MEMANTINE MULTIPLE MECHANISMS OF ACTION IN PRECLINICAL MODELS OF ALZHEIMER'S DISEASE

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Introduction: Memantine, a drug approved for the treatment of moderate to severe Alzheimer's disease (AD), is an uncompetitive antagonist of N-methyl-D-aspartate receptors (NMDARs). Recent preclinical evidence suggests that it has additional effects that may contribute to its clinical efficacy.

Aims: To review preclinical evidence supporting the clinical efficacy of memantine in AD through multiple mechanisms of action.

Methods: We compiled the findings of several preclinical studies that examined the effects of memantine treatment on amyloid-beta (Aβ) levels, plaque burden, tau phosphorylation, and acetylcholine levels in various rodent models, as well as cognitive performance after memantine and donepezil treatment in an animal model of AD.

Results: Memantine acts as an NMDAR antagonist, and can normalize LTP disruptions caused by Aβ oligomers. Memantine treatment is also associated with decreased plaque burden and alterations of both soluble and insoluble Aβ levels in multiple animal models of AD, and with decreased levels of total and phosphorylated tau. Memantine at therapeutic doses also increases brain acetylcholine (ACh) levels in both anesthetized and active rats, likely by increasing ACh release. Finally, in anesthetized, cognitively normal rats, the combination of systemic memantine and the cholinesterase inhibitor donepezil produces significantly greater increases in ACh than either drug administered alone, and significantly improves spatial memory (both acquisition and retention), compared to placebo treatment, in aged transgenic (3xAD) mice.

Conclusions: These data provide strong preclinical evidence for multiple effects of memantine in AD.