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

Michael A. Rogawski[1] and Gary L. Wenk[2]

[1]*National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD USA;*
[2]*Division of Neural Systems, Memory and Aging, University of Arizona, Tucson, AZ USA*

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## 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 chan-

Address correspondence and reprint requests to: Michael A. Rogawski, M.D., Ph.D., Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 49 Convent Drive MSC 4457, Bethesda, MD 20892-4457, USA.
Tel: +1 (301) 496-8013; E-mail: michael.rogawski@nih.gov

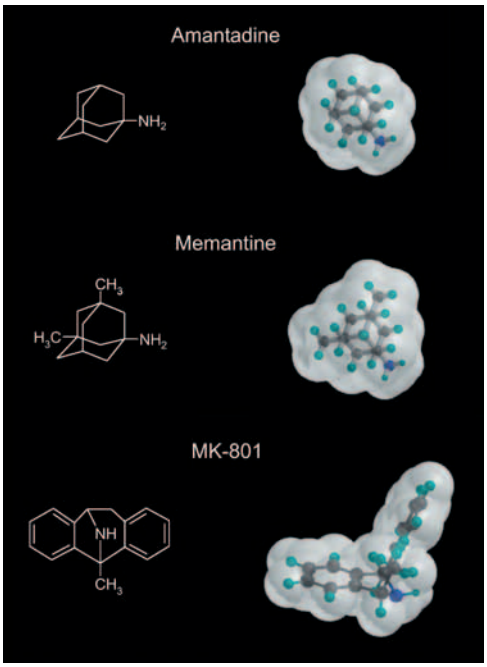


**Fig. 1.** Structures of the uncompetitive NMDA receptor antagonists amantadine, memantine and MK-801. The conventional representation is shown to the left; energy minimized three-dimensional ball and stick structures within a translucent solvent-accessible surface are shown to the right. The symmetrical, aspherical, three-dimensional structures of amantadine and memantine contrast with the more conventional planar structure of MK-801.

nel-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.

## INTRODUCTION

Memantine (1-amino-3,5-dimethlyadamantane) is a member of the aminoadamantane class of organic molecules. The aminoadamantanes are atypical drug compounds because of their unusual three-dimensional (non-planar) tricyclic structures (Fig. 1). The first aminoadamantane to be introduced into clinical use was amantadine, which was marketed in 1966 for the prophylaxis of respiratory infections due to the susceptible influenza A virus. For many years, amantadine was the only orally active antiviral agent available in the U. S. Its derivative, rimantadine, became available in 1993. Amantadine and rimantadine are believed to act by blocking an ion channel present in the viral coat. This ion channel, referred to as M2, is a tetrameric protein that allows protons to enter the virus and contributes to efficient viral replication (61,141).

Three years after amantadine was introduced onto the market, a woman with Parkinson's disease was observed to have a dramatic improvement in her symptoms during daily

administration for influenza prophylaxis (133). This anecdotal observation led to the demonstration that amantadine produces moderate symptomatic benefit in Parkinson's disease (particularly on tremor) and initiated interest in the aminoadamantanes for the treatment of neurological disease. Other anecdotal reports suggest that amantadine may have some activity in a variety of additional neurological conditions including tardive dyskinesia, chorea, and dementia (143).

Memantine is structurally similar to amantadine, with the exception of two methyl groups that are substituted for carbon atoms at the 3- and 5-positions. Memantine was first synthesized in the early 1960s in a program at Eli Lilly & Co. to identify putative hypoglycemic agents, but was found to be devoid of such activity. In early animal studies, memantine demonstrated greater potency than amantadine in pharmacological models of Parkinson's disease, and although memantine probably has similar clinical activity, it has not been extensively evaluated for this condition (45,63,132,143). Anecdotal reports suggest that, while memantine is effective in treating Parkinson's disease symptoms, it might not be as active as amantadine for this indication (33). Further studies with memantine revealed some similarities and differences in its pharmacological activity compared with amantadine. Although both drugs can act on a wide variety of target molecules resulting in numerous pharmacological effects, of particular importance in present-day theories regarding memantine's action was the observation first made by Kornhuber et al. (72) and Bormann (17) that the drug blocks NMDA receptors.

Although memantine has never been widely used for Parkinson's disease, it was registered in Germany in 1978 and became popular as an all-purpose neurological tonic, with anecdotal reports of utility in dementia, organic brain syndrome, acquired pendular nystagmus in multiple sclerosis (139), neurogenic bladder (57), alternating hemiplegia of childhood (71), neuroleptic drug-induced adverse reactions, spasticity and even coma (98). In 1989, memantine officially was launched in Germany for use in the treatment of dementia. In subsequent years, eight double-blind, placebo controlled trials have documented the efficacy and safety of memantine in the symptomatic treatment of AD and vascular dementia (4,64). These studies provide evidence that memantine is well tolerated, even in individuals compromised by dementing illnesses, and that memantine improves cognition in both AD and vascular dementia. In a population of care-dependent patients with severe dementia, encompassing both AD and vascular dementia, memantine use was associated with improvement in global assessments and functional capacities while decreasing care-dependence (158). Furthermore, a recent report of memantine in a moderate to severe community-dwelling AD population demonstrated that memantine confers improvements in cognitive, global and functional outcomes (120). Another recent report showed that memantine administered to moderate to severe AD patients on stable cholinesterase inhibitor (donepezil) therapy conferred greater improvements in cognition, activities of daily living, global assessment and behavior than in individuals treated solely with donepezil (42). While the practical utility of memantine has been documented in postmarketing studies examining the use of memantine in everyday outpatient practice by German general practitioners, internists and neurologists (129), the basis for the beneficial activity of memantine in dementia is not fully understood. Yet, it is reasonable to believe that the interaction of memantine with NMDA receptors may be relevant.

Here we review evidence that memantine blocks central nervous system NMDA receptors at clinically relevant doses and that it has beneficial activity in animal models of AD. Further, we present some ideas as to how the drug might produce the symptomatic

benefits observed in the treatment of AD without causing neurobehavioral side effects that occur with some NMDA receptor antagonists, and how it may perhaps even delay the progression of the disease.

## NMDA RECEPTORS AS A TARGET FOR MEMANTINE

### Glutamate and its Ionotropic Receptors

Glutamate is the main excitatory neurotransmitter in the central nervous system (35,135). It is responsible for interneuronal communication in local circuits within virtually every region of the brain and spinal cord and, in many instances, also for communication between distant regions. The rapid (millisecond) synaptic actions of glutamate are mediated by its interaction with ligand-gated ionotropic receptors, which are multisubunit protein complexes that span the neuronal plasma membrane. Ionotropic glutamate receptors have a central pore that allows conduction of cations ($Na^+$, $K^+$, and, in some instances, $Ca^{2+}$) across the membrane, and gating of the channel (i.e., whether it is closed and impermeable to ion flux or open and capable of allowing ions to flow) is determined by the binding of agonist (glutamate) to a specific recognition site on the receptor-channel complex. In addition, glutamate can exert slower synaptic actions through effects on metabotropic (G-protein coupled) glutamate receptors that do not contain intrinsic ion channels.

Through the use of pharmacological agonists and antagonists, ionotropic glutamate receptors have been classified into three families, referred to as AMPA, kainate and NMDA, so named because of the dicarboxylic acids that are selective agonists. Molecular cloning in the past decade has allowed the identification of the specific protein subunits that form each of these ionotropic glutamate receptors. AMPA receptors, which are composed of four subunits (GluR1–4) in different configurations, are the most abundant type of ionotropic glutamate receptor and are believed to participate in excitatory neurotransmission at all glutamatergic synapses. Kainate receptors have been less well studied, but also seem to play a role, albeit less prominent, in fast excitatory neurotransmission at many synapses. Kainate receptors also are present on presynaptic terminals where they regulate neurotransmitter release.

NMDA receptors also are present at many excitatory synapses (Fig. 2). Often they do not contribute to ordinary, ongoing synaptic transmission because of the unique property that they are blocked by ambient $Mg^{2+}$ in the extracellular environment. $Mg^{2+}$ ions enter the vestibule of the channel and, in contrast to the situation for AMPA and kainate receptors, are able to transiently occlude cation flux through the channel by binding to a site deep inside the ion conduction pathway or "pore" of the channel. At ordinary hyperpolarized resting potentials (e.g., –60 mV), the transmembrane electric field (negative on the inside of the cell) favors entry of $Mg^{2+}$ into the pore of NMDA receptors, so that the channels are largely blocked. Under such resting conditions, NMDA receptors do not conduct ions and they do not contribute to synaptic excitation. However, with large synaptic excitation (mediated mostly by AMPA receptors), the neuron sufficiently depolarizes so that $Mg^{2+}$ is no longer "strongly attracted into the pore" (actually, its effective binding-affinity for the channel-blocking site is reduced). Under such depolarized conditions, NMDA receptors activated by synaptically-released glutamate are able to pass an ionic

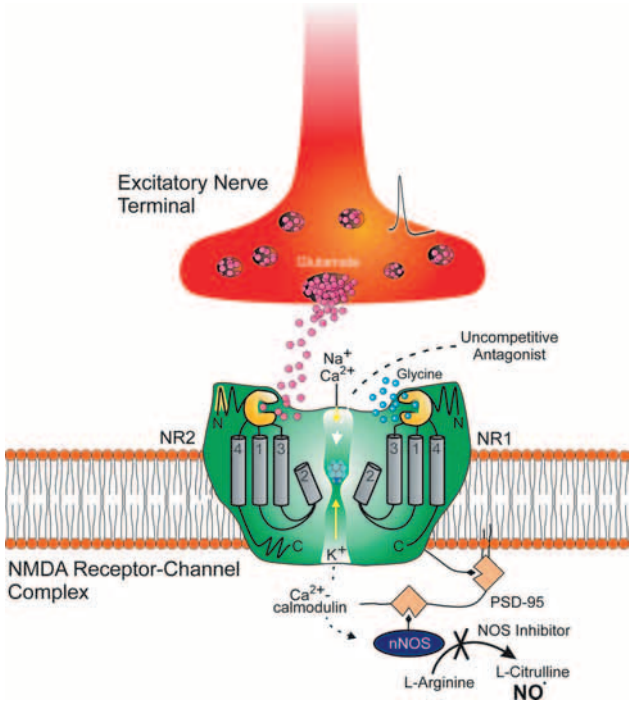


**Fig. 2.** Schematic illustration of the NMDA receptor at an excitatory synapse. Action potential invasion of the presynaptic excitatory nerve terminal releases vesicular glutamate into the synapse. The NMDA receptor channel-complex (composed of NR2 subunits containing the glutamate recognition site and NR1 subunits containing the glycine recognition site) in the postsynaptic membrane senses glutamate and is gated open, provided there are sufficient ambient levels of a glycine-site ligand. Only one NR2 subunit and one NR1 subunit are illustrated; NMDA receptors are believed to be tetramers. Cylinders represent probable α-helical membrane segments. Ion flux through the channel generally requires concomitant depolarization of the postsynaptic neuron to relieve the tonic block by ambient $Mg^{2+}$ (not illustrated). When the channel is open and conducting, $Na^{+}$ and $Ca^{2+}$ flow into the cell and $K^{+}$ flows out. $Ca^{2+}$ entering through the channel binds to intracellular proteins including calmodulin, which can activate nitric oxide synthethase (nNOS) and is tethered near the channel by postsynaptic density protein-95 (PSD-95). Uncompetitive antagonists, such as memantine (space-filling molecular structure illustrated), can enter the pore of the channel, which is formed by the second intramembrane loops from both the NR1 and NR2 subunits.

flux (largely $Na^{+}$ and $Ca^{2+}$) and contribute to postsynaptic excitation. Thus, the $Mg^{2+}$ block confers NMDA receptors with a pronounced voltage-dependence.

