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Reassessing the Amyloid Cascade Hypothesis of Alzheimer's Disease

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Abstract

Since its inception, the amyloid cascade hypothesis has dominated the field of Alzheimer's disease (AD) research and has provided the intellectual framework for therapeutic intervention. Although the details of the hypothesis continue to evolve, its core principle has remained essentially unaltered. It posits that the amyloid- β peptides, derived from amyloid precursor protein (APP), are the root cause of AD. Substantial genetic and biochemical data support this view, and yet a number of findings also run contrary to its tenets. The presence of familial AD mutations in APP and presenilins, demonstration of A β toxicity, and studies in mouse models of AD all support the hypothesis, whereas the presence of A β plaques in normal individuals, the uncertain nature of the pathogenic A β species, and repeated disappointments with A β -centered therapeutic trials are inconsistent with the hypothesis. The current state of knowledge does not prove nor disprove the amyloid hypothesis, but rather points to the need for its reassessment. A view that A β is *one* of the factors, as opposed to *the* factor, that causes AD is more consistent with the present knowledge, and is more likely to promote comprehensive and effective therapeutic strategies.

Introduction

With a rapidly aging population in the developed world and increasing life expectancy in the developing world, Alzheimer's disease (AD) is becoming a growing problem around the globe. AD is a slowly progressing, heterogeneous neurodegenerative disorder of uncertain etiology. Neurologically, it is initially manifested as a series of mild cognitive impairments, deficits in short-term memory, loss of spatial memory, and emotional imbalances. As the disease progresses, these symptoms become more severe, and ultimately result in total loss of executive functions. Pathologically, the disease is characterized by the presence of extracellular plaques of amyloid- β peptides (Glennner and Wong, 1984a, b; Masters et al., 1985) and intracellular tangles of hyperphosphorylated tau protein (Ballatore et al., 2007; Braak and Braak, 1998). The spatial and temporal connections between these two pathological hallmarks are not completely understood. The plaques first appear in the frontal cortex, and then spread over the entire cortical region, while hyperphosphorylated tau and insoluble tangles initially appear in the limbic system (entorhinal cortex, hippocampus, dentate gyrus) and then progress to the cortical region. The pioneering work of Braak and Braak suggests that the tangles appear before the plaque deposition is observed in AD brains, and that tangle pathology is more closely associated with disease severity than the plaque load (Braak and Braak, 1998; Giannakopoulos et al., 2003; Gosche et al., 2002; Josephs et al., 2008).

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About 5% of AD cases are 'familial' (fAD) with mutations found in amyloid precursor protein (APP) or in presenilin genes. Presenilin 1 (PS1) and presenilin 2 (PS2) are the catalytic core of the γ -secretase complex (De Strooper, 2003; Selkoe and Wolfe, 2007), and they cleave APP within the membrane-spanning domain generating A β peptide and APP intracellular domain (AICD). Little is known about the biological significance of AICD other than that it possesses transcriptional regulatory activity (Cao and Sudhof, 2001; Gao and Pimplikar, 2001; Zhang et al., 2007) and alters signaling pathways (Leisring et al., 2002; Ma et al., 2008; Ryan and Pimplikar, 2005). Most mutations in APP or presenilin invariably alter APP processing, often resulting in increased levels of longer form of A β (A β 42). The A β 42 peptide is more prone to aggregate and to form plaques, which are also frequently found in the brains of patients with sporadic AD. The familial AD afflicts patients in the 4th or 5th decade of life, whereas the sporadic AD cases are found in people in their 7th or 8th decade. Other than the age of onset, both forms of AD show similar neurological and histopathological features, and are thought to represent the same disease. Both APP and tau are integral to AD pathogenesis; mutations in APP and PS1 cause AD, and tau tangles are better correlated with the disease severity.

The Amyloid cascade hypothesis and its many avatars

Although the exact cause of AD has been the subject of considerable debate, the amyloid hypothesis remains the best defined and most studied conceptual framework for AD. The presence of amyloid plaques, as originally described by Alois Alzheimer in 1907, is considered as the defining characteristic of AD. Identification of A β peptides, the major constituents of the plaques, as the proteolytically derived products of APP (Glenner and Wong, 1984a, b) and cloning of the APP gene (Kang et al., 1987) allowed the disease to be examined at biochemical and molecular levels. Subsequently, mapping of several fAD mutations to the APP gene (Owen et al., 1990), the association of AD with Down's syndrome (which results from trisomy 21 and APP gene locus is present on chromosome 21), and higher prevalence of AD with increased copy number of APP, all established the primacy of APP in AD pathogenesis (Glenner and Wong, 1984a; Rovelet-Lecrux et al., 2006; Sleegers et al., 2006). The central role of APP in AD etiology was further confirmed by the identification fAD mutations in PS1, which cleaves APP and generates A β and AICD.

