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Causes versus effects: the increasing complexities of Alzheimer's disease pathogenesis

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Abstract

Amyloid plaques and neurofibrillary tangles are the hallmarks of Alzheimer's disease and have been the focus of disease etiology and pathogenesis. However, in the larger picture of a complex disease, the precise etiology of the lesions *per se*, as well as the clinical disease, remain to be defined. In this regard, to date no single process has been identified as a useful target and treatment efforts have shown no meaningful progress. Therefore, alternative ideas that may lead to new and effective treatment options are much needed.

Keywords

Alzheimer's disease; amyloid; fibrillary deposits; oxidative stress; tau

Amyloid plaques and neurofibrillary tangles (NFTs) are pathological hallmarks of the progression of Alzheimer's disease (AD). The questions of how, why and when they appear are, therefore, pertinent to understanding the disorder and, as a result, research efforts into the relationship between lesion and pathogenesis have been substantial. It is now known that specific molecular events are associated with the development of AD, although their exact relationship to lesion appearance is still controversial. Pathogenic mutations leading, for example, to amyloid- β (A β) deposition, are a primary piece of evidence [1–3], while a wide range of other metabolic abnormalities have been proposed [4–8]. During early AD stages, cell cycle deregulation has been related to the disease [9,10], which may also contribute to the protein aggregates. Other processes, such as oxidative damage to DNA and RNA, have

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also been implicated in the pathogenesis of AD [11], as well as lesion histogenesis [12–15]. Still others suggest tau protein metabolism as the rate-limiting factor in disease, specifically phosphorylation, conformational changes and cleavage [16–21]. A number of other mechanisms have been implicated, including such general mechanisms as apoptosis, inflammation and excitotoxicity. Nevertheless, while the disease effects are clear, the precise cause remains elusive, which is a concept that is sometimes forgotten in the enthusiasm over small molecules.

Genetic events: causative, but how?

Pathogenic mutations leading to familial autosomal-dominant AD involve the A β precursor protein (*APP*) gene [22,23], and presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes [24]. Apolipoprotein E (*APOE*) polymorphisms, sometimes referred to as familial late-onset AD, are not mutations *per se*, but are a significant predisposing factor [25,26]. In particular, the *APOE* gene has three isoforms (ϵ 2, ϵ 3 and ϵ 4), with the ϵ 4 isoform being the strongest predisposing allele [27]. *APOE* ϵ 3/ ϵ 4 heterozygotes have two- to three-fold higher risk of developing AD compared with ϵ 3/ ϵ 3 homozygotes, and ϵ 4/ ϵ 4 homozygotes have more than twofold the risk of the ϵ 3/ ϵ 4 genotype, while the presence of ϵ 2 is somewhat protective [28,29]. Thus, three polymorphisms of the *APOE* regulatory region (–219 G/T, –427 C/T and –491 A/T) are implicated in AD. Notably, however, after adjustment of the *APOE* status, a large French case–control study (388 AD cases and 386 controls) differed from the hypothesis of an independent involvement of the *APOE* promoter region polymorphisms in AD risk [30]. However, recently, the combined gene effects between tau (intron 9, rs2471738) polymorphism (discussed later in this section) and the low-density lipoprotein receptor-related protein 1 (exon 3, rs1799986) polymorphism were found to be associated with a six-times higher risk of developing AD than subjects without these risk genotypes, suggesting that *APOE* polymorphisms could have a synergistic effect, but, more importantly, the *APOE* gene could also be promoting other AD factors, such as tau deposition [31]. Indeed, in an attempt to clarify the mechanism that relates *APOE* and AD, a transgenic model that carries the Arg-61 region, which is specific for domain interaction, a structural property of *APOE*4 that distinguishes it from *APOE*3 and predicted to contribute to the association of *APOE*4 with AD, has been developed. Interestingly, the mice display synaptic, functional and cognitive deficits, with ‘domain interaction’ postulated as the causative factor. Domain interaction further results in astrocytic dysfunction, which some view as an early event in *APOE*4-associated AD development. The authors suggest domain interaction as a possible therapeutic target for AD treatment [32].

