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The molecular biology of senile plaques and neurofibrillary tangles in Alzheimer's disease

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Abstract

Since the earliest descriptions of the disease, senile plaques (SP) and neurofibrillary tangles (NFT) have been regarded as the pathological 'hallmarks' of Alzheimer's disease (AD). Whether or not SP and NFT are sufficient cause to explain the neurodegeneration of AD is controversial. The major molecular constituents of these lesions, viz., ß-amyloid (Aß) and tau, have played a defining role both in the diagnosis of the disease and in studies of pathogenesis. The molecular biology of SP and NFT, however, is complex with many chemical constituents. An individual constituent could be the residue of a pathogenic gene mutation, result from cellular degeneration, or reflect the acquisition of new proteins by diffusion and molecular binding. This review proposes that the molecular composition of SP and NFT is largely a consequence of cell degeneration and the later acquisition of proteins. Such a conclusion has implications both for the diagnosis of AD and in studies of disease pathogenesis.

Key words: *Alzheimer's disease (AD), senile plaque (SP), neurofibrillary tangle (NFT), ß-amyloid (Aß), molecular composition, gene mutation, disease pathogenesis.*

Introduction

Ever since the first descriptions of pre-senile dementia by Alois Alzheimer in 1907 [3], the formation of senile plaques (SP) and neurofibrillary tangles (NFT) have been regarded as the defining pathological features of Alzheimer's disease (AD). The Khachaturian [56] and 'Consortium to Establish a Registry of Alzheimer's Disease' (CERAD) [68] criteria emphasise the importance of SP in diagnosis, while the NIA-Reagan Institute criteria [54] suggest both SP and NFT should be considered. Whether SP and NFT are sufficient to cause the neurodegeneration of AD, however, is controversial and has been questioned by a number of authors [8,22,61].

Studies of the molecular biology of SP and NFT have played an important role in the development of hypotheses as to the pathogenesis of AD. For example, the discovery of β-amyloid (Aβ) as the most important molecular constituent of the SP [44] led ultimately to the 'Amyloid Cascade Hypothesis' (ACH), one of the most influential models of the molecular pathology of AD [50]. The ACH proposes that the de-

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position of Aβ is the initial pathological event in the disease leading to the formation of NFT, cell death, and ultimately dementia. Mutations of the amyloid precursor protein (*APP*) [28,45] and presenilin (*PSEN1/2*) genes [63,85], via the generation of pathological Aβ peptides, have been linked to familial forms of AD (FAD). Hence, the presence of Aβ within SP is regarded as the residue of the effect of a pathogenic gene mutation that via the accumulation of toxic and insoluble Aβ peptides leads to cell death. Since the pathological phenotype of familial AD (FAD) is similar, apart from age of onset, to that of sporadic AD (SAD) [13,51,75], studies of gene mutation have had a profound influence on the development of theories as to the pathogenesis of AD in general [92].

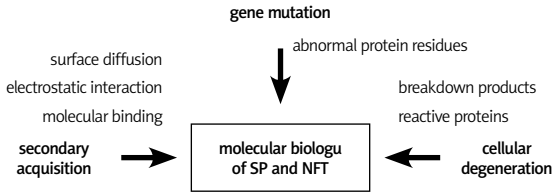

Fig. 1. Factors that influence the molecular composition of senile plaques (SP) and neurofibrillary tangles (NFT) in Alzheimer's disease (AD).

Table I. Molecular composition of senile plaques (SP) and neurofibrillary tangles (NFT) in Alzheimer's disease.

