Review

Alzheimer's disease is an inherent, natural part of human brain aging: an integrated perspective

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Abstract

Alzheimer disease is one of the most challenging demons in our society due to its very high prevalence and its clinical manifestations which cause deterioration of cognition, intelligence, and emotions – the very capacities that distinguish *Homo sapiens* from other animal species. Besides the personal, social, and economical costs, late stages of AD are vivid experiences for the family, relatives, friends, and general observers of the progressive ruin of an individual who turns into a being with lower mental and physical capacities than less evolved species. A human brain with healthy cognition, conscience, and emotions can succeed in dealing with most difficulties that life may pose. Without these capacities, the same person probably cannot. Due, in part, to this emotional impact, the absorbing study of AD has generated, over the years, a fascinating and complex story of theories, hypotheses, controversies, fashion swings, and passionate clashes, together with tremendous efforts and achievements geared to improve understanding of the pathogenesis and treatment of the disorder. Familal AD is rare and linked to altered genetic information associated with three genes. Sporadic AD (sAD) is much more common and multifactorial. A major point of clinical discussion has been, and still is, establishing the differences between brain aging and sAD. This is not a trivial question, as the neuropathological and molecular characteristics of normal brain aging and the first appearance of early stages of sAD-related pathology are not easily distinguishable in most individuals. Another important point is confidence in assigning responsibility for the beginning of sAD to a few triggering molecules, without considering the wide number of alterations that converge in the pathogenesis of aging and sAD. Genetic risk factors covering multiple molecular signals are increasing in number. In the same line, molecular pathways are altered at early stages of sAD pathology, currently grouped under the aegis of normal brain aging, only to increase massively at advanced stages of the process. Sporadic AD is here considered an inherent, natural part of human brain aging, which is prevalent in all humans, and variably present or not in a few individuals in other species. The progression of the process has devastating effects in a relatively low percentage of human beings eventually evolving to dementia. The continuum of brain aging and sAD implies the search for a different approach in the study of human brain aging at the first stages of the biological process, and advances in the use of new technologies aimed at slowing down the molecular defects underlying human brain aging and sAD at the outset, and transfering information and tasks to AI and coordinated devices.

Keywords: Alzheimer's disease, Human brain aging, Genetics, Epigenetics, New therapies

Index

Summary

This is a comprehensive historical and up-dated review on the pathogenesis of Alzheimer's disease (AD) in relation to intrinsic process of natural brain aging. The study covers, in addition to β-amyloid and tau pathology, alterations in multiple merging molecular pathways and sub-cellular structures underpinning brain aging and AD.

Familial AD (fAD) is rare and linked to altered genetic information associated with three genes. Sporadic AD (sAD) is much more common and multifactorial. A major point of clinical discussion has been, and remains, establishing the differences between brain aging and sAD. This is not a trivial question, as the neuropathological and molecular characteristics of normal brain aging and the first appearance of early stages of sAD-related pathology are not easily distinguishable in most individuals. Another important point is confidence in assigning responsibility for the beginning of sAD to a few triggering molecules, without considering the wide number of alterations that converge in the pathogenesis of aging and sAD. Recognized genetic risk factors covering multiple molecular signals are increasing in number. Molecular alterations of lipid rafts, protein synthesis from the nucleolus to the ribosome, protein phosphorylation, kinase activation, purine metabolism, epigenetic regulation of DNA and RNA, mitochondria and energy metabolism, inflammation, oxidative stress, cell-cycle re-entry, and cell death precede, in some regions (i.e., frontal cortex), abnormal tau deposition and amyloid plaques. Human brain aging and sAD do not follow a linear logic based on the assumption that a cause results in one or several effects; several separate alterations converge and potentiate each other to incorporate anomalies in additional pathways. Tau seeding and spreading are active intercellular and intracellular processes that explain, only in part, disease progression. Cell and region vulnerability are essential elements. Brain aging with neurofibrillary tangles (NFTs) restricted to the temporal lobe and selected nuclei of the brain stem, primary age-related tauopathy, preclinical AD, mild cognitive impairment (MCI) of Alzheimer type, typical AD, rapid progressive AD, and AD subtypes, are forms of sAD modulated by individual genetic and molecular factors. As in atherosclerosis, the progression of the process has devastating effects in a relatively low percentage of human beings. Future modulation of human brain aging and sAD will require the combined application of Artificial Intelligence, brain DNA editing, external electrical or wave-based signals to reduce energy consumption, and optimization of mitochondrial function, together with implantation of microdevices, to facilitate cooperative human-machine operation, pharmacological protection of lipid-protein interactions, high-throughput molecular technology, and resetting during sleep stages.

1. Introduction

The clinical and neuropathological characteristics and clinical correlates of Alzheimer disease (AD) have been described in several recent reviews (1-9). However, the study of AD has generated a fascinating and complex compendium of theories, hypotheses, controversies, fashion swings, and passionate clashes, together with tremendous efforts and achievements geared to improve understanding of the pathogenesis and treatment of the disorder. The present paper is a critical review of brain aging and AD that includes molecular abnormalities and early metabolic alterations beyond β-amyloid and tau pathology. These changes, together with genetic factors, converge in the pathogenesis of AD. Learning about early molecular modifications preceding by many years the appearance of clinical symptoms, when present, will serve to improve understanding of brain aging and the AD continuum.

Until the beginning of the last century, cognitive impairment and dementia were considered natural features of old age. Multiple brain infarcts were common in old people, and vascular dementia due to arteriopathy was thought to be the main cause of senile dementia. However, microscopic study of post-mortem brains stained with the dyes available at that time revealed the presence of certain structural anomalies in aged individuals. Paul Block and Georges Marinesco (10) described "amas ronds", and Emil Redlich (11) "miliare Sklerose" in the neuropil, interpreted at that time as nodules of glial sclerosis, which we now know as senile plaques (SPs). The introduction of the Max Bielschowsky silver method allowed visualisation of argyrophilic structures in neurons. Using this method, Alois Alzheimer described for the first time large numbers of argyr-

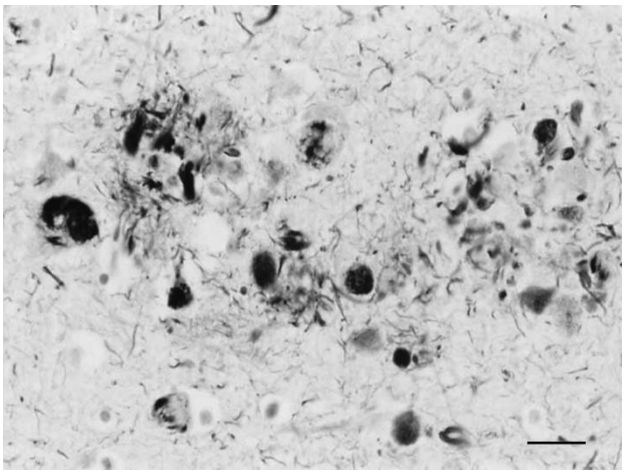

Figure 1: Dystrophic neurites of SPs and NFTs in the frontal cortex of a 76-year-old woman with dementia. Paraffin section, Gros-Bielschowsky silver method without counterstaining, black and white figure, bar = 25µm.

ophilic neurofibrillary tangles (NFTs) and aggregates of dystrophic neurites in the brain of a 51-year-old woman who had suffered from progressive dementia and hallucinations in the previous four and half years (12). Other cases were published shortly afterwards (13). The term Alzheimer's pre-senile dementia was introduced by Emil Kraepelin (14) to define the combination of pre-senile (before the age of 65) dementia in individuals with the morphological lesions described by Alzheimer. Oskar Fischer (15), using the same method, described the presence of 'Drusen' or 'drusige Nekrosen' in 16 cases of senile dementia characterized by loss of memory and sense of location, disorientation, and confabulation. Subsequent Fischer reports (16, 17) detailed the morphology of abnormal fibrils and abnormal neurites, and their stages of formation, in a large series of older individuals. The term ''senile plaque'' (SP) for these structures was proposed by Simchowitz (18). Fischer also described "drusige Entartung der Gefässe" which corresponds to amyloid angiopathy. Interestingly, Fischer also reported and illustrated the presence of NFTs in the same cases with dementia (19). Hundreds of articles appeared in the succeeding years. Alzheimer focused on NFTs as the main cause of dementia, whereas Fischer thought that SPs were the main substrate of dementia in older cases. Moreover, Alzheimer contemplated NFTs as aggregates of abnormal neurofibrils, while Fischer considered dystrophic neurites of SPs composed of abnormal neurofibrils, and NFTs a particular abnormality of nerve cells (19). Bielschowsky proposed a link between tangles and neuritic changes (20) (Figures 1 and 2). NFTs and SPs are now considered AD-related pathology or AD-neuropathologic change (ADNC) (https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf).

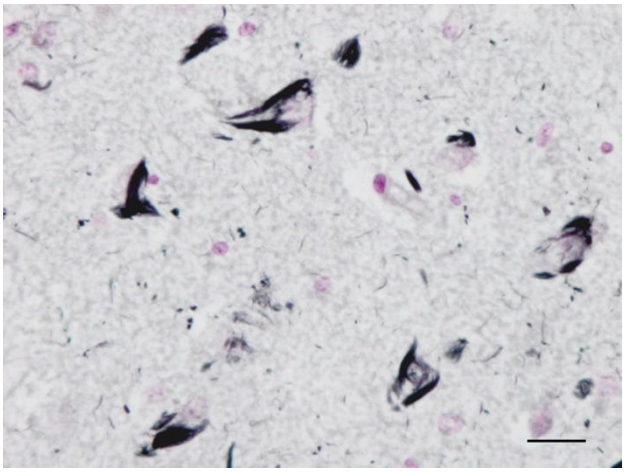

Figure 2: Neurofibrillary tangles in the CA1 region of the hippocampus of a man aged 69 years with no apparent cognitive impairment. Paraffin section, Gallyas staining, lightly counterstained with haemtoxylin, bar = 25µm.

The term Pick's disease (PiD) was coined in 1926 to distinguish AD from PiD primary frontotemporal degenerative atrophy (21). As late as the 1960s, AD and PiD were considered early dementias, whereas pure senile dementia, vascular dementias, and mixed (vascular and degenerative) were classified as dementias in old age (22). The frontiers between AD and pure senile dementia were not clear, as the onset of clinical symptoms in many cases classified as AD was after the age of sixty (23). It was not until the 1970s that Alzheimer's pre-senile dementia and senile dementia with changes of Alzheimer type were considered to be within the same spectrum (24-27). The inclusive term "Alzheimer-Fischer dementia" was never contemplated.

The first approach toward a clinical consensus on AD was made in 1984; clinical diagnosis of AD was set up in three categories – possible, probable, and definite (requiring neuropathological verification) (28). Definite AD was fixed as a neurodegenerative disease manifested by progressive dementia with a neuropathological substrate characterized by brain atrophy, neuronal death, and a particular distribution of abundant SPs and NFTs in the brain.

Box 1: Clinical classification of Alzheimer's disease (https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf).

Preclinical Alzheimer's disease

In this phase, individuals may have measurable brain changes that indicate the earliest signs of AD (biomarkers), but they have not yet developed symptoms such as memory loss.

Mild cognitive impairment due to Alzheimer's disease

People with MCI due to AD have biomarker evidence of Alzheimer's brain changes plus new but subtle symptoms such as problems with memory, language and thinking. These cognitive problems may be noticeable to the individual, family members and friends, but not to others, and they may not interfere with individuals' ability to carry out everyday activities.

Mild Alzheimer's dementia

In the mild stage of Alzheimer's dementia, most people are able to function independently in many areas but are likely to require assistance with some activities to maximize independence and remain safe. Handling money and paying bills may be especially challenging, and they may need more time to complete common daily tasks. They may still be able to drive, work and participate in their favorite activities.

Moderate Alzheimer's dementia

In the moderate stage of Alzheimer's dementia, which is often the longest stage, individuals experience more problems with memory and language, are more likely to become confused, and find it harder to complete multistep tasks such as bathing and dressing. They may become incontinent at times, and they may start having personality and behavioral changes, including suspiciousness and agitation. They may also begin to have problems recognizing loved ones.

Severe Alzheimer's dementia

In the severe stage of Alzheimer's dementia, individuals' ability to communicate verbally is greatly diminished, and they are likely to require around-the-clock care. Because of damage to areas of the brain involved in movement, individuals become bed-bound. Being bed-bound makes them vulnerable to physical complications including blood clots, skin infections and sepsis, which triggers body-wide inflammation that can result in organ failure. Damage to areas of the brain that control swallowing makes it difficult to eat and drink. Because of this, food particles may be deposited in the lungs and cause lung infection.

In contrast to AD dementia, well-tolerated progressive slower processing, memory loss particularly related to recent events, more trouble multitasking, slight cognitive decline, sleep disorder, emotional changes, slight or moderate depression, and bilateral brain activation for memory functions developing around the sixties are all consistent with "normal brain aging". Neuropathological alterations in normal old-aged individuals are NFTs in the hippocampus, entorhinal cortex, and inferior temporal cortex, and very rarely in the frontal neocortex; the distribution of SPs, if present, is more heterogeneous (29-35).

Clinical and neuropathological criteria to identify borderline cases between AD and cognitive impairment due to normal brain aging yielded only a

limited consensus (36, 37). A few years later, CERAD proposed a neuritic plaque score based on the number of plaques per mm^2 and the age of the individual to categorize AD in comparison to normal brain aging (38, 39).

Evidence of a clinical progression and postmortem neuropathological observations showing a concatenation of AD-related changes in old age and sAD (29-32, 40-43) prompted a clinical redefinition of AD at the beginning of the second decade of this century.

A crucial approach was the combination of clinical criteria, biochemical biomarkers in body fluids, and neuroimaging techniques to define the diagnosis of preclinical AD, mild cognitive impairment (MCI) due to AD, and AD (44-50).

More precise clinical definitions have been proposed to categorize different stages of AD (51). The classification shown in Box 1 is a summarized transcription of the Alzheimer's association report: 2022 Alzheimer's disease facts and figures (https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf).

The American Academy of Neurology estimates that MCI is present in about 8% of people age 65 to 69, in 15% of 75- to 79-year-olds, in 25% of those age 80 to 84, and in about 37% of people 85 years of age and older. About 7.5% will develop dementia in the first year after diagnosis of MCI; about 15% will develop dementia in the second year; about one third will develop dementia due to AD within five years (52, 53). The prevalence of dementia in 65-69-year-olds is approximately 0.01% of individuals; the prevalence of dementia doubles with increments of five years; thereby, between 25% and 50% of individuals over the age of 85 suffer from dementia (2). It is estimated that between 50% and 80% of cases with dementia have AD (2). Age, gender, race, living conditions, and genetic factors mark differences in the duration of preclinical and dementia stages in sAD (54, 55).

2. β-amyloid and Tau

Electron microscopic studies revealed that NFTs were composed of paired helical filaments (PHFs) that disrupted the architecture of the cytoskeleton. SPs were forged from a core of compact fibrils consistent with amyloids surrounded by dystrophic neurites filled with altered mitochondria, vesicles, numerous pleomorphic residual bodies, and PHFs (56-61) (Figure 3).

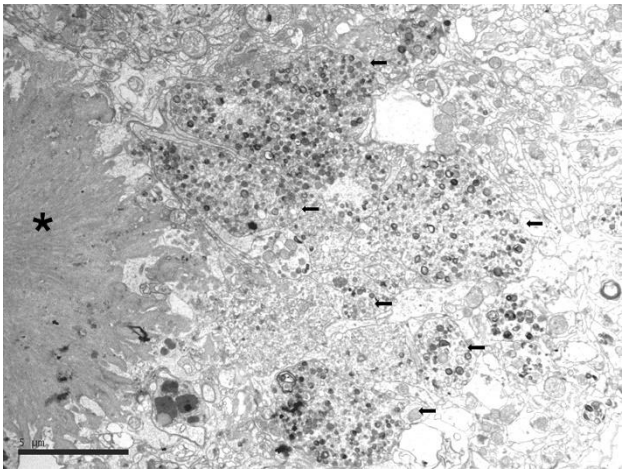

Figure 3: Electron microscopy of an SP showing the central core of amyloid fibrils (asterisk) and peripheral dystrophic neurites (black arrows) filled with vesicles, dense bodies, abnormal mitochondria, and paired helical filaments; bar = 5µm.

2a. β-amyloid (Aβ)

Subsequently, molecular studies identified β-amyloid as the main component of cerebral amyloid in β-amyloid angiopathy and SPs (62-66).

The amyloid precursor protein (APP) is a transmembrane protein which modulates brain cell adhesion, synaptic plasticity, and multiple intracellular signaling through the small endodomain of the molecule. APP processing is regulated by cytoplasmic phosphorylation (67). Cleavage of APP occurs through the combined action of α-, β-, and δ-secretases. β-secretase (BACE) is a GPI-anchored aspartyl protease (68). γ-secretase is a coprotein complex mainly composed of presenilin 1 (PSEN1) and presenilin 2 (PSEN2); components of the γ-secretase complex aph-1 homolog A; γ-secretase subunit (APH1A); APH1B; nicastrin (NCT/NCSTN); and presenilin enhancer γ-secretase subunit (PEN2/PSENEN), together with the modulators neprilysin (NEP/MME) and insulin-degrading enzyme (IDE). The γ-secretase complex is considered the "proteasome of the membrane" because of its capacity to act as a protelytic enzyme on more than 90 substrates (69-71). Cleavage of APP through α- and δ-secretase leads to the non-amyloidogenic pathway of APP degradation,

whereas the combined action of β- and δ-secretases generates small truncated C-teminal peptides at positions 42 ($A\beta_{1-42}$ or $A\beta_{42}$) or 40 ($A\beta_{1-40}$ or $A\beta_{40}$), depending on the thickness of the membrane, and many other small forms are amyloidogenic as well (72-75). Local cholesterol content affects the various secretase activities (76), including cholesterol derived from astrocytes (77).

Low physiological concentrations of Aβ seem necessary for long-term potentiation induction and for memory formation, probably acting on cAMP and cGMP (78). However, in aging and AD there is not only abnormal production of β-amyloid. Aβ is aggregated and accumulates in the extracellular space due to its hydrofobicity, facility for oligomerization, and transformation from an α-helix to a β-sheet conformation (66, 73, 74). Several enzymes can degrade β-amyloid such as neprilysin, plasmin, endothelin-converting enzymes, angiotensin-converting enzymes, insulin-degrading enzyme, several matrix proteinases, and cathepsins A and B (79, 80). Soluble Aβ is drained across the lymphatic wall, binding to low-density lipoprotein receptor-related protein (LRP-1). The expression levels of some of these enzymes and transporters are reduced in AD (81-85). Impaired lymphatic drainage and altered blood vessel walls impair the elimination of soluble β-amyloid via the circulatory system (86, 87) (see section 13).

Astrocytes followed by neurons are the main source of clusterin in brain; clusterin is then released to the extracellular space (88). Clusterin expression is increased in AD (87, 88), and co-localizes with β-amyloid deposits (91), more specifically with $A\beta_{1-40}$ (92). Clusterin may act as an extracellular chaperone (93) and it contributes to early stages of β-amyloid plaque pathology (94). In addition to being involved in Aβ aggregation and clearance and in the modulation of Aβ transport across the blood brain barrier (BBB) (95-97), clusterin is also known to reduce Aβ toxicity (98, 99). In addition, clusterin seems to interact with bridging integrator protein 1 (BIN1) and tau (100).

The main β-amyloid that circulates in brain interstitial fluid and cerebrospinal fluid (CSF) is soluble $A\beta_{40}$. β-amyloid deposits in AD are categorized as primitive or immature plaques, mature or neuritic plaques (classical SPs), compact or burned-out, cotton-wool plaques, diffuse plaques, subpial β-amyloid deposits, β-amyloid angiopathy, and perivascular plaques (dyshoric angiopathy) (Figure 4). β-amyloid can also be found in the cytoplasm of neurons, and in astrocytes at the periphery of SPs. β-amyloid is composed of a mixture of peptides of different molecular weight: $A\beta_{40}$ and $A\beta_{42}$ are predominant in SPs, while $A\beta_{40}$ is mainly located at the core of SPs and $A\beta_{42}$ at their periphery. Diffuse plaques contain $A\beta_{42}$ and truncated forms $A\beta_{17-42}$. Subpial β-amyloid deposits are mainly composed of amino-terminal truncated species. β-amyloid species have different aggregation properties. N-terminal truncated Aβ with pyroglutamate modification at position 3 and Aβ phosphorylated at serine 8 show enhanced aggregation into oligomers and fibrils. These forms appear at late stages (biochemical stages 2 and 3) of β-amyloid formation, whereas soluble and insoluble aggregates composed of non-modified Aβ are found at early stages (stage 1) (101, 102).

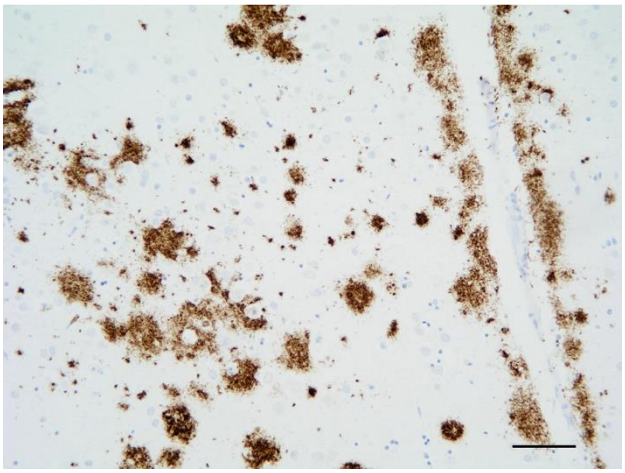

Figure 4: β-amyloid deposits in the temporal cortex. Paraffin section, β-amyloid immunohistochemistry, slight hematoxylin counterstaing, bar = 50µm.

Soluble β-amyloid oligomers (AβOs) and amyloid-β derived diffusible ligands (ADDLs), acting through specific cell surface receptors rather than fibrils, are toxic and cause neurodegeneration (103-115). High-molecular-weight β-amyloid oligomer levels are elevated in the CSF in AD (116). Yet in the cerebral tissue, the ratio of Aβ oligomer levels to plaque density distinguishes demented from non-demented patients (117).

Several membrane receptors can bind to Aβ oligomers. These receptors include the cellular prion

protein (PrP^C); the α7 nicotinic acetylcholine receptor (α7nAChR); Fcγ receptor II-b (FcγRIIb); the p75 neurotrophin receptor (p75NTR); the paired immunoglobulin-like receptor B (PirB); the PirB human orthologue receptor (LilrB2); the β-adrenergic receptors (β-ARs); and the Eph receptors (118), among others. PrP^C is one of the binding partners for Aβ oligomers (119-125), and PrP^C mediates impairment of synaptic plasticity by Aβ oligomers (124).

Besides β-amyloid species, several molecules are also components of SPs including metal ions, lipids, mucopolysaccharides, immunoglobulins, members of the complement system, molecules linked to lipid metabolism and lipid transport, blood coagulation/haemostasis factors, proteins linked to metabolism and molecular transport, neural, cell adhesion and extracellular matrix proteins, proteoglycans, and other cellular proteins (126, 127). The large amount of proteins in SPs is likely the consequence of co-aggregation and alteration of associated biochemical processes by which β-amyloid formation leads to neurodegeneration (127). Moreover, PrP^C co-localizes with Aβ in SPs (128).

