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From Mitochondrial Dysfunction to Amyloid Beta Formation: Novel Insights into the Pathogenesis of Alzheimer's Disease

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Abstract The non-Mendelian sporadic Alzheimer's disease (AD) is the most frequent form of dementia diagnosed worldwide. The most important risk factor to develop sporadic AD is aging itself. Next to hyperphosphorylated Tau, intracellular amyloid beta (Aß) oligomers are known to initiate a cascade of pathological events ranging from mitochondrial dysfunction, synaptic dysfunction, oxidative stress, and loss of calcium regulation, to inflammation. All these events are considered to play an important role in the progressive loss of neurons. The molecular mechanisms determining the balance between Aß production and clearance during the progression of the disease are not well understood. Furthermore, there is cumulating evidence that Aß formation impairs mitochondrial function and that mitochondrial dysfunction is an early event in the pathogenesis of AD. On the other hand, mitochondrial dysfunction, in particular increased formation of mitochondrially derived reactive oxygen species, promote Aß formation. Here, we review these latest findings linking mitochondrial dysfunction and Aß formation. We propose that mitochondrial dysfunction, which is well-known to increase with age, is an initial trigger for Aß production. As Aß itself further accelerates mitochondrial dysfunction and oxidative stress, its formation is self-stimulated. Taken together, a vicious cycle is initiated that originates from mitochondrial dysfunction, implying that AD can be viewed as an age-associated mitochondrial disorder. The proposed mechanism sheds new light on the pathophysiological changes taking place during the progression of AD as well as in the aging process.

Keywords Alzheimer's disease · Amyloid beta formation · Aging · Mitochondrial dysfunction

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Introduction

The non-Mendelian sporadic Alzheimer's disease (AD) is the most frequent form of dementia diagnosed world wide. Besides hyperphosphorylated Tau, intracellular amyloid beta (Aß) oligomers are considered to initiate a cascade of pathological events ranging from synaptic dysfunction, oxidative stress, mitochondrial dysfunction, loss of calcium regulation, and inflammation. All these different mechanisms are considered to play an important role in the loss of neurons. Aß peptides are natural products of metabolism. The exact mechanism why the balance between Aß production and clearance during the progression of the disease is lost is still not completely understood. However, the most important risk factor to develop sporadic AD is aging itself. Aging is associated with mitochondrial dysfunction and increased oxidative stress. Here, we review latest findings that mitochondrial dysfunction, which is associated with increased oxidative stress, might be an initial trigger for

enhanced Aß production during the aging process. Aß itself shows detrimental effects on mitochondrial function and further accelerates oxidative stress as well as mitochondrial dysfunction and apoptosis. The proposed mechanism sheds new light into the pathophysiological changes taking place during aging which might initiate, together with other factors such as the apoliprotein E4 (APOE4), the progression of AD.

Mitochondrial Dysfunction in the Aging Brain

Aging is the most prominent risk factor for a multiplicity of neurodegenerative diseases such as the non-Mendelian sporadic AD which affects most patients diagnosed for dementia above the age of 60. The prevalence for sporadic AD increases tremendously with age from 2 % in people aged 65–69 to 25 % in people aged above 90 [1]. A gradual increase of Aß levels over years or even decades is considered to play an important role in the pathogenesis of AD. Aß peptides are natural products of the amyloid precursor protein (APP) metabolism. Aß peptides contain of 36–43 amino acids. $Aß_{1\text{-}40}$ is the most abundant species whereas $Aß_{1\text{-}42}$ is reported to be more toxic and aggregation-prone than $Aß_{1\text{-}40}$. Enhanced amyloidogenic processing of APP by the ß-site APP cleaving enzyme (BACE) and the γ-secretase complex and reduced clearance lead to increased intracellular levels of soluble oligomeric Aß, resulting in cellular dysfunction comprising e.g., synaptic failure, mitochondrial dysfunction, enhanced oxidative stress, neurotransmitter and neurotrophin depletion, inflammation, and apoptosis which is reflected in patients as clinical symptoms such as cognitive deficits [2, 3]. However, the mechanism by which amyloidogenic APP processing is triggered in humans is still not known. This lack of knowledge certainly represents a major missing link in our understanding of the pathogenesis of this devastating disease.

