Review article

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Plaques and tangles and the pathogenesis of Alzheimer's disease

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Abstract

Since the earliest descriptions, senile plaques (SP) and neurofibrillary tangles (NFT) have been regarded as the pathological hallmarks of Alzheimer's disease (AD). Consequently, studies of the morphology, distribution, and molecular composition of SP and NFT have played an important role in developing theories as to the pathogenesis of AD; the most important being the 'Amyloid Cascade Hypothesis (ACH)'. Nevertheless, the significance of SP and NFT to the pathogenesis of AD remains controversial. This review examines three questions: 1) is there a relationship between the lesions and the degree of clinical dementia, 2) is the pathogenesis of the NFT linked to that of the SP, and 3) what is the relationship of SP and NFT to the pathogenesis of AD? These questions are discussed with reference to the morphology and molecular composition of SP and NFT, the effects of gene mutations, studies of head injury patients, experimental studies involving brain lesions and transgenes, and the degeneration of specific anatomical pathways. It was concluded that SP and NFT are not closely related to the developing dementia in AD, arise as relatively independent lesions, and may be the products of a degenerative process rather than being their cause.

Key words: *Alzheimer's disease (AD), Senile plaques (SP), Neurofibrillary tangles (NFT), Disease pathogenesis, Amyloid cascade hypothesis (ACH).*

Introduction

Since the first descriptions of pre-senile dementia by Alois Alzheimer in 1907 [4], the formation of senile plaques (SP) and neurofibrillary tangles (NFT) (Fig. 1) have been regarded as the defining lesions of Alzheimer's disease (AD) [58]. AD became a nosological entity in 1910 and was named by Kraepelin based on the description of the original cases. Of the two cases described by Alzheimer, however, both had numerous SP but only one case had significant numbers of NFT [35], thus creating a controversy as to the relative importance of the two lesions that still persists today.

Studies of the molecular composition of SP and NFT have played an important role in the development of hypotheses as to the pathogenesis of AD. The discovery of β-amyloid (Aβ), the most important molecular constituent of the SP [34], led to the formulation of the 'Amyloid Cascade Hypothesis' (ACH) (Fig. 2) [37]. The ACH proposes that the deposition of Aβ is the initial event in AD leading to the formation of NFT, cell death, and ultimately dementia. Nevertheless, there are observations that are difficult to reconcile with the hypothesis. First, in transgenic mice, genes overexpressing the amyloid precursor

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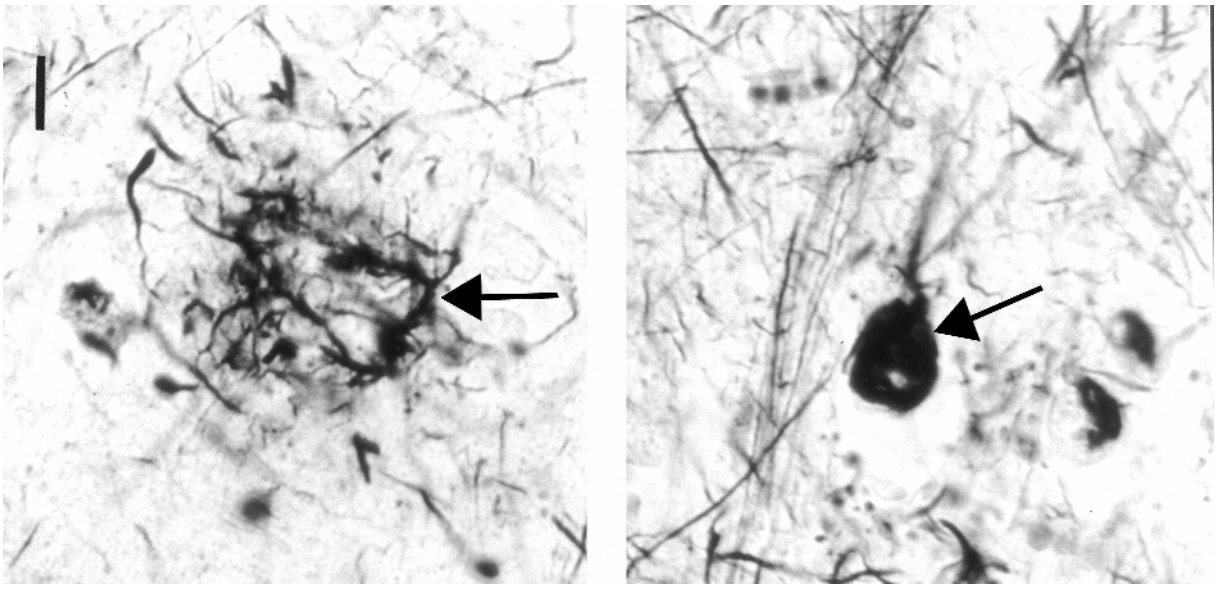