β-amyloid plaques are associated with variable alteration of neuronal processes, reactive astrocytes, and microglia. Altered synaptic protein deposition with a granular pattern is found in diffuse plaques (129). Neurotransmitter-containing and peptidergic dystrophic neurites precede those containing paired helical filaments within SPs (130-132). Altered neuronal structure, accumulation of abnormal molecules, and abnormal organelles and debris are characteristic of dystrophic neurites of mature SPs (133, 135). In addition to synaptic proteins, components of dense-core vesicles accumulate in dystrophic neurites of SPs (129, 135-138). Immunohistochemical studies have shown that dystrophic neurites of SPs contain 3Rtau and 4Rtau; several phospho-tau species; MAP2-P; phosphorylated neurofilaments light; medium and heavy chains; and active kinases p38, SAPK/JNK, GSK3β, and CK1-δ, in addition to markers of the ubiquitin-proteasome system (UPS) and autophagy (139). Mitochondria are altered in dystrophic neurites of SPs with variable vulnerability of the mitochondrial complexes of the respiratory chain (140, 141).

Dystrophic neurites are likely derived from axons arising from diverse neuronal populations, as revealed by specific neuronal markers (130-132, 142-146) therefore indicating that neuronal vulnerability is not restricted to a single cellular population.

Pyramidal cells in the vicinity of SPs show distorted dendrites and loss of dendritic spines (147-149).

2b. Tau

The microtubule-associated protein tau, encoded by *MAPT*, participates in microtubule stability, cellular polarity, and anterograde and retrograde axonal transport of organelles and vesicles. In addition to microtubules and actin, tau interacts with a large number of proteins and lipids in the cytoplasm, cell membranes, and synapses, and with DNA and proteins involved in DNA protection, among many other substrates (150, 151). The various functions of tau require interaction with multiple partners (151-157).

The main constituent of NFTs dystrophic neurites of SPs and neuropil threads is abnormal tau (158-173) (Figures 5, 6, and 7). A combination of all six hyperphosphorylated brain tau isoforms (3Rtau and 4Rtau expressed in brain), generated from alternative tau splicing, is characteristic of AD tau (163, 174, 175). The amount of 3Rtau is similar to 4Rtau in the human adult brain and in AD. However, possible variations in the ratio of 3Rtau/4Rtau among cell types in the human brain have not been adequately assessed. Abnormal tau in AD includes several species resulting from hyper-phosphorylation at different sites, acetylation, glycosylation, altered confor mation, truncation at glutamic acid 391 and at aspartic acid 421 (mediated by caspase 3), oligomerization, and β-sheet-rich fibril aggregation, among others (171-173, 176-196). The site of tau phosphorylation and other post-translational modifications in tau have commonalities and differences among tauopathies (197, 198). Tau inclusions in glial cells are not found in AD, unless accompanied by other tau co-morbidities including aging-related tau astrogliopathy (ARTAG) and argyrophilic grain disease (AGD) which are 4Rtau-only tauopathies.

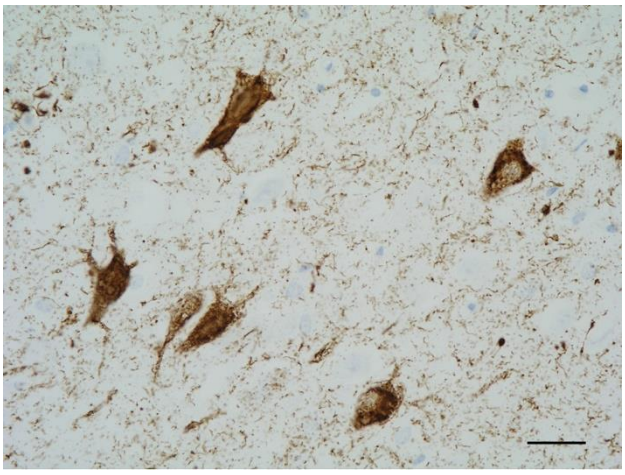

Figure 5: Neurofibrillary tangles in the CA1 region of the hippocampus. Paraffin section, AT8 immunohistochemistry, slight haematoxylin counterstaining, bar = 25µm.

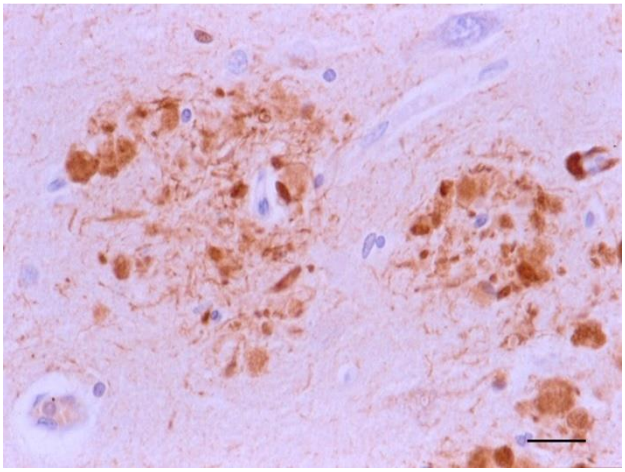

Figure 6: Dystrophic neurites of SPs in the entorhinal cortex containing hyper-phosphorylated tau. Paraffin section, AT8 immunohistochemistry, slight haematoxylin counterstaing, bar = 25µm

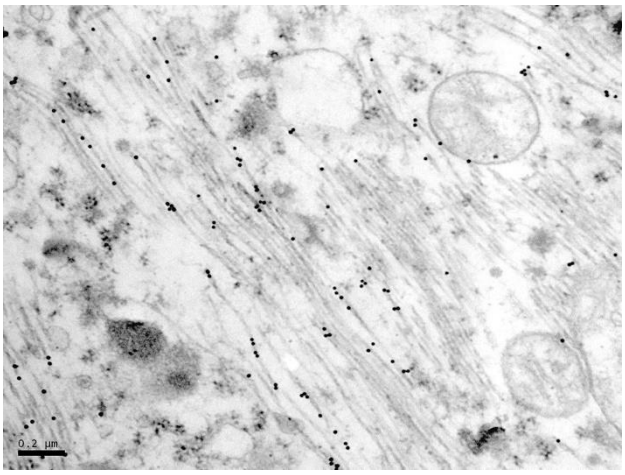

Figure 7: Immunoelectron microscopy showing phospho-tau deposits (black dots) in paired helical filaments. AT8 antibody, bar = 0.2µm.

Tau hyper-phosphorylation, the first step in NFT formation, is geared by the activation of specific kinases, and probably also by accompanying inhibition of phosphatases (171, 199). Several kinases are implicated in both the physiological and the pathological phosphorylation of tau, including glycogen synthase kinase 3β (GSK3β); cyclin-dependent kinase 5 (CDK5); protein kinase A (PKA); JUN N-terminal kinase (JNK); p38; and others (200). Co-localization of selected active kinases and tau deposits can be visualized in brain tissue (201-203). G-protein-coupled receptor (GPCR) kinases are also associated with NFTs and β-amyloid plaques in AD (204).

These alterations are cumulative but not homogeneous. More than one tau species may be present in a particular neuron. Furthermore, distinct defects may result depending on the type of accumulated tau, ranging from reversible dysfunction to irreversible disruption of the cytoskeleton, altered axonal transport, undermined cell signaling, synaptic dysfunction, and cell death. Tau-linked alterations can be the direct result of toxic species or the interactions of multiple partners (156). Soluble and insoluble tau oligomers, both phosphorylated and non-phosphorylated, may be involved in neurodegeneration (191, 205).

The association of tau with the plasma membrane is determined by its phosphorylation pattern. Tau associated with the plasma membrane can move to the cytosol upon tau hyper-phosphorlation (206, 207). The phosphorylation of tau also depends on phosphatidyl choline and phosphatidyl serine (208). Therefore, the composition of lipids at the membrane may modify the phosphorylation of tau and its capacity to shift its binding with actin and cytosolic proteins (209-211). Tau interactions with the membrane have several implications (155, 212). In addition to stabilizing membrane-cytosol interactions, tau is secreted associated to vesicles, or vesicle-free, key features in tau transmission (213-215).

Morphologically, abnormal neuronal tau deposits in AD are manifested as perinuclear tau deposits, granular cytoplasmic deposits, diffuse cytoplasmic deposits (all considered pre-tangle stages), neurofibrillary tangles (classical NFTs), ghost tangles (remains of NFTs in the neuropil), dystrophic neurites of SPs, and neuropil threads. The redistribution of abnormal tau from axons to the somatodendritic

compartment of neurons and dendritic spines is a characteristic consequence of tau pathology in AD and other tauopathies. PHFs induce tau accumulation into aggresomes that gather misfolded proteins when the protein degradation system is overloaded (216).

The structure of tau filaments in the different tauopathies largely depends on tau composition (3Rtau and 4Rtau) and on post-translational modifications including conformation and truncation, as revealed by transmission electron microscopy, and more recently by optimized cryo-electronmicroscopy and mass spectrometry (193, 217-222). The different structure of tau aggregates in tauopathies indicates the formation of different tau strains which are specific to each tauopathy (223). The accumulation rate of tau aggregates is greater in females and younger β-amyloid-positive subjects (224). Increased expression of 19 genes in chromosome X is associated with tau burden and slower cognitive decline in women but not in men, suggesting that specific X chromosome factors could confer risk or resilience in aging and AD (225).

In addition to abnormal tau, NFTs contain numerous proteins. Total tau interacts with a good number of proteins in AD (226, 227). Laser-capture micro-dissection of NFTs and liquid chromatography-/tandem mass spectrometry (LC-MS/MS) analysis in sAD followed by affinity purification mass spectrometry revealed that seventy-five proteins present in NFTs interacted with PHF1-immunoreactive phosphorylated tau (228). NFTs also contain markers of the sequestosome/p62, ubiquitin, and mutant ubiquitin (229, 230).

Increased PrP^{C} expression downregulates tau protein (231-234). Conversely, reduction or ablation of PrP^{C} levels induces an increase in tau 3Rtau/4Rtau balance through downregulation of GSK3β activity, thus indicating that PrP^{C} plays a role in tau exon 10 inclusion through the inhibitory capacity of GSK3β (235). Increased PrP^{C} levels at early and middle stages of NFT pathology yields lower tau and hosphor-tau. In contrast, PrP^{C} levels decrease at advanced stages of NFT pathology, which correlates with increased amounts of tau and hosphor-tau. Taken together, these observations suggest a protective role for PrP^{C} in early stages of AD (236). These observations linking an interaction of prion protein and tau may have implications in certain familial prion diseases grouped under the term Gerstmann-Sträussler-Scheinker disease, in which abundant PRP^{Res}-amyloid deposits are accompanied by extensive tau pathology (see section 3).

3. Familial AD (fAD; early-onset familial Alzheimer's disease: EOFAD), and the β-amyloid cascade hypothesis

From the early nineties, mutations in the genes *APP* (β-amyloid precursor protein), *PSEN1* (presenilin1), and *PSEN2* (presenilin2), all of them involved in the production of β-amyloid, have been identified in several families with pre-senile dementia of Alzheimer's type (early-onset familial Alzheimer disease: EOFAD, or fAD); increased APP dosage was also causative of AD and β-amyloid angiopathy (237-244). Recent genetic studies of the first Alzheimer's case identified that the patient carried a mutation in *PSEN1*. These groundbreaking discoveries led to the "β-amyloid cascade hypothesis", which supports the idea that the production of β-amyloid species is the primary factor triggering NFT formation and AD progression (245). The amyloid cascade hypothesis was further supported by the production of β-amyloid in transgenic mice bearing human mutations causative of AD. Yet mutations in these genes did not result in NFT formation in transgenic mice, although a few small hyper-phosphorylated tau deposits did appear in dystrophic neurites around β-amyloid plaques. At most, the joint production of SPs and tau deposits similar to NFTs in mice requires the cumulative expression of different mutated genes involved in human AD and tauopathies (246-248). However, *in vitro* and *in vivo* studies have shown the capacity of β-amyloid to phosphorylate tau and enhance tau aggregation, thus giving a boost to the β-amyloid cascade hypothesis (249). The β-amyloid cascade hypothesis fits with fAD linked to mutations of APP, *PSEN1*, and *PSEN2*.

Another genetic condition linked to increased risk of AD is Down syndrome. Middle-aged individuals (MA) with Down syndrome have neuropathological lesions of AD. Amyloid deposits may start as early as 12 years of age and they are universal by the age of 31. NFTs appear later in the entorhinal cortex, hippocampus, and neocortex (250-253).

The discovery of β-oligomers and cumulative evidence of their toxicity has led to modification of the "β-amyloid cascade" hypothesis, leading to the "amyloid-β oligomer hypothesis" (103-108). According to the new proposal, it is not the presence of fibrillar β-amyloid and deposition into definite aggregates, but rather soluble β-oligomers that are causative of cell damage and that trigger the process of neurodegeneration in AD (103-106, 254-257).

However, several points are still obscure. The level of insoluble Aβ rises with age and is further increased in AD whereas the total level of $A\beta_{40}$ in both soluble and insoluble fractions and the level of $A\beta_{42}$ in the soluble fraction decline with age before about 50 years. Differential production or retention of $A\beta_{40}$ and $A\beta_{42}$ likely contributes to the influence of age on the risk of sporadic AD, but the levels of soluble Aβ concentrations, higher in young adults than in older individuals and in subjects with AD, do not match the proposed toxic role of oligomers in AD (258, 259).

Tau deposits, other than those located in dystrophic neurites of SPs, are largely independent of β-amyloid. Other factors, including apolipoprotein E (ApoE), the endocytic system, cholesterol metabolism, and microglial activation, are regulators of tau pathology (260). Neurons derived from induced pluripotent stem cell (iPSC) lines from sAD and fAD linked to *PSEN1* mutations show increased phosphorylation of tau at different sites, increased levels of active GSK3β, and a significant upregulation of APP synthesis and APP carboxy-terminal fragment cleavage. However, significantly increased $A\beta_{1-42}/A\beta_{1-40}$ ratios are observed in fAD but not in sAD (261).

Other amyloids are the main constituents, in combination with NFTs, of different genetic neurodegenerative diseases causing dementia. Familial British dementia (FBD) and familial Danish dementia (FDD) are linked to specific mutations in the *BRI2* gene; the cleavage of Integral membrane protein 2B (BRI2) produces ABri and ADan amyloidogenic peptides, respectively. Amyloid plaques and amyloid angiopathy, and NFTs with a tau composition identical to AD tau, are found in both diseases (262, 263). Gerstmann-Sträussler-Scheinker disease (GSS) is linked to mutations in the prion protein gene (*PRNP*) that cause a prionopathy. Depending on the mutation, GSS is manifested pathologically by a combination of abundant prion-immunoreactive plaques surrounded by dystrophic neurites, together with numerous NFTs indistinguishable from AD-NFTs (264-266). Interestingly, APP, BRI2, and prion are proteins located at the cell membrane, and they interact with each other in normal conditions. The non-fibrillar, soluble BRI2-derived amyloids are also toxic, and probably play a central role in the pathogenesis of BRI2-linked dementias (267). The common structure of soluble amyloid oligomers suggests a common mechanism of pathogenesis (109, 113). Despite the differing genetic nature of these disorders, plaques and NFTs do not appear until middle age. Understanding of the mechanisms that control the metabolic pathways, that delay the beginning of the molecular and clinical manifestations of the disease for years, is a major challenge in neurodegenerative diseases linked to mutations in specific genes.

In contrast to mutations linked to β-amyloid production, mutations in *MAPT* are causative of familial tauopathy and are never associated with β-amyloid or other amyloid deposits (170, 171).

4. Sporadic AD (sAD; Late-onset Alzheimer disease: LOAD)

Most cases of AD (more than 95%) are sporadic (sAD) and occur in older individuals (late-onset Alzheimer's disease: LOAD). sAD has an insidious onset and a progressive course leading to death about 10-15 years after the first clinical symptoms of dementia. Aging is the main contributory factor. sAD is favoured by individual or combined low penetrating genetic factors, mainly allele ε4 of ApoE (268-271). Genome-wide association studies (GWAS) have identified other risk genes of sAD: LDL receptor related protein 1 (LRP1); low density lipoprotein protein receptor 1 (LDLR); interleukin 1a; clusterin (CLU); phosphatidylinositol binding clathrin assembly protein (PICALM); complement component (3b/4b) receptor 1 (CR1); bridging integrator 1 (*BIN1*), involved in synaptic vesicles and endocytosis; triggering receptor expressed on myeloid cells 2 (*TREM2*); sortilin-related receptor 1 (*SORL1*), involved in endocytosis and sorting; ADAM metallopeptidase domain 10 (*ADAM10*), involved in the cleavage of several proteins; ATP binding cassette

subfamily A member 7 (*ABCA7*); Spi-1 proto-oncogene (*SPI1*); paired immunoglobin like type 2 receptor alpha (*PILRA*); membrane-spanning 4-domains subfamily A (*MSA4*), linked to inflammation; CD2-associated protein (*CD2AP*) that regulates actin cytoskeleton; and ephrin receptor A1 (*EPHA1*), among others (272-288).

The regional and areal distribution of NFTs and SPs in the cerebral cortex is not homogeneous. In the hippocampal complex, NFTs predominate in the CA1 region and subiculum, the CA2, CA3 and hilus are less affected, and the dentate gyrus is spared in pure sAD cases. In the entorhinal cortex, NFTs are more abundant in layers II and V, whereas in the neocortex, NFTs predominate in layers III and V, with marked regional variations (the primary motor and sensory cortices have fewer NFTs than the association areas). NFTs are found more abundant in the temporal cortex, followed by the frontal and parietal cortex, and the occipital cortex. In subcortical regions, NFTs are localized in the basal nucleus of Meynert and nuclei of the basal forebrain, amygdala, hypothalamic nuclei, relay neurons within intralaminar and limbic thalamic nuclei, ventral tegmental area, raphe nuclei, locus ceruleus, and olfactory bulb. The cerebellar cortex is spared of NFT pathology. Cortical neurons with NFTs are mainly subpopulations of large pyramidal glutamatergic neurons (289-291). This is consistent with the observation that neurons with high content of neurofilaments are more susceptible to NFT formation (290-295).

GABAergic neurons are more resistant to NFT pathology, although the density of GABAergic neurons decreases and GABA-uptake is impaired in sAD (296-300) (see section 6 for details). Somatostain, which is expressed in a subpopulation of inhibitory neurons, and somatostatin receptors are also reduced in sAD (296, 301, 302).

Calcium-binding proteins parvalbumin (PV), calbindin D28K (CB) and caretinin (CR) are expressed in subpopulations of GABAergic neurons (303-305). PV-positive neuron numbers in the temporal, visual, and prefrontal cortex are preserved in AD (306-309), but PV-immunoreactive neurons are decreased in the entorhinal cortex and hippocampus in sAD (310-316). CB-immunoreactive neurons in the hippocampus, entorhinal cortex, and cortical layers V and VI are vulnerable, whereas CB-positive neurons in the occipital cortex and upper layers of the frontal cortex are resistant (309, 314, 314, 317). CR-positive neurons are not affected in the prefrontal, temporal, and visual cortices (309, 319, 320), but their number is reduced in the hippocampus and entorhinal cortex (314, 321). PV and somatostin, together with neuropeptide Y, cholecystokinin and substance P, are found in dystrophic neurites of SPs, thus evidencing the involvement of inhibitory and peptidergic neurons in SPs (130, 144).

Neuron loss is negligible in cognitively normal subjects, but the number of neurons decreases in the hippocampus and entorhinal cortex with NFT progression (322-324). The rate of this process is extremely variable among individuals.

A major achievement in improving our understanding of the progression of sAD pathology was the staging of NFTs and SPs in the post-mortem brain of large cohorts of non-demented and demented individuals covering a natural human population. In the telencephalon, the first NFTs appear in the entorhinal and transentorhinal cortex (stages I-II), followed by the hippocampus, temporal cortex, and other nuclei of limbic system (stages III-IV), and then continue on to most areas of the neocortex (stages V-VI). The spreading of NFTs is accompanied by a dramatic increase in the number of neurons with NFT pathology across stage progression (41, 325-327). About 85% of individuals aged 65 have NFT pathology, at least restricted to stages I-III (41, 325, 328, 329). All of them, excluding those having concomitant pathologies, are considered “cognitively normal for age” (330). Some individuals at stage IV-V suffer from moderate cognitive impairment; only about 5% have dementia. However, dementia of AD type accounts for about 25%-30% of the population at the age of 85 years, all of them categorized as NFT stages V-VI (331). Regional- and stage-dependent neuropathological alterations in sAD are accompanied by specified patterns of altered gene expression, that extend beyond the genes implicated in tau and β-amyloid pathology (332).

The Braak staging scheme does not rule out the occurrence of exceptions that do not fulfil the strict neuropathological criteria. These untypical cases are

considered AD subtypes: hippocampal sparing, limbic-predominant, and minimal atrophy sAD subtypes might account for about 25% of cases (333). In addition, several clinical sAD variants including non-amnestic, corticobasal syndromal, primary progressive aphasia, posterior cortical atrophy, behavioral/dysexecutive, and mild dementia variants have been categorized (334).

The olfactory bulb and tract, and several nuclei of the brain stem including the raphe nuclei and the locus coeruleus, are affected by NFT formation at the first stages of NFT pathology. The involvement of the olfactory bulb and tracts may contribute to the altered olfaction arising in sAD. Damage to selected nuclei of the brainstem, which are the origin of major serotoninergic and noradrenergic innervation of the entire brain, underlies a large series of clinical symptoms including impaired arousal, loss of attention and memory, impaired decision making, apathy, depression, anxiety, and altered reward processing, among others (335-340). Considered together, NFT generation and neuron loss largely depend on the specific cell and regional vulnerability of specific neuronal populations. Moreover, the simultaneous presence of NFT lesions in separate brain regions indicates that there is no single origin of NFT pathology that spreads through the brain, but rather various and cumulative original sources of tau pathology in the aging brain. Additionally, the rates of NFT progression, although variable from one individual to another, appear slowly at early NFT stages and progress rapidly at advanced stages of the disease (41).

The distribution of SPs differs from NFTs in the cerebral cortex in patients with sAD (341). Assessing the same series of cases for the study of NFT progression evidenced that the localization and distribution of SPs largely differ from NFT staging. The majority of individuals at NFT stages I-II and almost half of those at stage III do not have SPs or β-amyloid deposits (41, 342). Stages 0, A, B, C of Braak define the progression of SPs through the neocortex. The phases of Thal represent, from phase 1 to 6, the progressive and cumulative appearance of SPs from the neocortex, allocortex, diencephalic nuclei, striatum, and cholinergic nuclei of the basal forebrain, the brainstem, and the cerebellum (343).

The early appearance of tau pathology compared with the later appearance of β-amyloid plaques in a series of 2366 cases from children to centenarians has been recently revisited (344). Based on the results of these observations and many previous studies, the paper hypothesizes that tau pathology is an initiating factor in sAD (344).

Indeed, the lack of temporal and regional concordance between NFTs and SPs in sAD is intuitively barely consistent with the β-amyloid cascade hypothesis, unless non-identified soluble or other species of β-amyloid interact with neurons, thus triggering NFT pathology (345).

These comments do not mean that there is no interaction between the two proteins. Tauopathy fuelled by β-amyloid in a synergetic mechanism is well documented in AD (346-348).

The arguments between supporters of β-amyloid and of tau as the primal origin of sAD have consumed a great deal of effort, time, and financial investment (349). There is no doubt about the new acquisition of knowledge generated regarding sAD pathogenesis, but exclusive hypotheses have not produced the anticipated unequivocal results.

Cognitive impairment and dementia correlate with tau deposition and NFT pathology rather than with β-amyloid deposits and SPs (331, 350-358). Neuron loss occurs largely in parallel with tau pathology rather than with SPs in most regions (359). However, neuron degeneration and neuron loss are not restricted to neurons with NFTs (see section 10).