The ionic flux through NMDA receptors has two major consequences. First, NMDA receptors remain open for a longer time than AMPA receptors; therefore, the duration of the combined AMPA/NMDA receptor-mediated synaptic response is longer than that of a pure AMPA receptor response. Such prolonged synaptic activity alters the signaling properties of the synapse, and may play a role in certain pathological situations, including epileptic foci in which NMDA receptor-mediated excitation contributes to the prolonged synaptic depolarization that occurs during paroxysmal depolarization shifts (PDSs) believed to be the cellular correlates of interictal spikes. Second, in distinct contrast to some (but not all) AMPA receptors, NMDA receptors permit the flux of $Ca^{2+}$. The $Ca^{2+}$ that enters through synaptically-activated NMDA receptors can act as a messenger for various cel-

lular processes through the activation of $Ca^{2+}$-dependent protein kinases. Importantly, the $Ca^{2+}$ entry through NMDA receptors during strong synaptic excitation is believed to be the critical event that triggers the form of synaptic plasticity referred to as long-term potentiation (LTP) (85). In LTP, there is a functional strengthening of excitatory neurotransmission due to increased activity of AMPA receptors in the postsynaptic membrane, triggered by the $Ca^{2+}$ that enters through NMDA receptors.

NMDA receptors also can be activated in pathological situations by excessively high ambient levels of glutamate. Extracellular glutamate can reach supranormal levels during prolonged seizure activity or when neurons are damaged or die as a result of ischemia or neurodegenerative conditions. Under these pathological conditions, the neuronal membrane is chronically depolarized, relieving the $Mg^{2+}$ block of NMDA receptors. Activation of these unblocked NMDA receptors by ambient glutamate allows $Ca^{2+}$ flux which, if sufficiently prolonged, triggers a cascade of events leading to neuronal injury and death. A similar mechanism has been hypothesized to play a role in AD (82), but other mechanisms to chronically depolarize neurons, such as impaired metabolic function, may exist since increased ambient glutamate levels have not been observed in the AD brain (see "The Weak Excitotoxicity Hypothesis" below).

## The Structure and Function of NMDA Receptors

Molecular cloning has allowed the amino acid sequences of the proteins that serve as subunits of NMDA receptors to be determined (35, 94). Functional NMDA receptors are believed to be tetrameric complexes composed of one of 8 alternatively spliced forms of the NR1 subunit (the more common forms are denoted NR1a and NR1b) and one of the four NR2 subunits (NR2A, NR2B, NR2C, NR2D). Although glutamate is responsible for the millisecond-to-millisecond gating of the NMDA receptor during synaptic activity, NMDA receptors also require the presence of glycine or a glycine-like agonist (such as D-serine) (100) for functional activity. The binding site for glutamate is believed to be on the NR2 subunit and a homologous binding site for glycine on the NR1 subunit has been identified. A third type of NMDA receptor subunit, designated NR3, can assemble with NR1 and NR2, resulting in a receptor with diminished activity. (NR3 subunits also can assemble with NR1 alone to create a functional glycine receptor.) However, most NMDARs are made up of an NR1 subunit and at least one of the NR2 subunits. The NR2A and NR2B subunits are the major and most widespread NR2 subunits, with NR2C largely restricted to the cerebellum and NR2D most heavily expressed early in development and persisting to adulthood in only a few brain areas (153). The NR2B subunit predominates early in development and then gradually decreases, whereas expression of NR2A is low shortly after birth but continues to increase. Therefore, NR1/NR2A subunits are the major NMDA receptor subunits of relevance in adulthood. The switch from NR2B to NR2A is believed to be responsible for the reduced synaptic plasticity of older synapses, and presumably the diminished learning ability that comes with aging.

## NMDA Receptor Antagonists as Therapeutic Agents

The recognition that NMDA receptors play a key role in pathological neuronal excitation, as in epileptic seizures, and in glutamate-induced excitotoxicity, such as in stroke or brain trauma, stimulated intense interest in the development of drugs that could block

NMDA receptors and, therefore, ameliorate these pathological processes (84). NMDA receptor antagonists have dramatic activity in animal models of these conditions, but clinical trials have not been encouraging and interest in this approach for the treatment of stroke, epilepsy and brain trauma is waning in the drug industry. Nevertheless, it has been suggested that it is too early to abandon hope as methodological factors in the conduct of those clinical trials may have contributed to the failures (69). Early clinical trials focused on competitive NMDA receptor antagonists, such as CGS 19755 (selfotel), that reduce the functional activity of NMDA receptors by interfering with the ability of neurotransmitter glutamate to activate the receptor. More recently, trials of a glycine-site antagonist, GV 150526 (gavestinel), and a drug that selectively blocks NMDA receptors that contain the NR2B subunit, CP-101,606 (traxoprodil), have been conducted. While development of gavestinel has been halted, trials with traxoprodil in traumatic head injury have shown some promise, and trials for its use in stroke are continuing.

## Channel-Blocking (Uncompetitive) NMDA Receptor Antagonists

In relation to the enormous attention that has been focused on competitive NMDA receptor antagonists in the treatment of neurological disease, there has been relatively less attention given to agents that interact with the receptor in a noncompetitive fashion. (Noncompetitive antagonists either allosterically modify channel activity by binding to sites on the receptor-channel complex other than the agonist recognition sites, or interfere with the functional activity of the receptor in some other way; their blocking action cannot be overcome by increasing the agonist concentration.) The situation seems to be changing in that traxoprodil, a special type of noncompetitive NMDA receptor antagonist, is the only NMDA receptor antagonist currently under active development for stroke. In addition, it has been recognized for some time that a wide variety of structurally dissimilar compounds can block the activity of NMDA receptors by entering and binding to the cation pore. These agents act in a use-dependent fashion, meaning that the receptor-channel must be in the open state for the drug to exhibit its blocking activity (Fig. 2).

The presence of blocking drugs within the ionophore of the channel prevents cation flux and thereby inhibits the functional activity of the NMDA receptor. This form of block is often referred to as “uncompetitive” by analogy with uncompetitive enzyme inhibitors that are incapable of binding to free enzyme and only bind to the enzyme-substrate complex. Uncompetitive antagonism is a type of noncompetitive block (i.e., the block cannot be overcome by increasing the concentration of agonist; in the case of the NMDA receptor, either glutamate or glycine). Furthermore, uncompetitive antagonists have the added theoretical advantage of use-dependence, implying that their inhibitory action may be specifically potentiated at sites of excessive receptor activation (124,125). Dissociative anesthetics have been known to act as uncompetitive NMDA receptor antagonists since the demonstration in the early 1980s by David Lodge and his colleagues that ketamine and phencyclidine (PCP) block NMDA receptor-mediated excitation of spinal neurons (3).

A good portion of the resistance to the development of noncompetitive antagonists has been the belief that these agents — taking ketamine and PCP as examples — are more prone to cause neurobehavioral side effects than competitive antagonists. In fact, while some noncompetitive antagonists have a high propensity for side effects, others (such as memantine) are surprisingly free of toxicity (126). Indeed, it is now recognized that channel-blocking NMDA receptor antagonists fall into two broad categories: dissociative

anesthetic-like agents and low-affinity antagonists. In animals, dissociative anesthetics at low doses cause hyperlocomotion, stereotypies and ataxia; at higher anesthetic doses they induce a state of immobility, analgesia, and amnesia. In humans, these agents produce a variety of psychotropic effects at subanesthetic doses, including hallucinations and "dissociation" which refers to the perception of being separated from one's body. Thus, while PCP originally was developed in the 1950s as an anesthetic, it was later abandoned because it frequently induced a state of postoperative delirium. These effects are less frequent with ketamine, which was introduced in the 1960s and is still in limited use mainly in children. Nevertheless, ketamine is well recognized to produce a psychosis-like state with some features of schizophrenia (1,40). Because of their powerful psychotomimetic effects, these drugs were never seriously considered as candidates for clinical trials in epilepsy or neuroprotection; however, in contrast to PCP and ketamine, MK-801—which also acts as channel-blocking NMDA receptor antagonist but is far more potent (Fig. 1) — underwent clinical evaluation (146). In animals, MK-801 causes substantial neurobehavioral toxicity, including the induction of memory impairment (10), and at high doses induces dissociative anesthesia similar to that seen with ketamine (83). In human volunteers, low intravenous doses of MK-801 were well tolerated, but significant side effects were observed at doses associated with low nanomolar serum concentrations within the range that block NMDA receptors (84).

Dissociative anesthetic-like agents with high neurobehavioral toxicity, such as PCP or MK-801, typically have a high-affinity for NMDA receptors (<100 nM) (126). In recent years, a variety of other structurally diverse channel-blocking (uncompetitive) NMDA receptor antagonists have been identified with substantially lower behavioral toxicity. These better-tolerated antagonists, including memantine, exhibit lower affinity (>500 nM) for NMDA receptors than either PCP or MK-801. They have therefore been referred to as "low affinity uncompetitive NMDA antagonists" even though, as discussed below, we now recognize that low binding affinity is not the only factor that determines their improved tolerability and, indeed, certain neurobehaviorally toxic (dissociative anesthetic-like) uncompetitive NMDA antagonists, such as ketamine, may have binding affinities in the same range (126). Nevertheless, the term "low affinity antagonist" is useful to denote channel-blocking NMDA antagonists that have distinctly different neurobehavioral toxicity from dissociative anesthetic-like agents. In animals, neurobehavioral toxicity is often assessed by determining whether a drug induces gross neurological impairment (e.g., ataxia) at therapeutic doses. In addition, operant drug discrimination studies can demonstrate whether the subjective perception of two drugs is similar or dissimilar. Thus, although memantine has consistently been found to partially substitute for PCP and MK-801 in such paradigms, this activity occurs only at doses causing reductions in the rate of responding, indicating a nonspecific effect (50,56,102,165). The basis whereby low affinity antagonists have reduced toxicity and fail to crossgeneralize with dissociative anesthetics in drug discrimination experiments is not known with certainty; however, it has been proposed that a variety of factors may allow the level of block produced by the lower affinity antagonists to adjust in a more dynamic fashion in response to synaptic activity (see "Molecular Physiology of Memantine Block of NMDA Receptors" below).

