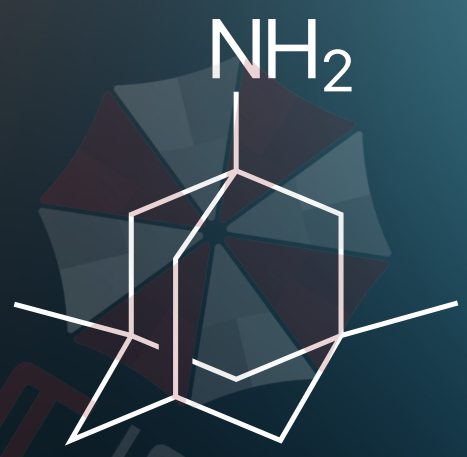

Memantine in Neurodegeneration: Pharmacokinetics and Mechanism of Action

History

Memantine was first synthesized in 1963, originally as an anti-diabetic medication. For this purpose it was however found to be inneffective.[1] As a derivative of amantadine, an anti-influenza agent, memantine was discovered by chance to be effective in Parkinson's disease (PD), as patients treated with amantadine against influenza demonstrated reduced symptoms. These observations led the pharmaceutical company Merz & Co. (now Merz Pharma) to apply for a patent (granted in 1975) describing memantine as bioactive within the CNS and of potential clinical use in neurological disorders. Memantine proved to be clinically well tolerated many years before the primary pharmacological target was identified. Much later, in 1989 it first approved for human use in Germany and is still used as prescription chemical today in many countries. Clinical and preclinical research into its mechanism of action is still ongoing to this day.

Mechanism of Action

Initially, it was thought that memantine at clinical dosages acts as a dopaminergic, serotonergic and noradrenergic compound,[2] with potential application in treatment of movement disorders, which ultimately proved false. Early research linking memantine to NMDA receptor (a subclass of glutamate receptors) antagonism hypothesized that memantine reduced NMDA-induced currents in a use-dependent fashion. Since then, extensive preclinical research has revealed the pharmacological mechanism of action of memantine to be a strong voltage-dependent but low potency NMDA receptor un-competitive antagonism at clinically relevant concentrations.

Memantine works by attaching to NMDA receptors in the brain more strongly than magnesium (Mg^{2+}) ions do. This helps block the long-lasting flow of calcium (Ca^{2+}) ions into brain cells, especially from receptors located outside of synapses (called extrasynaptic receptors). This is important because too much calcium can damage or kill brain cells. However, memantine only weakly blocks the NMDA receptors and leaves quickly after binding. This means it does not stop normal brain activity, such as the signals passed between neurons at synapses when glutamate is released during communication. Although the memantine works in several more targets

Memantine also acts as a non-competitive antagonist of the serotonin 5-HT3 receptor, with a potency similarly low to that for

the NMDA receptor. Interestingly, there is no clinical significance connected to this receptor interaction. Memantine also blocks certain brain receptors called nicotinic acetylcholine receptors (nAChRs), though not in a direct way. It likely affects these receptors with similar strength as it does with NMDA and 5-HT3 receptors.

One type of these nAChR, called the α7 receptor, is blocked by memantine. This may cause a short-term decline in thinking or memory when treatment with memantine first begins. However, the brain responds by increasing the number of these receptors over time, which may help explain the long-term improvements in memory and thinking seen with continued use of the chemical. In total, memantine has at least 8 identified molecular targets, also including dopamine, ELIC and ASIC receptors as well as voltage gated Ca2+ and K+ channels.[3]

Pharmacokinetiks[4,5]

Memantine is fully absorbed when taken by mouth, meaning 100% of the chemical enters the bloodstream. It reaches its highest levels in the blood about 3 to 7 hours after being ingested. The absorption is independent from food intake. After taking a single 20 mg dose, the highest blood levels are about 24 to 29 µg/L. When taken regularly (20 mg per day), stable blood levels are usually between 0.5 to 1.0 µM.