Lesion	Molecular composition
Diffuse SP	APP (lacking C terminus), Aβ oligomers especially $Aβ_{42/43}$, apolipoprotein E, α1-antichymotrypsin, HSPG, complement proteins (C1q, C_3, C_4), amyloid-P, may contain neuronal and astrocytic markers
Primitive SP	APP (N & C-terminal), $Aβ_{42/43}$, free ubiquitin, conjugated ubiquitin, PHF-antigen, phosphorylated tau, chromogranin-A, bFGF, apolipoprotein E, interleukin-6, actylcholinesterase, cholinergic, somatostatin, GABA, neuropeptide-Y, parvalbumin, and catecholamine immunoreactive neurites
Classic SP	$Aβ_{42/43}$ ('core'), α-synuclein ('ring'), Aβ40, actin, tubulin, phosphorylated tau, NF-protein, CAM, chromogranin-A ('ring'), α2-macroglobulin, complement proteins ('core'), immunoglobulins ('core'), amyloid-P, α1-antichymotrypsin, antitrypsin, antithrombin III, apolipoprotein E and D ('core'), DOPPEL, bFGF, PrP, may contain actylcholinesterase, cholinergic, somatostatin, GABA, neuropeptide-Y, parvalbumin, and catecholamine+ neurites ('ring'), silicon/aluminium ('core'), interleukin-6 ('ring')
Intracellular NFT	phosphorylated 3R/4R tau (C & N terminal), ubiquitin (C & N termini), MAP, NF-protein, apolipoprotein E, synaptophysin, bFGF, HSPG
Extracellular NFT	degraded tau (lacking N/C termini), GFAP, Aβ, ubiquitin (lacking N-terminus), amyloid-P, Apo E

Aβ – ß-amyloid, APP – amyloid precursor protein, bFGF – basic fibroblast growth factor, CAM – cell adhesion molecule, GFAP – glial fibrillary acidic protein, HSPG – heparan suphate proteoglycan, MAP – microtubule associated proteins, NF-protein – neurofilament protein, PHF – paired helical filament, PrP – prion protein.

Chemical analysis of SP and NFT in AD reveals them to have a complex and varied composition. There may be at least three types of factor that could influence the molecular biology of SP and NFT (Fig. 1) [17]. First, a molecular constituent could be the residue of a pathogenic gene mutation and therefore be directly related to the primary aetiology. Second, it could be the product of cellular degeneration and therefore, a consequence of the disease process [14]. Third, SP and NFT could acquire new molecular constituents as a result of diffusion and molecular binding to existing proteins [10,15,16]. This review examines the importance of these three factors in determining the molecular composition of SP and NFT in AD and discusses the implications in terms of diagnosis and pathogenesis.

The molecular composition of SP and NFT

Senile plaques

SP exist in various morphological forms including diffuse ('pre-amyloid'), primitive ('neuritic'), classic ('dense-cored'), and compact-type ('burnt-out') plaques [6,31]. A variety of Aβ peptides are present within these plaques and are formed as a result of secretase cleavage of the transmembrane glycoprotein APP (Table I) [47]. The most common of these peptides is $Aβ_{42/43}$ found largely in SP, whereas the more soluble $Aβ_{40}$ is also found in association with blood vessels [67,82] and may develop later in the disease [30]. Diffuse plaques contain $Aβ_{42/43}$ as well as APP fragments lacking the C-terminus while more mature classic plaques contain $Aβ_{40}$ in addition to $Aβ_{42/43}$. Moreover, SP have a variety of 'secondary' constituents [11] including silicon and aluminium [65], acute-phase proteins such as α-antichymotrypsin and α2-macroglobulin [38,64,99] and their mediator in-

terleukin-6 [84], intercellular adhesion molecules such as cell adhesion molecule 1 (CAM1) [38], apolipoprotein E (apo E) which is present in the earliest stages of SP formation [105] and D (apo D) [32], the heterodimeric glycoprotein clusterin, vibronectin, the complement proteins C1q, C4 and C3 [100], blood proteins such as amyloid-P (especially in classic SP), cathepsins B/D [86], and the sulphated glycosaminoglycans such as heparan sulphate proteoglycan (HSPG). In addition, the prion like protein DOPPEL encoded by the *PRND* gene may occur in peripheral regions of SP [39].

