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SPECIAL ISSUE

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The molecular significance of amyloid β-peptide for Alzheimer's disease

Abstract Alzheimer's disease is the most common form of dementia. Although the majority of the cases occur sporadically, in some rare cases Alzheimer's disease is genetically inherited. Pathologically, Alzheimer's disease is characterized by the accumulation of senile plaques within the extracellular space of brain regions known to be important for intellectual functions. In addition to senile plaques, deposits of identical biochemical composition are found in the walls of meningeal and cerebral blood vessels. Senile plaques are surrounded by degenerating neurons indicating a toxic interference of amyloid plaques with neurons. The major component of senile plaques is the 4 kDa amyloid β-peptide. This peptide has been shown to exhibit neurotoxic properties when added to cultured neurons, or injected into rat brains. Amyloid β-peptide is derived from a high molecular weight precursor, the β-amyloid precursor protein, by proteolytic processing. Mutations responsible for the early onset of Alzheimer's disease in some families are found within the gene coding for the β-amyloid precursor protein. These mutations strongly influence the generation of amyloid β-peptide resulting in a significant overproduction of the peptide or the generation of elongated forms which are known to aggregate and precipitate much faster. Moreover, mutations found in other genes known to cause early onset of Alzheimer's disease have been shown to interfere directly with the production or precipitation of amyloid β-peptide.

Key words β-Amyloid precursor protein · Proteolytic processing · S182

Introduction

Alzheimer's disease (AD) has gained a lot public interest during the past few years, especially after the former U. S. president, Ronald Reagan, was announced to be affected by this kind of neurodegenerative disorder. Currently, approximately 17 million AD cases exist worldwide causing one of the highest death rates of all known diseases. Thus far, no presymptomatic diagnosis or treatment for AD exists. Moreover, even the causative agent of AD is under permanent debate, and molecules as different as amyloid β-peptide (Aβ), apolipoprotein E (apo E) or an abnormally phosphorylated form of the cytoskeletal T-protein are believed to be the major players in the generation of the disease (e.g. Selkoe 1994; Strittmatter et al 1994).

The goal of this review is to outline the seminal role of Aβ peptide as a major causative agent of AD. This review focuses on evidence based on the molecular biology of Aβ generation. The pathogenic evidence of Aβ for AD has been described in more detail by Selkoe in several recent reviews (1991, 1994b and c).

Cerebral amyloid deposits are the major pathological hallmarks of Alzheimer's disease

A wide variety of pathological changes, including plaque formation, neurofibrillary tangles, neuronal cell loss, gliosis and reduced levels of certain neurotransmitters, have been described. Whereas most of these abnormalities can be found frequently in other neurodegenerative diseases, high densities of extracellular senile plaques are detected primarily in the brains of all AD patients (Fig. 1). Senile plaques are surrounded by a halo of dystrophic neurites showing abnormalities in dendrite and axon formation. The cell bodies of neurons in close proximity of these plaques are filled with neurofibrillary tangles. Neurofibrillary tangles are composed predominantly of an abnormally phosphorylated form of tau protein (Grundke-Iqbal et al. 1986; Ueda et al. 1990; for review see Selkoe 1991).

Because the major pathological changes are found in the immediate vicinity of senile plaques, it was expected that these plaques contain a component which might exhibit selective neurotoxicity. Therefore, a lot of efforts fo-

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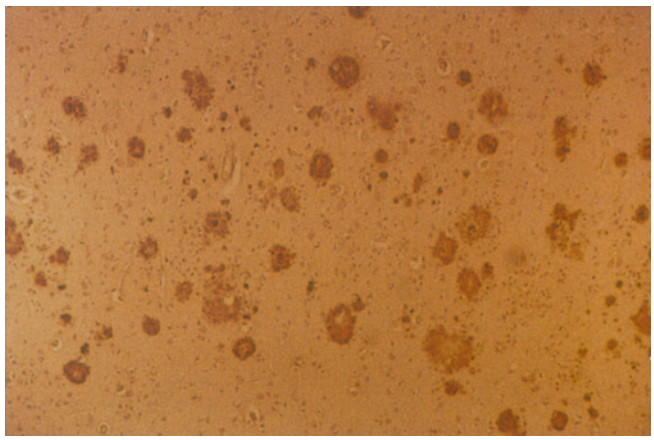


