

An update on the toxicity of A β in Alzheimer's disease

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Abstract: Alzheimer's disease is characterized histopathologically by deposition of insoluble forms of the peptide A β and the protein tau in brain. A β is the principal component of amyloid plaques and tau of neurofibrillary tangles. Familial cases of AD are associated with causal mutations in the gene encoding the amyloid precursor protein, APP, from which the amyloidogenic A β peptide is derived, and this supports a role for A β in disease. A β can promote tau pathology and at the same time its toxicity is also tau-dependent. A β can adopt different conformations including soluble oligomers and insoluble fibrillar species present in plaques. We discuss which of these conformations exert toxicity, highlight molecular pathways involved and discuss what has been learned by applying functional genomics.

Keywords: amyloid, mitochondria, oligomer, proteomic, tau, transgenic

Incidence of dementia

Alzheimer's disease (AD) is the most common cause of dementia, comprising 50%–70% of all cases and affecting more than 15 million people worldwide. Frontotemporal dementia (FTD), in comparison, is less common but may make up to 50% of dementia cases presenting before the age of 60 (Graff-Radford and Woodruff 2007). Dementia is defined as the significant loss of intellectual abilities such as memory functions, severe enough to interfere with social or occupational functioning. At present, AD cannot be cured which is different from memory dysfunction caused by malnutrition, drug abuse or depression where some form of treatment is available (Patel et al 2007).

Neuropathology of AD and FTD

The AD brain is characterized by massive neuronal cell and synapse loss at specific predilection sites (Selkoe 2002). The extracellular plaques and the intracellular neurofibrillary tangles are the key histopathological hallmarks of AD. The major proteinaceous component of the amyloid plaques is a 40- to 42-amino acid polypeptide termed A β (A β ₄₀ and A β ₄₂), which is derived by proteolytic cleavage from the amyloid precursor protein, APP, as part of normal cellular metabolism (Glennner and Wong 1984; Masters et al 1985). β -Secretase is the protease that generates the amino terminus of A β and γ -secretase cleavage at the carboxy-terminus dictates its length. A β ₄₀ is the most common species and A β ₄₂ is the more fibrillogenic and neurotoxic species. Recent evidence suggests that A β ₄₀ may prevent A β ₄₂ from aggregating and forming plaques (Yan and Wang 2007). β -Secretase activity has been attributed to a single protein, BACE 1 (Vassar et al 1999), whereas γ -secretase activity depends on four components, presenilin, nicastrin, APH-1 and PEN-2 forming a proteolytic complex (Edbauer et al 2003). α -Secretase is involved in the non-amyloidogenic pathway by cleaving APP within the A β domain, thus precluding A β formation (Gotz and Ittner 2008). Which higher order forms of A β exert toxicity is a matter of debate. The conflicting data as well as putative mechanisms of toxicity are discussed in detail below.

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The second histopathological hallmark of AD are the neurofibrillary lesions that are found in cell bodies and apical dendrites as neurofibrillary tangles, in distal dendrites as neuropil threads, and in the abnormal neurites that are associated with some β -amyloid plaques (neuritic plaques). Neurofibrillary tangles are also abundant, in the absence of overt plaques, in FTD and other so-called tauopathies (Lee et al 2001). The neurofibrillary lesions contain aggregates of the microtubule-associated protein tau that under physiological conditions is mainly localized to the axonal compartment of neurons (Goedert et al 1988). In tauopathies such as PSP (Progressive Supranuclear Palsy) or CBD (Corticobasal Degeneration), tau also forms aggregates in non-neuronal cells (Gotz 2001), emphasizing the important role of glia in disease (Kurosinski and Gotz 2002). Tau has an unusually high content of serine and threonine residues and many of these are phosphorylated under physiological conditions (Chen et al 2004a). Under pathological conditions, tau is hyperphosphorylated, which means that it is phosphorylated to a higher degree at physiological sites, and at additional “pathological” sites. Phosphorylation tends to dissociate tau from microtubules. Tau also undergoes a conformational change which likely assists in differential phosphorylation (Jicha et al 1997). Both tau and A β undergo nucleation-dependent fibril formation (Harper and Lansbury 1997). In the course of this process, initially dispersed polypeptide chains slowly come together to form a diverse array of fibrillation nuclei that enable the rapid outgrowth into higher order assemblies including fibrils (Hortschansky et al 2005; Pellarin and Caffisch 2006; Gotz et al 2008).