The mechanisms linking AD and aging are not well understood. The complex underlying mechanism of brain aging itself is still only partly understood. Several hypotheses were proposed to explain the complex phenomenon aging. One very prominent and well characterized alteration in the aging brain is the fact that mitochondrial efficacy is impaired in aged people, in different Alzheimer animal models, and in AD patients [4, 5].

Mitochondria, the powerhouses of our cells, are not only of major importance for ATP production but also control diverse cellular processes such as intermediate metabolic reactions, calcium homeostasis, apoptosis, proliferation, and differentiation. Mitochondria have their own genome (mtDNA) that encodes core subunits of four complexes (I, III, IV, and V) required for oxidative phosphorylation (OXPHOS). Electrons of NADH and $FADH_2$, intermediates of the Krebs cycle, are transferred from complex I and II to complex III, afterwards to complex IV, and finally to oxygen. During this electron transfer process, the accruing redox energy is used to pump protons from the mitochondrial matrix to the intermembrane space, generating a proton gradient across the inner membrane. This proton gradient is utilized by complex V to generate ATP. However, up to 2 % of electrons which are transferred through the respiratory chain lead to the formation of reactive oxygen species (ROS) in the form of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH.) at complex I and complex III [6, 7]. The superoxide anion radical might also react with other radicals such as nitric oxide (NO), producing reactive nitrogen species. In healthy organisms, the endogenous antioxidant system such as superoxide dismutase, catalase, glutathione reductase, or glutathione peroxidase detoxifies these harmful species. During the aging process and in the progression of age-associated neurodegenerative diseases, high ROS levels, also described as "oxidative stress", lead to accumulation of oxidized proteins, lipids, and nucleic acids and thereby might directly impair cellular function [8]. It should be emphasized that ROS next to their well-described toxic properties are also shown to have important roles as signaling molecules regulating a number of physiological processes (for review see [6, 9]).

Our brain is considered to be particularly vulnerable to oxidative stress due to three factors: first, it exhibits a high consumption of 20 % of consumed oxygen albeit only representing 2 % of the body weight; second, the exalted levels of polyunsaturated fatty acids; and third, its rather low extent of antioxidant defense compared to other organs [10]. Enhanced oxidative stress in the aging brain was repeatedly and consistently detected by different groups [11–15]. Findings of enhanced ROS levels in the aging brain led to a theory that ROS generated by OXPHOS induce oxidative modifications of the respiratory chain and somatic mutations in the mtDNA which in turn leads to reduced OXPHOS function contributing to the pathogenesis of AD [16]. Importantly, complex I activity was reported to decline substantially during normal brain aging, whereas complex III activity appears to be nearly unchanged [4, 17–19], suggesting complex I as a major player of the brain aging scenario and ROS generation. In addition, complex I function seems to be quite sensitive to oxidative stress for two reasons. First, complex I is spatially located such that it is well exposed to oxidative modifications. In particular, the various iron–sulfur clusters can be a site of direct ROS attack. These oxidative modifications can manifest in the impairment of enzymatic activity and mitochondrial dysfunction. Interestingly, for NO-mediated inhibition of complex I, three mechanisms were proposed: S-nitrosylation, tyrosine nitration, and damage to iron centers [20]. Second,

