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MEMANTINE HYDROCHLORIDE
Pharmacological and clinical profile

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Summary

Memantine (*Axura*®, Merz Pharmaceuticals GmbH; *Ebixa*®, H. Lundbeck A/S, *Namenda*™, Forest Laboratories, Inc.) is an uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist with low to moderate affinity for the (+)MK-801 binding site. It is characterized as a voltage-sensitive open-channel NMDA receptor blocker that antagonizes NMDA receptor–mediated inward currents *in vitro* with an IC_{50} of 1–3 μM. In animal models, memantine displays both neuroprotective (antiexcitotoxic) and cognition-enhancing properties at therapeutically relevant concentrations. The strong voltage dependency and rapid blocking/unblocking kinetics of memantine are thought to be the basis for its excellent clinical tolerability.

Recently completed clinical studies demonstrate positive effects of memantine in Alzheimer's disease both as a monotherapy and in patients receiving continuous donepezil treatment. Memantine treatment also has demonstrated significant improvement of cognitive performance in patients suffering from vascular dementia. Furthermore, the safety and tolerability of memantine in clinical trials has been excellent, with the incidence of premature withdrawals due to adverse events no greater

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than placebo and overall low frequencies of total adverse events. In 2002, memantine was approved by the European Medicines Agency (EMEA) for the treatment of moderately severe to severe Alzheimer's disease. More recently, memantine was approved in the US for the treatment of moderate to severe Alzheimer's disease (October 2003). Here, we review the most recent pharmacological and clinical data in dementia patients that has emerged from the systematic evaluation of memantine.

Introduction: NMDA receptor antagonists for dementia treatment

Dementia is a serious risk to aging individuals and places an enormous burden on healthcare systems in modern societies. Alzheimer's disease accounts for the majority of dementia cases, followed by vascular dementia and dementia of the Lewy-body type. Alzheimer's disease is characterized by intellectual deficits leading to functional impairment and eventually complete-care dependency. The main risk factor for Alzheimer's disease is age: the incidence of Alzheimer's disease increases from 0.5% per year at age 65 to 8% per year at age 85 (1). The prevalence of Alzheimer's disease also increases with age and may reach up to 47% in the very old (85 or more years) (2).

Until recently, approved treatments in Alzheimer's disease have focused on cholinergic neurotransmission, as loss of cholinergic neurons is observed in the process of Alzheimer's disease and is correlated with memory impairment. In the last decade, other neurotransmitter systems have been implicated in addition to the cholinergic hypothesis of Alzheimer's disease, and inhibition of pathological glutamatergic activity has emerged as a promising therapeutic approach for the treatment of patients with Alzheimer's disease (3, 4).

Glutamate is the principal excitatory amino acid neurotransmitter in cortical and hippocampal neurons. There is increasing evidence that cortical dementia with neuronal dysfunction may result, in part, from sustained elevation of glutamate levels and/or increased sensitivity of glutamate receptors to synaptic glutamate, leading to low-level, prolonged influx of calcium into neurons, impaired neuronal homeostasis and, eventually, neurodegeneration (5–9). Excessive glutamate release, with consequent neuronal dysfunction or even degeneration, follows cerebral energy deficit and hypoxia (10). Additionally, hyperactivity of the glutamatergic input to the hippocampus may result in excessive excitability of hippocampal cells, leading to disturbances in the signaling pathways thought to be critical for memory and learning.

One of the receptors activated by glutamate is the *N*-methyl-D-aspartate (NMDA) receptor, which has been found to be involved in learning and memory (11, 12). When activated, NMDA receptors allow calcium influx into neurons, which appears to be critical for the cellular processes involved in learning and memory. Overstimulation of NMDA receptors, however, can lead to excessive calcium influx, which ultimately results in neurodegeneration and cell death (13, 14). Under such conditions, temporally uncoordinated, tonic stimulation of NMDA receptors produces enhanced synaptic noise and deficits in synaptic plasticity and learning. Indiscriminate tonic stimulation of NMDA receptors results in increased frequency and amplitude of postsynaptic miniature potentials. It is postulated that this increased pathological synaptic noise, or chatter, impairs the ability of the synapse to recognize and transmit physiological signals, leading to deficits in synaptic plasticity and learning. Therefore, agents that selectively block pathological but not physiological activation of the NMDA receptor might restore the function of hippocampal neurons and improve memory-related symptoms of Alzheimer's disease (15).