Genetics of AD and FTD

In familial AD, autosomal dominant mutations have been identified in three genes: APP and the presenilin 1 (PS1) and presenilin 2 (PS2) genes. Together, they account for less than 1% of the total number of AD cases (Delacourte et al 2002). In addition, several susceptibility genes have been identified but only the apolipoprotein E (APOE) gene has been unanimously confirmed and found to be associated with sporadic AD (Rocchi et al 2003). Clinically and histopathologically, early-onset familial AD cannot be discriminated from late-onset sporadic AD (Gotz 2001).

Whereas in AD no mutations were found in the MAPT gene encoding tau, they were identified in FTD with Parkinsonism linked to chromosome 17 (FTDP-17) (Hutton et al 1998; Poorkaj et al 1998; Spillantini et al 1998). This established that dysfunction of tau in itself can cause neurodegeneration and lead to dementia. The existence of a subgroup of FTD

with no tau aggregation was enigmatic for some time leading to the coining of terms such as ‘dementia lacking distinctive histology’. This dementia with tau-negative and ubiquitin-positive lesions today is termed FTL-DU or FTDU-17 although this is misleading as it implies that the tau lesions in FTDP-17 are ubiquitin-negative which is not the case.

FTDU-17 is caused by loss-of-function mutations in the gene encoding progranulin (PGRN), a growth factor involved in multiple physiological and pathological processes including tumorigenesis (Baker et al 2006; Cruts et al 2006). The TAR DNA-binding protein of 43 kDa (TDP-43) is a constituent of the ubiquitin-positive inclusions in both FTL-DU and sporadic amyotrophic lateral sclerosis (ALS) arguing for an overlap in the pathology between these two entities (Neumann et al 2006). Similar to tau, in diseased brain, TDP-43 becomes hyperphosphorylated, ubiquitinated, and carboxy-terminally truncated. Mutations in the gene encoding valosin-containing protein cause frontotemporal dementia with inclusion body myopathy and Paget disease of bone (IBMPFD), a rare, autosomal-dominant disorder. As TDP-43, but not valosin-containing protein, is accumulating in the ubiquitin-positive inclusions in IBMPFD this would argue that valosin-containing protein gene mutations lead to a dominant negative loss or alteration of valosin-containing protein function culminating in impaired degradation of TDP-43. In other words, TDP-43 is a common pathologic substrate linking a variety of distinct patterns of FTL-DU pathology caused by different genetic alterations (Neumann et al 2007).

Clinical features of AD and FTD

AD is characterized by early memory deficits, followed by a gradual erosion of other cognitive functions such as judgment, verbal fluency and orientation. The most severe neuropathological changes occur in the hippocampal formation, followed by the association cortices and subcortical structures, including the amygdala and the nucleus basalis of Meynert (Arnold et al 1991). Neurofibrillary tangles develop and spread in a predictable manner across the brain providing the basis for distinguishing six stages of disease progression: the transentorhinal Braak stages I-II represent clinically silent cases; the limbic stages III-IV incipient AD; and the neocortical stages V-VI fully developed AD. By using phosphorylation-dependent anti-tau antibodies such as AT8, neuronal changes can be visualized well before the actual formation of neurofibrillary tangles (Braak and Braak 1991, 1995).

In contrast to AD, which is characterized predominantly by memory loss, FTD is mainly initiated with behavioral

impairment. The average age of diagnosis is about 60, which is around 10 years before the average sporadic AD patient is diagnosed (Snowden et al 2001; Weder et al 2007). Patients may have an often asymmetrical atrophy of the frontal and temporal cortex. There is evidence that motor neuron disease and FTD coexist, and the motor symptoms may precede, coincide, or follow the development of cognitive and behavioral changes (Graff-Radford and Woodruff 2007). In a significant subset of FTD, late parkinsonism is found (Lee et al 2001).