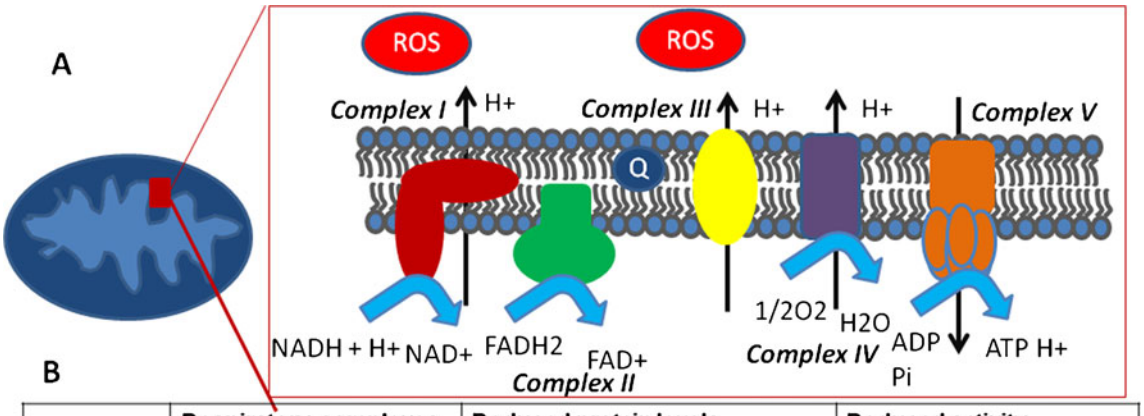
seven subunits of its catalytic core are encoded by mtDNA. Thus, this complex is tremendously susceptible to ROS-mediated mtDNA mutations which in turn can result in reduced complex I activity and enhanced ROS production. A reduced mitochondrial gene expression was observed in rats and humans [21, 22]. In addition, several groups showed reduced protein levels and activities of several complexes of the respiratory chain including complex I (please also see Fig. 1) [23–27]. Whether somatic mtDNA mutations and oxidative modifications are major factors contributing to aging, associated complex I dysfunction is an open question.

Mitochondrially Derived ROS Induce Aß Generation—Focus on Complex I

It is well established that mitochondrial dysfunction is an early event in the pathogenesis of AD, and several reviews beautifully summarize the recent findings about the effects of Aß on mitochondrial function, dynamics, and ROS production [28–30]. In this review, we rather aim to focus on the effect of mitochondrially derived ROS on Aß formation. Several lines of evidence suggest that elevated ROS production initiate toxic APP processing and thereby trigger Aß generation. The group of Tabaton reported that oxidative stress generated by hydroxynonenale (HNE) or H_2O_2 leads to enhanced Aß production in different cell models [31, 32]. In addition, HNE modifies the γ-secretase substrate receptor nicastrin. This leads to enhanced binding of the γ-secretase substrate APP, probably resulting in elevated Aß generation [33].

However, whether mitochondrially derived ROS promote amyloidogenic APP processing was unclear so far. In a recent study, we showed that complex I-derived ROS initiate enhanced amyloidogenic APP processing [34]. First, complex I dysfunction was induced in HEK293 and SY5Y cells using the complex I inhibitor rotenone. Rotenone leads to severe mitochondrial dysfunction including reduced mitochondrial membrane potential (MMP), ATP levels, mitochondrial fragmentation and increased ROS. In both cell models, $Aß_{1-40}$ levels were significantly increased. Importantly, the enhanced Aß generation could be attenuated by ROS scavenging using the antioxidant vitamin C. However, very high concentrations much above therapeutical levels were needed. Second, two different mouse models were used to support our hypothesis that mitochondrial derived ROS lead to enhanced APP processing. In a mouse model

A



B

	Respiratory complexes	Reduced protein levels	Reduced activity
Aging	complex I complex II complex III complex IV ATP-ase	18, 19 18,19 18,19 18,19 18,19	20, 21, 22
AD - Aß	complex I Complex II Complex III complex IV ATPase	46, 48, 49 49 48 46, 47, 49 49	45, 46 45, 46, 47
AD - Tau	Complex I ATP-ase	46, 51 46, 51	46, 51 46, 51

Fig. 1 **a** Simplified model of the respiratory chain. **b** Reduced protein levels and activity of the different complexes of the respiratory chain in aging and AD

deficient in complex I due to inactivation of the *Ndufs4* gene [35], Aß levels were increased even before there was notable pathology or behavioral effects. In addition, Thy-1 APP transgenic mice were treated with rotenone for 3 days. Again, $Aß_{1-40}$ levels were increased. In summary, our study shows for the first time using both cell and animal models that mitochondrially derived ROS, via complex I dysfunction, lead to enhanced Aß levels.

