Published in final edited form as:
J Alzheimers Dis. 2009 October ; 18(2): 447–452. doi:10.3233/JAD-2009-1151.

Reexamining Alzheimer's Disease: Evidence for a Protective Role for Amyloid-β Protein Precursor and Amyloid-β

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Abstract

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized clinically by cognitive decline and pathologically by the accumulation of amyloid-β-containing senile plaques and neurofibrillary tangles. A great deal of attention has focused on amyloid-β as the major pathogenic mechanisms with the ultimate goal of using amyloid-β lowering therapies as an avenue of treatment. Unfortunately, nearly a quarter century later, no tangible progress has been offered, whereas spectacular failure tends to be the most compelling. We have long contended, as has substantial literature, that proteinaceous accumulations are simply downstream and, often, endstage manifestations of disease. Their overall poor correlation with the level of dementia, and their presence in the cognitively intact is evidence that is often ignored as an inconvenient truth. Current research examining amyloid oligomers, therefore, will add copious details to what is, in essence, a reductionist distraction from upstream pleiotrophic processes such as oxidative stress, cell cycle dysfunction, and inflammation. It is now long overdue that the neuroscientists avoid the pitfall of perseverating on “proteinopathies” and recognize that the continued targeting of end stage lesions in the face of repeated failure, or worse, is a losing proposition.

Keywords

Alzheimer's disease; amyloid; amyloid-β protein precursor (AβPP) processing; antioxidant; cellular toxicity; oligomers; oxidative stress

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Authors' disclosures available online (http://www.jalz.com/disclosures/view.php?id=43).

INTRODUCTION

Reviews of the molecular pathogenesis of Alzheimer's disease (AD) tend to invite the reductionist approach to disease. Indeed, it is now customary in some circles to begin reviews, discussions, and lectures on AD with a schematic diagram of the amyloid-β protein precursor (AβPP) molecule, implying that this molecule encapsulates AD so completely that the disease itself is almost of secondary importance.

Such a mindset tends to ignore not only competing reductionist theories, but the complexity of chronic diseases in general. Moreover, referring to any one approach as “once controversial” highlights the magnitude of the problem, and the necessity to return to objective review of data that are generally soft and manipulable. In effect, how many patients need suffer an untimely demise at the hands of clinical trials driven by schools of thought that are no longer controversial, before a paradigm shift occurs?

This mindset tends further to lend a theological tone to pursuit of scientific data and thus invite not only a more objective assessment, but outright cynicism [1]. It may well be, however, that a return to objectivity, and indeed cynicism, are long overdue. Of the numerous hypotheses, none have resulted in a tangible treatment benefit, whereas millions would proffer themselves and their family members as guinea pigs, purely out of desperation.

Such is a clarion call to medical ethicists. Life is often eagerly risked in exchange for a mere modicum of hope because of what otherwise awaits the afflicted. At the same time, much more than a modicum of hope is all too palpable and equally unjustified, in even a cursory review of the scientific literature. Such a combination is a blueprint for exploitation.

Perhaps more disturbing are the schematic diagrams and modern graphics (i.e., cartoons) that demonstrate hypotheses in the mainstream press, which in effect give the “lay person” the illusion of understanding and the academic the illusion of progress, exacerbating the underlying problem. Titles and university affiliations decorate the work and provide unassailable credibility, while the entire package is sold like an elixir in the marketplace of public thought, as the waters of human suffering are trolled, intentional or not, for the afflicted and their families.

Realistically speaking, the perversion of the scientific method, and manipulation of a desperate public afflicted by an expanding, devastating, and incurable disease, characterize AD research and treatment in the 21st century; nevertheless, the peer review processes, the competition for public funds, and the embedded centers of opinion continue, unabated and unabashed, as knowledge of epiphenomena expands and progress toward effective treatment stagnates.

Pathological interpretation of neurodegenerative diseases has, for better or worse, focused on proteinaceous inclusions for no other reason than the fact that they can be visualized. Yet, implicit in the vast majority of studies on disease pathogenesis is the assumption that these lesions themselves are inherently toxic, and therefore represent disease per se rather than disease response. Such a conclusion is clear from the frenzy of studies that followed the identification of amyloid-β (Aβ) and tau in their respective lesions. Remarkably, in 2009, after nearly a quarter century of lesion primacy, and after targeting of Aβ as an avenue of treatment has repeated failed, the amyloid cascade concept is referred as “once controversial.”

