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Review

The unsolved relationship of brain aging and late-onset Alzheimer disease

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ABSTRACT

Late-onset Alzheimer disease is the most common form of dementia and is strongly associated with age. Today, around 24 million people suffer from dementia and with aging of industrial populations this number will significantly increase throughout the next decades. An effective therapy that successfully decelerates or prevents the progressive neurodegeneration does not exist. Histopathologically Alzheimer disease is characterized by extensive extracellular amyloid β (Aβ) plaques, intracellular neurofibrillary tangles (NFTs), synaptic loss and neuronal cell death in distinct brain regions. The molecular correlation of Aβ or NFTs and development of late-onset Alzheimer disease needs further clarification. This review focuses on structural and functional alterations of the brain during aging, age-associated imbalances of defences against oxidative stress and age-related alterations of the metabolism of Aβ, via a comparison of observations in healthy aged individuals and cognitively impaired or AD patients. Although our understanding of brain region-specific neuronal aging is still incomplete, the early structural and molecular changes in the transition from cognitive health to impairment are subtle and the actual factors triggering the severe brain atrophy during LOAD remain ambiguous.

1. Introduction

Alzheimer disease (AD) represents the most common form of dementia in the elderly and is linked to age. The prevalence of late-onset AD (LOAD) increases exponentially beginning at the age of 65, whereas early-onset variants of familial AD (FAD) emerge only in a small fraction (<5%) [1]. AD is a progressive neurodegenerative disease with one of the earliest symptoms being memory loss. Patients can suffer for up to 20 years, undergoing different disease stages: from mild (2–4 years) to moderate (2–10 years) up to severe (1–3 years) cognitive decline. AD is characterized by extensive extracellular deposits of amyloid β protein (Aβ), deriving from processing of the amyloid precursor protein (APP), and by intracellular neurofibrillary tangles (NFTs) of hyper-phosphorylated tau protein. These histopathological hallmarks partially correlate with synaptic alterations, cholinergic deficit, gliosis and neuronal cell death [2]. Interestingly, they are not an exclusive prerequisite for the development of the disease, since also brains of non-demented elderly can show substantial levels of Aβ plaques, NFTs and inflammation in regions typically affected by AD. FAD cases gave rise to defined genomic linkage regions and insights into genes connected to the development of FAD, which are all involved in the generation of Aβ [1]. A genetic polymorphism within the *ApoE* gene represents a well-accepted risk factor for sporadic AD and is also reported to influence the metabolism of Aβ [3]. However, the major non-genetic risk factor for development of sporadic AD is aging and the pathological circumstances causing LOAD are still under debate.

2. Demographic considerations

The demography of industrial populations is under a dramatic change. It is expected that taken the increase in life expectancy into account the world's population will continuously age throughout this century. By mid-century one-third of the people are above 60 years of age and also the proportion of people above the age of 80 will increase significantly [4]. Since age is the prevailing risk factor for several neurodegenerative diseases, including AD, aging of the population will lead to a rapid increase in number of affected people. Today, about 24 million people suffer from dementia worldwide and this number is expected to double every 20 years [5]. Since dementia care is particularly time and cost intensive, the increasing number of demented patients leads to a severe socio-economic burden. In 1998, the annual cost of informal caregiving for elderly with dementia was 18 billion dollars in the USA [6]. Despite enormous research efforts the etiology or pathobiochemical mechanisms responsible for LOAD still remain largely elusive. Nevertheless, there is a clear correlation between age and the probability to develop LOAD. The prevalence of LOAD increases in the elderly from around 1% at age of 65 to approximately 30% by the age above 80, with women showing a slightly higher risk than men [5,7,8].

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3. Classification of dementia

Dementia is one of the most common forms of disease in the elderly and causes a decline in cognitive functions, such as memory, language and attention. Of all late-onset dementias, LOAD is the most frequent form, accounting for 50% to 75%. Other types constitute vascular dementia, dementia with Lewy body and frontotemporal lobar degeneration, which are neuropathologically different to AD [9].

Mild cognitive impairment (MCI) is an established transitional state between cognitive aging and pathological dementia and represents a high risk for development of LOAD later in life [5,8,10–12]. Elderly people with MCI progress into dementia at a rate of 10% to 15% each year compared to only 1% to 2% within the general population. However, the discrimination between pathological dementia and a "normal" age-associated cognitive decline is difficult to define for clinicians. The severity of dementia can be assessed by brief cognitive ratings, such as the Mini-Mental State Examination (MMSE) [13]. The resulting scores represent cognitive aspects of dementia, but can be affected by education. In contrast, the clinical dementia rating (CDR) [14] and the global deterioration scale for aging and dementia (GDS) [15] include activities of daily living, behaviours as well as cognition and are not affected by educational levels. These tests allow the classification of age-associated cognitive deterioration, MCI and severe dementia.

4. Normative brain aging and the LOAD brain

4.1. Histological alterations of the aged brain and LOAD brain

The aging brain undergoes major alterations in functional performance, but obvious age-related changes at the level of brain structure are rather minor. In healthy aged brains the total number of neurons is not significantly reduced and the neuronal cell loss, which is observed during AD is, therefore, due to a distinct pathological process [16]. The cognitive decline of AD patients is strongly associated with atrophy in different brain regions. Neuronal atrophy can be due to shrinkage of neurons, neuronal cell death, or the loss of dendrites or axons, all of which have been observed in the brains of AD patients. The region that is initially affected by atrophy is the medial temporal lobe followed by distinct cortical regions [17]. The expansion of brain atrophy correlates with the cognitive decline observed in LOAD patients [17,18]. Even though non-demented elderly can show significant levels of NFTs in certain brain regions and by the age of 85 virtually everybody will have NFTs in the cerebral cortex [19], the progression of neurodegeneration during LOAD correlates with the total number and localization of NFTs [20–22]. NFTs are selectively deposited in brain regions that are temporarily and spatially associated with the cognitive impairment in LOAD. This implicates that NFTs are a possible early factor of AD and are widely used for post-mortem staging of the cognitive deficit [23,24].

The relationship between the severity of LOAD and Aβ is not fully clarified to date. A correlation of brain atrophy and Aβ levels or insoluble Aβ plaques has been demonstrated in some studies [25,26], but not in others [27,28]. Interestingly, Aβ levels are well-known to be already increased in cognitively healthy elderly [29,30], which can exhibit substantial amounts of Aβ plaques in distinct brain regions. A prominent difference in Aβ deposits found in non-demented or demented elderly is their regional distribution: non-demented elderly show deposits in the cerebral cortex, thalamus and hypothalamus as well as the basal ganglia. In AD patients they also occur in the midbrain, brainstem and cerebellum [31]. In fact, the deposition of Aβ starts in the neocortex and expands to further brain regions, following partially the neurodegeneration observed in AD patients. This hierarchal expansion of Aβ plaques is also observed in several mouse models overexpressing human APP at high levels [32,33]. Importantly, the plaque expansion is accompanied by an age-related memory impairment and gliosis, but is not necessarily associated with the development of NFTs or significant neuronal cell death [34].

Thus, at the level of histology changes of the brain during healthy aging are rather subtle and can include the appearance of considerable levels of NFTs and Aβ plaques. Only under pathological conditions histological alterations become significant. This suggests that the presence of NFTs and/or Aβ alone is not sufficient to explain the atrophy of brain tissue and the development of LOAD. Different or additional factors have to play a role during aging to initiate the neurodegenerative cascade.

4.2. Neurotransmission in the aged brain and LOAD brain

Prominent alterations occurring in the aged brain are functional changes in neuronal activity and neurotransmission, which are strongly influenced by already minor morphological alterations. Recent studies have demonstrated that age-related deficits in learning and memory are largely identical to functional alterations of the aged hippocampal neuronal network [35–37]. Passive membrane properties of neurons are maintained, but their excitability is altered and a critical factor for the deteriorated cognitive function of aged individuals. Dendritic spines are the primary site for excitatory synaptic transmission. Even in the adult brain spines are highly plastic and undergo frequent remodelling, which is a basis for learning and memory formation [38]. In the aged brain the complexity of dendritic arborization, spine volume, spine length and the total number of dendrites is significantly decremented in certain brain regions [39,40]. These changes in dendritic morphology are closely associated with an altered neurotransmission and age-related cognitive decline observed without any remarkable neuronal cell loss during brain aging and LOAD. The neurotransmission of the aged hippocampal network declines and this reduction concerns both the glutamatergic and cholinergic pathways, which represent the primary excitatory neurotransmitter systems for neuronal communication within the hippocampus.