Recently, a classification of AD has been proposed: AD autosomal dominant (fAD), ApoEε4 sAD, and non-ApoEε4 sAD (360). This categorization is not new, but rather recovers and further emphasizes the well-known relative importance of β-amyloid deposition in the different AD categories depending on genetic factors involved in the production of β-amyloid.

5. NFTs and SPs in non-human brain aging

β-amyloid plaques and β-amyloid angiopathy may be found in old-aged animals in some species including non-human primates, monkeys, dolphins

and other cetaceans, dogs, cats, bears, and pinniped species, among others; deposits are usually diffuse whereas core plaques surrounded by tau-containing dystrophic neurites are exceptional (361-372).

Phosphorylated-tau deposits in neurons are rarely encountered in most mammals, and they usually have the characteristics of pre-tangles rather than NFTs, as in a few vulnerable aged mouse lemurs (362). Intracytoplasmic tau inclusions in neurons, astrocytes, and oligodendrocytes may occur in aged baboons (373, 374), aged gorillas (369), and chimpanzees (371). Tau accumulation in the brain of old sea lions, seals, and walruses forms argyrophilic fibrillar 3Rtau and 4Rtau aggregates in the neuronal somata and neurites, and olny few tau aggregates are found in oligodendrocytes and microglia (372). Importantly, these changes are linked to aging, but they are not the only expression of brain aging (375, 376).

Hyperphosphorylated tau accumulation in neurons, intraneuronal β-amyloid deposits, and diffuse amyloid plaques may occur in the brain of aged domestic cats (377, 378). The characteristics and distribution of tau lesions in a few cats are reminiscent of sAD including the deposition of 4Rtau and 3Rtau (379). A unique 4Rtauopathy without β-amyloid deposits mainly involving neurons of the neocortex but not the hippocampus, accompanied by widespread coiled bodies in the cerebral white matter, has been reported in aged domestic cats (380).

These observations show that β-amyloid deposition and tau pathology may occur with high species variability, in aged mammals, and, particularly, in non-human primates and pinnipeds. However, we do not have evidence at present on whether these species show changes in the same way as human beings. In aged cynomolgus monkeys, β-amyloid plaques combine with 4Rtau deposits in pre-tangle neurons and coiled bodies in glial cells with a regional pattern reminiscent of progressive supranuclear palsy (370). Therefore, the old hypothesis suggesting that sAD is a phylogenetic disease (381) has a relative relevance unless applied to the search for mechanisms modulating similarities and differences between non-humans and humans regarding the tremendous prevalence, widespread localization, particular regional distribution, and composition and structure of tau deposits in humans in comparison with other species.

6. Synapses

Synaptic alterations were described in the 1960s in the seminal electron microscopic studies of AD (382). These findings were followed by the observation of decreased numbers of dendritic spines on cortical neurons assessed with the Golgi method in post-mortem and biopsy samples at a time when cerebral biopsies were still considered appropriate tools for diagnosis of dementia (383-389). Synaptic loss is the major morphological correlate of cognitive impairment (390). For this reason, AD is considered as the consequence of a synaptic failure (391). Subsequent studies have refined synaptic alterations using different methods (392; 393), including the use of intraneuronal dyes in post-mortem tissues (394, 395).

The Golgi method also provided evidence of dendritic degeneration and dendritic sprouting and re-growth in several brain regions in AD (396-401). Dendritic sprouting is reinforced by the presence of growth-associated protein 43 (GAP-43), a marker of neuritic growth and sprouting around SPs (143, 402). Aberrant sprouting seems to be triggered by pre-amyloid species and neurotrophic factors (401). Aberrant sprouting involves neurites, dendrites, and synapses, and it affects distinct connections in AD (401). Cycles of aberrant synaptic sprouting and neurodegeneration are common in AD (403).

Spine loss occurs mainly in clusters linked to tau pathology (404, 405). Immunohistochemistry also reveals altered expression of synaptic markers not only around SPs but also in diffuse plaques, suggesting a close relationship between synapses and β-amyloid deposition (129, 406, 407). Abnormal pre- and post-synaptic tau and tau oligomers damage the synapses and produce altered synaptic function (150, 408, 409).

Double-labeling of neurons also shows a direct relationship between tau deposition and loss of dendritic spines on cortical pyramidal neurons in AD (404). Abnormal tau and β-amyloid oligomers act synergistically to disrupt synaptic function (409). However, synaptic loss also appears not to be dependent on fibrillar β-amyloid in a murine model of

β-amyloid deposition (149). Abnormal neuronal expression of APP and cytoskeletal proteins in early stages of the disease might be involved in the mechanisms of synaptic pathology in AD (410).

Synaptic proteins are important components associated with β-amyloid in SPs (127). It has recently been postulated that altered synapses are the origin of amyloid plaques in AD (411; see also section 2a). Both β-amyloid and abnormal tau are accumulated at the synapses (412-421). Recent neuroimaging studies further support the association of tau pathology, synaptic loss, and altered synaptic function (422). It has been proposed that synaptic tau pathology is an early event, and synaptic tau seeding precedes tau pathology in sAD (423). Other factors are also important such as cytoskeletal actin dysregulation (424), and oxidative stress lipid and protein damage (425). No less significant is the association between cell-cycle dysfunction and failure of synaptic plasticity in AD (426).

Synaptic alterations include abnormalities in the synaptic and postsynaptic delivery of neurotransmitters and neuromodulators, and the selective vulnerability and responses of their receptors (see section 7).

Finally, lipid and protein alterations at the cell membrane, and altered cytoskeletal proteins, may affect synaptic integrity and function (see sections 22c and 22h).

In addition, synapses are organelles with high energy consumption, and therefore they are vulnerable to deficits in energy production linked to mitochondrial failure (427) (see section 22d).

7. Neurotransmitters, neuromodulators, and related receptors

An early relevant biochemical observation was the discovery of the involvement of the Meynert nucleus in AD, the correlation of this involvement with the number of plaques and cognitive impairment, and the accompanying impairment of cholinergic innervation in the cerebral cortex (428-430). The "cholinergic hypothesis" stated that AD was a disorder of cholinergic innervations (430, 431). The enthusiasm for the cholinergic theory was supported by the prior discovery of dopamine deficiency in the substantia nigra pars compacta in Parkinson's disease, and the success of L-dopa treatment for this disorder which is still in use 50 years later (432). Cholinergic drugs were used although their benefits were clearly lower than initially expected.

Later, the glutamatergic theory stated that excitotoxicity resulting from excessive synaptic or extrasynaptic activation of N-methyl-D-aspartate (NMDA) subtype of ionotropic L-glutamate receptors might enhance vulnerability of neurons in AD (433, 434). The role of glutamate in the pathogenesis of AD was driven, in part, by the discovery of altered glutamate transport and increased excitotoxicity in amyotrophic lateral sclerosis (435), and the interest at that time in excitatory amino acid neurotoxicity in the pathogenesis of neurodegenerative diseases (436). Glutamate overload increases mitochondrial Ca2+ influx and oxidative stress and leads to mitochondrial dysfunction (437). However, NMDA receptor blockers may also have undesirable effects due to their double effects on cell death as well as cell survival and plasticity (438). Now, neuroprotective therapies aim to both enhance the effect of synaptic activity and disrupt extrasynaptic NMDAR-dependent death signaling (438).

Cholinergic and glutamatergic neurotransmitter alterations play a significant role in the pathogenesis of brain aging and sAD (439-442). Other neurotransmitters and receptors are involved as well.

The important point is that alterations are not homogeneous; they depend on the type of neurotransmitter, the cells of origin, and the kind of receptor; not all receptors of a given neurotransmitter are equally vulnerable to aging and sAD.

In addition to the neurotransmitters, neuromodulators, and receptors discussed below, general aspects of GPCR, amylin receptors, netrin receptors, and dopamine receptors in sAD are detailed in other reviews (443, 444). Endorphins, enkephalins, dynorphins, and endomorphins are endogenous opioid peptides that bind to opioid receptors. β-endorphin has opioid activity through μ-receptors, but α-endorphin and γ-endorphin lack affinity for opiate receptors. Endorphins interact with the γ- aminobutyric acid (GABA), which in turn modulates the release of dopamine. The expression of endogenous

opioids and receptors is altered in human brain aging and sAD (445-448).

Many olfactory and taste receptors and molecules involved downstream are expressed in the human brain (449). Their ligands and functions remain unknown, although both olfactory and taste receptors might contribute to intercellular and intracellular cell signaling. The expression of some olfactory receptors is altered in sAD and other neurodegenerative diseases (450).

7a. Acetylcholine (Ach) and acetylcholine receptors (AChR)

ACh is synthesized in neurons by choline acetyl transferase (ChAT). ACh acts upon nicotinic acetylcholine receptors (nAChRs) and muscarinic acetylcholine receptors (mAChRs). ACh is degraded by acetylcholinesterase (AChE). Nicotinic receptors are ionotropic ligand-gated receptors, and muscarinic receptors are GPCR (451). The nAChRs are arranged into homomeric or heteromeric subunits consisting of a diverse set of complex subtypes including α1-7, α9-10, β14, γ, δ, and ε. Allosteric modulation of nAChRs increases pre-synaptic ACh levels and enhances the cholinergic nicotinic neurotransmission. α7 and α4β2 nAChR mediate the presynaptic release of ACh. nAChRs are also expressed in astrocytes and microglia (452, 453).

Through its receptors TRkA and $p75^{NTR}$, the nerve growth factor (NGF) plays an essential role in the survival and maintenance of cholinergic neurons in the basal forebrain (454-457).

Loss of basal forebrain cholinergic neurons occurs at early stages of NFT pathology (428, 458, 459). Pretangle pathology within cholinergic nucleus basalis neurons coincides with local neurotrophic and neurotransmitter receptor gene dysregulation (460). Loss of cholinergic neurons in the basal forebrain leads to reduced ACh levels and ChAT upregulation (461). In addition, nAChRs, particularly α7nAChRs, are altered in sAD (462-465). Importantly, nicotine and nAChRs also participate in the regulation of Aβ. On the one hand, nicotine inhibits the formation of $Aβ_{1-42}$ fibrils and disrupts preformed Aβ fibrils (466). On the other hand, $Aβ_{1-42}$ binds to α7nAChR and inhibits the release of ACh (467). Finally, α7 nAChRs mediate Aβ-induced neurotoxicity (468, 469). and Aβ-induced tau phosphorylation (470).

α7nAChRs also participate in microglial activation (471). Astrocytic and microglial nAChRs modulate Aβ phagocytosis and degradation, Aβ-related oxidative stress, and neurotoxicity (472).

The metabotropic mAChRs are classified into five M1-M5 subtypes (473). M1, M3, and M5 receptors interact with the Gq/11 protein, stimulate phospholipase C (PLC), phosphatidylinositol trisphosphate (PI3P), and activate protein kinase C (PKC). M2 and M4 receptors interact with Go/i proteins, inhibit adenylyl cyclase (AC) and protein kinase A (PKA), and decrease cAMP levels (474-476). There are no changes in the number of mAChRs in sAD; however, the interaction of Gq/11 protein is altered in sAD compared with controls (477). M1 muscarinic agonists reduce β-amyloid and tau pathology, whereas M1 muscarinic antagonists or deletion of M1 subtype augment β-amyloid and tau pathology in *in vitro* and *in vivo* murine models of AD (478-480).

SPs have low levels of AChE, but the activity of AChE increases around β-amyloid plaques (481, 482). AChE inhibitors such as donepezil, galantamine, tacrine, and rivastigmine are administered at the initial stages of sAD.

7b. Glutamate and glutamate receptors (GluRs)

Glutamate is released from synaptic terminals and acts on post-synaptic ionotropic glutamate receptors (iGluRs). This mechanism mediates fast excitatory synaptic transmission. Glutamate can also act on metabotropic glutamate receptors (mGluRs). The mechanism modulates various effects by coupling to G proteins with subsequent recruitment of second messenger systems. There are three families of iGluRs: NMDA (N-methyl-D-aspartate receptor), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and KA (kainate) receptors: NMDAR, AMPAR, and KAR, respectively. NMDARs are composed of different subunits encoded by *GluN1* (NR1), *GluN2A* (NR2A), *GluN2B* (NR2B), *GluN2C* (NR2C), *GluN2D* (NR2D), *GluN3A* (NR3A), and *GluN3B* (NR3B). AMPARs are composed of combinations of GluA1 (GluR1), GluA2 (GluR2), GluA3 (GluR3) and GluA4 (GluR4); and KARs by GluK1 (GluR5), GluK2 (GluR6), GluK3 (GluR7), GluK4 (KA-1)

and GluK5 (KA-2). In NMDARs, the binding of glutamate and glycine is necessary to activate glutamate-gated ion channels. The removal of magnesium ions (Mg2+) block permits the entry of calcium ions (Ca2+) and synaptic signaling (483, 484).

Both iGluRs and mGluRs are also localized presynaptically acting as auto-receptors and hetero-receptors. This localization facilitates neurotransmission in the short term and depresses neurotransmission in the long term (485). GluRs are localized non-synaptically and are also expressed by astrocytes and oligodendrocytes (486).

Glutamate binding to NMDARs, AMPARs, and KARs is reduced in the aging brain and sAD mainly in the cerebral cortex and hippocampus. These changes are receptor-, region-, and layer-dependent, thus indicating variable vulnerability. Altered expression is likely dependent on several factors and not necessarily correlated with local NFTs and SPs, although loss of neurons and reduced neuronal connectivity may account, in part, for the decreased receptor expression (440). The localization of the receptors also plays a cardinal role. NMDARs containing GluN2A subunits are located at synaptic sites and are implicated in the protective pathways. In contrast, GluN2B subunits are located mainly at extra-synaptic sites, and they increase neuronal vulnerability. β-amyloid activates GluN2B-containing NMDARs (487-489). In addition, NMDARs are necessary for synaptic targeting of Aβ oligomers (490) and neuronal Aβ production (491). NMDAR alterations are implicated in synaptic dysfunction in sAD (492, 493). NMDARs also participate in redox-mediated synaptic function impairment in brain aging and sAD (494).

Memantine, an NMDAR antagonist, is currently used at the middle clinical stages of AD to reduce the hyperactivity of glutamate, resulting in transient and limited success.

AMPARs are consistently endocytosed. The increase in the rate of AMPA endocytosis induces long-term depression and synaptic degeneration (495). Soluble Aβ oligomers are involved in synaptic damage via the subunit GluA3 AMPAR (496). Aβ also induces AMPAR ubiquitination and degradation (497).

Glutamate abnormalities in aging and sAD are not restricted to alterations in glutamate production and its effects on synaptic receptors in neurons and glial cells. Furthermore, glutamate effects in normal and pathological conditions also depend on glutamate transport by specific neuronal and glial transporters (498).

Excitatory amino acid transporters (EAATs) reuptake glutamate from the synaptic cleft and extra-synaptic sites, and transfer glutamate to glial cells and neurons. Vesicular glutamate transporters (VGLUTs) move glutamate from the cell cytoplasm into synaptic vesicles. EAATs can also transport L-aspartate and D-aspartate. EAAT1 and EAAT2 (SLC1A3 and SLC1A2, respectively) are localized in astrocytes whereas EEAT3 (SLC1A1), EAAT4 (SLC1A6) and VGLUTs 1/2/3 (SLC17A7, SLC17A6, SLC17A8, respectively) are found in neurons. Loss of EAAT2 occurs in many neurodegenerative diseases, including sAD (see section 12a). Abnormal expression of VGLUTs and EAATs may contribute to neuronal excitotoxicity and neuron demise in sAD (499-501).

mGluRs are G-coupled proteins that act upon different effector systems, including PLC and AC. mGluRs are classified into three groups based on their pharmacological profiles, molecular properties, and transduction mechanisms. Group I receptors (mGluR1, mGluR5) are coupled to PLC activation through Gq/11 proteins, whereas groups II and III are coupled to AC inhibition through Gi/o proteins. mGluR1/5 are primarily excitatory, and mGluR2/3 and mGluR4/5/6,7/8 are inhibitory (502-505). mGluRs, determined by radioligand binding assays, and expression levels of mGluR1, detected by western blotting, are significantly decreased in the frontal cortex in sAD. This decrease is already observed at NFT stages I-II and III-IV not involving the frontal cortex, and further decrease with the appearance of NFTs in the frontal cortex with disease progression. The expression levels of phospholipase Cβ1 (PLCβ1) isoform, which is the effector of group I mGluRs, is decreased in parallel. PLCβ1 decrease, in turn, is associated with reduced GTP- and l-glutamate-stimulated PLC activity in sAD. These results show that group I mGluRs/PLC signaling is downregulated and desensitized in the frontal cortex at the first stages of NFT pathology, and that these modifications worsen with the progression of sAD (506).

7c. γ-aminobutyric acid (GABA) and GABA receptors

The inhibitory neurotransmitter GABA is generated by α-decarboxylation from L-glutamate in neurons by the action of glutamic acid decarboxylase (GAD). GABA is then incorporated into the synaptic vesicles by vesicular GABA transporter (VGAT). After release from synaptic vesicles, GABA binds to ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors. $GABA_A$ receptor activation opens chloride ion channels; $GABA_B$ acts through G proteins, reduces calcium ion channels, and inhibits AC and intracellular production of cAMP (507-510). $GABA_A$ receptors are composed of combinations of five different subunits, α1-α6, β1-β3, γ1-γ3, δ, ε, θ, π, and ρ1-ρ2. The most frequent pentamers are 2α:2β:1γ (507). $GABA_B$ receptors are heterodimers composed of R1 and R2 subunits (508). GABA at the synapses is picked up by astrocytes that catalyze it to glutamine, which is then transported into neurons and converted to glutamate (511, 512). The involvement of astrocytes in GABA metabolism has suggested a potential role of astrocytes in GABA gliotransmission (513).

Several studies have shown inconsistent results regarding total GABA levels in sAD but there is a trend toward stressing abnormal GABAergic function (514-516). Reduced GABA, glutamate, and glutamine levels are observed in individuals with MCI and AD as revealed by magnetic resonance spectroscopy (517-520).

Regarding GABA receptors, electrophysiological studies reveal a reduction in GABA currents in the temporal cortex in sAD. This is associated with mRNA downregulation of α1 and γ2 subunits and upregulation of α2, β1, and γ1 transcripts (521). α1 and α5 subunit protein-immunoreactive levels are decreased in the CA1 region of the hippocampus (521-524), whereas α3, β1, β2, β3, and γ2 subunits are unaffected. In contrast, α1 subunits are increased in the CA3 region, granule cell layer, and hilus of the dentate gyrus in sAD (523-527). β3 subunit expression is decreased in the stratum oriens, radiatum of CA2 and CA3, and stratum moleculare (527), whereas γ1/3 subunits are upregulated in the hippocampus in sAD (525, 527).

Aβ induces the downregulation of $GABA_A$ receptors, inhibitory dysfunction, and sprouting of GABAergic axons (528-532).

7d. Serotonin and 5-hydroxytryptamine (5-HT) receptors

5-Hydroxytryptamine (5-HT) derives from the amino acid tryptophan via the intermediate 5-hydroxytryptophan and decarboxylation to form serotonin. In the brain, 5-HT is mainly produced in the raphe nuclei of the brain stem that constitutes part of the reticular formation. Ascending serotoninergic fibres innervate the whole telencephalon. Descending projections innervate the cerebellum and the spinal cord (443). Serotonin is stored at the synaptic vesicles and released into the synapse, where it binds to post-synaptic and auto-pre-synaptic receptors. Serotonin is then re-uptaken via serotonin transporters and reused or degraded by monoamine oxidase. 5-HT receptors are categorized into metabotropic and ionotropic receptors. Metabotropic GPCR are 5-HT1, 5-HT2, 5-HT4, 5-HT5, 5-HT6, and 5-HT7. The only ionotropic receptor is 5-HT3, permeable to sodium, potassium, and calcium ions. 5-HT1 and 5-HT5 receptors bind to Gαi/o proteins, inhibit AC, and decrease cAMP levels. 5-HT2 receptors bind with Gαq/11, activate PLC, generate PI3P, and activate PKC (533-541).

5-HT and receptors interact with the cholinergic, glutamatergic, noradrenergic, GABAergic, endocannabinoid, and glial cell systems (542-545). Orexins regulate serotonin neurons in the raphe nucleus (546).

The serotoninergic system is altered in aging and sAD (443, 547-549). The main alteration of the serotoninergic system in brain aging and sAD results from neuronal damage and NFT formation in the raphe nuclei in the independent origin of NFT pathology at early stages of AD-related pathology. Damage to the serotoninergic system contributes to mood changes and depression which are characteristic non-cognitive clinical manifestations of brain aging and sAD (443, 550-553).

Serotonin is linked to decreased β-amyloid production and modulation of soluble β-amyloid precursor protein (sAPPβ) (554-557). In addition, 5-HT4

receptors inhibit the secretion of β-amyloid peptides (558-560).

Due to the multiple facets of serotonin, serotonin receptors, and their interaction with other neurotransmitters, agonists, antagonists of the different 5-HT receptors, and principally selective serotonin re-uptake inhibitors are useful pharmacological agents to improve cognition and reduce depression in aging and sAD (444, 552, 561-568).

7e. Noradrenergic system

Norepinephrine or noradrenaline is synthesized from dopamine by the enzyme dopamine β-hydroxylase (DBH). Norepinephrine is metabolized by mono-amino oxidase (MAO) and catechol-O-methyltransferase (COMT). Norepinephrine is transported from the cytosol to the synaptic vesicles by the vesicular monoamino transporter (VMAT) (569, 570). Norepinephrine can bind both to metabotropic pre- and post-synaptic α1, α2, β1, β2, and β3 receptors. α1 are G_q-coupled and activate PLC; α2 are coupled to Gi/G0 proteins and inhibit AC; β1, β2, and β3 are coupled to Gs proteins and activate AC (571-574).

The locus coeruleus, which contains about 15,000 neurons in primates, is the principal source of brain noradrenaline. Noradrenergic terminals innervate the hippocampus, amygdala, cerebral neocortex, and hypothalamus (575-577). Post-synaptic α1 receptors are excitatory, whereas perisomatic and pre-synaptic α2 receptors are inhibitory (578). Adrenergic receptors are widely distributed in the brain (579, 580). Neurons of the locus coeruleus excite the cerebral cortex principally through α1 receptor signaling (581, 582). The locus coeruleus-noradrenergic system has a major role in arousal, attention, and stress responses. In the brain, norepinephrine may also contribute to long-term synaptic plasticity, pain modulation, motor control, and energy homeostasis (583). Noradrenergic terminals are also in contact with glial cells and blood vessels (584-586). Due to these connections, noradrenergic innervations also modulate inflammation and cerebral blood flow (583, 587-589).

In addition, the noradrenergic system interacts with the cholinergic and GABAergic systems (576, 590-592). Moreover, the locus coeruleus and the raphe nuclei are interconnected (593, 594). Finally, orexin/hypocretin, histamine and noradrenaline converge in the dorsal raphe nucleus (593).

The locus coeruleus is damaged at early stages of AD-related pathology (443, 595-598) (see also section 4). At these first stages, NFTs accompany neuron loss, but SPs only appear in some cases at advanced Thal phases of β-amyloid deposition. In contrast to the massive loss of noradrenergic neurons, calbindin-immunoreactive neurons are preserved in the locus coeruleus even at advanced stages of NFT pathology (599). Early neuronal alterations in the locus coeruleus are accompanied by abnormalities in the ascending noradrenergic system (600-602). Increased α_{2A} adrenergic receptor protein occurs in the amygdala and hippocampus in parallel with early NFT pathology in the locus coeruleus (338). In contrast, reduced DBH activity is found in the post-mortem hippocampus and neocortex, probably as a compensatory mechanism to noradrenaline lessening (603, 604). DBH levels are also reduced in plasma at early stages of AD (605). Moreover, connectivity between norepinephrine and dopamine brainstem centers is disrupted in sAD (606).

