INTRODUCTION

As the world’s population ages and life expectancy increases, many individuals are faced with an increased risk of developing dementia. The most common form of dementia is Alzheimer’s disease (AD). About 35.6 million people worldwide are now suffering from AD, and the disease is expected to affect 115 million by 2050.[1] Although this disease has been known about for over a century, there is no curative treatment available so far. At present, four drugs have been approved by the United States Food and Drug Administration for the symptomatic treatment of AD. The acetylcholinesterase (AChE) inhibitors donepezil, rivastigmine, and galantamine are suggested for managing mild-to-moderate AD, whereas donepezil and memantine, a noncompetitive antagonist of N-methyl-D-aspartate receptors (NMDAR), is indicated for patients with moderate or severe AD.[1-3]

Pathologically, AD is characterized by atrophy of the hippocampus and neocortex resulting from neuronal and synaptic loss, and the deposition of two proteinaceous lesions: senile plaques containing a core of amyloid-beta (Aβ) peptide and neurofibrillary tangles (NFT) composed of hyperphosphorylated microtubule-associated tau protein.[3,4] It is well-accepted that the accumulation of Aβ protein plays a central role in the pathogenesis of AD. The severity of dementia in AD correlates more strongly with cortical levels of soluble Aβ species than with insoluble amyloid plaque burden.[5,6] Experimentally, soluble Aβ oligomers have been specifically shown to block hippocampal long-term potentiation (LTP), an electrophysiological correlate of learning and memory, in vivo and in brain slices.[5-9] Understanding precisely how Aβ impairs hippocampal synaptic function could enable the development of potential therapeutics for AD.
Synaptic loss is one of the pathological hallmarks of AD and the best correlate of cognitive decline suggesting that it is a critical event in the pathophysiology of the disease. Several factors such as Aβ production, cholinergic dysfunction, NFT accumulation, inflammatory agents, oxidative stress, mitochondrial dysfunction, glutamate-mediated excitotoxicity, and genetic components are reported to be involved in the pathogenesis. Proposed explanations for the pathophysiology of AD include the cholinergic hypothesis, the soluble Aβ oligomers hypothesis, and the tau hypothesis.

CHOLINERGIC SYSTEM

Acetylcholine (ACh) is widely distributed in the nervous system and plays a critical role in cerebral cortical development, cortical activity, and learning and memory processes. Cholinergic neurons in the brainstem and basal forebrain project axons to many areas of the brain. All functions of the cholinergic system are controlled by the interaction of ACh with two families of receptors: muscarinic ACh receptors (mAChRs) and nicotinic ACh receptors (nAChRs).

Hippocampal cholinergic activity contributes to memory

Many studies have shown that hippocampal-dependent learning is associated with an increase in hippocampal ACh levels; thus, the elevation of extracellular ACh is thought to reflect hippocampal-dependent memory processes. Several behavioral studies have demonstrated that lesion-induced damage to cholinergic activity in the basal forebrain and its projections to the neocortex induced learning and memory deficits. Pharmacological experiments have further confirmed that cholinergic receptor agonists and acetylcholinesterase inhibitors (AChEIs) reduce the severity of cognitive dysfunction, whereas anticholinergic drugs cause learning and memory deficits in both animal and humans. Antagonists of mAChRs such as scopolamine, impair the encoding of new memories in animal models of learning and memory and produce cognitive impairment in humans.

It has been found that pharmacological activation of mAChRs or nAChRs produces an LTP-like increase in synaptic transmission in the hippocampal CA1 region. Blockade of the presynaptic inhibitory M2/M4 subtype of mAChRs by methoctramine increased ACh levels, and elicited a pharmacological LTP that shares a similar mechanism with tetanus-induced LTP. In accordance, both the endogenous release of ACh in vivo and the exogenous application of mAChR agonists in vitro facilitate the induction of LTP. Increasing endogenously released ACh specifically activates the nAChR, facilitating LTP induction. Selective depletion of medial septum LTP induction and glutamatergic synaptic current alteration in the hippocampus.