The neurotransmitter glutamate is essential for normal brain function since it is the principal component of excitatory neurotransmission in the brain. Moreover, it plays an essential role in neuronal plasticity or long-term potentiation (LTP) [41]. LTP is a cellular mechanism that is considered to be the fundamental mechanism for learning and memory [42]. Various receptors have been described for glutamate that include membrane channels (ionotropic glutamate receptors) and transmembrane receptors linked to intracellular signalling cascades (metabotropic glutamate receptors) [41,43]. The expression and distribution of glutamatergic receptors are affected by brain aging and the number of neurons that express certain glutamate and NMDA receptor subunits are significantly reduced [44,45]. At certain conditions, increased concentrations of glutamate can cause an exaggerated glutamatergic neurotransmission, resulting in excitatory neurotoxicity [46]. Various neurodegenerative diseases, including LOAD, have been linked to excitotoxicity. In particular the over activation of NMDA receptors leads to an immediate rise in intraneuronal calcium concentrations that ultimately result in neuronal cell death. This makes the NMDA receptor a central pharmacological target against acute and chronic excitatory neurodegeneration.

The drug memantine binds to NMDA receptors and blocks excitotoxicity without interfering with the important physiological function of NMDA receptors in neurotransmission [47]. Memantine is neuroprotective in multiple in vivo and in vitro systems and prevents NMDA- and glutamate-mediated neuronal cell death [48,49]. Recent randomized and controlled trials suggest that memantine provides measurable benefits for moderate to severe AD patients [50–52]. Interestingly, also mice overexpressing certain APP mutations derived from FAD show an improvement in learning and memory and a decreased Aβ plaque burden after treatment with memantine [53,54].

A second important neurotransmitter for modulation of learning and memory performance is acetylcholine. The cholinergic system is modified early in aging and MCI. Abnormalities in cortical cholinergic neurons are observed with an increased frequency during brain aging in non-demented subjects, leading to a general age-related hypofunction of cholinergic neurotransmission [55–57]. During AD, the decrease in cholinergic function is accelerated which gave rise to the "cholinergic hypothesis" of AD and aging [58,59]. It assumes that the degenerative decrease in cholinergic neurotransmission originates at the basal forebrain and innervates cortical regions and the hippocampus. Thus, the cholinergic degeneration is related to the impairment of cognitive performances during aging and AD. The clinical progression of LOAD correlates with the occurrence of cholinergic markers such as the reduction in choline acetyltransferase activity, total levels of acetylcholine and muscarinic and nicotinic receptor binding [60,61]. This confirms that age-related deficits of the cholinergic system are relevant for the progression of LOAD, rendering the cholinergic system an attractive therapeutic target. Since direct supplementation of acetylcholine was not successful to enhance cholinergic neurotransmission, other therapeutics were developed to increase the stability and levels of acetylcholine in the synaptic cleft, such as acetylcholinesterase inhibitors. A variety of studies support a short-term improvement of cognitive function in non-demented elderly and MCI patients after treatment with donepezil, a widely used acetylcholinesterase inhibitor, whereas long-term administration has failed to show any benefit [62–65]. Chronic treatment with donepezil may lead to a gain of physiological tolerance, possibly resulting in an up-regulation of acetylcholinesterase activity within the synaptic cleft.

Thus, neurotransmission is significantly influenced by brain aging and rapidly deteriorated during LOAD. The modulation of neuronal activity has proven short-term benefit for stabilization of cognitive function, but a long-term enhancement has not been successfully observed so far.

4.3. General age-related risk factors of brain aging affect LOAD

Since prevalence and onset of LOAD are not explainable simply by focusing on the regulation of single genes, a more complex picture involving a variety of risk factors and predisposition genes is likely. Indeed, several epidemiological studies illustrate that hypertension, hypercholesterolemia, obesity, diabetes and inflammation can significantly influence the onset and progression of LOAD.

The impact of hypertension on onset of LOAD was analyzed in several studies and there seems to be a positive correlation between the condition of high blood pressure in midlife and the onset of cognitive impairment later in life [66–68]. After manifestation of LOAD the blood pressure is decreasing compared to non-demented subjects to yet unknown reasons [69,70]. Hypertension results in vascular lesions that may promote the onset of cognitive decline. Interestingly, the ApoE polymorphism and the risk for vascular lesions in the white matter correlate significantly [71]. Randomized, placebo-controlled clinical trials have shown that the use of blood pressure-reducing drugs, such as beta blockers or inhibitors of the angiotensin converting enzyme, decrease the risk for development of dementia [72,73], but others did not find a significant benefit [74–76].

Hypercholesterolemia, obesity and diabetes are all of metabolic origin and represent a group of well-established age-related cardiovascular risk factors that influence the prevalence of cognitive decline, suggesting that cardiovascular diseases are associated with the risk of developing LOAD [68,77]. These risk factors have not only been observed in aged people, but in retrospective studies it was demonstrated that people with multiple cardiovascular risk factors in midlife show an increased probability for the development of dementia later in life [68,78].

Inflammation occurs in healthy aged brains and is a considerable contributor to age-related neurodegenerative disorders. Astrocytes mediate a variety of functions in the central nervous system, including the inflammatory response, the complement cascade and glutamate homeostasis [79,80]. The activation of astrocytes is progressively increasing during aging, rendering inflammation a common feature in the brains of healthy aged individuals [81]. Interestingly, astrocytes play an important role in Aβ clearance and the deposition of Aβ plaques is connected to astrocyte activation [82], resulting in an increased gliosis in AD brains compared to non-demented controls [83,84]. Nevertheless, a recent analysis of the astrocyte profile in the temporal cortex of aged human brains revealed that some areas of gliosis co-localize with Aβ plaques, but not all Aβ deposits were associated with inflammation and vice versa not all regions with dense gliosis showed Aβ plaques [81]. The inflammatory response of the brain leads to a cascade of cellular events that include an enhanced release of glutamate [85–87] and activation of NMDA receptors [88], which can cause neuronal cell death through excitotoxicity and impairment of neuronal calcium homeostasis. Epidemiological studies demonstrate that the long-term use of anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), is associated with a reduced prevalence of LOAD [89–91], whereas randomized control trials have not shown any benefit so far [92].

4.4. Oxidative stress in brain aging

It is generally assumed that the accumulation of oxidative damage within single cells is a driving force of aging. Decades ago Harman proposed that mitochondria play a central role in this process and that aging and age-associated degenerative diseases can partly be attributed to the harmful effects of reactive oxygen species (ROS) on cellular molecules [93]. The resultant "free radical theory of aging" describes that the permanent accumulation of ROS over an organism's lifespan causes cellular senescence and the organism to age. In fact, mitochondria are the primary site for ROS generation, consistent with their cellular function in electron transport and oxygen consumption for ATP production. Electrons eventually escaping the respiratory electron chain can reduce oxygen and form ROS that subsequently oxidize proteins, lipids and nucleic acids (Fig. 1). Oxidative damage contributes to a loss of function and impairs the cellular antioxidant defence causing an aggravation of the oxidative burden in a vicious cycle. Recently, the central role of oxidative stress in aging was further confirmed. We showed that the depletion of mitochondrial-encoded cysteine is directly correlated with lifespan in aerobic organisms [94]. In healthy cells the rate of ROS production is balanced by the cellular antioxidative defence system, consisting of antioxidative enzymes (eg glutathione peroxidase) and small antioxidant molecules (eg vitamin E) [95]. The brain is extraordinarily susceptible to oxidative damage because it has a high oxygen turnover and energy demand and a rather limited antioxidative capacity. Accumulation of oxidative damage in the brain is particularly deleterious since it is a generally post-mitotic tissue with neurons exhibiting only a weak self-renewal potential due to their low proliferative capacity.

4.5. Oxidative markers in normative brain aging, MCI and LOAD

An increased oxidative burden has been observed in the brain of non-demented elderly and of LOAD patients [96–98]. Membrane lipids are commonly attacked by ROS and peroxidation of lipids is the most frequently analyzed oxidative marker that is significantly increased during aging [98–100]. Peroxidation of polyunsaturated fatty acids is a deleterious process since it is self-propagating until either it is stopped by the antioxidative defence or until available lipids are exhausted by oxidation [101]. The oxidative modification of fatty acids leads to a structural damage of the membrane and the

