Neuropathologic Changes in Alzheimer's Disease: Potential Targets for Treatment

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The cognitive symptoms of Alzheimer's disease (AD) are believed to be caused not only by the loss of neurons in the cholinergic and glutamatergic neural systems but also by the irregular functioning of surviving neurons in these 2 systems. Aberrant cholinergic functioning in AD has been linked to deficits in the neurotransmitter acetylcholine, while AD-related abnormalities in glutamatergic signaling have been attributed to excitotoxicity caused by the persistent, low-level stimulation of glutamatergic neurons via the chronic influx of Ca^{2+} ions through the *N*-methyl-D-aspartate (NMDA) receptor calcium channel. Glutamatergic abnormalities in AD can be corrected to some extent by the NMDA receptor antagonist memantine, an agent whose therapeutic efficacy is believed to be related to its low to moderate level of affinity for the NMDA receptor calcium channel, a characteristic that allows memantine to prevent excessive glutamatergic stimulation while still permitting normal glutamate-mediated neurotransmission to take place. Although the mechanism underlying the chronic stimulation of glutamatergic neurons in AD has yet to be elucidated, one hypothesis is that the characteristic neuropathologic features of AD—β-amyloid deposits and neurofibrillary tangles—induce brain inflammation, which in turn impairs glutamatergic receptor function in such a way that the ability of these receptors to prevent the influx of Ca^{2+} in the absence of an appropriate presynaptic signal is compromised. If this hypothesis is correct, and if it is correct that β-amyloid deposits and neurofibrillary tangles arise long before the symptomatic onset of AD, then memantine, with its ability to alleviate glutamatergic receptor overstimulation, would be expected to provide therapeutic benefits beginning from the earliest stages of the disease. *(J Clin Psychiatry 2006;67[suppl 3]:3–7)*

Alzheimer's disease (AD) is a condition characterized by a series of specific neuropathologic changes, including the shrinkage of neurons, the formation of β-amyloid plaques, and the appearance of neurofibrillary tangles in the brain.[1,2] However, these features are not found uniformly throughout the brain. Instead, AD-related neuropathologic changes preferentially affect specific areas of the brain in a manner that is essentially consistent from patient to patient.[3]

The nonuniform distribution of pathologic changes in AD has been putatively linked to the observation of differential deficits across the spectrum of neurotransmission systems in this disease. In particular, it is believed that nerve terminal destruction occurs in the immediate vicinity of β-amyloid deposits in the brain. Thus, if these deposits, like other pathologic features of AD, were nonuniformly distributed, widespread neuronal death would be expected in certain areas of the brain, whereas extensive sparing of nerve cells would be expected in other areas. Similarly, it would follow that in AD, certain neurotransmission systems would exhibit a high degree of dysfunction while others remained relatively unaffected, since each neurotransmission system is associated with a specific region or regions of the brain.

THE CHOLINERGIC SYSTEM IN AD

Cholinergic Impairment in AD

One of the 2 neurotransmission systems that appear to be preferentially disrupted in AD is the cholinergic system, which uses acetylcholine to transmit neural signals. Evidence of cholinergic abnormalities is seen in a variety of forms in AD, and in general, these abnormalities are consistent with the hypothesis that reduced cholinergic neurotransmission is one of the hallmark features of AD. For example, an analysis of postmortem brain samples demonstrated that the average number of cholinergic neurons in the basal forebrain was 79% lower ($p < .004$) in a series of 5 patients with AD when compared with 5 unaffected control individuals.[4]

Cholinergic changes have also been observed on a molecular level in AD. A neuropathologic study conducted by Perry and colleagues[5] revealed that cortical activity of the

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enzyme choline acetyltransferase, which catalyzes the synthesis of acetylcholine from choline and acetyl coenzyme A, was 60% lower in patients with AD (N = 18) compared with patients who had no known neuropsychiatric abnormalities (N = 13). In the same study, a link was also found between postsynaptic cholinergic abnormalities and AD, as evidenced by a trend toward reduced muscarinic acetylcholine receptor binding in patients with increased β-amyloid plaque loads. Consistent with the hypothesis of reduced cholinergic neurotransmission in AD, Perry and colleagues also found that β-amyloid plaque burden was positively correlated with cortical activity of butyrylcholinesterase, an enzyme that is capable of catalyzing acetylcholine hydrolysis. However, cortical activity of acetylcholinesterase, the enzyme primarily responsible for catalyzing the hydrolysis of acetylcholine in the brain, exhibited an inverse correlation with β-amyloid plaque loads. The significance of this finding, which appears to be inconsistent with other changes that attenuate cholinergic neurotransmission, is unknown. Nonetheless, direct measurement reveals that, overall, levels of acetylcholine synthesis are reduced by approximately one half in patients with AD relative to healthy control individuals.[6]

