Alzheimer's Disease: From Animal Models to the Human Syndrome

Erika Orta-Salazar, Isaac Vargas-Rodríguez,
Susana A Castro-Chavira,
Alfredo I. Feria-Velasco and Sofía Díaz-Cintra

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Abstract

Some animal models, genetically modified (such as murine) and sporadic (as others species), enable the study of the origin of specific lesions observed in human neurodegenerative diseases. In particular, Alzheimer's disease (AD) models have been designed to test the hypothesis that certain lesions are associated with functional and morphological changes beginning with memory loss and impairment in activities of daily life. This review compares and evaluates the phenotypes of different AD animal models, on the basis of the specific objectives of each study, with the purpose of encompassing their contributions to the comprehension of the AD signs and symptoms in humans. All these models contribute to the comprehension of the human AD mechanisms regarding the heterogeneity of AD phenotypes: the overlap between AD and age-related changes, the variability of AD onset (early or late), the probable reactiveness of amyloid-β and tau proteins, the scarcity of senile plaques and/or neurofibrillary tangles in some AD cases, the spatial correlation of the pathology and cerebral blood vessels, and the immunological responses (microglial aging) and synaptopathy. Altogether, these considerations may contribute to find therapies to treat and prevent this disease.

Keywords: Alzheimer's disease, nutritional risk, murine, human, genetic Alzheimer's disease, sporadic Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is one of the major progressive and irreversible neurodegenerative diseases associated with aging [1]. The first case was identified by Dr. Alois Alzheimer in 1901 who presented the clinical and neuropathological characteristics of this disease on November 3, 1906 at the 37th meeting of the Society of Southwest German Psychiatrists in Tübingen, Germany [2]. AD is a progressively degenerative disease that destroys the patient's functional capacity and is the primary cause for loss of functional capacity among the elderly in developed countries [3]. AD accounts for 60–80% of all dementia cases, as described in the Organisation for Economic Cooperation and Development (OECD) report. The number of people worldwide living with AD was estimated at between 27 million and 36 million in 2016 [4, 5]. AD symptoms worsen over time at a variable rate; on average; AD patients live between 4 and 8 years after diagnosis, but they could live until 20 years, depending on various factors. Once installed, three main stages of pathological progression of AD have been defined, namely early, middle and late.

In the early stage, a person may have memory lapses, such as forgetting familiar words or names, losing or misplacing a valuable object, or being unable to plan or organize. The middle stage is the longest and can last many years. The person with middle stage AD may confuse words, become easily frustrated or angry, and has increased difficulty expressing thoughts and performing routine tasks. In late stage or severe dementia, the person loses the ability to respond to the environment, to carry on a conversation and, eventually, to control movement; memory and cognitive skills continue to worsen, personality changes may occur and individuals need extensive help with daily activities [5]. According to the age of onset, AD can be classified as: early-onset or familial AD accounting for only 5–10 % of AD cases, or late-onset or sporadic AD accounting for the rest of the AD cases. Familial AD is associated with mutations in the genes for presenilin (PS) 1 and 2 and/or amyloid precursor protein (APP); its symptoms appear at 30–50 years of age, whereas the majority of sporadic cases develop after age 65 [6].

AD is a multifactorial disease that is a pathologically and etiologically complex. There are a few causative genes which have been linked to the relatively small proportion of patients with early-onset familial AD [7]. The molecular analysis of families with early-onset AD has made it possible to identify mutations in genes associated with the disease: APP, PS 1 and PS 2, and the mean onset age is 45. Mutations in Apolipoprotein E ε4 (Apo E ε4) genes are present in 15–20% of AD cases appearing after 65 years of age. Three additional genes.

There are numerous hypotheses to explain the appearance of sporadic AD, such as head trauma, neuroinflammation, poor dietary habits and the lack of exercise, but the cause is still unknown [8, 9]. A possible explanation is that the abundant knowledge of AD biochemistry has not yet been well integrated into the cellular context of brain [10].

In order to elucidate the AD etiology, animal models that have genetic mutations linked to familial AD and show the same disease progression pattern have been developed. These models are either based on: (1) the overexpression of APP and secretases [11, 12]; (2) mutated APP [13, 14]; or (3) the overexpression of human APP (hAPP) together with mutated forms of

PS [15]. Notwithstanding these mutations, such mouse models rarely develop neurofibrillary tangles (NFTs). To simulate tau pathology, a microtubule-associated protein tau (MAPT) mutation associated with frontotemporal dementia is included in the 3xTg-AD mouse, in which the expression of hAPP and mutated forms of PS and tau are combined [16, 17]. Currently, at least 11 rodent models that exhibit AD characteristics, such as Aβ accumulation, tau pathology, neuronal loss and pathophysiology of glial cells, are being studied [6, 18].

2. Methods

For the AD definition, relevant representative book chapters, journal articles and a web page were selected aiming to first summarize the basics of well-established knowledge on Alzheimer's disease that included its biochemical, neuropathological and physiological features. Then, a literature search with the computerized PubMed data base was conducted in February, 2016 with no limit of date. We used the following search terms: (Malnutrition AND Senescence), (Malnutrition AND Alzheimer), and (Senescence). Then, relevant references cited in papers found via this search were reviewed. Studies were selected if they either provided updated information on the AD basics or regarding the biological mechanisms underlying Alzheimer's disease. Case studies were excluded. A total of 170 journal articles, four book chapters and a web page were selected.

3. Histopathological brain changes in AD

Autopsy studies examining the incidence of neuropathological lesions and clinical symptoms reveal that AD often occurs in conjunction with other pathologies, specifically, vascular and Lewy body dementias. The overlap of pathologies suggests the existence of common patho-physiological mechanisms [19].

In AD brains, many cellular and molecular changes coincide with changes in the proteins and genes implicated. The two primary lesions associated with AD are NFTs and the senile plaques first described by Alois Alzheimer. Graeber and co-workers explained in 1998 that the tissue sections of cerebral cortex from Auguste D had numerous NFTs and many amyloid plaques, especially in the upper cortical layer of the brain [20]. In this tissue, NFTs can be seen as accumulations of abnormally phosphorylated tau protein within the perikaryal cytoplasm of cortical neurons, and senile plaques consist of a central core of amyloid-β (Aβ), a 4-kD peptide, surrounded by abnormally configured neuronal processes or neurites; the neurites are localized similarly in animal models such as the PDAPP first model, which develops plaques and cognitive deficits similar to those in humans [13].