These results are in line with recently published findings showing that in APP transgenic mice (Tg2576), the pesticide paraquat which enhances ROS levels also increases Aß levels and leads to cognitive impairment [36]. Further support comes from a completely different aging model, the SAMP8 mouse. In this premature aging mouse model, a unique missense A11181G mutation in the mt-ND-4 gene was detected [37]. This gene encodes one of the subunits of complex I, NADH dehydrogenase subunit 4. Interestingly, these mice exhibit a 50 % increase of Aß during aging [38]. Another neurodegenerative disease which is highly associated with aging and complex I dysfunction is Parkinson's disease (PD). Several patients suffer from mixed forms of PD and AD associated with not only α-synuclein but also Aß plaques [39, 40]. The latter could be explained by our new findings that ROS generated by complex I dysfunction trigger Aß generation. However, other mechanisms might also contribute to enhanced Aß levels in PD such as increased secretion of Aß by α-synuclein [41]. Another genetic disease, the down syndrome, is associated with high levels of oxidative stress in early life and mitochondrial dysfunction [42]. Down syndrome patients have a high prevalence to develop AD which ranges between 8 % at an age of 35–49 and 75 % at an age above 60 years [43, 44] and show very early senile Aß plaques and neurofibrillary tangles. Recently, oxidative stress and mitochondrial dysfunction were proposed to be major factors linking down syndrome and AD [45]. Also, a selective impairment of complex I activity and increased ROS levels were detected in a down syndrome mouse model and in fibroblasts derived from down syndrome patients [46]. These defects might be partly explained by the triplication of both APP and SOD-1 genes. The increase of SOD-1 expression is considered to be associated with an increase in H_2O_2 outbalancing the reduction in superoxide [42].

One open question is whether only complex I-derived ROS or also other types of mitochondrial-derived ROS are able to induce amyloidogenic APP processing? We would propose that this is a shared property of all mitochondrially derived ROS. This hypothesis is supported by findings that in animal and cell models, several groups showed that hypoxia increases Aß production in vitro and in vivo [47–49] and that hypoxia increases ROS via reduced complex III activity [50]. Moreover, the AD prevalence is increased in patients with a stroke history [51, 52]. Our group also showed that antimycin, a selective complex III inhibitor, also leads to increased Aß levels in HEK293 cells [34].

Taken together, these findings demonstrate that ROS which are generated by mitochondrial dysfunction, e.g., as observed during aging or in pathological situations, act as a switch triggering amyloidogenic APP processing (Fig. 2). Together with other AD-associated risk factors such as the APOE4 status, low physical and cognitive activity, genetic mutations, or other diseases, mitochondrial dysfunction might be the crucial factor for the initiation of a vicious cycle which finally leads to AD. APOE4 expression was shown to reduce expression of several complexes of the respiratory chain including complex I and IV [53]. Furthermore, complex IV enzymatic activity was also reduced. Interestingly, treatment with small molecules that disrupt apoE4 domain interactions restored mitochondrial respiratory complex IV levels underlying the importance of this interaction [53].

How Do Mitochondrial ROS Trigger Aß Production?