Glutamatergic effect

The facilitation of LTP by mAChR activation is thought to be mediated by enhancement of synaptic NMDAR activity either by direct alteration of NMDAR channels or by induction of Ca2+ release from endoplasmic reticulum stores. The mAChRs also inhibit a variety of potassium channels including small conductance calcium-activated KCa2 channels (SK channels). Therefore, mAChR activation might induce a parallel long-term enhancement of both α-amino-3-hydroxy y-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDAR-mediated transmission.

It has been reported that chronic nicotine administration and in vitro acute nicotine treatment increases ACh release and enhances NMDAR responses in the hippocampus. One potential mechanism is that nicotine acts at presynaptic nAChRs to increase glutamate release onto postsynaptic NMDARs. The activation of nAChRs causes Ca2+ entry through receptor channels, which can trigger Ca2+ release from intracellular stores. Multiple lines of evidence also suggest that nicotine could act to ameliorate hippocampal-based learning deficits associated with changes in NMDAR function. Consistent with these studies, pretreatment with AChE inhibitors has been found to protect cortical neurons from glutamate neurotoxicity in a time- and dose-dependent manner through activation of nAChR.

Anti-inflammatory effect

The deposition of Aβ is the result of an imbalance between Aβ production and clearance. This imbalance leads to a situation of chronic inflammation in the brain. Aβ deposition contributes to the activation of astrocytes and microglia, and induces the production of a series of proinflammatory cytokines, chemokines, macrophage inflammatory proteins, leukotrienes, reactive oxygen species, and nitric oxide. The neuroinflammatory cytokines may not only contribute to neuronal death, but they might also influence classical neurodegenerative pathways such as amyloid precursor protein (APP) processing and tau phosphorylation.

A growing body of studies using donepezil has shown that donepezil does not function solely at the level of ACh, but also has potent anti-inflammatory effects in AD patients, a tauopathy mouse model and lipopolysaccharide (LPS)-treated animals. Donepezil inhibits proinflammatory gene expression directly.
resulting in reduced secretion of tumor necrosis factor-alpha, NO, and interleukin-1 beta in LPS-treated BV2 cells, a murine microglia cell line.[34] Furthermore, donepezil may inhibit neuronal death and cognitive decline by repressing oligomeric Aβ-triggered inflammatory pathways in microglia.[35] Thus, donepezil-mediated attenuation of the release of inflammatory mediators may result from inhibition of protein expression of proinflammatory molecules.

The cholinergic pathway has been shown to exert anti-inflammatory effects on several diseases such as rheumatoid arthritis,[36] inflammatory bowel disease,[37] sepsis,[38] and cardiovascular diseases.[39] On the other hand, nAChR has been shown to possess anti-inflammatory properties in macrophages,[40] and the activation of α7-nAChR significantly inhibits the production of proinflammatory cytokines.[41] It has been demonstrated that AChEI treatment may favor a Th2-mediated immune response by activating B-lymphocytes and increasing immunoglobulin production.[42] Galantamine-enhanced microglial Aβ phagocytosis to promote Aβ clearance requires the combined action of an ACh competitive agonist and the allosterically potentiating ligand for nAChRs.[43] Furthermore, plasma anti-Aβ1–42 antibody levels in AD patients were found to be significantly increased after AChEI treatment,[44] thus suggesting that increasing the endogenous response against Aβ might provide new insights for AD therapy. Recently, several promising studies have been conducted in phase II and phase III trials using active and passive immunotherapies, respectively.[45]

**GLUTAMATERGIC SYSTEM**

Glutamate is one of the most prominent neurotransmitters in the body. It is present in over 50% of the nervous tissue.[46] It plays a prominent role in a variety of brain functions including synaptic transmission, neuronal growth and differentiation, synaptic plasticity, learning and memory, and other cognitive functions.

