

Review Article

Development of memantine as a drug for Alzheimer's disease: A review of preclinical and clinical studies

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Abstract

Excitotoxicity contributes to neuronal cell death due to overstimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate, which plays a significant role in the development and progression of Alzheimer's disease (AD) and other neurodegenerative disorders. Studies have been conducted to identify a well-tolerated and selective NMDA receptor blocker in an effort to alleviate neurodegeneration. Memantine has been found to induce a distinct low-affinity NMDA receptor blockade in both preclinical and clinical studies. Therefore, FDA approved this drug as a well-tolerated noncompetitive NMDA receptor blocker for treating moderate to severe cases of AD. Further, memantine showed neuroprotective effects in preclinical studies by selectively blocking excessive NMDA receptor activation. Altogether, this novel drug is well-tolerated and effective for treating moderate to severe AD in various clinical studies. This paper is a review of preclinical and clinical studies on the drug development process of memantine.

Keywords: Memantine, Excitotoxicity, N-methyl-D-aspartate, Glutamate, Alzheimer's disease, neurodegeneration

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INTRODUCTION

The number of patients with Alzheimer's disease (AD) has been estimated to reach more than 13.5 millions by 2050 in the United States [1]. AD is a progressive neurodegenerative disease in which the functional and cognitive capabilities significantly deteriorate as the disease progresses [2]. Excitotoxicity contributes to neuronal cell death, which plays a significant role in the development and progression of AD and other neurodegenerative disorders. Excitotoxic neuronal cell death and injury occur primarily due

to the overstimulation of N-methyl-D-aspartate (NMDA) receptors by glutamate, which is the primary excitatory amino acid transmitter in the mammalian brain [3]. Studies have been conducted to identify selective NMDA receptor blockers as neuroprotective agents to treat neurodegenerative disorders. Unfortunately, most NMDA receptor antagonists failed due to disruption of the normal physiological function of NMDA receptors and the subsequent side effects [4]. However, memantine induced a distinct low-affinity NMDA receptor blockade in both preclinical and clinical studies. Therefore,

memantine was approved by FDA as a well-tolerated noncompetitive NMDA receptor blocker for treating moderate to severe AD [5]. The aim of this report was to review memantine drug development in preclinical and clinical studies.

NMDA receptors' role in neurodegenerative diseases

NMDA receptors are ionotropic glutamate receptors that are highly permeable to calcium [6]. Chronic activation of NMDA receptors leads to calcium influx and subsequent free radical formation that promotes cell death [3]. Studies have indicated that several neurodegenerative diseases, such as AD, Huntington's disease, and Parkinson's disease, are characterized by excessive glutamatergic activation of NMDA receptors causing neuronal cell injury and death [7]. Several studies have been undertaken to identify a well-tolerated selective NMDA receptor blocker in an effort to alleviate neurodegeneration in such diseases [8]. Unfortunately, most of the selective NMDA blockers failed in clinical trials due to disruption of normal glutamatergic functions and the resulting severe side effects [4]. Surprisingly, memantine, which was believed to be an anti-influenza agent, exhibited selective disruption of NMDA-mediated excitotoxic cell death at a well-tolerated clinical dose [9].

Discovery of memantine

Memantine is a polycyclic cage compound that was first synthesized in 1968 as a derivative of amantadine (Figure 1), which was believed to be an anti-influenza compound [10]. It was suggested that amantadine might block the ion channel of the influenza virus by forming a hydrogen bond with a histidine residue in the M2 transmembrane protein [11]. Upon the application of amantadine and memantine as treatment for influenza, the compounds exhibited, by serendipity, clinical efficacy in Parkinson's disease patients [12].

Consequently, investigators believed that memantine and amantadine may have some effect on the dopaminergic or cholinergic systems [13,14]. This belief was not opposed until the early 1990s when memantine was found to be devoid of dopaminergic or anticholinergic activities but was instead found to be a selective antagonist of NMDA receptors [15]. Memantine receptor blockade occurs during prolonged NMDA receptor activation, as observed in excitotoxicity, which confers memantine with a unique advantage over other NMDA receptor blockers [16]. This type of NMDA receptor

blockade allows for the normal physiological functioning of NMDA receptors and disrupts neuronal toxicity as a result of NMDA receptor overstimulation [17].