An additional toxicity of NMDA receptor antagonists in rodents — especially the dissociative anesthetic-like compounds MK-801, phencyclidine and ketamine — is the development of neuronal cytopathology in the posterior cingulate cortex and retrosplenial cortex. Reversible mitochondrial and cytoplasmic vacuolization occurs several hours after

low-dose systemic administration of these agents, while high doses can cause neuronal necrosis (5,103,160). At therapeutic doses memantine does not cause such vacuolization (26), although these effects have been observed in rodents with doses that lead to high peak serum levels. Neither vacuolization nor necrosis has been observed with memantine in primates, and these neuropathological changes have, in general, not been found in primates even with MK-801 treatment, suggesting that there are differences between the rodent and primate brain in their susceptibility to NMDA antagonist-induced neuronal injury (6). In fact, it has been proposed that the necrotizing effect is caused by the neuronal hypermetabolism that is well recognized to occur after administration of channel-blocking NMDA receptor antagonists (59,111). Since the primate brain has a lower density of neurons, it has a lower metabolic rate per gram of tissue, and might therefore be less susceptible to the necrotizing effects of these drugs.

### Interaction of Memantine and Amantadine with NMDA Receptors

The first clear evidence that memantine interacts with NMDA receptors came from radioligand binding studies in which memantine displaced [$^3$H]MK-801 from binding to postmortem human brain with a $K_i$ of 0.54 μM, which was noted to be below the brain concentration reached in the treatment of Parkinson's disease (about 2 μM) (72,154). At the same time, Borman (17) reported electrophysiological studies demonstrating that memanine blocks NMDA-evoked currents in cultured mouse spinal neurons. Numerous subsequent studies have confirmed that memantine inhibits NMDA receptor currents with $IC_{50}$ values in the range of about 2 μM (33). Subsequently, amantadine was also demonstrated to interact with NMDA receptors, but with lower affinity than memantine.

A critical issue for the NMDA receptor hypothesis of memantine action is whether levels in the brain extracellular microenvironment following the administration of clinically relevant doses of the drug are sufficiently high to affect NMDA receptors. It has been demonstrated that extracellular fluid concentrations of memantine are similar to those in the serum and cerebrospinal fluid (CSF), whereas whole brain concentrations are markedly greater (44-fold) (62). Thus, in rats treated chronically with memantine, serum concentrations of ~1 μM are associated with extracellular fluid concentrations of 0.4 to 0.7 μM. Serum levels of memantine in humans with the usual daily maintenance dose of 20 mg (120) are within the range of 0.5 to 1.0 μM (73,106). It has been estimated that free serum levels are 20–50% lower due to protein binding. Assuming extracellular fluid concentrations are similar to free serum concentrations in the human as in the rat, it can be expected (based upon affinity values given in the next section) that there is a low but significant block of NMDA receptors by memantine at nontoxic therapeutic doses.

## MOLECULAR PHYSIOLOGY OF MEMANTINE BLOCK OF NMDA RECEPTORS

### Inhibition of NMDA Receptor Currents

Whole-cell patch clamp recordings of native NMDA receptors expressed in cultured neurons have been the main method used to characterize the details of the interaction of memantine with NMDA receptors. Memantine has been found to inhibit NMDA receptor

currents in a concentration-dependent fashion with $IC_{50}$ values in the range of 0.5–3 μM at hyperpolarized membrane potentials (i.e., –60 to –70 mV) (14,24,67,108,138). The reported Hill coefficient of the concentration-response curve is close to 1 ($n_H = 0.92$) (138), compatible with the idea that a single memantine molecule binds and blocks the channel. However, an examination of the kinetic properties of the block of open NMDA channels revealed fast and slow components for block and recovery, and mathematical modeling using these data suggested the existence of two distinct blocking sites deep within the channel pore that can be simultaneously occupied by two blocking molecules (138,140). The blocking effect of memantine was (to a first approximation) use-dependent, indicating that block may require the channel to be in the open state. In addition, memantine block is strongly voltage-dependent, with the potency of block diminishing at more positive membrane potentials. Memantine exerts its blocking action by entering the channel from the outside (cytoplasmic) side, but is inactive when applied from the intracellular compartment (107). The antagonistic effects of memantine were not reversed by increasing the concentration of glycine, ruling out the possibility of an interaction between memantine and the NMDA receptor glycine binding site.

Studies with recombinant receptors expressed in heterologous cells that ordinarily do not express NMDA receptors have confirmed the results seen in native neurons (20). Additionally, such studies have shown that memantine has little selectivity for different isoforms of the NMDA receptor, at least in regard to those composed of the obligatory NR1 subunit and the NR2A, NR2B, and NR2D subunits. In HEK 293 cells transiently transfected with NR1a/NR2A, NR1a/NR2B, and NR1a/NR2D, memantine blocked L-glutamate-evoked currents with $IC_{50}$ values (at –70 mV) of 0.93, 0.82, and 0.47 μM, respectively (20). Studies with recombinant NMDA receptor subunits expressed in *Xenopus* oocytes have confirmed this modest subunit selectivity. The $IC_{50}$ values at –70 mV for NR1a coinjected with NR2A, NR2B, NR2C, or NR2D were 0.9, 0.4, 0.3, and 0.3 μM, respectively (105). Under conditions of membrane depolarization (–30 mV) and in the presence of 1 mM $Mg^{2+}$, the corresponding $IC_{50}$ values were 10.3, 10.9, 2.0, and 1.9 μM; the difference between the 2A and 2B subunits versus the 2C and 2D subunits is attributed to the reduced $Mg^{2+}$ sensitivity of the latter two subunits. It has been proposed that improved tolerability of low affinity NMDA receptor antagonists may be partly determined by their subunit selectivity, with a preference for receptors that do not contain the ubiquitious NR2A subunit (126). Although it is unclear how NR2C and NR2D selectivity relates to the improved tolerability of memantine, both subunits have rather restricted expression in comparison with NR2A and NR2B. It is not immediately obvious how selectivity for NR2C, which is mainly expressed in the cerebellum, could be of relevance in AD. On the other hand, while NR2D is much more strongly expressed in embryonic and neonatal brain, there is significant expression in certain adult brain regions including the basal ganglia, thalamus and subthalamic nuclei, which could participate in the pathophysiology of AD (153).

## Kinetics of Block

Understanding how low affinity, uncompetitive NMDA antagonists, such as memantine, have improved clinical tolerability relative to the dissociative-anesthetic like agents has been a focus of considerable research interest. A variety of pharmacodynamic factors,

including rapid intrinsic association kinetics, use-dependence, reduced closed channel block, partial trapping, multiple sites of block, and multiple sites of action on targets other than NMDA receptors, have been proposed as contributing to the improved tolerability of these drugs (126). Rapid channel-level kinetics was the first factor to be considered (124). Indeed, at equieffective concentrations, lower affinity antagonists necessarily have faster rates of block and unblock than high affinity antagonists, implying that the faster effective blocking rates could contribute to the improved clinical tolerability of the lower affinity antagonists. However, an extensive comparison between binding affinity and therapeutic index by Parsons et al. (109) demonstrated that reduced binding affinity alone could not completely explain the better tolerability. This lack of correlation between binding affinity and therapeutic index is particularly striking for ketamine, which is known to produce profound neurobehavioral toxicity yet has a blocking affinity in the range associated with better tolerated channel blocking agents, including memantine.

Lower affinity channel blockers generally have more rapid effective blocking rates because higher concentrations are required to exert similar degrees of fractional block. These higher concentrations, by the law of mass action, result in faster association rates and, assuming the dissociation rates are similar, a correspondingly faster approach to equilibrium block. However, there can be wide variability in the first order forward (association) rate constants ($k_1$). Apart from the concentration effect, compounds with faster intrinsic association rate constants would achieve equilibrium block more rapidly than those with slower association rates. While memantine and ketamine have similar blocking potencies, the forward rate constant of memantine ($k_1$) is ~6-fold greater than that of ketamine (95) and possibly as much as ~25-fold greater than that of PCP (109). The reverse (dissociation) rate constant ($k_{-1}$) of memantine is also correspondingly faster than that of ketamine, thus accounting for the similar equilibrium affinities ($K_D = k_{-1}/k_1$) of the two blockers. The rate of approach to equilibrium is given by the sum of the association and dissociation rates ($k_{eff} = k_1[\text{drug}] + k_{-1}$); therefore, the effective blocking rate for memantine would be substantially greater than that of ketamine even though the two drugs have similar equilibrium affinities, compatible with the idea that a faster association rate is related to improved tolerability.

The extent to which block can be reversed during synaptic activity could also play a role in the tolerability of channel blocking NMDA receptor antagonists. Factors affecting reversal of block include the rates of dissociation from open and closed channels (which may be voltage-dependent) and the phenomenon of trapping (discussed below). MK-801 is an example of an uncompetitive antagonist that dissociates very slowly from open channels (time constant >3 min vs. ~3 s for memantine) (95,109) and is also nearly fully trapped in closed channels (14). Therefore, during ordinary ongoing synaptic activation, NMDA receptors would slowly accumulate MK-801, resulting in near complete block that would be maintained during synaptic depolarization. In contrast, relief of block during synaptic depolarization can be achieved by antagonists with faster dissociation rates.

Considering the critical functional roles of NMDA receptors, it is apparent that in AD some NMDA receptor-mediated synaptic transmission must be maintained to avoid impairing the neurological, behavioral and memory functions that are dependent upon the integrity of these receptors. In fact, although the effects of memantine on NMDA receptor-mediated synaptic transmission have not been studied extensively, at least one study has shown that memantine (6 μM) only minimally reduced the NMDA receptor component of excitatory synaptic currents in cultured hippocampal neurons (26). In contrast, MK-801

caused a progressive use-dependent accumulation of block leading to complete inhibition of the NMDA receptor component. The poor tolerability of MK-801 may, therefore, relate to the accumulation of block and the virtual shutdown of all NMDA receptor-mediated synaptic transmission. However, it is important to note that the dissociation rate constant for memantine is only modestly faster than that of ketamine (95). In addition, other well-tolerated, uncompetitive NMDA antagonists also have equivalent or slower dissociation rates than ketamine (126). Therefore, the microscopic dissociation rate alone does not seem to determine tolerability, at least in regard to the moderate differences in rate that exist between uncompetitive antagonists other than MK-801.

In sum, blocking low, tonic levels of NMDA receptor-mediated excitation while at the same time permitting synaptic NMDA receptor responses may contribute to symptomatic improvement and also to potential neuroprotective effects (see "The Weak Excitotoxicty Hypothesis" below). The relatively faster channel-level kinetic properties exhibited by memantine may, at least in part, allow such differential blocking activity. Other factors of potential relevance are discussed in the following sections.

## Voltage-Dependence

Memantine block of NMDA receptors is highly voltage-dependent so that block is relieved by strong depolarization, as occurs during excitatory postsynaptic potentials (20). In other words, memantine can quickly exit the channel under depolarized conditions, allowing ongoing synaptic activity to be maintained (101). Because of their slow blocking kinetics, it is difficult to demonstrate voltage-dependent relief of block for dissociative anesthetic-like agents such as PCP and MK-801. While it is likely that these agents bind at a similar site deep within the channel pore as does memantine (see "Identification of the Memantine Binding Site" below), and that they have a similar intrinsic voltage dependence, the dissociative anesthetic-like agents remain in the channel during depolarization due to their slow dissociation rates and, therefore, exhibit functionally voltage-independent channel block on the time scale of ordinary synaptic activity.

