Role of Aβ and the α7 nicotinic acetylcholine receptor in regulating synaptic plasticity in Alzheimer’s disease

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Summary

Alzheimer’s disease (AD) is caused by the accumulation of β-amyloid protein (Aβ) in the brain. The aggregation of β-amyloid protein to higher molecular weight fibrillar forms is also considered to be an important step in the pathogenesis of the disease. The memory problems associated with AD are likely to be caused by changes in synaptic plasticity. Recent studies suggest that Aβ binds to the α7 nicotinic acetylcholine receptor (α7 nAChR), which plays an important role in synaptic plasticity and memory. A loop domain localized towards the C-terminus of the extracellular region of the receptor has been identified as forming part of a putative Aβ-binding site. In cell culture experiments, the binding of Aβ to the α7 nAChR has been found to cause an increase in the level of acetylcholinesterase, which is also increased around amyloid plaques in the AD brain. These studies indicate that the Aβ-binding site on the α7 nAChR receptor is an important new target for therapeutic development in AD.

Introduction

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. Clinically, the disease is characterized by a gradual loss of higher cognitive function, typically with memory problems [1]. Biochemically, AD is distinguished by the presence of proteinaceous deposits in the extracellular and intracellular compartments of the brain [2]. The major component of the intracellular deposits or neurofibrillary tangles is a hyperphosphorylated form of the cytoskeletal protein tau, whereas the extracellular deposits (amyloid) are made from a 4 kDa peptide known as the β-amyloid protein (Aβ). Aβ is a proteolytic fragment derived from the β-amyloid protein precursor (APP). Initially, cleavage of APP by an aspartyl protease known as the β-secretase or the β-site APP cleaving enzyme (BACE) produces a 99-residue C-terminal fragment. Subsequent cleavage of the C-terminal fragment by γ-secretase generates Aβ [3].

There is now very good evidence that accumulation and aggregation of Aβ in the brain leads to the neurodegeneration which causes AD [3]. Most of the Aβ contains 40 amino-acid residues (Aβ1–40). However, the production of a minor form which contains 42 residues (Aβ1–42, also known as long Aβ) is more closely associated with disease pathogenesis. A number of familial AD mutations have been identified in the APP gene as well as in genes encoding presenilins 1 and 2, which are associated with γ-secretase. All of these mutations have been found to increase
production of long Aβ, which aggregates more readily than Aβ1–40 [3, 4]. Both Aβ1–40 and Aβ1–42 can form amyloid fibrils (Figure 1) and both forms of Aβ are found in amyloid plaques. However, Aβ1–42 may help to seed Aβ1–40 aggregation, thereby accelerating the production of amyloid fibrils in AD [5].

One of the central unanswered questions in the field of AD, is the mechanism by which Aβ contributes to the cognitive decline. A large number of studies have suggested that Aβ is neurotoxic and that it can cause cell death [6, 7]. However, there are good reasons to doubt the idea that neuronal cell death can lead to dementia [8]. A more specific mechanism involving an alteration in synaptic plasticity seems more likely [9].

The α7 nicotinic acetylcholine receptor and Alzheimer’s disease

There is now increasing evidence that the α7 nicotinic acetylcholine receptor (nAChR) is involved in the regulation of synaptic plasticity [10]. nAChRs belong to the ligand-gated ion channel receptor family, which includes neurotransmitter receptors such as the GABA<sub>A</sub>, glycine and 5-HT<sub>3</sub> receptors [11]. All of these receptors possess a basic pentameric subunit structure which forms a central ion pore (Figure 2). In the central

Figure 1. Atomic force microscopy of a fibril of Aβ1–42 formed by aging under ambient conditions for 5 days on surface of highly oriented pyrolytic graphite. Fibrils are typically of 5–10 nm diameter and contain a helical periodicity of about 100 nm.

Figure 2. Ribbon representation of the extracellular domain of the acetylcholine-binding protein (protein data bank accession code 1I9B), a homologue of the α7 nAChR: (a) The figure shows both the loop domain homologous to a peptide to which Aβ binds. The figure also shows the central pore region which is permeable to sodium and calcium ions upon agonist binding. The axis through the central pore is tilted slightly to show both regions of the receptor; (b) Amino acid sequence of the putative Aβ-binding domain in the α7 nAChR. Amino acid residues are represented by the one-letter abbreviation. A disulfide bond between the two cysteine residues produces a hairpin bend in the peptide sequence.