Fig. 1 Accumulation of senile plaques in the brain of an Alzheimer's disease (AD) patient. A section through the temporal cortex of a 75-year-old AD case stained with antibody 3927 to Aβ (Haass and Teplow) is shown

cused on the isolation of the major components of senile plaques. Glenner and Wong (1984) finally isolated the component and found that senile plaques are composed predominantly of a 40–43 amino acid peptide which was called amyloid β-peptide.

Amyloid β-peptide is neurotoxic

Aβ was found to be a 4 kDa very hydrophobic peptide which tends to form insoluble aggregates. If Aβ is neurotoxic for surrounding neurons in the brains of AD patients, one would expect that this phenomenon could be demonstrated by in vitro experiments by adding Aβ to cultured neurons or injecting Aβ into the brains of animals. Indeed, Aβ exhibits neurotoxic properties and causes selective neuronal cell death in a dose-dependent manner when added to cultured neurons (Yankner et al. 1990). Moreover, Aβ is neurotoxic only if it is applied as preformed aggregates to cultured cells, thus mimicking the situation occurring during AD (Lorenzo and Yankner 1994). The neurotoxicity of Aβ is directly dependent on its ability to form fibrils whereas amorphous aggregates do not have neurotoxic activity (Lorenzo et al. 1994). Neurotoxicity of Aβ is not only found in cell culture systems. Injections of preaggregated Aβ into rat brains caused pathological changes similar to those found in the AD brain (Kowall et al. 1991). Taken together, these data clearly support the hypothesis that Aβ represents the neurotoxic component of senile plaques which may trigger neuropathological events finally resulting in AD.

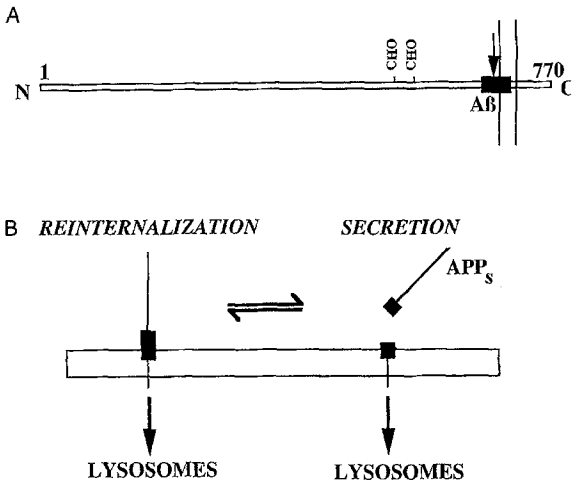
It has been argued that paired helical filaments are the primary neuropathological changes found in AD brains and all other morphological alterations including plaque formation are secondary events (Roses 1994; Strittmatter et al. 1994; Strittmatter and Roses 1995). In contrast to this hypothesis, it has been shown recently that addition of aggregated Aβ to cultured primary hippocampal neurons induces abnormal tau-phosphorylation and a loss of microtubule binding (Busciglio et al. 1995). This clearly shows a direct connection between Aβ neurotoxicity and cytoskeletal abnormalities found within the AD brain indicating again a primary role of Aβ for causing AD. In that paradigm abnormal phosphorylation of tau-protein is a secondary event caused by the neurotoxic properties of Aβ.

The genetics of Alzheimer's disease supports the seminal role of amyloid β-peptide

Alzheimer's disease usually occurs as a sporadic disease. However, in a few cases of early onset the disease results from dominant mutations found within at least three different genes localized on chromosomes 14, 19 and 21 (for review see Mullan and Crawford 1993). In the following sections, the influence of the different mutant gene products on the generation of Aβ is discussed.