## Partial Trapping

A key characteristic of the blocking action of dissociative anesthetic-like NMDA receptor antagonists such as MK-801, PCP and ketamine is that the drugs are "trapped" (Fig. 3). These drugs enter open NMDA receptor-channels and bind to a blocking site located deep in the pore. Although the presence of the drug molecule interferes with ion permeation, it does not prevent channel closure after removal of agonist. Therefore, the blocking drug can remain in the pore, trapped by the conformational change occurring during channel closure, and rebinding of agonist must occur to allow the blocker to leave the channel. "Trapping" block is distinct from "sequential" block, a classic mode of ion channel block in which the channel is unable to fully close when the drug molecule plugs its pore. In sequential block, a blocked channel is gated open with a subsequent application of agonist, allowing egress of the drug molecule followed by channel closing. Immediately after drug molecule egress, a transient current often can be detected as the channel closes. Accordingly, sequential block can be conceptualized as a situation where

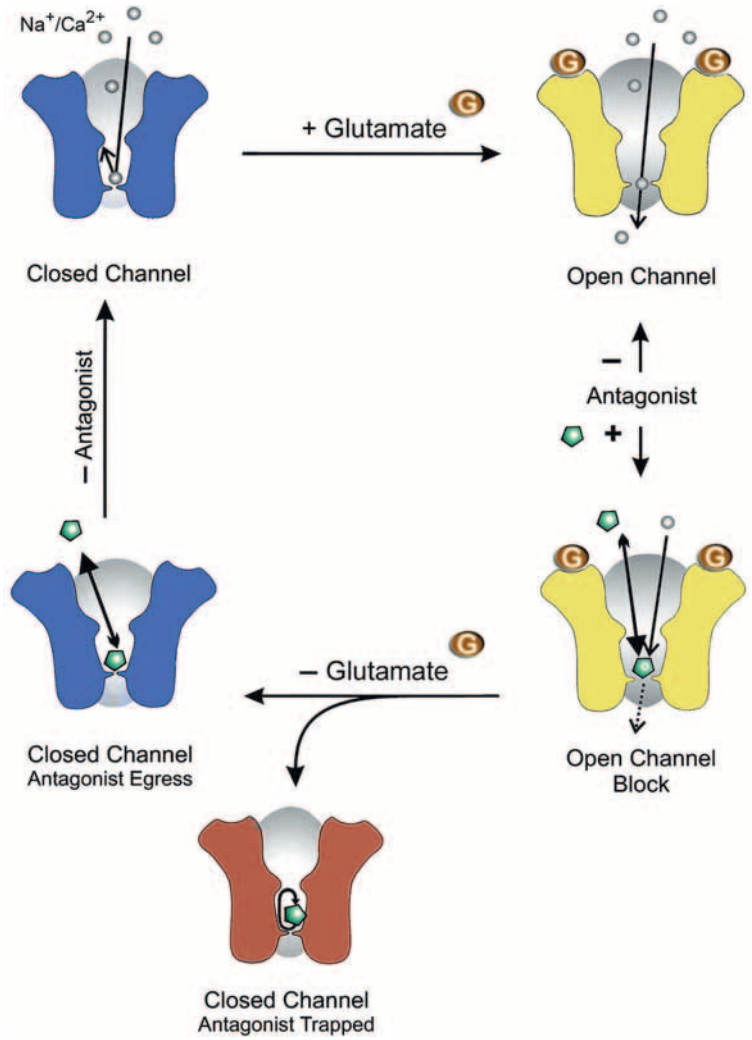


**Fig. 3.** Schematic illustration of uncompetitive (open channel) block and trapping. Upper left: NMDA receptor is shown in the unliganded, closed state. Upper right: In the presence of glutamate and a glycine site agonist (not shown) the channel is gated open, permitting cation flux. Lower right: A channel blocker (such as memantine) enters the open channel, producing block. Upon removal of agonist, the blocker may or may not be trapped in the closed channel. In a classical sequential blocking mechanism, the channel is unable to close when the agonist has dissociated until the blocker leaves the channel. Once the blocker exits the channel, the channel can return to the closed state. Memantine does not appear to block by this sequential blocking mechanism. Alternatively, the channel closes with the trapped blocker inside (bottom). It will then remain in this state until agonist is reapplied and the blocking drug is then able to leave the channel. This model is relevant to channel blockers such as memantine that access the channel through an aqueous pathway (from the extracellular space) and remain in the pore of the channel. Note that memantine block of the NMDA receptor exhibits partial trapping in which only a fraction of channels appear to exhibit trapped block. To explain partial trapping, Mealing et al. (96) propose that the blocking drug is prevented from entering the cytoplasm by a lower barrier (channel pore and selectivity filter of the channel) and by an additional upper barrier. Once the upper barrier closes, the antagonist is trapped in a "vestibule" that is formed by the space between these two barriers, and the receptor is in the closed, blocked state. If the "upper barrier" of the vestibule closes more slowly than the channel pore, some antagonist molecules may escape, resulting in partial untrapping (middle left). Partial trapping could occur if closure of the upper gate is separate from channel closure. From Mealing et al. (96) with permission.

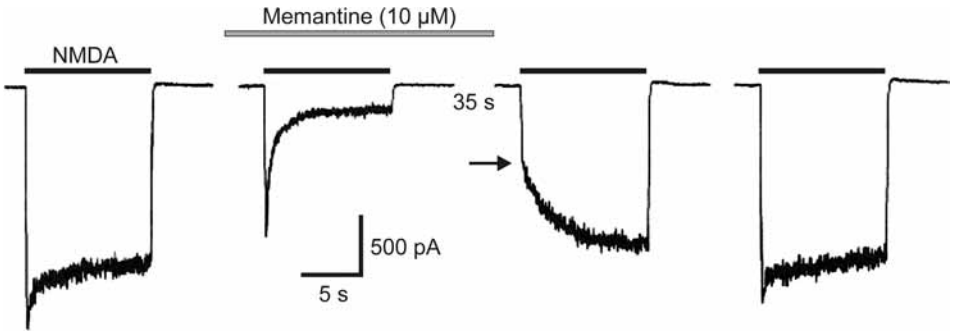


**Fig. 4.** Whole-cell voltage clamp recording demonstrating memantine block of NMDA receptor current with partial trapping. Perfusion of the cell with 200 μM NMDA (black bars) elicits an inward current response due to activation of NMDA receptors (first trace). Preincubation with 10 μM memantine for 20 s followed by coapplication of memantine and NMDA results in a current that shows a rapid reduction in the peak response to a steady-state level as memantine binds and blocks the open channels (second trace). After a 35 s period in the continued presence of memantine, the drug is washed off and 2 s later NMDA is applied alone (third trace). During this third response, the current shows a fast partial response (from the steady-state blocked level in the second trace to point indicated by arrow) and then a slower response to plateau. The fast portion of the response is generated by NMDA receptor channels that did not trap memantine (about 15% of total). The slower portion of the response represents those channels in which memantine is trapped; memantine must dissociate before the channels can pass current. The final trace shows the nearly fully recovered response to NMDA. From Parsons et al. (106) with permission.

drug binding interferes with the conformational change (i.e., movement of the gate that prevents ion flux) required for closure.

Like dissociative anesthetics, memantine also is trapped within closed NMDA receptor channels. However, Blanpied et al. (14) have proposed that the drug is trapped in only a proportion of the channels, a phenomenon they refer to as "partial trapping" (95,106). Partial trapping was demonstrated in experiments where both agonist and memantine are removed after block, and after trapping had reached steady-state (Fig. 4). Memantine was then observed to spontaneously unbind from roughly one-sixth of the channels, while persistently blocking the remainder of the channels. This is quite different from the situation with PCP and MK-801, which remain trapped in nearly all blocked channels. Indeed, the extent to which different blockers are trapped can vary from those that are not trapped (e.g., 9-aminoacridine) (11); those that exhibit partial trapping (e.g., memantine and AR-R15896AR); those that are nearly fully trapped (e.g., ketamine) (95); and, finally, those that are fully trapped (e.g., MK-801). It has been proposed that the lack of complete trapping is an important factor that accounts for the favorable tolerability of certain channel blocking NMDA receptor antagonists (96). This theory is based on the concept that relief of channel block, which occurs in a voltage-dependent fashion during synaptic activation, allows ongoing NMDA receptor-mediated synaptic transmission to continue to a sufficient degree so as to avoid disrupting the function of critical brain circuits that require the integrity of NMDA receptors. Trapping prevents the relief of block because the drug cannot be cleared from the channel between episodes of synaptic activation. Conversely, partial trapping (or perhaps more properly "partial untrapping") allows the maintenance of some degree of use-dependence and permits voltage-dependent relief of block.

Mealing et al. (96) have demonstrated that partial untrapping can occur even in the continuous presence of a blocking drug, so that the phenomenon is not only an experimental curiosity in studies where the blocker can be applied and removed rapidly, but also could be relevant in the clinical situation where the drug is tonically present. As of yet, a link between partial untrapping and the side-effect characteristics of lower affinity channel blocking antagonists has not been established with certainty. In fact, ketamine may be trapped only slightly more than memantine (86% versus 71%) (95), but it has dramatically greater toxicity than memantine.

## Closed Channel Block

Some authors have concluded that memantine does not block closed NMDA channels and, therefore, does not have access to the channel in its closed conformation (24). In this scheme, the drug molecule exclusively accesses its binding site via the hydrophilic permeation pathway. More recently, however, some authors have observed that memantine can interact with the channel in its closed state (138). This has been hypothesized to occur by entry of the drug into the channel pore through the route by which it normally accesses the channel ("hydrophilic pathway") (138) or by a distinct pathway (that may or may not require transit through the lipid membrane) that avoids the closed channel pore (14). While the significance of this closed channel block is not fully understood, it is apparent that it will reduce the use-dependence of the blocking action of memantine to some extent, since the receptor-channels will accumulate block even in the absence of synaptic activation. During chronic therapy, there could be substantial tonic block.

In addition to the block that occurs by memantine binding to the channel pore, Blanpied et al. (14) concluded that high concentrations of memantine also can block the channel through an interaction with a second, noncompetitive blocking site with an affinity that is about 100-fold lower than at the primary channel blocking site. Noncompetitive block at this site is not voltage-dependent and would only occur with high, nontherapeutically relevant memantine concentrations. It is interesting to note that many channel-blocking NMDA receptor antagonists can inhibit the channel through such secondary actions (140).