The role of the glutamatergic system is to convert nerve impulses into a chemical stimulus by controlling the concentration of glutamate at the synapse. It is well-accepted that LTP induction triggers the NMDAR, and therefore, activates the AMPA receptor in the CA1 region.[47,48] NMDAR activation allows Ca2+ to enter the postsynaptic cell, which subsequently triggers a number of kinase pathways and increases protein transcription. This process strengthens synapses and increases synaptic density, thus allowing fast adaptations of network activity which are critical for information processing.[49]

**Neuroexcitotoxicity**

Glutamate excitotoxicity has been hypothesized to have a role in AD pathogenesis. Dysfunction of glutamate transporters has been implicated in this pathway.[50] It has been reported that hippocampal excitatory amino acid transporter 1 (EAAT1) and EAAT2 expression is significantly reduced in AD,[49] further reinforcing the notion of a deficit in glutamate clearance in AD brain. In addition to uptake defects, the abnormal release of glutamate from vesicle stores has been implicated as a source of excess extracellular glutamate in AD.[51] Excessive activation of glutamate receptors leads to a number of deleterious consequences including impairment of calcium buffering, generation of free radicals, and activation of the mitochondrial permeability transition that results in release of apoptogenic proteins into the cytosol, where they trigger caspase-dependent apoptosis or promote autophagy.[52]

We and others have demonstrated that Aβ inhibits glutamate uptake in rat cortical synaptosomes, cultured cells, and acute brain slices.[59] These findings are also consistent with an intracerebroventricular injection of Aβ into rat brain, which causes a rapid increase in interstitial fluid glutamate levels without altering gamma-aminobutyric acid or aspartate.[53] The hydrophobic Aβ oligomers may bind principally to membrane lipids, and thereby, secondarily interrupt the structure and function of synaptic transmembrane transporters (glutamate transporters), leading to increases in extracellular glutamate concentration.

**Activation of extrasynaptic receptors**

Electron microscopic studies have shown that most plasmalemma receptors are extrasynaptically located, whereas only 1-2% of cell membrane receptors are located at synaptic sites in the hippocampus.[54] Thus, the chemicals distribute in the extracellular fluid and bind preferentially to these vastly extrasynaptic receptors. Extrasynaptic NMDARs, that is, receptors that are not activated during low-frequency synaptic events, can be found at various locations, such as the cell body, the dendritic shaft, the neck of the dendritic spine, and adjacent to the postsynaptic density. It has been found that synaptic NMDAR activity is extremely important for neuronal survival, whereas the extrasynaptic NMDARs are coupled to cell death pathways.[55] Using both whole-cell recording and Fluo-4 calcium measurements, we confirmed that Aβ rapidly and significantly increases extrasynaptic NMDA responses. Soluble Aβ oligomers activate extrasynaptic NR2B-containing NMDARs, thus increasing downstream calpain signaling and p38 mitogen-activated protein kinase activity.[9] Several studies have demonstrated that selective
NR2R antagonists prevent Aβ-induced synaptic dysfunction. [9] Consistent with these findings, low concentrations of memantine have been shown to target extrasynaptic NMDAR. [96] Both studies and related reports suggest that Aβ oligomers disrupt glutamate uptake or trigger glutamate release from glial cells, thus increasing glutamate levels to induce synaptic dysfunction.

**BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS IN DEMENTIA**

AD is a neurodegenerative disorder associated not only with a decline in cognitive abilities, but also with frequent manifestation of noncognitive symptoms (such as anxiety, depression, apathy, and psychosis) and other conduct disorders that impair daily living. [25] It has been proposed that the behavioral and psychological symptoms of dementia in AD patients are due to an imbalance of different neurotransmitters (ACh, dopamine, noradrenaline, and serotonin) in specific brain regions responsible for emotional activities (parahippocampal gyrus, dorsal raphe, and locus coeruleus) and cortical hypometabolism. [58]

There is increasing awareness that the cholinergic system plays a role in emotion and noncognitive behavior and may be involved in neuropsychiatric symptoms of AD. [59, 60] Other evidence indicates that monoamines, in addition to ACh, are also involved in the pathogenesis of AD and other dementia disorders. The increased activity and altered serotonergic modulation as a result of dopaminergic neurotransmission are associated with agitated and aggressive behavior, respectively. [61] Chronic administration of donepezil has been reported to reduce the incidence of neuropsychiatric symptoms in patients with mild to moderately severe AD. [62] Thus, the stimulation of monoaminergic activity in conjunction with AChE activity may provide an effective treatment option for AD and accompanying psychiatric disorders.