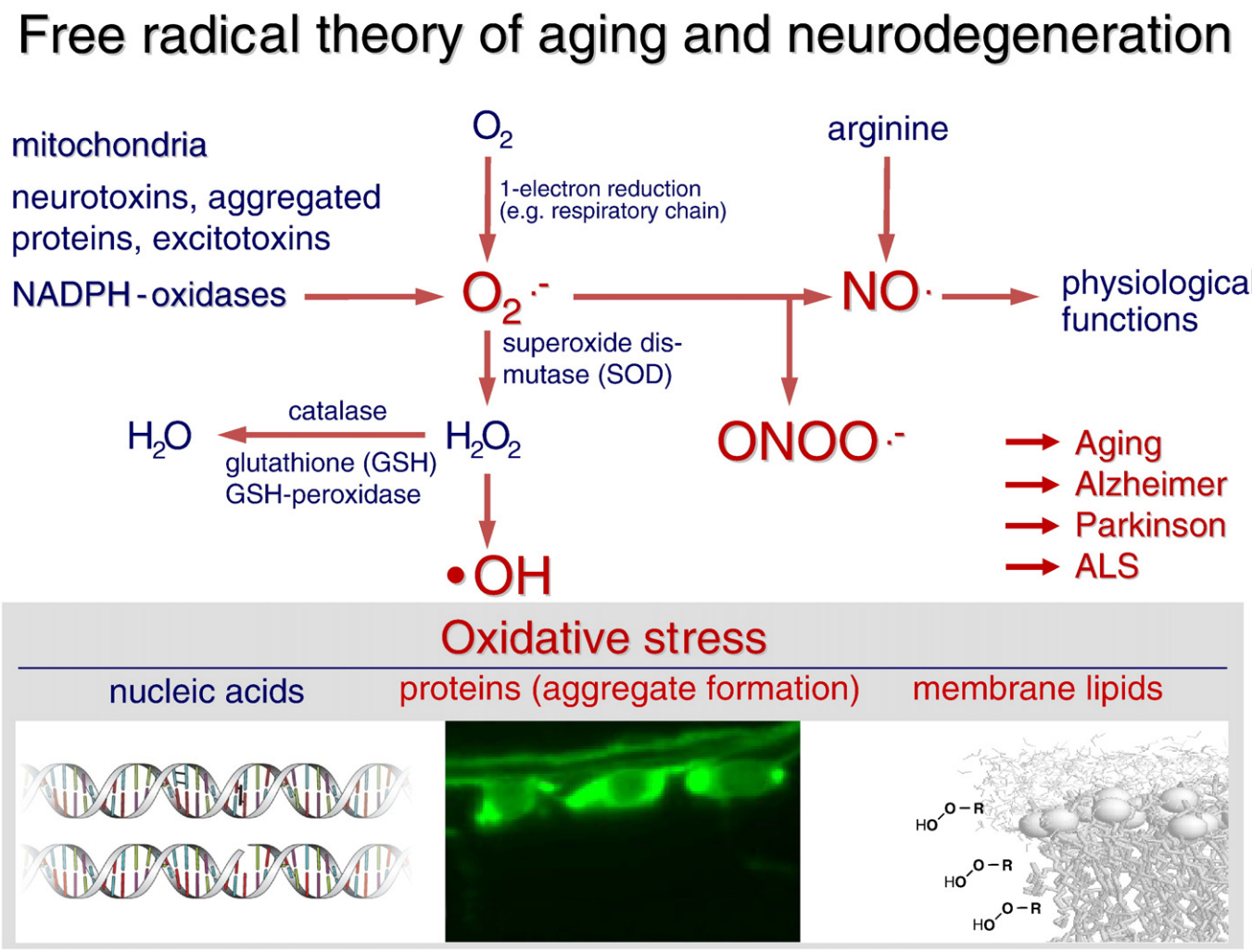

Fig. 1. Free oxygen and nitrogen radicals as driving force for aging and neurodegeneration. The free radical theory of aging and neurodegeneration summarizes the role of the accumulation of oxygen and nitrogen radicals in pathology. Basically all macromolecules can be attacked and oxidized by free radicals, leading to structural changes and molecule dysfunction. During neurodegeneration the oxidation of membrane lipid compounds and of proteins is especially well described, the latter is frequently leading to protein misfiling and aggregation.

generation of several aldehyde by-products, such as 4-hydroxy-2-nonenal, which have a high oxidative potential themselves and can severely impair cellular function [102]. Post-mortem analysis of the brains of MCI or LOAD patients found increased levels of lipid peroxidation in brain regions that are affected by neurodegeneration rather early [103,104].

Several studies have shown that also protein oxidation increases exponentially with brain aging [105–107] and is associated with a decreased capacity of the antioxidative defence machinery [107]. Importantly, also levels of oxidized proteins correlate with cognitive performance and patients with MCI or LOAD exhibit increased levels of protein carbonylation, a key marker for protein oxidation [108,109].

Another well-documented age-dependent modification is the oxidative damage of DNA. In particular mitochondrial DNA is susceptible to free radical-mediated damage due to its proximity to the site of ROS production, the lack of potentially protective histones and the limited function of the repair machinery. Mutations in mitochondrial DNA cause a respiratory chain dysfunction, which can increase cellular oxidative stress. It is well-established that mitochondrial mutations accumulate during brain aging and neurodegenerative diseases [110,111]. Compared to control subjects, MCI or LOAD patients show a significantly increased number of mutations in distinct mitochondrial and nuclear DNA bases in brain regions that are first to be affected by neuronal atrophy [112,113]. The increase in DNA mutations is expanding throughout the brain and correlates with the progression of neurodegeneration. Importantly, the number of mutations in mitochondrial DNA is approximately 10 times higher compared to nuclear DNA, consistent with its close location to the site of oxidative stress generation [113].

In summary, the oxidative burden observed in healthy brain aging and under neuropathological conditions confirms that the accumulation of oxidatively modified biomolecules is a general hallmark of brain aging and is enhanced during neurodegenerative conditions. Interestingly, the oxidative pressure in brain regions of MCI patients is comparable to those observed in the brain of LOAD patients [103,109]. This indicates that an advanced oxidative damage of affected brain regions occurs early in LOAD pathogenesis, even before the appearance of a cognitive deficit. Therefore, the therapeutical intervention of oxidative stress by increasing the capacity of the antioxidative defence machinery may delay onset or slow down progression of LOAD [114]. Indeed, in several epidemiological studies and clinical trials the use of antioxidants stabilized the cognitive function in elderly and prevented or decelerated memory and learning impairment in MCI or LOAD patients.

In the Cache County study the impact of a high vitamin C, vitamin E and carotene ingestion was analyzed in 3831 elderly residents for around seven years and it was observed that the combinatory

application of these antioxidants from food or supplements potentially delays the age-related cognitive decline [115]. The benefit of the ingestion of high levels of antioxidants for the reduced prevalence of LOAD has been demonstrated in several clinical trials [116,117], but also contradictory results have been published. For instance, a recent study analyzing the ingestion of vitamin E for prevention of MCI or LOAD failed to show a significant benefit [118] and using *Ginkgo biloba* extract in a randomized controlled trial did also not find a reduction in the incidence of dementia in cognitive normal and MCI subjects [119]. This discrepancy may be explained by the duration of treatment and the general poor blood brain barrier permeability of many used antioxidants and needs further clarification.

5. Amyloid in normative aged and LOAD brains

5.1. The amyloid precursor protein and generation of Aβ

After the discovery of Aβ as the major component of amyloid plaques in the AD brain [120,121], it was soon established that APP is the protein precursor of Aβ. APP is a ubiquitously expressed transmembrane protein and appears in three different isoforms (695, 751 and 770 amino acid residues) that arise from alternative splicing [1]. The longer isoforms of APP are predominantly expressed in non-neuronal tissue, whereas the shorter version is expressed at high levels in neurons [122].

APP is processed by the action of at least three different enzymes called secretases [123]. During non-amyloidogenic processing, α-secretase cleaves APP within the Aβ domain, which impedes the release of Aβ and results in secretion of sAPPα and the intracellular C-terminal fragment C83 (αCTF). This enzymatic activity refers to ADAM (a disintegrin and metalloprotease) family members, in particular ADAM10 and ADAM17 [124]. The amyloidogenic processing of APP is initiated by β-secretase (BACE; β-site APP cleavage enzyme) that cuts APP at the N-terminal site of the Aβ domain, generating sAPPβ and intracellular C99 (βCTF) [125]. Subsequently C83 and C99 are processed by the γ-secretase complex that cleaves at the C-terminal site of the Aβ domain and releases Aβ from the C99 fragment. In addition, this leads to generation of the AICD (APP intracellular C-terminal domain), the outermost C-terminal stub of APP. The AICD is known to be transcriptionally active after translocation into the nucleus [126]. γ-secretase is a multimeric enzymatic complex consisting of presenilin-1 (PS-1) or presenilin-2, nicastrin, APH-1 and PEN-2 [123,127]. It is unique in its enzymatic properties, since it cleaves within the transmembrane domain of type-I transmembrane proteins (eg APP, Notch). Recent evidence indicates that the proteolysis occurs at three different sites of the transmembrane domain [128,129]. The diversity of possible cleavage sites gives rise to Aβ peptides of different length. The most prominent forms consist of 40 and 42 amino acids (Aβ40/Aβ42), with a proportion of Aβ42 to Aβ40 of around 10% [1]. The C-terminus of Aβ has important implication for toxicity, as the longer version has a higher tendency to oligomerize and exhibit stronger neurotoxic properties.

