

Perspectives on the Amyloid- β Cascade Hypothesis

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Abstract. For the better part of the past two decades, studies on the molecular, biochemical and cellular mechanisms of Alzheimer disease have focused on amyloid- β protein, the major proteinaceous component of senile plaques. In fact, the Amyloid Cascade Hypothesis has come to dominate the field both in terms of proposed disease mechanism as well as potential for therapeutic intervention. In this review, we look at the Amyloid Cascade Hypothesis from the perspective of pathology, cell biology, and genetics. In all cases, alternate interpretations of old data as well as new evidence indicates that amyloid- β , far from being the harbinger of disease, actually occurs secondary to more fundamental pathological changes and may even play a protective role in the diseased brain. These findings bring into serious doubt the validity of the Amyloid Cascade Hypothesis as the central cause of Alzheimer disease and, consequently, the potential usefulness of therapeutic targets against amyloid- β .

Keywords: Alzheimer disease, amyloid- β , neurodegeneration, neuroprotection

1. Amyloid- β : Viewpoint from pathology

Pathology strengthens or refutes hypotheses concerning relationships between clinical disease and the neurodegenerative process and is therefore strategically positioned to identify primary processes versus epiphenomena. In this regard, several features of the basic clinicopathological assessment of Alzheimer disease (AD) are striking. For example, it is well established that neurofibrillary tangles and neuron number more closely correlate with both cognitive deficits and disease duration than do amyloid plaques [3,32]. Also widely accepted is the fact that numerous amyloid plaques are often found in elderly subjects who are not demented [21]. Moreover, amyloid- β ($A\beta$) staging poorly distinguished mild cognitive changes from dementia and showed marked overlap among the vari-

ous clinical stages of dementia in one study [34], while other studies have appropriately raised the question whether $A\beta$ deposition has any relationship at all with cognitive decline [25]. Amyloid burden further shows no correlation with neuronal loss (or with neurofibrillary tangles and disease duration) [36], in contrast to tau-positive neuritic pathology that is always minimal to absent in cognitively intact subjects [55].

It is clear that $A\beta$ deposits are a sensitive indicator, i.e., “marker,” of disease, but its specificity is doubtful for the reasons noted above. This phenomenon has led to the subtyping of plaques (e.g., “senile,” neuritic, diffuse, cored, etc) in an effort identify plaques that are more “pathogenic.” In this regard, it is generally accepted that diffuse plaques ($A\beta$ deposits without cores or a neuritic component) are decorative in nature, having little impact if any on cognitive function whereas neuritic plaques are more pathogenic. Parenthetically, often disregarded is the fact that $A\beta$ deposits with a prominent fibrillar $A\beta$ core (cored plaques) are numerous in the primary visual cortex of elderly individuals, again unassociated with dementia [60].

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Since neuritic plaques are better developed and thought to relate more closely to disease, it makes intuitive sense that diffuse plaques appear in preclinical disease and evolve into neuritic plaques with clinical expression of AD. The question therefore arises whether diffuse A β deposits, or for that matter neuritic plaques, correlate anatomically with clinical deficits typically found early in the disease. Conveniently, central nervous system diseases are the ideal setting in which this question might be addressed, given the overlay of neuroanatomy and the eloquence with which a single population of diseased neurons may express itself. Thus, there is a striking relationship between brain regions affected early in disease, and those regions having short-term and other memory functions – such as entorhinal cortex, perforant pathway, hippocampal pyramidal neurons, amygdala – particularly since memory loss is a prominent, early manifestation of AD. The pathology, however, is in the form of neurofibrillary tangles, while amyloid deposits (even of the neuritic variety) are much more evenly distributed and in fact more abundant in association cortices apart from the primary memory circuitry [2].

In non-demented, older control subjects, both neurofibrillary pathology and A β deposits may be encountered [8], raising the notion of “preclinical AD,” but here again the neurofibrillary pathology is scant and when present localizes to memory circuitry (e.g., entorhinal pre- α layer) while A β deposits in non-demented subjects are much more random. Similarly, olfactory deficits, which may be identified in preclinical stages of AD [74], are more associated with neurofibrillary pathology than with A β deposits [15], and tau pathology in the olfactory bulb correlates closely with Braak (neurofibrillary) stage as well as apolipoprotein E (ApoE) ϵ 4 allelotype [95].