The orexin system is compromised in sAD, thus contributing, in combination with the noradrenergic and serotonin decay, to altered sleep in sAD (607-611).

7f. Adenosine receptors

Adenosine is transported across the plasma membrane based on: a) its concentration gradients, and b) active Na^+-dependent transporters that carry adenosine against its concentration gradient.

Adenosine receptors are purinergic GPCR classified into A1, A2A, A2B, and A3 receptors. A1 and A3 receptors inhibit AC through Gi/o proteins, while A2A and A2B receptors stimulate AC through Gs proteins (612, 613). Adenosine receptors are present in subpopulations of neurons, astrocytes, oligodendrocytes, and microglia (614-616). Adenosine receptors modulate the release of glutamate, GABA, acetylcholine, noradrenaline, and serotonin (616-623).

Early autoradiographic studies showed decreased A1 expression in the hippocampus at advanced stages of sAD (624-627). However, A1 receptors accumulate in neurons with NFTs in sAD (628). More recent studies at first stages of NFT pathology have shown upregulation of adenosine receptors and sensitization of their specific signaling pathways preceding NFTs and SPs in the frontal cortex (629).

7g. Endocannabinoids and cannabinoid receptors (CBRs)

CBRs are classified as type 1 (CB1R) and type 2 (CB2R) (630). Anandamide (N-arachidonoyl ethanolamine, AEA) and 2-arachidonoyl glycerol (2-AG) are the main endogenous ligands of CBRs (631-634). Both endocannabinoids derive from arachidonic acid (AA). They are synthesized and metabolized by different pathways and induce specific biological functions. In the human brain, CB1Rs are mainly expressed in the limbic system. CB1Rs localize in the pre-synapses modulating glutamate and GABA neurotransmission (635-641). CB2Rs are expressed in microglia, and participate in inflammation and phagocytosis (642, 643). Low levels of CB2R expression have also been identified in some neurons (644-646).

Cannabinoid compounds may also bind to other receptors, such as GPR55, peroxisome proliferator-activated receptors PPARα and PPARγ, and transient receptor potential vannilloid-1 channels (647, 648). The study of expression of CB1Rs and mediators in sAD has yielded variable results (649). In contrast, increased CB2R expression in microglia surrounding SPs is consistently documented (650, 651). A few studies have shown altered expression levels of endocannabinoids and enzymes linked to their metabolism in sAD (652-654). Therefore, the endocannabinoid system plays a role in sAD although its precise contribution remains largely unknown. Treatment with exogenous cannabinoids and modulation of CBRs in murine models of AD has shown beneficial effects including reduction of β-amyloid plaques and β-amyloid burden, reduced tau phosphorylation, reduced inflammation, excitoxicity, mitochondrial dysfunction, and oxidative stress, and relief of cognitive impairment (649).

8. Trophic factors and receptors

The expression of trophic factors, particularly brain-derived neutrophic factor (BDNF) and nerve growth factor (NGF) and their receptors, is altered in sAD (655-659).

BDNF mRNA and protein are decreased in the frontal cortex and hippocampus in AD (660-662). BDNF immunoreactivity is reduced in tangle-bearing and non-tangle-bearing neurons, whereas immunoreactivity to full-length TrkB (the high affinity receptor for BDNF, neurotrophin-3 and neurotrophin-4) is reduced in tangle-bearing neurons. Strong BDNF immunoreactivity is observed in dystrophic neurites surrounding SPs, and strong TrkB in reactive glial cells, including those surrounding SPs. Truncated TrkB immunoreactivity occurs in individual neurons and reactive glial cells in the cerebral cortex and white matter in sAD (661). The cause of abnormal TrkB immunoreactivity in sAD is not known but β-amyloid modulates TrkB alternative transcript expression (663). ProBDNF is increased in sAD, and it is modified by reactive oxygen species (ROS)-derived advanced glycation end products, which prevent the processing of proBDNF to mature BDNF (664). Abnormal proBDNF/BDNF signaling impairs axonal transport, decreases trophic effects, and increases pathogenicity and cell death (661, 664, 665).

In contrast, the expression of NGF is increased in sAD (655, 666), but NGF-containing neurons in the basal forebrain are lost in sAD (454, 667). ProNGF is also increased in sAD (668, 669). This has relevant implications as proNGF induces processing and nuclear translocation of the intracellular domain of $p75^{NTR}$ (the low affinity neurotrophin receptor for NGF, BDNF, neurotrophin 3, and neurotrophin 4) and induces cell death in association with cofactor sortilin, a member of the Vps10p sorting receptor family (670-672).

9. Endoplasmic reticulum stress

The accumulation of abnormally misfolded proteins in the endoplasmic reticulum (ER) causes ER stress which is manifested by activation of one or more of the three signaling pathways of the misfolded protein response (UPR) (673). Glucose-related protein 78 (GRP78/BiP) is the master protein

that regulates the UPR (674). The cytosolic domains of the transmembrane ER proteins PKR-like endoplasmic reticulum kinase (PERK), inositol-requiring protein 1 (IRE1), and activating transcription factor (ATF)-6, trigger specific pathways once activated. PERK activates ATF-4, and the activation of ATF6 involves its displacement from the ER to the Golgi apparatus to be cleaved into ATF6c. IRE1 dimers phosphorylate and lead to the production of X-box binding protein 1 (XBP-1) which increases the ER capacity of protein folding and the degradation of abnormally folded proteins in the ER, thus reducing ER stress. IRE1 may also bind to the TRAF2 (TNF receptor-associated factor 2) adaptor molecule and activate the apoptosis signal-regulating kinase 1 (ASK1), which in turn causes the phosphorylation of c-Jun N-terminal kinase (JNK), thereby triggering cell death. ATF-4, truncated ATF6, and XBP-1, through downstream target genes, modulate ER homeostasis or apoptosis, depending on the saturation of the system (673, 675). The expression of several UPR components is altered in aging and sAD (676-679). ER stress also generates ROS which, together with mitochondrial ROS, is a major cause of oxidative stress damage. Mitochondrial dysfunction and ER stress are relevant promoters of apoptosis in sAD (680). ER stress is also linked to brain inflammation (681, 682). Moreover, β-amyloid may activate the UPR, either mediated by glutamate receptors and calcium uptake, or linked to mitochondrial dysfunction and ROS production; ER stress may also be induced by abnormal tau (683-685). Moreover, PERK, IRE1 and ATF6 signaling pathways activate autophagy (686-688).

10. Failure to remove debris: the ubiquitin-proteasome system (UPS) and autophagy in sAD

Autophagy and UPS are the two main mechanisms of intracellular protein degradation. There is a certain relationship between these two mechanisms, and there are some molecules in common that initiate compensatory effects to prevent disease progression (689, 690).

Autophagy includes macroautophagy, microautophagy, and chaperone-mediated autophagy (691). Microautophagy and chaperone-mediated autophagy involve lysosomal membrane invagination and chaperon recognition (692). Macroautophagy is mediated by autophagosome protein assembly of Beclin 1-Vps34 lipid kinase, Atg9-WIPI-1, Atg12 conjugation system, microtubule-associated protein light chain 3 (LC3), and Unc-51-like autophagy activating kinase 1 protein kinase. Lysosomal-associated membrane protein 1 (LAMP-1) is a transmembrane glycoprotein enriched in the membrane of lysosomes (693-695). Material digested by autophagy is incorporated into lysosomes.

Autophagy is impaired in brain aging and sAD (696-706). Altered macroautophagy in sAD is manifested in dystrophic neurites of SPs, in which mitochondria, dense bodies, and vesicles are common targets, and in synapses and granulovacuolar degeneration (see section 11). Autophagy is also involved in β-amyloid metabolism and clearance (707).

UPS activity is initiated by the conjugation of ubiquitin to the substrate following a three-step cascade to tag the protein into the proteasome. The 20S proteasome is a hetero-oligomer formed by heptameric rings organized into a structure resembling a hollow cylinder which has three main peptidase activities: chymotrypsin-like, trypsin-like, and peptidylglutamyl peptide hydrolyzing activities. The 20S proteasome can associate, in the presence of ATP, with two caps or 19S complexes, thereby forming the 26S proteasome complex. The 19S complex serves in the recognition of ubiquitylated proteins, protein unfolding, and translocation of the unfolded polypeptide to the inner chambers of the 20S proteasome for hydrolysis. The 20S proteasome can interact with other complexes. The PA28α/β activator (11S regulator) can also bind to 20S proteasome to form the PA28-proteasome complex. Additionally, the three catalytic β subunits of the 20S proteasome in response to γ-interferon are replaced by inducible homologous proteins LMP2, LMP7, and MECL1, forming the immunoproteasome (689). The immunoproteasome has a role in peptide production for antigen presentation by the major histocompatibility complex in most settings, but it is also involved in the clearance of oxidatively damaged proteins (708).

The UPS is altered in brain aging and AD (709-712). Impaired removal of altered proteins is manifested by the deposition of hyper-phospohorylated,

abnormally conformed, and truncated ubiquitinated tau species resistant to UPS degradation in NFTs, dystrophic neurites, and threads (197). In addition to ubiquitin, mutant ubiquitin is expressed in the aging brain and at early stages of sAD, whereas misframed ubiquitin contributes to the blockade of the proteasome by NFTs and other tau inclusions (229, 230, 713-716). Yet, mutant ubiquitin reduces Aβ plaque formation (717, 718).

The immunoproteasome is activated in AD and APP/PS1 double-transgenic mice (719-721). The reasons for immunoproteasome activation are not fully understood, but the presence of advanced glycation end products (AGEs) appears to induce activation of the immunoproteasome; the inhibition of AGE receptor (RAGE), and the downstream signalling Jak2 (Janus kinase 2)/STAT1 (signal transducer and activator of transcription 1) abolishes AGE-induced activation of the immunoproteasome (722).

11. Granulovacuolar degeneration (GVD)

GVD is characterized by the presence of vacuolar cytoplasmic lesions with a dense central core, mainly in CA1 hippocampal neurons (18). GVD is common in the hippocampus in the aging human brain and present in the majority, if not all cases, of sAD (Figure 8). GVD first appears in neurons of the hippocampal subfields CA1 and CA2, and the subiculum; this is followed by the entorhinal cortex, and CA4 neurons in stage 2, temporal neocortex in stage 3, amygdala and/or the hypothalamus in stage 4, and cingulate, frontal, and parietal cortices in stage 5 (723). GVD appears in relation to hippocampal phosphorylated tau accumulation in various neurodegenerative disorders, particularly AD (724). The most widely accepted model of AGD generation follows the scheme: abnormal tau in pretangles induces abnormal reticulum stress responses, which in turn trigger endocytic and autophagic pathways in the face of impaired proteolysis and altered function of the UPS. This scenario is consistent with the idea that GVD is the final stage of an active process linked to failed degradation of abnormal protein aggregates in the cytoplasm of a subpopulation of neurons (677, 725-727). Immunohistochemistry to

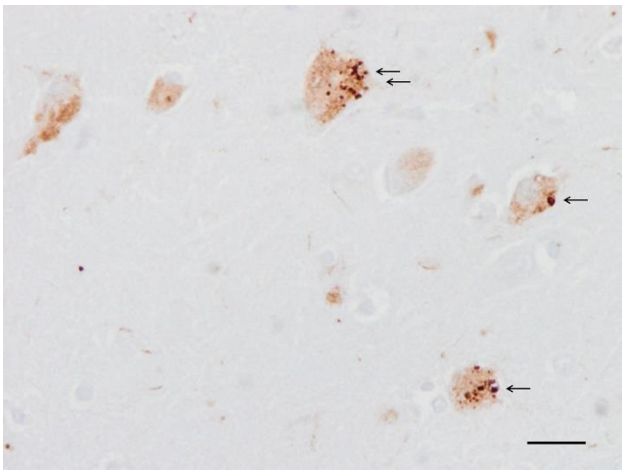

Figure 8: Granulovacuolar degeneration (black arrows) in neurons of the hippocampus. Paraffin section, p38-P immunohistochemistry, slight haematoxylin counterstaining, bar = 25 µm.

casein kinase 1δ (CK1-δ) and AT8 and laser microdissection have identified the proteomes of neurons containing GVD and NFTs, respectively, using label-free LC-MS/MS (728). A significant change in the abundance of 115 proteins in GVD-containing neurons and 197 in NFT-containing neurons was observed compared to control neurons (728). Differences in protein composition between NFTs and neurons with GVD are further supported by the demonstration of different activation of kinases and different profiles of phosphorylated proteins (139). Nonetheless, the same study of phosphoprotein expression showed that abnormal phosphorylation of various substrates is common at the first stages of NFT and GVD generation (139). These observations suggest that GVD is not restricted to tau pathology but rather involves a varied number of proteins. Since GVD is common in the older human population, it is not surprising to find a correlation between GVD pathology and cognitive impairment. However, when analysis is controlled for other associated neuropathologies, the associations between GVD and dementia lose significance (729).

12. Glial alterations in aging and sAD

Glial cells are altered in aging and sAD. Changes in glial cells have multiple facets, including cell senescence, astrocytic gliosis, microgliosis, activated inflammatory responses, and calcium homeostasis, among others. Astrocytes are key players in AD

modulating β-amyloid turnover, calcium homeosthasis, tripartite synaptic function, neuroinflammation, oxidative stress responses, and BBB dysfunction (730-734). Microglia and astrocytes, together with neurons and blood vessels, participate in the process of activation of inflammatory responses in aging and sAD (735-737). Moreover, microglia have the capacity to transform a subset of reactive astrocytes through the combination of IL-1α, TNF, and C1q (738). Both microglia and astrocytes are key participants in neuroinflammation in AD (739).

12a. Astrocytes

Astrocytes are key elements in the maintenance of the central nervous system (CNS) due to their role in brain homeostasis at all levels of organization from molecular to the whole organ (740). Astrocytes express neurotransmitter receptors, pumps, and transporters at their plasmalemma, along with transporters in the endoplasmic reticulum and mitochondria that regulate the cytosolic levels of ions which underlie most, if not all, astroglial homeostatic functions (741).

With aging, astrocytes show accumulation of lipofuscin, hypertrophy of cytoplasmic filaments, increased expression of glial fibrillary acidic protein (GFAP), S100β and vimentin, and modifications in morphology and number (742-744). Senescent astrocytes also exhibit senescence-associated secretory phenotype manifested by increased production of pro-inflammatory cytokines together with oxidative damage and increased superoxide production (745). Perivascular astrocyte senescence leads to altered BBB (746,747). This is accompanied by reduced expression of efflux transporter and increased expression of influx transporter receptors for AGEs. Abnormal transport of proteins through blood vessels affects the transfer of β-amyloid, leading to its accumulation in blood vessels (748, 749). Water aquaporin 1 (AQP1) expression in astrocytes is also altered in the frontal cortex at NFT stages I-II, suggesting early impairment of water transport linked to AD-related pathology (750). AQP4 expression is altered with aging and sAD; loss of AQP4 is associated with increased levels of β-amyloid and tau, suggesting that loss of AQP4 impairs the BBB and the gliolymphatic barrier (751).

Astrogliosis and astrocyte atrophy are relatively early events in AD (752-756). Reduced branching and reduced connexin 43 expression occur in sAD (757) which may compromise the extent of coverage domain and synaptic function in neighboring neurons (758). β-amyloid peptides also induce mitochondrial dysfunction and oxidative stress in astrocytes (759). Transcriptomics of laser-captured microdissection using GFAP as a marker revealed marked dysregulation of insulin, phosphatidylinositol 3-kinase (PI3K)/Akt, and mitogen-activated protein kinase (MAPK) signaling pathways at advanced Braak stages of the disease; minor and different abnormalities were observed at earlier stages, indicating different responses of astrocytes along disease progression (760). Recent transcriptomic studies in sAD have shown upregulation of genes related to perisynaptic astrocytic processes and downregulation of genes encoding endolysosomal and mitochondrial proteins; downregulation of astrocytic mitochondrial genes inversely correlates with the disease stages defined by Braak and CERAD scoring (761).

Reactive astrocytes are found mainly around Aβ deposits in SPs and blood vessels (752, 762, 763) and in areas without plaques then distributed in a layered pattern (762, 764). In response to vascular β-amyloid deposition, astrocytes produce cytokines, metabolizing enzymes, and ROS which in turn contribute to altered BBB and perivascular astrocytic function (765-769). Reactive astrocytes may contain Aβ (770-772) and N-terminal truncated β-amyloid (773), and they have the capacity to internalize and degrade β-amyloid fibrils (774). Activation of metalloproteinases (765, 775) and lysosomal degradation (776, 777) are the main complementary mechanisms by which astrocytes degrade β-amyloid. In addition, BACE may be expressed in astrocytes under appropriate conditions, facilitating the generation of β-amyloid in these cells (752, 778). Acquisition of a pro-inflammatory profile along with activation of the β-amyloidogenic pathway further potentiates toxicity of a subpopulation of astrocytes in AD (779). Curiously, β-amyloid seems to impair the phagocytosis of dystrophic synapses by astrocytes (780).

Astrocytes bearing β-amyloid show abnormal calcium homeostasis (758, 759, 781-783). In addi-

tion, β-amyloid-induced glutamate release by astrocytes may contribute to neuronal excitatory damage (784). De-regulation of specific metabotropic glutamate receptors in astroglia is also a putative harmful effect of β-amyloid (785).

NMDARs are expressed in a sub-population of astrocytes in the cortex and spinal cord. These receptors are composed of two GluN1, one GluN2C or D, and one GluN3 subunits. This composition makes astroglial NMDARs operational, modulating resting membrane potential (786).

EAAT2 clears excess extracellular glutamate from the synaptic cleft and extrasynaptic sites via glutamate re-uptake by glial cells and neurons to prevent neuronal hyperexcitability and excitotoxicity. Oxidative damage, splice variants, and altered solubility of EAAT2 may lead to functional alterations of glutamate transporters in AD (787-789). Moreover, EAAT2 expression is reduced with disease progression in parallel with increased GFAP expression in sAD (762, 790, 791). Furthermore, astrocytes surrounding SPs show altered immunoproteasome markers, and augmented expression of cytokines and mediators of the immune response (721, 735, 792, 793). Reactive astrocytes in sAD also have higher levels of complement component C3 which is required for both classical and alternative complement activation pathways (794).

Changes in the morphology of astrocytes are accompanied by alterations in the regulation and expression of GFAP and other astrocyte markers in cases with MCI and in pre-clinical AD (791, 795-797). These changes are preceded by expression of various cytokines and components of the inflammatory response (793, 798). Astrocytic responses are not homogeneous but rather variable, even in the same region (799-801). As for M1 and M2 suggested phenotypes for microglia (see section 12b), A1 and A2 astrocyte phenotypes have been proposed depending on their transcriptional profiles: A1 are neurotoxic and A2 neuroprotective (738, 802). However, this categorization is difficult to apply in the context of sAD (801-803).

Glucose hypometabolism is a characteristic metabolic feature associated with cognitive impairment in AD (804-807). Furthermore, neurons utilize lactate as a source of energy, and astrocytes are the main local source of neuronal lactate (808-811). Lactate levels are reduced in the brain of AD transgenic murine models (812). In the brain, the local source of ketone bodies results from fatty acid oxidation in astrocytes (813). In addition, astrocytes can produce ketones from amino acids (814). Considering that about 20% of cerebral ATP is generated from fatty acids (815), it may be inferred that impaired energy metabolism in astrocytes negatively impacts on neuronal energy metabolism, including maintenance of the energy requirements of the synapses (803, 816-818).

12b. Microglia

Microglial cells are multifunctional cells that respond to different stimuli leading to either beneficial or harmful effects depending on the production of specific molecules. Several studies have dealt with a proposed polarization of microglia into two types. M1 phenotype is stimulated by interferon-γ (IFN-γ) for the expression of pro-inflammatory cytokines, and M2 phenotype by IL-4/IL-13 for resolution of inflammation and tissue repair (819). However, the division between M1 and M2 microglial phenotypes with opposing effects in pathological conditions is probably a simplification, as complex microglial responses occur in the same setting, particularly in AD (820, 821). The term neuroinflammation, although widely used, sheds little light on the molecular consequences of microglial (and astrocytic) responses in any particular setting (822-824).

Microglia are modified in aging and AD (825-828). Dystrophic (senescent) microglia precede activated microglia in aging and sAD (826). Increased numbers of activated microglial cells occur in parallel with the production of β-amyloid and tau pathology (829). Microglial cells are found associated with SPs in contact with dystrophic neurites and internal to reactive astrocytes (7). Diffuse microgliosis involving the cerebral cortex and subcortical white matter occurs as well.

Microglial activation in AD is associated with upregulation of a large number of cytokines, chemokines, members of the complement system, and other mediators of the immune system (736, 830-837). Importantly, the inflammatory response is not homogeneous but is largely region and stage dependent (838). Inflammatory responses also occur

in transgenic mouse models of AD with specific region and stage profiles. Yet, the regulation of different components of brain inflammation and the immune system differ in transgenic mice when compared with sAD (838, 839). This is an important point, as inflammatory responses vary in different regions with disease progression; protective and deleterious microglia-associated effects may occur simultaneously in any individual at any stage of the disease.

Another relevant point is the role of lipids in activated microglia; increased expression of ApoE, triggering receptor expressed on myeloid cells 2 (TREM2), and lipoprotein lipase (LP2), is found in activated microglia (840).

A link between β-amyloid and microglia is well documented (829, 841, 842). A cell surface receptor complex for fibrillary-amyloid mediates microglial activation (843). Microglia, in turn, mediates the clearance of soluble Aβ through fluid phase macropinocytosis (844). Microglia-mediated synapsis loss in AD is enhanced by fibrillar Aβ and oligomeric Aβ aggregation onto neuronal post-synaptic terminals, complement deposition, C3 receptor (CD11b/CD18) activation, microglial activation, and synapsis phagocytosis (821, 845-849).

Microglia activation also correlates with tau pathology and NFT staging (829, 850-852). Positron emission tomography (PET)-based studies have also shown a correlation between tau pathology progression and microglial activation across Braak stages (853, 854). Abnormal tau at the synapsis also favors synapsis pruning and elimination by micoglial phagocytosis (855).

The notion that two types of microglial cells, unrelated to the proposed M1 and M2 subtypes, may play different roles in sAD is supported by recent observations. Using single nuclei RNA sequencing (snRNAseq) of isolated microglial nuclei in sAD brains, the abundance of phagocytic/activated named AD1-microglia correlates with tissue β-amyloid load and localizes with β-amyloid plaques; AD2-microglia are more abundant in association with tau pathology (856).

Microglial and altered expression of inflammatory markers is observed in children with Down syndrome, and it is modified in parallel with the appearance of tau and β-amyloid pathology and through disease progression. Microglial responses in Down syndrome with AD pathology differ from those of sAD (857-859). The profile of brain inflammatory responses also differs in human cases with AD-resilient pathology; levels of trophic factors are increased, whereas expression levels of chemokines are decreased (860).

The inflammasome is a multi-protein complex containing a member of the NOD-like family, such as pyrin-domain containing 3 (NLRP3R) that interacts with the inflammasome-adaptor protein ASC. The immune response elicited by β-amyloid functions through complex crosstalk between the toll-like receptor 4 (TLR4), complement, and inflammasome signaling pathways (861). The activation of the inflammasome in microglia triggers a cascade that involves caspase 1, and maturation of several cytokines including IL-1β and IL-18. The inflammasome in microglia participates in the nucleation of β-amyloid plaques and enhances tau pathology (862, 863). Aβ aggregates, and soluble Aβ oligomers and protofibrils, activate the NLRP3 inflammasome (864-866). Conversely, activation of NLRP3-ASC inflammasome aggravates amyloid pathology (867). Aggregated tau also activates NLRP3/ASC and exacerbates tau pathology (868). Loss of NLRP3 inflammasome function reduces tau hyperphosphorylation and aggregation by regulating tau kinases and phosphatases. Conversely, tau activates the NLRP3 inflammasome. Moreover, the intracerebral injection of fibrillar β-containing brain homogenates has been shown to induce tau pathology in an NLRP3-dependent manner (869).