5.2. Aβ toxicity and amyloid cascade hypothesis

Based on the evidence that mutations in *APP*, *PS-1* and *PS-2* genes are linked to FAD and result in an increased generation of Aβ42, effort to identify key-pathological mechanisms for development of AD gave soon rise to the "amyloid cascade hypothesis" [130]. This hypothesis focuses on Aβ as the principal component of neuronal cell death and depicts that an imbalance in Aβ production and clearance initiates a cascade leading to synaptic and neuronal dysfunction, hyperphosphorylation of tau and finally atrophy in distinct areas of the brain. Transgenic mouse models expressing human APP and/or PS with FAD-linked mutations partially support this hypothesis as the overproduction of Aβ42 mimics the pathophysiology observed in AD to a certain extent [34]. Although different transgenic lines vary in their phenotype and often no NFTs or neurodegeneration is observed, Aβ can independently cause an AD-related pathology. Interestingly, genetic polymorphisms associated with LOAD also directly or indirectly modify the metabolism of Aβ [3,131]. A correlation of Aβ and neurodegeneration is further supported by Trisomy 21 patients, which carry an extra copy of the *APP* gene, and show histopathological symptoms of AD in high frequency early in life [132].

What is the mode of toxicity of Aβ? The peptide shares a common feature with several proteins involved in neurodegenerative diseases, which is the strong propensity for oligomerization or aggregation. During the history of analyzing Aβ peptide chemistry and its toxic properties this attribute was driven into different directions, leading the AD field into diverse orientations. Initially the monomeric Aβ peptide was thought to be the crucial toxic component [133]. This view was modified by findings that rather high molecular weight aggregates and protofibrils of Aβ may represent the primary toxic species [134,135] and nowadays Aβ oligomers or even dimers are discussed to be the major harmful agent [136,137]. Mechanisms that have been approved to the toxicity of Aβ include activation of inflammation [138,139], damage to mitochondria [140,141] and membranes [142,143] and alterations of the cellular calcium homeostasis [144,145]. Interestingly, Aβ was shown to directly induce oxidative stress, leading to lipid peroxidation and cell death in vitro [146,147] (Table 1). Furthermore, evidence suggests that not only Aβ can induce oxidative stress but oxidative stress can even stimulate Aβ generation [148,149].

Despite the well-characterized toxicity of Aβ peptides and the cumulative analysis of an increased Aβ burden in FAD cases, the hypothesis of Aβ as the sole factor for age-associated AD-linked neurodegeneration is repeatedly challenged [150,151]. One prominent reason is the missing degeneration of neurons observed in transgenic rodent models expressing *APP* and/or *PS* genes carrying FAD mutations and producing high amounts of Aβ. A clear toxicity of Aβ is so far described in cell culture models, whereas in vivo convincing correlative data are still missing.

5.3. Aβ and neuronal transmission

The cognitive decline of demented elderly can temporarily occur before an obvious neuronal atrophy, which leaves questions about the mode of Aβ toxicity and the "amyloid cascade hypothesis" unanswered. In addition, also a deficit in memory and learning in APP-transgenic mice is often observed independent of a significant neurodegeneration. Recent effort to identify the impact of Aβ on neuronal function elucidated an association between Aβ and neuronal activity that can significantly influence cognition without neuronal cell loss. The injection of different Aβ fragments into hippocampal brain regions resulted in a decline in synaptic transmission [152–154] and the electrophysiological evaluation of aged APP-transgenic mice revealed an impairment of synaptic plasticity [155,156]. In an elegant experimental setting the group of Malinow was able to analyze the effect of Aβ on electrophysiology in detail [157]. Interestingly, they found that neuronal activity increased Aβ formation and that increased Aβ levels depress excitatory synaptic transmission. This interplay was confirmed in several in vitro and in vivo studies [158–160]. Thus, Aβ might function as a negative feedback modulator that is regulated by neuronal activity and also regulates itself neurotransmission. Interestingly, it was shown that Aβ inhibits neurotransmission by directly decreasing spine density [161], which can result in behavioural deficits due to a decreased glutamatergic neuronal signalling. This structural alteration is mediated by an increased endocytosis of AMPA receptors, which are necessary for stabilization of spines and synapse size [162,163]. Aβ seems to decrease the synaptic distribution of Ca(2+)/calmodulin-dependent protein

kinase II, which is important for AMPA receptor trafficking and function and may influence the removal of the AMPA receptor from the synaptic membrane [164]. Importantly, it was shown that the impact of Aβ on synaptic activity depends on the concentration of the peptide. Picomolar concentrations of Aβ42 positively modulate neurotransmission and memory, whereas concentrations in the nanomolar range result in the reduction of neuronal activity [165,166]. Thus, age-related disturbances in the metabolism of Aβ might regionally increase Aβ42 levels that negatively modulate neuronal activity and potentially lead to a decline in cognitive performance, culminating in dementia.

5.4. Age-related alterations of Aβ levels

Total levels of Aβ are increased in the cerebrospinal fluid or plasma of cognitively healthy subjects and AD patients [167,168]. Healthy elderly exhibiting increased Aβ42 levels remain cognitively normal over a period of years. To date there is no evidence that age-related increased Aβ levels result from an enhanced neuronal Aβ generation or a preference for amyloidogenic APP processing. In non-neuronal cells we have shown that the processing of endogenous APP is down-regulated during aging and that factors influencing this complex cleavage, such as secretase activity and membrane environment, are altered [169]. The activity of APP processing secretases has been analyzed during aging and already minor alterations of BACE activity have strong effects on AD pathology in transgenic mice [170]. Several groups found that β-secretase activity is increased during aging compared to non-demented controls [169,171,172]. This modification of enzymatic activity is apparently not mediated by enhanced β-secretase expression levels, but rather due to an altered post-transcriptional modification of the enzyme that influences its activity. The increased BACE activity was observed in brains bearing Aβ plaques and was often found to be located close to plaques [173]. This implies that an increase in β-secretase activity occurs as feedback of an exaggerated Aβ deposition and is not necessarily central for the age-related accumulation of Aβ itself.

One crucial parameter of increased Aβ levels is the efficiency of its degradation. Interestingly, the degradation of brain-derived Aβ seems to occur not only within the brain but also in peripheral tissues. Clearance experiments in rats depicted that after infusion of radiolabelled Aβ into the brain 30% of the injected peptides were found in blood and urine within minutes and were soon taken up by the liver or kidney [174]. In fact, transport of Aβ from brain parenchyma to blood has to occur across the blood brain barrier and is actively mediated by LRP-1 (LDL receptor-related protein-1) [175]. The subsequent transport of Aβ in the blood is supported by a soluble variant of LRP1 that acts as a sink and sequesters soluble Aβ to promote the passage across the blood brain barrier [176]. P-glycoprotein is a further protein, transporting Aβ from the brain parenchyma into the blood. Expression levels of this protein are inversely correlated with amyloid deposition in the brains of non-demented subjects [177]. Also the transport of Aβ from the blood into the brain has been demonstrated and is mediated through binding to the protein RAGE (receptor for advanced glycation end products) in endothelial cells [178].

In the brain multiple enzymes have been discovered that are responsible for degradation of Aβ, rendering the cleavage products less likely to aggregate and less neurotoxic. Neprilysin is one of the rate-limiting enzymes for Aβ degradation and overexpression of this protease reduces Aβ deposition, synaptic dysfunction and memory impairment in APP-transgenic mice [179,180]. Neprilysin expression levels in human post-mortem tissue are uniformly decreased in non-demented elderly and LOAD patients and are inversely correlated to age-related increased Aβ levels [181,182]. Importantly, neprilysin levels were found to be significantly associated with the ApoE genotype, resulting in a reduced expression in the presence of the ε4 allele [183]. This suggests that neprilysin is a key-player for clearance of Aβ, but the reduced activity alone is not sufficient to initiate neurodegeneration or cognitive impairment.

Thus, generation of Aβ by APP processing and total Aβ levels do not clearly suggest a crucial role of the peptide for the development of LOAD, since the observed differences between cognitive health and pathology are rather minor. Even though the in vitro neurotoxic potential of Aβ is without doubt, the impact of Aβ on LOAD-related neuronal cell death in vivo remains ambiguous and is by itself not sufficient to explain the heterogeneity and complexity of the disease.

6. Conclusions

Based on statistical calculations virtually everybody has a high chance to become demented if a certain age is reached and death is not due to other incidences or other age-associated degenerative diseases. Although this correlation is obvious, the molecular details of the link between aging and cognitive decline is not clear to date. Importantly, LOAD is influenced by several general risk factors of age-related degenerative disorders, such as hypertension, cardiovascular risk factors, inflammation, and increased oxidative burden. Comparing age-related alterations in brain histology, neurotransmission and Aβ metabolism during healthy brain aging confirms that it is only a small step from cognitive health to cognitive impairment and the causal triggers are still unknown. Even though FAD cases gave rise to defined genetic risk factors and genetic polymorphisms have been associated with sporadic AD, their involvement in onset and progression of LOAD is still ambiguous. To date not all facets of histological and molecular brain aging and particularly differences in aging of certain brain regions have been elucidated, but they may play a pivotal role for the development of LOAD.

