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Review

Amyloid-β: a chameleon walking in two worlds: a review of the trophic and toxic properties of amyloid-β

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Abstract

Although much maligned, the amyloid-β (Aβ) protein has been shown to possess a number of trophic properties that emanate from the protein's ability to bind Cu, Fe and Zn. Aβ belongs to a group of proteins that capture redox metal ions (even under mildly acidotic conditions), thereby preventing them from participating in redox cycling with other ligands. The coordination of Cu appears to be crucial for Aβ's own antioxidant activity that has been demonstrated both in vitro as well as in the brain, cerebrospinal fluid and plasma. The chelation of Cu by Aβ would therefore be predicted to dampen oxidative stress in the mildly acidotic and oxidative environment that accompanies acute brain trauma and Alzheimer's disease (AD). Given that oxidative stress promotes Aβ generation, the formation of diffuse amyloid plaques is likely to be a compensatory response to remove reactive oxygen species. This review weighs up the evidence supporting both the trophic and toxic properties of Aβ, and while evidence for direct Aβ neurotoxicity in vivo is scarce, we postulate that the product of Aβ's antioxidant activity, hydrogen peroxide (H_2O_2), is likely to mediate toxicity as the levels of this oxidant rise with the accumulation of Aβ in the AD brain. We propose that metal ion chelators, antioxidants, antiinflammatories and amyloid-lowering drugs that target the reduction of H_2O_2 and/or Aβ generation may be efficacious in decreasing neurotoxicity. However, given the antioxidant activity of Aβ, we suggest that the excessive removal of Aβ may prevent adequate chelation of metal ions and removal of $O_2^{-\cdot}$, leading to enhanced, rather than reduced, neuronal oxidative stress.

Theme: Disorders of the nervous system

Topic: Degenerative disease: Alzheimer's-beta amyloid

Keywords: Alzheimer's disease; Aβ; AβPP expression; Acute phase response; Metal ions; Iron; Copper; Antioxidant; Reactive oxygen species; Oxidation; Oxidative stress; Injury; Head trauma; Chelation; Neurotrophic; Neurotoxic; Zinc

Contents

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1. Introduction

Neuronal amyloidoses occur in Alzheimer's disease (AD) [1,2], Down syndrome [3], following head injury [4] and in healthy aging individuals [5], and are characterized by the extracellular deposition of a 39–43 amino acid protein, amyloid-β (Aβ), derived from the larger amyloid β protein precursor (AβPP). AβPP is processed in the brain by two competing pathways that involve different proteolytic enzymes that were initially termed secretases (α-, β- and γ-secretases). These pathways either promote the generation of Aβ (amyloidogenic pathway) or preclude its production (non-amyloidogenic pathway) [6]. Aβ is released as a soluble product from AβPP [7–9] via a series of metabolic cleavage steps through the combined actions of β- and γ-secretase [10]. β-Secretase was recently identified as a transmembrane aspartyl protease known as BACE (β-site AβPP cleavage enzyme; [11–14]). Presenilin-1 (PS1), a familial AD gene, and nicastrin, have been identified as components of the γ-secretase complex [15,16]. Although Aβ is released as a soluble protein, and is detected in biological fluids and tissue, it aggregates as diffuse amorphous (noncongophilic) deposits and dense, focal (congophilic), extracellular deposits in AD. The deposition of Aβ and numerous other components, into amyloid deposits, is associated with a chronic inflammatory response and oxidative stress (reviewed in Refs. [17,18]). We review here the physiochemical properties of amyloid-β in relationship to the potential biological functions of this protein. In particular, we review Aβ's propensity to bind copper and zinc, its redox activity and how these properties act on the one hand as a trophic agent, and on the other as a toxic agent.

2. Oxidative stress is an early event in the AD brain

One of the earliest pathological events in AD is oxidative damage to the brains of affected individuals [19]. The major site of increased oxidative damage is the cytoplasm of vulnerable neurons [20–23], while the lesions of AD [amyloid deposits and neurofibrillary tangles (NFTs)] also accumulate oxidative modifications over time. Whereas stable glycation, carbonyl and lipid peroxidation products are predominantly associated with NFTs and Aβ deposits [24] or granulovacuolar degeneration (Perry, Smith, Sayre, unpublished observations), reversible or rapidly degraded adduction products (e.g., oxidized nucleic acids) are predominantly found in the cytoplasm of neurons vulnerable to AD neuropathology, and precede lesion formation. Other neuronal cell types display limited oxidative damage.

The increased oxidative modification of cellular and lesion macromolecules likely result from increased intracellular production of membrane permeable H_2O_2 by abnormal mitochondria, increased extra-neuronal production of H_2O_2 from activated microglia [18] and by amyloid-β deposits. Reaction of H_2O_2 with reduced metal ions via Fenton and Haber–Weiss chemistry leads to the generation of the hydroxyl radical (·OH) that induces many oxidative modifications in macromolecules (e.g., 8-hydroxyguanosine, carbonyls). Since the ·OH cannot diffuse beyond nanometer distances, (reacting in the microsecond time span), sites of nucleic acid and protein modification are indicative of the site of ·OH generation and therefore sites of bound Cu and Fe. The ·OH-mediated oxidative modifications associated with AD neuronal cytoplasm and lesions are consistent with the chronic dysregulation of metal ion binding in the cytoplasm of pyramidal neurons and lesions of the AD brain. Dysregulation of transition metal metabolism and their extra- and intracellular accumulation in the AD brain have been repeatedly demonstrated (reviewed in Ref. [25]). For example, a well-controlled study using microparticle-induced X-ray emission analysis of the cortical and accessory basal nuclei of the amygdala indicated that Cu, Fe and Zn accumulate in the neurophil of the AD brain where their concentrations are increased 3–5-fold compared to age-matched controls. Such alterations in the localization of cytoplasmic metal ions appear to occur concurrently with increases in cytoplasmic RNA oxidation [20–22]. Additional evidence for abnormal metal ion homeostasis in AD includes a 2.2-fold increase in the concentration of cerebrospinal fluid (CSF) Cu [26], an accompanying increase in ceruloplasmin [27] in the brain and CSF of AD patients and numerous reports of abnormal levels of Fe and Fe-binding proteins [27–29].