As originally proposed in the early 90's (Hardy and Higgins, 1992; Selkoe, 1991), the essence of the amyloid hypothesis is that the increased production or decreased clearance of A β peptides causes the disease. Accumulation of the hydrophobic A β 40 and A β 42 peptides results in aggregation and formation of insoluble plaques, which trigger a cascade of deleterious changes, resulting in neuronal death and thus causing AD. Over time, this hypothesis has undergone alterations primarily in the description of the nature of pathogenic A β that is proposed to initiate deleterious events and cause AD (Figure 1). The original idea that the plaques are pathogenic has currently fallen out of favor because of two primary reasons. First, as indicated earlier the plaque load does not correlate well with the degree of dementia in humans (Terry et al., 1991), and many AD patients with severely impaired memory show no plaques at post mortem analysis. Moreover, many mouse models of AD show memory deficits long before the plaques are observed in the brain (Lesne et al., 2008). Second, recent advances in neuroimaging techniques *in vivo* (such as 11C-PiB retention) have shown the presence of robust plaques in otherwise cognitively normal people (Nordberg, 2008; Villemagne et al., 2008). Although it is possible that the PiB-positive individuals may represent individuals who are at high risk for AD, these findings, at a minimum, show that the presence of plaques does not necessarily equate with memory deficits. These observations have led to thinking that perhaps the insoluble plaques do not trigger the pathological events, and may be benign or even protective in nature (Caughey and Lansbury, 2003). There is also emerging interest in the observations that A β accumulates intracellularly in mouse models of AD and in human AD brains and could contribute disease progression (Gouras et al., 2000; Knobloch et al., 2007; LaFerla et al.,

2007). However, much remains to be known about its abundance relative to extracellular deposits, its location (intracytoplasmic or intravesicular), and how it could trigger the toxic effects.

A large portion of the fAD cases is accounted for by mutations in the PS1 gene (Cruts and Van Broeckhoven, 1998). PS1, a membrane protein with multiple spanning domains, associates with three other membrane proteins to form the γ -secretase complex. Unlike in APP, the fAD mutations in PS1 are scattered over the entire length of the molecule. Many of these mutations result in altered cleavage of APP, causing increased production of the longer A β 42 peptide, which is more prone to aggregate (Suzuki et al., 1994) and is shown to be more toxic *in vitro*. Since A β 42 levels are found to be higher in AD patients, it was proposed that increased levels of A β 42 triggered the cascade of the deleterious events resulting in AD (Younkin, 1995). Although, many fAD mutations in APP or PS1 result in increased A β 42, some mutations in PS1 do not increase the A β 42 levels, but rather decrease the A β 40 levels. This has led to yet another proposal that an increase in the 42/40 ratio, rather than the absolute levels of A β 42, is pathogenic, and triggers the deleterious events leading to the disease. This view is supported by the observation that increased 42/40 ratio is generally inversely related with the age of onset of AD (Bentahir et al., 2006).

Finally, the latest idea that higher order soluble aggregates of A β – the oligomers – are the disease causing pathogenic agents has attracted a lot of interest (Glabe, 2005; Klein et al., 2001; Walsh and Selkoe, 2004, 2007). Many groups have identified a number of poorly characterized but biochemically distinct forms of A β oligomers, and demonstrated their toxicity using *in vitro* and *in vivo* model systems. Distinct oligomeric species have been isolated from the brains from mouse models of AD (Lesne et al., 2006) and also from human AD brains (Shankar et al., 2008). The latter study also showed that the dimeric oligomers isolated from human AD brains potently inhibited long-term potentiation and enhanced long-term depression with IC₅₀ values in the picomolar range. Very little is known about how these distinct oligomers form *in vivo*, or whether A β 42 oligomers are more toxic than A β 40 oligomers, or how they trigger the deleterious changes.

From genetics to cell biology- evidence galore!

Studies from multiple disciplines have provided what seems like overwhelming support for the amyloid hypothesis. The supporting evidence has come from divergent areas such as genetics, histopathology, cell biology and animal models. These data have been discussed in detail in many excellent reviews (Crouch et al., 2008; Hardy and Selkoe, 2002; Price et al., 1998; Wakabayashi and De Strooper, 2008; Walsh and Selkoe, 2007; Yankner and Lu, 2008), and only the salient points are summarized below.

Genetics

Genetic studies of familial AD provide perhaps the strongest evidence supporting the amyloid hypothesis. Mutations in APP, PS1 and PS2 account for all the cases of fAD, whereas the E4 allele in the ApoE gene increases the risk of getting the disease. To date, approximately 180 fAD mutations have been identified in PS1, 20 fAD mutations in PS2 and 36 fAD mutations in APP (www.molgen.ua.ac.be/ADMutations). Most of the mutations in APP and presenilins seem to increase A β generation and/or increase A β 42 levels. Mutations in APP are localized at or near the cleavage sites that give rise to A β , although some mutations are mapped in the middle of the A β peptide and are thought to increase fibrillization. Mutations in PS1 and PS2, unlike those in APP, are distributed throughout the molecule. The question whether these mutations represent a toxic gain-of-function or a loss-of-function of APP and presenilins remains unsettled (De Strooper, 2007; Hardy, 2007; Van Broeck et al., 2007; Wolfe, 2007).