Microglial and inflammatory responses are dependent on genetic factors in sAD (280, 870-872). ApoE status is a modifier of the inflammatory response (873, 874). *CD33*, *TREM2*, and other genes linked with inflammation are expressed in microglia (871, 875, 876). Carriers of AD-associated risk variants in *TREM2* show a reduction in plaque-associated microglia, and an increase in dystrophic neurites and overall pathological tau compared with age- and disease stage-matched sAD patients without *TREM2* risk variants (877). Another study shows that TREM+ control cases have no pathological hallmarks of sAD, whereas TREM2+ sAD cases show

amoeboid microglia and upregulation of inflammatory markers when compared with TREM2+ controls and TREM2- sAD cases. These findings suggest that TREM2 influences, but does not trigger, the microglial responses in sAD (878).

12c. Oligodendrocytes

Myelin generation and maintenance, and axonal nurture in the CNS, are carried by oligodendrocytes. Oligodendrocytes may contain abnormal protein deposits in various neurodegenerative diseases with abnormal protein aggregates. Yet alterations in oligodendrocytes may occur without accompanying abnormal deposits. Oligodendrogliopathy is used to stress the role of altered oligodendrocytes in the pathogenesis of certain neurological diseases with or without abnormal oligodendroglial deposits (879).

Oligodendrocytes suffer a functional decline in aging and AD as revealed by combined morphological, biochemical, and neuroradiological methods. Neuroimaging and neuropathological studies have shown reduced white matter (WM) volume, WM lesions, and altered WM integrity and cortical disconnection in aging human brain (880-884). WM changes are associated with disruption of myelin and axons (885, 886). Alterations in the number of oligodendrocytes and oligodendroglial precursor cells (OPCs/NG2-positive cells) have been reported in aged primates and rodents (887). Neuroimaging studies show reduced WM size, WM hyper-lucencies, and myelin and axon damages in patients with MCI and dementia of Alzheimer's type (883, 888-896). WM atrophy, decreased myelin density, and demyelination are also observed in post-mortem neuropathological studies (881, 896, 897). Breakdown of WM integrity is considered a contributor to the loss of neuronal tract connectivity in aging and sAD (898, 899). Recent neuropathological studies have shown preservation of *MBP*, *PLP1*, *CNP*, *MAG*, *MAL*, *MOG*, and *MOBP* mRNA expression levels in the WM of the frontal cortex at NFT stages I-II/0-A when compared with MA individuals without NFT pathology, but a significant decrease at stages III-IV/0-C. This is accompanied by reduced expression of *NG2* and *PDGFRA* (platelet-derived growth factor receptor A) mRNA, reduced numbers of NG2-, Olig2-, and HDAC2 (histone deacetylase 2)-immunoreactive cells, and reduced glucose transporter immunoreactivity at stages III-IV/0-C. Curiously, partial recovery of some of these markers occurs at stages V-VI/B-C. These changes show that myelin loss is accompanied by reduced transcription of myelin-related proteins in the WM of the frontal cortex at middle-stages of AD (342).

Early myelin loss, decreased numbers of oligodendrocytes, and region-specific alterations, followed by partial reparative responses, also occur in transgenic mouse models of AD (900-903).

13. The neurovascular system in AD

The first highlighting of the role of vascular pathology in AD was in 1989 (904). The "vascular hypothesis" of sAD has been supported more recently (905-908). Interestingly, denervation probably due to the loss of inputs from the locus coeruleus and basal forebrain was initially considered a key factor (909); altered innervation of the cerebral blood vessels linked to cholinergic deficiency is still postulated as contributing to cerebral blood flow (CBF) reduction (910, 911).

There are hundreds of papers dealing with β-amyloid angiopathy and its effects on neurovascular function, as well as the role of lipid transporters and vascular receptors in the clearing of β-amyloid in the cerebral blood vessels (912-923). Yet, there is also overwhelming evidence of altered neurovascular functioning in sAD beyond that expected in association with β-amyloid angiopathy. Neurovascular dysfunction in individuals with MCI and advanced AD is manifested by reduced CBF (cerebral hypoperfusion), reduced cerebral glucose transport, impaired BBB function, altered lymphatic function, and altered structure of the capillaries (80, 910, 924-935).

In addition to atherosclerosis and small blood vessel disease that are common in the elderly, primary involvement of arterioles and capillaries is common in brain aging and sAD. Primary blood vessel damage in sAD is characterized by atrophy and irregularities of capillaries and arterioles, edema and increased numbers of pynocytotic vesicles in endothelial cells and pericytes, atrophy of smooth muscle fibers, thickening and focal disruption of the basal membrane, increase in collagen IV, heparan sulfate,

proteoglycans, and laminin in the basal membrane, increased aquaporin expression in perivascular astrocytes, and gliovascular dysfunction, among other defects (910, 936-941). Degeneration of endothelial cells is further supported by reduced staining of endothelial cell markers (942) accompanied by aberrant angiogenesis (943). Pericytes are decreased in number and show abnormal mitochondria, pinocytotic vesicles, and disorganization and accumulation of osmiophilic material in aging with cumulative damage with sAD progression (944-947). Aβ oligomers constrict human capillaries in AD by signaling to pericytes (948). Pericyte degeneration and impaired BBB function reduce Aβ clearance and increase β-amyloid accumulation in the brain. Importantly, pericyte alteration occurs at early stages of sAD and probably it has a determining role in the altered capillary permeability (949-950). It is difficult to ascertain the weight of each one of the vascular pathologies in the eventual neurovascular failure in a particular individual. Atherosclerosis, small blood vessel disease, β-amyloid angiopathy, brain hypoperfusion, altered BBB, and primary AD-linked non-amyloidotic angiopathy have cumulative effects (951, 952).

The timing and development of neurovascular failure in sAD is not a simple process. The "two-hit vascular hypothesis" suggests that early vascular damage leads to increased accumulation of Aβ deposits in the brain, which in turn provokes additional vascular damage. ApoE is one of the factors that modulate cerebrovascular integrity (953).

Impaired glucose uptake is an early event in pre-symptomatic fAD (954), and BBB breakdown is an early biomarker of human cognitive dysfunction (955), suggesting that the neurovascular system is dysfunctional at early stages of AD. Reduced expression of glucose transporter 1 (GLUT1) is manifested at early stages of sAD, and it impairs blood glucose uptake and vasculo-neuronal function (956, 957). Altered glucose transport accounts, in part, for the more complex brain glucose metabolism dysregulation in AD (958). More precise information has been obtained from the study of mouse models of cerebral β-amyloidosis mimicking β-amyloid deposits in AD (959). In the majority of these mice, cerebral blood vessels are altered and there is often impaired BBB at early stages of Aβ plaque deposition, usually preceding or in the absence of β-amyloid angiopathy (959). These observations are in line with the role of Aβ in the pathogenesis of neurovascular damage in AD (928). Unfortunately, little is known about the occurrence of different soluble, insoluble, and oligomeric amyloid species in these models.

The possible deleterious effects of abnormal tau on the integrity of the cerebral blood vessels have also been assessed (960). Tau expression is accompanied by BBB breakdown in tetracycline-regulable tau-transgenic mice; BBB function is recovered once tau levels are normalized (961). Non-structural but functional BBB dysfunction mediated by altered modulation of vasoactive factors including vasoconstrictor endothelin-1 has been suggested (962).

Altered CBF, impaired BBB, and structural anomalies in the blood vessels also occur in other neurodegenerative diseases such as Parkinson's and Huntington's diseases, amyotrophic lateral sclerosis, and multiple sclerosis (933, 934, 963), in which Aβ and AD-tau have no chance to play a causative role.

Neurons and astrocytes also play a role via glutamate in the regulation of CBF. Arteriole constriction depends on the metabolism of arachidonic acid (AA). Upon mGluR activation, increased AA in the plasma membrane is converted into 20-hydroxyeicosatetraenoic acid and induces vasoconstriction, or it is converted into prostaglandin 2 and produces vasodilatation (964).

Astrocytes have cardinal functions in the maintenance of BBB (see section 12a).

14. Purine and pyrimidine metabolism in sAD

Purines are heterocyclic double-ring aromatic organic molecules. Primary purines adenine and guanosine, together with one-ring primary pyrimidine nucleobases cytosine, thymidine, and uracil, are the core of DNA, RNA, nucleosides, and nucleotides. Adenosine and guanosine are purine ribonucleosides resulting from the binding of adenine or guanine to ribose, respectively. When adenine and guanine are attached to a deoxyribose ring, the resulting compounds are deoxyadenosine and deoxyguanosine, respectively. Nucleotides result from the incorporation of phosphate groups in nucleosides:

adenosine monophosphate (AMP), adenosine diphosphate, adenosine triphosphate (ATP), guanosine monophosphate (GMP), guanosine diphosphate, guanosine triphosphate, and cyclic forms cAMP and cGMP are primary purine-derived nucleotides. Modified purine nucleobases hypoxantine and xanthine result from the replacement of the amino-group by a carbonyl-group from adenine and guanine, respectively, whereas methyl-guanine results from the incorporation of a methyl group to guanine. Corresponding modified purine nucleosides are inosine, xanthosine, and methyl-guanosine, respectively. Nucleotides participate in a wide variety of crucial metabolic pathways including energy metabolism and cell signaling. In addition, purine bases are incorporated to other molecules to form cofactors of several enzymatic reactions such as coenzyme A, flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NADþ), nicotinamide adenine dinucleotide phosphate (NADPþ), and the corresponding reduced forms FADH2, NADH, and NADPH. S-Adenosyl methionine is made from ATP and methionine by methionine adenosyltransferase and is involved in the transfer of methyl groups to distinct substrates, including nucleic acids, proteins, lipids, and metabolites (965, 966). In addition, adenosine may act as neuromodulator on specific adenosine receptors (967) (see section 7f). Adenosine receptors also modulate the BBB (968).

Significantly decreased levels of adenosine, guanosine, hypoxanthine, and xanthine are found in the frontal cortex at stages I-II of NFT pathology, but the parietal cortex and temporal cortex show an opposing pattern at advanced stages of sAD. The activity of 5'-nucleotidase, which hydrolizes adenosine AMP to generate adenosine, is reduced in the frontal cortex mainly at NFT stages I-II, and only at NFT stages V-VI in the temporal cortex. Adenosine deaminase activity, which synthetizes inosine from adenosine, is decreased in the frontal cortex in sAD but is increased at NFT stages I-II in the temporal cortex. Finally, purine nucleoside phosphorylase activity, which metabolizes guanosine to guanine, is increased only in the temporal cortex at NFT stages I-II. Purine metabolism alterations are region- and stage-dependent and occur independently of NFTs and β-amyloid plaques (969).

In another study, 23 purine metabolism genes were analyzed with RT-PCR in the entorhinal cortex, frontal cortex area 8, and precuneus in MA individuals without NFT pathology and in cases at NFT stages I-II, III-IV, and V-VI (966). The mRNA expression levels of several enzymes were dysregulated at stages III-IV and V-VI in a region-dependent manner when compared with MA individuals. In addition, liquid chromatography mass spectrometry-based metabolomics in the entorhinal cortex identified decreased levels of xanthosine, guanine, and deoxyguanosine at stages I-II, followed by dGMP, inosine diphosphate, and glycine at NFT stages III-IV in sAD (966).

Some years ago, studies pointed to S-adenosylmethionine as a complementary candidate for therapeutic intervention in sAD (208, 970). More recently, several studies have scrutinized the modulation of purinergic signaling to ameliorate sAD (971-976). Considering the large number of different enzymes altered, this represents a tremendous endeavor.

15. Epigenetics in brain aging and sAD

Epigenetic regulation plays a crucial role in the final transcription of genes (977, 978). Three central mechanisms are briefly discussed: modifications of histones, DNA methylation and hydroxymethylation, and non-coding RNAs.

15a. Histone modifications, DNA methylation, and hydroxymethylation

Nucleosomes consist of DNA wound around a protein octamer composed of two molecules of the histones H2A, H2B, H3, and H4. The N-terminal of histones (histone tail) extends out from the surface of the nucleosome. Acetylations by histone acetyltransferases (HATs) and histone deacetylases (HDACs), and methylation mediated by histone methyltransferases (HMTs) and histone demethylases (HDMs), respectively, occur at the histone tails (979, 980). Histone acetylation decreases the interactions of histones with DNA, relaxes heterochromatin to euchromatin, and enables gene transcription (981-984). Methylation of histones can either increase or decrease gene transcription, depending on which

amino acids in the histones are methylated, and on the number of methyl groups involved. Methylations, which permit DNA uncoiling facilitate the access of transcription factors and RNA polymerase. The trimethylation of histone 3 at lysine 4 (H3K4m3) activates transcription, whereas dimethylation of histone H3 at lysine 9 (H3K9me2) is inhibitory. Likewise, methylation of lysine 4 of histone 3 (H3K4me1) facilitates gene transcription (985-988).

DNA methylation and DNA hydroxymethylation are biological processes by which methyl or hydroxymethyl groups are added to the DNA. Methylation and hydroxymethylation can change the activity of a DNA segment without changing the sequence. The methylation of a 5'-cytosine in cytosine-guanine-rich regions (CpG islands) of DNA promoters results mainly in the inability of transcription factors to bind DNA and compact heterochromatin; as a result, gene transcription is silenced. Four types of DNA methyltransferases, DNMT1, DNMT2, DNMT3a, and DNMT3b, carry out the process of DNA methylation. S-adenosyl-L-methionine (SAM) is the donor of methyl groups. DNA hydroxymethylation can occur as a result of oxidative stress or the action of ten-eleven-translocation-1 (TET1) proteins (989-994). SAM which is generated by adding adenosine to methionine, a reaction catalyzed by S-adenosyl-methionine transferase, transfers the methyl group to DNA methylation by DNA methyltransferase.

Brain aging and sAD is accompanied by epigenetic DNA modifications (995-1002). DNA modifications involve genes linked to β-amyloid production (1003-1006), ApoE-ε4 (996), tau phosphorylation (1007-1009), ribosomes (1010), BDNF (1011), and inflammation (1012, 1013). A large number of unrelated genes has also been assessed, showing either changes or no modifications in the methylation of DNA promoters (1014-1023). The expression of adenosine receptor A2A is modulated by DNA methylation in the gene promoter region (1024-1026). Therefore, epigenetic changes in DNA in aging and sAD are not widespread but selective for particular genes.

In monozygotic twins discordant for AD, significantly reduced levels of DNA methylation were observed in the neuronal nuclei of temporal neocortex in the AD twin (991).

Unfortunately, most studies are carried out on samples at advanced stages of sAD which precludes learning whether epigenetic changes in DNA are primary or secondary events (1027).

In addition to modifications in genomic DNA, increased mitochondrial 5-methylcytosine in most CpG and non-CpG sites in the D-loop region of mitochondrial DNA (mtDNA) has been identified in the entorhinal cortex at NFT stages I-II and III-IV compared with control samples (1028). These are relevant data as they indicate early mtDNA methylation linked to the pathogenesis of AD-related neuropathologic change (1028).

15b. Non-coding RNAs

Non-coding RNAs do not encode proteins, but most modulate protein translation targeting mRNAs. Transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs); small non-coding (snRNAs) such as microRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), extracellular RNAs (exRNAs), small Cajal-body specific RNAs (scaRNAs); and long non-coding RNAs (lncRNAs) are the principal types. miRNAs bind to complementary un-translated regions (3'-UTRs) of mRNAs to regulate target genes, resulting in translational repression or degradation (1029-1031). In animals, miRNAs are synthesized from primary miRNAs by the action of two RNase III-type proteins: Drosha, in the nucleus, and Dicer in the cytoplasm. Argonaute (Ago) subfamily proteins bind mature miRNAs to target mRNAs (1032, 1033).

Thousands of human genes are miRNA targets (1034, 1035). Ago2:RNA interactions using HITS-CLIP have been used to generate a transcriptome-wide map of miRNA binding sites in the human brain. About 7,000 stringent Ago2 binding sites were highly enriched for conserved sequences corresponding to abundant brain miRNAs. This interactome points to functional miRNA: target pairs across about 3,000 genes (1036).

Dysregulation of miRNAs is involved in the pathogenesis of sAD (1037-1040). Several miRNAs target genes, many of them abnormally regulated in AD, are associated with β-amyloid (1041-1060), tau phosphorylation, and cytoskeleton (1061-1074). It is

difficult to ascertain which miRNA alterations are primarily altered or secondary to β-amyloid and tau pathology in sAD (1075).

Several miRNAs can bind to specific mRNAs, modulating gene transcription differentially depending on the triggering factor (1038). miRNA 163, miRNA30a 5p, and miRNA206 bind to *BDNF* mRNA and modulate altered BDNF expression in sAD (1040, 1055, 1076).

Furthermore, one miRNA can bind to different mRNAs resulting in various functions. For example, reduced miRNA 132 is associated with downregulation of ChAT immunoreactivity in the nucleus basalis of Meynert (1061) and to AChE upregulation (1077, 1078). In addition, miRNA 132 targets CREB and promotes neuritogenesis and synaptic activity (1079).

Finally, miRNA dysregulation is stage- and region-dependent. For example, in the locus coeruleus, miRNA-27a-3p, miRNA-124-3p, and miRNA-143-3p show a trend to increase at NFT stages I-II and are significantly upregulated at NFT stages III-IV when compared with MA individuals without NFT pathology. In the entorhinal cortex of the same cases, only miRNA-143-3p is upregulated at stages III-IV. The expression levels of miRNA-27a-3p, miRNA-124-3p, and miRNA-143-3p are not modified in CA1 at any stage, whereas miRNA-124-3p is significantly downregulated in the dentate gyrus at NFT stages I-II (1080). The interpretation of these results is puzzling: downregulation of miRNA124 results in β-amyloid accumulation (1007); miRNA143-3p inhibition promotes neuronal survival in sAD (1081); and miRNA 27a-3p regulates the expression of intercellular junction proteins at the brain endothelium, while its downregulation increases BBB permeability (1082, 1083).

16. Microorganisms and sAD

The possibility that microorganisms participate in the pathogenesis of AD was suggested in a seminal publication in 1907 (1084). The role of bacteria, viruses, and fungi has been proposed to the present (1085-1088).

16a. Microorganisms in the brain and oral cavity

More than thirty years ago, *Borrelia burgdorferi* was reported in the brains of sAD cases (1089), although other studies did not validate this finding (1090). However, spirochetes, including *Borrelia* and *Treponema*, were postulated as contributing factors in the pathogenesis of the disease (1091-1094). rRNA sequencing has shown the presence of bacteria in Alzheimer's post-mortem brain (1095). β-amyloid exhibits potent antimicrobial activity against Candida albicans and some bacteria, pointing to the possibility that secretion of Aβ is triggered by microbial infection (1096).

Numerous periodontal bacteria have also been implicated in sAD in the context of chronic periodontitis (1097-1099). The association between periodontal inflammatory disease and sAD has raised much concern mainly because of the possibility of rapid therapeutic intervention (1100-1102). Increased levels of anti-*Helicobacter pylori*-specific antibodies were also reported in the CSF and serum of sAD patients (1099).

Histological and immunohistochemical techniques have detected fungi and bacteria in the brain of sAD (1103-1105). PCR analysis revealed various fungal species in the brain and CSF in sAD (1106-1108). A combination of bacteria and fungi was observed in several cases, and several fungi were identified in different brain regions in the same individual, suggesting multi-fungal infection (1107). The corpora amylacea are particularly enriched in fungal and bacterial peptides, acting as scavengers of microbial debris (1109). The presence of fungi is not restricted to sAD as they have also been identified in the CNS and CSF in amyotrophic lateral sclerosis (1110, 1111).

Herpes viruses were proposed as participants in the pathogenesis of sAD about four decades ago (1112, 1113). Since then, several studies have implicated herpes viruses in sAD (1114- 1116). Herpes simplex virus 1 (HSV-1) has received much attention due to the presence of high expression levels in the brain and HSV-1 IgG antibodies in the CSF (1117-1121). Interestingly, HSV-1 DNA is localized in senile plaques (1122). The link between herpes zoster and sAD is still controversial (1123). Human cytomegalovirus (CMV) seropositivity was associated with a risk

of sAD (1124). Human herpes virus 6 (HHV-6) has focused on several studies (1125-1128). Viral associations have also been reported, including HSV-1 and CMV, HSV-1 and HHV-6, HHV-6 and EBV (Epstein-Barr virus), and HHV-6 and HHV-7 (1115, 1126, 1129, 1130). A relationship is established between β-amyloid and herpes virus, suggesting a mechanism against brain infection (1131). Since differences in sAD and controls are not always significant, it is still difficult to conclude that a direct causal relationship exists between herpes virus and sAD.

The hypothesis of multi-pathogen infections in the pathogenesis of sAD has recently been discussed (1085). Moreover, exposure to systemic infections in 5xFAD transgenic mice, carrying mutated genes associated with fAD, causes neurodegeneration in brain regions displaying β-amyloid pathology and high local microglia density (1132).

Together, the available information shows that the human brain, particularly the aged brain, accommodates viruses, bacteria, and fungi, together with the debris of these microorganisms over time. Whether brain and oral microorganisms might contribute to "neuroinflammation" and facilitate the course of sAD remains obscure. Nonetheless, a recent review postulates a link between the β-amyloid cascade hypothesis and chronic infection in sAD: β-amyloid deposition is produced in response to brain microbial inflammation (1133).

16b. Gut microbiota

In recent years, several studies have implicated the "gut-brain-microbiota axis" in the pathogenesis of sAD; altered gut microbiota may promote neuroinflammation, Aβ aggregation, and oxidative stress (1134-1140). The putative mechanisms producing effects include changes in the systemic metabolism that may influence brain functions, transfer of microbiota metabolites to the brain through the BBB, and direct impact of microbiota reaching the brain parenchyma. Serotonin may play a role in the gut-microbiota axis (1141). The opioid system has been postulated to be contributory as well (1142).

Conversely, the infusion of tracers into the lateral ventricle of rats has permitted their visualization in the nasal cavity, nasal pharynx, soft palate, and esophagus, thus suggesting that at least rats can swallow waste from the brain (1143).

17. Seeding and spreading of β-amyloid and tau

17a. Seeding β-amyloid

The intracerebral injection of diluted extracts from AD brains or from old AD-like transgenic mice accelerates β-amyloid deposition in transgenic mice bearing *APP* and/or *PSEN1* mutations (1144-1148). Soluble forms of Aβ are particularly effective at inducing plaque formation (1149). Plaques not only develop locally but extend as well to the cerebral cortex distant from the injection site. These findings support the possibility that once the first β-amyloid deposits appear they may accelerate the accumulation of additional seeding in other parts of the brain, thereby contributing to the exponential deposition of β-amyloid (1150). Neuronal activity regulates the regional vulnerability to β-amyloid deposition (1151).

β-amyloid seeding and spreading may also occur following peripheral inoculation of β-amyloid seeds (1152). However, the intracellular mechanisms linked to the formation and fibrillisation of host β-amyloid and recruited β-amyloid spreading need clarification.

Intraventricular injection of Aβ oligomers in cynomolgus macaques leads to diffusion into the brain, causing tau hyperphosphorylation, NFT formation, synaptic loss, and astrocyte and microglial activation in regions of the macaque brain where Aβ oligomers are abundant (1153).