In terms of strictly genetic factors, the autosomal dominant mutations in the *PSEN1* and *PSEN2* have also been widely implicated in the development of AD through the abnormal processing of A β protein, which leads to deposition as A β plaques [33,34]. Noteworthy also, is a *PSEN1* double mutation (E318G plus G394V), which evidently affects γ -secretase activity [33], and a heterozygous missense mutation in exon 11 of the *PSEN2* gene with a substitution from valine to methionine in position 393. However, experimentally, *in vitro* expression of *PSEN2* V393M cDNA does not show a detectable increase in the secreted A β ₄₂/A β ₄₀ peptide ratio [35], suggesting a possible new mechanism for presenilin mutations apart from A β processing as traditionally proposed. Supporting this hypothesis, a *PSEN1* polymorphism was found to be associated with decreased AD risk among carriers of the *APOE*4 allele [36]. Interestingly, presenilin mutations may also be useful for diagnosis, as cerebrospinal fluid analysis in sporadic AD cases showed a causative L424R *PSEN1* mutation, as well as a correlation of increased total tau and phosphorylated-tau levels with decreased A β ₄₂ [37], suggesting again that presenilin mutations could be interacting with the other disease factors of AD, such as tau depositions. While a number of publications

demonstrate that PSEN mutations result in the production of A β peptides that contribute to the neurodegeneration seen during AD, it is also clear that other mechanisms are involved.

Mutations in the A β sequence probably contribute to the formation of the pathological structures seen in AD, at least in the rare instances where they occur. The support for this concept includes recent data that showed single residue mutations P7S decreased the thermodynamic stability and greatly enhanced its capacity to form amyloid-like fibrils in systemic amyloid light-chain amyloidosis [38]. Similarly, another report shows that a single tyrosine residue difference in the stop codon in the gene encoding the prion protein C-terminus may significantly affect the site of A β deposits [39].

In addition to A β , deposits mainly composed of tau protein constitute the second prominent pathological feature of AD. Over 40 mutations in the tau gene have been identified, mainly in families with autosomal-dominant frontotemporal dementia and parkinsonism phenotype linked to chromosome 17, but also in sporadic families with Pick's disease and AD. Specifically, mutations in tau have appeared to result in an imbalance in the ratio of the synthesized 3R and 4R tau isoforms, which stimulates protein aggregation and initiates neurodegeneration [40]. The aggregation of 4R-tau isoform has been found to be significantly higher than 3R isoform in *in vitro* aggregation assays [41] and is predominant in the typical deposits (NFTs) observed during AD [42].

Pursuing this further and incorporating many confounding risk factors for the disease, a genotyping of AD cases of single nucleotide polymorphisms has been published in a public database called Alzgene, naming close to 600 genes and 1900 polymorphisms [43]. The majority of the variations remain to be mechanistically related to the disease; nevertheless, this opens an interesting opportunity to characterize the relationships between genetics and AD development. Beyond individual genes as noted above, additional susceptibility regions, including those on chromosomes 9, 10 and 12, were found to be related to AD [44], although the precise risk remains unproven. Overall, since 1990, no more than six genes have been related to the development of AD; however, they only account for a minority of AD cases around the world. Notably, the majority of the genes discussed so far that are involved in the disease are related to the deposition of A β , lesions that characterize disease development and progression [45,46]. It should also be pointed out that although genetic factors do not account for all AD cases, their effects may be regarded as causal when they are present.

Fibrillar A β depositions: cause or effect?

Identification of the histochemical properties of senile plaque cores, with A β being the major protein component, understandably raised the possibility of a protein-mediated neurotoxic process that laid the foundation for a hypothesis that has changed only marginally in the past 20 years. The perceived strength in the amyloid cascade hypothesis is reflected in the scientific literature, which is voluminous and dominated by experimental studies that strictly adhere to the following assumptions: A β accumulates in senile plaques in the AD brain; specific point mutations in the gene for APP cause familial, early-onset AD; and, increased copy numbers of APP in some cases of Down's syndrome lead to relatively early A β deposits and pathology generally associated with AD [47].