Pathology

Histopathologically, A β plaques and tau tangles are considered the diagnostic hallmarks of AD. Thus, by definition A β plaques are the essential component of AD pathogenesis. Indeed, one carefully controlled study with low sample size showed strong correlation between cognitive dysfunction and A β plaques in the entorhinal cortex (Cummings et al., 1996). However, detailed examination of a large number of AD brains upon autopsy has shown that tau tangles appear initially in the limbic system of the brain and spread to the cortex as the disease progresses. A β plaques, on other hand, appear first in the cortical regions and spread to the rest of the brain as the disease progresses (Braak and Braak, 1998).

Cell Biology

Tissue culture studies *in vitro* have proved valuable in demonstrating the neurotoxic nature of A β peptides. A number of early studies showed that when added to neuronal cultures, fibrillar A β produced deleterious changes such as apoptosis, neuronal cell death, and synaptic and dendritic loss. By contrast, monomeric or non-fibrillar A β was incapable of producing such changes. These deleterious events were also observed *in vivo* when fibrillar A β was injected in mouse brains. However, as pointed out above recent studies have implicated the soluble oligomeric A β , rather than the fibrillar A β , to be the toxic moiety.

Animal models

Many groups have generated mouse models of AD that develop A β plaques and exhibit memory deficits. These transgenic mouse models, based on overexpression of fAD mutant APP or PS1 (or both), have yielded significant information on AD pathogenesis, and have been used to evaluate the efficacy of both immune and non-immune therapeutic strategies. In some cases, reduction in total A β or A β plaque load was accompanied by improved memory function in behavioral paradigms (Radde et al., 2008).

Would the real oligomers please stand up?

The idea of soluble 'A β -oligomers' as the toxic, disease-causing agent is receiving increasingly greater attention. A β peptides are amphiphilic in nature, with the first 28 residues being polar and last 12 (or 14 in A β 42) being nonpolar. At neutral pH, the polar part of the peptide contains 6 positively charged and 6 negatively charged residues, further exaggerating the polarity of differences between two termini of A β . Because of this amphiphilic property, A β aggregates and forms higher-order oligomers *in vitro* (Bitan et al., 2003; Teplow et al., 2006). Such oligomers have also been isolated from culture medium (Walsh et al., 2005), brain extracts of AD patients (Shankar et al., 2008) or AD mouse models (Lesne et al., 2006). Yet, as discussed below, aggregation of the amphiphilic A β is extremely sensitive to experimental manipulations raising a possibility that the conclusions of some of the investigations may be open for interpretation.

The molecular pathway by which A β forms soluble oligomers and insoluble fibrils and protofibrils *in vivo* is not clear (Figure 2). The currently available information is based on two experimental approaches. The *in vitro* approach involves the use of synthetic A β peptides under controlled conditions (Teplow et al., 2006), whereas the *in vivo* approach relies on isolating such oligomers from tissue culture media, brain extracts, etc. The biophysical and computational approaches have revealed a complex pattern of A β assembly, and have uncovered subtle differences between oligomerization of A β 40 vs. A β 42 (Urbanc et al., 2004). A common picture emerging from the use of multiple experimental approaches suggests that A β exists in a 'natively unfolded' conformation, and undergoes nucleation-dependent polymerization. It is suggested that A β forms hexameric 'paranuclear' units, which self-

associate end-on-end to form beaded protofibrils (Roychaudhuri et al., 2008). These protofibrils further aggregate to form fibrils, ultimately leading to plaque formation.

Using *in vitro* approaches, various groups have formed discreet oligomeric structures from pure, synthetic A β peptides. ADDLs (A β -derived diffusible ligands) are formed from A β 42 using special solvent conditions, and seem to be composed of 12 monomers (Catalano et al., 2006; Klein, 2002; Roychaudhuri et al., 2008). By atomic force microscopy, these oligomers appear as globular structures of 6 nm. On the other hand, A β 42 forms distinct 12-mer units in the presence of SDS called 'globulomers', with the C-terminal region of A β forming the hydrophobic core (Gellermann et al., 2008). However, these globulomers do not form fibrils. Larger A β -oligomers, comprising 15–20 monomeric units have also been formed *in vitro* (Deshpande et al., 2006). In addition, several larger assemblies that form pore-like structures with diameter up to 15 nm have been described *in vitro* using synthetic A β peptides (Hoshi et al., 2003). Thus, by employing different experimental conditions, distinct oligomeric structures can be formed from A β *in vitro*.

So, what happens under *in vivo* conditions? It is obvious that the *in vivo* environment is very different from that found *in vitro*, and the hydrophobic nature of A β makes it doubtful that the pathways of A β assembly observed *in vitro* also work *in vivo*. Not surprisingly, the A β oligomers isolated from the biological systems rarely resemble those formed *in vitro* from synthetic peptides. For example, the naturally secreted, A β -oligomers have been isolated from tissue culture media of cells stably expressing fAD mutant APP_{V717F} protein. However, unlike the large oligomers formed *in vitro* (12-mers and larger), these oligomers are small, mostly dimers and trimers (Townsend et al., 2006). Such dimers and trimers have been reported in the brains of AD patients, but not normal individuals. Interestingly, the neurotoxicity was associated only with the A β dimers and not with the higher oligomers (Shankar et al., 2008). In contrast, another set of studies showed that neurotoxicity was associated not with the smaller dimeric/trimeric aggregates, but with much larger oligomers termed A β *56 (Cheng et al., 2007; Lesne et al., 2006). These oligomers, possibly composed of 12 monomers, are first observed in a transgenic mouse model at the approximate age when memory deficits become apparent. Unlike the pathogenic dimers/trimers, so far there have been no reports indicating the presence of A β *56 in AD brains but not normal brains.