3. Aβ deposition is a response to altered metal ion metabolism and oxidative stress

Increases in metal ion accumulation and oxidative stress in the AD brain are associated with changes in the concentration of soluble and deposited Aβ. A number of stress conditions upregulate AβPP expression and Aβ generation. One common endpoint leading to this change

in the expression and processing of AβPP and Aβ deposition is the shortage of energy supply, related oxidative stresses and apoptosis. Ischemia, hypoglycemia and traumatic brain injury, a condition that has been shown to put neurons under metabolic stress [30], all upregulate AβPP and/or its mRNA in animal models and culture systems [31–38]. Not only does energy shortage [and Ca(II) dysregulation] promote AβPP expression, but they also route the metabolism of AβPP from the non-amyloidogenic to the amyloidogenic pathway. Inhibition of mitochondrial energy metabolism alters the processing of AβPP to generate amyloidogenic derivatives [39,40], while oxidative stresses (H_2O_2 and UV) have been shown to increase the generation of Aβ peptides in monkey eye lenses [41] and neuroblastoma cells [42–44]. H_2O_2 increases concentrations of both intracellular [42,45] and secreted Aβ [43] in neuronal cell lines. Importantly, the antioxidants Trolox and dimethyl sulfoxide are able to block the increase in neuronal Aβ generation [42]. Other sources of oxidative stress such as paired helical filament-induced superoxide radical generation [46], inorganic mercury-induced decreases in cellular glutathione [22] and oxidative stress induced by micromolar concentrations of Aβ [43] also increase neuronal Aβ production. That Aβ (at concentrations sufficient to induce oxidation) can induce its own production suggests the potential for the development of a 'vicious feedback cycle' of increasing Aβ generation and oxidative stress [44]. Serum deprivation (trophic factor withdrawal), which is known to increase reactive oxygen species (ROS) generation [47,48], also increases Aβ production in human primary neurons [49]. This observation may explain why estrogen withdrawal increases the generation of Aβ in neuroblastoma cells [50,51]. Although hypoglycemia and ischemia promote AβPP mRNA and protein expression (see above), increased production of Aβ in the presence of H_2O_2 is not related to increased synthesis of AβPP but rather to increased generation of Aβ from AβPP [42]. This suggests that AβPP is upregulated under these conditions for functions other than the chelation and antioxidant activities of Aβ, such as its role in enhancing neurite outgrowth [52] and mediating the axonal transport of the membrane compartment containing β-secretase and presenilin-1 [53].

Taken together, these results suggest that Aβ synthesis is modulated by stress conditions, perhaps as a result of altered metal ion metabolism. In support of this role, Perry and colleagues have shown that amyloid plaque and NFT load in the cortex are inversely correlated with oxidative stress [20,21,54,55]. That is, as amyloid load increases, cytoplasmic oxidative damage decreases. A similar negative correlation between Aβ deposition and oxidative damage was found in patients with Down syndrome (DS) [20]. Notably, Aβ deposits observed in both studies mainly consist of early diffuse plaques. These findings indicate that in brains of patients with AD and DS, early Aβ deposition is correlated to decreased oxidative stress. Thus, formation of diffuse amyloid plaques may be considered as a compensatory response that reduces oxidative stress [18,19,56]. Consistent with this, in situ, soluble Aβ levels are inversely correlated with synaptic loss [57]. These observations also suggest that the accumulation of Aβ in the AD brain may be related to the increased oxidative challenge experienced by the brain as we age [58].

An increase in Aβ generation in the AD, DS and aging brains, and under the oxidative experimental conditions described above may be aimed at chelating metal ions in order to prevent oxidation. We and others have proposed that Aβ deposition may act as a sink for trapping potentially harmful transition metal ions (particularly redox active metal ions) that can be released from metal-binding proteins by oxidative and mildly acidotic conditions, and that would otherwise catalyze adverse oxidation of biomolecules [18,19,59,60]. Such conditions are present during inflammation as observed in the AD brain and following head trauma (see Ref. [25] for a review). The capture of metal ions in turn promotes the aggregation of Aβ that deposits as 'diffuse' amyloid. It is not surprising that the brain, which concentrates transition metal ions [25], has developed mechanisms to sequester metal ions to prevent their abnormal distribution under stress conditions.

Given this response to oxidative stress and metal ion accumulation, it is not surprising that Aβ deposition is detected in the human brain after traumatic brain injury [61,62]. Both $Aβ_{1-40}$ and, especially, $Aβ_{1-42}$ increase in CSF during the first week following the trauma [63]. Fatal head injury results in the formation of diffuse parenchymal deposits of Aβ in the brain, all of which contain $Aβ_{1-42}$ as a major component [64]. Irrespective of the stress, Aβ production appears to be a regulatory response that helps cells to cope with abnormal metabolism of transition metals. Together, these data provide a plausible physiological explanation for the increased generation of Aβ in AD and following head trauma, one that is aimed at chelating metal ions, reducing oxidative damage (thereby preventing ROS-mediated neuronal apoptosis), sealing vessels (see Refs. [65,66]) and promoting neurite outgrowth. We will discuss the biochemical data supporting the activation of Aβ antioxidant activities following metal ion chelation in the following sections.

4. Chelation and redox properties of Aβ

4.1. Aβ possesses metal ion binding/chelation sites

A number of physiochemical properties of Aβ support the above-mentioned functions of Aβ. Over the last 5 years we have characterized Aβ as a metalloprotein that binds transition metal ions via the 3 histidine (positions 6, 13, and 14) and 1 tyrosine (position 10) residues located in the hydrophilic N-terminal part of the peptide [59,67]. While Aβ binds transition metals such as Zn and Fe, it is a

particularly strong Cu chelator [59,67]. Aβ has two binding sites for Cu (and Zn) between residues 6–14 that differ in affinity. Importantly, $A\beta_{1-42}$ has a much higher binding affinity for Cu(II) (4.5×10^{-17} M and 5×10^{-9} M) than Zn(II) (1×10^{-9} and 40×10^{-9}) at both sites, with $A\beta_{1-40}$ having a lower binding affinity for Cu than $A\beta_{1-42}$ [67]. Cu has recently been shown to bind to the nitrogen atoms of the imidazole ring of the three histidine residues of Aβ [68] and to be coordinated between bridging histidine residues [69]. These strong chelating properties of Aβ for Cu(II), Zn(II) and perhaps Fe(III) explain the reported enrichment of these metal ions in amyloid plaques in AD [70], and suggest that one function of Aβ is to sequester these metal ions. Recent studies of amyloid deposits in the AβPP2576 transgenic mouse model of AD [71] have identified enrichments of Zn [70] and Fe [23], resembling those seen in AD amyloid (Cu levels are not yet established in this model). Further support that Aβ is a metalloprotein comes from our recent Raman microscopy studies that identify both Cu and Zn bound to histidine residues in amyloid core plaques [72]. Binding of redox active Cu (and Fe) by Aβ would remove this potentially redox active species from oxidative reactions.