Hence, it is extrapolated that A β synthesis and deposition and, in particular, a relative increase in the synthesis and deposition of 'pathogenic' A β_{42} , is the 'rate-limiting' factor in AD pathogenesis, while the accompanying pathologies (neurofibrillary pathology, neuronal loss and synaptic dysfunction) are secondary, end-organ phenomena. Such deposition is also closely related to genetic mutations in the presenilins, and, given that presenilins are necessary components of the γ -secretase complex in Notch proteolysis, thus provides

evidence that presenilin-mediated β -secretase cleavage of APP (necessary along with β -secretase for cleavage of APP and production of A β_{42}) is a causal process [48–52]. That said, genetics might also be considered as only one aspect in the A β deposition cascade and, thus, its deposition is a compensatory response during the neurodegenerative scenario rather than a causal factor itself [46,53]. For example, by using cultured cortical neurons, A β induces apoptosis through the JNK–c-Jun–FasL–caspase-dependent extrinsic apoptotic pathway [54]. Furthermore, A β modulates redox factor-1, thus affecting both the cell death signaling pathways and DNA repair [55]. A β induces oxidative stress, predominantly via mitochondria, and also affects cholesterol balance [56], and NMDA and oligomeric A β_{42} can induce reactive oxygen species production in cortical neurons through activation of NADPH oxidase [57]. A β also binds with nanomolar affinity to the cellular prion protein, inducing synaptic dysfunction by affecting long-term potentiation [58]. The finding that A β oligomers decreased RACK1 distribution in the membrane fraction of cortical neurons suggests that the A β -induced loss of RACK1 distribution in the cell membrane may underlie the impairment of muscarinic regulation of PKC and GABAergic transmission [59]. Regarding this issue, application (1 h) of A β_{42} or A β_{25-35} (proto-)fibrils but not oligomers induced significant membrane depolarization of pyramidal cells and increased the activity of excitatory cell populations as measured by extracellular field recordings in the juvenile rodent brain, confirming the pathogenic significance of A β fibrils [60]. However, others suggest that monomers and oligomers are more toxic than the fibrillary structure itself, since upon A β_{42} fibrillization, neurotoxicity is reduced [61], suggesting that the aggregated form of A β is protective rather than pathological. Furthermore, oligomers directly extracted from AD patients are able to inhibit long-term potentiation, enhance long-term depression and reduce dendritic spine density in normal rodent hippocampus, suggesting that A β dimers are, as matter of fact, synaptotoxic [62]. It was also found that A β oligomers, by promoting reactive oxygen species, trigger neuronal damage through NMDA receptor-dependent calcium flux, emphasizing a synaptotoxic role [63]. Taken together, despite the dichotomy between the actions of the A β species, it is clear that A β is playing a crucial role during neurodegeneration, with actions that could be considered either a cause or effect.

Fibrillary tau deposition: cause or effect?

The NFTs, mainly comprised of the pathologically self-aggregated tau protein, were characterized around the same time [64] or even earlier than the A β deposits [65,66]; however, until the presence of NFTs along the hippocampal area was found to be congruous to the cognitive decline seen in AD patients, and even since, tau phosphorylation is generally regarded as a downstream event [67–69]. Several post-translational events of the tau protein, such as phosphorylation [70–72], conformational changes [73,74] and cleavage [18], are specifically noted in AD, possibly resulting from the following pathological behavior of modified tau protein: lack of microtubule associations, migrations to the cell cytoplasm and self-aggregation. A growing body of data supports the hypothesis of post-translational events as causative for the tau aggregation seen during AD. In this regard, phosphorylation of tau protein at residues 262, 293, 324 and 356 was found to modify the structural properties in repeats 1 and 2, in particular for Gln265–Lys26, which are in close proximity to Ser262 [75], the phosphorylation site that most strongly attenuates binding to microtubules [19]. Thus, phosphorylation of truncated tau protein at residues Ser396/404 was found to attenuate the ability of tau to stabilize the microtubules [76], suggesting that two or more events are needed for the protein to show its pathological effect. In the same vein, events that truncate tau protein have been found to affect the normal capacity of the tau protein to confer stability to the microtubules, and instead lead to self-aggregation into the NFTs [77,78]. In the same regard, the conformational non-native α -structure is related to the microtubule repeat tau protein domain and directly associates with filament development at the start of paired helical filaments formation [79].