**COMPARISON OF DONEPEZIL AND MEMANTINE**

It is well-established that AChEIs inhibit the action of the ACh-hydrolyzing enzyme AChE to boost ACh levels, and thus, alleviate disease symptoms associated with the progressive loss of cholinergic function in AD. In contrast, memantine acts at the NMDAR to lower the pathologically increased tonic level of excitation of the glutamatergic synapse at rest. Although AChEIs significantly improve learning and memory, memantine behaves like other NMDAR antagonists and has been reported to inhibit hippocampal LTP, [63] disrupt cognitive flexibility, and impair memory and locomotor behaviors. [64, 65] Interestingly, a comparison between the effects of donepezil and memantine on spatial memory in the APP23 mouse model using a complex dry-land maze test showed that donepezil treatment significantly improved moving time, whereas memantine improved resting time, thus suggesting that donepezil may influence memory acquisition and memantine influences memory retrieval. [66]

Donepezil administration increases dopamine and norepinephrine levels in the dorsal hippocampus and decreases extracellular norepinephrine and serotonin levels in the ventral hippocampus. [67] In contrast, memantine decreases dopamine and serotonin in the dorsal hippocampus and increases 3-methoxy-4-hydroxyphenylglycol in the ventral hippocampus. Although memantine is recognized as a moderate affinity, noncompetitive, reversible NMDAR antagonist, it has been demonstrated that memantine enhances synaptic transmission in an mAChR-dependent manner in the mouse hippocampus, [68] and may interact more potent with cholinergic receptors than with NMDAR. [69] Acute systemic or local administration of either memantine or donepezil significantly increases ACh levels in the neocortex and hippocampus of rats. [70]

**EFFICACY OF DONEPEZIL AND MEMANTINE ON THE TREATMENT OF AD**

AChEIs are considered the standard treatment of the mild-to-moderate stage of AD, [71] whereas memantine is suggested for moderate-to-severe AD patients. [72] Clinically, donepezil at 10 mg/day significantly improves cognitive, neuropsychiatric, and global function, thus reducing caregiver burden. [62, 72] Increasing the daily dose to 23 mg/day was found to be safe and tolerated in patients with moderate-to-severe AD. [73, 74] Memantine has been found to improve global cognition, functional communication, and some behavioral symptoms (agitation and aggression). [75, 76] Interestingly, donepezil and memantine also have differential behavioral effects: donepezil affects depression, anxiety, and apathy whereas memantine mainly affects agitation, aggression, and delusions. [77, 78] A recent clinical review suggests that combination therapy with donepezil and memantine for AD could be safe and well-tolerated for moderate-to-severe AD. [79] However, there are no significant benefits of the combination of donepezil and memantine over donepezil alone on cognitive function. [80] Thus, combination therapy may be more effective in improving neuropsychiatric behaviors than cognition because of their complementary activity.
AChE inhibitors ameliorate the cognitive and psychiatric symptoms in AD patients through increased synaptic ACh levels to activate AChRs and protect against glutamate neurotoxicity and inflammation, whereas memantine appears to mainly protect against excitotoxicity and consequent neurodegeneration. AChE inhibitors exert neuroprotective effects by improving cholinergic mediated memory function, enhancing glutamatergic responses and acting as anti-inflammatory agent. Memantine is efficient at preventing the deleterious actions of Aβ oligomers mainly due to its selectivity for the extrasynaptic NMDARs. Therefore, AChE inhibitors could be used for the earlier to later stages of AD, but memantine should preferentially be used only in the later phase of AD.

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Conflicts of interest
There are no conflicts of interest.

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