4.2. Cu and Zn alter the conformation of Aβ

Binding of Cu and Zn by synthetic human Aβ induces its aggregation [59,67,73–75], but not fibrillization [76] in vitro. Early studies indicated that histidine residues were important for Aβ aggregation since the loss of histidine residues, such as in rat Aβ which contains three amino acid substitutions (Arg→Gly, Tyr→Phe and His→Arg at positions 5, 10 and 13, respectively) [77] or histidine modification, results in greatly diminished aggregation of Aβ by Cu(II), Zn(II) or Fe(III) [59,78]. These results indicate that histidine residues are essential for metal-mediated assembly of Aβ and may explain why cerebral Aβ deposition is not a feature of aged rats [77] even though soluble $A\beta_{1-40}$ is produced by rat neuronal tissue [79]. Miura et al. [68] using Raman spectroscopy have demonstrated that Zn(II) binds to the N(τ) atom of the histidine imidazole ring and the peptide aggregates through intermolecular His(N(τ))–Zn(II)–His(N(τ)) bridges. Zn(II)-induces considerably more aggregation of Aβ compared with other metal ions at physiological pH [59,68,73,74].

Unlike other biometals, marked Cu(II)-induced aggregation of $A\beta_{1-40}$ and $A\beta_{1-42}$ emerges as the solution pH is lowered below neutrality [59]. Although the N(τ)-metal ligation also occurs in Cu(II)-induced Aβ aggregation at mildly acidic pH, below neutral pH, Cu(II) binds to N(π), and to deprotonated amide nitrogens of the peptide main chain. Bridging histidine residues also would explain the multiple metal-binding sites observed for each peptide and the high degree of cooperativity evident for subsequent metal binding [67,69]. Although three histidines are bound to the metal center several potential sites still exist for further coordination of metal ions, such that continued metal-mediated cross-linking of the peptides would lead to aggregation. Cu(II)-induced precipitation at pH 6.6, which is specific for certain proteins, is completely reversible with either alkalinization returning the pH to 7.4, or chelation [59]. Similar pH specific aggregation has recently been found for Zn(II) in the presence of heparin [76].

Confirming the role that transition metal ions play in the assembly of diffuse Aβ in the brain, Cu/Zn chelators were shown to significantly enhance the solubilization of Aβ from post-mortem AD brain [80]. The high concentrations of redox active Cu and Fe, and redox inactive Zn present in the cortex and hippocampus and the release of Cu (~15 μM) [81] and Zn (200–300 μM) [82,83] from the synapse during transmission coupled with the lowered pH of the inflammatory AD brain provide an ideal environment in which Aβ could aggregate. That Aβ deposits during inflammatory conditions such as following head injury and in AD where pH is low, and where Cu, Zn and Fe are released from other metalloproteins, indicates a unique role for Aβ in sequestering metal ions during times of inflammation/oxidative stress. Interestingly, Aβ simultaneously binds equal amounts of Cu(II) and Zn(II) in phosphate-buffered saline (PBS) at pH 7.4 (~1.7 atoms each) when equimolar concentrations of both metal ions are present [67]. However, when the pH is lowered to pH 6.6, Cu effectively competes almost all Zn from Aβ. This may be a trigger for the initiation of the redox properties described below.

4.3. Aβ possesses redox properties

Aβ has two major sites that are important for its redox activity. The first site involves the binding of redox active Cu or Fe to human $A\beta_{1-40}$ and $A\beta_{1-42}$ via histidine residues that directly produces H_2O_2 by a mechanism that involves the reduction of these metal ions [18,69,84–87]. The second site is Met at position 35 in the lipophilic C-terminal region. Aβ peptides lacking Met35 (e.g., $A\beta_{1-28}$) have a decreased capacity to reduce Cu(II) and generate H_2O_2 [69,85,86], while addition of methionine to $A\beta_{1-28}$ greatly increases the reduction of Cu(II), thereby indicating its importance for Cu reduction [69]. In addition, substitution of this residue by another amino acid abrogates the prooxidant action of $A\beta_{25-35}$ towards liposome oxidation [88] and decreases protein oxidation (and neurotoxicity, see below) induced by $A\beta_{25-35}$, $A\beta_{1-40}$, and $A\beta_{1-42}$ [89]. The presence of Met35 alone is not sufficient for redox activity and neurotoxicity since rat Aβ, which has Met 35 but lacks a key redox metal ion binding site (histidine 13), has low toxicity. Thus, the coordination of redox metal ions by Aβ is crucial for the redox activity and neurotoxicity of the peptide.

The high affinity of Aβ for Cu [67], its strong redox

potential and recruitment of O_2 [69,85,86] are features that resemble the electrochemistry of Cu,Zn-superoxide dismutase (SOD) [90]. We have found that Aβ, when bound to an appropriate amount of Cu(II) and Zn(II), also can catalyze the dismutation of superoxide (O_2^-) to H_2O_2, and could therefore operate as an antioxidant [91,92]. Conversely, under certain conditions, in the presence of either Cu(II) or Fe(III), Aβ produces a positive thiobarbituric reactive substance assay [85] and electron spin resonance spin-trapping spectra [93] compatible with the generation of the hydroxyl radical (OH·). The amounts of reduced metal and ROS are both greatest when generated by $Aβ_{1–42}$>$Aβ_{1–40}$>>rat $Aβ_{1–40}$=$Aβ_{1–28}$, a chemical relationship that correlates with the relative neurotoxicity of these peptides. Methionine also can scavenge free radicals [94] and reduce transition metals to their high-active low-valency form [95], thereby exhibiting both anti- and prooxidative properties. Thus, Aβ possesses physiochemical properties consistent with both an antioxidant and a prooxidant. In the following sections we will review evidence for both these activities.