While the relationship and pathological consequence between post-translational modification of tau protein and NFT formation is undeniable, what is causative is not so clear. In an attempt to address this issue, several studies suggested models accounting for the appearance of the three main events: phosphorylation, conformational changes and cleavage. Indeed, these translational events were proposed as sequential steps in a tau pathological processing model [80–83]. These events appeared in a chronological fashion, thus fostering an interesting debate about which step was responsible for tau aggregation. Ultimately, phosphorylation was proposed as the earliest event in tau processing despite the need to explain its origins [83]. That is, phosphorylation itself requires other events, such as kinase deregulation, in which oxidative stress and metabolic homeostasis (discussed later) clearly play a role. In fact, some authors have suggested that the NFT deposits could just be a dynamic reservoir that reflects the kinetics of the disease [84].

From this perspective, it is clear that the modified tau protein is dependent on earlier events, and, therefore, its fibrillar deposits are not a cause but are rather an effect of the disease.

Oxidative stress & metabolic malfunction: is this the strongest candidate for a cause?

By definition, detection of damage resulting from reactive oxygen species is indicative of oxidative stress [85]. Reactive oxygen species are a byproduct of cellular oxidative metabolism and are generated in the mitochondria during oxidative phosphorylation as molecules with unpaired electrons, such as superoxide (O_2^-). Indirect evidence of cellular oxidative stress is the increased expression of molecules involved in oxidant defense, such as heme oxygenase, superoxide dismutases, glutathione transferases and catalase [85]. It is important to note that neurons displaying signs of oxidative stress are not necessarily succumbing to oxidative stress, but may be adapting by way of oxidant defenses. Thus, neurodegenerative disorders where oxidative stress is postulated to play a role are associated with mechanisms that maintain a balance between oxidative stress and adaptation to this stress, ultimately reflecting the ability of living systems to dynamically regulate their defense mechanisms in response to oxidants. In the case of disease, the normal balance between production of and defense against oxidative stress has been challenged. These challenges become clear during the AD process, and include a strong presence of increased sulfhydryls, induction of heme oxygenase-1 and increased expression of Cu/Zn superoxide dismutase [86–88], which indicates loss of homeostasis. Thus, such oxidative stress is reflected in several targets, such as DNA alteration [89–91], kinase deregulation [92–94], metabolic dysfunction [95,96] and cell cycle perturbation [97,98]. These phenomena provide a case for protein malfunction such as occurs with A β [99] and tau protein aggregation, and, therefore, it has been suggested that neurons actually respond to oxidative stress by increasing A β production [100], an increase associated with a consequent reduction in oxidative stress [101,102]. Similarly, A β itself can act as a genuine antioxidant, such as a potent superoxide dismutase [103]. Therefore, AD cases with APP mutations lose effective antioxidant capacity (due to mutation-driven protein dysfunction), while the extensive A β deposits themselves are signatures not of neurotoxicity *per se*, but of oxidative imbalance and an oxidative stress response. This is consistent with the data that A β deposits begin to appear around the age of 40 years [102].

Relating oxidative stress and tau protein, phosphorylation plays a pivotal role in redox balance, and it is, therefore, not surprising that oxidative stress, through activation of MAPK pathways, leads to phosphorylation [104–106], or that conditions associated with chronic oxidant stress, such as AD, are associated with extensive phosphorylation of targets such as tau protein.

Notably, oxidative stress extends its effects beyond AD-related proteins; the formation of hydroxyl radicals affects all cellular macromolecules, including RNA [12]. While RNA alteration may lead to protein sequence anomalies [107], RNA destruction is more easily accommodated in cellular metabolism than is damage to DNA [13,108] or enzyme active site destruction.

