Research and development of therapeutics for Alzheimer disease.

○Masayasu Okochi, Shinji Tagami, Masatoshi Takeda
(Dpt. of Neuropsychiatry, Osaka Univ. Sch. of Med.)

Donepezil, an acetylcholine esterase inhibitor, has been introduced for the treatment of Alzheimer disease in Japan. Its action, consisting of modulation of neurotransmission in synapses, is similar to that of drugs for functional psychiatric diseases. As many symptoms of dementia are thought to reflect quantitative/qualitative impairment of synaptic functions in neural networks, there are good reasons to believe that the main aim of therapeutic intervention for Alzheimer disease should be the maintenance and enhancement of synaptic functions. However, this strategy cannot impede the neurodegenerative and pathological processes involved in Alzheimer disease. Basic research results indicate that elimination of amyloid-β peptide (Aβ), a major constituent of senile plaques in Alzheimer disease, impedes these processes. The Aβ hypothesis makes it clear that insolubilization of Aβ42 contained in secreted Aβ, originally produced as a soluble peptide, is the initial step in the pathological process of Alzheimer disease. Physiologically, the Aβ42 domain in the βAPP sequence is in an α-helical structure. However, transition from the α-helical to a β-strand structure is likely to start oligomerization, which induces synaptic toxicity and amyloidosis in senile plaques, the former causing clinical symptoms and the latter pathological hallmarks. Thus, many clinical trials aiming to eliminate brain Aβ have been and are being performed. The current status of research and development of therapeutic interventions will be summarized here.