5. The good side: neurotrophic and antioxidant properties of Aβ

Although largely neglected, numerous studies have demonstrated that Aβ exhibits neurotrophic and neuroprotective properties when present at physiological concentrations (nM) in deprived conditions and neonatal cells (Fig. 1) [96–106]. Included in these neurotrophic properties, we have found that nanomolar concentrations of Aβ can block neuronal apoptosis following trophic factor withdrawal [92]. These results are consistent with the metal binding and redox properties of Aβ described above whereby Aβ chelates Cu which in turn ‘switches on’ the antioxidant activities of Aβ (Fig. 1) [91,92]. In this respect, we have found that the anti-apoptotic activity of Aβ is modulated by Cu concentration [92]. Recently, the antioxidant properties of Aβ were confirmed by Kontush et al. [107] who showed that Aβ prevents lipoprotein oxidation in CSF and by Zou et al. [108] who showed that monomeric $Aβ_{1–40}$ inhibits the reduction of Fe(III) induced by vitamin C and the generation of O_2^-. That Aβ

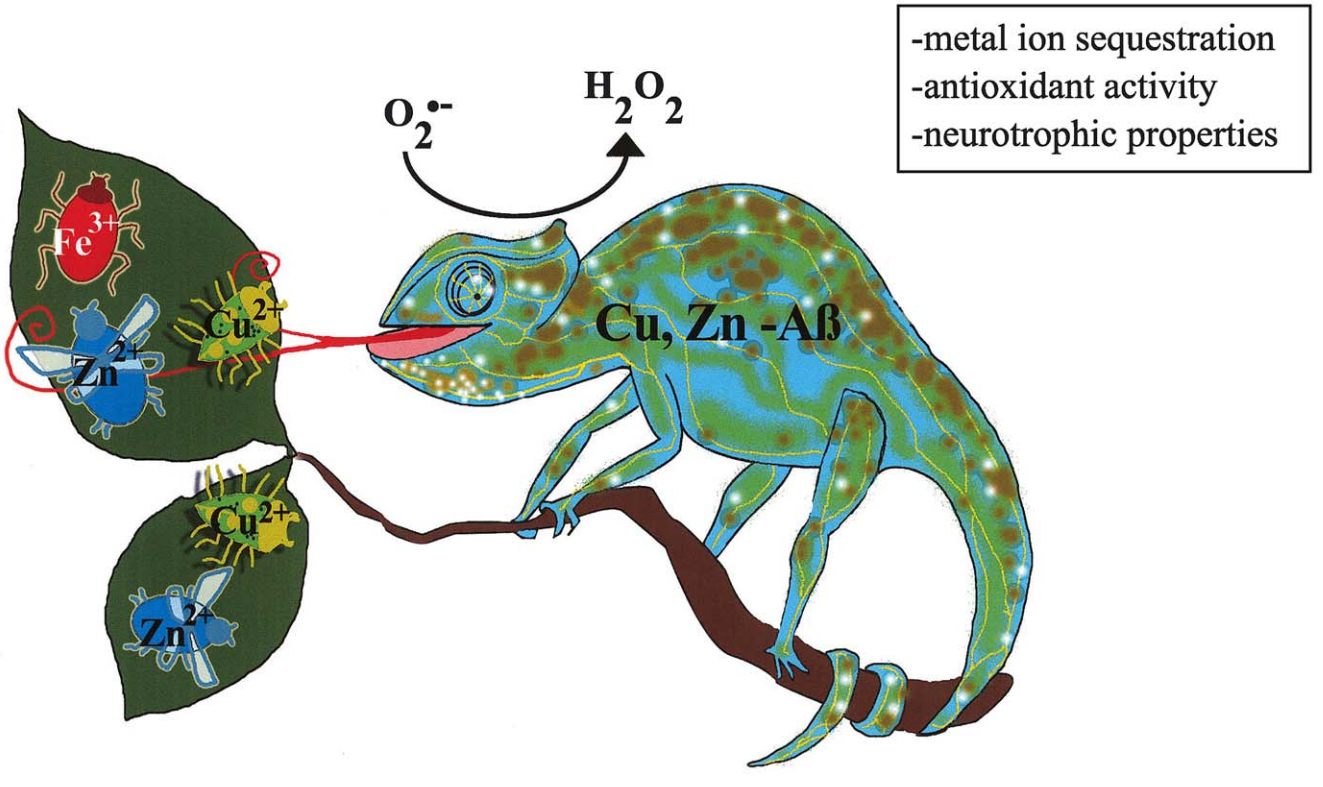

Fig. 1. The power of sacred animals in mythology and folklore is directly related to their ability to live in two worlds. This ability to straddle one or more ecological niches or divide their time between the land and the water or the sky is cause for veneration. Anthropologists use the notion of liminality as a tool to describe these attributes. In this regard, animals such as birds, frogs and chameleons provide a metaphor for liminality and an abstract frame of reference that can be employed in attempts to understand further actual data. This notion only achieves analytical worth by way of the dialectical relationship between the structure/anti-structure contrast. Nevertheless, the Aβ protein has been shown to possess ‘liminal-like states’. We chose the chameleon as a metaphor, as it is known to change its skin color and pattern to match its surroundings. Analogous to the chameleon, Aβ somehow partakes in this power to walk at once in two worlds, whereby it too changes its properties in response to its environment. In this review, we explore how Aβ liminally spans the gap between the trophic (A) and the toxic (B) to serve the brain at one time and perhaps contribute to problems at another.