Fig. 1. Hallmark lesions of Alzheimer's disease, viz., senile plaques (SP) and neurofibrillary tangles revealed using a silver impregnation stain (Modified Bielschowsky method, magnification bar 15 μm)

protein (APP) do not produce the predicted cascade [29]. Second, SP and NFT appear to be separated in the brain both temporally [54] and spatially [10] suggesting that the two lesions may develop independently. Indeed, in the entorhinal cortex, NFT may actually precede the appearance of SP [29].

This review is a reappraisal of the significance of SP and NFT in AD and examines three questions: 1) is there a relationship between the lesions and the degree of dementia, 2) is there a pathogenic relationship between the SP and NFT, and 3) what is the relationship of SP/NFT to disease pathogenesis?

The morphology and molecular composition of SP and NFT

Senile plaques

Senile plaques are classified into a number of morphological subtypes, viz., diffuse, primitive, and classic plaques [9,24]. A unique combination of histological features appears to be associated with the formation of each type of plaque [8]. Hence, diffuse plaques have a close spatial association with neuronal perikarya [3], primitive plaques with synapto-axonal degeneration not involving the cell body [31], and classic plaques with blood vessels [8]. Hence, degeneration of a particular cell type or anatomical structure could result in the formation of a plaque with a specific morphology.

The molecular composition of SP (Table I) includes Aβ, apolipoprotein E (Apo E) [88], α_1-antichymotrypsin, sulphated glycosaminoglycans, and complement factors [83]. Moreover, the mature primitive and classic plaques contain dystrophic neurites immunoreactive to the protein tau, the most important component of the NFT. Classic SP are especially complex and contain a variety of molecular constituents within the amyloid 'core' and the surrounding 'ring' [8]. Hence, chromogranin-A and paired helical filament (PHF) antigens appear to be localised to the 'ring' while complement factors and immunoglobulins are found in the plaque 'core' (Table I). The presence of immune system proteins within the 'core' has suggested that blood proteins and more specifically immunological factors [55] may be involved in the pathogenesis of the Aβ deposits and hence AD.

Neurofibrillary tangles

The morphology and molecular composition of NFT appears to be dependent on cell type and location within the brain. Hence, cortical and subcortical NFT comprise morphologically similar but chemically different PHF [78] suggesting that the formation of NFT

