Alzheimer’s disease (AD) is a progressive neurodegenerative disorder with characteristic clinical and pathologic features. Although multiple neural systems are affected, a key component of the degenerative process is a loss of cholinergic neurons and a subsequent reduction in nicotinic acetylcholine receptors (nAChRs), which are widely distributed and influence the release of multiple neurotransmitters including glutamate, serotonin, and acetylcholine. The deficit in nAChRs seen in AD is predominantly associated with loss in the α4 subunits, although modest reductions in α3 occur in some individuals. The changes in nAChRs seen in AD patients are distinct from those in normal aging and could contribute to the clinical features and neuropathology of the disease.

In this special issue of Biological Psychiatry the mechanistic basis for the effect of nicotine and nACh receptors in AD are reviewed by a group of international experts. Nicotine is a natural alkaloid, and its effects in the central nervous system are mediated by the activation of nAChRs. Clinical studies using nicotine patches have demonstrated the short-term efficacy of nicotine in treating cognitive impairments associated with AD. Stimulation of nAChRs in AD patients can improve the acquisition and retention of verbal and visual information and decrease errors in cognitive tasks. Furthermore, nicotinic stimulation could influence processes implicated in the pathophysiology of AD. When administered directly to the hippocampus in rats, nicotine elevates production of nerve growth factor.

A neuropathologic hallmark of AD is deposits of β-amyloid peptide in senile plaques. β-Amyloid is a 39– to 43–amino acid fragment of a larger precursor protein, amyloid precursor protein. The neurotoxicity of β-amyloid and the association between nicotine and β-amyloid are intriguing. Protein kinases are activated by β-amyloid, and these kinases act as secondary messengers to signal neuronal death. Nicotine administration protects against β-amyloid neurotoxicity in vivo and in vitro. These data suggest that nicotinic stimulation may facilitate neuron survival and delay degeneration in AD. If so, nicotinic stimulation may have more than just palliative effects and could alter the clinical course of AD.

Cholinesterase inhibitor therapy remains the mainstay of AD treatment, but there is a need for new and more effective treatments. Additional treatment strategies, including direct and indirect stimulation of nAChRs, offer promise. Galantamine inhibits acetylcholinesterase and positively modulates nAChRs through an allosteric interaction. By binding to a site on the nAChR distinct from that occupied by acetylcholine, galantamine increases receptor sensitization to acetylcholine, thereby enhancing nicotinic neurotransmission. Hence, galantamine is a particularly interesting compound that enables the effects of nicotinic modulation in AD to be studied further.

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