Acetylcholine dysfunction in Alzheimer’s

At a macroscopic level, AD is characterized by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus (Wenk, 2003)

One of the first explanations of Alzheimer’s is the cholinergic hypothesis.

This is supported by the finding of reduced choline uptake (Rylett et al., 1983), reduced ACh release (Milsson et al., 1986) and loss of cholinergic perikarya from the nucleus basalis of Meynert (Whitehouse et al., 1982) confirming a substantial presynaptic cholinergic deficit.

This loss of basal forebrain (nbM is in this area) ACh is a classical sign of dementia, especially Alzheimer’s Dementia.

These findings along with the role of ACh in learning and memory led to the hypothesis that ACh reduction is involved with the development of Alzheimer’s disease.

Further support for this come from:

- A reduction in the number of nAChR in the cerebral cortex of AD patients has been detected using ligand binding techniques (Whitehouse et al. 1986).
- Shimohama et al. (1986) showed that, not only nicotinic receptors, but also muscarinic acetylcholine receptors are decreased in AD brains.
- The selective cholinergic channel activator (nicotinic agonist), ABT-418, significantly improved recall failure on a verbal learning task in AD patients (Potter et al. 1999).

However, loss of ACh is only one symptom in a triad of three:

- ACh cell loss
- Extracellular plaque accumulation (Amyloid plaques)
- Intracellular fibrillary tangles

Amyloid plaques and neurofibrillary tangles are changes characteristic of Alzheimer’s disease (Anderton, 2002)

Amyloid plaques are where protein (beta-amyloid) fragments are snipped from an amyloid precursor protein by an enzyme and instead of being broken down further they accumulate into hard, insoluble plaques.

Tangles are also insoluble; they are twisted fibres found inside neurons and are primarily made up of tau protein.

Support for plaques comes from the finding of the first Alzheimer’s genetic mutation to be in the APP gene (Goate et al., 1991).

Additionally, these plaques are believed to be toxic to the brain by disrupting calcium ion homeostasis and thus inducing apoptosis (Yanker et al., 1990)

However, individuals without the disease also show evidence of these plaques (Arrigada et al., 1992) and the occurrence of plaques does not correlate with neuron loss (Schmitz et al., 2004)

This lead to the formation of the Tau hypothesis which proposes the loss of Tau (a microtubule-stabilising protein) leads to degradation of the cytoskeleton (Gray et al., 1987).