Proteolytic processing of β-amyloid precursor protein

Aβ is derived by proteolytic processing from a high molecular weight precursor protein encoded on chromosome 21, called β-amyloid precursor protein (βAPP; Kang et al. 1987). βAPP is a type-1 transmembrane protein (Dyrks et al. 1988) with a small C-terminal cytoplasmic domain, one transmembrane domain and a large N-terminal extracellular domain (Fig. 2a; Weidemann et al. 1989). The Aβ domain is partially embedded within the phospholipid bilayer protecting it from proteolytic cleavage. Moreover, a major processing pathway clearly inhibits Aβ generation (Fig. 2b). βAPP is cleaved during its transport to the cell surface by an unknown protease called α-secretase. This results in the secretion of the extracellular domain of βAPP (Weidemann et al. 1989) and the generation of a membrane-bound 10 kDa C-terminal fragment (Oltersdorf et al. 1990). As shown in Fig. 2b, α-secretase cleavage occurs at position 17 of the Aβ domain, thus clearly preventing amyloid formation (Esch et al. 1990). However, an additional trafficking pathway has been shown which involves reinternalization of the uncleaved precursor and its targeting to endosomes and lysosomes (Fig. 2b, left panel; Haass et al. 1992a; Yamazaki et al. 1995). This pathway has been claimed to be involved in the generation Aβ (Haass et al. 1993; Koo and Squazzo 1994). Suprisingly, Aβ was found to be generated in a physiological pathway by tissue-cultured cells (Haass et al. 1992b; Shoji et al. 1992; Busciglio et al. 1993; for review see Haass and Selkoe 1993). In that pathway βAPP is alternatively processed by two additional hypothetical enzymes called β- and γ-secretase (Fig. 2c). It is believed that βAPP is reinternalized and cleaved within endosomes by β-secretase at the N-terminus of the Aβ domain (Koo and Squazzo 1994). This creates a 12-kDa intermediate (Haass et al. 1992a), which recycles back to the cell surface. On the cell surface the precursor is cleaved again by γ-secretase in an unknown mechanism resulting in the im-



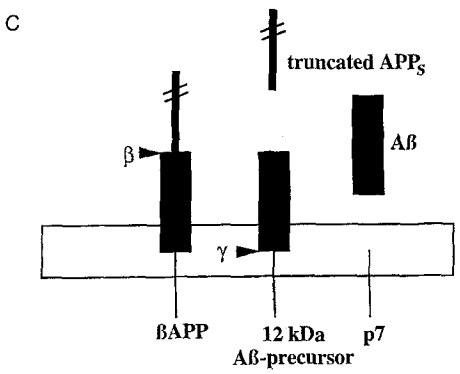


Fig. 2 a–c βAPP and its proteolytic processing pathways. **a** Representation of the βAPP molecule. Black box = Aβ; CHO = glycosylation sites. **b** Processing of βAPP by α-secretase and the reinternalization pathway. **c** Aβ generation by cleavage of β- and γ-secretase; β-secretase cleavage creates a truncated form of amyloid precursor proteins (APPs) (Seubert et al. 1993) and a 12-kDa amyloidogenic precursor. γ-secretase cleavage of the 12-kDa precursor results in the formation of a putative 7-kDa fragment and the secretion of Aβ

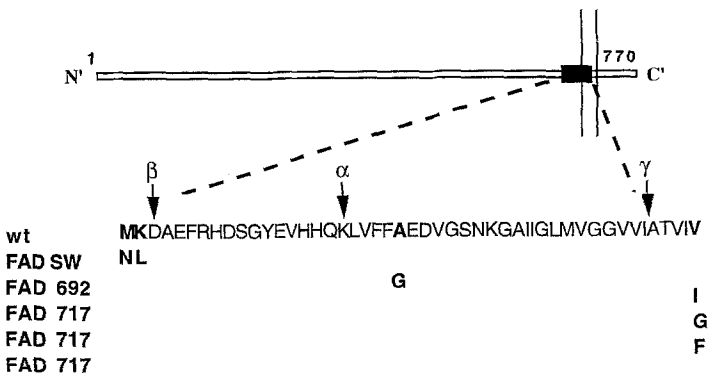


Fig. 3 Localization of familial AD (FAD) mutations found within the βAPP gene. The Aβ domain and its amino acid sequence is shown enlarged