These histopathological features start in the temporal lobe and extend to the Meynert nucleus that projects to the hippocampus and to the frontal, parietal and occipital cortices, all of which have important roles in the control of cognitive functions; gradually, these lesions destroy a person's memory and ability to learn, to reason, to communicate and to carry out daily activities

[21, 22]. The first histopathological lesion is the intracellular NFT, which consists largely of twisted, hyperphosphorylated filaments of the microtubule-associated protein tau. The second lesion type is the extracellular plaque of differently sized, small amyloid peptides called Aβ that are derived via sequential proteolytic cleavages of APP [23]. The two types of lesions seem to form independently, with tangles appearing first [24]. Affected regions typically exhibit synaptic and neuronal loss, with cholinergic and glutamatergic neurons being the most affected [25], as well as inflammation, gliosis, oxidative stress and neuronal dystrophy [8].

3.1. Brain atrophy and traumatic brain injury

New technologies based on structural and functional neuroimaging and on the biochemical analysis of cerebrospinal fluid have established interesting correlates of intracerebral amyloidosis in individuals with mild, pre-dementia symptoms.

Whole brain volume changes are used as surrogate markers for AD neuropathology in clinical studies; the extent to which these changes can be attributed to pathological features of AD in the aging brain may be established using other signs of brain atrophy in patients showing cognitive impairment [26]. The relationship between pathology and brain atrophy is not simple and linear; neither is the distinction between normal aging and the disease, which is a complicated issue. Aging, dementia diagnosis and AD pathologies closely correlate with enlargement of the brain ventricles but not with reduced total brain volume. Ventricle enlargement may be a response to various conditions and reflect changes in both white and gray matter of the brain, and may be related to cerebrovascular disease and AD. Clinically, brain atrophy in AD patients precedes symptoms. Researchers have proposed using brain atrophy as a surrogate marker for pathology in clinical trials and longitudinal studies. For example, decreased hippocampal volume is considered an acceptable marker in people with mild cognitive impairment (MCI) and at early stages of AD.

It is well established that AD leads to nerve cell death and tissue loss throughout the brain. As more neurons die, more brain regions are affected and over time, the brain shrinks dramatically leading to functional impairment. The atrophy pattern involves white matter and largely spares the isocortex and hippocampus, which is different from that reported in AD patients [27]. The atrophy of the medial temporal lobe, including the entorhinal cortex, amygdala and hippocampus, is closely related to impairment for forming new memories. The hippocampus in AD patients may lose 3–4% of its volume in a year, whereas average loss in a normal brain is less than 1%. Thus, these hippocampal alterations are one of the best-established signs of AD. Furthermore, the hippocampus is more susceptible to reduced blood flow, which occurs in cortical amyloid angiopathy.

Some studies evaluating brain atrophy in the transgenic PDAPP mouse model found a reduction in hippocampal volume and severe atrophy or agenesis of fiber tracts, fornix and corpus callosum [28–30]. ApoE ε4 is associated with increased risk of sporadic AD and of conversion from mild cognitive impairment to AD. ApoE ε4 also plays an important role in brain atrophy and memory impairment by modulating amyloid production and deposition [31].

Microglia is the innate immune cell in the brain that, as a result of brain injury like infection or traumatic injury, produces cytokines and may remain primed in a state where a second stimulus produces an exaggerated activation (hyper-reactivity). This response may be triggered by traumatic brain injury, infection or aging [32, 33], which are risk factors for developing AD. Hyper-activated microglia is importantly involved in this process [33–35].

3.2. Neuronal and synaptic loss

Extracellular accumulation of Aβ protein and intracellular accumulation of tau in brain tissues have been described in animal models of AD, as well as in some mechanical stress-based diseases with different mechanisms, such as traumatic brain injury, arterial hypertension and normal pressure hydrocephalus.

Numerous studies dealing with AD have shown evidence for synaptic dysfunction, which correlates with cognitive decline along with an abundance of plaques or tangles [36]. Synapse abnormalities in AD brain tissue were first described by Gonatas and colleagues [37]. Quantitative ultrastructural and immunohistochemical *postmortem* studies of brain samples from patients with MCI to early-mild AD confirmed previous results that synapse loss was an early structural finding that correlated with AD severity. These studies showed a marked loss of synaptic proteins, such as synaptophysin, SV2 and p65, in the brains of AD patients [38–41]. Numerous factors have been associated with increased risk of AD: diabetes, hypertension, smoking, obesity and dyslipidemia [3].

Dysfunction of synaptic communication in cortical and hippocampal networks has been suggested as one of the neuropathological hallmarks of the early stages of AD and has been increasingly referred to as a "synaptopathy", in which the soluble oligomeric Aβ peptide plays a pivotal role in disrupting synaptic function and, thus, in neuronal network activity [42, 43]. In addition, high levels of soluble Aβ oligomers show a strong correlation with synaptic dysfunction, which contributes to neurodegeneration. This reflects the loss or damage to synapses that occurs as the disease progresses, which in turn produces functional degeneration of specific neuronal circuits and consequent aberrant activity in neural networks; however, the exact mechanisms are still unknown. One possibility is the immediate-early gene Arc/Arg3.1 (early-expression activity-regulated cytoskeletal gene, here referred to as Arc), one of the genes known to be vital for memory consolidation and synaptic plasticity. Also, the mapping of Arc expression patterns in brain networks has been extensively used as a marker of memory-relevant neuronal activity history. A recent study by Morin et al. proposes that in 3xTg-AD mice, intraneuronal Aβ expression in the hippocampus could increase unspecific neuronal activation and subsequent Arc protein expression, which might impair further memory-stabilizing processes [44]. Understanding the link between intracellular Aβ and Arc/Arg3.1 protein function should help disentangle the molecular and cellular mechanisms underlying episodic memory deficits during the early phases of AD and could clarify the role of disrupted hippocampal excitability in memory retrieval deficits occurring in early-stage AD-like pathology.