Neurofibrillary tangles

The microtubule associated protein (MAP) tau is the most important constituent of the paired helical filaments (PHF) and straight filaments which comprise cellular NFT in AD. There is a single gene for tau and different isoforms result from alternative splicing and post-transcriptional changes [37]. AD is therefore considered to be a tauopathy, a group of disorders that also includes Pick's disease (PiD), corticobasal degeneration (CBD), the NFT predominant form of senile dementia (NFT-SD), argyrophilic grain disease (AGD), progressive supranuclear palsy (PSP), and parkinsonism-dementia complex of Guam (Guam PDC) [26,34]. The composition of tau differs between the different tauopathies. For example, PiD is characterised by tau with three microtubule repeats (3R tau) while PSP and CBD are composed of four repeat (4R) tau [33,70]. In AD both 3R and 4R tau are present, the 3R/4R tau ratio being highly variable but specific to individual types of neuron [96]. In addition, the molecular composition of the NFT varies markedly depending on whether they are intracellular NFT (I-NFT) or extracellular NFT (E-NFT). Hence, unlike I-NFT, E-NFT are glial fibrillary acidic protein (GFAP) and Aβ immunoreactive [104], and also contain significant amounts of amyloid-P [77] and ubiquitin [21].

The effect of pathogenic gene mutations

The first demonstration of a direct association between a pathological protein and a gene mutation in neurodegenerative disease was made in AD [28,45]. A primary pathogenic role for the *APP* gene was suggested by the discovery of missense mutations in a small number of families, mutations in exons 16 and 17 being the first established genetic link with FAD [46]. There are three isoforms of APP, viz., APP_{695}, APP_{751}, and APP_{770}, all of which are cell surface glycoproteins with a single membrane-spanning region [25]. Aberrant degradation of APP is believed to result in Aβ formation, especially the peptide $Aβ_{42/43}$, the major constituent of the SP. APP has a large extracellular N-terminal domain and a short intracellular C-terminal domain while the Aβ sequence itself has 15 amino acids lying within the membrane and 28 extracellular amino acids. The metabolism of APP is mediated by α-, β-, and γ-secretase and in cultured cells that overexpress APP, there are two catabolic pathways. First, the 'non-amyloid' pathway in which APP is cleaved within the Aβ sequence by α-secretase and second, the 'amyloid' pathway in which APP is cleaved by β- and γ-secretase after endocytosis of the trans-membrane portion [76]. It was originally believed that soluble Aβ was non-toxic but became extremely toxic once fibrils were formed [76]. More recent evidence suggests that Aβ oligomer intermediates are more likely to be the dominant toxic species [57]. Hence, altered proteolytic processing of APP and the accumulation of excess Aβ is assumed to be an early pathological event in FAD, a process which also occurs to a limited extent in aged humans [79]. Following Aβ deposition, the formation of SP, microglial activation, astrocytosis, and neuritic dystrophy presumably lead to the formation of NFT, cell death, and dementia as proposed by the ACH [50].

Subsequently, the most common subtypes of FAD were linked to mutations of the *PSEN* [63,85] genes and the effect of these mutations was also assumed to lead, albeit more indirectly, to the enhanced deposition of amyloidogenic species of Aβ [47]. The normal function of the *PSEN* genes, and how gene mutations result in Aβ deposition in these cases is unclear. *PSEN1* may be involved in notch signalling [88] and may therefore be important in cell differentiation. *PSEN1/2* genes may also be implicated via the perturbation of cellular calcium homeostasis [106] or in interactions with the transcriptional coactivator cAMP-response element binding (CREB-binding) protein which plays a key role in regulating gene expression [41]. In addition, *PSEN* genes are part of the γ-secretase complex which are important in generating Aβ from APP. Hence, mutant *PSEN1* could enhance 42-specific-γ-secretase cleavage of normal APP resulting in increased deposition of $Aβ_{42/43}$ [93].

Hence, there is a close relationship between specific gene mutations, amyloid deposition, and FAD.

In the case of *APP*, the product Aβ can be directly related to the gene. In other FAD cases, e.g., those linked to *PSEN* genes, the connection between the gene mutation and the accumulation of Aβ may be more indirect. These processes, however, account for only a small proportion of cases of AD; the *APP* and *PSEN1/2* genes together accounting for less than 5% of cases [52]. In addition, various questions remain, e.g., if the ACH is correct, how does Aβ lead to the formation of tau [8], how do Aβ and tau cause cell death in AD, why is the density of lesions so low in some AD cases, and why is the pathology of FAD and SAD so similar?