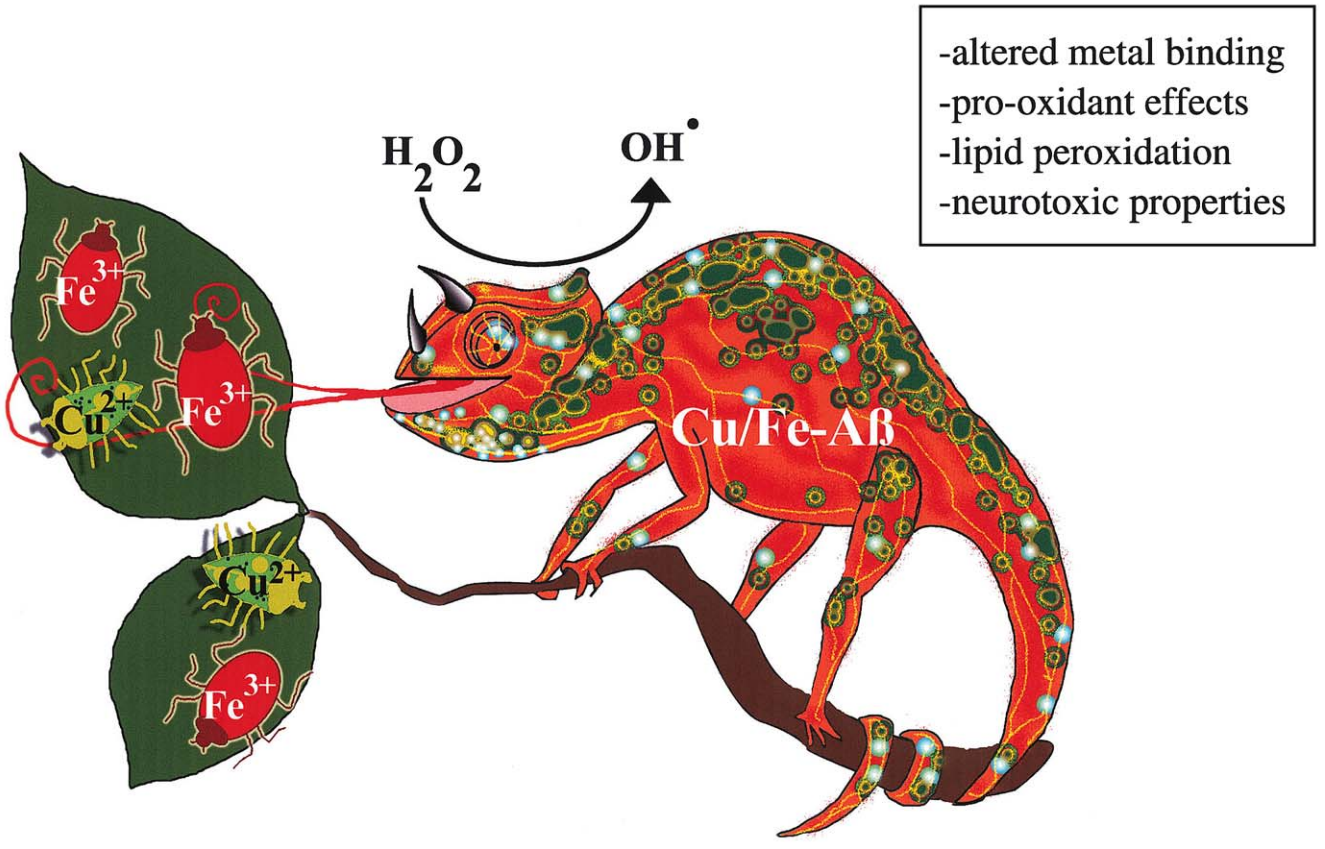

Fig. 1. (*continued*)

protects against H_2O_2 induced death implies that its substrate is not H_2O_2.

Evidence that Aβ has antioxidant activity is accumulating and is summarized in Table 1. Strong cellular evidence that Aβ acts as an antioxidant comes from studies showing that the increased production of Aβ by mutant PS1 fibroblasts is accompanied by a decrease in the production of ROS, particularly ·OH formation [110]. Consistent with this finding is that primary cortical neurons infected with wild-type or mutant PS1 are not associated with increased sensitivity to apoptosis [111]. Moreover, the increased production of Aβ induced by the over-expression of wild-type PS1 in brains of transgenic mice results in increased brain resistance to metal-induced oxidation [112]. Conversely, primary hippocampal neurons from PS1M146V mutant knock-in mice have been shown to exhibit increased superoxide production, mitochondrial membrane depolarization, and caspase activation when treated with Aβ [117,118]. However, it is likely that the high concentrations of Aβ used in this study promoted ROS generation (see below) that exceeded the capacity of the cellular antioxidant defense systems. Monomeric Aβ also has been shown to protect neurons from Fe(II) induced toxicity [108]. Thus, Aβ generation appears to protect cells from oxidation (by metal ions).

In addition to its cellular protective role, addition of physiological concentrations of $A\beta_{1-40}$ and $A\beta_{1-42}$ also has been shown to protect lipoproteins from oxidation in cerebrospinal fluid and plasma [107]. Since these Aβ peptides do not prevent metal-independent lipoprotein oxidation, and $A\beta_{25-35}$ was shown to be less effective at inhibiting lipoxidation, it is likely that the mechanism by which Aβ inhibits lipoxidation [107] is via metal ion sequestration as described above. Free radical scavenging by Met 35 does however contribute to this effect since $A\beta_{25-35}$ (which has only weak, metal-binding properties) is able to inhibit lipid peroxidation [107] and replacement of Met35 by Leu considerably weakens the effect [88]. Supporting this effect, there is a positive correlation between CSF resistance to oxidation and its levels of Aβ [60], but not to the level of ascorbate, a major chain-breaking antioxidant in human CSF [119], illustrating the importance of Aβ in CSF as an antioxidant. The concentration of $A\beta_{1-42}$ also correlates better with CSF oxidative resistance than that of $A\beta_{1-40}$ [60], in accordance with the stronger metal binding of $A\beta_{1-42}$ compared to $A\beta_{1-40}$ [59,67]. Moreover, Andorn and Kalaria [109] have shown that Aβ peptides possess significant antioxidant activity in an ascorbate-stimulated-lipid-peroxidation assay of post-mortem human brain membrane preparations.

Neuronal cell cultures secrete a high molecular weight

Table 1
Summary of evidence that Aβ acts as an antioxidant

	Refs.
Peptide studies	
SOD activity, dismutation of $O_2^{-\cdot}$ to H_2O_2 (spectrophotometrically)	[92]
SOD activity, dismutation of $O_2^{-\cdot}$ to H_2O_2 (spectrophotometrically; pulse radiolysis)	[91]
Antioxidant activity against ascorbate-stimulated-lipid-peroxidation in post-mortem human brain membrane preparations	[109]
Protection against CSF and plasma lipoxidation (at nanomolar concentrations)	[107]
CSF concentrations positively correlate with CSF resistance to oxidation	[60]
Inhibition of $O_2^{-\cdot}$ generation and metal induced lipid peroxidation	[108]
Cellular studies	
Anti-apoptotic (at nanomolar concentrations)	[92]
PS1 overexpression induces Aβ generation and decreased ROS generation; not associated with increased sensitivity to apoptosis	[110,111]
PS1 transgenic mice have increased neuronal resistance to metal-induced oxidation	[112]
Monomeric Aβ protects neurons from Fe(II) induced toxicity (but not H_2O_2)	[108]
Animal studies	
Injection of Aβ into brains is not toxic to cortical neurons in young monkeys, or in young or old rats	[113,114]
Fibrillar $A\beta_{1-42}$ injections reduce neuronal loss in the adult rat cerebral cortex compared with saline vehicle	[115]
Brain Aβ+iron injections are significantly less toxic than iron alone in the adult rat cerebral cortex	[116]

product, likely a lipoprotein complex that possesses an antioxidative activity [120]. Cu,Zn-SOD has recently been detected in, and shown to associate with serum lipoproteins (mainly low and high density lipoproteins) in a saturable fashion [121]. Thus, it is likely that Cu,Zn-SOD exerts a physiological protective role against oxidative damage of lipoproteins that transport cholesterol. Since Aβ also binds cholesterol present in apolipoproteins, and given the properties of Aβ eluded to above, it is likely that Aβ also may function to either scavenge 'free' redox metal ions in serum and/or act as an antioxidant. The amphiphilic properties of Aβ [122] would allow its insertion into the apolipoprotein and extracellular chelation of metal ions that might otherwise promote lipoprotein oxidation. Indeed, endogenous Aβ is largely associated with lipoproteins in CSF and plasma [123,124]. In this respect, it is of interest that Aβ generation has been shown to be positively correlated with cholesterol concentration in a number of different systems including cell culture [125], hypercholesterolemia heart disease [126], AβPP-transgenic mice [127] and in Niemann–Pick type C cells [128].