3.3. Synaptopathy

Activated Arc/Arg3.1 is targeted to the post-synaptic density of synaptically active dendritic spines where it associates with polysomes. Arc interacts with endophilin 2/3 and dynamin, contributing to α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) type glutamate receptor (AMPAR) modulation by enhancing receptor endocytosis. The Arc-endosome also traffics APP and physically associates with PS 1, thereby increasing the amount of activity-dependent Aβ [45]. This may be a positive feedback mechanism in which removal of the AMPAR from the synapse will produce a significant loss of dendritic spines and synaptic activity, resulting in synaptic failure similar to that observed in AD. Activity of the *N*-methyl-D-aspartate receptor (NMDAR) in the hippocampus is also known to be crucial for long-term spatial memory formation and to play a role in AD pathogenesis. The NMDAR is localized at synaptic and extra-synaptic sites where it has diverse functions, from modulating memory strength to neurotoxicity and neuroprotection, and one of the components of the NMDAR-associated signaling complex is Arc/Arg3.1. Other postsynaptic elements are the lipid rafts (subdomains of the plasma membrane that contain high concentrations of cholesterol and glycosphingolipids), which are involved in cell signaling and with the NMDAR complex. Thus, physiological and pathological events such as ischemia and spatial learning can induce movements of NMDAR signaling complexes between the postsynaptic density and lipid raft subdomains. Synaptopathy and lipid raft disruption may be related to the onset of episodic memory deficits during the early stages of AD [46–48]. In order to analyze this possibility, studies have been initiated to determine the content of NMDA and AMPA receptors as well as Arc/Arg3.1 levels in the lipid raft microdomains of the 3xTg-AD murine model of AD at the pre-plaque stage and to understand perturbations in neurons, which may help to explain the synaptic plasticity deficits and long-term memory impairments observed in AD models.

4. Proteins in the pathophysiology of AD

4.1. The amyloid precursor protein (APP)

The APP is a type 1 transmembrane glycoprotein of 110–130 kDa, one of the most abundant proteins in the central nervous system (CNS), and is cut by α-secretase within the sequence of amino acids that comprise the Aβ peptide, precluding formation of amyloid peptides [49]. In the amyloidogenic pathway, APP is cleaved instead by β-secretase, releasing a smaller N-terminal fragment (sAPPβ) and a longer C-terminal fragment (C99) that contains the full amyloidogenic sequence of amino acids. A further cleavage of APP by γ-secretase yields the Aβ peptide. In brain, there is an equilibrium between Aβ peptide production and its clearance [50]. How Aβ is removed from the brain is not entirely clear, but is mediated by two proteins: apolipoprotein E (APOE) and the insulin-degrading enzyme (IDE) that may inhibit its aggregation [51]. Disadvantageous genetic polymorphisms (such as the ε4 allele of APOE) and pathological conditions related to abnormal IDE homeostasis (e.g., diabetes mellitus) that may favor the amyloidogenic cleavage of APP and/or decrease Aβ clearance from the brain will

therefore facilitate Aβ accumulation in neural tissues and the downstream effects of the amyloid cascade [52].

4.2. Deposition of Aβ

Aβ is produced by endoproteolysis, post-translational processing of the amyloid precursor protein (APP), which is achieved by the sequential cleavage of APP by groups of enzymes or enzyme complexes termed α-, β- and γ-secretases [53]. The first transgenic mouse (PDAPP) model that developed amyloid plaque pathology was generated by Games and colleagues to express human APP containing mutations associated with early-onset AD; results obtained in these mice support a primary role for APP/Aβ in the genesis of AD and show they could provide a preclinical model for testing therapeutic drugs [13]. Since then, other mouse models have been created that recapitulate all aspects of AD including processing of the APP. However, not all APP transgenic mice have cognitive impairment, cellular loss and other AD characteristics, and they fail to replicate the full human disease. Some models actually confirm that the reduction of Aβ is insufficient to rescue memory function once downstream processes are underway. Conversely, other studies in mice predict that immunization against Abfix might prevent cognitive decline if administered early enough [54]. Also, Schenk et al. [55] studied transgenic mouse models and reported that their active immunization alleviated the burden of amyloid plaque, suggesting a potential therapeutic strategy [56].

Brain injury is reported to accelerate Aβ deposition and exacerbate Alzheimer's disease associated with impairment of cognition prior to the emergence of Aβ plaques. However, the relationships between Aβ levels (Aβ 40, A β42, or the ratio of Aβ 42 to Aβ 40), gender, age and cognitive function were measured in five mouse models (Tg2576, APP, PS 1, APP(OSK)-Tg, 3xTg-AD), see reference [57]. They used behavior tests such as escape latency times in the Morris water maze or exploratory preference percentage in the novel object recognition test. Tg2576 mice, overexpressing human APP_{695} concentration six times greater than that of normal mouse APP levels, show higher levels of Aβ40 and Aβ42 and Aβ deposits that begin at 9 months of age [58]. The APP models express hAPPSw and APP751 isoforms under the control of the murine Thy1 promoter. As a result, this mouse exhibits levels of human APP seven times greater than that of wild-type mice, and its Aβ plaques begin at 6 months of age. The APP(OSK)-Tg mouse expresses APP harboring the Osaka (E693) mutation, and it exhibits intraneuronal Aβ oligomers and memory impairment from 8 months of age. The PS 1 model expresses human PS with the mutation M146L or M146V via the PDGF-β promoter and higher levels of endogenous mouse Aβ1-42/43 [59]. The 3xTg-AD, triple-transgenic model exhibits both Aβ and tau pathologies and mimics human AD [60]. Thus, the possible role of Aβ in AD cognitive decline needs to be further investigated, fueled by other possible hypotheses and explanations [57].

4.3. Apolipoprotein E

Genetic association studies reveal that several genes such as ApoE are associated with multiple age-related disorders, indicating that these genes could play a crucial role in their causation. The e4 allele of the apolipoprotein E (ApoE) gene is the best-known genetic risk factor for AD,

because it has been suggested to affect both Aβ and NFT pathology in AD. ApoE is a 34-kDa lipid-binding protein that functions in the transport of triglycerides and cholesterol in multiple tissues by interacting with lipoprotein receptors on target cells; these functions are particularly critical for the central nervous system where ApoE transport of cholesterol is important for the maintenance of myelin and neuronal membranes [60]. Polymorphism of the ApoE gene has been implicated in many chronic cardiovascular (myocardial infarction, hypertension, coronary heart) and neuronal diseases. The ApoE ε4 genotype not only is a risk factor for cardiovascular disease but also it combines synergistically with age, atherosclerosis, peripheral vascular disease or type-2 diabetes to increase the risk of AD [62–66].

The ApoE gene is expressed most highly in the liver and brain; genome-wide association studies have confirmed the ε4 allele of ApoE as the strongest genetic risk factor for AD [67, 68], because over 60% of persons with AD harbor at least one ApoE-ε4 allele, and recent data indicate complex interactions between age, ApoE genotype and gender [61]. In reference [69], Dowell et al. used NMR to study two age groups: a young group (average age, 21 years) and a mid-age group (average age, 50 years); they reported that there are regional white matter brain volume and cortical thickness differences between genotype groups at each age. They raised the possibility that an over-engagement with these regions by e4+ individuals in youth may have a neurogenic effect that is observable later in life. According to a genome-wide association study of cerebrospinal fluid (CSF) from AD subjects, several single nucleotide polymorphisms (SNPs) in the ApoE gene region of the brain were also associated with phosphorylated tau (p tau) elevated levels in the CSF. When cerebrospinal fluid levels of Aβ 1–42 were analyzed together with tau/p tau, a significant correlation was found with SNPs of the ApoE gene. ApoE is also a crucial regulator of the innate immune system, which promotes pro-inflammatory responses that could exacerbate AD pathogenesis [70].

