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Review

The Unexpected Role of A$\beta_{1\text{-}42}$ Monomers in the Pathogenesis of Alzheimer's Disease

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Abstract. Amyloid-β (Aβ) has been proposed as a biomarker and a drug target for the therapy of Alzheimer's disease (AD). The neurotoxic entity and relevance of each conformational form of Aβ to AD pathology is still under debate; Aβ oligomers are considered the major killer form of the peptide whereas monomers have been proposed to be involved in physiological process. Here we reviewed some different effects mediated by monomers and oligomers on mechanisms involved in AD pathogenesis such as autophagy and tau aggregation. Data reported in this review demonstrate that Aβ monomers could have a major role in sustaining the pathogenesis of AD and that AD therapy should be focused not only in the removal of oligomers but also of monomers.

Keywords: Alzheimer's disease, Aβ monomers, Aβ oligomers, autophagy, tau protein

INTRODUCTION

Alzheimer's disease (AD) is the most common age-related disease [1], and it has become a very serious social and health problem with the increase of life expectancy. Indeed, the risk of AD increases dramatically in individuals above the age of 70, and it is predicted that the incidence of the disease could further increase by 3-fold over the next 50 years [2].

Extracellular amyloid plaques formed by aggregated amyloid-β peptides (Aβ) and intracellular neurofibrillary tangles composed by polymers of altered tau protein are the two main pathological hallmarks of the disease.

According to the amyloid cascade hypothesis, a series of clues indicate that the accumulation of Aβ in the brain is the primary and early event that induces neuronal degeneration, characterized by accumulation of conformational altered and aggregated tau protein.

Aβ, a 39–43 residue polypeptide, is cleaved from the amyloid-β protein precursor (AβPP) by β- and γ-secretases and consists of a largely hydrophilic N-terminal domain (1–16) and a C-terminal hydrophobic domain [3]. The predominant Aβ species end at 40 and 42 residues; the latter shows a greater propensity for aggregation and is considerably more neurotoxic because of two additional hydrophobic amino acids [3].

Although many details in the pathogenesis of AD remain elusive, Aβ has been proposed as a biomarker and a drug target for the therapy, being expected to

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ameliorate the accuracy of early diagnosis, and to investigate the influence of drugs on Aβ removal and aggregation. The neurotoxic entity and relevance of each conformational form of Aβ to AD pathology is still under debate; Aβ oligomers are considered the major killer form of the peptide [4] but a role for fibrillary form of Aβ to neurotoxicity cannot be ignored [5]. Monomers instead have been proposed to be involved in physiological process. Their role in the pathogenesis of AD is unknown. Here we reviewed some different effects mediated by monomers and oligomers on mechanisms involved in AD pathogenesis.

Aβ MONOMERS AND OLIGOMERS

Aβ monomers are predominantly α-helical and random coil in structure. $A\beta_{42}$ monomers are highly prone to aggregation and they form a wide range of soluble oligomers which vary in morphology and size from dimers to trimers and then up to large prefibrillar structures [6].

Monomers are the prevalent species of the lag phase and fibrils dominate at the final plateau, while during the growth phase their concentrations are similar. The concentrations of any intermediates, small aggregates or oligomers, appear low at all time [7].

Monomers have been proposed to be involved in physiological processes. There is concern in the field about technical limitations of working with such small peptides and their derivatives. The problem in studying $A\beta_{42}$ monomers derives by their tendency to aggregate as well as by the heterogeneity of the peptide solution that can assume different conformational states [8]. Despite these technical limitations, some researchers developed methods to obtain a homogeneous population of $A\beta_{42}$ monomers [9–11]. These pure monomeric preparations have been found able to protect neurons by trophic deprivation and excitotoxicity [9] through the activation of the phosphatidyl-inositol-3-kinase pathway. More recently, it was also demonstrated that $A\beta_{42}$ monomers mediated the glucose uptake in neurons by selectively activating the member of the insulin receptor superfamily, IGF-IRs, and promoting the translocation of glucose transported Glut3 to the plasma membrane from the cytosol [12]. These results suggest a positive role of $A\beta_{42}$ monomers that would be important for neuronal survival; therefore, therapeutic approaches should take into account this neuroprotective function.