Tamagno et al. (2005) showed that BACE1 protein and activity are significantly increased by H_2O_2 and HNE in the NT2 cell line. In addition, the authors propose that enhanced γ-secretase activity also positively enhance BACE1 activity and expression, and thereby might lead to a positive feedback loop which further triggers the generation of Aß. These findings are in line with recently published results by Jo et al. (2011) which confirm that γ-secretase regulates BACE1 expression. Several pathways are discussed to be involved in this phenomenon such as HIF-1α, NF-KB, and JNK/cjun [47, 54, 55]. These data together with our findings might suggest that in a physiological context, mitochondrially derived ROS trigger APP processing via enhanced BACE1 and γ-secretase activity. Yet, whether this is indeed the case and what signaling pathways are involved needs to be resolved in future studies.

Aß Itself Causes Mitochondrial Dysfunction, ROS, and Thereby Initiates a Vicious Cycle

Several groups, including our group, showed that oligomeric Aß as well as fibrillar Aß leads to a drop on MMP and ATP production [56–58]. In Thy-1 APP transgenic mice, MMP was already reduced at an age of 3 months when only oligomeric Aß is present and amyloid plaques are not detectable [56]. This decrease is mainly induced by reduced complex IV activity which is also reflected in impaired oxygen consumption [56]. However, fibrillar Aß preparations lead to similar decrease in MMP as oligomeric Aß, suggesting that

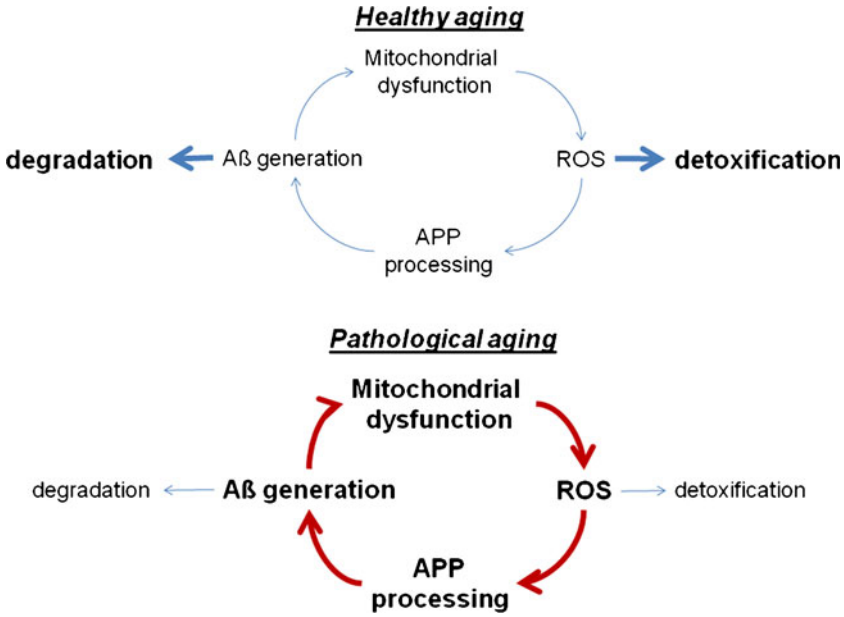


Fig. 2 The effect of mitochondrial dysfunction on ROS, APP processing, and Aß generation during healthy aging (*top panel*) compared to pathological aging (*bottom panel*)

mitochondrial dysfunction is mediated by both species in contrast to defects in long-term potentiation (LTP) where only oligomeric Aß inhibits LTP [59]. The group of Eckert showed that several subunits of complex IV are downregulated in APP/PS2 mice [58]. Here, a direct correlation between complex IV activity and protein levels was detected. These findings are supported by another study reporting decreased activity of complex IV in a triple transgenic animal model (P301Ltau/APP/PS1) [60]. In other AD animal models (Tg2587 [61] or PS1 [62]), decreased protein levels of several complexes of the respiratory chain including complex IV (Fig. 1) was observed. However, the activity of these complexes or other parameters for mitochondrial function such as MMP was not determined in these studies.

