The Neuropharmacological Basis for the Use of Memantine in the Treatment of Alzheimer’s Disease

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Keywords: Alzheimer’s disease — Amantadine — Channel block — Dementia — 5-HT3 receptor — Memantine — Nicotinic receptor — NMDA receptor — Uncompetitive antagonist.

ABSTRACT

Memantine has been demonstrated to be safe and effective in the symptomatic treatment of Alzheimer’s disease (AD). While the neurobiological basis for the therapeutic activity of memantine is not fully understood, the drug is not a cholinesterase inhibitor and, therefore, acts differently from current AD therapies. Memantine can interact with a variety of ligand-gated ion channels. However, NMDA receptors appear to be a key target of memantine at therapeutic concentrations. Memantine is an uncompetitive (channel blocking) NMDA receptor antagonist. Like other NMDA receptor antagonists, memantine at high concentrations can inhibit mechanisms of synaptic plasticity that are believed to underlie learning and memory. However, at lower, clinically relevant concentrations memantine can under some circumstances promote synaptic plasticity and preserve or enhance memory in animal models of AD. In addition, memantine can protect against the excitotoxic destruction of cholinergic neurons. Blockade of NMDA receptors by memantine could theoretically confer disease-modifying activity in AD by inhibiting the “weak” NMDA receptor-dependent excitotoxicity that has been hypothesized to play a role in the progressive neuronal loss that underlies the evolving dementia. Moreover, recent in vitro studies suggest that memantine abrogates β-amyloid (Aβ) toxicity and possibly inhibits Aβ production. Considerable attention has focused on the investigation of theories to explain the better tolerability of memantine over other NMDA receptor antagonists, particularly those that act by a similar channel blocking mechanism such as dissociative anesthetic-like agents (phencyclidine, ketamine, MK-801). A variety of channel-level factors could be relevant, including fast channel-blocking kinetics and strong voltage-dependence (allowing rapid relief of block during synaptic activity), as well as reduced trapping (permitting egress from closed channels). These factors may allow memantine to block channel activity induced by low, tonic levels of glutamate — an action that might contribute to symptomatic improvement and could theoretically protect against weak excitotoxicity — while sparing synaptic responses required for normal behavioral functioning, cognition and memory.