Animal models of AD and FTD

To better understand the role of A β and tau in AD and related disorders, experimental animal models have been developed which reproduce aspects of the neuropathological characteristics of these diseases (Gotz et al 2007; Gotz and Ittner 2008).

In 1995, Games and coworkers established the first A β plaque-forming mouse model by targeting high levels of the disease-linked V717F mutant form of APP in brain, using the platelet-derived growth factor mini-promoter for expression. These PDAPP mice showed many of the pathological features of AD, including extensive deposition of extracellular amyloid plaques, astrogliosis and neuritic dystrophy (Games et al 1995). Similar features were observed in a second transgenic model established by Hsiao and coworkers by expressing the APP^{sw} mutation inserted into a hamster prion protein cosmid vector (Hsiao et al 1996). The APP23 strain was established by expressing APP^{sw} under the control of the neuronal mThy1.2 promoter, with a seven-fold overexpression of APP (Sturchler-Pierrat et al 1997; Stalder et al 1999). Subsequently, many more models have been developed such as the TgCRND8 or J20 mice (Janus et al 2000; Mucke et al 2000). These mouse models have been instrumental in addressing aspects of A β toxicity and testing therapies such as vaccination trials (Gotz 2001; Gotz et al 2004b; Kulic et al 2006).

The first tau transgenic model was established by us in 1995, expressing the longest human brain tau isoform, without a pathogenic mutation, in mice using the hThy1 promoter for neuronal expression (Gotz et al 1995). Despite the lack of a neurofibrillary pathology, these mice modeled aspects of human AD, such as the somatodendritic localization of hyperphosphorylated tau and, therefore, represented an early 'pre-tangle' phenotype. The subsequent use of stronger promoters caused a more pronounced tau phenotype in transgenic mice (Ishihara et al 1999; Spittaels et al 1999; Probst et al 2000; Gotz and Nitsch 2001). Once the first

pathogenic FTDP-17 mutations were identified in the MAPT gene in 1998, several groups expressed them in mice and achieved neurofibrillary tangle formation, both in neurons and in glial cells (Gotz and Ittner 2008). We, for example, expressed G272V and P301L mutant tau and obtained mice with aggregated tau and neurofibrillary tangles (Gotz et al 2001a; Gotz et al 2001b; Gotz et al 2001c; Deters et al 2008). The P301L tau-expressing pR5 mice showed a behavioural impairment in amygdala- and hippocampus-dependent tasks; aspects of the behavioral impairment could be correlated with the aggregation pattern of the transgene (Pennanen et al 2004; Pennanen et al 2006). K369I transgenic mice, on the other hand, model Parkinsonism in FTD, in parts owing to expression of the transgene in the substantia nigra (Ittner et al 2008).

Cross-talk between A β and tau

The amyloid cascade hypothesis claims, in simplistic terms, that in the pathogenic cascade of AD, A β is upstream of tau (Hardy and Selkoe 2002). To address the interaction between A β and tau (Gotz et al 2004a), A β plaque-forming Tg2576 mice were crossed with tangle-forming P301L tau-transgenic JNPL3 mice; also, P301L tau transgenic pR5 mice were intracerebrally injected with fibrillar preparations of A β ₄₂ (Gotz et al 2001b; Lewis et al 2001). Both strategies caused an increased tau phosphorylation at pathological epitopes and neurofibrillary tangle formation, establishing a link between A β and tau in vivo (Gotz et al 2001b; Lewis et al 2001). Similarly, tangle formation was aggravated by infusing brain extracts of aged plaque-forming APP23 mice intracerebrally in P301L tau transgenic mice or by crossing APP23 and P301L tau transgenic mice (Bolmont et al 2007). Together, these studies established that A β exaggerates a pre-existing tau pathology supporting, at least in parts, the amyloid cascade hypothesis in mice.