Brain regions associated with memory and learning are innervated by cholinergic neurons, and as a result, the cholinergic abnormalities seen in AD are believed to underlie the characteristic cognitive changes that occur in patients with this disease. In particular, the loss of cholinergic functioning in the cerebral cortex leads to attentional deficits in patients with AD,[7] while cholinergic dysfunction in the hippocampus has been linked to impairments in memory.[8,9] Nonetheless, the ramifications of cholinergic disruptions in AD do not appear to be limited to the realm of cognition, as it has been hypothesized that deficient cholinergic neurotransmission in the amygdala is associated with the emotional changes that frequently occur in affected patients.[10]

Therapeutic Targeting of Cholinergic Dysfunction in AD

Due to its apparent role in the pathogenesis of AD, the cholinergic system has become an important target for pharmacotherapeutic interventions. Available evidence suggests that the core symptoms of AD can be linked to decreased cholinergic neurotransmission in affected patients,[11] as cholinergic neurons are progressively lost throughout the course of the disease and acetylcholine molecules, which mediate cholinergic signaling, are found at lower levels relative to what is seen in healthy individuals. This acetylcholine deficit lies at the heart of the rationale for the use of cholinesterase inhibitors (ChEIs) in patients with AD. Cholinesterase inhibitors are designed to suppress the activity of the enzyme cholinesterase, whose primary function is to mediate the degradation of synaptic acetylcholine molecules. In doing so, ChEIs block the destruction of acetylcholine, thereby increasing synaptic levels of this neurotransmitter and presumably restoring cholinergic neurotransmission to levels closer to what is seen in healthy individuals.[12] It is important to remember, however, that while ChEIs appear to counteract AD-related deficiencies in cortical acetylcholine, they are not capable of slowing or reversing cholinergic neuronal loss, which is believed to be responsible in part for the degenerative course of AD. Therefore, ChEIs may provide cognitive benefits to patients with AD by boosting synaptic acetylcholine levels, but they are unable to slow the natural progression of the disease.[13]

THE GLUTAMATERGIC SYSTEM IN AD

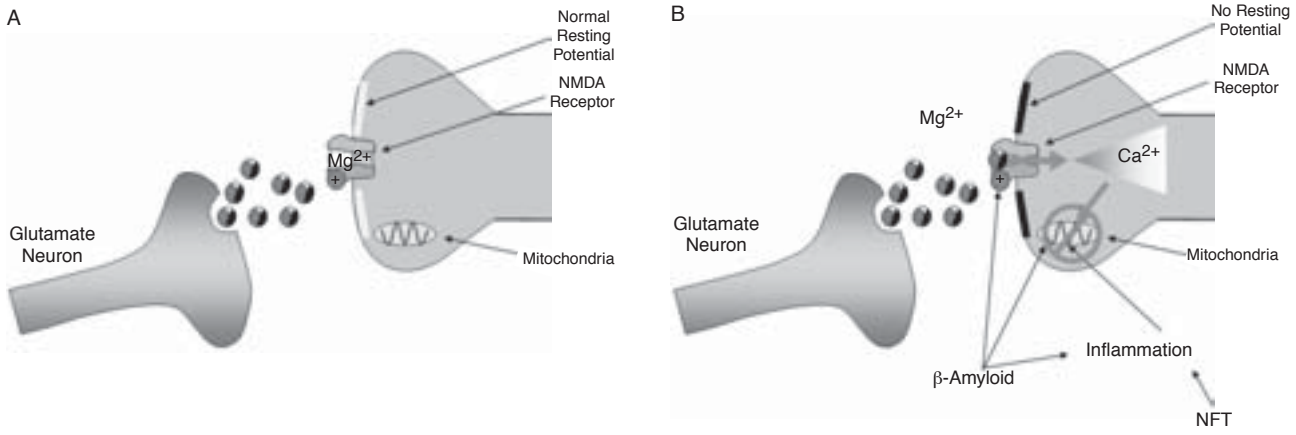
Glutamatergic Dysfunction in AD

The neurotransmitter glutamate is involved in a diverse array of physiologic processes, ranging from cognition to drug tolerance and responsiveness to pain. With regard to cognition, glutamatergic neurotransmission is believed to play a key role in the neural processes underlying learning and memory,[14] and it has been hypothesized that glutamatergic function is disrupted in patients with AD.[15] Specifically, it is thought that, in AD, sustained, low-level activation of glutamatergic receptors—in particular, the *N*-methyl-D-aspartate (NMDA) receptor—occurs as a result of impairments in glutamatergic receptor function, with these impairments possibly being due to oxidative stress and the consequences of chronic brain inflammation. However, the exact nature of these impairments remains to be elucidated.