While it is important to appreciate the technically challenging nature of the A β oligomerization studies, it should be recognized that they are fraught with experimental artifacts (Rahimi et al., 2008). In a series of careful studies, Teplow and colleagues showed how A β could be artifactually formed into oligomers simply by experimental manipulations (Bitan et al., 2005; Teplow et al., 2006). Thus, it remains a serious concern as to whether A β oligomers are induced during isolation procedures or actually pre-exist in the biological samples prior to the experimental manipulations. This argument becomes even more plausible (Rahimi et al., 2008) when one considers that different groups, employing different isolation procedures, arrive at different oligomeric structures from biological samples, e.g. A β *56 (Lesne et al., 2006) vs. dimers/trimers (Shankar et al., 2008) vs. the ADDLs (Catalano et al., 2006; Lesne et al., 2006; Shankar et al., 2008). Nonetheless, it is interesting that these groups were not able to isolate the respective oligomeric species from normal brains. Thus, formation of A β oligomers from the AD brains may not be simply due to the isolation protocols employed. In any case, from the discussion above it should become obvious that despite the growing attention, the biology and chemistry of 'oligomeric A β ' is fraught with experimental artifacts increasing the odds of arriving at erroneous conclusions.

Reassessing the amyloid hypothesis: is the glass three-quarters full or the wrong size?

The amyloid hypothesis dominates the AD research field because it is the best described and most scrutinized model, and is supported by a large volume of data. Nevertheless, it is not universally accepted in the field, and if anything criticism of the hypothesis is becoming more pointed. One reason for this development is the accumulation of new data that are inconsistent with the main tenets of the hypothesis. Moreover, as discussed below, a strong case can be made that even the existing supporting data may not be as strongly supportive as initially perceived.

Genetics

The presence of mutations in APP and presenilins has been considered amongst the strongest evidence in support of the hypothesis (Hardy and Selkoe, 2002; Price and Sisodia, 1998) but they are not the evidence that A β is the prime cause of AD. Presently, over 225 fAD mutations in APP, PS1 and PS2 combined have been reported that initiate the disease at various ages. However, different mutations result in different molecular outcomes- some increase total A β , some increase A β 42 selectively, some do not affect A β levels, while some others selectively decrease A β 40 without affecting A β 42 levels (Van Broeck et al., 2007). Similarly, with about 180 distinct mutations distributed throughout the PS1 molecule, it is difficult to see how all of them can result in a single molecular outcome, namely increase in A β 42 levels (Shioi et al., 2007). Thus, taking into account that APP is the substrate and PS1 is the protease, the common denominator amongst all the mutations is that they *alter* APP processing, and increase in the A β 42 levels is just one of the *many* possible consequences. This point of view remains consistent with the genetics of AD, but does reduce the importance of A β as a causative agent. In addition, many studies have shown that mutations in PS1, which account for the majority of fAD cases, also cause neuronal dysfunction by pathways that are independent of APP and A β (Baki et al., 2008; Baki et al., 2004; Kallhoff-Munoz et al., 2008; Neve, 2008; Shen and Kelleher, 2007; Shioi et al., 2007). Thus, there is a substantial body of data indicating that PS1 mutations by themselves can trigger the toxic events, and that the increased A β load and plaques may be a secondary effect, perhaps less consequential to disease causation and progression.

Pathology

The original tenet of the amyloid hypothesis that the plaques cause the disease is now falling out of favor. The shift in thinking can be traced to a number of factors. First, exhaustive histopathological observations showed a poor correlation of the 'plaque load' with the degree of dementia in AD patients (Terry et al., 1991). Second, the early observations that many non-demented normal individuals had significant plaque load upon autopsy has now been confirmed by live PiB imaging. Third, many mouse models of AD that overexpress fAD mutant APP show memory deficits prior to plaque depositions. The J20 transgenic mouse line expressing Swedish (K670N/M671L; numbering according to APP₇₇₀) and Indiana (V717F) mutations shows robust plaque pathology and memory deficits. Interestingly, insertion of an additional mutation in the APP cytoplasmic tail (D664A; numbering according to APP₆₉₅) ameliorated the memory deficits without any reduction in the plaque pathology (Galvan et al., 2006). This finding proves that plaques alone do not necessarily underlie memory deficits, as also confirmed in Tg2576 line, another mouse model of AD (Lesne et al., 2008). Finally, data from recent human studies showed that in a small number of AD patients, removal of the plaques by vaccination did not result in improved memory function (Holmes et al., 2008). Such findings, together with studies suggesting neurotoxicity is associated with the soluble oligomers of A β , have started to displace the notion that plaques are the cause of the disease.