## Identification of the Memantine Binding Site

Electrophysiological studies can provide an estimate of the depth of the voltage-dependent blocking site for channel blockers based upon the Woodhull model (159). This analysis uses information about the "steepness" of the relationship between membrane potential and the relative amount of steady-state block in order to estimate the fraction of the membrane electric field sensed by a charged blocking molecule at its blocking site within the channel pore. Assuming that the amino group gives memantine a single, positive charge at physiological pH, and that only one memantine molecule blocks each channel, Blanpied et al. (14) determined that the meantime blocking site senses 87% of the membrane electric field, placing it deep within the channel; Kashiwagi et al. (67) obtained an almost identical value of 89%. If two molecules of memantine bind simultaneously within the channel as suggested by Sobolevsky and Koshelev (138), the corrected value would be about 45%, consistent with the idea that the blocking site is about one-half of the way

across the membrane field which would place it near the blocking sites of many other channel blockers (140).

Each NMDA receptor subunit is believed to be situated in the neuronal membrane with its N-terminus on the extracellular side and its C-terminus on the intracellular side. The polypeptide chain traverses the membrane three times in what are referred to as the M4, M1 and M3 transmembrane segments. In addition, an M2 segment is believed to be a re-entrant loop that does not cross the membrane, but rather dives into and out of the membrane from the intracellular side. Substantial evidence from site-directed mutagenesis indicates that the M2 loop forms the pore of the channel and that it is a critical determinant of both divalent cation permeability and $Mg^{2+}$ block (35). Asparagine residues in this region form part of the binding site for $Mg^{2+}$ and contribute to the selectivity filter of the channel; these residues also influence block by channel blockers such as MK-801 (67).

Attempts to identify the memantine pore blocking site by mutagenesis of NR1 and NR2B subunits (forming NR1/NR2B heteromers) have revealed that mutations in M2 can influence blocking potency, which is compatible with the idea that the drug binds in the pore/selectivity filter region of the channel, near the $Mg^{2+}$ blocking site (Fig. 5). Interestingly, while block by MK-801 is dramatically reduced by mutations in the M1, M3, and M4 membrane-spanning regions of the channel, memantine block is largely unaffected by these same mutations. This indicates that block by the high-affinity antagonist MK-801 may be more complex than that of memantine, and may be dependent upon subtle conformational changes in the protein. Regardless, the actual binding site for MK-801 may be similar to that of memantine.

## OTHER TARGETS OF MEMANTINE

Although NMDA receptors are the most memantine-sensitive ion channels identified to date, memantine can affect other ion channels. In particular, the drug has been reported to block 5-$HT_3$ receptors (116,121) and nicotinic acetylcholine receptors (nAChRs) (106). Memantine does not affect other ionotropic receptors, including AMPA and $GABA_A$ receptors. Memantine inhibits nAChRs at the frog neuromuscular junction (89), and both memantine and amantadine exert use-dependent and voltage-dependent block of human α4β2 nAChRs stably expressed in human embryonic kidney cells (HEK 293) with $IC_{50}$ values at –100 mV of 3.4 and 6.6 μM, respectively (21). Human α7 neuronal nAChRs expressed in *Xenopus* oocytes were blocked by memantine slightly less potently than α4β2 nAChRs ($IC_{50}$ value, 14 μM) (88), but in the same range as native nAChRs in cultured hippocampal neurons ($IC_{50}$ value, 12.3 μM) (107).

To the extent that nAChRs are relevant to the cholinergic deficit in AD, the actions of memantine on nAChRs theoretically could have a negative therapeutic effect. The fact that amantadine is a more potent nAChR antagonist than memantine and is used at doses that cause greater serum levels, may, in part, explain why amantadine has not been found to be as useful as memantine in AD treatment. It is also noteworthy that some clinically approved cholinesterase inhibitors (ChEIs) block nAChRs at higher doses, while others, including galantamine, are allosteric potentiating ligands that promote the activity of nAChRs at low concentrations and can also block these receptors at somewhat higher concentrations (130).

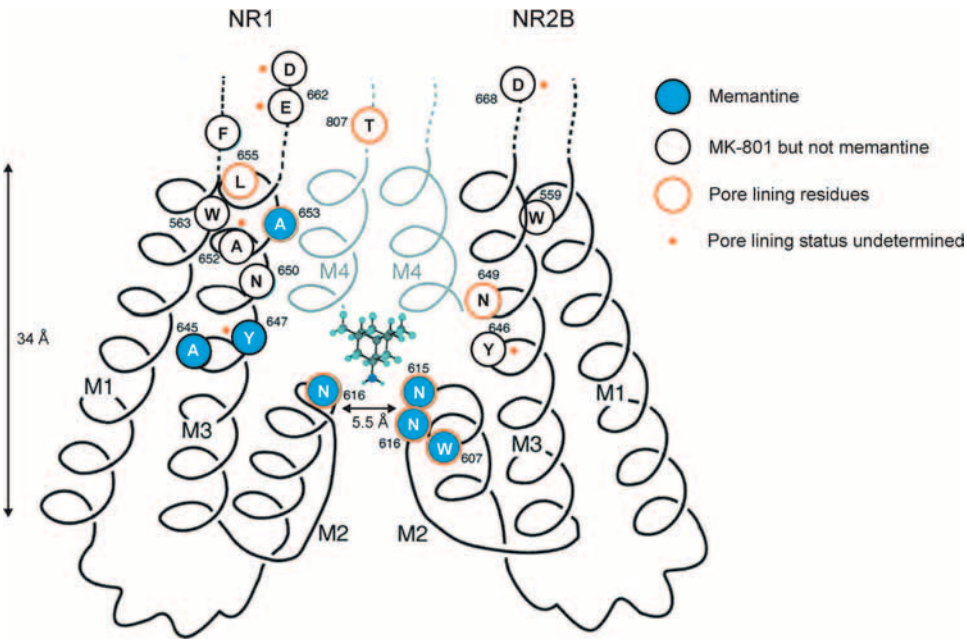


**Fig. 5.** Deduced structure of the pore and extracellular vestibule region of the NMDA receptor. The membrane spanning M1 and M3 domains of the NR1 and NR2B subunits are depicted as helices, with the pore-forming M2 loops shown as a helix followed by a random coil. The asparagine (N) residues critical to divalent cation permeability and $Mg^{2+}$ block are located at the tips of the M2 helices (79). Residues that strongly affect memantine (and also MK-801) block when mutated are shown as blue circles. Additional mutations that strongly influence MK-801 block but not memantine block are shown as open circles; these residues may influence MK-801 block either by altering its access to the deep channel blocking site or by allosterically disrupting the structure of the deep high-affinity binding site. Memantine binding is influenced by fewer M3 and M1 residues than MK-801, indicating that its access is less restricted or that its binding is less critically dependent upon the structure of the binding site, compatible with its lower binding affinity. Letters within circles are standard single-letter amino acid codes; numbers indicate sequence positions. Solvent accessible residues that line the pore (as determined by the substituted cysteine accessibility method) (9) are indicated with an orange border. A single memantine molecule is positioned at the ring of asparagines forming the selectivity filter; the orientation is arbitrary. This model does not exclude the possibility of occupancy by two memantine molecules as proposed by Sobolevsky and Koshelev (138). Adapted from Kashiwagi et al. (67) with permission.

In addition to the interaction with nAChRs, memantine has the potential to interfere with the therapeutic activity of ChEIs by affecting their interaction with cholinesterase enzymes. Indeed, there is evidence from *in vitro* studies with striatal homogenates that memantine can partially reverse the activity of irreversible ChEIs such as diisopropylfluorophosphate, but in the same system, memantine at concentrations as high as 5 μM does not significantly affect cholinesterase activity (151). However, no interaction of memantine with the reversible ChEIs used for the treatment of AD, including tetrahydroaminoacridine, donepezil and galantamine has been reported. Additionally, substantial clinical evidence demonstrates that memantine administered to AD patients on stable doses of a ChEI (donepezil) is both efficacious and well tolerated (42), and a German postmarketing study indicates that this may extend to other ChEIs as well (60).

Recent studies indicate that memantine may functionally block 5-$HT_3$ receptors with a potency similar to its action on NMDA receptors ($IC_{50}$, 1 μM; Merz, personal communication). 5-$HT_3$ receptors are ligand-gated ion channels that are expressed widely in the central and peripheral nervous systems where, like NMDA receptors, they mediate fast excitatory synaptic transmission. There is now considerable evidence that 5-$HT_3$ receptor activation can inhibit LTP and memory, and, conversely, that 5-$HT_3$ receptor blockade facilitates learning and cognitive performance (28a). Therefore, it is conceivable that the interaction of memantine with 5-$HT_3$ receptors could be relevant to its beneficial activity in AD. Interestingly, dissociative anesthetics such as ketamine and PCP do not block 5-$HT_3$ receptors at the low concentrations that block NMDA receptors, raising the possibility that 5-$HT_3$ receptor blockade could contribute to the behavioral tolerability of memantine. 5-$HT_3$ antagonists are used clinically in the treatment of nausea and they also may have beneficial activity in gastrointestinal motility disorders. The most common adverse events associated with ChEIs in the treatment of AD are nausea, diarrhea and vomiting. In view of the 5-$HT_3$ blocking activity of memantine, it is noteworthy that there was a reduced incidence of such gastrointestinal side effects in AD patients treated with both donepezil and memantine than with donepezil alone (42).

In addition to effects on ionotropic receptors, memantine is a very weak blocker of L- and N-type voltage-gated $Ca^{2+}$ channels in hippocampal neurons, P-type $Ca^{2+}$ channels in cerebellar Purkinje neurons, and $Na^+$ channels in dorsal root ganglion ($IC_{50}$s > 100 μM) (107). Parsons et al. (106) discusses additional reported effects of memantine at high concentrations on other ion channel types that are of uncertain significance.

## MEMANTINE, SYNAPTIC PLASTICITY AND MEMORY

Overwhelming evidence has implicated NMDA receptors in learning, with particular importance in the encoding of memory (15,122). NMDA receptors are also well recognized to be required for the induction of some forms of synaptic plasticity such as long-term potentiation (LTP), in which certain patterns of synaptic activity are associated with enduring alterations in the strength of synaptic transmission. The link between LTP and learning was first made by R. G. M. Morris on the basis of studies showing that NMDA receptor antagonists cause parallel impairment of water-maze learning and LTP in rats (87,131). More recently, knockout mice lacking hippocampal NMDA receptors have been shown to exhibit deficits in both spatial and non-spatial learning tasks, supporting a critical role for NMDA receptors in memory function (39,127). Although it is generally accepted that NMDA receptor antagonists interfere with many forms of learning, under certain circumstances NMDA receptor antagonists can paradoxically enhance learning (34). Indeed, it has been noted that hippocampal LTP is dependent upon partial blockade of NMDA receptors by $Mg^{2+}$. LTP does not occur under $Mg^{2+}$-free conditions probably because induction of LTP requires periodic reversal of ongoing NMDA receptor activity.