The oligomeric forms of Aβ are the major toxic agents in AD [13–15]. Interestingly, concentration of $A\beta_{42}$ oligomers are higher in plasma of AD patients than control subject [16]. Several pathogenetic mechanisms of $A\beta_{42}$ oligomers have been proposed. Oligomers are able to bind neurons and directly induced cell death mediating phagocytosis and oxidative stress [17, 18]. They can also impair the electrochemical signals by forming small channels [19–21] or by interfering with the cell signaling pathways [22] and cause neuronal death. Finally, it has been demonstrated that oligomers can accumulate in mitochondria, damaging the respiratory chain [23]. During the Aβ aggregation process, small prefibrillar aggregates are first formed and then these assemble into protofibrils and protofilaments. The level of Aβ polymers with fibrillary conformation also correlates with AD onset and severity, thus although oligomers are believed to be more toxic to cells, strong evidence indicates that the fibril formation is related to the rates of disease progression of AD patients [5].

We found that $A\beta_{42}$ monomers at physiological concentrations upregulated BACE1 activity [24] suggesting that the limit between the physiological and pathological functions of Aβ is very subtle. Our recent studies showed different effects of $A\beta_{42}$ monomers and oligomers in autophagy, apoptosis, and tau aggregation.

$A\beta_{42}$ MONOMERS VERSUS OLIGOMERS IN AUTOPHAGY AND APOPTOSIS

Autophagy and apoptosis are two mechanisms closely involved in the pathogenesis of AD.

The misfolded proteins, in particular those that tend to form aggregates, are directed to autophagy, a degradation system in which substrates are segregated into autophagosomes which are then fused with lysosomes for degradation into amino acids [25]. In turn, an increased level of apoptosis, the programmed cell death that leads to the destruction of cells and organelles through the activation of catabolic pathway, has been found increased in neurodegenerative disease such as AD [26].

The role of autophagy and its connection with apoptosis in AD pathogenesis is far from being clear. This relationship has many facets since autophagy in some cases represents a mechanism for adaptation to stress conditions that suppresses apoptosis, while in other cases, it is an alternative death mechanism.

Some studies reported that the induction of apoptosis by rapamycin, an inducer of autophagy, significantly reduces the permeability of mitochondrial outer membrane, which represents a crucial event to mediate apoptotic cell death [27]. On the other hand, stressors are able to induce damage in apoptotic machinery, for example inhibiting caspase activities, mediating autophagic cell death [28, 29].

Given the central role of Aβ in the pathogenesis of AD, it is plausible that it can play a role in linking the two mechanisms. Thus, it is well known that impairment of autophagy leads to Aβ accumulation in vacuoles and cell death. AβPP and Aβ peptides colocalized in autophagosomes in AD cellular and murine models [30, 31]. Moreover, it has been reported that the accumulation of $A\beta_{42}$ and p62, a marker of the autophagic flux, precedes the derangement of autophagic clearance and mediates the lysosomal impairment [32]. On the other hand, strong evidence indicates that Aβ is also produced during autophagy [30]. Probably, physiologically, autophagy does not influence the production of Aβ because of the efficient clearance of lysosomal degradation [33]. In pathological conditions, autophagy becomes a site for AβPP processing and Aβ generation, thus many autophagic vacuoles are found in AD brains particularly in dystrophic neurites [34] and in perikarya of neurons containing tangles [35]. Moreover, in dystrophic neurites, an accumulation of phagophores has been shown, suggesting that their maturation to lysosomes may be impaired in AD [30].