Further relating oxidative stress to the cell cycle perturbation, it has been found that impairment of nucleolar function in response to stress is accompanied by perturbation of nucleolar structure, cell cycle arrest and stabilization of p53 [109]. The nucleolar target for downregulation of rDNA transcription is TIF-IA, an essential transcription factor that modulates the activity of RNA polymerase I. Upon stress, TIF-IA is phosphorylated by JNK2, and phosphorylation prevents TIF-IA from interaction with polymerase I, thereby impairing transcription complex formation and rRNA synthesis. Furthermore, stress-induced inactivation of TIF-IA is accompanied by translocation of TIF-IA from the nucleolus to the nucleoplasm [98]. Additionally, oxidative balance has been related to upregulation of Cdc42/Rac in select neuronal populations in cases of AD, which suggests an oncogenic process during AD [104,110,111].

Overall, the establishment that oxidative stress is linked to cell cycle re-entry is probably one of the earliest insults encountered in vulnerable neurons, as well as kinase deregulation, and with further research support, this may be considered a causal event [112,113].

Potential therapeutic targets

Cholinesterase inhibitors are one of the therapeutic approaches used for AD, for which the rationale is as follows: inhibition of cholinesterase increases extracellular levels of brain acetylcholine and improves cognitive processes as a consequence, significantly so in experimental animals [114]. However, when they are used in AD patients the results are much less efficient in terms of improvement; indeed, some researchers have tried to explain why this treatment does not show significant memory improvement, postulating that other events, such as alteration of other neurotransmitter systems and diffuse synaptic loss, are also playing an important role [115]. That said, attacking just one event would not be enough; therefore, some researchers have tested combined therapies, such as cholinergic and adrenergic drugs in rat models, but unfortunately, the data have not shown an advantage for their use as a therapeutic alternative [114].

Using A β as a pharmacological target has also been tested [116]. Many efforts have been made in order to approach the A β therapeutic target rationale. Indeed, data have emerged from novel strategies, such as intracerebral sequestration of A β by an anti-A β monoclonal antibody 266 that inhibits the accumulation of multi-meric toxic A β . Such data, however, have only recently been tested in rat models [117]. In addition, the newly proposed DNA A β ₄₂ trimer immunization of mice that was developed to produce specific Th2-type antibodies [118], which in principle should reduce A β deposition, has not yet been demonstrated. On the other hand, it should be pointed out that many animal models have shown improvement after immunization, despite data in humans that have been disappointing [119].

Another specific drug that inhibits the A β aggregation is 3-amino-1-propane sulfonic acid (tramiprosate, 3-APS, AlzhemedTM); however, a recent study has shown that it also favors tau aggregation [120], reinforcing the notion that multi-targets should be carefully considered.

Antioxidant use has also entered into the field and, in this regard, population studies have reported that intake of antioxidants or poly-unsaturated fatty acids may be associated with a

reduced incidence of dementia, and it has been reported that people who are mentally, socially and physically active have a reduced risk of cognitive impairment [121]. However, results from randomized trials of risk factor modification have been mixed and have not demonstrated any conclusive evidence of improvement for AD patients.

Since novel therapies have not yet proven successful, other strategies that address the increased complexities between all the events related to the disease should be pursued.

Summary – jumping to a risky but necessary conclusion

The original goal of this report was to discuss the various and probably related AD pathogenic theories, encompassing genetics, metabolic dysfunction, cell cycle re-entry, fibrillar deposits or oxidative stress, in an attempt to segregate those aspects that more accurately reflect cause versus those that are downstream effects. In spite of the numerous studies and the vast new knowledge of molecular pathogenesis, the empirical features of the pathological progression still appear most relevant and most accurately reflect the etiopathogenesis. In this regard, and according to the data resulting from the study of human disease, such as, cell models and transgenic models, all the events seems to be followed or even promoted by previous events, such that they are eliminated as potential causes of disease. Consistent with such an analysis, oxidative stress appears closest to a causal event, acknowledging that previous events may be promoting the oxidative stress itself. However, it should be noted that while not all the events are, strictly speaking, causal, they may nevertheless affect disease progression (Figure 1). This may explain why the efforts in treatment have been singularly unsuccessful, but nevertheless may be useful in a ‘cocktail’ approach [122]. Ultimately, we propose that future attempts at AD treatment should recognize the multitude of complex, yet inter-related pathogenic mechanisms, and perhaps new promising data will emerge, if not by hypothesis-driven constructs, then by accident.