Here we will scrutinize the findings that 1) advanced protein aggregation, in addition to serving protective functions in other tissues, may protect cells from toxic intermediates; 2)

amyloid protein fragments have antioxidant properties; 3) protein modifications upstream of AβPP processing affect plaque formation and promote neurogenesis; and 4) treatments that specifically target amyloid do not affect disease prevalence nor progression. Overall, based on these data, we propose that Aβ is not responsible for the clinical manifestations of AD.

AMYLOID IN FAMILIAL AND SPORADIC ALZHEIMER'S DISEASE

Emil Kraepelin was the first to use Alzheimer's name in association with dementia in the eighth edition of his textbook of Psychiatry [2] and was justified as a new disease not because of the association of dementia with lesions. Indeed, senile dementia in association with senile plaques had been known previously. Rather, it was the early age at onset that justified “Alzheimer's disease” as a new condition, worthy of a new disease. We now know that early-onset disease is commonly associated with familial disease in the strict sense, and the presence of germline mutations [3,4]. Therefore “Alzheimer's disease” as it was originally named, is essentially familial early-onset AD, whereas different process, or a process demeaned to be sufficiently different to require a different name, that is “senile dementia,” refers essentially to sporadic late onset disease.

Silver staining techniques and Congo red birefringence [5,6] were the mainstay of amyloid plaque analysis until the small protein Aβ, a metabolic product of AβPP transcribed on chromosome 21, was found to be the major component [7,8]. During this time period, a conspicuous shift from the notion that senile plaques are an accompaniment of disease, to plaques being directly tied to etiology and pathogenesis [9–12] occurred. The identification of kindreds of familial AD linked AβPP germline mutations, as well as the development of neuropathology in cases of Down's syndrome, in which patients have an extra copy of AβPP, reinforced this notion.

While the genetic mutations involving AβPP, presenilin (PS), and trisomy 21 result in an AD-like phenotype, it is important to remember that the total identified familial early-onset AD kindreds with known mutations number only about 450. Clinical presentation in familial disease is also heterogeneous and can present with cerebral hemorrhage without dementia, spastic paraparesis with delayed dementia, subcortical dementia with Parkinsonism, and seizures [13–15] – clearly differing from sporadic AD. Also different from sporadic AD are the extensive Aβ burden often throughout the white matter, deep gray matter, cerebellum, and “cotton wool” plaques that lack fibrillar Aβ as in PS1 mutation cases, such that early-onset familial AD imperfectly mimics the far more common sporadic condition.

The cohort of dementia subjects number at least 20 million across the globe. Moreover, in sporadic disease, a variety of other specific risk factors come into play (e.g., head trauma, diet, sex hormones, educational background, and aluminum exposure) [13], which are unaccounted for by simplistic reductionist theories.

Should amyloid be used as a diagnostic tool?

Shortly after the initial description of AD, it was realized that senile plaques, as well as neurofibrillary tangles, occur with advanced age in most non-demented individuals [13]. The diagnosis of AD at autopsy, therefore, became a quantitative exercise [13]. Importantly, both clinical dementia and *numerous* plaques and tangles are required for the diagnosis of AD. Pathological lesions, as qualitative phenomena, are therefore diagnostically meaningless.

It is further interesting to note that among the various neurodegenerative diseases, AD is the only condition with features that overlap substantially with “normal aging.” Cortical Lewy bodies, Lewy neurites, and the various inclusions associated with subtypes of tauopathy, are generally not features in the brain in cognitively intact elderly. Without a detailed

neurological history, confounding factors such as polypharmacy, hydrocephalus, and metabolic derangements are limitations for making an accurate pathological diagnosis, and the often mythical concept of “autopsy-proven” AD [16].

Looking at this from another angle, AD is a chronic, non-neoplastic disease, routinely examined pathologically at its end-point, i.e., at autopsy. Other chronic, non-neoplastic disease processes use biopsy as a diagnostic tool, e.g., chronic renal failure, chronic liver disease, interstitial lung disease, and neuromuscular disease, in which pathology invariably loses specificity with increased disease duration [13]. However, in interpreting neurodegenerative disease, the neuropathologist is required to distinguish among clinicopathological entities with *increasing* specificity. Such an exercise is counterintuitive to the basic concept of chronic disease pathology; nevertheless, attempts standardize diagnostic criteria through lesion quantitation have been made.