The connection between the constant stimulation of NMDA receptors and the cognitive deficits seen in AD is based primarily on the principle of excitotoxicity—that is, nerve cell death caused by chronic neuronal activation. Nonetheless, the sustained activation of NMDA receptors may also play a role in the symptomatology of AD by acting to produce a type of "background noise" in the complex network of neuronal signaling processes. More specifically, if one views the ratio of the extent of NMDA receptor stimulation during neuronal firing to the extent of NMDA receptor stimulation in the absence of neuronal firing as a type of "signal-to-noise ratio," then it is conceivable that elevated levels of NMDA receptor activation under resting conditions could lead to a reduction in this ratio and therefore cause impaired neurotransmission.[15]

One model that has been put forth to explain the neuronal overactivity seen in AD centers on the loss of the resting potential in glutamatergic neurons due to mitochondrial injury and dysfunction (Figure 1). In neurons, the mitochondria serve primarily to produce adenosine triphosphate (ATP), a charged compound that helps to maintain the electric potential gradient between the interior of the neuron and the surrounding extracellu-

Figure 1. (A) Normal Resting State of Glutamatergic Neurons in Healthy Individuals[a] and (B) Proposed Role of β-Amyloid Deposits, Neurofibrillary Tangles, and Inflammation in the Genesis of Glutamatergic Dysfunction in Alzheimer's Disease[b]



[a]In healthy patients, in the absence of a presynaptic glutamatergic signal, Mg^{2+} occupies the postsynaptic NMDA receptor calcium channel, held in place by the potential energy gradient between the interior of the postsynaptic glutamatergic neuron and the extracellular space.
[b]In patients with Alzheimer's disease, β-amyloid plaques and neurofibrillary tangles induce brain inflammation, which has a damaging effect on neuronal mitochondria. In addition, neuronal mitochondria may be damaged directly by β-amyloid plaques. This mitochondrial damage impairs the ability of the neuron to maintain the appropriate resting potential, and Mg^{2+} therefore vacates the postsynaptic NMDA receptor calcium channel pore, allowing the influx of excessive levels of Ca^{2+}. β-Amyloid may further exacerbate the problem of chronic Ca^{2+} influx by binding to NMDA receptors in a way that enhances the ability of Ca^{2+} to enter the postsynaptic glutamatergic neuron through the NMDA receptor calcium channel.
Abbreviations: NFT = neurofibrillary tangles, NMDA = *N*-methyl-D-aspartate.

lar space. Mitochondrial dysfunction has been linked directly to β-amyloid deposits,[16] as well as to inflammation induced by these deposits and by neurofibrillary tangles,[17,18] the other hallmark feature of AD. Thus, it has been suggested that, in AD, these stressors disrupt normal mitochondrial functioning in glutamatergic neurons and lead to the loss of the membrane potential, causing NMDA receptor calcium ion channels to be vacated by resident Mg^{2+} ions; according to this model, NMDA receptor calcium ion channels would remain vacated even under resting conditions. Such chronic opening of NMDA receptor calcium channels would lead to the constant influx of Ca^{2+} ions (perhaps exacerbated by the ability of β-amyloid to bind directly to NMDA receptors in a way that enhances the ability of Ca^{2+} to enter the postsynaptic neuron[19]) regardless of whether normal neurotransmission was taking place, and neuronal overactivation would be expected to occur as a result.