Expert commentary

For more than a decade, the field of AD has focused on two hypotheses positing A β and/or tau phosphorylation as key pathogenetic mediators. While hypothetical constructs, these hypotheses have dictated the direction of the field. Recent experimental data, coupled with a number of clinical trial failures targeting these hypotheses, are now casting doubt that these hypotheses are fundamentally flawed. That is, the role of upstream mediators of disease, such as oxidative stress, should be investigated with the hope of establishing an effective means to reduce and/or prevent disease.

Five-year view

As much as one swallow does not make a summer, one failure should not lead to an abandonment of amyloid as a target. However, over the next 5 years, the amyloid hypothesis will have been repeatedly tested in clinical trials. Multiple failures will not be for a lack of effort, and should therefore lead investigators to re-organize their mindset.

Additionally, over the next 5 years, it is likely that clinical trial data from other therapeutic targets will be available. Success in any one of these areas may lead to new directions and increased attention to ‘new’ and perhaps more promising therapeutic pathways.

Key issues

- Distinguishing causal phenomena in Alzheimer’s disease (AD) from their associated epiphenomena is an essential step toward establishing a universal avenue to disease control.

- The pathological hallmarks that characterize the disease, such as A β and neurofibrillary/tau tangles, are not primary events in disease pathogenesis, although they indeed mediate neurodegeneration.
- Although only relevant in cases of familial, early onset AD, genetic mutations in *APP*, *PSEN1/2* and *APOE* genes are responsible for the origins of disease pathogenesis (i.e., oxidative stress, cell cycle aberrations and amyloid- β [A β] deposition).
- A β is initially instituted in the brain as a compensatory response to neuronal environmental changes (unless otherwise produced from point mutations), and it induces its destructive effects only after substantial aggregation and overaccumulation.
- A β is thus a secondary aspect to AD development and not a primary event.
- Similarly, tau phosphorylation and deposition is merely a secondary event in disease pathogenesis that results from environmental changes in the AD brain.
- Oxidative stress is the best candidate for a primary causal factor in the neurodegeneration in AD.
- Imbalances in the generation of reactive oxidative species, due to high demand of the brain for oxidative phosphorylation, induce oxidative stress on neuronal macromolecules (i.e., DNA, RNA and proteins, phospholipids) and require the brain to initiate antioxidant compensatory mechanisms that render the brain vulnerable to other damage.
- This damage includes cell cycle aberrations, A β overaccumulation and neurofibrillary tangle aggregation: events that then mediate further neurodegeneration via autoimmune response, neuroinflammation, further oxidative stress and so on.
- Oxidative stress and its immediate products are thus an avenue for future therapeutic intervention.

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Figure 1. Tentative model for protein deposition and oxidative stress relationship

Soluble amyloid- β oligomers could activate ionic channels (Ca^{2+}) leading to an increase of Ca^{2+} entry prior to amyloid- β fibrilization. Increased Ca^{2+} additionally influences mitochondria and metabolic enzyme production of reactive oxygen species that in turn could affect proteins, DNA and lipids, and subsequently lead to necrosis, apoptosis and altered proteolysis – all events directly relating to tau processing and deposition. Additionally, reactive oxygen species abnormally activate kinases and phosphatases, which also directly affect tau processing and deposition. AA: Arachidonic acid; JNK: c-Jun N-terminal kinase; NOS: Nitric oxide synthase; PLA_2 : Phospholipase A2; PP2A: Protein phosphatase 2A; SOD: Superoxide dismutase.