How does Aß affect complex IV activity? Some studies suggest that Aß is partly localized into mitochondria and might thereby inhibit complex IV activity. One possibility proposed was that Aß is taken up by the mitochondrial translocase of outer membrane which might inhibit protein import including nuclear encoded complex IV subunits [63]. Other groups suggested that the sequestration of heme or the interaction between Aß and the Aß-binding alcohol dehydrogenase might explain the observed complex IV deficits [64]. It was also proposed that Aß is generated within mitochondria by mitochondrially localized γ-secretase [65]. Degradation of mitochondrial Aß might occur via the human presequence protease PreP [66]. Interestingly, the activity of the latter protease as well as complex IV activity was reduced in AD brains compared to age-matched controls [67].

The early measured defects in MMP, oxygen consumption, and complex IV dysfunction induced by Aß are accelerated by hyperphosphorylated tau, the other hallmark of AD, during the aging process. Hyperphosphorylated Tau induces complex I dysfunction which is further exaggerated during the aging process [58, 68]. Importantly, complex I dysfunction was present in tau transgenic animals (pR5) of 12 months as well as in triple transgenic animals at an age of 12 months (pR5/APP/PS2) but not in APP/PS2 transgenic animals. Changes in oxygen consumption and mitochondrial respiration and a drop in MMP levels were not detectable before an age of 24 months in these animals, indicating that Aß might initiate mitochondrial damage which is further accelerated by hyperphosphorylated tau.

In all these different animal models for AD, increased amount of oxidative stress were found in the form of HNE, O_2^-, or enhanced H_2O_2 production [56, 58, 60]. This oxidative stress might further impair mitochondrial function by oxidative modifications or mtDNA mutations and thereby contribute together with decreased OXPHOS functionality to the progression of Aß production. Thereby, a vicious cycle is started which is further self-propagated during the progression of the disease.

As discussed above, complex IV might be a specific target of Aß. However, complex IV dysfunction alone is not sufficient to induce Aß generation [69, 70]. In a complex IV deficient AD mouse model (COXd/AD), even less amyloid plaque burden was detected compared to AD mice. Importantly, no enhanced ROS production could be detected in this animal model. Therefore, complex IV dysfunction appears not to directly cause enhanced APP processing and Aß generation. Future studies need to clarify how Aß promotes mitochondrial dysfunction.

Are Other Mitochondrial Diseases also Characterized by Cognitive Deficits and Aß Burden?

In case the hypothesis that mitochondrial derived ROS lead to enhanced Aß production is correct, patients suffering from mitochondrial disorders such as mitochondrial encephalopathy, lactatacidosis, stroke like episodes (MELAS), myoclonic epilepsy with ragged red fibers, or Kearns Sayre syndrome are predicted to also show cognitive decline and dementia (mitochondrial dementia) and Aß plaques. This is certainly difficult to test as many patients suffering from these severe diseases die during childhood. Still, cognitive impairment and dementia are documented findings in individual patients suffering from mitochondrial disorders. Several clinical, morphological, functional, and chemical manifestations were detected in these patients [71]. Only in few cases, cognitive function, Aß levels in the cerebrospinal fluid, or Aß plaques in post mortem brain samples were investigated. However, a sporadic case of progressive cognitive and behavioral decline was identified in a patient with a rare m.3291T>C MELAS mutation [72]. Interestingly, AD-like Aß plaques were found in a female MELAS patient, who was only 54 years old at the time of testing, even though no evidence for familiar AD resulting from APP mutations was found [73]. Taken together, these findings strongly support the view that that mitochondrial dysfunction is an early trigger in the pathogenesis of AD indicating that AD possibly needs to be regarded as a mitochondrial disorder. This opens a number of new strategies for therapeutic intervention. From our point, ROS scavengers as well as mitoprotective strategies might be one part of a complex treatment strategy for AD also comprising drugs lowering the early oligomeric Aß species which all need to be applied decades before the disease is diagnosed. The proposed therapy would need to be continued for decades. This strategy first requires reliable biomarkers which are indicative for the development of AD.

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