Memantine spreads widely throughout the body and easily crosses the blood–brain barrier with help from a special transporter called OCTN1. The chemical has a medium plasma protein binding of 45 % which means it's less likely to interfere with other chemicals like warfarin or digoxin.

Memantine is not heavily broken down in the body. It does not interact much with liver enzymes, which reduces the chance of interactions with other medications. The small amount of memantine that is broken down forms inactive substances that don't significantly affect its main action.

Most memantine is removed from the body through the urine — around 75 % leaves the body unchanged. The chemical has a half-life of about 60 to 80 hours. How quickly memantine is cleared from the body depends on the pH of the urine: if the urine is more alkaline (less acidic), the chemical stays in the body longer; if the urine is more acidic, the chemical is cleared more quickly. Urine acidity is affected by other medications, physical conditions, activity and food intake.

Pre-Clinical Trials

In neurodegenerative disorders and in Alzheimer's disease in particular, substances that lead to the formation of reactive oxygen species (ROS) play a defining role. ROS lead to a variety of biochemical changes to neurons and glia cells (neuron support cells), eventually leading to cell death. In AD, these ROS can be generated by amyloid-β peptide (Aβ). Oxidative damage was inhibited by d(−)-2-amino-5-phosphonopentanoic acid and memantine, two different NMDA receptor antagonists, suggesting action of Aβ through the NMDA receptor.[6]

So called ADDLs (Amyloid β-Derived Diffusible Ligands) constitute metastable alternatives to the disease-defining Aβ fibrils deposited in amyloid plaques from Alzheimer's. same size oligomers occur in transgenic mouse AD models. In mice, ADDLs appear concomitantly with memory failure, consistent with the ability of ADDLs to inhibit long-term potentiation (LTP) and block reversal of long-term depression (LTD). Memantine completely protected against ADDL-induced ROS formation in mice, as did other NMDA receptor antagonists. Memantine and the anti- NR1 antibody also attenuated a rapid ADDL-induced increase in intraneuronal calcium, which was essential for stimulated ROS formation. These results show that ADDLs bind to or in close proximity to NMDA receptors like memantine, triggering neuronal damage through NMDA-R-dependent calcium flux.[7]

Another pathogenic protein in AD is the so called Tau protein. In Alzheimer's disease and other tauopathies, tau proteins can become abnormally phosphorylated, leading to the formation of neurofibrillary tangles (NFTs) that disrupt neuronal function and contribute to neurodegeneration. Memantine (20 µM) also prevents toxicity and tau hyperphosphorylation in cultured

cortical neurons exposed to the mitochondrial toxin NaN3 together with the oxidative stressor H2O2 . This shows that it does not only protect neurons from Aβ fibrils, but also from NFTs.[8]

Memantine affects the process of long-term potentiation (LTP), which is important for learning and memory, in animals models of Alzheimer's disease (AD). Memantine helps protect LTP from damage caused by Aβ and even restores it in some cases. However, very high doses of memantine might harm the brain's ability to change and adapt. In another type of model using genetically modified mice with AD-like symptoms, memantine also restored LTP and improved how nerve signals worked. It improved memory impairments in these mice too. This was linked to stronger brain signals and activity of certain brain chemicals. In some cases, blocking certain potassium channels could stop memantine's effects. In another model that mimics late-onset AD, memantine helped improve brain function and reversed some of the damage over a long period of treatment.[9]

Effects in non-disease model animals

Low doses of memantine (e.g., 0.3–0.56 mg/kg) enhance working memory and reduce errors in tasks such as the radial maze, while higher doses (above 1 mg/kg) tend to impair performance. In several behavioural tasks, memantine improved memory function at moderate doses but caused deficits at higher ones (e.g., 20 mg/kg) as well. Some studies found no effect in animals without cognitive impairments, and high doses often caused side effects like impulsivity or performance disruptions. Sub-chronic and high-dose treatments were associated with impairments in various tasks, such as passive avoidance, spontaneous alternation, and discrimination learning. While low, therapeutically relevant doses were generally neuroprotective, higher doses could impair different aspects of memory and learning. Overall, memantine shows potential for enhancing cognition, particularly under non-pathological conditions, but its benefits are dose-dependent. Effective use requires careful balancing to avoid adverse cognitive and behavioural effects.[10–12]

