AMYLOID-β AND τ SERVE ANTIOXIDANT FUNCTIONS IN THE AGING AND ALZHEIMER BRAIN

MARK A. SMITH,* GEMMA CASADESUS,+ JAMES A. JOSEPH,† and GEORGE PERRY*
*Institute of Pathology, Case Western Reserve University, Cleveland, OH, USA; and †USDA-Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA
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Abstract—Historically, amyloid-β and τ (tau), the major components of senile plaques and neurofibrillary tangles, respectively, have been considered central mediators of the pathogenesis of Alzheimer disease. Therefore, efforts to understand disease mechanisms have concentrated on understanding either the processes involved in amyloid-β deposition as senile plaques or on the phosphorylation and aggregation of τ as neurofibrillary tangles. However, in light of recent evidence, such “lesion-centric” approaches look to be inappropriate. In fact, rather than initiators of disease pathogenesis, the lesions occur consequent to oxidative stress and function as a primary line of antioxidant defense. Given this, it is perhaps not surprising that the increased sensitivity to oxidative stress in the aged brain, even in control individuals, is invariably marked by the appearance of both amyloid-β and τ. Additionally, in Alzheimer disease, where chronic oxidative stress persists and is superimposed upon an age-related vulnerable environment, one would predict, and there is, an increased lesion load. The notion that amyloid-β and τ function as protective components brings into serious question the rationale of current therapeutic efforts targeted toward lesion removal. © 2002 Elsevier Science Inc.

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INTRODUCTION

Amyloid-β and the microtubule-associate protein tau (τ) are, without a shadow of a doubt, the best-studied proteins relating to the pathogenesis of Alzheimer disease (AD). While perhaps not surprising since the pathological diagnosis of Alzheimer disease is dependent upon both amyloid-β and τ depositions [1,2], the amalgamation of diagnostic and mechanistic views relating to the disease has unfortunately led researchers astray. Amyloid-β and τ are crucial diagnostic indicators; however, as we discuss below, their mechanistic importance has far less to do with their consequences than with the factors that led to their formation. Thus, the goal of this review is to present an alternative hypothesis for the role of amyloid-β and neurofibrillary tangle (NFT) deposition in this disease.

Amyloid-β

The overwhelming view currently held concerning disease pathogenesis is the premise that amyloid-β causes the disease [3]. Champions of the amyloid-β hypothesis argue that diagnostic, clinical, and pathological studies all support a central role for amyloid-β. First, amyloid-β is an obligate feature of the disease and correlates, albeit weakly, with disease severity [4]. Second, amyloid-β is often, though not always, found in regions of the brain that degenerate during the disease and amyloid-β is a potent neurotoxic agent in vitro. Third, and most touted, both in vivo in the disease and in vitro in transfected cells, amyloid-β is increased by all of the mutated genes (including the source of amyloid-β,
AβPP) that are associated with the autosomal dominant inheritance of AD [5]. However, the aforementioned points are, at best, circumstantial and may also be used as evidence that amyloid-β is playing a protective role. First, the correlation of amyloid-β with dementia (i.e., neuronal dysfunction and loss) appears to be a protective compensation mounted in response to the underlying disease process [6]. Indeed, there is insurmountable evidence that oxidative stress is one of, if not the, earliest pathological alteration in the disease [7,8]. Importantly, neurons respond to oxidative stress, both in vitro and in vivo, by increasing amyloid-β production [9], and this increased amyloid-β is associated with a consequent reduction in oxidative stress [7,8]. Proteins, such as amyloid-β, that are induced under oxidative conditions and act to lessen oxidative damage, are typically thought of as antioxidants and, in this regard, we recently demonstrated that amyloid-β is a bona fide antioxidant that can act as a potent superoxide dismutase [10].

Viewing amyloid-β as a protective response element provides a valid mechanism for why the brains of almost everyone over the age of 40, an age, coincidently, where redox alterations first manifest [8], contain amyloid-β deposits. The alternate view, that everyone at mid-life is on the verge of developing AD is not only unsound from a biological perspective but also does a great disservice to the large percentage of cognitively normal aged individuals whose brains contain amyloid-β loads equivalent to patients with AD [11]. Indeed, although fibrillary or aggregated forms of amyloid-β, like those present in the senile plaques, cause cytotoxicity in vitro [12], the presence and density of amyloid-β in vivo correlates weakly with the onset and severity of AD [13]. Instead, the presence of the soluble form of amyloid-β in the brain may be a better predictor of the disease [14]. Specifically, SDS-stable oligomers and not monomers of this form of amyloid-β seem to play an important role, as shown by augmented presence of these oligomers during the expression of mutations in AβPP or presenilin [15], as well as by their capacity to inhibit neuronal plasticity parameters (LTP) in vivo when micro-injected into the brains of rodents [16]. Conversely, amyloid-β is not always present in the brains of cognitively normal elderly. Nevertheless, these differences can be explained in terms of genetic and environmental variability across individuals. One possibility is that some people are genetically endowed with more efficient endogenous antioxidant defense systems and thus age better/slower. Alternatively, these people may have supplemented their diets with foods rich in antioxidants throughout their lifespan, compensating for age-related declines in these endogenous systems and thus slowing down oxidative stress-related declines seen during aging [17–19]. If amyloid-β and NFT deposition provides an antioxidant function, it is likely that these processes will be recruited during times when oxidative stress is high and the endogenous antioxidant-defenses are compromised. Nevertheless, if these systems remain relatively efficient or are supported by exogenous antioxidant supplementation, the presence of amyloid-β and NFT may not be necessary, and thus lead to little amyloid-β and NFT deposition. Preliminary data from in vitro studies support this hypothesis. Incubation of primary cortical neurons with blueberry extract, a fruit rich in antioxidants [17–19], prevents τ phosphorylation when neurons are presented with an oxidative stress insult (Casadesus, Smith, and Joseph, in preparation), analogous to the effects of endogenous antioxidants [20].