The existence of exceedingly rare kindreds bearing mutations that affect A β processing (A β PP and presenilin mutations) is still perhaps the most compelling clinicopathological argument in favor of the Amyloid Cascade Hypothesis. However, it may likewise be argued that these rare kindreds represent more of an aberration compared to the infinitely more common sporadic, late-onset AD and thus a fundamentally different disease process. Indeed, close analysis of the pathology of subjects with presenilin mutation discloses prodigious A β deposits, but also discloses such structures as the “cotton-wool” plaque and extensive white matter, deep gray matter, and posterior fossa involvement that are uncommon or unheard of in sporadic AD. It might also be noted that cases formerly interpreted

as “plaque-only” AD often demonstrate Lewy body pathology [41]; thus A β deposition is not only a poor predictor of dementia in AD, but seldom if ever exists in isolation in demented subjects.

In short, objective review of the available evidence concerning A β deposition in AD, versus clinical disease progression and the entire neuropathological substrate, limits us to the conclusion that A β deposition, while a convenient marker of disease, is nonetheless epiphenomenal. Thus, on a pathological basis alone, we are compelled to search for a more fundamental etiology.

2. Amyloid- β : Viewpoint from cell biology

The original findings from pathology led those interested in cell biology to explore the biology of A β . In this regard, A β is derived by proteolytic cleavage of the amyloid- β precursor protein (A β PP), a protein of unknown cellular function that has the general properties of a cell surface receptor [54,68]. While it was originally thought that A β was an abnormal cleavage product, A β has since been established as a normal metabolic product of neuronal A β PP and is found in the cerebral spinal fluid (CSF) and serum of healthy individuals [39,86]. The regulatory activity of three different proteolytic enzymes, α , β and γ -secretases, at their specific cleavage sites yields a number of different products, including A β_{1-40} and A β_{1-42} [88]. While A β_{1-40} is the predominant product of this proteolytic pathway, A β_{1-42} is far more fibrillogenic *in vitro* and is the major A β species present in the core of senile plaques (both AD and non-AD related) [10,50]. The deposition of A β_{1-40} and A β_{1-42} into senile plaques likely begins with the nucleation of soluble A β_{1-42} into fibrils followed by accumulation of normally soluble A β_{1-40} [50].

A crucial finding by cell biologists was that A β is toxic to neurons in *in vitro* culture experiments. In fact, while debate still continues regarding which A β molecule, oligomer or fibril, is the real culprit, A β is inherently toxic in cell culture models [24,75,106]. Additionally, A β also causes synaptic degeneration and is therefore synaptotoxic as well as neurotoxic [83]. The source of A β toxicity, whether synaptotoxic or neurotoxic, has yet to be established, however a number of theories have been advanced. For example, numerous studies support the idea that an oxidative event is critical for A β toxicity (reviewed by [63]). Certainly, it is clear that A β is capable of generating reactive oxy-

gen species (ROS), including H_2O_2 [43,48,49], which can stimulate inflammatory cells to further propagate ROS production [1,11,98]. Given the role of ROS, it is not surprising that $A\beta$ -neurotoxicity can be attenuated by administration of antioxidants and free radical scavengers, such as vitamin E [6]. However, while it is clear that $A\beta$, either directly or indirectly, promotes oxidative stress and that $A\beta$ toxicity can be attenuated by antioxidants, the precise mechanism by which $A\beta$ leads to increased oxidative stress remains elusive. Indeed, while studies have suggested that the neurotoxicity of aggregated $A\beta$ is mediated by its ability to induce oxidative stress via the spontaneous generation of free radicals and ROS [43], this proposition is unlikely based on theoretical as well as methodological grounds [26,80,96]. Instead, it now appears that the oxidant effects of $A\beta$ are mediated by its interaction with redox-active metals such as iron and copper since chelation treatment of $A\beta$, to remove bound metals, significantly attenuates toxicity [78]. Significantly, $A\beta$ has an unusually high affinity for both iron and copper [4,22] and is capable of reducing these metals with subsequent production of hydrogen peroxide and oxidized amyloid [48,49]. The relevance of this mechanism to disease pathogenesis is highlighted by the association of redox active metals with senile plaques in AD [81,89].