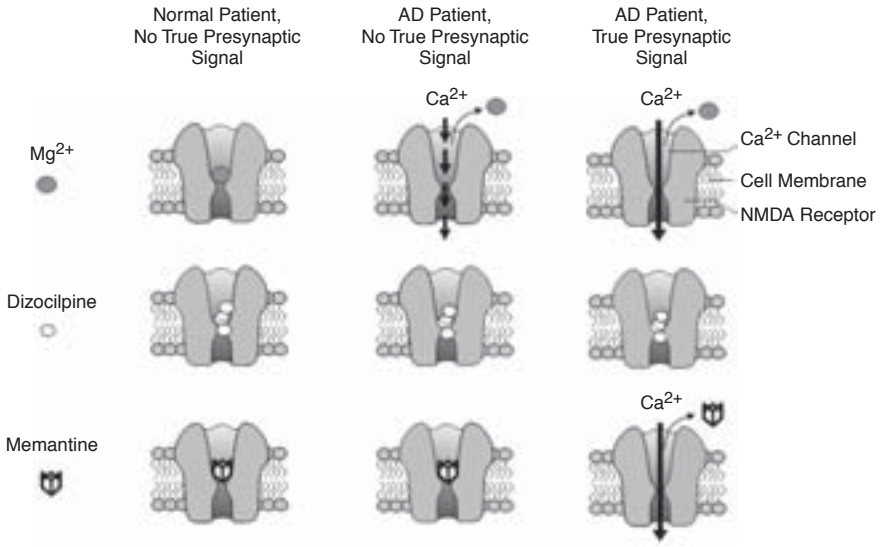
Therapeutic Targeting of Glutamatergic Dysfunction in AD

With the emergence of NMDA receptor overactivation as a key process in the etiology of AD-related cognitive impairments, recent efforts have focused on treatment of the cognitive symptoms of AD using agents that block NMDA receptor calcium channels. The logic behind the use of such agents is that they are capable of blocking NMDA receptor stimulation by preventing the passage of Ca^{2+} ions through the calcium channels associated with these receptors.

Early efforts to treat AD using NMDA receptor open-channel antagonists involved molecules such as dizocilpine and phenylcyclidine, which have a high affinity for the NMDA receptor calcium channel. However, studies conducted in animal models and in humans revealed that these 2 compounds caused memory impairment and other significant neurobehavioral side effects. Ultimately, it was hypothesized that dizocilpine and phenylcyclidine were producing these side effects precisely because of their inhibitory potency. In particular, it was thought that while these 2 compounds were able to block the influx of Ca^{2+} through the NMDA receptor calcium channel in the absence of neuronal firing, as was desired, they remained bound within the channel pore and therefore halted the flow of Ca^{2+} at times when channel opening would otherwise have been a normal consequence of neuronal firing.[15,20] Based on this model, strong NMDA receptor open-channel antagonists such as dizocilpine and phenylcyclidine would not only block the constant, low-level NMDA receptor activation seen in AD but also inhibit normal neurotransmission, leading to cognitive impairment.[15,20]

This hypothesis regarding the cognitive toxicity profiles of dizocilpine and phenylcyclidine serves as a possible basis for the clinical effectiveness of memantine, a noncompetitive, low- to moderate-affinity antagonist that nonetheless has a higher affinity than does Mg^{2+} for the NMDA receptor open channel. Clinical trials involving patients with AD have demonstrated that memantine improves cognitive functioning (or slows cognitive decline)

Figure 2. Proposed Differential Antagonism of the *N*-Methyl-D-Aspartate (NMDA) Receptor Calcium Channel by Mg^{2+}, Dizocilpine, and Memantine[a,b]



[a]*Top:* In healthy patients, Mg^{2+} serves as a physiologic blockade of the NMDA receptor open channel, preventing the influx of Ca^{2+}. However, in Alzheimer's disease (AD), Mg^{2+} vacates the NMDA receptor calcium channel even when a true presynaptic signal is not present, leading to the chronic influx and accumulation of Ca^{2+} within the postsynaptic neuron. The eventual consequence of this Ca^{2+} accumulation is excitotoxic cellular dysfunction or death and, ultimately, impaired cognitive processing. *Middle:* When administered to patients with AD, dizocilpine, a high-affinity NMDA receptor open-channel antagonist, blocks the NMDA receptor calcium channel and thus prevents the chronic excitotoxic inflow of Ca^{2+}. However, due to its high affinity, dizocilpine does not vacate the calcium channel to allow Ca^{2+} influx when a true presynaptic signal is present, and as a result, normal cognitive processes that depend on Ca^{2+} influx as a response to such a signal are impaired. *Bottom:* When administered to patients with AD, memantine, a low- to moderate-affinity NMDA receptor open-channel antagonist, blocks the NMDA receptor calcium channel and thus prevents the excessive influx of Ca^{2+}. In addition, due to its affinity profile, memantine is capable of exiting the calcium channel pore to allow Ca^{2+} to enter the channel in response to true presynaptic activation, thereby allowing normal cognitive processes to occur unhindered.