In 2002, Colton et al. demonstrated that ApoE regulates the production of nitric oxide (NO), a critical cytoactive factor released by active macrophages. Thus, due to greater NO production, ApoE4 carriers characteristically have high levels of oxidative/nitrosative stress and a higher incidence of AD, a mechanism that explains the genetic association between ApoE4 and human diseases [71].

4.4. Tau accumulation

Besides the accumulation of soluble and toxic Aβ-aggregates, tau accumulation causes oxidative stress and mitochondrial dysfunction, and it is linked to the initiation of the tau cascade. The tauopathies are a group of degenerative diseases with histopathology character-ized by filamentary inclusions composed of tau protein in neurons (NFT pathology). These are abundant in many neurodegenerative diseases, including AD, Pick's disease, argyrophilic grain disease and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) [72]. In AD, the presence of neurofibrillary tangles (NFT) composed of tau is prominent, and their density correlates with neuronal loss and clinical severity [72, 74]. Dystrophic neurites are all sites of accumulation of pathological paired helical filaments (PHFs) that appear to be central to neurofibrillary degeneration of neuropathology and that contain

(the microtubule-associated protein) tau as an integral structural component [75–78]. Also, tau processing in AD, leading to the formation of paired helical filaments, is driven by aggregation and polymerization, and appears to be associated with abnormal phosphorylation and truncation processes [79]. Mouse models expressing the P301L mutation causing neurofibrillary degeneration have been generated to study neurofibrillary pathologies [80]; and this mutation facilitates the development in transgenic mice of tauopathies [81–83] that recapitulate human tauopathies [83]; these mice provided the opportunity to test experimentally whether the distribution or timing of neurofibrillary pathology is influenced by the pathogenic mutations that cause AD. However, the physiology of tau protein is different in adult mice and humans; because mouse brain contains only isoforms like 4R, while in normal adult human there is a balance between 3R and 4R isoforms [85].

There is a clear link between type 2 diabetes mellitus and AD, and the use of antidiabetic drugs such as metformin has been proposed as a potential therapy for AD. There is also experimental evidence that metformin may have beneficial effects on cognition [86]. However, it remains unknown whether, in the absence of insulin resistance or diabetes, chronic treatment with metformin ameliorates tau pathology and behavioral performance in a transgenic model of neurodegenerative tauopathy *in vivo*. A recent study by Barini et al. shows how metformin modulates tau pathology in vivo. In P301S mice, they found similar levels of tau and ptau in the cortex and hippocampus with or without metformin, but metformin enhanced hyperactive behavior in the open field test. Due to dual actions on tau phosphorylation and aggregation, metformin may unpredictably impact the development of tauopathy in elderly diabetic patients at risk for AD [87].

In order to elucidate the molecular mechanisms underlying the post-translational modifications of Aβ and tau, several transgenic mouse models have been developed. One of these models is the 3xTg-AD transgenic mouse, carrying three transgenes encoding the APPSWE, S1M146V and TauP301L proteins. Ontiveros-Torres et al. reported the hippocampal accumulation of fibrillar Aβ as a function of age and hyperphosphorylation patterns of TauP301L at both its N- and C-termini: the expression of activated protein kinases and mediators of inflammation was monitored from 3 to 28 months as well. These authors reported that the accumulation of Aβ oligomers results in an inflammatory environment that upregulates kinases involved in hyperphosphorylation of the TauP301L polypeptide. The 3xTg-AD mouse is an excellent model for further studying pathological modifications of key factors in AD [88].

5. Hypotheses explaining AD

5.1. Developmental origins of health and adult disease in dementia

Today, an increasing number of epidemiological, clinical and experimental studies suggest an association between toxicant and drug exposure during the perinatal period and the development of metabolic-related diseases and neurotoxicity later in life. A study called 'The developmental origins of health and adult disease' (DOHaD) addressed fundamental issues in the emerging areas of lifetime neurotoxicity testing, differential vulnerable periods of

exposure, non-monotonic dose-response effects and neurotoxic risk assessment. Neurotoxicity during central nervous system development results in permanent changes.

The DOHaD hypothesis proposes an association of early fetal environment with adult size, later ischemic heart disease, hypertension, metabolism, diabetes and insulin resistance, which are risk factors for dementia, obesity and deficits in behavior and learning [89–91]. Aβ-derived diffusible ligands (ADDL) also contribute to insulin deficits and insulin resistance in the brain of AD patients, and ADDL levels can be used to diagnose AD [92].

The brain of patients with AD has deficits in cerebral glucose utilization due to insulin/IGF resistance associated with increased oxidative stress, DNA damage, reactive oxygen species and mitochondrial dysfunction. The consequences of insulin and IGF resistance in the brain compromise neuronal survival, energy production, gene expression, and cerebral plasticity [93]. Thus, inhibition of insulin/IGF signaling mediates AD neurodegeneration by an increase in activity of kinases which phosphorylate tau; accumulation of AβPP – Aβ; mitochondrial dysfunction; generation of reactive oxygen and nitrogen species, oxidative and endoplasmic reticulum stress, and signaling through pro-inflammatory and pro-apoptotic cascades [93, 94].

Since Hoyer [95] proposed that the deficits in cerebral glucose utilization and energy metabolism worsen with progression in cognitive impairment. In addition, Steen et al. proposed that chronic deficits in insulin signaling mediate the pathogenesis of AD [96]. Additionally, AD could be regarded as a brain disorder that has composite features of type 1 (insulin deficiency) and type 2 (insulin resistance) diabetes. Thus, AD could be referred to as "type 3 diabetes", because both molecular and biochemical consequence overlap with type 1 and type 2 diabetes [94, 97]. Recently, experimental studies consider that glucose hypometabolism is an early and persistent sign of AD because brains present features of impaired insulin signaling, a model using intracerebroventricular streptozotocin injections (icv STZ model) to generate sporadic AD that emulates the AD characteristics of Aβ deposits on the wall of meningeal and cortical blood vessels, mitochondrial abnormalities and oxidative stress [98].

