

Figure 5. Glutamatergic transmission in memantine-treated AD patients.

and the hyperphosphorylation of tau. Lahiri et al.[31] demonstrated in cell cultures that memantine, at a nontoxic dose, decreased secreted β-amyloid levels without altering cellular amyloid precursor protein (APP) levels, suggesting that memantine may potentially inhibit the amyloidogenic pathway. In addition, memantine was able to restore the tau phosphatase and kinase activities and the phosphorylation/ dephosphorylation imbalance associated with neurodegeneration.[32]

In vivo studies

In vivo studies have also shown the neuroprotective properties of memantine, by demonstrating that the infusion of low doses of memantine may prevent the loss of cholinergic neurons. Wenk et al.[33] studied the neuroprotective effect of memantine on the cholinergic neurons of the nucleus basalis of Meynert. They demonstrated that a continuous infusion of memantine, given intraperitoneally, produced a dose-dependent protection in the NMDA-lesioned rat. Miguel-Hidalgo et al.[34] showed that memantine was able to protect against β-amyloid-induced neurotoxicity and learning impairment in rats. They found significant reductions in the amount of neuronal degeneration and pyknotic nuclei in the hippocampal neurons of memantine-treated animals as compared with vehicle-treated animals. These data suggest therapeutically relevant concentrations of memantine can protect against ß-amyloid-induced neuronal degeneration. Chronic treatment with memantine at therapeutically relevant doses also increased the maintenance of the LTP in moderately aged rats, showed a trend to improved memory retention in the Morris maze,[35] and improved cognition in transgenic mice coexpressing human presenilin and APP mutations.[36] In summary, these studies provide evidence that memantine can increase the durability of synaptic plasticity and provide preclinical information of the potential neuroprotective effect of memantine.

Clinical trials: therapeutic efficacy

Recently, two double-blind, randomized, placebo-controlled parallel-arm trials have shown the efficacy of memantine in AD and vascular dementia (VaD).[37,38] Smaller trials conducted over the last decade in Northern European countries also suggest the positive effects of memantine for the treatment of dementia and other related indications.[39-40]

subscore and the Nurses' Observation Scale for Geriatric Patients "disturbing behavior" dimension also showed differences in favor of memantine (P = 0.04 and P = 0.07, respectively). Memantine was well-tolerated, with a frequency of adverse events comparable to placebo. In summary, both trials show that memantine is well-tolerated presenting efficacy in the improvement of cognitive symptoms, without significant changes in the clinician's global impression. In addition, prospectively defined subgroup analyses by severity at baseline have been performed for both trials, demonstrating the largest benefit in the subgroup of patients with advanced disease (baseline MMSE < 15).[45]

Combination studies with acetyl-cholinesterase inhibitors (ChEI) have also been performed. At the 16th Congress of the European College of Neuropsychopharmacology, Periclou et al.[46] presented a pharmacokinetic study of memantine and donepezil in healthy young subjects. The administration of single memantine doses with multiple donepezil ones was well-tolerated without evidence of pharmacokinetic interaction. Farlow et al.[47] preliminarily reported a randomized, double-blind, placebo-controlled, parallel group study with a one- to two-week single-blind placebo screening period followed by 24 weeks of double-blind treatment. Probable AD patients (NINCDS-ADRDA criteria) were on stable donepezil monotherapy and had an MMSE score of 5 to 14. A total of 404 patients at 37 sites were randomized to memantine 20 mg per day (202) versus placebo (201). Patients treated with memantine/donepezil showed a statistically significant superiority in cognitive performance as measured by the SIB, in function (ADCS-ADLsev and BGP-care dependency subscale), in behavior (Neuropsychiatric Inventory, or NPI, total score) and in global improvement (CIBIC-PLUS) compared with the placebo/donepezil group. Furthermore, combination therapy resulted in improved cognitive performance, while treatment with ChEI alone was associated with continued cognitive decline. The combination therapy was safe and well-tolerated. These results demonstrate that the combination of an NMDA receptor antagonist and a ChEI drug in patients with severe AD is beneficial and superior to treatment with ChEI alone.

Conclusion

Preclinical studies have demonstrated, both in vitro and in vivo, the neuroprotective efficacy of memantine, which is able to increase the LTP and synaptic plasticity and decrease the glutamatergic NMDA receptor-mediated neurotoxicity. Well-designed clinical trials have demonstrated its safety and efficacy on patients with severe AD and VaD. The crucial question, subjected to a methodologically difficult approach, is whether memantine will be able to show its neuroprotective properties in a prospective clinical trial. The answer to this complex question will confer clinical veracity to memantine's double effect derived from its mechanism of action.