Cell biology

A large body of evidence shows that synthetic A β , when added to neuronal cultures or injected into mouse brains, causes deleterious events such as activation of kinases, tau hyperphosphorylation, oxidative stress, neuroinflammation, apoptosis, etc. Thus, the toxic effects of A β are unambiguously demonstrated in various experimental paradigms. However, considering the amphiphilic structure of A β , which imparts detergent-like properties, the toxicity reported with A β peptides is not surprising. A more relevant pathophysiological question is—does this represent what could be happening in human AD? A vast majority of these studies have used micromolar or higher concentrations of purified A β 40–42, which are orders of magnitudes higher than observed inside the body. Moreover, because of its hydrophobic nature, A β peptides inside an organism will not be free, but will be associated with other hydrophobic proteins. The disease relevance of several early studies conducted using A β 25–35 is even less clear since this peptide has not been observed inside a living organism (Du et al., 2007). Also, the ICV injection paradigm limits the relevance of the studies because it is difficult to imagine a pathophysiological situation where an organism receives such an acute bolus of purified A β . In short, although A β undoubtedly possesses toxic properties *in vitro*, it is difficult to prove that this is also true in the pathophysiological conditions *in vivo* that are relevant to AD.

Animal model of AD

Development of mouse models of AD that reproduce the major AD features, such as A β plaques and memory deficits, has yielded significant information about AD. Such models have been generally considered to be favorable to the amyloid hypothesis. However, the limitations of mouse models are becoming alarmingly clear (Phinney et al., 2003; Radde et al., 2008). Most mouse models expressing fAD mutant APP/PS1 develop plaques and exhibit memory deficits from anywhere 2–3 months until 18–20 months of age and none of these transgenic models display tau tangle pathology or neurodegeneration, two hallmark features of human AD. However, it should be noted that transgenic mice can be ‘pushed’ to display tau tangles or neurodegeneration by subjecting them to additional manipulations such as deleting p73 gene (Wetzel et al., 2008) or simultaneously expressing multiple APP and PS1 mutations as in the case of 5xFAD transgenic mice (Oakley et al., 2006). Neurodegeneration observed in 5xFAD mice can be prevented by crossing with BACE1 knock-out animals indicating that BACE processing of APP is essential for the deleterious effects (Ohno et al., 2007). Nonetheless, the observation that most ‘straight forward’ mouse models of AD do not show tau pathology or neurodegeneration has led many in the field to classify these transgenic mice as models of amyloidopathy, rather than AD *per se*. Also, the rate of plaque deposition as well as the deficits in memory paradigms (Wolfer et al., 1998) are critically dependent on the mouse strain, and show tremendous strain-to-strain variation (Brown and Wong, 2007; Crabbe et al., 1999; Wahlsten et al., 2003). Finally, therapeutic strategies, such as immunization (Morgan et al., 2000) or NSAID treatment (McGeer, 2000), that showed positive effects in mouse models failed to do so in human trials. Thus, although mouse models of AD may have added to our knowledge of amyloidopathy and helped identifying factors that promote plaque formation, their limitations in capturing the essence of AD or producing a successful drug are becoming increasingly evident.

Not throwing the baby out with the bathwater

The debate regarding the exact cause of AD has been ongoing, and is likely to continue for the foreseeable future till an effective therapeutic strategy has been achieved. At one end of the spectrum are those who harbor no doubts that A β , in a yet undefined form, is *the* cause of AD and, therefore, eliminating this pathogenic A β will be the ultimate cure for AD. At the other end of the spectrum are those who consider A β to be an inconsequential bystander (or, worse,

a beneficial mediator of cellular response), and believe the amyloid hypothesis to be completely wrong (Lee et al., 2007). Because of the enormous amount of data in the literature, it is easy to seek support for either view by selectively focusing on the data favorable to one's view and ignoring the studies that runs contrary to it. From the discussion above, it should become clear that although the amyloid hypothesis remains the best defined and more widely accepted view, the evidence that A β causes the disease is not as strong as the proponents would like to believe. Similarly, those who believe the amyloid hypothesis to be completely wrong do not have data to support such a claim.

Since both views are unsatisfactory and are partially inconsistent with the available data, it may be helpful to reassess the hypothesis anew. The classical view of the amyloid cascade hypothesis (Fig 3A) proposes A β as the starting point of the cascade. Other deleterious events found in AD, such as hyperphosphorylation of tau, neuroinflammation, neurodegeneration, synapse loss, etc., lie downstream of A β . Over time, these deleterious events contribute to synaptic dysfunction, and ultimately cause AD. Thus, blocking the events at the A β level itself will prevent the downstream harmful events and prevent AD. However, a review of the literature supports a view that A β , instead of acting upstream of the deleterious events, exerts its effects at the same level as the other events that can also be caused by non-A β factors (Fig 3B). The view that there is no single primary factor that causes the disease, and that non-A β factors also contribute to AD as well as A β does, is more consistent with the present data. The concept that A β is only *one* of the factors that cause AD, explains the less than perfect correlation between A β and the disease severity, and may explain the recent findings why A β -targeted therapies are not effective against AD. An intriguing possibility (suggested by an anonymous reviewer) that the toxic form of A β creates a self-sustaining loop of deleterious events could also explain why A β -targeted therapies at the advanced stages of AD are not particularly effective. The preliminary findings reported at the 2008 ICAD meeting that multiple tau-targeted therapies (Rember, AL-108), are more effective in combating AD may be the harbinger of the idea that, perhaps, an effective therapeutic strategy can only be achieved by going beyond the amyloid hypothesis (Gong and Iqbal, 2008).