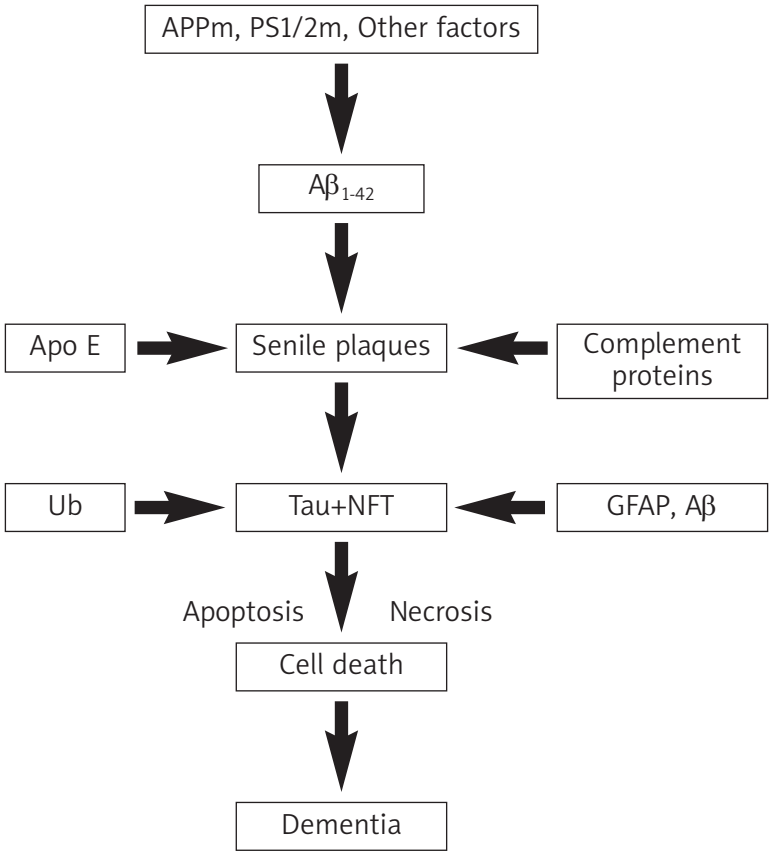

Fig. 2. The 'amyloid cascade hypothesis' (ACH). Abbreviations: amyloid precursor protein mutation (APPm), presenilin 1/2 mutation (PS1/2m), Apolipoprotein E (Apo E), Glial fibrillary acidic protein (GFAP), Neurofibrillary tangles (NFT), Ubiquitin (Ub)

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), $A\beta_{42/43}$, Apolipoprotein E, α_1-antichymotrypsin, Sulphated glycosaminoglycans, Complement factors (C1q, C3, C4)
Primitive SP	APP (N & C-terminal), $A\beta_{42/43}$, Free ubiquitin, Conjugated ubiquitin, PHF-antigen A68, Phosphorylated tau, Chromagranin-A, s100b
Classic SP	$A\beta_{42/43}$ ('core'), α-synuclein ('ring'), $A\beta_{40}$, Actin, Tubulin, Phosphorylated tau, A68, NF-protein, Chromagranin-A ('ring'), α_2-macroglobulin, Complement factors ('core'), Immunoglobulins ('core'), Serum amyloid-P, α_1-antichymotrypsin, Antitrypsin, Antithrombin III, Apolipoprotein E ('core')
Intracellular NFT	Phosphorylated tau (C & N terminal), tau 55/64/69, Ubiquitin (C & N terminal), MAP, NF-protein
Extracellular NFT	Degraded tau, GFAP, Aβ, Ubiquitin (lacking N-terminus), Amyloid-P, Serpins, HSPG

Abbreviations: Aβ (Amyloid-beta), APP (Amyloid precursor protein), GFAP (Glial fibrillary acidic protein), HSPG (Heparan sulphate proteoglycan), MAP (Microtubule associated proteins), NF-protein (Neurofilament protein), PHF (Paired helical filament)

may be related to the degeneration of specific types of neuron. One of the most important molecular markers of NFT is tau (Table I). In AD, by contrast with progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), all six isoforms of tau are abnormally phosphorylated and aggregated into PHF. Hence, differences in the protein composition of NFT could depend on the antigens expressed by cells of specific pathways [17]. In addition, NFT may acquire a variety of molecular constituents as tau undergoes post-translational modification [20]. These include hyperphosphorylation and glycosylation crucial to the development of NFT, as well as ubiquitination, glycation, polyamination, nitration and proteolysis, which may represent mechanisms within neurons to remove damaged or aggregated proteins. Subsequently, degeneration of NFT results in the loss or modification of many tangle proteins. Hence, extracellular NFT contain modified tau and ubiquitin and also acquire new proteins such as glial fibrillary acidic protein (GFAP) and Aβ (Fig. 2) [16,21,53,87].

What is the relationship of SP and NFT to dementia?

Several studies have attempted to correlate the numerical density of SP and NFT with clinical aspects of the disease such as patient age, duration of disease, or to the degree of clinical dementia [14,69,86]. Significant correlations have been reported between the total quantity of Aβ in the entorhinal cortex and the degree of cognition [22], between the density and surface area of Aβ and months of severe dementia [14], between dementia and NFT counts in sectors CA1 and CA4 of the hippocampus and the subiculum [69], and between neuritic SP and NFT and the degree of dementia [86].

Hyman et al. [40], however, found that no quantitative measure of Aβ correlated with disease duration in AD and suggested that Aβ may not continue to accumulate in the brain throughout the course of the disease. The complex relationship between the presence of SP and NFT and the development of dementia was also emphasised by Bennett et al. [15]. No change in SP/NFT density was found from biopsy to autopsy suggesting that the pathology was well advanced prior to the development of overt clinical symptoms. In addition, SP density may actually decline with advancing AD as a result of the removal of lesions by glial cells [9]. A similar conclusion was reported by McKenzie [56] who found that neither the mean nor the maximum density of SP increased with age. Hence, SP may not progressively accumulate over the course of the disease but develop over a limited period of time and then stabilise to a constant level or even decline. These results a question whether there is a close association between the formation of SP and NFT and the developing dementia in AD.