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In 1992, Görtelmeyer and Erbler[39] evaluated the efficacy and tolerability of memantine in patients affected with mild to moderate dementia through a randomized two-center placebo-controlled clinical study. This study included 88 patients and lasted 42 days. Efficacy was assessed with several clinical scales and an activities of daily living (ADL) scale. Tolerability was assessed on the basis of the doctor's global assessment and through structured documentation forms. After six weeks of treatment with 20 mg of memantine, clinical and statistically significant improvements were observed and improvement in ADL was detected. Memantine was also safe and well-tolerated. In 1993, Pantev et al.[40] performed another randomized, double-blind, placebo-controlled study in 60 patients affected with mild to moderate dementia who lived in nursing homes. Neuroimaging was performed to rule out secondary causes of dementia, although an etiological diagnosis was not established. In this small sample of patients, memantine showed clinical efficacy with rapid improvement of cognitive symptoms and ADL.

More recently, Winblad et al.[8] performed a multicenter, randomized double-blind, parallel group study of memantine, 10 mg per day, versus placebo in 166 severely demented patients (Mini-Mental State Examination (MMSE) <10 and Global Deterioration Scale (GDS) stages 5-7). Dementia was defined by DSM-III-R criteria and primary end points were determined through the Clinical Global Impression of Change (CGI-C) and the Behavioral Rating Scale for Geriatric Patients (BGP) "care dependence" subscore. An AD subgroup (49 percent of the population) analysis was defined prospectively in the protocol based on the classification by the modified Hachinski ischemic scale at baseline (as defined by a total score of < 5). At week 12, the intention to treat endpoint analysis showed a positive response in the CGI-C in 73 percent of the memantine-treated group versus 45 percent of the placebo group (stratified Wilcoxon $p < 0.001$) independent of the etiology of the dementia. The results in the BGP subscore showed an improvement of 3.1 points under memantine and 1.1 points under placebo ($p = 0.016$). No significant differences in adverse events were observed between treatment groups.[41] This study shows that treatment with memantine produces functional improvement and reduced dependency in patients affected with dementia. However, the study's methodological drawbacks are the small number of patients, the short study length, and the lack of research diagnostic criteria for AD and VaD.

By contrast, Reisberg et al.[37] conducted a 28-week, multi-center, randomized, double-blind, placebo-controlled parallel-arm trial on the efficacy of memantine in patients with moderate to severe AD. Patient eligibility criteria included: a diagnosis of AD with NINCDS-ADRDA criteria, GDS stage 5 or 6, Functional Assessment stage (FAST) greater or equal to 6a, and a MMSE score from 3 to 14. Patients were randomized to memantine, 20 mg per day (n = 126), or placebo (n = 126). The primary efficacy variables were the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev). The secondary efficacy end points included the Severe Impairment Battery (SIB) and other measures of cognition, function, and behavior. Patients receiving memantine had a better outcome than those receiving placebo, ($p < 0.05$) on both primary outcome assessments: the CIBIC-Plus and the ADCS-ADLsev and in the secondary end points ($p < 0.01$). Memantine treatment was safe and well-tolerated.

In summary, in patients with moderate to severe AD, memantine showed significant improvements in the cognitive, functional, and global end points, while safety and tolerability assessments confirmed the already known favorable profile. The same group of investigators have presented the results of a 24-week extension study performed on 175 patients who completed the double-blind study. Patients who switched from placebo to memantine improved relative to their projected rate of decline. These results support the use of memantine in the long-term treatment of patients with moderate to severe AD.[42]

The efficacy and tolerability of memantine has also been studied in patients diagnosed with probable VaD based on a pharmacological rationale previously reported.[43] In 54 centers of the United Kingdom, Wilcock et al.[44] performed a 28-week, double-blind, parallel, randomized controlled trial of memantine (20 mg daily) versus placebo. Primary efficacy parameters were the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) and the CGI-C. A total of 579 patients with an MMSE score between 10 and 22 were randomized. In this study, memantine was able to only show efficacy with the ADAS-cog, while CGI-C ratings showed no significant differences between treatment groups. A total of 77 percent of all memantine-treated patients, versus 75 percent of the placebo-treated patients, experienced adverse events, dizziness being the most common (11 percent versus 8 percent, respectively).[44]

A similarly designed trial, performed by Orgogozo et al. in France,[38] also showed significant improvement in the ADAS-cog scale. Among the secondary efficacy parameters which were analyzed, the MMSE significantly improved with memantine compared with the deterioration observed in the placebo group ($P = 0.003$). The Gottfries-Brane-Steen Scale "intellectual function"

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