5.2. Mitochondria, aging and AD

A major risk factor in patients who progress to dementia is aging, which is characterized by defects in energy metabolism and mitochondrial function. Mitochondrial dysfunction is a hallmark of aging, and it plays a central role not only in Alzheimer's but also in Parkinson's disease [99]; it causes the accumulation of soluble and toxic Aβ-aggregates and oxidative stress, and it is linked to the initiation of the tau cascade. In addition, signaling from the nucleus to mitochondria may be crucial for the regulation of mitochondrial function and aging, possibly contributing to the development of age-associated diseases such as AD. Mitochondria not only play a central role in metabolic pathways, they also regulate cell fate through crosstalk between autophagy and apoptosis. Macroautophagy (autophagy) and apoptosis are intimately interconnected and determine whether cells survive or die [100].

On the other hand, genes define a baseline mitochondrial function, where maternal mtDNA contributes more, and environmental factors determine the rate of mitochondrial function, with less durability producing faster brain aging. Mitochondrial function influences AD, APP

expression and processing and Aß accumulation [101, 102]. Also in familiar AD (FAD), the impaired mitochondrial function is caused by PS (either PS 1 or PS 2) mutations, but about 10% are inherited, most of the cases are sporadic AD (SAD). Both FAD and SAD share the features of accumulated extra and intracellular Aβ plaques, as well as intracellular NFTs and cell atrophy and cell death, suggesting a common pathogenic origin on the basis of the intracellular Ca^{2+}-homeostasis disruption tested in a mutant PS with a mitochondrial dysfunction with potential cell death [103]. Xie et al. used APP/PS1 transgenic mice to study the temporal relationship among Aβ plaque deposition, oxidative stress, and cell death, identified Aβ as the mediator of oxidative stress and subsequent neurodegeneration. Oxidative stress began in neurites and was followed by the appearance of Aβ plaques in the surrounding tissue ultimately leading to oxidation in neuronal soma, but the oxidized neurites survived for several weeks. The oxidation in neuronal soma was associated with caspase-dependent apoptosis [104]. In addition, intermediate cellular players, including astrocytes or microglia, responded to amyloid deposits with chemokine or cytokine signaling which, in turn, led to oxidation in neurites.

The Glutamate (Glu) and mitochondria have a relationship in oxidative stress that underlies AD; Glu is an important neurotransmitter in neurons and glial cells, and is strongly dependent on calcium homeostasis and mitochondrial function [105]. Mitochondrial deficits occur early in AD, even before plaque formation [106]. Decreased expression of cytochrome c oxidase (COX) and pyruvate dehydrogenase (PDH) has also been detected in postmortem brain tissue of patients with AD, as well as in animal models. Substances used to maintain brain metabolism in the 3xTg-AD mouse model, such as icariin active component of the traditional Chinese herbal medicine *Epimedium*, could modulate neuronal cell activity, preserve mitochondria and functional synaptic proteins, inhibit Abfix expression and improve cognitive functions in AD mice [107].

5.3. Nutrition and AD

Genetic and environmental factors are particularly important for the sporadic form of AD. Diets rich in saturated fatty acids and alcohol but deficient in antioxidants and vitamins appear to promote the onset of the disease. In contrast, diets rich in antioxidants, vitamins B6, B12 and folate, unsaturated fatty acids, and fish suppress its onset [108]. During the last decade, many investigations have shown metabolic disturbances (obesity and metabolic syndrome) to be risk factors for the development of dementias and even AD [109]. Obesity is related to vascular diseases, and there is increasing evidence linking vascular risk factors to dementia and AD [109]. Instead of exploring the effect of its subcomponents, several studies have assessed the relationship between metabolic syndrome as a whole and the risk of AD or cognitive decline [111–113]. The cellular mechanisms involved in the AD associated with metabolic alterations are now becoming more understandable. It is well known that an optimal supply of nutrients is necessary to maintain normal functioning of the brain. Thus, the impact of poor nutrition (overweight, obesity) on the development of AD and the importance of good nutrition as a preventive strategy to reduce the incidence of dementias and AD are clear.

Malnutrition is associated with increased morbidity and mortality in patients with AD, with sleep disturbances, psychological problems, immobility, falls and increased hospitalization risk [114]. Normal human aging is also associated with vitamin deficiencies. One study in an Alzheimer transgenic mouse (VCT2+/-APP/PSEN1) found decreased ascorbic acid and increased oxidative stress in the brain as well as for Alzheimer's disease [115].

Antioxidant nutrients may help to protect these affected brain regions. Plasma vitamin C levels are lower in subjects with dementia compared to controls, supporting the free radical theory of oxidative neuronal damage [116]. Despite years of scientific, medical and clinical advances in this area, much work remains to discover specific nutritional interventions for the prevention of AD. Promising agents such as vitamins, energy substrates, flavonoids, lipids and modified diets functioning as antioxidants, metabolic enhancers, immune modulators and direct disease-modifying agents await further investigation [117].

5.4. Malnutrition and senescence hypothesis of AD progression

It is well known that adequate nutrition is an important factor in order to maintain cognitive function, particularly during aging. Malnutrition is among the risk factors for developing mild cognitive impairment and AD in which a cognitive decline is correlated with synaptic loss. The synapses are part of the neuronal membrane and are continuously being remodeled; therefore, ensuring the availability of sufficient levels of nutritional precursors (i.e., uridine monophosphate, choline and omega-3 fatty acids) to make the phospholipids required to build neuronal membranes may reduce synaptic degeneration in AD. Also, B-vitamins, phospholipids and other micronutrients act as cofactors to enhance the supply of precursors required to make neuronal membranes and synapses. Vitamin D has a role in brain physiology as well, for instance, by promoting neurotransmission, neurogenesis, synaptogenesis, amyloid clearance and preventing neuronal death [118].

Undernutrition during early life results in deficits in the spatial learning capacity of the animals [118], as shown by a wide variety of behavioral tests, and it is known to cause changes in the developing brain that affect the morphology, particularly in the granule cells of the dentate gyrus [120–122]. Prenatal malnutrition and chronic malnutrition in the aged rats cause abnormal mitochondrial, swollen Golgi membrane system, increase in multivesicular bodies and lypofuscine density in neurons of the hippocampus [123]. Since the mitochondrion is responsible for the production of ATP, its dysfunction induces a senescence response [124]. Furthermore, mitochondrial autophagocytosis is believed to be a major contributor to lipofuscin formation [125]. Autophagocytosis of mitochondria is also prominent in AD, because the accumulated autophagic vacuoles in dystrophic neurites contribute to the local production of Aβ within plaques, and the generalized increase in autophagy in the neuropil could be a significant source of Aβ overproduction in the AD brain. Thus, a link between mitochondrial dysfunction/oxidative stress and autophagy has been reported to occur in AD [126]. In addition, lipofuscin can be used as a biomarker to detect senescence [127], since it is one of the "age pigments", autofluorescent cell products from lysosomes that diverge in number and size among brain regions.