Conclusions and Perspectives

The amyloid hypothesis and the notion that A β is the critical primary factor in disease causation have long dominated the AD research area. However, there is growing realization that the role of A β in AD pathogenesis may be more limited than previously thought. The changing view is more consistent with both sets of observations- those that are supportive of the amyloid hypothesis as well as those that run against it. The notion that A β plays no role in AD is just as likely to be wrong as the belief that A β is the prime or sole cause of AD. The concept that A β , even if most visible, is only *one* of the factors that contributes to AD is likely to give a more accurate, albeit complex, picture of AD pathogenesis, and yield more comprehensive therapeutic strategies against AD.

Finally, a note on the continuing debate regarding 'to what degree the amyloid hypothesis is right or wrong'. The proponents on both sides of this debate seem to hold strong and passionate views and are unlikely to change their minds based on the reasoning put forward here. Ultimately, the availability of an effective therapy against AD, which is the goal of both the proponents as well the critiques, will prove or disprove the amyloid hypothesis. Meanwhile, the school of thought that does not accommodate the contradictory evidence will only become less and less relevant to the field of AD.

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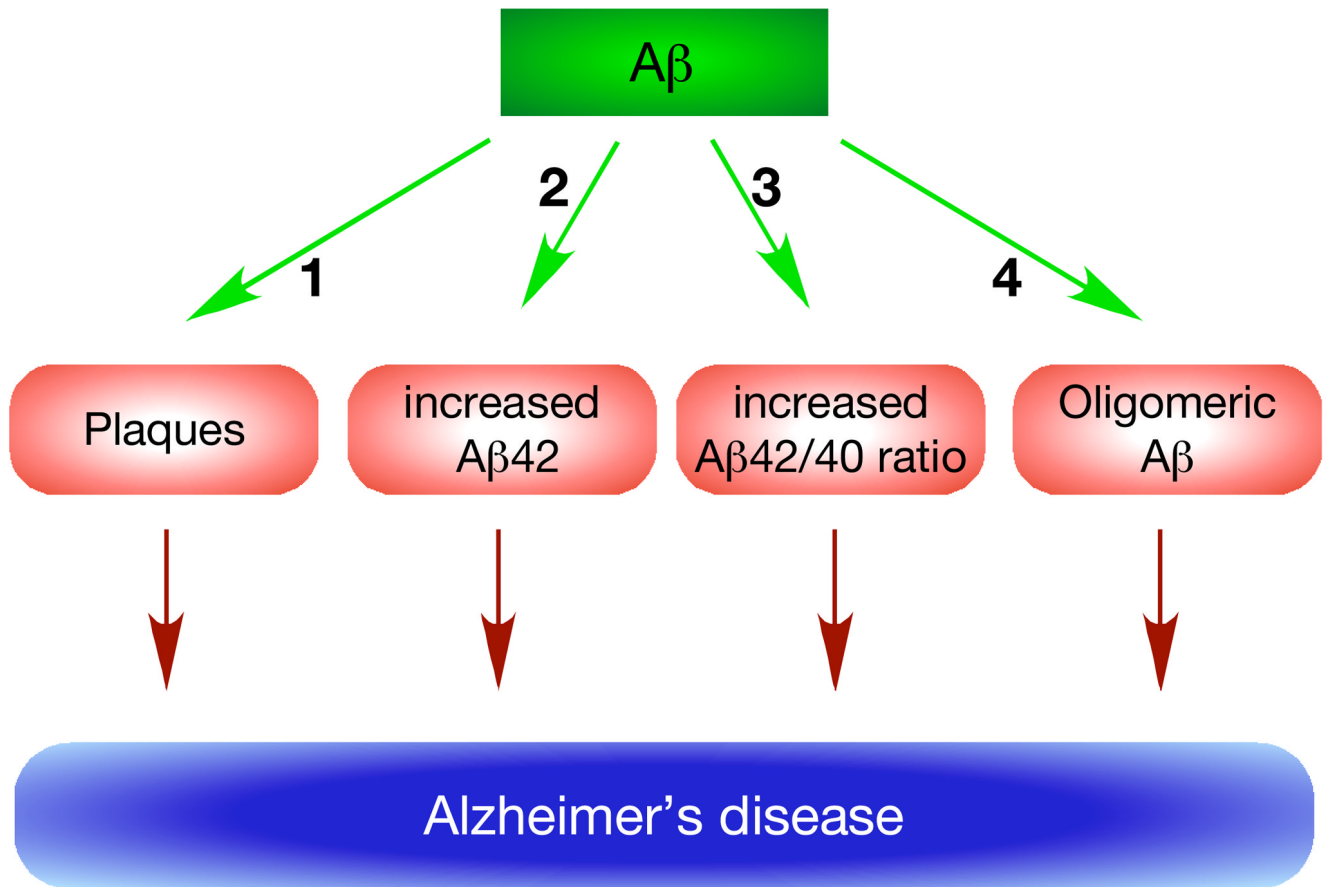


Figure 1. Many avatars of the amyloid hypothesis

The main tenet of the amyloid hypothesis is that A β is the primary cause of the disease. It was originally proposed that increased levels of A β resulted in plaque formation (1), which caused AD. Subsequent observations that fAD mutations increase A β 42 generation, led to a proposal that it is the increased levels of A β 42 peptide that is pathogenic and caused AD (2). Another variation on the theme is that the absolute levels of A β 42 are less important than the ratio of A β 42/40 in causing AD (3), and there seems inverse correlation between A β 42/40 ratio and the age of disease onset. However, the currently most favored idea is that A β forms soluble oligomers (4), which are pathogenic in nature and cause AD. Despite intense investigations, there is no consensus regarding the chemical nature of such pathogenic oligomers.