LTP typically is induced by brief (usually 1 s), high frequency (generally 100 Hz) tetanic stimulation. The summated synaptic depolarization produced by such trains is greater than that produced by a single stimulus, and there is a correspondingly greater relief of $Mg^{2+}$ block of NMDA receptors. The subsequent $Ca^{2+}$ entry can trigger intracellular events that lead to synaptic strengthening. A similar process is assumed to occur during

memory formation when excitatory pathways are strongly activated. Interestingly, although $Mg^{2+}$ is required for LTP, Coan et al. (28) demonstrated that low levels of block produced by the competitive NMDA receptor antagonist AP5 can counteract the deficit in LTP induction that is seen upon $Mg^{2+}$ removal. Memantine, like all NMDA receptor antagonists, blocks hippocampal LTP, although its potency ($IC_{50}$, 11.6 μM) is lower than the potency at which it binds to NMDA receptors and blocks NMDA receptor-mediated synaptic transmission, probably because memantine blocking affinity is reduced by the strong depolarization that occurs during LTP induction (26,49). However, in an analogous series of experiments to those of Coan et al. (28), Frankiewicz and Parsons (48) found that low concentrations of memantine could actually restore the deficit in LTP produced by low $Mg^{2+}$. In contrast, MK-801 did not have any restorative activity. It has been proposed that memantine can substitute for $Mg^{2+}$ because, like $Mg^{2+}$, it exhibits strong voltage-dependence and fast blocking kinetics so that it can rapidly exit the NMDA receptor channel during the depolarization required for LTP induction. Unblock of the NMDA receptor during an LTP-inducing stimulus is critical to LTP induction since NMDA receptors mediate the $Ca^{2+}$ entry that triggers the process. In contrast, MK-801 is functionally far less voltage-dependent because of its high affinity and extremely slow unblocking rate, rendering it a nearly irreversible blocker.

In behavioral studies, memantine does not cause dramatic impairment of memory function and, in some cases, can actually improve memory. In an operant test of short-term memory in rats, memantine was found to reduce accuracy (indicating memory impairment), but only at doses that reduced the rate of responding (indicating generalized behavioral toxicity) (157). In the same task, other NMDA receptor antagonists, including the channel blockers PCP and MK-801 and two competitive antagonists, selectively impaired memory at doses below those that reduced response rates. Moreover, passive avoidance learning in day-old chicks was improved by pretreatment with memantine (7), and in moderately-aged rats, Barnes et al. (8) found that memantine prolonged the maintenance of LTP *in vivo* and was associated with a trend in improved memory retention in the Morris water-maze. While other researchers did not note improved performance with memantine, they found little decrement in water-maze performance compared with control (26). Similarly, memantine reversed learning deficits in reference memory following lesions of the entorhinal cortex, whereas MK-801 caused a worsening of learning deficits (166). Since treatment with memantine was started a few days after the lesion and improvement was observed several days later, the effects of memantine were probably not a consequence of its neuroprotective activity, but rather of its ability to enhance or restore NMDA receptor-mediated neurotransmission.

It has been proposed that tonic activation of NMDA receptors (that is, gating of the channel unassociated with synaptic activity), could contribute to impairment of cognition and memory in AD. In fact, low levels of NMDA can impair the induction of LTP as well as inhibit learning in passive avoidance models (66,164). Such tonic glutamatergic activation presumably reduces the magnitude of the change in NMDA receptor activation that can be produced by a relevant signal. Interestingly, low levels of NMDA receptor blockade with either MK-801 or memantine (but not the competitive NMDA antagonist CGP-39551) were found to reverse the learning deficit in rats produced by systemic NMDA injections (164). In addition, memantine, at a therapeutically relevant concentration (1 μM), was found to restore the LTP deficit produced by perfusion with NMDA (Fig. 6).

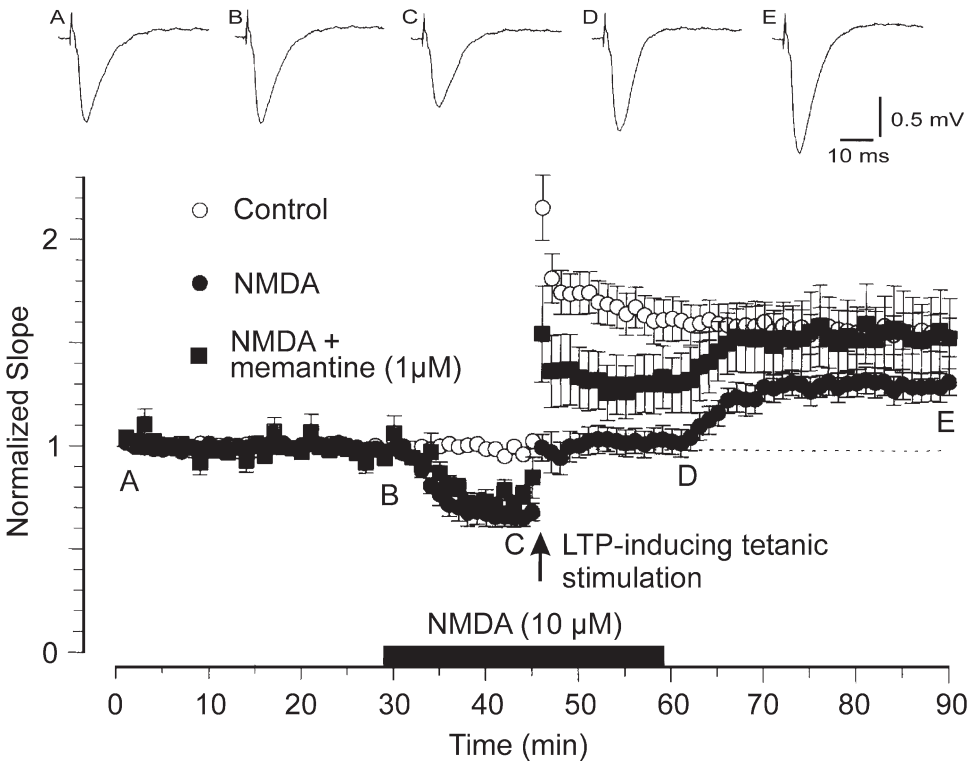


**Fig. 6.** Inhibition of long-term potentiation (LTP) in area CA1 of a rat hippocampal slice by NMDA perfusion and reversal of this inhibition by preincubation with memantine. LTP was induced by high frequency (100 Hz, 1 s) tetanic stimulation of the Schaffer collateral commissural pathway. Perfusion with 10 μM NMDA during the period indicated by the bar reduced the slope of the evoked field response and led to a diminution in the level of LTP. The continuous presence of 1 μM memantine only slightly reduced the depression of the slope by NMDA (not clearly visible prior to LTP induction), but reversed the inhibitory effect of NMDA on the induction of LTP, which reached control levels of potentiation after removal of NMDA. The failure of this low (clinically relevant) concentration of memantine to substantially block the depressant effect NMDA demonstrates that such low memantine concentrations only partially block NMDA receptors. The $Mg^{2+}$ concentration in the extracellular solution was 1 mM. Representative traces shown at the top are taken from an experiment with NMDA alone; letters show corresponding positions on the time course. From Zajaczkowski et al. (164) with permission.

Overall, in both *in vitro* and *in vivo* paradigms, memantine was observed to have positive effects on synaptic plasticity and learning at the same concentrations and doses that are associated with neuroprotective activity (see below). In the hippocampal slice, memantine confers neuroprotection at concentrations 5-fold lower than those that significantly block LTP, and even at high concentrations (30 μM), full inhibition of LTP by memantine is not observed (49). In contrast, while MK-801 has demonstrated neuroprotective activity in model systems, it generally inhibits synaptic plasticity and learning at neuroprotective doses. MK-801 completely blocks LTP at concentrations similar to those required for neuroprotective effects (49). Hence, it is theoretically possible for memantine to exert protective effects against glutamate-induced excitotoxicity while preserving fundamental synaptic plasticity mechanisms that underlie learning and memory, whereas this is unlikely to occur with MK-801.

## SYMPTOMATIC AND DISEASE-MODIFYING TREATMENT APPROACHES IN ALZHEIMER'S DISEASE

Presently approved drugs for the treatment of AD are cholinesterase inhibitors (ChEIs). Inhibition of cholinesterases, a family of acetylcholine-degrading enzymes (53), increases the synaptic concentration of the neurotransmitter acetylcholine (ACh), thereby enhancing and prolonging the action of ACh on muscarinic and nicotinic acetylcholine receptors (AChRs). In addition to beneficial effects on cognition, ChEIs may cause unwanted peripheral and central side effects. Excessive activation of muscarinic AChRs can lead to nausea, vomiting and diarrhea, while overactivation of nicotinic AChR can produce tremors and muscle cramps. Currently marketed ChEIs include donepezil, rivastigmine and galantamine. In contrast to donepezil and rivastigmine, galantamine, the newest ChEI, also allosterically potentiates the activity of nicotinic AChRs. In fact, it has been argued that sensitization of nicotinic AChRs may be its primary mode of action in AD (130).

ChEIs have been demonstrated to stabilize cognitive and behavioral function in AD, producing a symptomatic benefit. Overall, they have a modest, but nonetheless significant, beneficial impact on neuropsychiatric and functional outcomes in AD patients (145). On the other hand, there is no definitive evidence that ChEIs specifically affect the underlying pathological process or have any beneficial effect on the long-term, inexorable downward course of the disease. However, it has been noted that approximately 20% of patients being treated with ChEIs exhibit a cognitive stabilizing effect that can last up to 2 years, and it has been suggested that this long-lasting effect could indicate an effect on the disease process in a subset of patients (54). Similarly, memantine not only temporarily slows the cognitive and behavioral decline, but may produce some improvement during the initial 3 months of treatment (120). As is the case with ChEIs, the effect, if any, of memantine on the underlying disease process is unknown. However, current theories of the pathogenesis of AD make it possible to speculate that chronic blockade of NMDA receptors could conceivably produce a long-term disease-modifying effect.