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References

[1] D.J. Selkoe, Alzheimer's disease: genes, proteins, and therapy, Physiol. Rev. 81 (2001) 741–766.
[2] H. Braak, E. Braak, Neuropathological stageing of Alzheimer-related changes, Acta Neuropathol. 82 (1991) 239–259.
[3] D.B. Carter, The interaction of amyloid-beta with ApoE, Subcell. Biochem. 38 (2005) 255–272.
[4] W. Lutz, W. Sanderson, S. Scherbov, The coming acceleration of global population ageing, Nature 451 (2008) 716–719.
[5] C.P. Ferri, M. Prince, C. Brayne et al., Global prevalence of dementia: a Delphi consensus study, Lancet 366 2112–2117.
[6] K.M. Langa, M.E. Chernew, M.U. Kabeto, et al., National estimates of the quantity and cost of informal caregiving for the elderly with dementia, J. Gen. Intern. Med. 16 (2001) 770–778.
[7] A. Lobo, L.J. Launer, L. Fratiglioni, et al., Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts, Neurology 54 (2000) S4–9.
[8] R.N. Kalaria, G.E. Maestre, R. Arizaga, et al., Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors, Lancet Neurology 7 (2008) 812–826.
[9] J.A. Levy, G.J. Chelune, Cognitive-behavioral profiles of neurodegenerative dementias: beyond Alzheimer's disease, J. Geriatr. Psychiatry Neurol. 20 (2007) 227–238.
[10] R.C. Petersen, G.E. Smith, S.C. Waring, R.J. Ivnik, E.G. Tangalos, E. Kokmen, Mild cognitive impairment: clinical characterization and outcome, Arch. Neurol. 56 (1999) 303–308.
[11] R.C. Petersen, J.C. Stevens, M. Ganguli, E.G. Tangalos, J.L. Cummings, S.T. DeKosky, Practice parameter: Early detection of dementia: mild cognitive impairment (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 56 (2001) 1133–1142.
[12] J.E. Graham, K. Rockwood, B.L. Beattie, et al., Prevalence and severity of cognitive impairment with and without dementia in an elderly population, Lancet 349 (1997) 1793–1796.

[13] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198.
[14] C.P. Hughes, L. Berg, W.L. Danziger, L.A. Coben, R.L. Martin, A new clinical scale for the staging of dementia, Br. J. Psychiatry 140 (1982) 566–572.
[15] B. Reisberg, S.H. Ferris, M.J. de Leon, T. Crook, The Global Deterioration Scale for assessment of primary degenerative dementia, Am. J. Psychiatry 139 (1982) 1136–1139.
[16] S.N. Burke, C.A. Barnes, Neural plasticity in the ageing brain, Nat. Rev. Neurosci. 7 (2006) 30–40.
[17] R.I. Scahill, J.M. Schott, J.M. Stevens, M.N. Rossor, N.C. Fox, Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 4703–4707.
[18] C.R. Jack Jr., M.M. Shiung, J.L. Gunter, et al., Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD, Neurology 62 (2004) 591–600.
[19] T.G. Ohm, H. Muller, H. Braak, J. Bohl, Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes, Neuroscience 64 (1995) 209–217.
[20] P.T. Nelson, G.A. Jicha, F.A. Schmitt, et al., Clinicopathologic correlations in a large Alzheimer disease center autopsy cohort: neuritic plaques and neurofibrillary tangles "do count" when staging disease severity, J. Neuropathol. Exp. Neurol. 66 (2007) 1136–1146.
[21] P. Giannakopoulos, F.R. Herrmann, T. Bussiere, et al., Tangle and neuron numbers, but not amyloid load, predict cognitive status in Alzheimer's disease, Neurology 60 (2003) 1495–1500.
[22] P. Tiraboschi, L.A. Hansen, L.J. Thal, J. Corey-Bloom, The importance of neuritic plaques and tangles to the development and evolution of AD, Neurology 62 (2004) 1984–1989.
[23] I. Alafuzoff, T. Arzberger, S. Al-Sarraj, et al., Staging of neurofibrillary pathology in Alzheimer's disease: a study of the BrainNet Europe Consortium, Brain Pathol. 18 (2008) 484–496.
[24] J.L. Whitwell, K.A. Josephs, M.E. Murray, et al., MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study, Neurology 71 (2008) 743–749.
[25] H.A. Archer, P. Edison, D.J. Brooks, et al., Amyloid load and cerebral atrophy in Alzheimer's disease: an 11C-PIB positron emission tomography study, Ann. Neurol. 60 (2006) 145–147.
[26] L.C. Silbert, J.F. Quinn, M.M. Moore, et al., Changes in premorbid brain volume predict Alzheimer's disease pathology, Neurology 61 (2003) 487–492.
[27] K.A. Josephs, J.L. Whitwell, Z. Ahmed, et al., Beta-amyloid burden is not associated with rates of brain atrophy, Ann. Neurol. 63 (2008) 204–212.
[28] R.L. Neve, N.K. Robakis, Alzheimer's disease: a re-examination of the amyloid hypothesis, Trends Neurosci. 21 (1998) 15–19.
[29] J. Naslund, V. Haroutunian, R. Mohs, et al., Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline, Jama 283 (2000) 1571–1577.
[30] N. Schupf, M.X. Tang, H. Fukuyama, et al., Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 14052–14057.
[31] D.R. Thal, E. Capetillo-Zarate, K. Del Tredici, H. Braak, The development of amyloid beta protein deposits in the aged brain, Sci. Aging Knowledge Environ. 2006 (2006) re1.
[32] D. Games, D. Adams, R. Alessandrini, et al., Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein, Nature 373 (1995) 523–527.
[33] M.C. Irizarry, F. Soriano, M. McNamara, et al., Abeta deposition is associated with neuropil changes, but not with overt neuronal loss in the human amyloid precursor protein V717F (PDAPP) transgenic mouse, J. Neurosci. 17 (1997) 7053–7059.
[34] T.L. Spires, B.T. Hyman, Transgenic models of Alzheimer's disease: learning from animals, NeuroRx 2 (2005) 423–437.
[35] D.A. Clayton, M.H. Mesches, E. Alvarez, P.C. Bickford, M.D. Browning, A hippocampal NR2B deficit can mimic age-related changes in long-term potentiation and spatial learning in the Fischer 344 rat, J. Neurosci. 22 (2002) 3628–3637.
[36] T.C. Foster, Involvement of hippocampal synaptic plasticity in age-related memory decline, Brain Res. Rev. 30 (1999) 236–249.
[37] E.S. Rosenzweig, C.A. Barnes, Impact of aging on hippocampal function: plasticity, network dynamics, and cognition, Prog. Neurobiol. 69 (2003) 143–179.
[38] F. Engert, T. Bonhoeffer, Dendritic spine changes associated with hippocampal long-term synaptic plasticity, Nature 399 (1999) 66–70.