To this end, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) sought “to produce more accurate and reliable neuropathologic criteria for AD, to determine the neuropathologic spectrum of AD, and to establish the types and frequencies of other disorders coexisting with AD or occurring alone.” [17]. Routinely, three neocortical areas among other regions, stained with Bielschowsky silver, are reviewed and the presence senile plaques are categorized into sparse, moderate, and frequent. The senile plaque frequency is then correlated with age (younger than 50 years, 50–75 years, and older than 75 years).

The underlying concept of these standard consensus criteria are that the older the patient, the more plaques are required for the diagnosis of AD. The precursor Khachaturian criteria employed a similar concept [18]. The Braak diagnostic method, in contrast, presumes, rather remarkably, that everyone with a lesion has some degree of AD regardless of clinical signs. The stages depend on the brain regions affected and also enumerate neurofibrillary pathology rather than senile plaques, because of the stepwise progression from transentorhinal to limbic to neocortical regions affected as opposed to the variation of the plaque distribution. The NIA-Reagan consensus criteria, published six years after CERAD and Braak, is a combination of the two methods completely different methodologies [19].

The fact that these competing standardized methods for assessing AD quantitate different lesions comprised of different proteins belonging to different metabolic pathways is *prima facie* evidence of the poor correlation between lesion and cause. According to CERAD, Khachaturian, and NIA-Reagan, with age, the more plaques are “forgiven,” and more senile plaques are required to diagnose AD, such that instances exist in which the same number of senile plaques results in different diagnoses. Applying standard criteria, a 49-year old patient with a sparse number of senile plaques and dementia, by CERAD criteria, would have definite AD, whereas a 76-year old patient with the same number of senile plaques would yield an “uncertain” diagnosis of AD or possible AD. Yet we are led to presume that lesions are indicative of disease.

Amyloid as a host response

The relationship between AD pathology, clinical disease, and advanced age, could suggest that pathology is a variable *host response* to an underlying etiology, and a response that accumulates with age. Upstream to Aβ processing from its precursor are events which, upon further discernment, could begin the shift the focus from resultant amyloid deposition.

A newly discovered factor, sortilin-related receptor, controls the processing of AβPP to Aβ and the soluble fragment. Interestingly, this factor has reduced expression in AD cases, which could expectedly result in uncontrolled processing of AβPP, and therefore, increased Aβ. In fact, when combined with an AD mouse model, SORLA gene deficiency does in fact

result in increased Aβ plaque burden. Yet, importantly, the increased soluble AβPP fragment correlates with neuronal ERK activation and neurogenesis such that Aβ accumulation could be considered secondary to the the neuronal survival mechanism [20].

The formation of amyloids is a generally common occurrence in biology. Varied points of view have been proposed regarding protein polymerization. It has been suggested that there has been an evolutionary selection of specific amino acid residues within proteins to select against aggregation potential [21]. Yet other examples are naturally protective (i.e., eggshell), or in some fish, amyloidogenic structures protect cells from freezing [22]. Amyloid in the brain is common among many mammals, and therefore, may not be indicative of a specific human disease. The rather recent focus on amyloid protofibrils being the culprit exhibiting toxic properties is not unfounded [23]. Other examples of toxic oligomeric species, other than Aβ causing cellular destruction include prion protein, lysozyme, cystatin C, and others [24]. Yet, the amino acid sequences foster elongation of these intermediates and promote self-assembly, often limiting the destructive properties of the oligomeric phases. Another prime example extremely relevant to the environment within the brain, are the studies of the protein Pmel17. This protein acts as a template for the polymerization of melanin. Melanin is an important compound within cells that confers protection from oxidative damage and other cytotoxic insults. Importantly, Pmel17, by promoting this polymerization, effectively removes the toxic precursors of melanin formation [25]. Additionally, another amyloid-like peptide, microcin E492, exists as aggregates within bacterium where it is functionally toxic, yet readily forms a more structured amyloid, rendering it nontoxic [26]. It is suggested by these examples that amyloid formation is a conserved property for promoting cellular survival.