As a result, memantine is favored over other NMDA receptor antagonists for its tolerability and safety and an improved side effects profile [17]. It is noteworthy that the mechanism by which memantine interacts with NMDA receptors is not fully understood. However, it has been suggested that the ammonium group of memantine might interact with the side chain of the GluN1 subunit of the NMDA receptor and block its action [18].

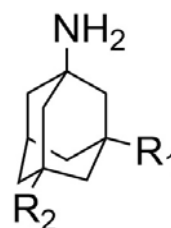


Figure 1: Chemical structures of amantadine ($R_1 = H$, $R_2 = H$) and memantine ($R_1 = CH_3$, $R_2 = CH_3$)

In vitro studies

Memantine NMDA receptor antagonism assay

Rat retinal neurons have been studied *in vitro* to evaluate the functional activity of NMDA receptors [19]. The use of rat retinal ganglionic neurons in evaluating the pharmacological effect of different compounds on NMDA receptors is well established [20]. Studies have been conducted to investigate the effect of memantine on the N-methyl-D-aspartate-evoked current in rat retinal neuron cell culture [21], and memantine was found to disrupt this current with a 50% inhibition concentration of approximately 1 μM [22].

Memantine inhibition of NMDA-induced calcium influx

In a study that utilized digital calcium imaging technology, memantine strongly inhibited excessive calcium influx simulated by a high concentration of N-methyl-D-aspartate. However, memantine allowed a low level of calcium influx similar to that evoked by a low concentration of N-methyl-D-aspartate. This observation was the basis of the hypothesis that memantine inhibits only the overstimulation of NMDA receptors as in excitotoxicity and allows for the normal physiological functioning of NMDA receptors. As

a result, memantine exhibits a unique advantage over other NMDA receptor antagonists [21].

Memantine disrupted NMDA receptor-mediated neurotoxicity

In this type of neurotoxicity assay, retinal or cortical neuronal cell culture is exposed to glutamate in the presence of a high concentration of calcium and low concentration of magnesium [23]. As a result, neurotoxic cell injury is specifically mediated through NMDA receptors. It has been demonstrated that the neurotoxic effect mediated by NMDA receptors is ameliorated by memantine in both cortical neurons and rat retinal ganglion cell culture [22,24]. Likewise, memantine strongly blocked the neurotoxic effects of glutamate in cortical neuron cell culture [25].

In vivo studies

Memantine ameliorated NMDA-mediated convulsions in mice and rats

Pretreatment with memantine significantly ameliorated convulsions caused by the intracerebroventricular application of N-methyl-D-aspartate in rats [26]. Similarly, memantine was administered to mice before systemic administration of N-methyl-D-aspartate and was found to block N-methyl-D-aspartate-provoked convulsions in the pretreated mice when compared to that in the control mice [26, 27]. Prevention of N-methyl-D-aspartate-mediated convulsions demonstrated the selective action of memantine on NMDA receptors.

Neuroprotective effect of memantine

The neuroprotective action of memantine has been demonstrated in many *in vivo* studies using cerebral ischemic animal models [28, 29]. In a mouse model of cerebral ischemia, pretreatment with memantine reduced the infarct size and acute excitotoxic cell damage, thus confirming its neuroprotective ability [30]. Interestingly, one study investigated whether memantine has a neuroprotective effect after the induction of brain damage. In this study, traumatic brain injury was induced in rats using specialized devices and followed by memantine treatment for 7 days. Memantine significantly reduced neuronal cell death and injury in the treated rats when compared to that in the control untreated rats [28]. In another study, memantine significantly upregulated brain-derived neurotrophic factor in the brains of treated rats in contrast to the control rats, thereby confirming its neuroprotective effect [31].

Chronic neurodegenerative disease animal models

The chronic administration of memantine in rats significantly protected them against hippocampal neuron damage induced by intracerebroventricular injection of quinolinic acid [32]. In another study, memantine significantly prevented striatal neuronal injury due to mitochondrial toxicity induced by the administration of malonate [33]. It is noteworthy that the use of malonate to induce mitochondrial toxicity is based on the notion that neurodegenerative diseases are associated with chronic excitotoxicity and the production of free radicals and mitochondrial toxicity. Another study investigated the effect of memantine in an animal model of neurodegeneration due to β -amyloid-provoked excitotoxicity; the neurodegenerative effects were significantly alleviated in memantine-treated rats when compared to that in vehicle-treated rats [34].