[39] J.M. de Brabander, R.J. Kramers, H.B. Uylings, Layer-specific dendritic regression of pyramidal cells with ageing in the human prefrontal cortex, Eur. J. Neurosci. 10 (1998) 1261–1269.
[40] S. Nakamura, I. Akiguchi, M. Kameyama, N. Mizuno, Age-related changes of pyramidal cell basal dendrites in layers III and V of human motor cortex: a quantitative Golgi study, Acta Neuropathol. 65 (1985) 281–284.
[41] J.C. Watkins, D.E. Jane, The glutamate story, Br. J. Pharmacol 147 (Suppl. 1) (2006) S100–S108.
[42] T.V. Bliss, G.L. Collingridge, A synaptic model of memory: long-term potentiation in the hippocampus, Nature 361 (1993) 31–39.
[43] N.J. Sucher, M. Awobuluyi, Y.B. Choi, S.A. Lipton, NMDA receptors: from genes to channels, Trends Pharmacol. Sci. 17 (1996) 348–355.
[44] P. Liu, P.F. Smith, C.L. Darlington, Glutamate receptor subunits expression in memory-associated brain structures: regional variations and effects of aging, Synapse 62 (2008) 834–841.
[45] K.R. Magnusson, The aging of the NMDA receptor complex, Front. Biosci. 3 (1998) e70–80.
[46] M.F. Beal, Mechanisms of excitotoxicity in neurologic diseases, FASEB J. 6 (1992) 3338–3344.
[47] S.A. Lipton, Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders, J. Alzheimers Dis. 6 (2004) S61–74.
[48] C. Heim, K.H. Sontag, Memantine prevents progressive functional neurodegeneration in rats, J. Neural. Transm. Suppl. 46 (1995) 117–130.
[49] M. Weller, F. Finiels-Marlier, S.M. Paul, NMDA receptor-mediated glutamate toxicity of cultured cerebellar, cortical and mesencephalic neurons: neuroprotective properties of amantadine and memantine, Brain Res. 613 (1993) 143–148.
[50] S. Bakchine, H. Loft, Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study, J. Alzheimers Dis. 13 (2008) 97–107.
[51] B. Reisberg, R. Doody, A. Stoffler, F. Schmitt, S. Ferris, H.J. Mobius, Memantine in moderate-to-severe Alzheimer's disease, N. Engl. J. Med. 348 (2003) 1333–1341.
[52] P.N. Tariot, M.R. Farlow, G.T. Grossberg, S.M. Graham, S. McDonald, I. Gergel, Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial, Jama 291 (2004) 317–324.
[53] R. Minkeviciene, P. Banerjee, H. Tanila, Memantine Improves Spatial Learning in a Transgenic Mouse Model of Alzheimer's disease, J. Pharmacol. Exp. Ther. 311 (2004) 677–682.
[54] H. Scholtzova, Y.Z. Wadghiri, M. Douadi, et al., Memantine leads to behavioral improvement and amyloid reduction in Alzheimer's-disease-model transgenic mice shown as by micromagnetic resonance imaging, J. Neurosci. Res. 86 (2008) 2784–2791.
[55] C. Geula, N. Nagykery, A. Nicholas, C.K. Wu, Cholinergic neuronal and axonal abnormalities are present early in aging and in Alzheimer disease, J. Neuropathol. Exp. Neurol. 67 (2008) 309–318.
[56] R. Goekoop, P. Scheltens, F. Barkhof, S.A. Rombouts, Cholinergic challenge in Alzheimer patients and mild cognitive impairment differentially affects hippocampal activation—a pharmacological fMRI study, Brain 129 (2006) 141–157.
[57] G. Gron, I. Brandenburg, A.P. Wunderlich, M.W. Riepe, Inhibition of hippocampal function in mild cognitive impairment: targeting the cholinergic hypothesis, Neurobiol. Aging 27 (2006) 78–87.
[58] R.T. Bartus, On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis, Exp. Neurol. 163 (2000) 495–529.
[59] P.J. Whitehouse, D.L. Price, R.G. Struble, A.W. Clark, J.T. Coyle, M.R. Delon, Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain, Science 215 (1982) 1237–1239.
[60] L.M. Bierer, V. Haroutunian, S. Gabriel, et al., Neurochemical correlates of dementia severity in Alzheimer's disease: relative importance of the cholinergic deficits, J. Neurochem. 64 (1995) 749–760.
[61] M.D. Ikonomovic, E.J. Mufson, J. Wuu, D.A. Bennett, S.T. DeKosky, Reduction of choline acetyltransferase activity in primary visual cortex in mild to moderate Alzheimer's disease, Arch. Neurol. 62 (2005) 425–430.
[62] B. Benjamin, A. Burns, Donepezil for Alzheimer's disease, Expert Rev. Neurother. 7 (2007) 1243–1249.
[63] H.M. Bryson, P. Benfield, Donepezil, Drugs Aging 10 (1997) 234–239.
[64] S.M. Greenberg, M.K. Tennis, L.B. Brown, et al., Donepezil therapy in clinical practice: a randomized crossover study, Arch. Neurol. 57 (2000) 94–99.
[65] R.A. Hansen, G. Gartlehner, A.P. Webb, L.C. Morgan, C.G. Moore, D.E. Jonas, Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis, Clin. Interv. Aging 3 (2008) 211–225.
[66] D. Knopman, L.L. Boland, T. Mosley, et al., Cardiovascular risk factors and cognitive decline in middle-aged adults, Neurology 56 (2001) 42–48.
[67] I. Skoog, B. Lernfelt, S. Landahl, et al., 15-year longitudinal study of blood pressure and dementia, Lancet 347 (1996) 1141–1145.
[68] R.A. Whitmer, S. Sidney, J. Selby, S.C. Johnston, K. Yaffe, Midlife cardiovascular risk factors and risk of dementia in late life, Neurology 64 (2005) 277–281.
[69] J. Verghese, R.B. Lipton, C.B. Hall, G. Kuslansky, M.J. Katz, Low blood pressure and the risk of dementia in very old individuals, Neurology 61 (2003) 1667–1672.
[70] O. Hanon, F. Latour, M.L. Seux, H. Lenoir, F. Forette, A.S. Rigaud, Evolution of blood pressure in patients with Alzheimer's disease: a one year survey of a French Cohort (REAL.FR), J. Nutr. Health Aging 9 (2005) 106–111.
[71] F.E. de Leeuw, F. Richard, J.C. de Groot, et al., Interaction between hypertension, apoE, and cerebral white matter lesions, Stroke 35 (2004) 1057–1060.
[72] F. Forette, M.L. Seux, J.A. Staessen, et al., The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study, Arch. Intern. Med. 162 (2002) 2046–2052.
[73] C. Tzourio, C. Anderson, N. Chapman, et al., Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease, Arch. Intern. Med. 163 (2003) 1069–1075.
[74] W.B. Applegate, S. Pressel, J. Wittes, et al., Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program, Arch. Intern. Med. 154 (1994) 2154–2160.