mediate secretion of the peptide into the tissue culture media. Such cell culture systems are currently used to analyse the details of Aβ generation. The relevance of this system is supported by the finding that soluble Aβ is also found in biological fluids such as cerebrospinal fluid and plasma (Seubert et al. 1992; Shoji et al. 1992).

Mutations found within the gene coding for the β-amyloid precursor protein

Not surprisingly, mutations found in some families with familial AD (FAD) mapped to the βAPP gene. These mutations are localized in a very characteristic pattern close to the cleavage sites of all three secretases (Fig. 3). In the case of a Swedish family, a double mutation is found at the N-terminus of the Aβ domain exactly at the β-secretase site (Mullan et al. 1992). Another mutation occurs in the middle of the Aβ domain very close to the α-secretase site (Hendriks et al. 1992). A third set of those mutations is localized close to the γ-secretase site (Goate et al. 1991; Chartier-Harlin et al. 1991; Murrell et al. 1991). These three types of FAD mutations directly influence Aβ formation.

The Swedish mutation results in a three- to sixfold overproduction of Aβ in transfected tissue culture cells (Citron et al. 1992; Cai et al. 1993) and primary fibroblasts derived from gene carriers of the Swedish family (Citron et al. 1994; Table 1). It has been shown that this mutation provides a substrate which is recognized with higher efficiency by β-secretase (Citron et al. 1995) resulting in an overproduction of Aβ due to an earlier cleavage not within endosomes, but within secretory vesicles (Haass et al. 1995). The resulting overproduction of Aβ leads to an earlier plaque formation and consequently to a very early onset of AD (Table 1).

The mutation close to the α-secretase site seems to inhibit α-secretase activity, thus resulting in a modest overproduction of Aβ and the generation of N-terminal truncated Aβ-like peptides (Haass et al. 1994). N-terminal truncated Aβ-like peptides lack negative charges, which might together with enhanced Aβ production facilitate aggregation and therefore lead to an earlier amyloid deposition (Table 1).

All three mutations found at the C-terminus of Aβ are known to result in the production of Aβ species with a higher proportion of peptides ending at amino acid 42, instead of amino acid 40 (Suzuki et al. 1994). These elongated peptides are known to aggregate much faster (Jarret and Lansbury 1993) which again leads to an accelerated amyloid plaque formation (Table 1).

Taken together, all three types of βAPP mutations directly influence Aβ production by either causing enhanced production of Aβ or by increasing the rate of peptides which aggregate with much faster kinetics. These very different mechanisms finally result in an early deposition of Aβ and therefore an early onset of AD.

Table 1 Molecular and pathogenic effect of FAD mutations on Aβ generation. Mutations occurring within the βAPP gene are shown above the *dashed line*. FAD familial Alzheimer's disease

FAD gene/ mutation	Influence on Aβ generation	Molecular mechanism	Pathogenic mechanism
MK/NL	Three- to sixfold increase of Aβ production	Mutation provides a better substrate for β-secretase, resulting in an early cleavage within secretory vesicles	Overproduction of Aβ leads to earlier plaque formation
A/G	Modest increase of Aβ production and generation of N-terminal truncated Aβ-like peptides	Inhibition of α-secretase activity	N-terminal truncated peptides might aggregate faster, which leads to earlier plaque formation
V/I V/F V/G	Increased amounts of Aβ peptides ending at amino acid 42 instead of 40	Mutations might provide a new recognition sequence for γ-secretase	Aβ peptides ending at amino acid 42 aggregate faster, which leads to earlier plaque formation
Apo E4	Triggers Aβ aggregation	Allele-specific binding of apo E to Aβ	Accelerated aggregation of Aβ leads to earlier plaque formation
S182 (chromosome 14)	Increased amounts of Aβ peptides peptides ending at amino acid 42 instead of 40	Unknown	Aβ peptides ending at amino acid 42 aggregate faster, which leads to earlier plaque formation