The increase in lipid components is possibly due to modifications in neuronal metabolism with age [128]. In Ref. [129], Giacone et al. proposed the "lipofuscin hypothesis of AD", in which the first step in the genesis of senile plaques is the release of lipofuscin free into the neuropil, where it cannot be rapidly degraded due to its biochemical characteristics. Therefore, the lipofuscin may persist in the extracellular milieu, giving rise to a focal impairment that can initiate the senile plaque and serving as a source of Aβ oligomers for a prolonged period of time. This idea is supported by the hydrophobic and insoluble characteristics of lipofuscin, which mimic those of substances that are the most effective in inducing an innate immune response [130]; the rate of lipofuscin formation is also closely related to oxidative stress [131].

5.5. Senescence hypothesis and microglial aging

Cellular senescence is a terminal phase of mitotic cells characterized by permanent cell-cycle arrest; it can be induced by a variety of stressors, including reactive oxygen species. One hypothesis is that senescent cells contribute to aging by altering cells and its secretory phenotype, as well as to the development of age-associated diseases such as AD [132].

It has been suggested that neuroinflammation, mediated by the brain's innate immune system, contributes to AD neuropathology and exacerbates the course of the disease. Some studies found that a systemic immune challenge during late gestation predisposes mice to develop AD-like neuropathology during aging when there are elevated levels of inflammatory cytokines and hippocampal amyloid precursor protein (APP), altered tau phosphorylation and missorting to somatodendritic compartments. All these effects produced significant impairments in working memory in old age [34]. Also, AD and brain aging share common molecular changes, and AD could be a form of accelerated brain aging. In addition, in AD senescent mechanisms are present in all cells, including glia and neurons. Evidence indicates that vascular impairment is a fundamental contributor to AD pathology, and platelets are generally considered a key element because they represent the link between Aβ deposition, peripheral inflammation and endothelial senescence. AD is superimposed onto the normal process of aging and one important facet of aging is the accumulation of senescent cells that lose the ability to proliferate, and also release cytokines and proteases, collectively known as the senescence-associated secretory phenotype, which contribute to the chronic inflammatory environment seen in the old age [133]. In brain, astrocytes clearly play a role in modulating neuronal function and survival in health but in disease are senescent [134]. Also, human astrocyte lines expressing the toxic form of Aβ rapidly reached a senescent state in vitro [135].

In the other hand, observations suggest that chronic systemic inflammation induces in middle-aged rats intense neuroinflammation evoked by senescent-type microglia and may contribute to the initiation and progression of AD, resulting in cognitive impairment. Also, with chronic inflammatory bone disorders, pro-inflammatory blood cells and bacterial components including lipopolysaccharides (LPS), activate the receptors localized on the surface of leptomeningeal cells, which in turn activate brain-resident microglia to evoke neuroinflammation [136]. Furthermore, the maternal immune response predisposes the offspring to develop neuropsychiatric disorders and can prime microglia cells to produce high levels of cytokines with a second stimulus [137]. Prenatal immune activation of offspring changes the

integrity of the gastrointestinal barrier [138], which probably increases exposure to antigens with pathogen-associated molecular patterns, such as LPS. Exposure to Poly (I:C) on the late gestational day can alter cognitive performance in the adult or aged animals [34, 139]. High-fat diets can also cause metabolic endotoxemia (an increased LPS concentration in plasma from microbiota in the gut) with a pro-inflammatory response [140]. This gut microbiota LPS accelerates aging, with an increase in the concentration of pro-inflammatory cytokines and of protein 16 (p16), which is a senescence biomarker in the colon [141]. The senescent cells produce chemokines, cytokines, growth and differentiation factors and matrix-remodeling enzymes, collectively known as the senescence-associated secretory phenotype [142, 143], which can contribute to tissue dysfunction [142] as Alzheimer's diseases [144]. The possible mechanism is that chronic systemic inflammatory challenges induce differential age-dependent microglial responses. Microglia are the resident immune cells in the brain, providing its first line of defense and initiating the release of pro-inflammatory mediators to trigger neuroinflammation in response to autoimmune injury, infection, ischemia, toxic insults and trauma. They recognize a broad spectrum of molecular targets, such as glycolipids, lipoproteins, nucleotides, abnormally processed peptides, modified or aggregated proteins (i.e., Aβ), inflammatory cytokines, and damaged neurons, which are the strongest inducers of microglia activation [145]. In Ref. [99], Wu et al. propose a strong relationship between nutrients, microglia, aging and brain based on the concept of "microglia ageing." This concept considers microglia as the key contributor to the acceleration of cognitive decline, which is the major sign of brain aging. Senescent microglia display morphological changes: fewer and shorter processes, increased soma volume, and formation of spheroid swellings, collectively referred to as "dystrophic microglia." Furthermore, inflammation induces oxidative stress and DNA damage, leading to the overproduction of reactive oxygen species, including macrophages and microglia and promoting aging. Therefore, providing early treatment of inflammatory disorders and controlling microglia aging, may delay the onset and limit the severity and/or progression of AD [136].

Animal models are used to test changes in microglia. For example, in adult APP/PS1 mice, exercise enhances memory test performance and is associated with increased numbers of cholinergic and serotoninergic neurons, and reduced Aβ levels and microglia activation [146]. Dietary restriction also appears to attenuate age-related activation of microglia, resulting in beneficial effects on neurodegeneration and cognitive decline [147]. Dietary restriction suppresses LPS-induced secretion of inflammatory cytokines, and shifts hypothalamic signaling pathways to an anti-inflammatory bias [148].

5.6. β-Amyloidopathy and neuroinflammation in the pathogenesis of age-related AD

The study of the aging organism allowed selection of a group of neurodegenerative diseases which have a similar mechanism of pathogenesis, including the pathological processes of protein aggregation and deposition in nerve tissue. The AD pathogenesis in β-amyloidopathy is a manifestation of proteinopathy leading to cytotoxicity, neurodegeneration and the development of pathological apoptosis activated by the formation of intracellular Aβ [166].