[75] H. Lithell, L. Hansson, I. Skoog, et al., The Study on COgnition and Prognosis in the Elderly (SCOPE); outcomes in patients not receiving add-on therapy after randomization, J. Hypertens. 22 (2004) 1605–1612.
[76] M.J. Prince, A.S. Bird, R.A. Blizard, A.H. Mann, Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults, Bmj 312 (1996) 801–805.
[77] M. Vanhanen, K. Koivisto, L. Moilanen, et al., Association of metabolic syndrome with Alzheimer disease: a population-based study, Neurology 67 (2006) 843–847.
[78] S. Kalmijn, D. Foley, L. White, et al., Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study, Arterioscler. Thromb. Vasc. Biol. 20 (2000) 2255–2260.
[79] M. Sastre, T. Klockgether, M.T. Heneka, Contribution of inflammatory processes to Alzheimer's disease: molecular mechanisms, Int. J. Dev. Neurosci. 24 (2006) 167–176.
[80] M. Pertusa, S. Garcia-Matas, E. Rodriguez-Farre, C. Sanfeliu, R. Cristofol, Astrocytes aged in vitro show a decreased neuroprotective capacity, J. Neurochem. 101 (2007) 794–805.
[81] J.E. Simpson, P.G. Ince, G. Lace, et al., Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain, Neurobiol. Aging (in press). doi: 10.1016/j.neurobiolaging.2008.05.015.
[82] R.G. Nagele, J. Wegiel, V. Venkataraman, H. Imaki, K.C. Wang, J. Wegiel, Contribution of glial cells to the development of amyloid plaques in Alzheimer's disease, Neurobiol. Aging 25 (2004) 663–674.
[83] R.W.T.G. Beach, E.G. McGeer, Patterns of gliosis in Alzheimer's disease and aging cerebrum, Glia 2 (1989) 420–436.
[84] A.K. Vehmas, C.H. Kawas, W.F. Stewart, J.C. Troncoso, Immune reactive cells in senile plaques and cognitive decline in Alzheimer's disease, Neurobiol. Aging 24 (2003) 321–331.
[85] S.W. Barger, A.S. Basile, Activation of microglia by secreted amyloid precursor protein evokes release of glutamate by cystine exchange and attenuates synaptic function, J. Neurochem. 76 (2001) 846–854.
[86] H. Takeuchi, S. Jin, J. Wang, et al., Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner, J. Biol. Chem. 281 (2006) 21362–21368.
[87] I.F.A. Timothy, J. Harrigan, David Jourd'heuil, Alexander A. Mongin, Activation of microglia with zymosan promotes excitatory amino acid release via volume-regulated anion channels: the role of NADPH oxidases, J. Neurochem. 106 (2008) 2449–2462.
[88] A.M. Floden, S. Li, C.K. Combs, Beta-amyloid-stimulated microglia induce neuron death via synergistic stimulation of tumor necrosis factor alpha and NMDA receptors, J. Neurosci. 25 (2005) 2566–2575.
[89] K. Andersen, L.J. Launer, A. Ott, A.W. Hoes, M.M. Breteler, A. Hofman, Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study, Neurology 45 (1995) 1441–1445.
[90] J.C. Breitner, B.A. Gau, K.A. Welsh, et al., Inverse association of anti-inflammatory treatments and Alzheimer's disease: initial results of a co-twin control study, Neurology 44 (1994) 227–232.
[91] B.A. in't Veld, L.J. Launer, A.W. Hoes, et al., NSAIDs and incident Alzheimer's disease. The Rotterdam Study, Neurobiol. Aging 19 (1998) 607–611.
[92] B.K. Martin, C. Szekely, J. Brandt, et al., Cognitive function over time in the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT): results of a randomized, controlled trial of naproxen and celecoxib, Arch. Neurol. 65 (2008) 896–905.
[93] D. Harman, The biologic clock: the mitochondria? J. Am. Geriatr. Soc. 20 (1972) 145–147.
[94] B. Moosmann, C. Behl, Mitochondrially encoded cysteine predicts animal lifespan, Aging Cell 7 (2008) 32–46.
[95] R.J. Reiter, Oxidative processes and antioxidative defence mechanisms in the aging brain, FASEB J. 9 (1995) 526–533.
[96] C. Behl, B. Moosmann, Antioxidant neuroprotection in Alzheimer's disease as preventive and therapeutic approach, Free Radic. Biol. Med. 33 (2002) 182–191.
[97] B. Moosmann, C. Behl, Antioxidants as treatment for neurodegenerative disorders, Expert. Opin. Investig. Drugs 11 (2002) 1407–1435.
[98] Y. Zhu, P.M. Carvey, Z. Ling, Age-related changes in glutathione and glutathione-related enzymes in rat brain, Brain Res. 1090 (2006) 35–44.
[99] M. Cini, A. Moretti, Studies on lipid peroxidation and protein oxidation in the aging brain, Neurobiol. Aging 16 (1995) 53–57.
[100] E. O'Donnell, M.A. Lynch, Dietary antioxidant supplementation reverses age-related neuronal changes, Neurobiol. Aging 19 (1998) 461–467.
[101] C. Mylonas, D. Kouretas, Lipid peroxidation and tissue damage, In Vivo 13 (1999) 295–309.
[102] J.N. Keller, M.P. Mattson, Roles of lipid peroxidation in modulation of cellular signaling pathways, cell dysfunction, and death in the nervous system, Rev. Neurosci. 9 (1998) 105–116.
[103] W.R. Markesbery, M.A. Lovell, Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment, Arch. Neurol. 64 (2007) 954–956.
[104] M.M. Mielke, C.G. Lyketsos, Lipids and the pathogenesis of Alzheimer's disease: Is there a link? Int. Rev. Psychiatry 18 (2006) 173–186.
[105] M.M. Abd El Mohsen, M.M. Iravani, et al., Age-associated changes in protein oxidation and proteasome activities in rat brain: modulation by antioxidants, Biochem. Biophys. Res. Commun. 336 (2005) 386–391.
[106] H.F. Poon, H.M. Shepherd, T.T. Reed, et al., Proteomics analysis provides insight into caloric restriction mediated oxidation and expression of brain proteins associated with age-related impaired cellular processes: mitochondrial dysfunction, glutamate dysregulation and impaired protein synthesis, Neurobiol. Aging 27 (2006) 1020–1034.
[107] I. Rodrigues Siqueira, C. Fochesatto, I.L. da Silva Torres, C. Dalmaz, C. Alexandre Netto, Aging affects oxidative state in hippocampus, hypothalamus and adrenal glands of Wistar rats, Life Sci. 78 (2005) 271–278.
[108] J. Greilberger, C. Koidl, M. Greilberger, et al., Malondialdehyde, carbonyl proteins and albumin-disulphide as useful oxidative markers in mild cognitive impairment and Alzheimer's disease, Free Radic. Res. 42 (2008) 633–638.
[109] J.N. Keller, F.A. Schmitt, S.W. Scheff, et al., Evidence of increased oxidative damage in subjects with mild cognitive impairment, Neurology 64 (2005) 1152–1156.
[110] A. Bender, K.J. Krishnan, C.M. Morris, et al., High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease, Nat. Genet. 38 (2006) 515–517.
[111] M. Corral-Debrinski, T. Horton, M.T. Lott, J.M. Shoffner, M.F. Beal, D.C. Wallace, Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age, Nat. Genet. 2 (1992) 324–329.
[112] J. Wang, W.R. Markesbery, M.A. Lovell, Increased oxidative damage in nuclear and mitochondrial DNA in mild cognitive impairment, J. Neurochem. 96 (2006) 825–832.
[113] J. Wang, S. Xiong, C. Xie, W.R. Markesbery, M.A. Lovell, Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease, J. Neurochem. 93 (2005) 953–962.
[114] P. Hajieva, C. Behl, Antioxidants as a potential therapy against age-related neurodegenerative diseases: amyloid Beta toxicity and Alzheimer's disease, Curr. Pharm. Des. 12 (2006) 699–704.
[115] H.J. Wengreen, R.G. Munger, C.D. Corcoran, et al., Antioxidant intake and cognitive function of elderly men and women: the Cache County Study, J. Nutr. Health Aging 11 (2007) 230–237.
[116] F. Grodstein, J.H. Kang, R.J. Glynn, N.R. Cook, J.M. Gaziano, A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II, Arch. Intern. Med. 167 (2007) 2184–2190.
[117] M. Sano, C. Ernesto, R.G. Thomas, et al., A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study, N. Engl. J. Med. 336 (1997) 1216–1222.
[118] M.G. Isaac, R. Quinn, N. Tabet, Vitamin E for Alzheimer's disease and mild cognitive impairment, Cochrane Database Syst. Rev. (2008) CD002854.
[119] S.T. Dekosky, J.D. Williamson, A.L. Fitzpatrick, et al., *Ginkgo biloba* for prevention of dementia: a randomized controlled trial, Jama 300 (2008) 2253–2262.
[120] G.G. Glenner, C.W. Wong, Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein, Biochem. Biophys. Res. Commun. 122 (1984) 1131–1135.
[121] C.L. Masters, G. Multhaup, G. Simms, J. Pottgiesser, R.N. Martins, K. Beyreuther, Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels, EMBO J. 4 (1985) 2757–2763.
[122] C. Haass, A.Y. Hung, D.J. Selkoe, Processing of beta-amyloid precursor protein in microglia and astrocytes favors an internal localization over constitutive secretion, J. Neurosci. 11 (1991) 3783–3793.
[123] C. Haass, Take five—BACE and the gamma-secretase quartet conduct Alzheimer's amyloid beta-peptide generation, EMBO J. 23 (2004) 483–488.
[124] S. Lammich, E. Kojro, R. Postina, et al., Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 3922–3927.
[125] R. Vassar, B.D. Bennett, S. Babu-Khan, et al., Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, Science 286 (1999) 735–741.
[126] X. Cao, T.C. Sudhof, Dissection of amyloid-beta precursor protein-dependent transcriptional transactivation, J. Biol. Chem. 279 (2004) 24601–24611.
[127] T. Sato, T.S. Diehl, S. Narayanan, S. Funamoto, Y. Ihara, B. De Strooper, H. Steiner, C. Haass, M.S. Wolfe, Active gamma-secretase complexes contain only one of each component, J. Biol. Chem. 282 (2007) 33985–33993.
[128] Y. Gu, H. Misonou, T. Sato, N. Dohmae, K. Takio, Y. Ihara, Distinct intramembrane cleavage of the beta-amyloid precursor protein family resembling gamma-secretase-like cleavage of Notch, J. Biol. Chem. 276 (2001) 35235–35238.
[129] Y. Qi-Takahara, M. Morishima-Kawashima, Y. Tanimura, et al., Longer forms of amyloid beta protein: implications for the mechanism of intramembrane cleavage by gamma-secretase, J. Neurosci. 25 (2005) 436–445.
[130] J.A. Hardy, G.A. Higgins, Alzheimer's disease: the amyloid cascade hypothesis, Science 256 (1992) 184–185.
[131] U. Dreses-Werringloer, J.C. Lambert, V. Vingtdeux, et al., A polymorphism in CALHM1 influences Ca2+ homeostasis, Abeta levels, and Alzheimer's disease risk, Cell 133 (2008) 1149–1161.
[132] M.L. Margallo-Lana, P.B. Moore, D.W. Kay, et al., Fifteen-year follow-up of 92 hospitalized adults with Down's syndrome: incidence of cognitive decline, its relationship to age and neuropathology, J. Intellect. Disabil. Res. 51 (2007) 463–477.
[133] B.A. Yankner, L.R. Dawes, S. Fisher, L. Villa-Komaroff, M.L. Oster-Granite, R.L. Neve, Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease, Science 245 (1989) 417–420.
[134] N. Suzuki, T.T. Cheung, X.D. Cai, et al., An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants, Science 264 (1994) 1336–1340.
[135] A. Lorenzo, B.A. Yankner, Beta-amyloid neurotoxicity requires fibril formation and is inhibited by Congo red, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 12243–12247.
[136] M.P. Lambert, A.K. Barlow, B.A. Chromy, et al., Diffusible, nonfibrillar ligands derived from Abeta1–42 are potent central nervous system neurotoxins, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 6448–6453.