A number of studies have examined the physiological effects of Aβ peptide after it's injection into the cerebral cortex or hippocampus of rats. Such Aβ injections are frequently reported to alter neuronal metabolism and to decrease the expression of neurotransmitters [129], although decreases are temporary and expression normally returns to the affected area [130]. In one of the few studies undertaken to determine quantitative measurements of neuronal loss, Frautschy et al. [131] found that infusion of Aβ into rat brain for 4 weeks increased the density of TUNEL-labeled profiles by 1.8-fold in piriform cortex and 1.4-fold in frontal cortex. This increase was statistically significant but numerically trivial, since the overall frequency of dying cells was very low. In another study, infusion of Aβ for 1 week did not result in any TUNEL-labeled profiles around the infusion site [132].

Recent quantitative studies have shown that large injections of fibrillar human $A\beta_{1-42}$ cause less neuronal loss in the adult rat cerebral cortex than equivalent volumes of the saline vehicle [115]. Furthermore, the injection of Aβ containing 1.0 mM iron is significantly less toxic than injections of 1.0 mM iron alone, while there is a trend towards significance for saline vehicle [116]. These results indicate that while Aβ–iron complexes (at the concentrations found in neuritic plaques) are neurotoxic, Aβ attenuates the neurotoxicity of iron, and therefore serves a neuroprotective function. Two semi-quantitative studies that have injected Aβ into the brains of monkeys also have concluded that pure Aβ is not toxic to cortical neurons in young monkeys, or in young or old rats [113,114]. Aβ injections have however, been shown to produce neurotoxicity in aged monkeys [114]. The reason for this difference is unclear, but it may be related to the unusually high levels of extracellular iron that are present in the cortices of old monkeys compared with young monkeys and old rats [133]. Alternatively the concentrations of the complimentary antioxidant enzymes such as glutathione peroxidase and catalase may be reduced in the old primate brain and are too low to combat Aβ-induced ROS production.

These data support the view that Aβ functions as an antioxidant and is produced for this purpose by neurons and many other cells, such as astrocytes, neuroblastoma

cells, hepatoma cells, fibroblasts, and platelets. Further, the above discussion indicates that Aβ may have a metal ion binding/antioxidant role both intracellularly and extracellularly in diffuse amyloid deposits, CSF and plasma.

6. The dark side: neurotoxic and prooxidant properties of Aβ

The identification of Aβ as the major protein component of amyloid, the defining feature of AD neuropathology, led to the idea that this protein might be the cause of AD. With this in mind, much research effort has been directed at determining if this deposited protein was toxic, thereby explaining the loss of neurons and synapses in the disease. Indeed, Aβ has been shown to be toxic, but only convincingly so in vitro (e.g., Refs. [106,113,134–139]), and only using high concentrations of aged Aβ. So what is the exact mechanism of this toxicity? Does iron or copper potentiate Aβ neurotoxicity? We attempt to answer these questions in the following sections.

6.1. Does iron or copper potentiate Aβ neurotoxicity?

Evidence supporting a neurotoxic role for Aβ comes primarily from experiments on cultures of primary neuronal cells from neonatal rodents or from cultures of neuroblastoma cell lines. Such studies typically report neurotoxic effects from the addition of micromolar concentrations of Aβ peptide to the culture media. Aβ is not always neurotoxic to cultured cells however, and a closer examination of discordant studies provides an insight into the possible reasons for the neurotoxicity that has been reported in vitro. For example, when droplets of pure fibrillar Aβ are dried onto the surface of cell culture flasks to form artificial ‘plaques’ they provide excellent substrates for neurons that are subsequently plated in these flasks. Indeed, the neurons preferentially grow on these plaques and thrive [140]. By contrast, if the neurons are plated first, and Aβ is then dissolved in the culture media, neurotoxicity results. This difference may be due to Fe(III) or Cu(II) which is generally present in high concentrations in culture media (neurons have a metabolic requirement for both metal ions). We have shown that high concentrations of Aβ incubated with Cu(II) are neurotoxic to primary neurons, but that Zn(II), which competes for Cu(II) binding sites on Aβ, can partially attenuate this toxicity (Fig. 1) [86,105]. Likewise, Aβ dissolved in Fe(III)-containing media is toxic to neurons but Aβ dissolved in Fe(III)-free media is not [141]. We have speculated that Fe(III) [or Cu(II)] in culture media may bind to soluble Aβ, and given its amphiphilic nature, bind to cell membranes thereby inducing oxidative injury [54,142,143]. This potential for toxicity may be exacerbated by the tendency for batches of resolubilized synthetic Aβ to be contaminated with Fe(III) and/or Cu(II). The removal of Fe(III) by incubation of the Aβ with the chelator deferoxamine significantly decreases the toxicity of the peptide to neuroblastoma cells, while the toxicity of the suspended Aβ can be restored by addition of 0.1 mM Fe(III) [143]. Another study has confirmed that significant concentrations of Cu(II) and Fe(III) are present in synthetic samples of Aβ and the presence of these metals can catalyze the production of hydrogen peroxide [144].

Plaque cores contain both Cu(II) and Fe(III), but presumably the toxicity of these metals is neutralized, either by Aβ itself, or by the cocktail of other components bound to the plaques. It should be noted that the neurotoxic interactions that occur between Aβ and Fe(III) are in contrast to the neuroprotective and antioxidant functions ascribed to the low concentrations of Aβ–Cu(II) complexes described earlier in this review. However, under certain conditions, such as high Aβ concentrations, aggregation state, accessibility to lipid membranes and altered metal (Cu) binding (e.g., Cu,Cu–Aβ vs. Cu,Zn–Aβ), Cu:Aβ complexes are equally toxic (Fig. 1) [54,86]. Therefore, altered coordination of metal ions to Aβ may alter the normal redox properties of Aβ (see below), resulting in oxidative damage and neurotoxicity.