We recently obtained data shedding light on the interaction between autophagy and apoptosis in response to oligomeric as well as monomeric forms of $A\beta_{42}$ [36]. We demonstrated that oligomers induce apoptosis allowing the formation of a complex between the anti-apoptotic protein Bcl-2 and Beclin1, a protein implicated in the autophagosomes formation [37]. Other authors demonstrated that the regulation of this complex represents a crucial mechanism by which cells turn off autophagy [38], leading to apoptosis. The mechanism through which the inhibition of autophagy predisposes cells to apoptosis is not completely clear and could be due to a bioenergetics deficiency [39] or to oxidative stress induction [40]. The latter mechanism is in agreement with our previous reports demonstrating that oligomers, but not monomers, increase oxidative stress in different cellular models [41]. On the other hand, monomers lead to autophagy and hamper the formation of the complex formed by Bcl-2 and Beclin 1, through activation of the JNK pathway and inducing Bcl-2 phosphorylation [42]. Monomers also cause a significant accumulation of autophagosomes and also a reduction of lysosomal activity and an accumulation of substrates that are not digested such as BACE1 [36]. These findings confirm our previous data demonstrating that $A\beta_{42}$ monomers upregulate BACE1 expression interfering with its lysosomal degradation, inducing a cycle of Aβ production [43]. We also found that monomers of $A\beta_{42}$, but not oligomers, inhibit the activity of Uch-L1, an abundant neuronal enzyme that mediates the proteosomal degradation; our data suggest that Uch-L1 inhibition interferes with the lysosomes as demonstrated by the decrease of cathepsin D, a marker of lysosomal activity [43].

$A\beta_{42}$ MONOMERS VS OLIGOMERS ON TAU AGGREGATION AND PHOSPHORYLATION

The causal relationship between 'plaques and tangles', i.e., whether and how Aβ induces the formation of intracellular altered and aggregated protein tau, is a crucial and a much-debated issue.

We investigated whether $A\beta_{42}$ could modify the conformation and/or the phosphorylation of tau protein to render it more prone to aggregate [44]. Previous data reported three major mechanisms through which Aβ peptides may induce tau aggregation: 1) Aβ phosphorylates tau through the activation of specific kinases and this event alters the ability of tau to bind tubulin [45, 46]; 2) Aβ interferes with proteasomal degradation of tau, thus increasing the free-state of the protein [47]; 3) Aβ aggregates exert a nucleation effect on tau [3, 4]. The latter hypothesis is supported by the notion that tau pathology often coexists with cerebral amyloidosis [48, 49].

We demonstrated that $A\beta_{42}$ monomers, but not oligomers, intraventricularly injected in mice expressing wild type human tau, produce a pathological conformational change of tau protein [44]. In the same experimental model, we also found that monomers induce phosphorylation of pathological tau epitopes activating GSK3β, JNK, and ERK kinases and that the inhibition of these kinases rescues the tau conformational change [44]. Finally, we investigated whether the observed modification of tau mediated by Aβ monomers could be ascribed to an increase of tau protein levels. It is well known that the increase of total tau is a condition that favors phosphorylation and conformational change of tau,

as demonstrated with mutant tau [50]. We found that Aβ monomers inhibit its proteasomal degradation. Thus, Aβ monomers alter tau conformation through two different mechanisms: hyperphosphorylation and increase of protein levels [44].

CONCLUSIONS

Results of our previous works suggest that oligomeric neurotoxicity is higher than in monomers, possibly through the production of reactive oxygen species or others mediators, and kill neurons inducing apoptosis. Monomers, on the other hand, are able to modulate AβPP processing, increase BACE1 activity sustaining its continuous production and favoring tau aggregation. Thus, both Aβ species may be considered relevant in the pathogenesis of AD. Our results suggest that AD therapy may be focused not only in the removal of oligomers but also of monomers and help to develop new therapeutic approaches to treat the disease.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/17-0581r1).

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