Interestingly, recent evidence suggests that A β toxicity is also tau-dependent (Roberson et al 2007). Reducing endogenous tau levels prevented behavioral deficits as assessed in the Morris water maze, without altering A β levels. This was achieved by crossing plaque-forming APP transgenic mice onto hetero- and homozygous tau knockout backgrounds (Roberson et al 2007). Tau reduction also protected both transgenic and non-transgenic mice against pentylenetetrazole (PTZ)-mediated excitotoxicity as shown by dramatic changes in seizure severity and latency. We were able to reproduce these findings in a second plaque-forming APP transgenic mouse model (Ittner et al submitted). Earlier findings in cultured hippocampal neurons derived from tau

knockout and transgenic mice supports the model that tau is required for A β toxicity (Rapoport et al 2002). Together, this suggests that a reduction in tau levels is a potentially powerful treatment strategy for AD and other neurological conditions that are associated with neurotoxicity. A mechanistic explanation is lacking and therefore the importance of this information should encourage more research groups to work on the interaction between A β and tau.

Functional genomics and A β toxicity

An unbiased approach to address the toxicity of tau and A β is by functional genomics, which encompasses transcriptomic and proteomic techniques (Chen et al 2004b; Hoernkli et al 2004; David et al 2005a; Hoernkli et al 2005). These highlighted a role for oxidative stress (see below) and impaired axonal transport in disease (Gotz et al 2006). When we analyzed the proteome pattern of total brain from P301L tau transgenic pR5 and wild-type mice by proteomics, we discovered that it was mainly metabolic related proteins including mitochondrial respiratory chain complex components, antioxidant enzymes and synaptic proteins that were modified in P301L tau mice. Importantly, mitochondrial dysfunction could be functionally validated in the P301L tau mice. Furthermore, the reduction in mitochondrial complex V levels in the P301L tau mice was also decreased in human P301L FTDP-17 brains. Finally, P301L tau mitochondria displayed an increased vulnerability towards fibrillar preparations of A β ₄₂, suggesting a synergistic action of tau and A β pathology on the mitochondria (David et al 2005b).

In a follow-up study we investigated the toxicity of oligomeric A β species that in recent years have been suggested to be the main culprit, rather than fibrillar A β (Hartley et al 1999; Necula et al 2007). The identity of the A β toxic species in both AD brains and in experimentally generated systems correlates best with the soluble, rather than the insoluble fibrillar forms. However, at present, there is little chemical and structural detail at the molecular and atomic level about the various aggregates to properly define the toxic species (Cappai and Barnham 2008). Interestingly, in cortical brain cells obtained from P301L tau transgenic pR5 mice both oligomeric and fibrillar, but not monomeric A β ₄₂ caused a decreased mitochondrial membrane potential (Eckert et al 2008a). This was not observed with cerebellar preparations indicating selective vulnerability of cortical neurons. Furthermore, we measured reductions in state 3 respiration, the respiratory control ratio and uncoupled respiration when incubating P301L tau mitochondria either

with oligomeric or fibrillar preparations of A β ₄₂. We also found that aging specifically increased the sensitivity of mitochondria to oligomeric A β ₄₂ damage indicating that while oligomeric and fibrillar A β ₄₂ are both toxic, they exert different degrees of toxicity in mitochondria from older animals (Eckert et al 2008a).

To understand which processes are disrupted by A β ₄₂ in the presence of tau aggregates a comparative proteomics study was performed in both a cellular and an in vivo system (David et al 2006). P301L tau expressing neuroblastoma cells were treated with A β ₄₂ as prior studies had shown that this caused tau filament formation (Ferrari et al 2003; Pennanen and Gotz 2005). In parallel, the amygdala of P301L tau transgenic mice was stereotaxically injected with A β ₄₂ as this causes increased tangle formation (Gotz et al 2001b). When the deregulated proteins in the two experimental paradigms were classified, it was found that a significant fraction of the altered proteins belonged to the same functional categories, ie, stress response and metabolism. We also identified model-specific effects of A β ₄₂ treatment such as differences in cell signaling proteins in the cellular model and changes in cytoskeletal and synapse proteins in the amygdala. By Western blotting and immunohistochemistry, we were able to show that 72% of the tested candidates were altered in human AD brain with a major emphasis on stress-related unfolded protein responsive candidates. This highlights these processes as important initiators in the A β ₄₂-mediated pathogenic cascade in AD and further supports the role of unfolded proteins in the course of AD (David et al 2006).