Perhaps most noteworthy regarding Aβ’s toxicitiy is that plaque cores (containing fibrillized Aβ, and presumably metal ions) isolated from AD brains appear to be non-toxic to cultured cells and can be degraded by microglial cells in vitro [145]. In addition, cultured retinal ganglion cells grow avidly on a substrate of plaque cores [145]. Taken together, the preceding observations suggest that when soluble Aβ binds and concentrates Cu(II) and Fe(III) in solution it becomes neurotoxic, whereas preformed deposits of pure Aβ tend to be neurotrophic. Another major caveat to the argument that Aβ is toxic is that transgenic mice with massive accumulations of Aβ amyloid deposits (mainly diffuse) show no neuronal death [146,147], in marked contrast to in vitro findings of Aβ mediated neurotoxicity and apoptosis. Recently, it has been shown that expression of human tau is required in order to induce neuronal death in vitro [148], although it is not known if τ-Aβ transgenic mice will display accelerated neuronal loss.

6.2. What is the mechanism of Aβ neurotoxicity in vitro?

Early studies indicated that aging the peptide [106] in order to promote the transition of the peptide from monomeric to fibrillar that results from a change in the secondary structure of the protein from random coil and α-helical to β-sheet [137,150,151] was required for toxicity [152]. However, Aβ fibril formation per se is not required for neurotoxicity because replacement of methionine by norleucine (see Ref. [89]) or the C-terminus with other type I transmembrane proteins [149] allows for

fibril formation but is not toxic. The neurotoxic activity of Aβ appear to be dependent on two main factors.

(1) Redox metal ion binding. Both Cu [54,86] and Fe [141,143] potentiate the neurotoxicity of human $A\beta_{1-40}$ and $A\beta_{1-42}$. Conversely, metal ion chelators and Zn displacement of Cu from Aβ peptides protects neurons from Aβ toxicity in vitro [54,141,143]. Since Aβ in the presence of Cu(II) or Fe(III) produces H_2O_2 [85,86] Aβ toxicity is likely to be mediated by a direct interaction between Aβ and transition metals with subsequent generation of ROS (Fig. 1) [86,143]. Indeed, the amounts of TBARS reactivity are greatest when generated by $A\beta_{1-42}$>>$A\beta_{1-40}$>rat $A\beta_{1-40}$, a chemical relationship that correlates with the participation of the native peptides in amyloid pathology, as well as correlates with the peptide's relative Cu binding affinity and neurotoxicity in cell culture.

Why then in earlier studies was the 'aging' (fibrillization) of Aβ required in order to induce neurotoxicity? In the absence of metal ions Aβ is monomeric, has an α-helix conformation and does not form aggregates [78,150,153]. However, trace metal ions present in laboratory buffers [67,154] promote fibrillization of Aβ since high-affinity chelators limit Aβ fibrillization with aging (Huang, Atwood and Bush, unpublished results). This is consistent with the fact that $A\beta_{1-42}$, which is more prone to aggregation, has a higher metal ion affinity compared with $A\beta_{1-40}$ [67]. In addition, the concentration dependent toxicity of Aβ (typically≥10 μM) may in part be explained by the fact that fibrillization rate is directly dependent upon Aβ concentration, which in turn will dictate redox metal ion binding. Thus, aggregation of Aβ required for neurotoxicity may in fact be due to the sequestration of redox metal ions from buffers, thereby allowing for ROS generation.

(2) Methionine 35. The neurotoxicity of Aβ in vitro also is dependent upon Met35, the substitution of which for another amino acid abrogates the neurotoxicity induced by $A\beta_{1-42}$, $A\beta_{1-40}$ and $A\beta_{25-35}$ [155,156]. Met35 likely acts to mediate ROS generation since its substitution decreases liposome oxidation [88] and protein oxidation [155,156]. The $A\beta_{25-35}$ peptide, although not a native peptide, also has been reported to exhibit H_2O_2-like reactivity towards aqueous Fe(II), nitroxide spin probes, and synaptosomal membrane proteins [157]. $A\beta_{25-35}$ also promotes ROS generation in a mitochondrial fraction from rat cortex, but only in the presence of Fe(III) or Cu(II) [158]. Rat Aβ, which contains $A\beta_{25-35}$ has very low toxicity. Therefore, while $A\beta_{25-35}$ may possess some of the electron transfer elements necessary to cause the redox activity observed in the intact native Aβ peptides, ROS generation via this oligopeptide may be through indirect mechanisms, such as the reaction with factors in the cortical membranes as studied by Bondy et al. [158].

These studies indicate that the presence of transition metals may not only be required for Aβ fibrillization, but also for the initiation of ROS generation through Met35. Recent experimental and theoretical studies have examined the exact mechanism by which Aβ:metal complexes might induce ROS generation. Aβ binding of Cu (or Fe) to its N-terminal hydrophilic metal-binding site(s) as described above allows for their reduction in its C-terminal metal-reducing site to produce H_2O_2. This mechanism suggests that in order for metal ions to be reduced, Met35 must come into contact with the C-terminus. This might be achieved by folding of the peptide or by fibrillization where metal atoms bound to the N-terminal of one Aβ, can be simultaneously available for the reductive Met35 residues on an adjacent Aβ. Cu induced radicalization of Met35 via this mechanism also would induce the generation of a stable ·C radical on the peptide backbone, likely glycine, that would then be available to participate in lipid peroxidation reactions [191]. Thus, the reduction of metal ions by Aβ [85,86] and of Aβ by other cellular reductants allows it to act as an oxidant via the production of H_2O_2 and ·C radicalization.

Taking into account these properties of Aβ, and its lipophilic nature, it is possible to explain the numerous publications reporting pro-oxidative and neurotoxic effects of the peptide in vitro. Synthetic Aβ peptides have been shown to induce oxidation of different cellular substrates, including lipids of synaptosomes [159], lipoproteins [160], transport enzymes [161] and DNA [162]. Functionally, Aβ alters neuronal metabolism, inactivating glutamine synthetase and creatine kinase enzymes in brain cytosolic extract and cell free preparations [163]. Aβ fragments also have been shown to induce in a time- and dose-dependent manner decreases in catalase activity, and increases in Cu/Zn-SOD and Mn-SOD activities and cellular peroxides in neuronal cell cultures, a pattern that is similar to that found in the AD brain [165]. This divergent shift in antioxidant enzymes may contribute to the cascade of neuronal injury [163]. In this respect, in cell culture, Aβ has been shown to exert its neurotoxicity through a mechanism that induces intracellular generation of $O_2^{-\cdot}$/H_2O_2 [164] and 4-hydroxy-2-nonenal [161], thought to lead to calcium ion accumulation and subsequent neuronal or vascular endothelial death [164,166,167]. This toxicity is abolished by the presence of SOD [167], catalytic synthetic $O_2^{-\cdot}$/H_2O_2 scavengers [165], the spin-trap compound phenyl-*tert*.-butyl-nitrone [157], or chain-breaking antioxidants, such as vitamin E or vitamin C [89,161,168–170]. In support of these findings, neurons cultured from subjects with Down syndrome, a condition complicated by the invariable premature deposition of cerebral Aβ [171] and the overexpression of soluble $A\beta_{1-42}$ in early life [172], exhibit lipid peroxidation and apoptotic cell death caused by increased generation of H_2O_2 [173].