Moreover, unbiased stereological counting indicates that during normal aging there may be little or no cell loss despite, as pointed out above, the presence of an increasing number of plaques [21]. This testifies to the protective function of amyloid-β. Importantly, even the hyper-physiologic levels of amyloid-β found in engineered AD transgenic mice [22] only lead to senile plaque formation in middle-aged mice and are, like their human counterparts, preceded by oxidative stress [23–25]. Taken together, these findings indicate that amyloid-β is not driving the pathogenic process, rather it is a consequence of the pathogenic oxidative process that serves an antioxidant function. In normal aging, the production and deposition of amyloid-β successfully staves off age-related redox imbalances, but in AD where there is a profound and chronic redox imbalance, the presence of amyloid-β, even at high levels, proves insufficient.

The idea that amyloid-β is protective represents a major paradigm shift but is really not surprising. Neuronal degeneration is associated with a number of responses including the induction of heat shock proteins such as heme oxygenase-1 [26] and ubiquitin [27,28] that, like amyloid-β, show a relationship with cognitive decline. Why is it that only amyloid-β is considered pathogenic? The answer, according to the proponents of the amyloid-β hypothesis is that amyloid-β is neurotoxic in vitro and is associated with neuronal loss in vivo. However, that amyloid-β is age-and region-specific is further consistent with a key role in redox homeostasis. Cell culture studies showing neurotoxicity may be artifacts of in vitro conditions [29], an aspect further buttressed by the fact that neither isolated senile plaques nor immobilized amyloid-β elicit neurotoxicity in vivo or in vitro [30–32]. Nonetheless, as a bioactive substance, we should remain cognizant that antioxidants can also serve as pro-oxidants, dependent upon the conditions and that, in certain nonphysiological circumstances, amyloid-β can be made damaging [33,34]. In this regard, and although the capacity of amyloid-β to induce oxidative
stress remains controversial [35], recent data illustrate that the oxidant properties of amyloid-β may stem from its capacity to interact with transition metals and mediate toxicity via redox-active ions that precipitates lipid peroxidation and cellular oxidative stress [29].

Based on the evidence presented above, the few reports demonstrating, under some circumstances, neuronal loss in some transgenic mice with amyloid-β deposits [36] argue only that amyloid-β is a bioactive substance. Indeed, there is little evidence in the literature showing behavioral deficits in mice transgenic for only AβPP mutations. The most consistent findings of behavioral deficits have been shown in mice transgenic for more than one mutation, e.g., AβPP/PS1 [37,38], and even then it is superimposed upon an aged environment.

Finally, the notion that genetic linkage mutations cause increased amyloid-β causes disease is simplistic, pays scant regard for biological and cellular homeostasis, and is clearly not as direct as often assumed, even in the case of mutations in AβPP. While it is true that AβPP and presenilin-1 and -2 mutations are deterministic for the onset of AD and that these mutations produce increases in amyloid-β in the brain, it is against logic to conclude with certainty that there is a casual relationship between the two. For example, and perhaps not surprising, in light of the antioxidant function of amyloid-β, oxidative stress is among the best inducers of AβPP protein expression and consequent amyloid-β production [9]. Therefore, if a mutation causes oxidant stress then one would also find an increase in amyloid-β. Indeed, together with the in vivo findings showing that increased amyloid-β deposition is associated with reduced oxidative stress [7,8], the finding of increased amyloid-β with the mutants simply highlights that perturbations in the cellular system lead to a protective response, i.e., increased amyloid-β production.

Our arguments supporting amyloid-β as a crucial antioxidant defense mechanism are extremely relevant to current pharmacological efforts targeted at either removing amyloid-β or lessening amyloid-β production, and will likely leave neurons without one of their fundamental compensatory responses to aging and disease.

**SUMMARY**

While amyloid-β and τ are often viewed as harbingers of disease, the observed decrease in oxidative damage
Fig. 1. As a consequence of age-related oxidative stress, there is an upregulation of phosphorylated \( \tau \) and amyloid-\( \beta \) that result in NFT and senile plaques, respectively. Both lesions serve antioxidant functions and limit age-related neuronal dysfunction. However, in AD, this age-related oxidative stress is compounded by metabolic [43] and metallic [44, 45] sources of oxidant stress that, despite greatly enhancing amyloid-\( \beta \) production and \( \tau \) phosphorylation, lead to neurodegeneration and consequent dementia.

with amyloid-\( \beta \) and \( \tau \) accumulation points towards an alternate, contrary interpretation that they represent important survival responses (Fig. 1) [6, 37, 55–57]. If this proves to be the case, current efforts targeted at their elimination will actually exacerbate the disease.

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REFERENCES