β-amyloid deposits were also observed in the brains of patients with iatrogenic Creutzfeldt-Jabob disease (iCJD) secondary to cadaveric dura mater grafts, treatment with cadaveric human growth hormone obtained from hypophysis of CJD-affected donors, or contaminated neurosurgery early in life (1154).

17b. Tau seeding

Physiological release of neuronal tau is stimulated by neuronal activity and extracellular tau *in vivo* (1155-1158). Intercellular tau transmission may

have physiological functions that permit the transfer of tau status information from one neuron to another, enabling them to modify the status of the host tau according to this information. This mechanism may lie behind the activation of post-translational modifications of tau in the host neuron following the transfer of pathological tau in models of tau seeding and spreading. Tau is secreted by exosomes, and the extracellular appearance of tau does not depend on neuronal death, but rather physiological tau transfer from one neuron to another (1159). Tau phosphorylation facilitates tau transmission and propagation (1160).

Several studies have suggested that the progression of sAD and other neurodegenerative diseases with abnormal protein aggregates occurs in a similar way to prions in prion diseases (1161-1164).

In favor of this hypothesis, many experimental designs in mouse and rat models have provided evidence that cells have the capacity to transfer tau from one cell to another. The over-expression of human tau P301L restricted to the entorhinal cortex shows the progression of tau without detectable transgene expression anterogradely from the entorhinal cortex to the dentate gyrus and CA1 region of the hippocampus and subiculum, and retrogradely to scattered neurons in the perirhinal and secondary somatosensory cortex (1165, 1166). Using a lentiviral-mediated rat model, tau protein is axonally transferred from hippocampus neurons to neurons of distant brain regions such as the olfactory and limbic systems (1167)

Several mechanisms of tau release and uptake have been proposed, mainly in the context of synaptic transmission. However other processes may occur as well. Tau release may occur via (SNAP: Soluble NSF Attachment Protein Receptor) SNARE-mediated exocytosis, release by secretory vesicles from lysosomes, microvesicle shedding, and direct plasma membrane crossing. Tau uptake may occur via endocytosis, adsorptive endocytosis, macropinocytosis, transmembrane diffusion, and nanotunneling. Binding of phosphorylated tau to AMPA and NMDA receptors is another putative mechanism (1168-1179).

Tau seeding and spreading is produced following the intracerebral inoculation of synthetic tau fibrils (1180, 1181), and the inoculation of fibrillar-enriched fractions from human and mouse brain homogenates of tauopathies, including sAD, containing hyper-phosphorylated tau (1182-1186). Tau seeding and spreading in neurons also occur following intracerebral inoculation of similar tau aggregates in wild type mice (WT) and in transgenic WT mice (1183, 1187-1194). Propagation in these models occurs through connectivity rather than proximity (1182). In addition to neurons, deposits may also occur in astrocytes, and the morphology of glial inclusions appears to mimic the glial aggregates of the corresponding human tauopathies (1183, 1188, 1189, 1195). Differences in the type of inoculum that produce different protein aggregate deposits in the host and variable involvement of astrocytes have led to the proposal that tau strains are behind the different phenotypes and progression of human tauopathies (1161, 1196-1198).

More refined situations probably occur in human neurodegenerative diseases. For example, sAD brain contains different tau strains with particular properties (1199); different tau strains may contribute to the clinical heterogeneity of AD (1200).

Moreover, tau seeding and spreading also occur in oligodendrocytes in WT mice following inoculation of sarkosyl-insoluble fractions in the hippocampus and corpus callosum of human brain homogenates from sAD and cases with primary age-related tauopathy (PART) (1191-1193). Yet, tau deposits in oligodendrocytes never occur in humans affected by sAD and PART without co-morbidities (see section 21 for PART details). These discrepancies between human diseases and mouse models may be explained by the differences between human and murine tau (1201, 1202). Whether different types of tau occur in neurons and glial cells, or even in different neuron populations granting selective vulnerability, deserves further research.

Tau seeding and spreading have also been generated in rhesus monkeys after the inoculation of adeno-associated virus expressing a *double-4Rtau* mutation in the left hemisphere (1203). Tau spreading was accompanied by robust TREM2+ microglial proliferation (1203), an unexpected observation not seen in other models.

Another curious observation that deserves validation is the triggering of tau deposits in tau transgenic mice following peripheral administration of tau aggregates (1204).

Neuropathological studies in humans reveal the beginning of tau seeding in the telencephalon in sAD in the transentorhinal and entorhinal cortex, and from these brain regions tau spreads to others (1205, 1206). Neuroimaging analysis further support tau spreading along functional connectivity networks (1207). However, combined post-mortem regional seed amplification and PET studies in living individuals suggest that from NFT Braak stage III onward, local replication rather than spreading between regions is the main mechanism to explain progressive tau burden in sAD (1208).

Together, tau seeding and spreading differ from seeding and spreading of prions. Grossly, tau seeding and spreading circumvent certain regions that should be involved according to the hypotheses of either neuronal connectivity or neuronal proximity. Most importantly, once up-taken by the receptive neuron, abnormal tau triggers a series of molecular processes that include activation of several tau kinases, post-translational modifications of tau—for instance, hyperphosphorylation, nitration, and altered conformation; recruitment of additional substrates in tau deposits; and modifications in the ratio of 3Rtau/4Rtau in the host neuron (1209), which implies the capacity of foreign abnormal tau to modulate exon 10 splicing in *MAPT* in the host (1190, 1191, 1202, 1209).

17c. Multiple seeding foci of β-amyloid and tau pathology; vulnerable and resistant populations to tau seeding in brain aging and sAD

Another important point is the characteristics of tau spreading in the human brain that seem to skip over obligate regions on the basis of cell connectivity. The dentate gyrus does not show tau pathology in AD and other 3R+4R tauopathies without co-morbidities, but the dentate gyrus is affected in 3R-tauopathies and 4R-tauopathies. Alternative pathways from the entorhinal cortex to the hippocampus proper are possible but there is no clear explanation for this particular pattern in AD. It may be suggested that certain populations are able to transfer abnormal tau from one neuron to the next in the connecting pathway without recruiting host tau and forming local aggregates within themselves. Regional vulnerability plays a cardinal role in tau spreading in AD-related animal models (1210).

In summary, tau seeding and spreading is not the only cause of tau progression in sAD and other tauopathies. Cellular vulnerability, including neuronal, astroglial, and oligodendroglial, together with regional vulnerability, already highlighted several years ago, are also key points to understanding tau progression in sAD and other tauopathies.

Finally, several studies implicate microglia in the process of tau seeding with apparent enhancing and mitigating effects (868, 1211-1216). Another study concludes that microglia have a complex role; they are capable of taking up and breaking down seed-competent tau, but do so inefficiently and could hardly play a role in the spread of tau pathology (1217).

The capacity for seeding of β-amyloid and tau does not imply a unique origin of β-amyloid and tau pathology in sAD. Neuropathological studies at early stages of NFT and SP pathology have shown that independent tau deposits are localized in separate regions such as the raphe nuclei and locus ceruleus, transentorhinal and entorhinal cortex, and olfactory bulb, in addition to isolated tau-positive neurons in other parts of the brain. Similarly, β-amyloid deposits in the brain parenchyma are not connected; likewise there is not an intimate connection of blood vessels affected by β-amyloid angiopathy.

Aβ and tau pathology, like other molecular alterations in brain aging and sAD, have multiple and separate foci; lesions in aging and sAD do not start in a single region only to progress from that site to the whole brain.

18. Neuronal death

Neuronal depletion in AD is the result of cell death and lack of neuronal renewal. Apoptosis was postulated as a major mechanism of neuronal death in AD and most neurodegenerative diseases based on the positivity of cells stained with the method of *in situ* end-labeling of nuclear fragmentation, and immunoreactivity to cleaved caspase 3 (1218-1220). Caspase 3-mediated and caspase 3-non-mediated

apoptosis is also supported by studies in cell lines (1221-1224). However, DNA fragmentation occurs during the agonic state and post-mortem delay, and active caspase-3 participates in tau truncation during the genesis of NFTs. Therefore, the weight of apoptosis as a cause of neuron demise in AD is probably unevenly represented. Necroptosis is another type of programmed cell death, frequently linked to inflammation that depends on the kinase activity of receptor interacting protein 3 (RIP3) and RIP1, and the subsequent activation of the mixed lineage kinase domain-like protein (MLKL). This pathway is activated in AD and other neurodegenerative diseases (1225-1227).

Neuronal degeneration and demise in AD is not correlated with tau pathology (1228, 1229), although ghost tangles are not rare in advanced stages of AD. Intraneuronal accumulation of β-amyloid is involved in synaptic dysfunction, cognitive impairment, and the formation of amyloid plaques in AD (416, 1230, 1231). In addition, excessive production of Aβ peptides and APP activates death signaling pathways including apoptosis, necrosis, necroptosis, oxytosis (GSH-mediated oxidative cell death), pyroptosis (inflammasome-mediated cell death), and autophagy *in vitro* (1232).

In summary, although β-amyloid and tau pathology may induce cell death in sAD, they are not the only factors triggering active cell death pathways. Other alterations, such as aberrant cell-cycle re-entry, energy metabolism failure, oxidative stress damage, and altered cell membrane signaling, are relevant contributory factors (see section 21).

19. Neuronal connectivity networks in brain aging and sAD

The notion that clinical manifestations in brain aging may correspond solely to early stages of AD-related pathology restricted to the hippocampus, inner regions of the temporal cortex and selected nuclei of the brain stem is simplistic, and probably untrue. Functional neuroimaging techniques have shown selective modifications of the intrinsic connectivity network in aging that exceed the domains of these regions. The default mode, salience, dorsal attention, fronto-parietal control, and auditory, visual and motor networks decline by middle adulthood, but the motor network shows increased connectivity in middle adulthood, followed by a lessening (1233-1237). Disruption of neuronal connectivity networks appears in aging and is intensified in AD (1237-1243).

However, functional connectivity alterations do not always correlate locally to tau and β-amyloid deposition; hyper- and hypo-connectivity cycles can occur repeatedly at different stages of the disease (1244). Moreover, greater segregation of functional connections into distinct large-scale networks is associated with cognitive resilience at early stages of sAD (1245, 1246). Additional studies suggest a compensation phase followed by a degenerative phase in aging, and in early, preclinical AD (1247). This is important information, as plasticity changes may circumvent, at least temporarily, deficient functioning during brain aging and early stages of sAD. Plasticity may explain the particular capacities of the adult brain to manage information in creating new networks, manifested as “experience”.

Considering the areas affected in functional neuroimaging studies, it may be inferred that molecular changes take place in the aging brain in regions other than those affected by tau and β-amyloid pathology.

20. Human brain aging and preclinical AD

The combination of clinical manifestations and complementary biomarkers has established consensus criteria to define different clinical phases of AD (See Box 1). At preclinical stages, individuals may have measurable brain changes that indicate the earliest signs of AD (biomarkers), but they have not yet developed symptoms such as memory loss (https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf). The preclinical phase is further categorized into three stages. Preclinical AD stage 1 includes cognitively normal individuals with abnormal β-amyloid markers and no neurodegeneration; stage 2, individuals with abnormal β-amyloid and neurodegeneration as revealed by magnetic resonance imaging (MRI); and stage 3, individuals with abnormal β-amyloid deposition and neurodegeneration, and “subtle” cognitive changes

(2, 48, 1248-1252). The refinement of the diagnosis of preclinical stages has improved with the acquisition of new neuroradiological methods, and optimization of CSF and blood biomarkers (1253-1256).

However, improvement in detection using CSF, blood, and plasma biomarkers largely depends on the availability of optimized instruments and markers. Current CSF and plasma biomarkers used in the diagnosis of AD are levels of β-amyloid, phospho-tau, tau, and phospho-tau ratio, neurofilaments, synaptic proteins, markers of activated astrocytes, and inflammatory markers. At present, the available methods cannot detect differential levels of tau, phospho-tau, β-amyloid, and structural and synaptic proteins unless the degenerative process is at least at undetermined middle stages of AD neuropathological change. Hippocampal atrophy, as revealed by computed tomography (CT) and MRI, and currently used to correlate cognitive impairment and altered neuropathological substrate, is a late marker of AD that is only positive when there is advanced NFT pathology and neuron loss in the hippocampus.

A recent meta-analysis to estimate the prevalence of Aβ pathology as measured with biomarkers in participants with normal cognition, subjective cognitive impairment, or mild cognitive impairment revealed that about 25-35% of cognitively normal older adults harbored a significant amount of β-amyloid (1257). Further studies have shown that β-amyloid CSF-based estimates using adjusted data-driven cutoffs are up to 10% higher than PET-based estimates in people without dementia thus suggesting that preclinical AD may be more prevalent than previously suspected (1258).

In contrast, tau PET imaging using optimized tracers provides more precise information *in vivo* at the different stages of NFT progression (855, 1259-1267). Improved neuroimaging methods corroborate earlier neuropathological observations in post-mortem brains. Individuals without cognitive impairment may have tau or β-amyloid positive signal alone, or β-amyloid and tau pathology, or tau and β-amyloid PET negativity (1268-1270). Neuroimaging studies have also identified tau pathology in the entorhinal region and mesial temporal cortex in normal aged individuals with or without minimal cognitive impairment (1271-1276). Tau PET observations are also useful to show that tau deposits appear before β-amyloid deposits in most individuals. Finally, neuroimaging allows the visualization of a continuum of lesions from "normal" brain aging to Alzheimer's type dementia in sAD and fAD (1277, 1278).

Therefore, neuroimaging observations further suggest that tau pathology is predominant in normal brain aging that overlaps with tau pathology in individuals with preclinical AD. Clinical criteria of AD are biased by the consideration that Aβ pathology precedes tau pathology in sAD. In other words, the conception of the β-amyloid cascade hypothesis permeates the diagnosis of sAD.

In addition to clinical and biomarker criteria, new neuropathological standards, based on the study of a wide number of selected brain regions stained with selected immunohistochemical markers, take into consideration AD pathology progression and the presence of comorbid pathologies were proposed by the National Institute on Aging–Alzheimer's Association (NIA-AA) in 2012 (49, 50). The main considerations are a) recognition that AD neuropathologic changes may occur in the apparent absence of cognitive impairment, (b) consideration of an "ABC" score for AD neuropathologic change that incorporates histopathologic assessments of β-amyloid deposits (named A, based on Thal phases), staging of neurofibrillary tangles (named B, based on Braak stages), and scoring of neuritic plaques (named C, based on CERAD), and (c) assessment of co-morbid conditions such as Lewy body disease, vascular brain injury, hippocampal sclerosis, and TDP-43 proteinopathy; also including ARTAG and AGD. At present, the post-mortem neuropathological examination is still the most precise approach to identify the morphological changes linked to a brain aging and sAD (49, 50, 325) (Table 1).

Following this classification, the score levels of AD neuropathologic change are classified as "not", "low", "intermediate", and "high" (Table 2). The presence of Aβ is mandatory. It is also stated that "medial temporal lobe NFTs in the absence of significant Aβ or neuritic plaques occurs in older people and may be seen in individuals without cognitive impairment, with mild impairment, or with cognitive impairment from causes other than AD" (49, 50). To

"A" Thal phase for Aβ plaques		"B" Braak and Braak NFT stage		"C" CERAD neuritic plaque score	
0	0	0	none	0	none
1	1 or 2	1	I or II	1	sparse
2	3	2	III or IV	2	moderate
3	4 or 5	3	V or VI	3	frequent

Table 1: "ABC" score for AD neuropathologic change modified from ref. 49 and 50. National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines for the neuropathologic assessment of Alzheimer's disease.

support this assertion, a previous work is cited: "Brains that have many NFTs in medial temporal lobe structures (Braak stage III or IV) but no cortical SPs may be a diagnostic dilemma; they also raise questions about the amyloid cascade hypothesis of AD in which NFT development is thought to occur downstream of the development of amyloid plaques" (1279). More recently, the introduction of the term PART has been used to name cases with NFT pathology without SPs (see section 21a).

A key point of this neuropathologic classification is the notion that β-amyloid deposition is the first "*sine-qua-non*" condition to consider the possibility of AD. The occurrence of NFTs without β-amyloid plaques is not consistent with AD at any stage. The neuropathological proposal of the National Institute on Aging-Alzheimer's Association assumes the "amyloid cascade hypothesis" as the cause of sAD. Yet the cognitive status correlates with NFT burden rather than with β-amyloid plaques (331).

AD neuropathologic change		**B**		
A	**C**	0 or 1	2	3
0	0	not	not	not
1	0 or 1	low	low	low
	2 or 3	low	intermediate	intermediate
2	Any C	low	intermediate	intermediate
3	0 or 1	low	intermediate	intermediate
	2 or 3	low	intermediate	high

Table 2: "ABC" score level of AD neuropathologic change. Aβ/amyloid plaques (A), NFT stage (B), and neuritic plaque score (C). The combination of A, B, and C scores is designated as "not", "low", "intermediate" or "high" AD neuropathologic change. "Intermediate" or "high" AD neuropathologic change is considered sufficient for dementia. National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines for the neuropathologic assessment of Alzheimer's disease.

21. Primary age-related tauopathy (PART), rapidly progressive sAD, and sAD resilience

21a. PART

In 2014, the term PART, a common pathology associated with human aging, was proposed to categorize a subpopulation of individuals with normal cognition or with MCI showing NFT pathology at stages I-IV of Braak and no SPs, and slower progression to the clinical stage of dementia in some individuals (1280-1283).

The concept of PART derives from the interpretation of the "β-amyloid cascade hypothesis" as the cause of AD. In other words, it is assumed that the presence of NFTs without Aβ deposition is not AD and therefore, cases with NFTs and without SPs do not match with the neuropathologic assessment of AD proposed by the NIA-AA.

PART includes the majority of individuals aged 65 or older with first stages of NFT pathology and without SPs. The individuals represent about 85% of human beings at the age of 65 (328, 329, 1284), and are considered clinically affected by "normal brain aging". Therefore, PART appears to be a predominant disorder until the emergence of SPs (41, 329, 336, 1284). Once a substantial number of SPs appears in the brain, AD is overriding, whereas dementia with only tangles (or tangle-predominant dementia) which would be the logical progression of PART decays and becomes rare (1285). It has been stated that the frequency of PART increases at the age of 85 years (1286). However, most individuals with NFT pathology at stages I-III without SPs are younger in largest series of cases (41, 329, 1284).

The distribution of tau pathology in CA1 and CA3 regions of the hippocampus is reported to be different in PART and sAD. However, in one series, the mean age of the individuals was about 88 but the NFT stages varied in the samples with PART and sAD (1287). In another series (mean age 84.3 ± 9.4 years), tau pathology was high in both CA1 and subiculum, followed by CA2/3, entorhinal cortex, CA4, and dentate gyrus in sAD. In PART, the severity of tau pathology in CA1 and subiculum was high, followed by enthorinal cortex, CA2/3, CA4, and dentate gyrus (1288). Differences appear to be minimal and were probably modified by the presence of tau pathology in SPs in sAD.

The proposal of PART as a new tauopathy is not widely accepted. PART has also been interpreted as being within the spectrum of sAD (a part of sAD) in cases with a particular genetic background characterized by lower prevalence of *ApoEε4*, *PTK2B*, *BIN1*, and *CR1* genes, and higher prevalence of *ApoEε2* (1282, 1289, 1290). In contrast, tangle-predominant dementia has been associated with *MAPT H1* haplotype (1291).

21b. Rapidly progressive AD

Patients with rapidly progressive AD (rpAD) are younger and have a median survival time after diagnosis of about 7-10 months (1292); the neuropathological hallmarks and peripheral biomarkers are similar to those seen in current sAD excepting for a low frequency of ApoEε4 allele and increased serum levels of specific pro-inflammatory cytokines (1293, 1294). Yet $A\beta_{42}$ oligomers in rpAD have distinct properties which promote the faster spread of $A\beta_{42}$ pathology (1295). The composition of SPs also differs in rpAD, with significantly higher levels of neuronal proteins, decreased levels of astrocytic proteins, and particular abundance of synaptic-derived proteins (1296). Moreover, high-density oligomers of the prion protein and a significant 1.2-fold decrease in di-glycosylated PrP isoforms occur in rpAD. Fifteen proteins appear to interact with PrP^C while only two proteins, 3/4histone H2B-type1-B and zinc alpha-2 protein3/4, are specifically bound with the PrP isoform isolated from rpAD cases (1297). Abnormal PrP isoforms in rpAD are accompanied by altered localization of distinct interactors including the growth arrest-specific 2-like protein and associated end-binding protein 1, α-tubulin, and β-actin (1298).

Molecular profiles of β-amyloid proteoforms differ in rpAD when compared with typical sAD (1299). Moreover, the presence of highly hydrophobic Aβ seeds in rpAD brains that seeded reactions at a slower pace in comparison to typical sAD has been validated (1299).

Another anomaly is the downregulation and dislocalization from the nucleus to the cytoplasm of the splicing factor proline and glutamine rich (SFPQ), its colocalization with TIA-1 in stress granules, and its association with tau oligomers in the brain of rpAD (1300).

21c. sAD resilience

Centenarians have resistance to sAD or very low progression to advanced Braak stages of tau and β-amyloid pathology (1301-1303). Curiously, AD-related changes in the oldest-old population also show a particular neuropathological distribution including high densities of NFTs, mainly in the hippocampus, without apparent major clinical deficiencies (1302-1307).

Multiple factors are associated with increased or reduced structural and behavioral patterns linked to cognition in the elderly and sAD. The cognitive reserve, linked to educational and occupational acquisition, social networks, and leisure activities in later life, have a protective effect (1308-1312). Glycolitic dysfunction reduces resilience (1313) whereas coffee and cacao favour protection from sAD (1314).

Comorbidities, including TDP-43 proteinopathy and mesial sclerosis, reduce resilience (1315-1317).

Genetic factors also participate in cognitive resilience (1318, 1319). A greater number of genes apply in women (225, 1320). A top variant on chromosome 18 upstream of *ATP8B1* is significantly associated with methylation in prefrontal cortex tissue at multiple CpG sites, including one just upstream of *ATPB81*, and present in individuals with unimpaired cognition (1321). A rare variant in the 3'-UTR of *RAB10* is protective for sAD (1322). HDAC4, REST, and G_i intracellular signaling are sAD-specific pathways involved in regulating the onset of memory deficits (1323). Molecular modulators of neuronal vulnerability, such as RAR related orphan receptor B (RORB), and glial dysfunctions are also involved in neuronal vulnerability (1324). The myocyte-specific enhancer factor 2C (MEF2C) is upregulated in a subpopulation of glutamatergic neurons in resilient individuals. Over-expression of *Mef2a/c* in the PS19 transgenic mouse model of tauopathy improves cognitive flexibility and reduces hyperexcitability (1325). The profiles of brain inflammatory responses also differ in resilient sAD cases, with expression levels of chemokines decreasing and trophic factors increasing (860, 1326). Yet a consensus is needed on how to define the concepts of cognitive reserve, resilience, and resistance linked to cognition in aged individuals (1327).

The genetic and molecular factors linked to the AD spectrum are listed in Table 3.