Are SP and NFT pathologically related?

A primary pathogenic role for APP in AD was suggested by the discovery of nonsense mutations within the gene [19]. These observations led to the formulation of the ACH (Fig. 1) [37] in which the deposition of Aβ is the primary pathological event in AD and of all subsequent pathology. The Aβ peptide exists in alternative spliced forms but normal processing does not lead to amyloid forming species. Hence, APP mutations are likely to result in an increase in the highly amyloidogenic peptide $A\beta_{42}$ and the formation of Aβ deposits or plaques [36].

Subsequently, cases of AD linked to mutations of presenilin genes (PS1 and PS2) were identified. These mutations also lead to the deposition of $A\beta_{42}$ in plaques and subsequently, to the formation of NFT, neuronal loss, and dementia [73]. Familial cases of AD, linked to the substitution of valine by isoleucine at codon 717 of the APP gene also have significant numbers of NFT thus supporting a close link between APP and the cytoskeleton [49]. In addition, cases linked to PS1 have greater numbers of SP and NFT compared with cases of sporadic AD suggesting that PS1 may increase tau deposition [73].

There is, however, no established mechanism by which the deposition of Aβ directly promotes the formation of NFT. Giasson et al. [32] conclude that Aβ promotes the formation of intracellular tau and α-synuclein although the mechanism of this interaction is uncertain. Attempts have also been made to demonstrate a synergistic interaction between NFT and Aβ [61,74]. In addition, when foetal rat hippocampal neurons and human cortical neurons were treated with Aβ, fibriller forms of Aβ apparently induced tau phosphorylation [18]. It was concluded that amyloid fibril formation might alter

the phosphorylation state of tau resulting in the loss of microtubule binding capacity.

The effect of specific antigens on neuronal degeneration

Injection of synthetic $A\beta_{40}$ into the cortex and hippocampus of rats results in the appearance of focal degenerative lesions and loss of neurons within seven days; the degree of pathological change being proportional to the dose of Aβ [47]. In addition, a significant increase in Alz-50 positivity may be observed within neurons that could represent a degenerative process preceding the formation of NFT [26]. *In vitro* Aβ fibrils can induce neuronal degeneration by increasing the level of cell surface full-length APP and the level of secreted AβPP [38]. The level of AβPP was also elevated before significant cell death occurred suggesting involvement of APP at an early stage. Furthermore, treatment of neuronal cell cultures with Aβ increased the levels of tau protein kinase-1 and induced the appearance of tau proteins that were recognised by the antibody Alz-50 [79]. These results suggest that Aβ is neurotoxic and can induce changes that may lead to the formation of NFT and cell death by apoptosis or necrosis.

Transgenic experiments

A variety of transgenic models employing one, two, or three mutations have been used in the study of AD. In the APP:V642I mouse, there was an increase in the deposition of $A\beta_{42}$ but no mature SP or NFT were observed [46] and this result is fairly typical of such experiments. In the 'double Swedish model' (APP: K670N, M671L) Aβ deposits similar to those of AD were observed, the deposits being immunopositive for Apo E but no NFT were present [71]. In the 'Indian/Swedish mutation model', both diffuse and compact type Aβ deposits were observed at 9-10 months of age. Amyloid deposition increased with age with the neocortex and amygdala being affected first followed by the hippocampus and thalamus [28]. Using the APP:Tg2576 mouse, evoked synaptic responses of neurons were impaired in areas of the cortex where substantial numbers of SP were present [76]. The responses of younger animals, before plaque formation was evident, were similar to those of controls suggesting that it was the formation of the SP that was associated with neuronal dysfunction. In addition, using the APP:Tg2576 mouse, Puig et al [64] found that increased Aβ induced oxidative stress thus increasing the activity of stress kinases and increasing tau phosphorylation in the neurites surrounding amyloid plaques.