[137] R. Roychaudhuri, M. Yang, M.M. Hoshi, D.B. Teplow, Amyloid beta-protein assembly and Alzheimer's disease, J. Biol. Chem 284 (2009) 4749–4753.
[138] B.D. Gitter, L.M. Cox, R.E. Rydel, P.C. May, Amyloid beta peptide potentiates cytokine secretion by interleukin-1 beta-activated human astrocytoma cells, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 10738–10741.
[139] H. Jiang, D. Burdick, C.G. Glabe, C.W. Cotman, A.J. Tenner, beta-Amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain, J. Immunol. 152 (1994) 5050–5059.
[140] A.Y. Abramov, L. Canevari, M.R. Duchen, Beta-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase, J. Neurosci. 24 (2004) 565–575.
[141] M. Manczak, T.S. Anekonda, E. Henson, B.S. Park, J. Quinn, P.H. Reddy, Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression, Hum. Mol. Genet. 15 (2006) 1437–1449.
[142] N. Arispe, H.B. Pollard, E. Rojas, Giant multilevel cation channels formed by Alzheimer disease amyloid beta-protein [A beta P-(1–40)] in bilayer membranes, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 10573–10577.
[143] M. Kawahara, N. Arispe, Y. Kuroda, E. Rojas, Alzheimer's disease amyloid beta-protein forms Zn(2+)-sensitive, cation-selective channels across excised membrane patches from hypothalamic neurons, Biophys. J. 73 (1997) 67–75.
[144] M.P. Mattson, B. Cheng, D. Davis, K. Bryant, I. Lieberburg, R.E. Rydel, beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity, J. Neurosci. 12 (1992) 376–389.
[145] S.K. Rhee, A.P. Quist, R. Lal, Amyloid beta protein-(1–42) forms calcium-permeable, Zn2+-sensitive channel, J. Biol. Chem. 273 (1998) 13379–13382.
[146] C. Behl, J.B. Davis, R. Lesley, D. Schubert, Hydrogen peroxide mediates amyloid beta protein toxicity, Cell 77 (1994) 817–827.
[147] D.A. Butterfield, J. Drake, C. Pocernich, A. Castegna, Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide, Trends Mol. Med. 7 (2001) 548–554.
[148] C. Goldsbury, I.T. Whiteman, E.V. Jeong, Y.A. Lim, Oxidative stress increases levels of endogenous amyloid-beta peptides secreted from primary chick brain neurons, Aging Cell 7 (2008) 771–775.
[149] Y. Tong, W. Zhou, V. Fung, et al., Oxidative stress potentiates BACE1 gene expression and Abeta generation, J. Neural. Transm. 112 (2005) 455–469.
[150] A. Abbott, Neuroscience: the plaque plan, Nature 456 (2008) 161–164.
[151] A. Mandavilli, The amyloid code, Nat. Med. 12 (2006) 747–751.
[152] W.K. Cullen, Y.H. Suh, R. Anwyl, M.J. Rowan, Block of LTP in rat hippocampus in vivo by beta-amyloid precursor protein fragments, Neuroreport 8 (1997) 3213–3217.
[153] D.B. Freir, C. Holscher, C.E. Herron, Blockade of long-term potentiation by beta-amyloid peptides in the CA1 region of the rat hippocampus in vivo, J. Neurophysiol. 85 (2001) 708–713.
[154] A. Stephan, S. Laroche, S. Davis, Generation of aggregated beta-amyloid in the rat hippocampus impairs synaptic transmission and plasticity and causes memory deficits, J. Neurosci. 21 (2001) 5703–5714.
[155] P.F. Chapman, G.L. White, M.W. Jones, et al., Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice, Nat. Neurosci. 2 (1999) 271–276.
[156] M.A. Westerman, D. Cooper-Blacketer, A. Mariash, et al., The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease, J. Neurosci. 22 (2002) 1858–1867.
[157] F. Kamenetz, T. Tomita, H. Hsieh, et al., APP processing and synaptic function, Neuron 37 (2003) 925–937.
[158] J.R. Cirrito, K.A. Yamada, M.B. Finn, et al., Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo, Neuron 48 (2005) 913–922.
[159] C. Priller, T. Bauer, G. Mitteregger, B. Krebs, H.A. Kretzschmar, J. Herms, Synapse formation and function is modulated by the amyloid precursor protein, J. Neurosci. 26 (2006) 7212–7221.
[160] J.T. Ting, B.G. Kelley, T.J. Lambert, D.G. Cook, J.M. Sullivan, Amyloid precursor protein overexpression depresses excitatory transmission through both presynaptic and postsynaptic mechanisms, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 353–358.
[161] H. Hsieh, J. Boehm, C. Sato, et al., AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss, Neuron 52 (2006) 831–843.
[162] Z. Nusser, R. Lujan, G. Laube, J.D. Roberts, E. Molnar, P. Somogyi, Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus, Neuron 21 (1998) 545–559.
[163] Y. Takumi, V. Ramirez-Leon, P. Laake, E. Rinvik, O.P. Ottersen, Different modes of expression of AMPA and NMDA receptors in hippocampal synapses, Nat. Neurosci. 2 (1999) 618–624.
[164] Z. Gu, W. Liu, Z. Yan, {beta}-Amyloid impairs AMPA receptor trafficking and function by reducing Ca2+/calmodulin-dependent protein kinase II synaptic distribution, J. Biol. Chem. 284 (2009) 10639–10649.
[165] D. Puzzo, L. Privitera, E. Leznik, et al., Picomolar amyloid-beta positively modulates synaptic plasticity and memory in hippocampus, J. Neurosci. 28 (2008) 14537–14545.
[166] A. Garcia-Osta, C.M. Alberini, Amyloid beta mediates memory formation, Learn. Mem. 16 (2009) 267–272.
[167] I. Blasko, K. Jellinger, G. Kemmler, et al., Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine, Neurobiol. Aging 29 (2008) 1–11.
[168] R. Mayeux, L.S. Honig, M.X. Tang, et al., Plasma A[beta]40 and A[beta]42 and Alzheimer's disease: relation to age, mortality, and risk, Neurology 61 (2003) 1185–1190.
[169] A. Kern, B. Roempp, K. Prager, J. Walter, C. Behl, Down-regulation of endogenous amyloid precursor protein processing due to cellular aging, J. Biol. Chem. 281 (2006) 2405–2413.
[170] L. McConlogue, M. Buttini, J.P. Anderson, et al., Partial reduction of BACE1 has dramatic effects on Alzheimer plaque and synaptic pathology in APP Transgenic Mice, J. Biol. Chem. 282 (2007) 26326–26334.
[171] H. Fukumoto, D.L. Rosene, M.B. Moss, S. Raju, B.T. Hyman, M.C. Irizarry, Beta-secretase activity increases with aging in human, monkey, and mouse brain, Am. J. Pathol. 164 (2004) 719–725.
[172] S.J. Tyler, D. Dawbarn, G.K. Wilcock, S.J. Allen, alpha- and beta-secretase: profound changes in Alzheimer's disease, Biochem. Biophys. Res. Commun. 299 (2002) 373–376.
[173] J.H. Stockley, R. Ravid, C. O'Neill, Altered beta-secretase enzyme kinetics and levels of both BACE1 and BACE2 in the Alzheimer's disease brain, FEBS Lett. 580 (2006) 6550–6560.
[174] J.F. Ghersi-Egea, P.D. Gorevic, J. Ghiso, B. Frangione, C.S. Patlak, J.D. Fenstermacher, Fate of cerebrospinal fluid-borne amyloid beta-peptide: rapid clearance into blood and appreciable accumulation by cerebral arteries, J. Neurochem. 67 (1996) 880–883.
[175] M. Shibata, S. Yamada, S.R. Kumar, et al., Clearance of Alzheimer's amyloid-ss(1–40) peptide from brain by LDL receptor-related protein-1 at the blood–brain barrier, J. Clin. Invest. 106 (2000) 1489–1499.
[176] A. Sagare, R. Deane, R.D. Bell, et al., Clearance of amyloid-beta by circulating lipoprotein receptors, Nat. Med. 13 (2007) 1029–1031.
[177] S. Vogelgesang, I. Cascorbi, E. Schroeder, et al., Deposition of Alzheimer's beta-amyloid is inversely correlated with P-glycoprotein expression in the brains of elderly non-demented humans, Pharmacogenetics 12 (2002) 535–541.
[178] R. Deane, S. Du Yan, R.K. Submamaryan, et al., RAGE mediates amyloid-beta peptide transport across the blood–brain barrier and accumulation in brain, Nat. Med. 9 (2003) 907–913.
[179] M.A. Leissring, W. Farris, A.Y. Chang, et al., Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death, Neuron 40 (2003) 1087–1093.
[180] R. Poirier, D.P. Wolfer, H. Welzl, et al., Neuronal neprilysin overexpression is associated with attenuation of Abeta-related spatial memory deficit, Neurobiol. Dis. 24 (2006) 475–483.
[181] E. Hellstrom-Lindahl, R. Ravid, A. Nordberg, Age-dependent decline of neprilysin in Alzheimer's disease and normal brain: inverse correlation with A beta levels, Neurobiol. Aging 29 (2008) 210–221.
[182] R. Russo, R. Borghi, W. Markesbery, M. Tabaton, A. Piccini, Neprylisin decreases uniformly in Alzheimer's disease and in normal aging, FEBS Lett. 579 (2005) 6027–6030.
[183] J.S. Miners, Z. Van Helmond, K. Chalmers, G. Wilcock, S. Love, P.G. Kehoe, Decreased expression and activity of neprilysin in Alzheimer disease are associated with cerebral amyloid angiopathy, J. Neuropathol. Exp. Neurol. 65 (2006) 1012–1021.