FAD	mutations in the genes *APP*, *PSEN1* (presenilin1), and *PSEN2*; increased APP dosage
sAD	ε4 of ApoE, LRP1, LDLR, interleukin 1a, CLU, PICALM, CR1, *BIN1, TREM2, SORL1*, *ADAM10*, *ABCA7, SPI1*, *PILRA, MSA4*, *CD2AP*, and *EPHA1*
PART	lower prevalence of *ApoEε4*, *PTK2B*, *BIN1*, and *CR1* genes, and higher prevalence of ApoEε2
rpAD	low frequency of ApoEε4 allele; increased inflammation; different Aβ oligomers; different amyloid-β proteoforms; different seeding capacities of β-amyloid; high-density PrP oligomers; decreased PrP di-glycosylated isoforms; specific PrP isoform; altered localization of the growth arrest-specific 2-like 2 protein (G2L2), α-tubulin and β-actin; downregulation and dislocalization from the nucleus to the cytoplasm of SFPQ, their colocalization with TIA-1 in stress granules, and their association with tau oligomers
resilient AD	variant of chromosome 18 upstream of *ATP8B1*; rare variant in the 3'-UTR of *RAB10*; *MEF2C* upregulation in a subpopulation of glutamatergic neurons; decreased expression levels of chemokines and increased levels of trophic factors
Tangle-predominant dementia	association with *MAPT H1* haplotype

Table 3: Genetic and molecular factors linked to the AD spectrum (see sections 3, 4 and 21 for references).

Considering the previous data, and the preponderance of tau pathology over β-amyloid deposits at the first and middle stages of AD-related pathology (344), a modification to the NIA-AA "ABC" score level of AD neuropathologic is hereby proposed. The added value is the reflection of tau pathology at the same diagnostic value as β-amyloid (Table 4).

AD neuropathologic change				
A	**C**	**B**		
0	0	0 or 1	2	3
0	0	low	low	intermediate
1	0 or 1	low	low	intermediate
	2 or 3	low	intermediate	intermediate
2	Any C	low	intermediate	intermediate
3	0 or 1	low	intermediate	intermediate
	2 or 3	low	intermediate	high

Table 4: Modified "ABC" score level of AD neuropathologic change. Aβ/amyloid plaques (A), NFT stage (B), and neuritic plaque score (C). The combination of A, B, and C scores is designated as "not", "low", "intermediate" or "high" AD neuropathologic change. "Intermediate" or "high" AD neuropathologic change is considered sufficient for dementia. Here, NFTs are considered with equal relevance to SPs in the progression from normal brain aging with NFT changes, PART, preclinical AD, and sAD (including AD variants, rpAD and ADNC in centenarians).

22. Biochemical changes beyond tau and β-amyloid at the the first stages of NFT pathology

In addition to the classical neuropathological hallmarks restricted to the inner region of the temporal lobe and selected nuclei of the brain stem which characterize the first stages of NFT pathology, there is cumulative evidence of molecular and biochemical alterations in other regions in the same brains. Several brain regions such as the frontal cortex, which does not show NFT pathology at stages I-III (and very rarely, if present, β-amyloid deposition at these stages), show altered lipid and protein membrane composition, abnormal mitochondrial function, oxidative stress damage, altered protein synthesis, activation of kinases, dysregulated protein phosphorylation, and abnormal inflammatory responses, among other disruptions. All of these alterations advance in parallel with the progression of NFT pathology; most of them have implications in tau and β-amyloid pathology, and they all persist or increase at middle and advanced NFT stages and sAD. The terms NFT and sAD in these sections are those used in the original publications.

22a. Aberrant cell-cycle re-entry, and altered adult neurogenesis

The nervous system has plastic capacities and this is manifested in many ways in sAD. One of these is the activation of pathways geared to activate cell cycle re-entry. However, neurons are post-mitotic cells that activate cell death programs at G1/A and G2/M points in response to cell cycle reactivation (1328). Aberrant neuronal cell-cycle re-entry, as revealed by the expression of various proteins involved in the activation and progression of the cell cycle, is produced in a subpopulation of neurons in sAD (1329-1340). The expression of cell-cycle-related proteins occurs before the appearance of NFTs and SPs and may trigger programmed cell death or the activation of kinases leading to oxidative stress damage, tau hyperphosphorylation, and activation of β-amyloid pathways (1341-1346).

The expression of $p75^{NTR}$ in doublecortin (DCX)-immunoreactive dentate gyrus progenitors is reduced in AD and related transgenic models. The inoculation of pro-NGF neutralizing antibodies into the dentate gyrus restores memory performance of APP/PS1 animals and significantly increases the percentage of DCX+ progenitors in the dentate gyrus of these animals, thus suggesting that impaired proNGF-p75NTR signaling blocks adult neurogenesis in AD (1347). Moreover, the proNGF/p^{75NTR} signaling pathway blocks adult neurogenesis and neuron cell death in AD (670-672).

Altered adult neurogenesis is not restricted to sAD, as it occurs as well in the dentate gyrus in other neurodegenerative diseases such as Huntington's disease, amyotrophic lateral sclerosis, Lewy body disease, and frontotemporal dementia (1348).

22b. Brain lipids

The brain is the second richest organ in lipids after the adipose tissue. Cholesterol accounts for 20-25% of the total lipids in the plasma membrane of neurons; most local cholesterol is synthesized by astrocytes in the adult brain (1349). Glycerophospholipids are the main phospholipid components ubiquitously found in cell membranes, and they are found in abundance in membranes from neural cells. Lipids carry out, in addition to structural functions, the roles of mediators or second messengers. These are lipophilic molecules involved in signal transduction processes. Lipid mediators are derived from the enzymatic degradation of glycerosphingolipids, sphingolipids, and cholesterol by phospholipases, sphingomyelinases, and cytochrome P50 hydroxylases, respectively. Eicosanoids such as prostaglandins, leukotrienes, and lipoxins are derived from oxidation of the AA. Docosanoids, including neuroprotectins, resolvins, and maresin, are mediators of docosahexanoic acid (DHA). These mediators are important modulators of oxidative damage, inflammation, and apoptosis. Other glycerophospholipid-derived lipid mediators are diacylglycerols (DAGs) phosphatidylinositol 1,4,5-triphosphates, platelet-activating factor, lysophosphatidic acid, and endocannabinoids (1350). Degradation of sphingolipids also results in the generation of mediators, such as ceramide, ceramide 1-phosphate, sphingosine, and sphingosine 1-phosphate. These mediators are involved in differentiation, growth, cell migration, and apoptosis. Cholesterol-derived lipid mediators, including 24- and 25-hydroxycholesterol, produce apoptosis (1351-1354).

The physical-chemical properties of the membrane bilayer and the chemical reactivity of fatty acids determine their susceptibility to oxidative damage (1355-1357). ROS and reactive nitrogen species (RNS) are more soluble in the fluid lipid bilayer than in the aqueous solution (1358, 1359). More importantly, polyunsaturated fatty acid (PUFA) residues of phospholipids are very sensitive to oxidation (1360). As a result, neural cell membrane lipids become primary targets of oxidative damage and lipid peroxidation.

In the aging brain, there is a progressive decrease in the levels of cholesterol, phosphatidylethanolamine, phosphatidyl inositol, phospholipid, ethanolamine plasmalogen, and sphingomyelin (1361-1366). Increasing age is associated with progressive modifications in the composition of PUFA, including DHA and AA levels (1367). The age-related reduction in PUFAs is inversely correlated with stearoyl-CoA desaturase expression and activity, resulting in higher levels of monounsaturated fatty acids (MUFAs).

Lipofuscin located in secondary lysosomes increases with age in neurons and glial cells (1368, 1369). The “aging pigment” is composed of two-thirds protein and one third lipids (1370, 1371). Proteins in lipofuscin belong to the cytoskeleton, mitochondrial bioenergetics, synapse, and membrane receptors (1372). This proteome is practically identical to the proteome derived from lipoxidation reactions identified in the frontal cortex of aged humans (1373).

Levels of glycerophospholipids, sphingolipids, DAGs, and plasmalogens are altered in the brain in sAD (1374-1379). The disturbance of human brain lipid content in sAD pathology may be categorized into four main groups (i) decreased expression of phospholipids, specifically plasmalogen PE and plasmalogen PC, due in part to abnormal peroxisome activity; (ii) reduced sulfatide content; iii) increased levels of ceramides; and (iv) increased lipoxidative stress (1354). Plasmalogen PE plays a particular role as anti-oxidant (1380). Moreover, in gray matter, the major PPE molecular species are enriched in DHA and AA.

Modifications in DHA, AA, and PUFAs in sAD produce an imbalance between their protective role (the adaptive responses derived from their lipid mediators) and a deleterious role (derived from their susceptibility to oxidation) (1381, 1382). Lipid peroxidation is an early event and a major cause of oxidative stress damage in sAD progression (1373, 1381). β-amyloid plays an important part since SPs are always surrounded by oxidized lipids, as revealed using Fourier transform infrared microscopy (1383). One mechanism to modulate oxidative damage is mediation by the upregulation of DHA synthesis, which occurs in selected regions at early stages of sAD; this is followed by an adaptation, and then decreased DHA contents. This change is not uniform,

but rather region- and stage-dependent. DHA content in sAD progression is like a shock wave manifested in three steps: upregulation, adaptation, and depletion.

Crucial information connecting lipid alterations and sAD comes from genetic data. In addition to allele ε4 of *ApoE* (268-271, 1384, 1385), many genes involved in sAD are linked to cholesterol and lipid metabolism (284, 1386-1391). Most of them increase the risk of β-amyloid deposition but *ApoEε2* allele appears to decrease it (1392, 1393).

22c. Lipid rafts and cell membranes

Lipid rafts are microdomains of cell membranes enriched in glycosphingolipids, cholesterol, and protein receptors which favor multiple cell signaling interactions at the cell membrane, necessary for signal transduction (1394, 1395). The exoplasmic leaflet is enriched with glycosphingolipids and sphingomyelin, the cytoplasmic leaflet is enriched with glycerolipids; cholesterol is present in both. The lipid composition makes this system highly dynamic in that several proteins act as structural proteins, transmembrane signaling proteins, and protein anchors linked to protein-protein interactions (1396).

Cholesterol in lipid rafts facilitates the clustering of α- and β-secretases. Although cholesterol does not have a direct effect on γ-secretases, the increment of local cholesterol facilitates the production of β-amyloid (1397, 1398).

The lipid composition of membranes is altered in sAD. β-amyloid oligomers and peptides are recruited in lipid rafts (1399-1402). Altered lipid raft composition also occurs in APP/PS1 double-transgenic mice, a model of familial cerebral β-amyloidopathy. Altered composition of lipid rafts is observed at the age of three months in parallel with the appearance of the first plaques in these mice (1403).

Prion protein expression in SPs further supports alteration of lipid raft-enriched cell membrane in association with β-amyloid deposition at advanced stages of sAD (128, 1404, 1405).

Lipid raft alteration in AD does not occur abruptly. The composition of lipid rafts changes with age in a gender-dependent manner. The main changes affect levels of plasmalogens, polyunsaturated fatty acids (especially DHA and AA), total polar lipids (mainly phosphatidylinositol, sphingomyelin, sulfatides, and cerebrosides), and total neutral lipids (particularly cholesterol and sterol esters) (1406).

Importantly, the lipid composition of lipid rafts in the entorhinal cortex and frontal cortex, but not the cerebellum, is already altered in human brain at NFT stages I-II without β-amyloid deposits; lipid rafts at these stages display higher anisotropy, indicating that lipid changes in brain at NFT stages I-II increase membrane order and viscosity in these domains (1407). Among other alterations, the structure of lipid rafts at stages I-II is associated with increased BACE1/AβPP interaction (1408).

There is also a close functional relationship between cytoskeletal proteins and cell membranes through protein-protein interactions, electrostatic interactions with lipid membranes, and lipid tails. These complementary interactions are ruined once one of the components is altered. Altered composition of lipid rafts and membrane proteins increases Aβ pathways and tau fibrilisation. At the same time, tau monomers and β-sheet-rich tau structures disrupt cell membranes (156, 212, 1389, 1409-1413). Tau connections with lipid tails depend on electrostatic interactions and phospholipid composition with high affinity for anionic lipids and anionic vesicles (1414, 1416). Tau monomers may concentrate at the membrane and form oligomers and fibrils under pathological conditions. These β-sheet-rich tau structures are capable of disrupting membrane organization and function (212). Deposition of abnormal tau at the pre- and post-synaptic membranes may appear prior to the appearance of NFTs, and it contributes to early synaptic dysfunction (409). Conversely, there is also the possibility that alterations at the cell membrane involving the lipid composition and post-translational modifications of membrane proteins trigger abnormal phosphorylation of tau and induce formation of tau fibrils (1417) (see section 21h).

Plasma membrane specializations containing caveolin are invaginated and form caveolae which are closely related to lipid rafts (1418). Caveolae in sAD participate in a wide number of processes including internalization of tau oligomers and β-amyloid metabolism (1419-1421).

Other factors influence membrane damage, in particular, microglial pro-inflammatory mediators generating membrane damages (1422).

22d. Mitochondria

Mitochondrial alterations were identified in the pioneering ultrastructural research of AD and were later sustained by functional studies (1423-1427). Mitochondrial alterations in sAD led to the formulation of the "mitochondrial cascade hypothesis", proposing that mitochondrial alterations and failed energy metabolism trigger sAD (1428, 1429). Recent reviews have stressed the importance of mitochondrial failure in the pathogenesis of AD (1430-1432). Functional defects in ATP-synthase are considered a main contributory factor to explain failure of energy production in mitochondria (1433). Other studies have stressed the impairment of complex I in mild cases of AD (1434). Besides energy metabolism deterioration, abnormal mitochondrial function also causes increased production of ROS (1435-1437).

Mitochondrial ATP-synthase is a target of oxidative damage in the entorhinal cortex at stages I-II of NFT pathology; total levels of ATP-synthase are preserved but ATPase function is impaired (1438). Altered mitochondrial DNA methylation is manifested in the entorhinal cortex at stages I-II of NFT pathology and advances with disease progression (1028). Increased mitochondrial 5-methylcytosine levels are found in the D-loop region of mtDNA in the entorhinal cortex. Interestingly, this region shows a dynamic pattern in the content of mitochondrial 5-methylcytosine in APP/PS1 transgenic mice in parallel with the progression of β-amyloid pathology in these mice (1028). Aβ deposits have been considered a main cause of mitochondrial dysfunction in AD (1439). Additionally, mitochondrial abnormalities are observed in tau transgenic mice (1440). Aβ and tau pathology have synergistic effects on mitochondria in triple transgenic mice (1441). It has been proposed that there are mitochondrial links between brain aging and AD (1442).

The mitochondria-associated lipid raft-domain of the ER in close contact with the mitochondria, called MAM (mitochondria-associated ER membrane), facilitates functional and biochemical interaction between these structures, mainly linked to metabolism of the cholesterol, phospholipids, glucose, fatty acids, and calcium signaling (1443, 1444). MAM functions are altered at early stages of sAD (1445, 1446), thus prompting the "MAM-hypothesis" as a determinant in the pathogenesis of sAD (1447). There is growing evidence of impaired physical and proteome crosstalk between ER and mitochondria in sAD (1444).

22e. Oxidative stress damage

The mitochondria respiratory chain generates ROS which participate in cell signalling under physiological conditions. Peroxisomes, ER, microsomes, nucleus and plasma membrane are potential sources of ROS. Excess production of ROS and deficient anti-oxidant responses lead to oxidative stress damage to DNA, RNA, carbohydrates, lipids, and proteins. Ion-catalyzed oxidation of some amino acid residues may result in the production of carbonyl derivatives such as glutamic semialdehyde and aminoadipic semialdehyde. In addition to direct effects, oxidative modifications may induce the production of reactive carbonyl species such as glyoxal, glycoaldehyde, methylglyoxal, malondialdehyde (MDA), and 4-hydroxynonenal (HNE), derived from the oxidation of carbohydrates and lipids. Carbonyl species react with lysine, arginine, and cysteine residues, leading to the formation of advanced glycation and lipoxidation end-products (AGE/ALEs) in proteins. Typical AGEs/ALEs adducts are carboxymethyl-lysine (CML), carboxyethyl-lysine (CEL), and MDA-lysine (MDAL), among others (1357, 1373, 1381, 1448, 1449). Regarding RNS, nitric oxide damage to thiols, amines, and hydroxyls leads to nitrosative damage. Reactions with RNS lead to the formation of 3-nitrotyrosine (nitration) and to oxidation of distinct substrates. Reactive peroxinitrite is able to nitrate tyrosine residues and to oxidize methionine residues of proteins (1450).

Oxidative stress damage is a major component of brain aging. Protein oxidative and glycoxidative damage significantly increases with age; 60 years of age is the breakpoint of human frontal cortex aging (1451).

Oxidative stress damage in the aging brain is region- and age-dependent (1452). Regional vulnerability to neurodegeneration based on energy demands, oxidative stress, and other metabolic factors

can predict neurodegeneration (1453). For example, lower energy demand, lower mitochondrial stress, and one-carbon metabolism (particularly restricted to the methionine cycle), together with lower target of rapamycin (TOR) signaling and better antioxidant capacity, occur in the frontal cortex compared with the entorhinal cortex and the hippocampus. These differences suggest that the frontal cortex is relatively resistant to stress compared to the entorhinal cortex and hippocampus (1454).

However, this hypothesis does not apply universally when assessing different brain regions of individual brains in parallel (1455). The results are more complex and their interpretation is more difficult. Vulnerable cortical and diencephalic regions are in fact more resistant to degeneration in aging (1455). However, differences in vulnerability to protein oxidation are dependent on the subcellular localization, secondary structure, and external exposition of certain amino acids. Lipoxidized proteins are mainly those involved in energy metabolism, cytoskeleton, proteostasis, neurotransmission, and O_2/CO_2/heme metabolism (1452).

AGEs are produced in aging and sAD, but their levels and the levels of their receptor (RAGE) do not correlate with Aβ levels, tau levels, or dementia (1456, 1457).

Most studies of oxidative stress damage in sAD are centered on stages V-VI (cases with dementia) and III-IV (cases with MCI). Proteins involved in glycolysis and energy metabolism, in electron transport chain, oxidative phosphorylation, and other mitochondrial components; structural proteins; chaperones; stress proteins, and stress responses; and proteins of the UPS are all targets of oxidative damage (1373, 1458-1467). Protein oxidative damage is usually accompanied by decreased functional activity (1468). Altered enzymatic activity has been demonstrated for the oxidized protein creatine kinase BB, enolase 1, glutamine synthetase, Pin-1, carbonic anhydrase 2, UCHL-1, α-enolase, GAPDH, GDH, H^+ transporting ATPase, LDH, ATP synthase, and pyruvate kinase in sAD. A few studies have included the identification of oxidatively damaged protein, the quantification of total protein levels, and the reduction of enzymatic activity (1381). In an attempt to correlate oxidative stress damage and regional vulnerability in sAD, a meta-analysis of MDA, HNE, protein carbonylation, 8-hydroxyguanine levels and superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase activities showed that changes linked to oxidative stress were variable from one region to another and dependent on the type of adduct. No correlation was seen between oxidative damage and regional vulnerability (1469).

Oxidative damage was advocated to be the earliest event in sAD (1470). Further research revealed that oxidative damage was more marked in younger cases, in cases with rapid disease progression, and in neurons without NFTs when compared with neurons with tangles in the same individual (1471). Moreover, oxidative stress precedes β-amyloid deposition in pre-symptomatic fAD and Down syndrome (1472, 1473). Early observations suggested that oxidative post-translational modifications might play a role in the formation of SPs and NFTs (1474). Following this argument, aggregation of Aβ and tau was considered a compensatory response to underlying oxidative stress (1475). However, β-amyloid is also a cause of oxidative stress, thereby potentiating the loop (1476). Oxidative stress generates mitochondrial dysfunction by damaging structural proteins and components of the mitochondrial respiratory chain in sAD (1438, 1477-1479). Oxidative damage also causes synaptic dysfunction (425).

As indicated in previous paragraphs, oxidative damage of ATP-synthase resulting in the loss of its function occurs at stages I-II of NFT pathology (1438). Mitochondrial dysfunction, abnormalities in lipid rafts, and oxidative stress damage potentiate each other and are major players in neuronal energy failure at the first stages of NFT pathology (1480). Another relevant consequence of oxidative stress is the effect of advanced glycation end products on cell-cycle re-entry and arrest, also occurring at the first stages of sAD (1481).

22f. Inflammation

Aging is accompanied by low levels of activated innate inflammatory responses (1482, 1483).

The role of microglia and inflammation in the aging brain and sAD has been discussed in previous paragraphs. Here, the focus is on the relevance of inflammatory changes in brain aging and at early stages of AD pathology. Several reports in the 1990s

described a protective effect of non-steroidal anti-inflammatory drugs used for the treatment of auto-immnune diseases on the manifestation and progression of sAD (1484-1490). Further studies delineated their positive effects when the treatment was initiated before the appearance of cognitive impairment, but the effects of the same treatments were minimal when administered in advanced AD. These observations show that inflammatory responses modulate the history of AD at the early stages of the process. More importantly, there is also a chance for anti-inflammatory drugs in the treatment of sAD when administered at the appropriate time (1491-1493).

Molecular studies disclosed that multiple cytokines are involved at the early/middle stages of AD (1494). More detailed studies in MA and in cases at first (I-II), middle (III-IV), and advanced (V-VI) NFT stages examined the expression of cytokines and mediators of the immune system in different regions progressively affected in sAD: the entorhinal cortex, orbitofrontal cortex, and frontal cortex area 8 (838). Changes in mRNA expression correlated with the corresponding protein levels as revealed by immunohistochemistry and western blotting (838). Moreover, gene regulation at first stages of AD pathology (NFT I-II, SPs: 0) was not related to NFTs, β-amyloid plaques, concentration of $A\beta_{40}$ and $A\beta_{42}$, or membrane-bound fibrillar β-amyloid in the frontal cortex (838). These observations do not contradict previous studies showing a relationship between membrane-associated β-amyloid and inflammatory changes in cases with more advanced preclinical AD and SPs in the cerebral cortex (101), but they highlight the observations that: (a) inflammatory markers appear at the first stages of NFT pathology (stages I-III) in regions with no NFTs and SPs; (b) inflammatory changes are modified with disease progression; and (c) different inflammatory responses occur simultaneously in different regions in the same individual.

22g. Protein synthesis impairment

Protein synthesis is altered in sAD, and this is due to multiple alterations at different subcellular levels from the nucleolus to the ribosome. The relation nuclear organizer region (NOR) surface/total nucleus surface is reduced; the rDNA promoter is hyper-methylated, and dimethylated histone H3K9 and acetylated histone H3K12 are decreased in the CA1 region of the hippocampus; nuclear tau declines; specific transcription factors are abnormally regulated; rRNA levels are decreased and RNA is oxidatively damaged; the expression of nucleolar proteins as well as the expression of RNAs involved in the generation of ribosomal proteins decreases; the expression levels of translation initiation and elongation factor of the protein synthesis in ribosomes is dysregulated; and the capacity of isolated ribosomes to incorporate S^{35} methionine into protein is impaired (1010, 1473, 1495-1506). Tau protein disrupts nucleocytoplasmic transport in AD (1507), but the role of tau, if any, in the other steps of the protein synthesis pathway is not known.

Alterations of protein synthesis pathways are already identified in the hippocampus at the first stages of NFT pathology. Nucleophosmin 1 (*NPM1*) mRNA is significantly increased, and upstream binding transcription factor RNA polymerase I gene (*UBTF*) mRNA and 28S rRNA significantly decreased in CA1, but not in the dentate gyrus at NFT stages I-II. Dimethylated histone H3K9 (H3K9m2) immunoreactivity is reduced in neurons of the dentate gyrus and CA1 at NFT stages I-II. mRNA expression of ribosomal proteins RPL23A, RPL26, RPL31RPS5, RPS6, RPS10, and RPS13 is significantly reduced in the dentate gyrus at stages I-II when compared with MA individuals without NFT pathology. In contrast, *RPL5* and *RPL26* mRNA expression is increased, and *RPS5* and *RPS6* mRNA decreased in CA1 at the same stages I-II (1508). These results show early alterations not only in the CA1 region, which will be involved in NFT pathology, but also in the dentate gyrus, which does not contain abnormal tau deposits at any time in the process. Seven upregulated miRNAs (*miR-125b*, *miR-146a*, *miR-200c*, *miR-26b*, *miR-30e*, *miR-34a*, and *miR-34c*) and three downregulated miRNAs (*miR-107*, *miR-210*, and *miR-485*), all of which associated with oxidative stress, are found in vulnerable brain regions of sAD at the clinical prodromal stage (1501). Together, these observations show that alterations in protein synthesis pathways appear at early stages of AD-related pathology and they are not linked to tau and β-amyloid deposits.