The effect of structural degeneration within the cell

How do gene mutations result in pathology?

That a more complex relationship may exist between *APP* mutation, Aβ and AD was first proposed in 1993 [71]. Amino acid changes associated with the codon 717 mutation of the *APP* gene (APP_{717}) appeared to shed little light on the pathogenic mechanism of AD and existing data from neurotoxicity experiments did not establish a primary role for Aβ in disease pathogenesis [71]. In addition, deposition of Aβ occurs only in areas of cortex with viable neurons, i.e., functional neurons were necessary for the presence of Aβ [65]. Hence, Aβ may not necessarily kill neurons but may be secreted in response to cellular damage. Furthermore, generation of the pathological Aβ sequence requires cleavage by β- and γ-secretase at the N and C-terminal sites [66,103]. As the C-terminal domain lies within the membrane, membrane damage resulting from cellular breakdown, might therefore be a prerequisite for the Aβ fragment to be generated [17].

Senile plaques

Animal models suggest that Aβ peptides may be formed in response to cellular degeneration. Lesions of the nucleus basalis of Meynert (nBM) in the rat, for example, elevate APP synthesis in cortical neurons [101]; the production of excess APP being a response to loss of functional innervation. Similarly, subacute and prolonged neuronal damage in humans can induce the formation of APP [20]. In the rat, injury to an area of brain results four to seven days later in the presence of APP in axonal swellings, cell bodies, and dystrophic neurites [89]. Lesions of the fimbria-fornix pathway in the rat also result in a marked accumulation of APP in regions of the hippocampus associated with degenerating cholinergic fibres [23,35]. Injections of toxins into the brain produce very similar results, e.g., there are changes in the expression or induction of APP in brain cells after intrathecal or intraparenchymal injections of various toxins [20] while administration of chloroquine results in the production and accumulation of C-terminal fragments of APP in the cell bodies of pyramidal cells [19]. Furthermore, APP shares structural features with precursors of epidermal growth factor suggesting that APP is an endogenous protectant activated by injury to brain cells [81]. These observations have suggested alternative schemes of pathogenesis in which Aβ is not the primary cause of AD. Hence, theories involving perturbations of vesicular trafficking, the cytoskeletal network, and the distribution of membrane cholesterol are increasingly being explored [35].

Many other constituents of SP may be a consequence of structural degeneration of the cell. Approximately 40% of diffuse plaques contain degenerating neuronal perikarya [5,7,69] and many contain the processes of astrocytes. Acetylcholinesterase rich neurites have been found in SP and may be the degenerating axonal terminals of neurons originating in the nBM [91]. Cholinergic neurites, and neurites positive for somatostatin, γ-amino butyric acid (GABA), neuropeptide Y [59], and the catecholamines have all been recorded in SP [91]. As a consequence of neuritic degeneration, PHF antigens, tau, A68 protein, ubiquitin, and NF epitopes are also present [83]. In addition, the presence of neuronal markers such as parvalbumin suggests the preferential incorporation of processes of pyramidal neurons into SP [1]. The presence of chromogranin A, a soluble protein in dense-core synaptic vesicles within the dystrophic neurites of the 'coronas' of classic plaques, may also be the result of cellular degeneration [72,80].

Neurofibrillary tangles

The formation of NFT could be a part of the neurons limited response to injury [103] as neurons will often respond to degeneration by increasing the synthesis of tau [43]. Dopamine denervation and sep-

tal lesions affecting cholinergic and GABA neurons projecting to the dentate gyrus result in the loss of dendritic MAP2 and tau immunostaining [97]. Hence, transynaptic changes affecting dentate gyrus neurons may result in the precursor stages of NFT. NFT may also contain additional constituents that result from cellular degeneration [12] such as NF proteins and synaptophysin [4].