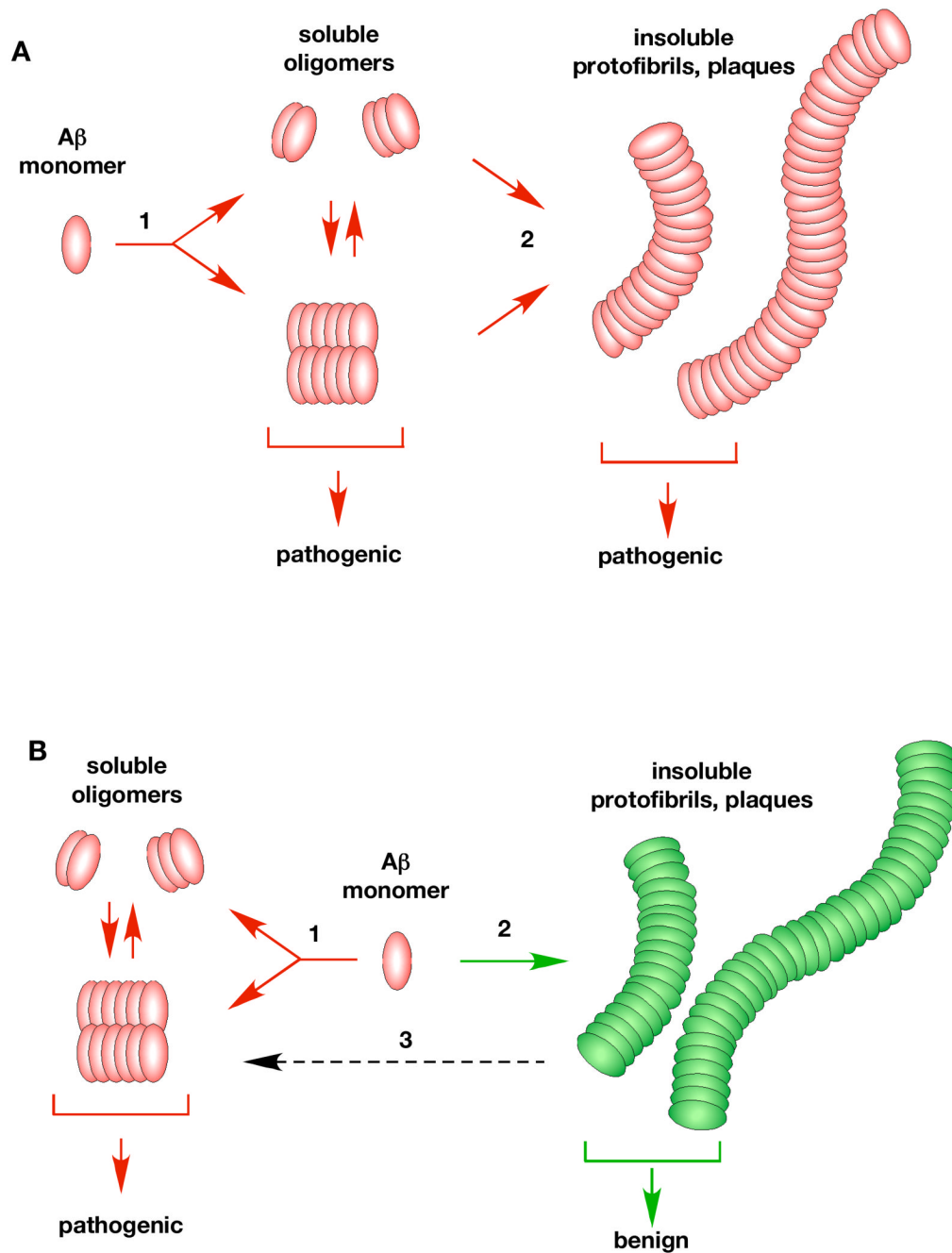


Figure 2. Potential pathways of A β oligomerization *in vivo*

Almost nothing is known about how A β oligomerizes *in vivo*. One possibility (A) is that there is a single linear oligomerization pathway with A β monomers initially forming low molecular weight soluble aggregates (1). These oligomers further aggregate (step 2) into insoluble protofibrils, fibrils and plaques (2). In this view, both soluble oligomers and insoluble fibrils are considered to be pathogenic. An alternate possibility (B) is that there are two distinct pathways. A pathogenic pathway (1) that forms soluble oligomers (dimers/A β *56/ADDLs) which cause the disease, and a second non-pathogenic pathway (2) that leads to the formation of insoluble aggregates and plaques. The insoluble aggregates are thought to be benign, a view more consistent with the available data. It has also been suggested that the benign insoluble

aggregates may slowly leach (3, dashed arrow) forming the pathogenic soluble oligomers (Meyer-Luehmann et al., 2008).

