Alzheimer's disease

According to a recent study, Alzheimer's disease is identified as an age-related dementia disease because of revealed specific genetic and molecular mechanisms underlying AD. The common symptoms of AD are difficulty remembering names and recent events, loss of executive functioning, apathy and depression.

**Pathogenesis of Alzheimer's disease**

AD is associated with brain shrinkage and loss of neurons in many brain regions, especially the hippocampus and frontal brain which play a crucial role in memory formation. The loss of cholinergic neurons in these two parts is a feature of the disease and is thought to underlie the cognitive deficit and loss of short-term memory that occurs. This loss is caused by accumulating two proteins, the amyloid plaques, consisting of amorphous extracellular deposits of beta-amyloid protein(known as Aβ) and the phosphorylated filaments of a microtubule-associated protein(Tau). The early appearance of amyloid deposits presages the development of AD, although symptoms may not develop for many years.

Amyloid deposits consist of aggregates of Aβ, Aβ40 and Aβ42. These two are segments of amyloid precursor protein(APP) and are generated by the action of specific proteases called secretase. Both proteins aggregate to form amyloid plaques, but αβ 42 shows a stronger tendency than αβ 40 so it appears to be the main component in amyloid formation. APP is a 770 amino acid membrane protein and cleavage by α-secretase releases the large extracellular domain as soluble APP, which is believed to serve a physiological trophic function. Formation of Aβ involves cleavage at two different points which need one of the enzymes called the γ-secretase. The γ-secretase lacks precision, so it may cut at the wrong point in the APP's transmembrane domain, leading to the generation Aβ 40 and Aβ 42. Mutation of the APP gene also favours the formation of Aβ 42. There is a lipid transport protein called apolipoprotein-E, which is responsible for the clearance of Aβ oligomers. Mutation of the ApoE4 gene will cause the accumulation of Aβ oligomers. The other main player in the biochemical stage is Tau. Tau is a normal constituent of neurons associated with the intracellular microtubules that serve as a track for transporting materials along nerve axons. When Tau is abnormally phosphorylated by various kinases, like CDK5, it dissociates from microtubules to be deposited intracellularly. When the cells die, these filaments aggregate as extracellular neurofibrillary tangles. And these tangles could be a factor in causing AD. Tau phosphorylation is enhanced by the presence of Aβ, possible by activation of kinases. Conversely, hyperphosphorylated Tau favours the formation of amyloid deposits.

**Loss of cholinergic neurons**

The loss of cholinergic neurons by following protein accumulation will lead to biochemical changes. Ach transferase activity, Ach content and Ach transport in the cortex and hippocampus are all reduced considerably in AD but not in other disorders. The nicotinic receptors particularly in the cortex, are reduced. The loss of the projection Ach from the forebrain of the hippocampus will influence the short-memory formation.

Therapeutic approaches

The pharmacological approaches to restoring cholinergic function might be feasible, leading to the use of cholinesterase inhibitors to treat AD. The currently approved for the treatment of AD is memantine. It is an orally active weak antagonist at NMDA receptors. By binding the NMDA receptor, it can reduce the secretion of glutamate and maintain the concentration of Ach. Other AchE inhibitors such as donepezil, rivastigmine and galantamine also can be used to treat AD.