## MOLECULAR PATHOGENESIS OF ALZHEIMER'S DISEASE

### The Central Role of Aβ Peptide

AD is characterized by progressive deterioration of cognition and memory, and disturbed emotional reactivity caused by dysfunction and degeneration of neurons in the limbic system and cerebral cortex. Affected brain areas typically contain extracellular neuritic plaques comprised of fibrillar β-amyloid peptide (Aβ) deposits and intracellular neurofibrillary tangles comprised of paired helical filaments of hyperphosphorylated tau. While tau likely plays a contributory role in the pathogenic process of AD (118), the deposition of Aβ is believed to be a key element leading to the neuronal loss seen in the AD brain (91). Aβ, a ~4 kDa protein, is formed through the so-called "amyloidogenic pathway" in which amyloid precursor protein (APP) is sequentially cleaved by β- and γ-secretase enzymes rather than through nonamyloidogenic processing by α-secretase (Fig. 7). APP is cleaved by α-secretase within the Aβ region to produce APPsα (the secreted ectodomain of APP) and CT83 (the 83-residue C-terminal fragment, α-stub). The amylodoge-

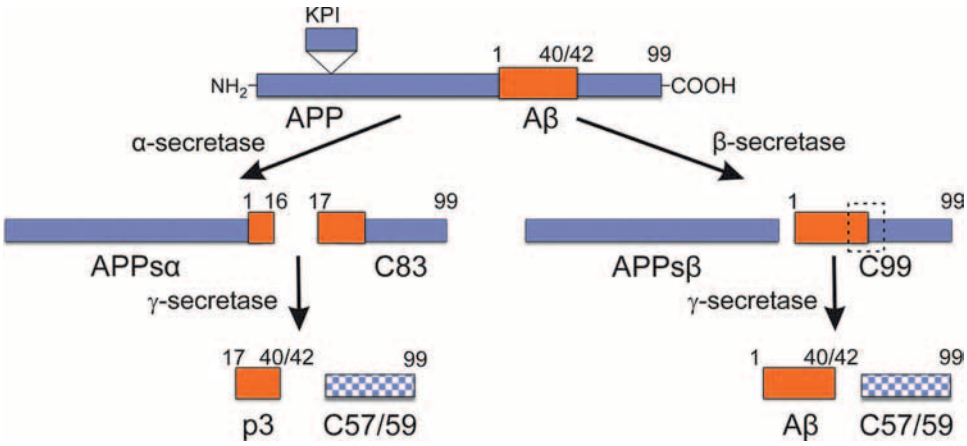


**Fig. 7.** Proteolytic processing of the β-amyloid precursor protein (APP) whose largest alternate splice form is comprised of 770 amino acids (with a 56-amino acid insert that is homologous to the Kunitz-type of serine protease inhibitors, KPI). The Aβ domain is shown in orange. Numbers refer to the amino acid sequence, relative to the first amino acid of the Aβ domain. α-Secretase cleavage of APP generates APPsβ (the secreted ectodomain of APP) and C83 (the carboxyl-terminal 83 amino acids of APP). β-secretase cleavage of APP generates APPsβ and C99. γ-Secretase cleavage of C83 and C99 yields, respectively, the p3 and Aβ peptides. A single membrane-spanning domain is indicated by a dashed box; Aβ includes 28 residues just outside the membrane plus the first 12–14 residues of the transmembrane domain.

nic Aβ peptides are generated by two proteolysis steps: APP is cleaved by β-secretase to form APPsβ and C99; C99 is then further cleaved by γ-secretase within its membrane spanning region, releasing Aβ(1–42) or Aβ(1–40).

Much of the fibrillar Aβ found in neuritic plaques is the slightly longer, more hydrophobic Aβ(1–42) that is particularly prone to aggregation; however, the typically more abundant Aβ(1–40) is usually colocalized with Aβ(1–42) in plaques. The "amyloid hypothesis" of AD posits that the gradual accumulation of Aβ(1–42) in the interstitial fluid of the brain oligomerizes, providing a focus for the subsequent deposition of Aβ(1–40) and other proteins (134). This accumulation of toxic fibrillar Aβ injures neurites within the plaques and in the surrounding neuropil. Such focal injury disrupts both neuronal function and homeostasis, and eventually causes neuronal death.

Although the manner in which Aβ damages neurons is not completely understood, both oxidative stress and disruption of neuronal $Ca^{2+}$ homeostasis, resulting in excitotoxicity, have been implicated in the neurodegeration of AD (86,93,113). Aβ induces oxidative stress and perturbs neuronal ion homeostasis by promoting membrane lipid peroxidation (22), which can impair the function of membrane-bound ion, glucose, and amino acid (including glutamate) transport proteins. Ultimately, Aβ toxicity is believed to lead to neurofibrillary tangles consisting of aggregated tau protein.

## The "Weak Excitotoxicity" Hypothesis

Some *in vitro* experiments indicate that Aβ, in addition to producing oxidative stress and affecting $Ca^{2+}$ homeostasis, increases the vulnerability of cultured neurons to glutamate, leading to glutamate excitotoxicity. Glutamatergic neurotransmission is required for

normal brain function and is critical to normal learning and memory, in part because LTP and other NMDA-dependent forms of synaptic plasticity may underlie these processes. However, inappropriately timed or sustained glutamate activation of NMDA receptors, either acute or chronic, can lead to neuronal injury and death (38). This scenario has become known as the "weak excitotoxicity" model (2,80). NMDA receptors normally are activated by synaptically released glutamate in a phasic manner. In AD, increased extracellular glutamate hypothetically could lead to chronic membrane depolarization. Alternatively, factors present in the AD brain could cause membrane depolarization even in the absence of abnormally elevated glutamate (80). Interest in mechanisms of non-glutamate-induced chronic depolarization has intensified in recent years with reports that endogenous levels of glutamate are not elevated in AD (32,44,65,78).

Several factors potentially contribute to chronic depolarization of neurons in the AD brain. For example, Aβ(1–42) can chronically depolarize neurons through its action on the metabotropic glutamate receptor, mGluR1 (13). Such Aβ-induced membrane depolarization would be expected to partially relieve voltage-dependent $Mg^{2+}$ block of NMDA receptors. Under these conditions, subsequent activation of NMDA receptors by ordinary glutamatergic synaptic activity could permit a continuous "leak" of $Ca^{2+}$ into neurons, theoretically overwhelming the endogenous mechanisms that regulate $Ca^{2+}$ homeostasis. Therefore, neurons that express NMDA receptors would become selectively vulnerable to normal glutamatergic stimulation. Accordingly, there are a number of reports that NMDA receptors are depleted in selected regions of the AD brain (81).

Other factors that could lead to chronic membrane depolarization are oxidative stress or impaired intracellular $Ca^{2+}$ buffering, potentially resulting in impaired energy production. This, in turn, might lead to impairment in the function of membrane ion pumps required for maintenance of the resting potential. In any of these situations, excessive $Ca^{2+}$ influx through NMDA receptors could mediate glutamatergic excitotoxicity (27,128) by activating a host of $Ca^{2+}$-dependent signaling pathways, ultimately leading to neuronal degeneration (37,92). For example, $Ca^{2+}$ entry through NMDA receptors stimulates nitric oxide ($NO^{\cdot}$) production through closely associated neuronal nitric oxide synthase (nNOS) (see Fig. 2). $NO^{\cdot}$ can then react with a superoxide anion to form peroxynitrite, which disintegrates into extremely toxic hydroxyl free radicals that can damage cells in a variety of ways (58).

## Interaction of Aβ with NMDA Receptors

In recent years, evidence has accumulated that Aβ can interact with NMDA receptors and enhance NMDA receptor-mediated excitotoxicity. For example, radioligand binding experiments in rat cortical membranes suggest that Aβ selectively binds to the glutamate and glycine binding sites of the NMDA receptor, and not to non-NMDA glutamate receptor subtypes (31). This binding may be functionally important inasmuch as *in vitro* application of Aβ(1–40) to rat dentate gyrus can enhance NMDA receptor-mediated postsynaptic neuronal responses (161). The enhancement of NMDA receptor responses would be expected to increase neuronal vulnerability. Indeed, mature cultured murine cortical neurons and fetal human cerebral cortical cell cultures exposed to Aβ were more susceptible to excitotoxic injury by glutamate or NMDA as compared to neurons that were not exposed to Aβ (70,92).

### NMDA Receptors and Tau

In addition to the evidence that Aβ can influence the activity of NMDA receptors, several recent studies have suggested the intriguing possibility that NMDA receptor activation can affect the expression and functional state of tau. As noted above, tau is a microtubule-associated protein that promotes microtubule polymerization and stabilization. Hyperphosphorylated tau accumulates in paired helical neurofilaments to form neurofibrillary tangles. A link between glutamate excitotocity and tau first was suggested by studies in cultured rat hippocampal neurons in which glutamate-induced neurodegeneration was associated with immunostaining specific for neurofibrillary tangles (90). More recently, it has been shown that acute or chronic NMDA-induced excitotoxicity in neuronal cultures augments tau production (114,136) and specifically increases tau that is phosphorylated at serine 202 (29). Since evidence suggests that neurofibrillary tangles are a critical determinant of the clinical progression of AD (12), and that augmented tau phosphorylation is prevented by NMDA receptor antagonists (30), it is conceivable that NMDA receptor-dependent effects on phosphorylated tau could promote the evolution of AD pathology. Interestingly, treatment of neuronal cultures with a specific tau antisense oligonucleotide (to decrease the glutamate-induced elevation of tau synthesis) protected neurons against glutamate-induced excitotoxicity (114). This experimental evidence supports a role for tau in the cascade of events involved in excitotoxic neurodegeneration.

## MEMANTINE AND ALZHEIMER'S PATHOLOGY

### Neuroprotective Activity of Memantine

Like other NMDA receptor antagonists, memantine has neuroprotective activity in a wide variety of model systems. For example, early studies demonstrated that memantine protects chick retinal neurons and cultured rat cortical neurons against excitotoxicity induced by either glutamate or NMDA, but not by kainate and the AMPA receptor agonist quisqualate (41,104). More recently, memantine has been shown to protect against NMDA receptor-mediated, agonist-induced excitotoxicity in cultured rat retinal ganglion cells (25,43), cultured rat hippocampal neurons (76,77), and chick telencephalic neurons (43,112). Memantine also is protective in *in vivo* models of brain hypoxia and ischemia (26,75). Overall, these studies demonstrate that memantine has powerful protective activity against glutamate excitotoxicity. To the extent that similar mechanisms contribute to cell death in AD, memantine could theoretically slow the progression of the disorder.

### Activity of Memantine in Models of Alzheimer's Disease

A deficit in cholinergic markers and degeneration of the cholinergic neurons in the nucleus basalis of Meynert (NBM) are common elements of AD pathology (155). The loss of NBM neurons is thought to underlie, at least in part, the memory and attentional impairment components of the dementia syndrome (68,147). As such, experimental destruction of cholinergic neurons in the rodent has been used as an animal model for these components of AD pathology (47,147,151). Moreover, drug therapies designed to attenuate the memory and attentional impairments associated with AD have focused on

cholinergic neurotransmitter systems (52) (see above "Symptomatic and Disease-Modifying Treatment Approaches in Alzheimer's Disease"). Although the basis of the vulnerability of cholinergic neurons in AD is not understood, one possibility is that the degeneration of these neurons might be due to inappropriate activation of the NMDA receptors they express. Indeed, infusion of NMDA, or glutamate receptor agonists such as quinolinic acid, into the rodent nucleus basalis magnocellularis (a structure analogous to the human nucleus basalis of Meynert) is associated with a loss of cholinergic neurons, as demonstrated by a decrease in the release of ACh and a decline in the activity of the acetylcholine synthesizing enzyme choline acetyltransferase (ChAT) (148–150,152). Furthermore, the loss of these neurons was associated with impaired spatial memory (152).

Several studies have shown that the loss of cholinergic neurons caused by injection of NMDA into the rat NBM can be attenuated by pre-treatment or co-treatment with therapeutically-relevant doses of memantine (148–150,152). Memantine also protects against destruction of cholinergic neurons by the mitochondrial toxin 3-nitropropionic acid, which may act through a "weak excitotoxicity" mechanism (see above). Consistent with these findings, other studies have shown that learning deficits caused by NMDA injection into the rat NBM can be averted by memantine (148).