Promotion of polymeric structures, inhibiting oligomeric toxicity, therefore, is a cellular survival technique. Again, pursuing upstream events, perhaps initiated by reactions for neuronal survival such as that demonstrated by the correlation of soluble AβPP fragment and neurogenesis, will yield useful answers to the clinical signs of mental deterioration. Emphasis on controlling amyloid load, which very well could be a direct (i.e., elongation of toxic oligomers) or indirect (i.e., byproduct of soluble amyloid fragment which may be involved in survival) host response, may not be warranted.

TOXICITY OF AMYLOID LESIONS

Aβ was first purified and identified from visible microscopic lesions, the amyloidogenic blood vessels in Down's syndrome, and amyloid plaque cores of AD. Therefore, the microscopic pathology of AD is the foundation for the amyloid hypotheses [13], suggesting the amyloid is toxic. The $A\beta_{1–42}$ species is commonly accepted as “pathogenic,” and an increased ratio of $A\beta_{1–42}$: $A\beta_{1–40}$ is seen in familial AD. Yet this is due to a marked *decrease* in $A\beta_{1–40}$ [27,28]. As such, mutations that cause AD do so by producing less $A\beta_{1–40}$ [29].

Aβ has been shown to be toxic *in vitro* by a variety of mechanisms, including induction of apoptosis [30], promotion of inflammatory mediators [31], and as an accelerant of oxidative stress [32]. Many in the field realize the technical difficulties when working with amyloid protein and peptide fragments. The variation of fragmentation, insolubility, and self-assembly proficiency are some of the issues, as are reproducibility inconsistencies due to concentration, pH, or different effects in *in vivo* versus *in vitro* studies. The ratio of the various cleavage products is one of intense scrutiny. Even if you disregard the notion presented earlier that AβPP processing is a host response, the variability and different ramifications reported for amyloid fragments and their ratios merits discussion. Not all studies conclude with or promote the idea amyloid toxicity. In a large epidemiological

analysis using pooled data from many studies, non-steroidal anti-inflammatory drug (NSAID) use was shown to reduce the risk of AD. Another variable in this group was the further identification of use of NSAIDs that specifically reduce $A\beta_{1–42}$, called selective $A\beta_{42}$-lowering agents. Neither this class of NSAIDs nor aspirin alone had any additional advantage for the protective effect seen [33]. $A\beta_{1–40}$ has been shown to be protective, thus targeting $A\beta_{40}$ formation pharmacologically, or immunologically, could be deleterious [34]. When mice specifically bred for overexpression of $A\beta_{1–40}$ were crossed with both the Tg2576 mouse model as well as mice specifically overexpressing $A\beta_{1–42}$, the overall higher levels of $A\beta_{1–40}$ inhibited amyloid deposition by 60–90%. Soluble $A\beta_{28}$ has proven antioxidant properties and readily chelates metals, albeit not efficiently [35]. Increased redox-active metal accumulation is a feature of amyloid plaques and is likely a result of mitochondria dysfunction. Therefore, neuronal survival mechanisms in which soluble AβPP fragments promote neurogenesis, and in which some Aβ fragments confer antioxidant or protective properties may be driving the equilibrium toward increased AβPP processing. The byproduct, amyloid aggregation, is a further protective response to protect cells from the rather toxic protofibrils or oligomers. Targeting AβPP processing therefore will not protect neurons, unless an underlying cause responsible for the increased AβPP expression is determined.

On the other hand, widely recognized defects stemming from the pathological standards of identifying AD is: 1) the weak correlation between Aβ deposits and cognitive status [36–41]; 2) the lack of correlation between loss neural function within the regions responsible for memory and the extent of Aβ deposits in that brain region [37–40]; and 3) large amounts of amyloid may be encountered in the brains of cognitively intact elderly [40,42]. There is a consistently better correlation between neurofibrillary pathology and the above indices.

CONCLUSION

Amyloid pathology, and its irregular association with disease, has remained essentially unchanged since its original description and lesion-based therapies thus depend on the concept that the host response is deleterious. Driving the recent expansion of knowledge has been the genetics associated with AD and the resulting enthusiasm over identification and treatment of the underlying cause. Lost in this frenzied activity is the poor relationship between Aβ deposits, as detected neuropathologically, and neuronal dysfunction in brain regions affected by those deposits. Until there is a fundamental paradigm shift and blunting of the negative impact of an outright misconception, the discovery of upstream processes that lead to lesions will be hampered.

Acknowledgments

Work in the authors' laboratories is supported by the National Institutes of Health (AG026151 to MAS).

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