Human SH-SY5Y neuroblastoma cells were also investigated by transcriptomics to assess the role of P301L mutant tau expression and treatment with or without A β on gene regulation. We found that A β and P301L tau expression independently affected the regulation of genes controlling cell proliferation and synaptic elements. Moreover, A β and P301L tau acted synergistically on cell cycle and DNA damage genes, yet influenced specific genes within these categories. By using neuronally differentiated P301L tau cells, it was shown that A β treatment induced an early up-regulation of cell cycle control and synaptic genes. Together, the study showed that A β treatment and human tau over-expression in a cell culture model acted synergistically to promote aberrant cell cycle re-entry supporting the mitosis failure hypothesis in AD (Arendt 2003; Hoernkli et al 2007).

The Yin and Yang of A β

AD has been termed a synaptic failure (Selkoe 2002). While A β can kill neurons, it can also act by causing synaptotoxicity

which may be more relevant for the earlier stages of AD that are best characterized by synaptic loss rather than neuronal death. Loss of synaptic terminals or dendritic spines could cause the associated decline in cognitive functions that characterizes AD. Whether the neurotoxic and synaptotoxic actions of A β are separate activities or whether they share common mechanisms is not known (Cappai and Barnham 2008).

How cells respond to A β varies depending upon the concentration of A β used, which adds another level of complexity. While A β peptide added at micromolar concentrations to primary neuronal cultures induces cell death (Yankner et al 1990), low, subnanomolar concentrations are neurotrophic arguing in favor of a physiological function of A β (Yankner et al 1990). As discussed above, the neurotoxic activity of A β is dependent upon its aggregation state. When A β aggregation was induced this increased its neurotoxic activity suggesting that the toxic species was associated with the formation of fibrils (Pike et al 1991a; Pike et al 1991b; Pike et al 1993). At present, however, there is a major research focus on the role of non-fibrillar soluble A β as the toxic species in AD (Lambert et al 1998; Walsh et al 2002; Smith et al 2007). These species have been given different names, including A β -derived diffusible ligands (ADDLs) (Lambert et al 1998), globulomers (Barghorn et al 2005) and the A β star species 56 (A β *56) (Lesne et al 2006). To assist in identifying these species, conformational antibodies have been developed that not only stabilize the A β protofibrils but also prevent mature amyloid fibril formation (Habicht et al 2007).

A β can inhibit long-term potentiation (LTP), a model system for synaptic strengthening and memory (Lambert et al 1998; Walsh et al 2002; Cleary et al 2005; Klyubin et al 2005; Trommer et al 2005). When cell medium containing abundant A β monomers and proposed oligomers, but not amyloid fibrils was microinjected into rat brain, this markedly inhibits hippocampal long-term potentiation (LTP) (Walsh et al 2002). Immunodepletion from the medium of all A β species completely abrogated this effect. Pretreatment of the medium with insulin-degrading enzyme, which degrades A β monomers but not oligomers, did not prevent the inhibition of LTP, indicating a role for A β oligomers. These were shown to disrupt synaptic plasticity *in vivo* at concentrations found in human brain and cerebrospinal fluid, in the absence of monomeric or fibrillar amyloid. When cells were treated with γ -secretase inhibitors at doses which prevented oligomer formation but allowed appreciable monomer production, this no longer disrupted LTP, indicating that synaptotoxic A β oligomers can be targeted therapeutically (Walsh et al 2002; Walsh et al 2005).