Some models include mutations of both the APP and PS1 transgenes. In one study (APP: K670N, M671L; PS1: M146L), long-term potentiation (LTP) of neurons was observed as early as three months with reduced LTP paralleling the appearance of SP [81]. In a similar model, which also incorporated an APP: V717I mutation, there was age-related loss of pyramidal neurons in the hippocampus CA sectors including at sites devoid of plaque deposition [70]. In a further APP:PS model, Aβ deposits were observed at eight weeks and hyperphosphorylated tau as punctate deposits at 24 weeks but dystrophic neurites were not as heavily labelled as in AD [48].

A few transgenic experiments have been carried out employing three mutations (APP, PS1, and tau). In one experiment (APP: Swedish mutation, PS1: M146V, tau: P301L), Aβ and tau pathology were present with a temporal and regional specificity similar to AD, the Aβ deposits developing prior to tau positive lesions as predicted by the ACH [59]. In further experiments involving this model, AD immunotherapy was found to reduce both Aβ and early tau epitopes suggesting a relationship between the two pathologies [60].

Anatomical pathways

Studies have suggested that SP and NFT may occur in distinct but independently distributed patterns in AD [10,39]. Studies of the spatial patterns of SP and NFT show them to be clustered with, in a significant proportion of cortical areas, a regular distribution of the clusters parallel to the pia mater [11]. The clusters of SP and NFT, however, are nearly always distributed independently, which does not support a direct pathogenic link. Perez et al [63], however, showed that $A\beta_{25\text{-}35}$ could induce the aggregation of tau proteins and that a decrease in aggregation of Aβ was induced by tau peptides. Hence, aggregation of tau may be associated with disassembly of Aβ and this observation could explain the lack of co-localisation of SP and NFT.

There may be a spatial association between SP and NFT in brain areas that are anatomically connected. In

the hippocampal formation, there is a correlation between the density of SP in the outer two-thirds of the dentate gyrus molecular layer and the NFT in the adjacent entorhinal cortex; areas directly connected via the perforant path [72]. Hence, in adjacent cortical gyri, NFT may develop in cell bodies that give rise to the cortico-cortical fibres and SP may develop at their ends or on the collateral branches [23,62]. These observations could be interpreted in two distinct ways. First, as support for the ACH [37], i.e., amyloid formation at the axon terminals of an anatomical projection could result in the appearance of NFT in the cell bodies. Second, degeneration of specific groups of neurons could result in the formation of both SP and NFT. The distribution of the SP and NFT in regularly distributed clusters, however, suggests that the clusters of lesions develop in relation to specific groups of neurons associated with a neuronal projection and therefore, it is more likely that they reflect a response to synaptic disconnection and the degeneration of neurons [7].

The results of transgenic studies suggest that the presence of APP mutations alone or in combination with PS1 results in the formation of Aβ deposits, but apart from some evidence of hyperphosphorylated tau in neurites associated with the plaques, do not appear to induce NFT. The additional presence of tau transgenes is usually necessary to completely replicate AD pathology. This evidence together with that of the anatomical studies indicating that clusters of SP and NFT appear to be distributed more or less independently suggests the pathogenesis of the NFT may not be closely connected to that of the SP as predicted by the ACH.

What is the relationship of SP and NFT to disease pathogenesis?

Degeneration caused by head injury

In survivors of head injury, APP is found in neuronal perikarya and in dystrophic neurites surrounding Aβ deposits, similar pathological features to AD [30]. The processing of APP into Aβ in these cases occurs within the synaptic terminal fold of the axons; the presence of glial cells not being necessary for this conversion. Hence, the production of APP may be a response of the brain to neuronal injury [30]. Subsequently, it was shown that specific neurons in the medial temporal lobe secreted large quantities of APP and that there were more APP positive neurons in these areas in head injury patients [57]. Hence, increased expression of APP in head trauma cases may be an acute phase response to neuronal injury [68], the overexpression of APP leading to the deposition of Aβ. Several acute phase proteins are localised within Aβ deposits (Table 1) including amyloid-P, complement factors, and α-antichymotrypsin [43] supporting this hypothesis. Furthermore, Regland and Gottfries [66] proposed that APP was involved in disease processes secondarily to help maintain cell function. APP may maintain neuronal growth and survival and its putative neurotrophic action is supported by the observation that APP shares structural features with the precursor for epidermal growth factor [66]. NFT may also be part of the neurons response to injury [67].