In the early stages of AD, neurofibrillary tangles, deposition of Aβ and neuronal loss are restricted to the entorhinal cortex (18,19,51). Lesions of the entorhinal cortex have been used to model early AD since rats with entorhinal cortex lesions demonstrate reliable learning deficits. In one study, chronic infusion of memantine did not affect memory function of normal rats, and actually improved memory in quinolinic acid-induced entorhinal cortex lesioned rats (166). In contrast, the same study showed that MK-801 produced memory disturbances in normal animals and worsened memory function in animals with entorhinal cortex lesions.

Long-term (2 week) intracerebroventricular infusion of the NMDA receptor agonist quinolinic acid was used to model the possible chronic changes occurring during weak excitotoxicity (99,162,163). This treatment produced a persistent, short-term memory deficit as assessed by a simple behavioral task (T-maze alternation). The reduced density of choline uptake sites in the hippocampus, as assessed by [$^3$H]hemicholinium-3 binding, confirmed that among the effects of the treatment, a cholinergic deficit is produced. Chronic infusion of memantine producing steady-state serum levels similar to those obtained during memantine treatment in AD (1.2 μM) prevented the quinolinic acid-induced reduction in [$^3$H]hemicholinium-3 binding and the deterioration in learning, but had no effect on learning in unlesioned animals. Of note, chronic infusion of memantine did not affect the magnitude of LTP observed in the CA1 region of hippocampal slices taken from treated animals (see "Memantine, Synaptic Plasticity and Memory" above).

## Memantine and β-Amyloid Toxicity

As noted above (in "Molecular Pathogeneis of Alzheimer's Disease"), Aβ itself can be toxic to neurons, and also may augment NMDA receptor-mediated excitotoxicity. Recently it was shown that chronic infusion of memantine in rats reduced the local neuronal cell loss produced by intrahippocampal injection of Aβ(1–40), thus protecting against Aβ toxicity (Fig. 8) (97). At present, it is uncertain whether this effect is specifically due to an interaction of memantine with NMDA receptors or the result of another mechanism. Future studies with other NMDA receptor antagonists will be of interest in this regard.

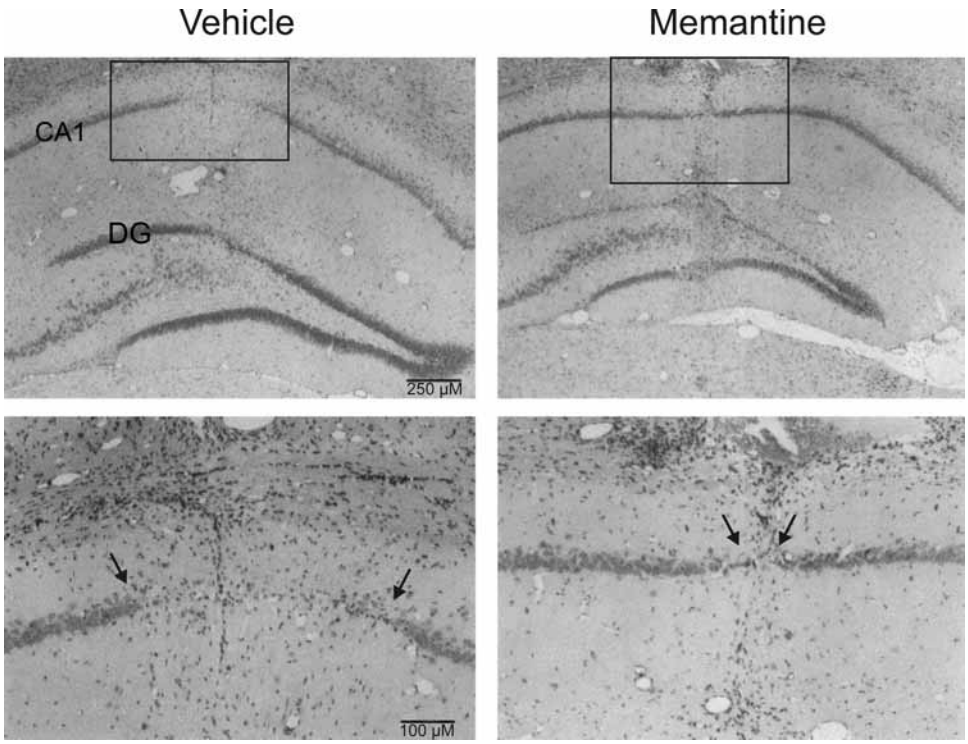


**Fig. 8.** Memantine protects against neurodegeneration induced by Aβ(1–40). Sections through the hippocampus from two rats that received injections of a small amount of Aβ(l–40) (3 nmole) into the hippocampus are shown above. The sections to the left and right are from animals treated with vehicle or memantine, respectively, by osmotic pump for 9 days to produce a plasma concentration of ~2 μM. The Aβ injection was on day 2. High magnification images below correspond to the rectangles in the upper images. The extent of neuronal degeneration is marked by arrows and is limited to the needle tract in the memantine-treated animal. CA1 subfield and dentate gyrus (DG) are marked. From Miguel-Hidalgo et al. (97) with permission.

It also has been reported that brief exposure of cultured cortical neurons to memantine (producing transient block of NMDA receptors) can "precondition" the cells in such a way that Aβ(1–40) toxicity is inhibited for as long as 48 h post-treatment (144). It is proposed that the transient inactivation of NMDA receptors triggers a rapid compensatory survival response that provides long-term protection from both apoptotic and nonapoptotic death. The relevance of these effects to chronic memantine therapy in AD remains to be defined.

Recent *in vivo* experiments have begun to provide confirmation of the positive effects of memantine on amyloid-related toxicity. For example, a transgenic mouse model has been developed that expresses a mutant form of APP present in Swedish familial Alzheimer's disease (FAD) kindreds as well as a presinilin 1 (PS1) variant, PS1(A246E), linked to early onset FAD (16). (PS1 is a member of the γ-secretase complex and is required for γ-secretase activity; 137). These mice have accelerated amyloid deposition in hippocampus and cortex that is associated with dystrophic neurites and reactive astrocytes (115). Treatment of these animals with memantine improved performance in both T-maze and Morris water-maze paradigms for spatial working memory and spatial long-term memory, respectively (142).

Very recently, evidence has shown that memantine also may affect APP processing in a beneficial manner. In cultured human neuroblastoma (SK-N-SH) cells, treatment with memantine (50 nM to 50 μM) for 24 to 48 h increased the levels of APPsα in the condition media (~30–50%) without affecting the levels of total intracellular APP, suggesting that the drug may enhance APP processing by the α-secretase (non-amyloidogenic) pathway (Fig. 7) (23). It remains to be determined how this occurs and whether memantine has similar effects in the AD brain. If memantine can enhance non-amyloidogenic APP processing, a new dimension of disease modifying activity of memantine would be uncovered.

Another recent study has found that memantine reduces abnormal tau hyperphosphorylation in tissue culture, suggesting that it could also have a beneficial effect on neurofibrillary degeneration (62a).

## CLINICAL EVIDENCE

Memantine, typically administered orally in a daily dose of 20 mg, is rapidly and completely absorbed. The time to maximum plasma concentration following single oral doses of 10–40 mg ranges between 4 to 8 h. With daily administration, steady-state levels are reached within 21 days (110; Forest Laboratories, personal communication), and while memantine is generally well tolerated in human subjects, it can produce some neurocognitive defecits. Thus, in healthy young volunteers, memantine (30 mg) produced a substantial performance decrement in delayed (80 min) object recognition but it did not affect memory for faces (117). The drug also has been shown to impair perceptual learning in human volunteers (35a).

Numerous studies have been reported that demonstrate the positive benefits of memantine therapy in AD and vascular dementia (36,55). Moreover, recent studies have provided evidence that the drug is effective in the treatment of moderate to severe AD, in which the response to ChEIs is not well documented. In a large 28-week, multicenter, randomized, double-blind, placebo-controlled study of moderate to severely affected AD patients, memantine-treated subjects showed significantly less functional and cognitive decline than those taking placebo (119). Other studies using a mixed group of patients (including AD and other forms of dementia) have shown comparable results (129). Similarly, in patients with severe dementia (AD and vascular dementia) who were treated with memantine 10 mg/day or placebo for 12 weeks, 73% showed functional improvement and reduced care-dependence (158). A more recent clinical trial found that memantine administered to patients stably maintained on the ChEI donepezil provided greater improvement on a series of dementia scores than that produced by treatment with donepezil alone (42). Interestingly, the combination of memantine and ChEI improved cognitive performance relative to the original baseline, while those patients receiving the ChEI alone continued to show progressive cognitive decline.

The clinical administration of memantine has been well tolerated with few side-effects (64,106). Although a few isolated case reports of delirium, delusions, hallucinations, restlessness or other central nervous system side effects have been reported with memantine use, it is difficult to dissociate the roles of concomitant medications and underlying neurological disease (46,55,123). In a recently published large scale, multicenter trial of memantine in a moderate to severe AD population, adverse events were no more frequent

among patients receiving memantine than among those receiving placebo, with a notable decrease in both agitation and urinary tract infection in the memantine-treated group (120). In another study of vascular dementia patients, dizziness was slightly more frequent (11% versus 8%) in the memantine group, but overall the drug was well tolerated (156).

## CONCLUSIONS

On the basis of extensive clinical experience, it has now been convincingly demonstrated that memantine is both efficacious and well tolerated in the symptomatic treatment of AD and other dementing illnesses, including vascular dementia. The mechanism by which memantine exerts its beneficial clinical actions is not well understood; however, after nearly four decades of extensive investigation, the only verified molecular targets that are likely to be relevant at therapeutic doses are neurotransmitter-gated ionotropic receptors, NMDA receptors, and possibly 5-$HT_3$ serotonin and nicotinic acetylcholine receptors. There have been extensive studies on the NMDA receptor blocking activity of memantine, but a satisfying explanation as to how interfering with NMDA receptor function leads to symptomatic improvement is still elusive. On the other hand, the good tolerability of memantine compared with other channel-blocking NMDA receptor antagonists is likely due to the specific biophysical details of its interaction with NMDA receptors which have been extensively characterized. Since 5-$HT_3$ antagonists can have beneficial effects on memory and cognition, there will be considerable interest in exploring whether effects on 5-$HT_3$ receptors play a role in the positive effects of the drug on dementia symptoms. It is conceivable that in the future more compelling targets may emerge, and indeed the recent studies on APP processing are intriguing in this regard. Yet, for the present, attention is directed toward the NMDA receptor, particularly given its critical role in learning and memory. In view of the potential neuropathological role of NMDA receptor mediated excitotoxicity in the evolution of AD, the exciting possibility exists for disease modification with memantine. Clinical trials reported to date show reduced deterioration over the short-term (<1 year) and certainly are compatible with this possibility; but, longer-term trials are needed to convincingly confirm that memantine modifies the course of the disease. Memantine is an incremental step in the road to an eventual cure for the scourge of AD, and, for the present, it offers significant improvements in the quality of life for persons affected by the disorder — the patients themselves as well as their families and caregivers.

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