Before we take this further however, and since the foundations of the Amyloid Cascade Hypothesis were founded on the *in vitro* toxicity of $A\beta$, it is obviously important to investigate $A\beta$ toxicity further. In this regard, we have suggested that the *in vitro* toxicity that has been shown in culture, and very unreliable in animal models, may in fact be an artifact of culture and not intrinsic to the peptide itself [78]. In fact, contrary to *in vitro* scenarios, $A\beta$ occurs after oxidative stress and, rather than increasing stress, appears to blunt oxidative stress *in vivo* [70,71] by acting as an antioxidant [23]. Notably, nanomolar concentrations of $A\beta$ can block neuronal apoptosis following trophic factor withdrawal [108]. These findings are consistent with the trophic and neuroprotective action of $A\beta$ at physiological concentrations in deprived conditions and neonatal cells that have been reported during the last decade [6,53,56,61,87,100,106]. Indeed, as mentioned above, while amyloid can be toxic in cell culture “models”, in animals and humans, despite massive amyloid concentrations, there is generally little associated cell death [62] and consequently only a weak correlation to cognitive decline [67]. In fact, $A\beta$ appears to be a response to neuronal injury [31], rather

than the mediator of such an injury and this scenario is consistent with a protective function for $A\beta$ [5,52,79]. In this regard, it is notable that depletion of the energy supply induces upregulation of $A\beta$ PP expression such that ischemia, hypoglycemia and traumatic brain injury, a condition that has been shown to put neurons under metabolic stress [103], all upregulate $A\beta$ PP and its mRNA in animal models and culture systems [40,51,66,84,85,107]. Also, inhibition of mitochondrial energy production alters the processing of $A\beta$ PP to generate amyloidogenic derivatives [27,29,64], while oxidative stress has been shown to specifically increase the generation of $A\beta$ [27,65,73]. Consistent with this response, $A\beta$ has been detected in the human brain several days after traumatic brain injury [31]. This fits well with the role of $A\beta$ PP as an acute phase reactant upregulated in neurons, astrocytes and microglial cells in response to inflammation and a multitude of associated cellular stresses including axonal injury [7,31], loss of innervation [99], excitotoxic stress [72,94], heat shock [16], oxidative stress [27,104], aging [44,69,97] and inflammatory processes [9,12,13,35].

Therefore, from the perspective of cell biology, while cell culture “models” were keys in formulating the Amyloid Cascade Hypothesis, they do not appear to be an accurate reflection of any *in vivo* or diseased conditions. In this regard, it is now clear that the amyloid toxicity seen *in vitro* is a reflection of artifactual cell culture conditions [78]. With this in mind, and rejecting the cell culture toxicity data as artifact, the strength of the Amyloid Cascade Hypothesis is clearly diminished.

3. Amyloid- β : Viewpoint from genetics

A strong piece of evidence supporting the Amyloid Cascade Hypothesis is that familial forms of the disease (FAD) involve mutations or polymorphisms in $A\beta$ PP or in genes that are directly involved in $A\beta$ PP processing [42,82]. In fact, a tremendous amount of effort and resources have been dedicated in the past decade to determining the mechanisms of AD using models based on these mutations. The most straightforward form of FAD is caused by point mutations in $A\beta$ PP in regions that are involved in the proteolytic processing of the peptide [33,59]. It is thought that these mutations accelerate the onset of AD into the fourth decade by increasing the ratio of $A\beta_{1-42}/A\beta_{1-40}$, thereby increasing the relative amount of the more fibrillogenic form [92]. A double mutation at positions 670/671

(Swedish mutation) increases the production of total $A\beta$ and thereby increases the load of $A\beta_{1-42}$ without changing the relative ratio [14,17]. The fact that an increase in total $A\beta$ load can accelerate the deposition of $A\beta$ is supported by the neuropathology demonstrated in patients with Down syndrome, a disorder caused by trisomy of chromosome 21, where the $A\beta$ PP gene is localized. It is thought that the overexpression of $A\beta$ PP in these individuals [38] causes the formation of $A\beta$ plaques very similar to those seen in the AD brain. Additionally noteworthy is that the most common form of FAD is caused by mutations in one of the two presenilin genes (PS1 on chromosome 14 or PS2 on chromosome 1) (reviewed by [37]). While the function of the presenilin genes is not completely elucidated, it is known that they localize to the endoplasmic reticulum and Golgi apparatus [57] and form stable complexes with $A\beta$ PP [102]. Such missense mutations in the presenilin genes increase the ratio of $A\beta_{1-42}/A\beta_{1-40}$ [18, 93]. Finally, it has been demonstrated that one allele of the apolipoprotein E gene, namely ApoE4 predisposes individuals to the development of late-onset AD [19]. Of the three alleles (also including ApoE2 and ApoE3), ApoE4 has the greatest affinity for $A\beta$, is found associated with senile plaques and is thought to accelerate fibrillogenesis [101]. Interestingly, the ApoE2 is capable of inhibiting the formation of fibrils and is protective against the development of AD [20].