Lesion experiments

Experimental lesions that damage the nucleus basalis in the rat result in a decrease in cortical choline acetyltransferase and an elevation of cortical peptides such as somatostatin and neuropeptide Y [5]. In addition, neuronal loss and the development of neuritic plaque-like structures occur within cortical tissue. In subsequent experiments, it was demonstrated that lesions of the nucleus basalis also elevated APP synthesis in the cerebral cortex suggesting that the production of APP could be a specific response to loss of functional innervation [84]. In addition, four to seven days after a lesion of the nucleus basalis, APP was demonstrated in axonal swellings, cell bodies, and dystrophic neurites [75]. Chemically induced lesions of the brain produce similar results. For example, lesions of the nucleus basalis using N-methyl-D-aspartate (NMDA) elevated APP synthesis in cortical polysomes [84] and, in areas of the brain damaged by kainite [45], APP695 was recorded in dystrophic neurites near to the lesion. In addition, intrathecal or intraparenchymal injections of a toxin induced APP in hippocampal neurons subsequent to neuronal damage [44]. All of these studies support the hypothesis that APP is produced in cells as a response to neuronal injury or loss of functional input and therefore, that the early development of diffuse Aβ deposits in AD could be a consequence of neuronal degeneration. In the majority of experiments of this type, no mature amyloid deposits are observed [84] and there is no evidence that APP fragments are subsequently

processed into amyloid [45]. This observation suggests that additional factors, e.g., the endoproteolysis of APP by β and γ secretase, may be necessary to produce the APP fragments that can form mature amyloid deposits [82].

The production of Aβ may also have beneficial effects in the brain. For example, $A\beta_{42}$ can induce neurogenesis, a property of Aβ oligomers but not fibrils [52]. In addition, Aβ has trophic properties derived from its ability to bind metals [13]. As a consequence, oxidative stress may promote the release of Aβ, a process that may represent a compensatory response to this damage.

Lesion experiments may also induce pathological changes leading to the development of NFT. Denervation of the dopamine pathways and septal lesions affecting both the cholinergic system and γ-aminobutyric acid (GABA) neurons projecting to the dentate gyrus, result in a loss of dendritic microtubule associated protein-2 (MAP2) and the appearance of tau positive dentate gyrus granule cells [80]. Hence, denervation causes transynaptic changes in dentate gyrus neurons and these changes may represent a precursor stage to NFT formation.

Experimental models

Nasal infection induced in a mouse using *Chlamydia* extracted from an AD brain led to the formation of Aβ deposits within the brain three months post-infection, the density, size, and number of deposits increasing as the infection progressed [51]. In addition, in *Drosophila*, expression of $A\beta_{42}$ led to the appearance of diffuse amyloid deposits, age-dependent learning defects, and extensive neurodegeneration [41]. Furthermore, in neuroblastoma cells overexpressing APP, deposition of Aβ occurred and there were morphological changes and death of cells consistent with the presence of apoptosis [65]. It was concluded that Aβ was not responsible for the death of the cells but was secreted by the damaged cells.

Anatomical pathways

In AD, several studies have emphasised the connection between SP and the degeneration of specific anatomical pathways [23]. First, acetylcholinesterase rich neurites have been found in cortical SP and may represent the degeneration of axon terminals from neurons originating in the nucleus basalis of Meynert [77]. Second, the diffuse-type of SP are spatially correlated with clusters of neuronal cell bodies [3], the shape of the deposit often matching that of the dendritic fields of the cells. Third, large diffuse SP are observed in the parvopyramidal layer of the presubiculum at the site of the convergence of inputs from several cortical areas and may represent the degeneration of these neuronal pathways [2]. Fourth, neuronal mRNAs predominate within SP suggesting that the plaques form at the sites where neurons degenerate [33]. Fifth, chromogranin A, an antigenic determinant of dense-core synaptic vesicles, are incorporated into SP suggesting that synaptic disconnection is involved in plaque formation [1]. Finally, in a transgenic mouse model, the cortico-cortical fibres were significantly disorganised with the terminal fields of local and distant cortical areas containing swollen dystrophic neurites [25]. These results suggest that AD is a 'disconnection syndrome' resulting from the disruption of all afferent and efferent connections between the hippocampus and the rest of the brain [23]. The pathological process appears to proceed in a stepwise manner via the cortico-cortical pathways [62].