Clinical studies on memantine

The first randomized clinical trial investigating the efficacy and safety of memantine in patients with severe AD was conducted in the late 1990s [35]. A total of 166 patients were randomly divided to receive either 10 mg/day of memantine (n = 82) or placebo (n = 84) for 12 weeks. The memantine-treated group exhibited significant functional improvement and required less time for supportive care when compared to the placebo-treated group [35].

In a randomized placebo-controlled clinical trial, a total of 252 patients with moderate to severe AD in more than 30 US centers were randomly assigned to receive a dose of 10 mg memantine or placebo twice daily for 28 weeks [36]. At the end of 28 weeks, a significant improvement in clinical symptoms and functional activities was observed in the memantine-treated patients in contrast to that in the placebo-treated patients. Moreover, memantine was well-tolerated, and there were no signs or symptoms of any significant side effects in the treated patients [36].

The last clinical trial that was submitted to the FDA investigated the effect of combination therapy with a cholinesterase inhibitor (donepezil) and memantine [37]. This randomized, double-blind, placebo-controlled study was conducted in 322 patients with moderate to severe AD who were already receiving donepezil. Patients from 37 US centers were randomly assigned to receive either 20 mg/day memantine or placebo for 24 weeks. The

results of this trial were consistent with those of previous studies indicating the benefits of memantine over placebo treatment when added to donepezil [37]. It is noteworthy that one retrospective study to analyze three previous clinical trials focusing on AD patients with agitation or aggression provided significant evidence that memantine is well-tolerated and effective for treating patients with moderate to severe AD [38].

Table 1: Examples of preclinical studies on memantine

Study	Experiment/assay	Findings	Reference
<i>In vitro</i>	NMDA receptor antagonism assay	Memantine was found to antagonize the current that was evoked by NMDA with a 50% inhibition concentration of approximately 1 μ M	[22]
<i>In vitro</i>	NMDA-induced calcium influx inhibition assay	Memantine strongly inhibited excessive calcium influx that was simulated by a high concentration of NMDA. Memantine allowed a low level of calcium influx similar to that evoked by a low concentration of NMDA	[21]
<i>In vitro</i>	NMDA receptor-mediated neurotoxicity antagonism assay	Memantine exhibited strong antagonism of the neurotoxic effects mediated by NMDA receptors in cortical neurons, rat retinal ganglion and cortical neuron cell cultures	[22, 24, 25]
<i>In vivo</i>	NMDA-mediated convulsions experiments	Memantine was found to block NMDA-provoked convulsions in rats and mice	[26, 27]
<i>In vivo</i>	Neuroprotection experiments	Memantine reduced the infarct size and the acute excitotoxic cell damage in cerebral ischemic model. Memantine induced neuroprotection by significantly reducing neuronal cell death and injury in rats with traumatic brain injury. Memantine significantly upregulated the brain-derived neurotrophic factor in the brains of rats	[28, 30, 31]
<i>In vivo</i>	Chronic neurodegenerative disease animal models	Memantine significantly protected rats against hippocampal and striatal neuronal damage induced by quinolinic acid and malonate. Memantine protected against the neurodegenerative effects of β -amyloid-provoked excitotoxicity in rats	[32-34]

Table 2: Examples of completed clinical trials on memantine's efficacy and safety in AD

Reference	N	Treatment	Results
[35]	166	Memantine Placebo	The memantine-treated group exhibited a significant functional improvement and required less time for supportive care compared to the placebo-treated group
[36]	252	Memantine Placebo	Significant improvement in clinical symptoms and functional activities was observed in the memantine-treated patients as compared to the placebo-treated patients. Memantine was well-tolerated, and there were no signs or symptoms of any significant side effects in the treated patients
[37]	322	Memantine Donepezil Placebo	Memantine showed significant improvements as compared to placebo when added to donepezil in cognition and was well tolerated
[39]	677	Memantine Placebo	Patients on cholinesterase inhibitors who were treated with memantine showed earlier improvements in cognitive functions as compared to placebo

CONCLUDING REMARKS

The exact molecular mechanisms underlying the interaction of memantine with NMDA receptors still need to be studied more to improve the efficacy and outcomes of this treatment strategy in the management of AD. Although clinical studies have demonstrated that memantine is effective for treating AD, it is not a cure. The limited curative effects of memantine could be attributable to the late administration of this drug when neuronal cell death has already started. Further studies are needed to investigate the early administration of this drug with other antioxidants that might improve its curative effect in AD.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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