Proteinopathy-induced cell senescence is caused by the accumulation of misfolded proteins and activation of the innate immune system, with the production of pro-inflammatory cytokines, chemokines and oxidative stress that trigger chronic inflammation and ultimately, senescence. Components of SASP and proteinopathy can induces more senescent cells. These cells are resistant to apoptosis, but can die by autophagy. Senescent cells can be the link between Aß and secondary proteinopathies such as tau, α-synuclein and TDP-43 [149]. Indirect evidence that infection could be a cause of AD has been reported, and it was suggested that invasion by a virus could cause activation of microglia and pericytes and ultimately, amyloid deposition [150].

Systemic infections and persistent neuroinflammation are risk factors for developing AD [151]. Mice injected on gestational day 17 with poly I:C (a mimic of virus exposure) show, at 15 months, an increase in APP and its proteolytic fragments, hyperphosphorylation of tau without NFTs and the absence of significant Aβ accumulation, but these parameters have not yet been determined in aged mice [34]. Indirect evidence that infection could be a cause of AD has been reported by Wisniewski et al., who suggested that invasion by a virus could cause activation of microglia and pericytes and ultimately, amyloid deposition [152].

The infectious hypothesis is suggested by the altered blood-brain barrier and the activation of neuroinflammation in the brain, which could decrease Aß peptide clearance. For example, infection by *Helicobacter pylori* is acquired during childhood and often persists for life, inducing a chronic gastric inflammation that remains asymptomatic but can induce systemic inflammation and increase homocysteine levels, contributing to the risk of AD. In animal models of AD (5xFAD), in which glutamate excitotoxicity through NMDA receptors involves neuroinflammation, however, apart from Aβ reductions, improvements were no longer observed in the 5xFAD model during advanced stages of the disease, which may reflect the limited efficacy of memantine in clinical settings [153].

5.7. Amyloid cascade hypothesis

The amyloid cascade hypothesis postulates that memory deficits are caused by increased brain levels of Aβ peptide, which are derived from the larger amyloid precursor protein (APP) by sequential proteolytic processing [154]. This hypothesis is a neuron-centric, linear and quantitative model postulating direct cause and consequences in a cascade initiated by Abfix deposition and leading progressively to Tau pathology, synaptic dysfunction, inflammation, neuronal loss and ultimately, to dementia. Earlier AD mouse models have generated a wealth of information that has significantly improved our knowledge about AD; however, the amyloid cascade hypothesis remains controversial, because the majority of these models are based on transgenic overexpression of APP in combinations with different familial AD-associated mutations in APP or PS 1. Overexpression of APP generates elevated Aβ levels to mimic the Aβ amyloidosis of AD brains, but concomitant with this it produces non-physiological effects and a number of undesirable side effects. One strategy is to introduce mutations into the mouse APP gene and new models (APP^{NL-F} and APP^{NLG-F}) that develop robust Aβ amyloidosis, which induces synaptic degeneration and memory impairments [155].

The quantitative aspects of the hypothesis imply that reducing the number of Aβ-plaques or the concentration of Aβ-oligomers should be sufficient to halt progression of AD. Thus, a minor increase in the $A\beta_{42}:A\beta_{40}$ ratio stabilizes toxic oligomeric species with intermediate conformations. The toxic impact of these Abfix species on the synapse but can spread into cells, producing neuronal death; Kuperstein et al. [156], suggest that there is a dynamic equilibrium between toxic and non-toxic intermediates.

In addition, it is well known that diffusible Aβ oligomers are the major toxic agents in AD, and both monomers and oligomers are important for the early diagnosis of dementia because they are potential predictors for the progression of AD and are useful to evaluate new drugs against AD [157, 158].

A quarter to a third of older people has amyloid burdens without symptoms of dementia [159]. Various APP transgenic mice do not have all the characteristics of AD: they exhibit little or no neuron loss and not all of them develop cognitive impairments, even if for three-quarters of their lives they have deposits of amyloid, suggesting that Aβ alone is not sufficient. Thus, they are a model of asymptomatic AD [159, 160].

6. Animal models for AD study

AD investigations have been conducted traditionally by studying human brains (autopsy) or by producing specific brain lesions in mice. The generation of animal models is particularly relevant, because they have been designed to test neurodegeneration with characteristics similar to those in the human brain, allowing us to design new therapeutic approaches. These models are key tools for in-depth studies of neurodegenerative diseases like AD.

Many studies of AD are based on experimental models in mice since their genome is nearly 99% homologous with human [161]. Transgenic mouse models recapitulate the major hallmarks of AD and have been utilized since the early 1990s to explore in detail mechanisms underlying the disease pathology; they have provided excellent opportunities to analyze the bases for the temporal evolution of AD brains and to delineate the basic mechanisms that cause cellular dysfunction.

At present, there are many transgenic mouse and knockout models to analyze certain aspects of AD pathology, allowing the exploration of uncharted territories; they have revealed new pathogenic possibilities, many of which have not yet been demonstrated in humans. On the other hand, some discrepancies between the data obtained in the mice and in man remain unexplained [162]. Mice lack certain important aspects of AD; for example, age is an important factor in AD, but these animals have a short life, between 2 and 4 years. Also, the amyloid protein in mice, derived from proteolysis of the APP precursor, is different from that in human [163]. In spite of that, diverse studies in this mouse model showed the presence of soluble Aβ oligomers at prefibrillar stages that can act as toxic ligands at postsynaptic compartments, driving the synaptic in neuronal populations localized in similar areas to those affected in the human pathology with memory alterations. They have also been instrumental in validating dug targets in special cerebral areas to control memory.

The triple transgenic (3xTg-AD) mouse, which develops pathologies associated with AD, was created in 2003 (**Figure 1**). To produce this model, Oddo's team simultaneously microinjected two genes (APP and tau) into single-cell PS1M146V mouse embryos (transgenic mice that overexpress human or wild-type APP, and are hybrids from the 129/C57BL6 strain). These mice develop both amyloid plaques and NFT-like pathology in a progressive and age-dependent manner associated with anatomical and temporal analogously to that observed in the human AD brain [16]. In this 3xTg-AD, Aβ deposits initiate in the cortex and progress to the hippocampus with aging (**Figure 2**). Amyloid accumulation is localized in the basal neocortex as well as in entorhinal areas, but this accumulation can also expand into the hippocampus. The conformational or hyperphosphorylation changes characteristic of tau pathology occur particularly in pyramidal neurons of the hippocampal CA1 subfield and in cortical structures (**Figure 3**) and evolve in the AD brain [164].