Discussion

This review examined three questions concerning the relationship of SP and NFT in AD: 1) the relationship between the lesions and dementia, 2) whether the SP and NFT were interrelated, and 3) the relationship of SP and NFT to disease pathogenesis. The literature supports the conclusion that the formation of SP and NFT is a reactive change that occurs in response to neuronal degeneration and is not closely related to the developing dementia. However, $A\beta_{42}$ is also neurotoxic, and once formed, is likely to initiate phases of secondary neurodegeneration. The evidence also suggests that NFT are a degenerative change within cell bodies in response to synaptic disconnection. Whether the formation of NFT is directly related to Aβ is particularly controversial. Although some transgenic and anatomical studies indicate a possible link, there is no established mechanism that links NFT directly to Aβ pathology. By contrast, much of the evidence suggests that SP and NFT pathology arise independently [10], but once formed, there could be synergistic reactions between Aβ and tau [29,63].

If SP and NFT are the products of neurodegeneration, then a number of further questions need to be considered. First, what is the role of gene expression in the pathogenesis of AD? The genes expressed in particular cells, such as APP, PS, and Apo E may not be the direct 'cause' of AD but could influence the molecular composition of a resulting lesion, and therefore, indirectly its level of toxicity and the extent of secondary degeneration. The uncertainty as to the significance of SP and NFT in AD raises the question as to the 'actual' cause of AD. Hence, alternative models have been proposed based on perturbation of vesicular trafficking at synapses, disruption of the cytoskeletal network, or the distribution of membrane cholesterol [27].

Second, what are the factors that determine the morphology and molecular composition of SP and NFT? The data suggest that the morphology of a lesion is the consequence of the neurodegeneration of specific anatomical structures, e.g., SP are a consequence of synaptic disconnection affecting cell bodies or axonal terminals while NFT result from changes within the perikaryon and processes of neurons [62]. Variations in the morphology of SP (Aβ deposit subtypes) may depend on brain area and/or the specific anatomical structures involved [8]. The ultimate molecular composition of a lesion may reflect a combination of factors, viz., the residue of gene mutation, post-translational processes, the process of cellular degeneration, and the reaction of the surrounding tissue to the degenerative process. Some of the constituents of brain lesions may also be acquired secondarily by surface diffusion.

Third, should the presence, distribution, and molecular determinants of SP and NFT continue to play a significant role in the pathological description and classification of AD and should these lesions be defining features of the disease? There are three problems that need to be considered. If SP/NFT are the products of brain degeneration then they may represent relatively late stages in the pathogenic cascade. Hence, there may be many cases of AD that are difficult to classify pathologically because they may have insufficient numbers of SP and NFT or possess early developmental stages of these pathologies. There is also a substantial overlap between the densities of SP and NFT in AD and normal elderly brain [6] that further complicates diagnosis. Furthermore, SP and NFT are observed in many other disorders [12] leading to disease overlap. Numerous examples of such cases have been reported, e.g., dementia with Lewy bodies (DLB) with associated AD pathology, Creutzfeldt-Jakob disease (CJD) with AD, Parkinson's disease (PkD) with AD, and these cases can be difficult to classify within the existing system [12]. These observations raise the question as to the status of AD as a nosological disorder and whether it should be redefined and if so, by what criteria [42,85].

Fourth, if the role of SP and NFT in the pathogenesis of AD is unclear, should significant effort continue to be devoted to immunotherapy and other treatments designed to remove Aβ from the brain? Such treatments could be beneficial in limiting the degree of secondary degeneration caused by Aβ deposition. Nevertheless, some studies suggest that Aβ deposition could be actually beneficial and promote neurogenesis [52], the Aβ having a range of protective functions [50]. In addition, excessive removal of Aβ could reduce chelation within the brain and result in enhanced oxidative stress [13].

In conclusion, the degree to which SP and NFT are a reflection of the primary pathological process occurring in AD remains controversial. The development of these lesions during the course of the disease may be due to a complex series of factors determined by host genotype, the anatomical pathways affected, and the degeneration of specific cell populations, and their abundance is only weakly related to the degree of dementia. In addition, there is no established mechanism that links Aβ and tau pathologies thus questioning one of the major tenets of the ACH. As a result, further research to establish the actual role of SP and NFT in the pathogenesis of AD is urgently needed.

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