Apolipoprotein E4 is associated with late onset familial Alzheimer disease

Besides mutations linked to the βAPP gene on chromosome 21, AD is also associated with a gene mapped to chromosome 19. The responsible gene was identified as the gene encoding the apolipoprotein E (apo E). Apo E occurs as three different alleles, apo E2, apo E3 and apo E4 (for review see Strittmatter and Roses 1995). The apo E4 allele is clearly associated with late-onset FAD (Strittmatter et al. 1993). Moreover, it was shown that each inherited apo E4 allele increases the risk and lowers the distribution of the age of onset (Corder et al. 1994). Based on these results, it was argued that Aβ plays only a secondary, if any, role in causing AD (Roses 1994). However, evidence indicating that the apo E phenotype directly influences the amyloid burden in the AD brain has accumulated. The brains of apo E4/E4 patients were clearly shown to contain a higher amount of senile plaques (Rebeck et al. 1993) indicating an influence of the apo E phenotype on the rate of plaque formation. In contrast, the apo E phenotype has no influence on the density of tangles. This is further supported by data indicating that apo E binds allele specifically to Aβ (Ma et al. 1994; Wisniewski et al. 1993; Sanan et al. 1994; Strittmatter et al. 1993). In that regard it was claimed that apo E4 binds to Aβ with higher avidity as compared with other apo E alleles (Strittmatter et al. 1993). However, these in vitro experiments have to be interpreted carefully because purified apo E molecules might undergo chemical modifications influencing Aβ binding (LaDu et al. 1994, 1995). Nevertheless, recent work has shown that binding of apo E4 to Aβ triggers amyloid fibril formation (Ma et al. 1994; Sanan et al. 1994). This indicates that binding of apo E to Aβ might initiate accelerated amyloid aggregation and therefore cause earlier plaque formation, a pathogenic mechanism remarkably similar to that of mutations found at the C-terminus of Aβ (Table 1).

A gene encoded on chromosome 14 is involved in Aβ metabolism

A gene on chromosome 14 was linked to early-onset FAD in a variety of families (Schellenberg et al. 1992, St. George-Hyslop et al. 1992). The gene (called S182) was recently cloned by Sherrington et al. (1995) and shown to be an integral membrane protein with seven potential transmembrane domains. The biological function of the gene product is unknown, but based on sequence homologies it was argued that S182 might be involved in the cellular trafficking of membrane vesicles or might represent a receptor or channel protein (Sherrington et al. 1995).

Although the biological function of S182 is still unknown, the influence of this mutation on βAPP processing has been analysed by using primary fibroblast derived from members of these families. Interestingly, it has been shown that cells derived from carriers of the chromosome-14-associated mutation show an increased rate of Aβ peptides ending at amino acid 42 (Younkin, personal communication). Therefore, S182 seems to directly influence proteolytic processing of βAPP resulting in the generation of peptides known to aggregate much faster. Again, this mechanism is remarkably similar to that found in the case of βAPP mutations at the C-terminus of the Aβ domain.

Taken together, AD is not caused by a single gene product or failure of this gene product. However, all known mutations, including those not linked to the βAPP gene, strongly influence Aβ production qualitatively or quantitatively. In all cases we find either a simple overproduction of Aβ or the generation of modified peptides. Overproduction and generation of modified Aβ molecules leads to accelerated aggregation and amyloid plaque formation. Moreover, aggregated Aβ is neurotoxic and causes pathological changes such as the formation of paired helical filaments and finally neuronal cell death. Therefore, the molecular biology of βAPP processing

strongly supports a seminal role for Aβ in the generation of AD.

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