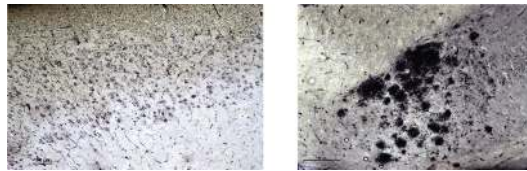**Figure 1.** Triple transgenic mouse (3xTg-AD).

Figure 2. Photomicrographs of the amyloid beta in triple transgenic mouse in the cerebral cortex of 11-month-old female showing the staining for amyloid beta aggregates mice stained by immunohistochemistry using a BAM-10 antibody.
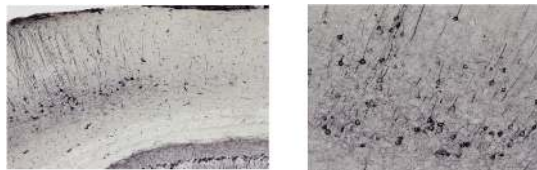

Figure 3. Photomicrographs of the cerebral cortex of an 11-month-old female mouse stained by immunohistochemistry using 499 tau antibody, showing the presence of human tau protein in two magnifications.

Another characteristic of the 3xTg-AD mouse is that the brain regions severely affected, including the hippocampus, entorhinal cortex, amygdala, neocortex, and some subcortical areas such as basal forebrain where the acetylcholine (Ach) neurotransmitter is altered in the brains of individuals with mild AD due to low choline acetyltransferase (ChAT) activity [165–167].

The 3xTg-AD mouse has fewer ChAT-immunopositive neurons in the Meynert nucleus (primary source of cholinergic neurons), as well as a reduced density of ChAT-positive cholinergic fibers projecting to the primary motor cortex and the CA1 area of the hippocampus [168]. These cognitive dysfunctions are caused by massive loss of cholinergic neurons in the anterior basal brain, the area most vulnerable to the development of the pathological characteristics associated with AD. Alterations in cholinergic neurotransmission in the patients' neocortex and hippocampus are associated with the early stages of memory loss [168]. We also found a 50% reduction in nest-building quality (a task controlled by the hippocampus), associated with a significant increase in damaged neurons in the CA1 hippocampal area (26%) compared to wild-type mice [170]. The decreased ability to carry out activities of daily living (humans) or to perform nest building correctly (3xTg-AD mice) are behavioral symptoms that can be studied and related to anatomical and morphological signs in the complex Alzheimer's disease syndrome.

6.1. Sporadic models for Alzheimer's study

A variety of animals can serve as experimental models of AD, which are valuable tools for the design of new therapeutic strategies and to explore some other aspects of the disease, as some specimens develop amyloid plaques in their brain and cognitive dysfunctions similar to those of AD. Like humans, dogs develop amyloid plaques in their brains with advancing age, and some specimens suffer sporadic cases of Alzheimer's disease, age-related cognitive impairment with loss of short-term memory or working memory, changes in behavior, irritability, incontinence, and orientation problems [171]. Sarasa cloned and sequenced the canine APP, finding it virtually identical to human APP, including the peptide sequence corresponding to β-amyloid peptide. They analyzed the presence and distribution of amyloid plaques in the brains of healthy young and old dogs with severe cognitive dysfunction. With specific antibodies against AB40 and AB42, they found that the old demented animals had many amyloid and more mature plaques than older control dogs [163].

A nontransgenic rodent *Octodon degus*, which develops hallmarks of AD, could be a natural model to understand how sporadic AD, between 12 and 36 months of age, develop the accumulation of Aβ oligomers and phosphorylated tau proteins. Moreover, age-related changes in Aβ oligomers and tau phosphorylation levels are correlated with decreases in spatial and object recognition memory, postsynaptic function, and synaptic plasticity [172].

Sparks and Schreurs proposed studying AD in rabbits fed a diet rich in cholesterol and copper. These animals develop amyloid plaques in their brains and deficiencies in learning complex tasks. They exhibit increased immunoreactivity to amyloid β in neurons, the presence of extracellular plaques in the meninges, microgliosis, apoptosis, vascular activation of SOD,

rupture of the blood-brain barrier and elevated brain levels of cholesterol; these data provide strong support for the suggestion that copper is implicated in the accumulation of Abfix [173].

Alzheimer's disease is of special interest to neuroscientists, not only because it is the most common of the brain degenerations but also because it is a multifactorial disorder of unknown etiology. In addition, recent evidence supports the hypothesis that persistent chronic infections produce increased Aβ (amyloidosis) in brain, and may be mediated by a response of the innate immune system. This hypothesis may give an explanation of the common pathogenic mechanisms and inflammatory gene polymorphisms involved in both AD and type 2 diabetes. In both diseases amyloidosis, that is, the accumulation of insoluble aggregates of fibrillar proteins, occurs in various organs and is often associated with bacterial infections [174]. Thus, the accumulation of intraneuronal amyloid-β peptide (Aβ) appears to be an early event in AD, suggesting its important role in the neurodegenerative process of AD, because Aβ aggregates, particularly oligomers, may lead to synaptic dysfunction and neuronal loss, which are associated with memory and neural plasticity loss. Transgenic animal models are established to study the pathological role of intracellular Aβ and to screen for drugs against Aβ aggregation and associated toxicity, and they suggest that soluble, nonfibrillar Aβ oligomers may induce synaptic failure early in AD. Despite their undoubted value, the transgenic models rely on genetic manipulations that represent the inherited and familial but not the most abundant, sporadic form of AD [175].

7. Conclusions

This review poses a historical overview of the pathology of Alzheimer's disease and provides an up to date of its features. Then, a molecular and histological follow-up of the proteins most strongly associated with this pathology is delivered. Finally, the diverse molecular and cellular current hypotheses seeking to disentangle the mechanisms of Alzheimer's disease and supported by research in animal models are analyzed. These models have been extremely useful in elucidating the mechanisms of Alzheimer's disease, including the numerous factors and conditions that contribute to the pathogenesis, which may have important implications providing new insight for current and future strategies to treat Alzheimer's disease and to reduce or delay its onset by preventing infection, inflammation and amyloidosis.

Acknowledgements

Author details

Erika Orta-Salazar[1], Isaac Vargas-Rodríguez[1], Susana A Castro-Chavira[1],
Alfredo I. Feria-Velasco[2] and Sofía Díaz-Cintra[1*]

*Address all correspondence to: yodi@unam.mx

1 Institute of Neurobiology (INB), Developmental Neurobiology and Neurophysiology
UNAM-JuriquillaQuerétaro, México

2 Laboratory of Cellular Neurobiology, Department of Cellular and Molecular Biology,
CUCBA, University of Guadalajara Zapopan Jalisco, México

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