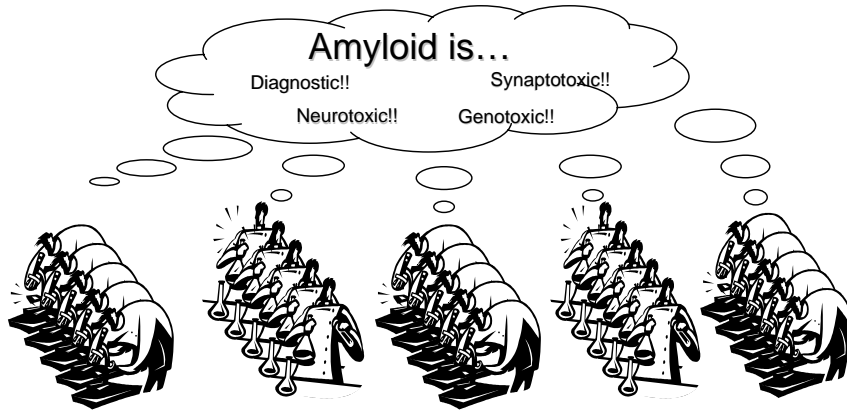
This strong evidence implicating $A\beta$ in AD pathogenesis led to the supposition that generation of transgenic animals either over expressing $A\beta$ PP or containing a mutation in $A\beta$ PP that affects processing of the full length protein thereby leading to an increase in the $A\beta_{1-42}/A\beta_{1-40}$ ratio, may mimic the symptomatology of AD. Taken as a group, the various transgenic mice strains that have been produced have demonstrated that overexpression $A\beta$ PP or overproduction of the $A\beta_{1-42}$ peptide fragment is sufficient to cause deposition of the peptide into senile plaque-like structures and may in fact be responsible for at least some of the neurodegeneration in AD (reviewed by [45]). Indeed, despite the fact that each of the different constructs introduced yielded somewhat different phenotypes, some aspect of AD pathophysiology are apparent in each. For example, Games and colleagues created a transgenic mouse expressing human $A\beta$ PP with the Val717Phe mutation at ten times the endogenous level and these animals developed $A\beta$ plaques in the hippocampus, cerebral cortex and corpus collosum by 6–9 months of age and also show synaptic loss and astroglycotoxicity, although they show no behavioral abnormalities [30]. Among the

first models to demonstrate behavioral changes reminiscent of those seen in AD were those overexpressing $A\beta$ PP containing the Swedish double mutation (Lys670Asn/Met671Leu). In addition to a marked increase in levels of $A\beta$ in the CSF and deposition of $A\beta$ plaques, these mice demonstrated marked deficits in spatial learning, as demonstrated by Morris water maze, by the age of 9 months [47]. Although no neurotoxicity is observed in these mice, it is thought that their impaired spatial learning, which is correlated with long-term potentiation, is related to synaptic loss. Interestingly, these mice also displayed oxidative stress in association with the plaques, much like that seen in AD [90]. Neurotoxicity has also been seen accompanied by an increased mortality rate, with 50% of mice dying by 12 months of age compared to an average of 24 months in controls, in mice overexpressing $A\beta$ PP [58]. Although there are differences in the details of these studies, it is clear that $A\beta$ can independently cause AD-related pathology and some behavioral defects.