In Neuro-2A cells, oligomers were shown to induce a tenfold greater increase in neurotoxicity as compared to fibrils (Stine et al 2003). However, whereas LTP seems to be inhibited by oligomeric A β only and not fibrillar A β , in a different experimental paradigm, the two species seem to have both toxic, yet diverse effects (White et al 2005). Using rat astrocyte cultures, oligomeric A β_{42} was shown to induce initial high levels of the pro-inflammatory molecule IL-1 β that decreased over time, whereas fibrillar A β caused increased levels over time (White et al 2005). It has been suggested that their neurotoxic activity is associated with dimeric and trimeric species however the exact composition of these higher molecular weight A β species has not been determined (Walsh et al 2002; Cleary et al 2005) and remains a crucial point to definitively establish their molecular identity. Together, this shows that the relative role of the toxicity of monomeric compared to oligomeric compared to fibrillar species is far from being resolved.

A β and downstream signaling

What are the down-stream effectors of A β toxicity? A β may act via a plethora of pathways to induce synaptic and neuronal degeneration (Small et al 2001). A β 's anti-LTP activity can be modulated with antagonists to the p38 MAP kinase (Wang et al 2004) and the Jun NH $_2$ -terminal kinase (JNK) pathways (Minogue et al 2003), both of which have also been implicated in tau phosphorylation (Kins et al 2001; Kins et al 2003). While inhibitors of p38, JNK, GSK-3 β and phosphatidylinositol 3-kinase showed either no or only minor inhibition of A β oligomer-mediated cell death in mouse hippocampal slices, inhibitors of MAPK kinase kinase, which is upstream of the extracellular signal-regulated kinases, significantly inhibited A β -mediated neuronal death (Chong et al 2006).

Another interesting kinase is the non-receptor tyrosine kinase Fyn, as it links A β and tau. Fyn is a known interaction partner of tau (Lee et al 1998). Furthermore, Fyn is necessary for the toxicity of ADDLs (an oligomeric form of A β) as Fyn knockout neurons are resistant to ADDL-mediated neuronal cell death (Lambert et al 1998). Moreover, Fyn knockout mice display reduced synaptotoxicity without affecting aberrant sprouting, when crossed with APP transgenic mice (Chin et al 2004). Fyn has a role in modulating synaptic activity and plasticity, by phosphorylating the NMDA receptor (Braithwaite et al 2006). This finding is consistent with the fact that A β oligomers alter the transport of the NMDA receptor by promoting its endocytosis and resulting in decreased NMDA receptor activity both

in vitro and in APP transgenic mice (Snyder et al 2005). Work in neuronal and astrocyte cultures further suggests that A β causes Ca²⁺-dependent oxidative stress by activating an astrocytic NADPH oxidase, with neuronal death following through a failure of antioxidant support (Abramov et al 2004). Together, this suggests a fine-balanced network of molecular interactions (Cappai and Barnham 2008).

At present it is not understood whether A β acts via a receptor or whether membrane binding alone is sufficient (Cappai and Barnham 2008). If A β acts via a receptor, this receptor may have specificity for A β or it may bind proteins or peptides with shared amyloid properties. Work in primary cortical and hippocampal cultures treated with A β and human amylin, respectively, indicates that the latter may be the case, as rat amylin, which is not amyloidogenic, turns out not to be toxic (Lim et al 2008). Membrane interaction of A β can occur via its hydrophobic carboxy-terminal domain (Bhatia et al 2000; Ambroggio et al 2005) or by electrostatic interactions mediated by the charged amino acids in the amino-terminal domain (Lau et al 2006). A β may bind to the cell membrane forming channels or pores that disrupt ion homeostasis, hence leading to neuronal dysfunction (Arispe et al 1993; Pollard et al 1995; Holscher 1998; Bhatia et al 2000; Lin et al 2001). As several molecules associated with disease (such as the Prion protein, the British peptide, or human amylin) can form soluble oligomers and bind to membranes and disrupt ion homeostasis, this may be an inherent property of amyloidogenic proteins or peptides (Demuro et al 2005).