Together, the above findings are very compelling for Aβ toxicity in vitro, and indicate that the accumulation of Aβ in vivo may contribute directly to free radical damage in AD. There is however a paucity of data indicating Aβ is

actually toxic in vivo, as most clearly illustrated by the lack of toxicity in AβPP-transgenic mice, though the latter is recognized not to be a complete model as it lacks the human form of tau and thus can not give rise to neurofibrillary tangles. The relevance of these mechanisms to neuronal toxicity in vivo therefore remains to be determined.

7. Transition to the dark side?

The redox properties of Aβ indicate that the peptide could act as an antioxidant and a prooxidant (Fig. 1). But under what conditions would the peptide act to reduce, or increase, oxidative stress? And what is the biological role of intracellular and extracellular Aβ?

The increased generation of Aβ by oxidative stress indicates a response to preserve normal cellular function by dampening oxidative insults. The accumulation of early or diffuse amyloid deposits could be considered an early pathological stage that limits lipid/lipoprotein oxidation, crucial for preventing neuronal apoptosis. Given the above discussion, the accumulation of amyloid plaques in cognitively normal individuals could be considered as a successful compensation to aging. Indeed, we have recently shown that Aβ deposition is inversely correlated with oxidative damage in the AD and DS brains [20,21,54,55]. In addition, Zn binding to Aβ may 'detoxify' Aβ by displacing Cu from the redox active site [54]. However, at some threshold level of ROS generation, efficient removal of Aβ–metal complexes would be overtaken by their disproportionably high generation, resulting in the uncontrollable growth of plaques. Aβ's only known catalytic activity serves to dismutate $O_2^{-\cdot}$ to H_2O_2 and tissues will only be protected from subsequent H_2O_2-mediated damage where peroxide clearance mechanisms (e.g., catalase, glutathione peroxidase) are fully competent. Thus, excessive deposition of Aβ:Cu may well overwhelm antioxidant defense systems incapable of handling the accumulating H_2O_2. Conversely, Aβ:Cu deposits would not be predicted to be neurotoxic except if H_2O_2 is produced above this threshold level of removal. This would result in a feedback loop mechanism that could exacerbate both plaque growth and ROS generation, leading to the functional demise of neurons [174]. Therefore, to accelerate oxidation, Aβ must be present in concentrations greatly exceeding those normally measured in biological fluids or tissues (i.e., micromolar vs. nanomolar; see Refs. [89,170]). This has been reported for cerebrospinal fluid, where Aβ acts as an antioxidant at peptide concentrations measured in these biological fluids (0.1–1.0 nM), while at higher Aβ concentrations its antioxidant action is abolished [60]. Likewise, nanomolar concentrations are anti-apoptotic, while micromolar concentrations are toxic (see previous discussion).

An analogous trophic/toxic scenario exists with Cu,Zn-SOD (SOD1) (and ascorbate). At normal physiological concentrations, SOD1 is known to increase cellular resistance to oxidative stress [175]. However, when SOD is overexpressed at levels that are much higher than other antioxidant enzymes such as glutathione peroxidase, or the ability of cells to supply reducing equivalents, increased oxidative stress is observed [176]. Oxidative damage is likely due to the generation of ·OH from the interaction of accumulating H_2O_2 with redox cycling proteins (such as Cu,Zn-SOD1) via Fenton-like chemistry [177]. Similar chemistry may be involved in familial amyotrophic lateral sclerosis, where mutant SOD aggregates in the central nervous system [178,179]. Oxidative modification by H_2O_2 of the histidine in the active site of SOD1 [180,181] and in growth hormone results in the formation of 2-oxo-histidine [182,183], which is thought to led to inactivation of the enzyme and/or to further aberrant redox chemistry. Amyloid-β extracted from the AD brain also is oxidatively modified [184], however the influence of such post-translational modifications on the redox cycling of the peptide has yet to be determined.

8. Amyloid removal as a therapy?

The prominence of the 'amyloid hypothesis' of neurodegeneration has led to therapeutic strategies aimed at preventing or reversing amyloid deposition in the hope that this will stabilize and/or reverse cognitive deficits. These strategies have included attempting to inhibit either of the two proteases, β- and γ-secretase, that generate Aβ from AβPP [185], active or passive Aβ immunization [186,187], modulation of cholesterol homeostasis [188], inhibition of metal-induced Aβ aggregation via metal ion chelation [189] and lowering amyloid associated inflammation with anti-inflammatory drugs [190]. Examination of the known neuroprotective functions of Aβ described earlier would indicate that the removal of Aβ would also remove the neuroprotection that Aβ affords. Removal of Aβ would be predicted to increase oxidative damage and exacerbate inflammation in the AD brain. Another likely function for Aβ is the maintenance of cellular integrity, the loss of which would lead to the breakdown of the blood–brain barrier, and neuroinflammation [65]. Indeed, Aβ vaccination therapy in human clinical trials has not proven successful, instead leading to clinical signs of neuroinflammation (meningitis and encephalitis). These results, taken together with the known function of Aβ, suggest that any strategy aimed solely at removing Aβ will result in the loss of neuroprotection and induce subsequent side-effects.

9. Conclusion

Aβ possesses trophic/antioxidant and prooxidant/toxic properties that are modulated by redox metal ions. Under

normal physiological conditions, Aβ released in response to injury appears to be purposive by providing neuroprotection against oxidative stresses, afterwhich it is cleared. If however the rate of clearance is insufficient with respect to production (e.g., decreased neprolysin, insulin degrading enzyme, Apo E4 allele), the progressive accumulation of neuronal Aβ:Cu in response to oxidative challenges or AβPP/PS1 mutation induced amyloidogenesis may lead to the generation of H_2O_2 that exceeds the capacity of antioxidant defense systems. This in turn would lead to a vicious cycle of increased Aβ generation and ROS production. Progressive amyloid deposition also would promote microglial activation and increased respiratory burst activity (reviewed in Ref. [18]), further exacerbating amyloid deposition and ROS generation. Therefore, Aβ may not be directly toxic but rather act indirectly via the generation of H_2O_2 which induces rampant oxidative damage and neuronal dysfunction.

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