[b]Based on Danysz et al.[15] and Rogawski and Wenk.[20]

without producing serious cognitive side effects,[21,22] and it has been posited that this lack of side effects is related to memantine's reduced affinity (relative to dizocilpine and phenylcyclidine) for the NMDA receptor calcium channel. Specifically, it has been hypothesized that memantine, because of its low to moderate binding affinity, blocks the passage of Ca^{2+} through the NMDA receptor calcium channel in the absence of a presynaptic signal but, due to its fast on-off kinetics within the channel pore, is also capable of quickly exiting the channel during normal neuronal signaling, when the influx of Ca^{2+} through the channel is appropriate (Figure 2). In this way, it is believed that memantine prevents the neurotoxicity associated with NMDA receptor overactivation while still allowing normal glutamatergic neurotransmission.[15,20]

At present, the efficacy of memantine therapy has been definitively established only in patients with moderate to severe AD. However, preclinical findings suggest that this agent may also provide benefit in the earlier stages of AD.[23] In particular, it has been demonstrated that memantine, presumably because of its ability to halt the chronic influx of Ca^{2+} through NMDA receptor calcium channels, protects neurons against the cytotoxic effects of inflammation induced by the slow, prolonged intraventricular infusion of lipopolysaccharide into rat brain. Thus, if it is correct that glutamatergic signaling becomes dysfunctional in AD as a result of neuronal loss triggered by brain inflammation, and if the neuropathologic changes responsible for this inflammation (i.e., β-amyloid deposits and neurofibrillary tangles) are first seen in early (or preclinical) AD and help to determine the subsequent course of the disease, as has been hypothesized,[3,24] then it may be the case that memantine, by preventing inflammation-induced neurotoxicity, can also provide benefit to patients during the very early phases of the disease.

SUMMARY

Alzheimer's disease is a condition whose cognitive symptomatology is believed to be caused by the dysfunction of cholinergic and glutamatergic neural systems and also by the irregular functioning of NMDA receptors. Aberrant cholinergic functioning in AD has been linked to deficits in the neurotransmitter acetylcholine, and as a result, therapeutic efforts have focused on increasing levels of this neurotransmitter in the brain. Cholinesterase inhibitors, which increase acetylcholine levels by inhibiting cholinesterase, an enzyme that mediates the synaptic deg-

radation of acetylcholine, have been shown to provide significant symptomatic benefits to patients with mild to moderate AD.

While neurotransmitter deficits appear to be responsible for the dysfunctional state of cholinergic neurotransmission in AD, another culprit—the persistent, low-level stimulation of neurons—has been implicated in the glutamatergic signaling abnormalities seen in this disease. Specifically, the chronic influx of Ca^{2+} through the NMDA receptor calcium channel, even in the absence of glutamatergic signals from an active presynaptic neuron, is believed to result in neuronal death via an excitotoxic route, and it has also been hypothesized that the constant inflow of Ca^{2+} acts as a type of "background noise," making it more difficult for affected neurons to recognize the electrical impulses that result when an actual glutamatergic signal is sent by a presynaptic neuron.

The mechanism underlying the chronic inflow of Ca^{2+} into glutamatergic neurons in AD has yet to be elucidated. However, one hypothesis is that mitochondrial damage mediated by β-amyloid– and neurofibrillary tangle–induced inflammation leads to the loss of the neuronal resting potential, causing Mg^{2+}, the body's own NMDA receptor open-channel antagonist, to vacate the channel even in the absence of a glutamatergic signal from a firing presynaptic neuron, allowing Ca^{2+} to enter the channel more readily.[15] If this hypothesis is correct, and if it is correct that β-amyloid deposits and neurofibrillary tangles arise even before the symptomatic onset of AD,[3,24] then glutamatergic irregularities would be expected to be present from the earliest stages of AD.

The glutamatergic abnormalities seen in AD can be corrected to some extent by the NMDA receptor antagonist memantine, an agent whose therapeutic efficacy is believed to stem from its low to moderate level of affinity for the NMDA receptor calcium channel. In particular, because the binding affinity of memantine is greater than that of Mg^{2+}, it is believed to attenuate the chronic stimulation of glutamatergic neurons in AD by blocking calcium channels that have been aberrantly vacated by Mg^{2+} during periods of neuronal inactivity. Furthermore, memantine does not appear to have significant cognitive side effects, as its affinity for the NMDA receptor calcium channel is sufficiently low to allow the passage of Ca^{2+} through the channel during periods of normal neuronal activity. At present, memantine has confirmed efficacy only in the setting of moderate to severe AD. However, given the possible presence of glutamatergic abnormalities long before the onset of symptoms in AD, targeting of the glutamatergic system using this agent might be expected to result in neuroprotection throughout the entire natural course of the disease.

Drug name: memantine (Namenda).

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