The clinical development of several NMDA receptor antagonists was abandoned or had never been considered due to serious adverse effects, mainly psychotomimetic and cardiovascular in nature. The NMDA receptor antagonist memantine is a clinically well-tolerated treatment, and it is the only compound targeting the glutamatergic system in dementia that has been extensively tested in clinical studies. Memantine is a low to moderate affinity, uncompetitive NMDA receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics. Given these pharmacological features, it is hypothesized that memantine blocks the sustained activation of NMDA receptors by µM concentrations of glutamate under pathological conditions, but rapidly leaves the NMDA receptor channel upon transient physiological activation by low mM concentrations of synaptic glutamate (16, 17). These pharmacological properties are thought to be the basis for the excellent safety and tolerability of memantine in clinical use, differentiating memantine from other NMDA receptor antagonists.

In contrast to a number of other NMDA receptor antagonists, memantine has been shown to prolong the duration of learning and synaptic plasticity *in vivo* and to improve learning and memory in animal models (18, 19). These findings, together with the data that demonstrate neuroprotection in animal models of ischemia and chronic neurodegenerative disease (20), suggest a role for memantine in both symptomatic improvement and neuroprotection in Alzheimer's disease and vascular dementia. Although specifically designed long-term clinical trials have yet to be undertaken to assess a possible disease-modifying effect, symptomatic improvement from memantine treatment has been demonstrated in Alzheimer's disease and vascular dementia patients by several recent double-blind, placebo-controlled trials (21–24). This review will provide an overview of memantine, highlighting the most recent clinical data concerning the use of this compound in the treatment of dementia.

Memantine history

Memantine was first investigated for the treatment of Parkinson's disease (25), neurogenic bladder dysfunction associated with spasticity (26), various forms of dementia and other symptoms in psychogeriatric patients (27–29). It was also tested for vigilance enhancement in comatose patients and may ameliorate vigilance disturbances (30, 31). Based on such studies, and the recognition that memantine was an NMDA receptor antagonist, a clinical program was initiated to further investigate the drug as a treatment for dementia (20, 32).

Chemical characteristics

- Empirical formula: $C_{12}H_{21}N.HCl$
- Molecular weight: 215.76 (memantine hydrochloride)
- INN: memantine
- IUPAC name: 1-amino-3,5-dimethyladamantane hydrochloride

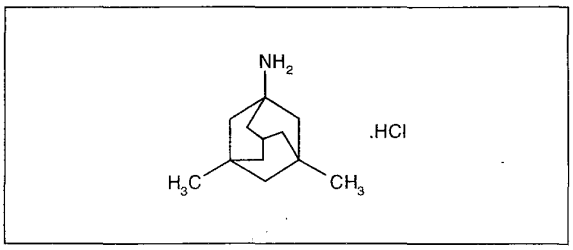

Fig. 1. Structural formula of memantine hydrochloride.

Memantine pharmacodynamics

Preclinical data

Within the therapeutic dosage range, memantine acts on NMDA receptors in the brain and has no relevant affinity for most other central nervous system (CNS) receptors, including the other ionotropic glutamate receptors AMPA and kainate (16, 33–35). Memantine binds to the (+)MK-801 recognition site of the NMDA receptor channel with a K_i of about 0.5–1 μM and antagonizes NMDA receptor–mediated inward currents *in vitro* with an IC_{50} of 0.5–3 μM (16, 36, 37). In addition to NMDA receptor antagonism, antagonism of 5-HT_3 receptor channels by memantine may have some therapeutic relevance, although this aspect of memantine pharmacology remains to be elucidated (15, 38).

Also apart from its antagonism of NMDA receptors, the agent has been found to modulate protein phosphatase (PP)-2A signaling in rat hippocampal slices. Here, memantine inhibited and reversed abnormal hyperphosphorylation and accumulation of tau resulting from inhibition of PP-2A, a process associated with neurofibrillary degeneration in Alzheimer's disease (39).

NMDA receptors in the CNS are tetrameric complexes formed mainly by two NR1 and two NR2 subunits (see ref. 40 for review). Neurons in the hippocampus and cortical areas predominantly express NR1, NR2A and NR2B subunits. Memantine has been shown to block glutamate-activated currents in a concentration-dependent manner in different recombinant rat NR1A/NR2(A-D) receptor combinations expressed in human embryonic kidney cells (HEK 293) (41) and Xenopus oocytes (42) with about 2–3 times higher potency for NR1A/2D and NR1A/2C receptors than for NR1A/2A receptors, and with intermediate potency for NR1A/2B receptors.

Memantine shows receptor-blocking kinetics and voltage-dependency characteristics between those of the endogenous NMDA receptor antagonist, Mg^{2+}, and the high-affinity NMDA receptor channel blockers such as (+)MK-801 (dizocilpine). Intermediate voltage dependency and fast blocking/unblocking kinetics appear to enable memantine to block NMDA receptors under pathological conditions (*e.g.*, chronic glutamatergic activity) without adversely affecting the physiological activation of the receptors by transient mM levels of synaptically released glutamate (15, 16). The pharmacological properties of memantine are thought to be the basis not only for its demonstrated neuropro-

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