A β binding proteins

A number of A β -binding proteins have been identified on the plasma membrane of neurons and glial cells. These include the α 7 nicotinic acetylcholine receptor, the receptor for advanced glycosylation end-products (RAGE), APP itself, the NMDA receptor, the P75 neurotrophin receptor (P75NTR), the scavenger receptors, CD36 and low-density lipoprotein receptor-related protein (LRP) members (Verdier et al 2004). RAGE can bind both non-fibrillar and fibrillar forms of A β (Yan et al 1996). Transgenic mice co-expressing mutant APP and RAGE revealed an earlier onset of memory defects and synaptic dysfunction than single APP transgenic mice (Arancio et al 2004). LRP, apoE and the serum protein α 2-macroglobulin (α 2M) probably modulate A β toxicity via clearance of apoE:A β and α 2M:A β complexes or A β alone from the brain and hence reduce A β levels (Shibata et al 2000; Deane et al 2004). The addition of an anti-NMDA receptor antibody can block A β oligomer binding to neurons and reduce ROS stimulation in hippocampal cultures (De

Felice et al 2007) suggesting a direct interaction between these two proteins. Alternatively, A β may be interacting with NMDA receptor via an integrin-mediated effect (Bi et al 2002). P75NTR can bind a variety of A β oligomeric species and modulate A β toxicity in a cell type- and P75 isoform-dependent manner (Coulson 2006; Sotthibundhu et al 2008). Full-length P75NTR blocks toxicity of fibrillar and non-fibrillar A β in primary neurons (Zhang et al 2003), but promotes toxicity of fibrillar A β in neuroblastoma cells (Perini et al 2002).

A β may not only bind to the cell surface but also act on intracellular organelles such as mitochondria (Lustbader et al 2004; Caspersen et al 2005; Crouch et al 2005; Devi et al 2006; Manczak et al 2006) whose function it impairs (Keil et al 2004; David et al 2005b; Eckert et al 2008a; Eckert et al 2008b). Mitochondrial dysfunction was also linked to full-length and carboxy-terminally truncated APP, that was shown to accumulate exclusively in the protein import channels of mitochondria of human AD, but not age-matched control brains (Devi et al 2006). Similarly, accumulation of full-length APP in the mitochondrial compartment in a transmembrane-arrested form, but not lacking the acidic domain, was shown to cause mitochondrial dysfunction and impair energy metabolism (Anandatheerthavarada et al 2003). A β can disrupt mitochondrial cytochrome *c* oxidase activity (Crouch et al 2005; Takuma et al 2005) in a sequence- and conformer-dependent manner (Crouch et al 2005). The A β binding protein alcohol dehydrogenase (ABAD) is a short-chain alcohol dehydrogenase that binds to A β in the mitochondrial matrix. This lead to mitochondrial failure via changes in mitochondrial membrane permeability and a reduction in the activities of enzymes involved in mitochondrial respiration (Lustbader et al 2004). ABAD can bind to the oligomeric A β ₄₂ present in the cortical mitochondria of APP transgenic mice (Yan et al 2007). Protease sensitivity assays suggest that A β gains access to the mitochondrial matrix rather than simply being adsorbed to the external surface of mitochondria (Caspersen et al 2005). The interaction between A β and the mitochondria may explain how A β induces apoptosis and caspase activation (Ivins et al 1998; White et al 2001; Lustbader et al 2004). Intracellular A β may be derived from internalized extracellular A β or from intracellularly generated A β (Casas et al 2004; Gomez-Ramos and Asuncion Moran 2007; Wegiel et al 2007). The presence of intracellular A β adds a further level of complexity to the mechanism of A β toxicity as this enables direct access to organelles that are vital for the function and viability of neurons. It is needless to say, that this has important implications for treatment strategies.

Conclusions

What can be expected in the forthcoming years? Some of the current therapeutic trials targeting A β may come to fruition (Gotz and Ittner 2008). With the advent of new tools it will likely become easier to discriminate A β conformations and hence allow establishing a defined role of specific conformers in toxicity (Habicht et al 2007). The mode of A β uptake and/or binding by neurons and other cell types will be elucidated and interacting proteins, both under physiologic and pathologic conditions, will be identified. Finally, how A β and tau interact and contribute to disease will assist in the development of treatment strategies for AD and related disorders.

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Disclosures

The authors have no conflicts of interest to disclose.

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