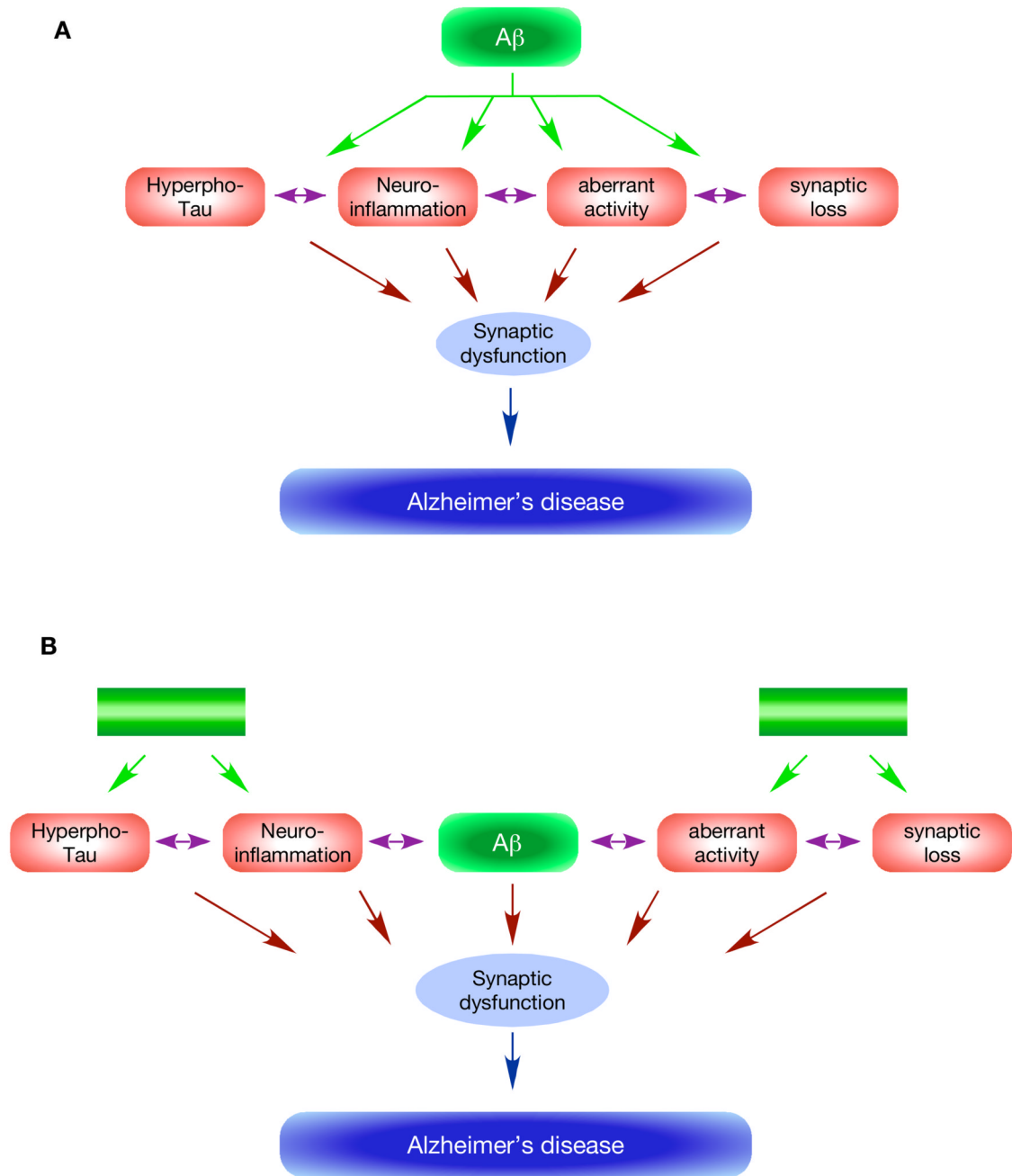


Figure 3. Reassessing the amyloid hypothesis

The classical view (A) of the amyloid hypothesis posits that A β is the primary cause of AD and occupies the top position in the cascade (green oval). Increased production or decreased degradation results in accumulation of A β , which in a yet uncertain pathogenic form (see Figure 1) triggers a number of downstream deleterious events (purple ovals). These events are caused by A β as a primary effect (green arrows) and/or as a secondary effect (double-headed purple arrows). A cumulative effect of these events over time results in synaptic dysfunction, and causes AD. A distinguishing feature of this view is that A β acts upstream of all other events, and blocking its effects will prevent all downstream events and prevent AD. A modified view (B), which is more consistent with the presently available data, suggests that the deleterious

events leading to AD are caused by A β as well as non-A β factors (green boxes). One prediction of this model is that blocking the A β effects will be effective only in a limited number of cases, as has been observed in the recent drug trial.