Clinical Trials

Alzheimer patients

Several meta-analyses have indicated beneficial effects of memantine as monotherapy or in association with stable AChEI treatment in patients with mild to severe Alzheimer'sdisease.[13,14]

Two meta-analyses combining data from trials in patients with moderate to severe Alzheimer's disease,[15,16] indicate significant effects of memantine on global status, cognition, function and behaviour. In both meta-analyses, combining data from trials in patients with mild to moderate Alzheimer's disease (table IV) favoured memantine over placebo in terms of global status and cognition, but not function or behaviour.[13]

The overall effects in mild to severe Alzheimer's disease, assessed by combining data from six trials, were significant improvements in global status, cognition and function, but not in behaviour.

In a further meta-analysis, data from patients with low cognitive function at entry (1826 of 2311 patients) from six trials were combined, and suggested significant standardised mean improvements in global status, cognition and function.[16]

In total, the efficacy of memantine treatment in Alzheimer patients has been conclusively proven.

Healthy subjects

Seven studies examined the acute effects after a single dose of memantine in healthy subjects. In a parallel design study, placebo or 30 mg of memantine were administered to 16 male volunteers. No significant effect on mood, attention or immediate and delayed verbal and spatial memory was found.[17] In three crossover design studies, in which young male volunteers were given 30 mg memantine or placebo further effects have been investigated. The first study focused mainly on long-term visual memory e.g. assessing delayed recognition of line drawings of objects and photographs of faces after an interval of 80 min. Recognition performance for objects was significantly impaired after

memantine intake, whereas face recognition was not affected. Also, attention and temporal discrimination remained unaffected.[18] Temporal processing was the focus of a second study of the same author.[19]

Memantine impaired the estimation for tones in the range of seconds, but the estimation for tones in the range of milliseconds was not impaired. Again, outcome in attention tasks was not significantly altered. In a third study, a decline of attentional span was found, but only for participants scoring high for introversion.[20] In a further study examining mainly the subjective evaluations of memantine, some stimulant-like subjective effects were reported. However, this study included participants with previous stimulant use.[21] Similarly, two other studies reported on the subjective effects of memantine. Korostenskaja et al. found that 30 mg of memantine impaired “arousal” but increased the subjective rating of “speed of thinking”.[22] In the other study, 20 mg increased ratings of “happiness”, while 30 mg increased ratings of “dizziness”, the latter effect being however most likely side effect of a relatively high first dose.[23] From these experiments, there is no clear evidence that memantine increases cognitive performance in healthy subjects.

Conclusion

Memantine is in general well tolerated. Common side effects include confusion, dizziness, drowsiness, headache, insomnia, agitation, and/or hallucinations. Severe side effects may include blood clots, psychosis, and heart failure. Less common adverse effects include vomiting, anxiety, hypertonia, cystitis, and increased libido.

Memantine helps reduce symptoms in people with Alzheimer’s disease. Still, there is no strong evidence yet that it can slow down or stop the progression of the disease in humans, although some animal studies suggest it might.

In healthy human individuals, most studies found no significant improvement in mood, attention, or memory. One study reported impaired object recognition but not face recognition. Another found that memantine affected estimation of time in the seconds range but not in milliseconds. Some subjective stimulant-like effects were reported, especially in those with prior stimulant use. Additional studies found mixed subjective effects, such as impaired arousal, increased "speed of thinking," and changes in mood or dizziness depending on dose. Overall, the evidence does not support cognitive enhancement from memantine in healthy individuals.

The data and published literature are so extensive that not every aspect could be covered by this summary.

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