Disruption at many steps of the protein synthesis pathway increases in all regions with sAD progression (1508), making it difficult to establish a causative relationship between tau and β-amyloid pathology and the progressive decay of protein synthesis at advanced stages of sAD.

22h. Dysregulated protein phosphorylation

Early phosphoproteomics studies identified a few abnormally phosphorylated proteins in the hippocampus and cerebral cortex in small numbers of cases with sAD compared with controls (1509-1511). Subsequent work with more accurate methods in advanced sAD identified a large number of abnormally phosphorylated proteins, some of them with increased phosphorylation, and others with decreased phosphorylation. Abnormally phosphorylated proteins corresponded to cytoskeletal proteins, integral membrane proteins, synaptic proteins, adhesion molecules, serine/threonine kinases, transport/cargo proteins, heat-shock proteins, and others mostly involved in cell growth and/or maintenance, cell communication, and metabolism (1417, 1513, 1514). Multi-omics integration highlighted relevant altered networks including amyloid cascade, inflammation, complement, WNT protein signaling, transforming growth factor-β and bone morphogenic protein signaling, lipid metabolism, iron homeostasis, and membrane transport (1515).

Recent studies performed in the entorhinal cortex and frontal cortex in human brain aging and sAD at different NFT stages identified sixty-five dysregulated phosphoproteins in the entorhinal cortex, and eighty-one phosphoproteins in the frontal cortex at NFT stages I-II when compared with MA individuals without NFT pathology. Dysregulated protein phosphorylation of selected proteins occurs in parallel with the appearance of NFTs in the entorhinal cortex but precedes the appearance of NFTs and SPs in the frontal cortex. The number of dysregulated phosphoproteins increases in both regions with NFT stage, most of them added to those already dysregulated at stages I-II. Considering the total number of identified dysregulated phosphoproteins, the most active period corresponds to NFT stages III-IV, at a time when a subpopulation of people might be clinically categorized as suffering from MCI (1417).

The main group of dysregulated phosphoproteins at NFT stages I-II are membrane proteins; proteins of the cytoskeleton; proteins of the synapses and dense core vesicles; proteins linked to membrane transport and ion channels; kinases; proteins linked to DNA and protein deacetylation; proteins linked to gene transcription and protein synthesis, and proteins involved in energy metabolism (1417). Altered phosphorylation of selected proteins, accomplished by activation of several kinases, may alter membrane and cytoskeletal function, among these synaptic transmission and membrane/cytoskeleton signaling, in addition to energy metabolism, protein synthesis, and DNA homeostasis (1417).

DAGs are constituents of cell membranes that participate in intermediate lipid metabolism, and they are key components in lipid-mediated signaling. In neurons, DAGs modulate several signal transduction proteins linked to the activation of protein kinases, traffic and fusion of synaptic vesicles, ion channels, axonal guidance, and cytoskeletal homeostasis, among others (1516-1518). Tau and β-amyloid phosphorylation may also be mediated by DAGs and PKC (1519). DAG levels are increased in the sAD frontal cortex (1520, 1521). Further studies are needed to learn about possible links between DAGs and abnormal phosphorylation of cell membrane proteins.

23. Concluding comments

Linear logic based on the assumption that a cause results in one or several effects does not explain complex biological phenomena such as brain aging and sAD; there is no single cause of aging and sAD. Rather, the biological processes involved in generation, development, living, decline, and death are complex concatenations of complementary, disruptive, and adaptive responses. Not surprisingly, the mutually exclusive hypotheses formulated to explain sAD are not satisfactory.

Genetic studies in sAD have also provided a wealth of information identifying genetic risk factors

which principally cover cholesterol and lipid metabolism, inflammation, and cell membranes and synapses (1390).

A scheme of the several factors involved in brain aging and sAD is presented in figure 9. In addition to genetic factors, there is an interaction between molecular alterations in cellular structures that may favor the production of β-amyloid and abnormal tau. Conversely, the presence of β-amyloid and abnormal tau has a negative effect on the majority of cellular structures, contributing to a detrimental loop in sAD pathogenesis.

Molecular alterations are similar and cumulative in brain aging and sAD. Therefore, a continuum of brain aging and sAD primarily based on an archetypal distribution of NFTs usually followed by the deposition of β-amyloid plaques is a factual possibility.

The pathogenesis and evolution of arteriosclerosis is another example of cumulative age-related degenerative changes in blood vessels. Almost all people are affected to some degree by the age of 65. However, the first lesions in atherosclerosis, characterized by macrophage infiltration and intracellular lipid accumulation in the blood vessel wall, may occur in the first or second decade; inflammation, endothelial and perycite damage, altered metabolism of muscle fibers, extracellular lipid cores and atheromatous plaques develop later. Clinical manifestations may appear at advanced stages of fibroatheroma, as well as complicated lesions in MA individuals. Thus, the atheromatous plaque, the characteristic lesion of atherosclerosis, is not the first requirement to identify atherosclerosis as a biological process which is expressed by cumulative stages of blood vessel damage leading or not to clinical manifestations of variable severity.

Searching possible therapies for sAD has been constant over the years. Cholinesterase inhibitors, NMDA receptor antagonists, membrane protectors, anti-oxidants, and anti-inflammatory agents, all assayed at middle and advanced clinical stages of sAD, have proven poorly effective. Other treatments are directed to reducing β-amyloid or tau accumulation. Several Aβ-protein-targeted drugs, including β-secretase inhibitors, γ-secretase inhibitors and modulators, α-secretase activators, direct inhibitors of Aβ aggregation, and immunotherapy have been assayed or are under different phases of clinical trial (1522). β-amyloid immunization in humans has been successful in the sense that SPs are largely reduced in the brain of treated patients; yet the abundance of tau deposits and the progression of the disease are not substantially modified by β-amyloid immunization (719, 1523, 1524). The clinical improvement seen with β-amyloid immunotherapy has been null or negligible, or at best arguable (1525-1530). Treatment with a BACE1 inhibitor has yielded very limited neuropathological improvement (1531). Trials with new generation Aβ immunotherapy are in progress.

Following the same line of thinking, tau immunization, although putatively preventing tau accumulation, is unlikely to be a unique alternative treatment (1532-1534). Various tau-based therapies have been developed or are under development. These therapies include the use of inhibitors of tau phosphorylation, glycosylation, and acetylation; microtubule stabilizers; inhibitors of tau aggregation; and anti-tau immunotherapy (1535-1538). Various tau therapies based on active and passive immunization are effective in murine and primate models. However, some of these attempts have failed in sAD (1539). Although encouraging, it is not clear how such treatments will reduce the different forms of abnormal tau and decrease Aβ burden. In short, there is no evidence that merely lessening the abnormal levels and deposits of tau or β-amyloid at middle and advanced stages of the illness will cure sAD. Therefore, it is crucial to re-consider the optimal age to start combined anti-tau- and anti-β-amyloid-based treatments to combat two main representative components of AD. The identification of new putative targets for therapeutic intervention before the appearance of tau and amyloid deposits is a promising endeavor.

Gene therapy has also been assessed in transgenic mouse models with variable success using both vector-based therapies and genetically modified cell replacement (1540-1542). Studies in humans are limited, at this time, to upregulated NGF in sAD patients, with little evidence of benefit (1543-1545).

Exosomes are a class of membrane vesicles derived from endolysosomal compartment implicated

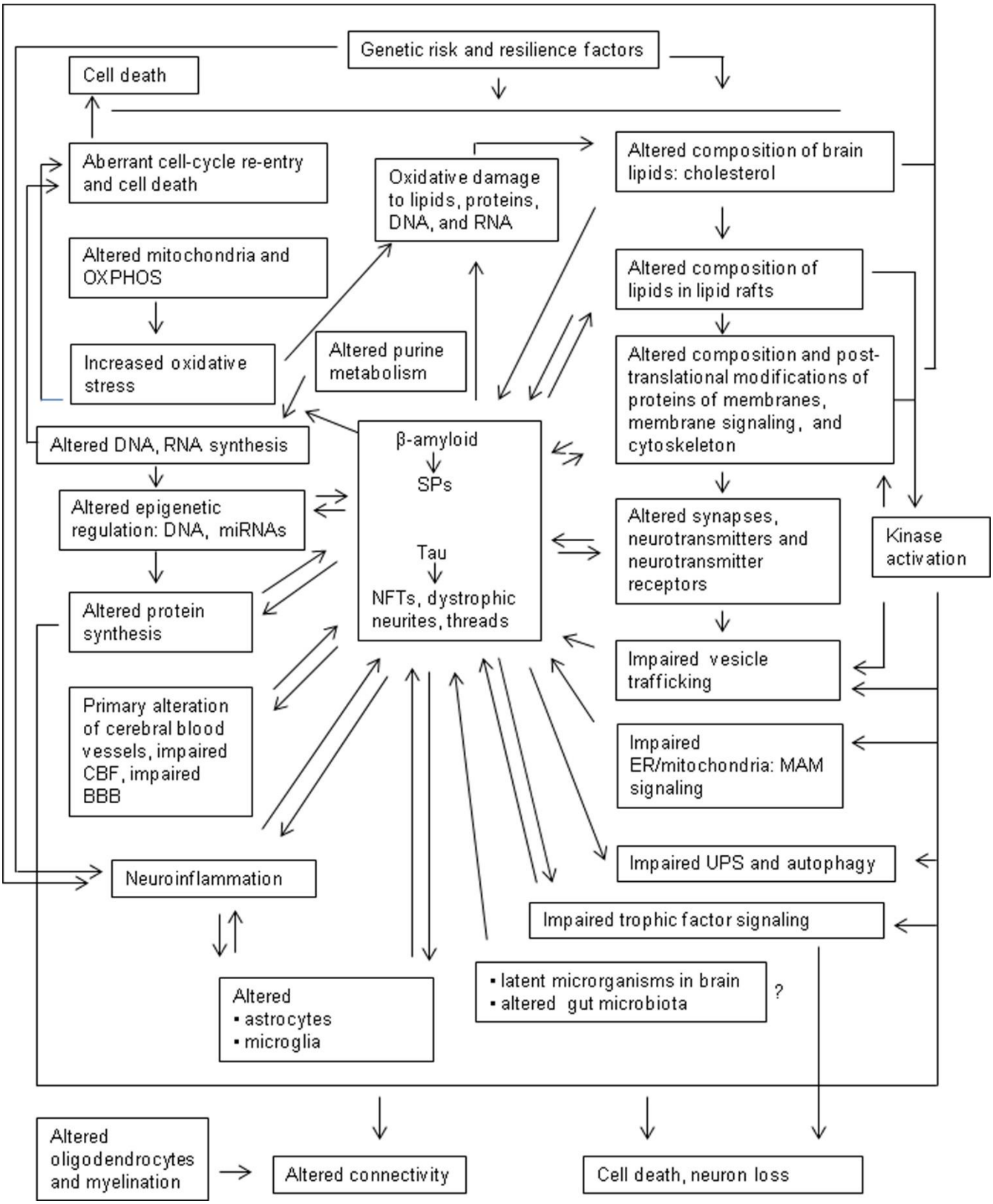

Figure 9: Factors involved in brain aging and sAD. In addition to genetic factors, molecular alterations in cellular structures may induce the production of β-amyloid and abnormal tau. Conversely, the presence of β-amyloid and abnormal tau has a negative effect on the majority of cellular structures, contributing to a harmful loop in sAD pathogenesis.

in cell-cell communication by shuttling different lipids, protein, and RNAs between cells. The use of shuttles including exosomes to deliver selected molecules into the cells is still at the early stages.

The meager success of available therapies to curb the effects of human brain aging and sAD is a matter of concern. Besides disease modification and symptomatic therapies for sAD (1546-1549), other relevant and long-term ventures may also be considered.

One of these is a revision of animal models used to test sAD therapies, because they have failed when applied to humans (1550). To make this clear: for 25 years, many AD-like mouse models have been "cured" in the lab, only for the treatments to fail in clinical trials in humans (1551, 1552). It seems that mice have the ability to remodel complex metabolic defects once one of the factors involved in the process is normalized. This does not occur in humans.

These considerations are made yet more compulsory because a number of molecular function derangements take place before or concurrent with the appearance of β-amyloid and tau pathology morphologically manifested as NFTs and SPs. Altered lipid and protein composition of cellular membranes accompanied by impaired subcellular cell signaling from the cell membrane to the ER, mitochondrial membranes, altered synapses, altered mitochondria and energy metabolism, and reactivation and abortion of developmental programs leading to neuronal death, together with dysfunctional BBB and singular brain inflammatory expression, all point to sAD as a human brain age-related disorder of convergent mechanisms that shatters brain self-organization (329, 1343, 1553, 1554).

A great data analysis covering the tremendous body of information on AD must be updated in real time.

We need to think of the coming decades as an opportunity to take advantage of the rapid growth of artificial intelligence (AI) and cell reprogramming. We will be able to redesign some aspects of the human brain in the near future using advanced technologies. To this end, we also need to identify the main targets and appropriate intervention times. Timing is crucial since it will be difficult to reprogram molecular pathways in old-adult individuals that have already suffered brain deterioration. Brain reprogramming would likely be undertaken before the beginning of the slow-pace functional decline in MA adults. Brain reprogramming may cover different areas including brain DNA editing, utilization of external electrical or wave-based signals to reduce energy consumption of basic neuronal networks, optimization of mitochondrial function, implanting of microdevices to facilitate cooperative human-machine function, pharmacological combined protection of lipid-protein interactions, and program resetting during stages of sleep. Improvement of brain function in aging and sAD has a chance in the application of high-throughput molecular technology, AI, and robotics (1394, 1555-1561). This new era is certain to present formidable ethical challenges.

Abbreviations

2-AG: arachidonoyl glycerol; 5-HT: 5-hydroxytriptamine; 3'-UTR: complementary un-translated regions; AA: arachidonic acid; Aβ: beta amyloid; ABCA7: ATP binding cassette subfamily A member 7; AβOs: soluble β-amyloid oligomers; AC: adenylyl cyclise; ACh: acetylcholine; AChE: acetylcholinesterase; AD: Alzheimer disease; ADAM10: ADAM metallopeptidase domain 10; ADDLs: amyloid-β derived diffusible ligands; ADNC: AD-neuropathologic change; AEA: N-arachidonoyl ethanolamine; AGD: argyrophylic grain disease; AGEs: advanced glycation end-products; Ago: argonaute subfamily proteins; AI: artificial intelligence; ALEs: advanced lipoxidation end-products; AMP: adenosine monophosphate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; APHH1A: α-secretase subunit A; ApoE: apolipoprotein E; APP: amyloid precursor protein; AQP: aquaporin; ARTAG: aging-related tau astrogliopathy; ASC: inflammasome-adaptor protein; ATF-6: activating transcription factor 6; ATP8B1: ATPase phospholipid transporting 8B1; ATP: adenosine triphosphate; BACE: β-secretase; β-AR: β-adrenergic receptor; BBB: blood brain barrier; BDNF: brain-derived neurotrophic factor; BIN1: bridging integrator 1; C1QTNF7: complement C1q tumor necrosis factor-related protein 7; C3AR1: complement C3a receptor 1; Ca2+: calcium ion; cAMP: cyclic adenosine monophosphate; CB: calbindin D28K; CBF: cerebral blood

flow; CBR: cannabinoid receptor; CD2AP: CD2-associated protein; CDK5: cyclin-dependent kinase 5; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CEL: carboxyethyl-lysine; cGMP: cyclic guanosine monophosphate; ChAT: choline acetyl transferase; CK1-δ: casein kinase I isoform delta; CLU: clusterin; CML: carboxymethyl-lysine; CMV: human cytomegalovirus; CNP: 2',3'-cyclic-nucleotide 3'-phosphodiesterase; CNS: central nervous system; COMT: catechol-O-methyltransferase; CpG: cytosine-guanine-rich regions ; CR: calretinin; CR1: complement component (3b/4b) receptor 1; CREB: cAMP response element-binding protein; CSF: cerebrospinal fluid; CSF1R: colony stimulating factor 1 receptor; CSF3R: colony stimulating factor 3 receptor; CT: computed tomography; DAG: diacylglycerol; DBH: dopamine β-hydroxylase; DCX: doublecortin; DHA: docosahexanoic acid; DNMT: DNA methyl transferases; GSH: glutathione; EAAT: excitatory amino acid transporter; EBV: Epstein-Barr virus; EOFAD: early onset Alzheimer disease; Eph: ephrin; EPHA1: ephrin receptor A1; ER: endoplasmic reticulum; exRNAs: extracellular RNAs; fAD: familial Alzheimer disease; FAD: flavin adenine dinucleotide; FBD: familial British dementia; FcγRIIb: FCγ receptor II-b; FDD: familial Danish dementia; GABA: γ- aminobutyric acid; $GABA_A$ receptors: ionotropic $GABA_A$ receptors; $GABA_B$ receptors: metabotropic $GABA_B$ receptors; GAD: glutamic acid decarboxylase; GAP-43: growth-associated protein 43; GDH: glutamate dehydrogenase; GFAP: glial fibrillary acidic protein; GluRs: glutamate receptors; GLUT 1: glucose transporter 1; GMP: guanosine monophosphate; GPCR: G-protein-coupled receptor; GRP78/BiP: glucose-related protein 78; GSK3β: glycogen synthase kinase 3β; GSS: Gerstmann-Sträussler-Scheinker; GVD: granulovacuolar degeneration; GWAS: genome-wide association studies; H3K4me1: methylation of lysine 4 of histone 3; H3K4m3: trimethylation of histone 3 at lysine 4; H3K9me2: dimethylation of histone H3 at lysine 9; HAT: histone acetyltransferase; HDAC: histone deacetylase; HDM: histone demethylase; HHV-6: human herpes virus 6; HMT: histone methyltransferase; HNE: 4-hydroxynonenal; HSV-1: herpes simplex virus 1; iCJD: iatrogenic Creutzfeldt-Jabob disease; IDE: insulin degrading enzyme; IFN-γ: interferon γ; iGluR: ioinotropic glutamate receptor; IL: interleukin; iPSC: indiuced pluripotent stem cells; IRE 1: inositol-requiring protein 1; Jak2: janus kinase 2; KA: kainate; KAR: kainate receptor; LAMP-1: lysosomal-associated membrane protein 1; LC3: protein light chain 3; LC-MS/MS: liquid chromatography (LC) tandem mass spectrometry (MS); lcnRNAs: long non-coding RNAs; LDH: lactate dehydrogenase; LDLR: low density lipoprotein protein receptor 1; LilrB2: PirB human orthologue receptor ; LOAD: late onset Alzheimer disease; LP2: lipoprotein lipase 2; LRP1: HLDL receptor related protein 1; MA: middle-aged; mAChR: muscarinic acetylcholine receptor; MAG: myelin associated glycoprotein; MAL: myelkin and lymphocyte protein; MAMs: mitochondria-associated ER membranes; MAP2- microtubule associated protein 2; MAPK: mitogen-activated protein kinase; MAPT: microtubule associated protein tau; MAPT H1: microtubule-associated protein tau haplotype 1; MAO: mono-amino oxidase; MBP: myelin basic protein; MCI: mild cognitive impairment; MDA: malondialdehyde; MDAL: MDA-lysine; MEF2C: myocyte-specific enhancer factor 2C; Mg2+: magnesium ion; mGluR: metabotropic glutamate receptor; miRNA: microRNA; MLKL: mixed lineage kinase domain-like protein; MOBP: myelin-associated oligodendrocyte basic protein; MOG: myelin-oligodendrocyte glycoprotein; MRI: magnetic resonance imaging; MSA4: membrane-spanning 4-domains subfamily A; mtRNAs: mitochondrial RNAs; MUFA: monounsaturated fatty acids; nAChR: nicotinic acetylcholine receptor; NADþ: nicotinamide adenine dinucleotide; NADPþ: nicotinamide adenine dinucleotide phosphate; NCT/NCSTN: nicastrin; NEP/NME: neprelysin; NFT: neurofibrillary tangle; NG2: neural/glial antigen 2; NGF: nerve growth factor; NIA-AA: National Institute on Aging–Alzheimer's Association; NLRP3R: pyrin-domain containing 3; NMDA: N-methyl D-aspartate; NMDAR: N-methyl-D-aspartate receptor; NOR: nuclear iorganizer region; NPM1: Nucleophosmin 1; nRNAs: small non-coding RNAs; OPC: oligodendroglial precurosor cells; PART: primary age-related tauopathy; $P75^{NTR}$: p75 neurotrophin receptor, low affinity nerve growth factor receptor; PDGFRA: platelet-derived growth factor receptor A; PEN2/PSENEN: presenilin enhancer γ-secretase subunit; PERK: PKR-like endoplasmic reticulum kinase; PET: positron emission tomography; PHF: paired helical filament; PI3K: phosphatidylinositol 3-kinase; PI3P: phosphatidylinositol trisphosphate; PICALM: phosphatidylinositol binding clathrin assembly protein; PiD: Pick disease; PILRA: paired immunoglobin like type 2 receptor alpha; PirB:

paired immunoglobulin-like receptor B; piRNAs: PIWI-interacting RNAs; PKA: protein kinase A; PKC: protein kinase C; PLC: phospholipase C; PLP1: proteolipid protein 1; PPAR: peroxisome proliferator-activated receptors; PRNP: prion protein gene; PrP^{C}: cellular prion protein; PSEN1: presenilin 1; PSEN2: presenilin 2; PTK2B: protein tyrosine kinase 2 beta; PUFA: polyunsaturated fatty acids; PV: parvalbumin; RAB10: Ras-related protein Rab-10; RAGE: AGE receptor; REST: RE1-silencing transcription factor; RIP3: receptor interacting protein 3; RNS: reactive nitrogen species; RORB: RAR related orphan receptor B; ROS: reactive oxygen species; RP: ribosomal protein; rpAD: rapidly progressive AD; rRNA: ribosomal RNA; sAD: sporadic Alzheimer disease; SAM: S-adenosyl-L-methionine; SAPK/JNK: stress-activated protein kinase/JUN N-terminal kinase; scaRNAs: small Cajal-body specific RNAs; SFPQ: splicing factor proline and glutamine rich; siRNAs: small interfering RNAs; SNAP: soluble NSF attachment protein receptor; SNARE: SNAP receptor protein; snRNAseq: single nuclei RNA sequencing; snRNA: small nuclear RNAs; snoRNAs: small nucleolar RNAs; SORL1: sortilin-related receptor 1; SPI1: Spi-1 proto-oncogene; SP: senile plaque; STAT1: signal transducer and activator of transcription 1; TET1: ten-eleven-translocation-1 protein; TGF: transforming growth factor; TLR : Toll like receptor; TNF: tumor necrosis factor; TOR: target of rapamycin; TRAF2: TNF receptor-associated factor 2; TREM2: triggering receptor expressed on myeloid cells 2; TrkA: specific NGF receptor; tRNA: transfer RNAs; UBTF: upstream binding transcription factor RNA polymerase I gene; UCHL-1: ubiquitin C-terminal hydrolase L1; UPR: misfolded protein response; UPS: ubiquitin proteasome system; VGAT: vesicular GABA transporter; VGLUT: vesicular glutamate transporter; VMAT: vesicular monoamino transporter; WM: white matter; WT: wild type; XBP-1: X-box binding protein 1.

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