The effect of secondary acquisition of proteins

Proteins already present within SP and NFT may bind additional molecular constituents, e.g., PHF and amyloid fibres can 'decorate' themselves with various proteins [10,102]. In addition, Aβ has a number of trophic properties and can bind metals such as copper, iron, and zinc [18]. Furthermore, during aging, long-lived proteins accumulate post-translational modifications ('Maillard reaction products') such as cross-linking, decreased solubility, and increased protease resistance [87]. These changes may alter the chemical composition of a lesion with time and significantly change its binding properties [95]. Electrostatic interactions may also be important in binding exogenous components to Aβ [42].

Senile plaques

Apo E labels a proportion of SP [98] and is usually detected after the appearance of Aβ [62] suggesting that it is not a prerequisite for plaque formation even in individuals expressing allele ε4 but is acquired secondarily. Apo E itself can bind to several proteins including Aβ and in the cell targets lipoprotein particles [90]. Several acute-phase proteins and proteins associated with the immune system accumulate in SP. Interleukin-6 is enhanced in both mild and moderate AD, is a mediator of acute-phase proteins, and may be responsible for their accumulation within SP [84]. The membrane attack complex (MAC) has been identified in the dystrophic neurites of SP [60], and whereas immunoglobulin G (ImG) has not been identified, SP are associated with a variety of complement proteins, CAM, and proteins that may have originated in the blood plasma [11,38]. The presence of C_3 and antichymotrypsin suggest that the classic pathway is activated in association with diffuse plaques but it is unclear whether the process proceeds beyond C_3. C_3 is abundant in serum and therefore, could originate in blood but is also produced by macrophages and astrocytes [48]. Amyloid-P is a complex glycoprotein made in the liver and present in blood serum [2] and is found in both SP and NFT suggesting that the substance accumulates following impairment of the blood brain barrier [9,36,55]. Approximately 90% of Aβ positive SP contain amyloid-P [58]. The staining pattern of amyloid-P parallels that of the complement proteins suggesting that it may assist microglia during phagocytosis [2].

SP also contain basic fibroblast growth factor (bFGF), a substance that appears to attract neurites into the plaque [29]. As a consequence, SP acquire various markers associated with the processes of neurons and glial cells. In addition, prion protein (PrP) may accumulate at the periphery of Aβ positive plaques [49].

Neurofibrillary tangles

The maturation of NFT is associated with several changes in their molecular biology. Hence, E-NFT contain many SP constituents including Aβ, HSPG, amyloid-P, and various serpins [77,78]. I-NFTs are less compact, silver positive, and eosinophilic compared with E-NFT [106]. E-NFTs are also immunoreactive for GFAP and Aβ, both of which are likely to be deposited after cell death. The acquisition of Aβ by E-NFT suggests either that Aβ is inaccessible to I-NFT or that there are conformation changes of the proteins in the extracellular space that facilitate binding of Aβ [95]. A major constituent of NFT is ubiquitin, which is found either as a free molecule or as a protein-ubiquitin conjugate. Ubiquitin may contribute to the polymerization of abnormal fibriller structures in an attempt to eliminate them [21]. As I-NFT develop into E-NFT, they lose the N/C termini of tau and two-thirds of the N-terminus of ubiquitin [95]. NFT are also immunopositive for apo E [73]. In AD, all apo E positive neurons are positive for PHF proteins but not all PHF, tau-2 positive neurons exhibit apo E immunoreactivity [24]. These results suggest that apo E plays a secondary role in NFT formation and is accumulated within neurons in response to repair processes induced by NFT. In the presence of calcium ions, HSPG will bind to the free carboxyl groups of NFT proteins and this binding may play a role in increasing the insolubility of PHF [78]. In addition, bFGF binds to heparinase sensitive sites in NFT due to the presence of HSPG [78]. The MAC has also been iden-

tified in association with NFT [53]. Neurons remove membrane inserted MAC fragments by endocytosis and hence, retrograde transport to cell bodies may result in the attachment of MAC to abnormal cytoskeletal proteins such as tau [53].

Discussion

What determines the composition of SP and NFT?

The SP and NFT of AD have a rich molecular biology and a summary of the possible origins of their major molecular constituents is shown in Fig 2. The only constituent unequivocally related to a gene product is Aβ, being directly related to mutations of *APP*.