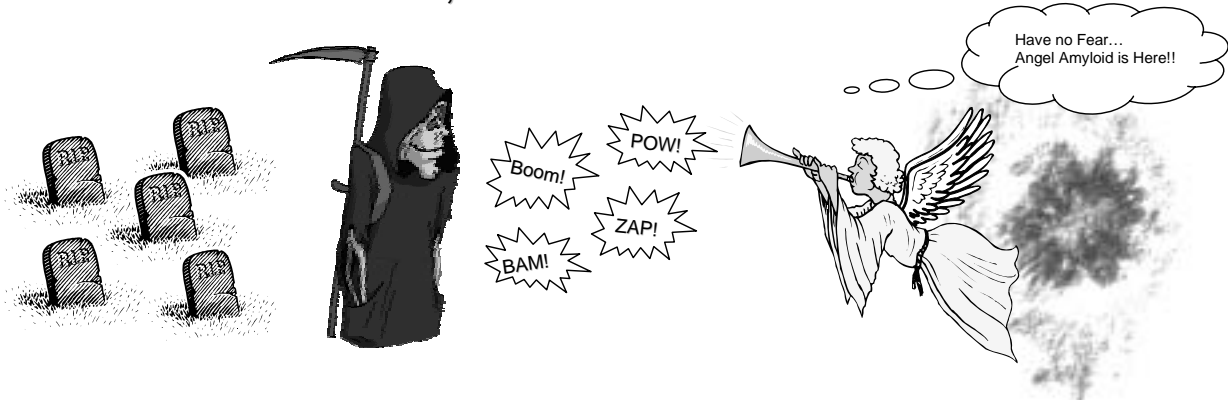
On the other hand, it is fair to state that characterizing FAD has proven only marginally useful to our understanding of sporadic AD, which by far represents the majority of cases. In fact, mutations in $A\beta$ PP have been identified in only 20–30 families worldwide and represent less than 0.1% of the 15 million known cases of AD. Mutations in both presenilin (PS) 1 and 2, which are the most common genetic determinant of AD, only contributes an additional 120–130 families. While it is clear that mutations in these proteins involved in $A\beta$ PP processing are capable of inducing amyloid neuropathies and dementia, no aberrant neurologies are observed usually for many decades. Moreover, while one interpretation of the available data is that “mutation leads to increased $A\beta$ leads to disease” an equally valid explanation is that “mutation leads to disease leads to increased $A\beta$ ”. Support for the latter is becoming ever apparent since mutations lead to cellular stress which, as discussed earlier, in turn leads to increased $A\beta$ [77, 105]. Therefore, all of the data showing how mutations cause alterations in $A\beta$ could be equally interpreted as showing that these mutations cause a perturbation in redox balance and therefore mutations could both cause increased $A\beta$ and, independently, cause disease.

The claim that the positive correlation between ApoE4 genotype and incidence of AD supports a causative role for $A\beta$ is likewise flawed. While it is true that ApoE4 has the greatest affinity for $A\beta$, is found associated with senile plaques and is thought to accelerate fibrillogenesis [101], this is not the sole or even the major physiological role of ApoE proteins.

The scientific clones busy at work in the lab...



...MEANWHILE, IN AN AD BRAIN NEAR YOU...



In the periphery, it is known that ApoE helps to regulate the transport and metabolism of lipids. It is also well established that the level of ApoE is elevated in response to injury in the peripheral and central nervous system [46] and, like $A\beta$, ApoE may thereby serve a protective role after ischemia or traumatic brain injury by distributing phospholipids and cholesterol to injured neurons [76]. ApoE may also protect against oxidative injury and prevent the accumulation of lipid peroxidation end products, such as hydroxynonenal, which are prominent features in AD and acute brain injury. In this vein, several studies showed that patients with homozygous ApoE4 genotype have longer periods of unconsciousness and higher incidence of post-traumatic coma following severe traumatic brain injury [28,91]. In short, ApoE4 predisposes patients for any number of neurodegenerative processes and is another factor that is completely nonspecific to AD. Therefore, much like

in acute injury, ApoE4 may be associated with a higher incidence of AD because it is less efficient in protecting neurons from the causative insult and therefore may have very little to do with its affinity for $A\beta$.

4. Conclusions

From the perspectives of pathology, cell biology, and genetics, the Amyloid Cascade Hypothesis has a number of critical flaws that seriously question the validity of the construct and necessitates rejecting the hypothesis as currently structured. Obviously, a new hypothesis will need to include $A\beta$ but as a downstream consequence rather than a pathogenic mediator. With this in mind, therapeutic targets for AD will need to be radically revised.

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