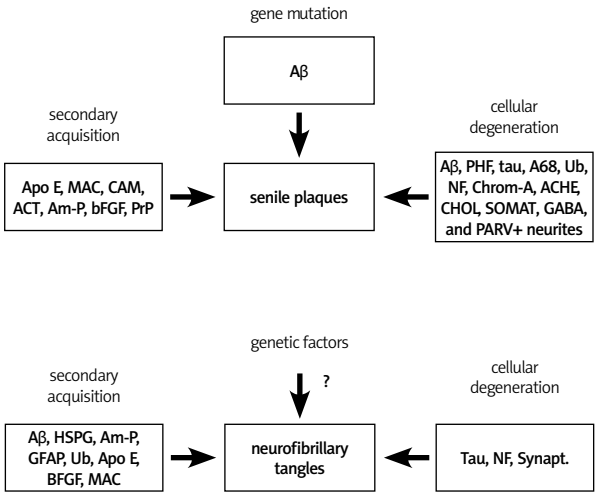

Fig. 2. The proposed origin of the main molecular constituents of senile plaques (SP) and neurofibrillary tangles (NFT) in Alzheimer's disease (AD): Aβ (b-amyloid), ACHE (acetylcholinesterase), ACT (α1-antichymotrypsin), Am-P (Amyloid-P), APP (amyloid precursor protein), Apo E (Apolipoprotein E), bFGF (basic fibroblast growth factor), CAM (cell adhesion molecule), CHOL (cholinergic), Chrom-A (chromogranin-A), GABA (γ-amino butyric acid positive neurites), GFAP (glial fibrillary acidic protein), HSPG (heparan suphate proteoglycan), MAC (membrane attack complex), MAP (microtubule associated proteins), NF-protein (neurofilament protein), PARV (parvalbumin positive neurites), PHF (paired helical filament), PrP (prion protein), SOMAT (somatostatin positive neurites), Ub (ubiquitin), Synapt (synaptophysin).

The degree to which Aβ 'directly' promotes cell death, however, is more controversial. First, FAD cases are similar, apart from age at onset, to SAD [51,75] and hypotheses such as the ACH do not specify what initiates the common late-onset form of AD [94]. Second, it is difficult to establish a mechanism that directly links a specific *APP* mutation to cell death. A variety of mechanisms have been proposed by which abnormal and misfolded proteins may affect cellular homeostasis including disruption of the ubiquitin degradation system, axonal transport, synaptic function, and protein sequestration and these are reviewed in detail by Forman et al. [40]. Third, the presence of Aβ within SP may obscure the primary aetiology because of secondary toxicity effects. Fourth, many of the molecular constituents of SP and NFT may be formed as a response to cellular degeneration including Aβ and tau [14,74,81,101].

SP and NFT also contain several constituents that are directly related to cellular degeneration (Fig. 2). Hence, synaptic disconnection, neuritic degeneration, and invasion by glia add various constituents to developing SP. These processes may explain the presence of tau, PHF antigens, synaptic proteins, and specific neurotransmitter-positive neurites within SP. Subsequently, as lesions age, the activity of some constituents is lost and new compounds acquired. Many of these newly acquired proteins may be made by glial cells or be derived from the bloodstream as a result of breakdown of the blood brain barrier. Hence, GFAP, complement proteins, and acute phase proteins become incorporated into SP. Acquisition of substances by SP as a result of surface diffusion and molecular binding may cause further changes in plaque morphology and alter the properties of the plaque so that it can bind yet further proteins [10,15,16].

Implications for diagnosis

Aβ and tau are currently the most important molecular markers of AD and the various diagnostic criteria emphasise the presence of either SP alone or both SP and NFT in pathological diagnosis [66,68,103]. Nevertheless, the molecular complexity of SP and NFT and the possible origins of the various constituents raise questions about the reliability of using any constituent as the sole pathological marker of disease. First, when many chemical constituents are present, there is the problem of distinguishing

the primary 'pathological' proteins from reactive products, the breakdown products of the cell, and the compounds acquired by surface diffusion. Studies of FAD have had the most significant influence in identifying the 'primary' pathogenic protein, viz., Aβ, the results then being extrapolated to SAD. Aβ, however, may itself be a reaction to cellular degeneration rather than being its cause [14]. Second, the chemical composition of SP and NFT changes as the lesions mature and, in some cases, activity of the primary molecular constituents may be reduced or become substantially altered, and this may cause problems in the diagnosis of AD especially of longer duration cases. Nevertheless, if the value of SP and NFT in the diagnosis of AD is questioned, there is the problem of how AD is to be defined [17].

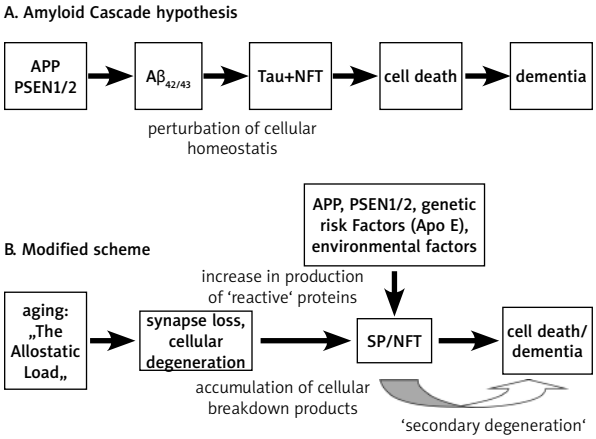

Fig. 3A-B. Relationships between gene mutation and disease phenotype in Alzheimer's disease (AD). A. The amyloid cascade hypothesis (ACH) to explain the pathogenesis of familial AD (FAD). B. Modified scheme to explain the pathogenesis of FAD and sporadic AD (SAD): APP (amyloid precursor protein), Aβ (β-amyloid), Apo E (Apolipoprotein E), NFT (neurofibrillary tangle), SP (senile plaque), PSEN (presenilin).

Implications for disease pathogenesis

In the conventional view of AD pathogenesis as illustrated by the ACH (Fig. 3A), a causal pathway is hypothesised linking mutations of *APP* to cell injury and death; the latter mediated presumably by a variety of changes in cellular homeostasis [40] and caused by the accumulation of Aβ peptides [50]. This review, however, proposes a more complex interrelationship between these elements (Fig. 3B) in which the primary factor is the age-dependent breakdown of anatomical systems and pathways within the brain and the consequence loss of synapses [27]. The extent of this aging effect, which begins early in life, is mediated by the degree of lifetime stress (the 'allostatic load'). The brain is the ultimate mediator of stress-related mortality through hormonal changes resulting in hypertension, glucose intolerance, cardiovascular disease, and immunological problems [27]. The consequence is gradual synaptic disconnection, neuronal degeneration, and the upregulation of genes determining various reactive and breakdown products [14,74,81,101]. Second, in small numbers of families, specific APP or *PSEN* mutations influence the outcome of this age-related degeneration by determining the solubility and/or toxicity of the molecular product. Cells have mechanisms to protect against the accumulation of misfolded and aggregated proteins including the ubiquitin system and the phagosome-lysosome system. Neuronal degeneration in individuals with specific mutations results in the accelerated formation of Aβ and tau, and then a further phase of 'secondary' neurodegeneration, which overwhelms the protection systems. Early-onset FAD is the consequence of this process.

By contrast, in individuals without a specific genetic mutation, but where more complex genetic and environmental risk factors are present, the outcome of age-related loss of synapses is mainly soluble and smaller quantities of insoluble proteins which are degraded by the cellular protection systems and do not significantly accumulate to form SP and NFT. With advancing age, however, the protective systems become less effective resulting in slowly accumulating quantities of Aβ and tau. The result of these insidious processes is that the cellular protection systems do not become overwhelmed until much later in life; the consequence being late-onset SAD. The advantage of this modified scheme is that it may explain why the phenotypes of FAD and SAD are similar, why SP and NFT often appear to be distributed independently within the brain, and reflects data suggesting that Aβ and tau are formed as a response to cellular degeneration.

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