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Amyloid- β Oligomers and Aluminum Co-Aggregate to Form Toxic Amyloid Channels in Alzheimer’ s Disease Brain: A New “Amyloid- β Channel-Aluminum Hypotheses”

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Abstract

Large numbers of senile plaques are thought to be characteristic of Alzheimer’s disease (AD), but these deposits are also a by-product of normal senescence. In AD and normal brains, senile plaques are primarily composed of amyloid-β peptides (Aβ P) with aluminum (Al). Evidence suggests the oligomerization of Aβ P is part of the molecular mechanism of AD pathogenesis by forming neurotoxic amyloid channels. However, the relationship between Al and AD has been a subject of scientific debate for many years. The complex nature of Al bioavailability has made it difficult to evaluate its toxicity to the human brain. In 2004, Al concentration in CSF of AD patients analyzed to be 1.6 ± 0.4 times higher than normal people. Importantly, AD patients with more Al in CSF showed less MMSE score, indicating Al may decrease cognitive ability. Recently, Al accumulations in sporadic AD and familial AD brains were reported to be much higher than in normal control brains. Above its neurotoxicity, Al^{3+} has a crucial role as a cross-linker in β-amyloid oligomerization. Therefore, I propose a hypothesis that β-amyloid oligomerizes with Al, forming non-specific cation amyloid channels in cell membranes, which allows calcium to enter cells and finally causes neuronal death by together with Al’s own neurotoxicity.

Keywords: Beta amyloid; Senile plaque; Aluminum; Amyloid channel; Calcium influx; Oligomer; Alzheimer’s disease

Abbreviations:

Aβ P: Amyloid β Peptides: Al: Aluminum; AD: Alzheimer’s Disease; ALS: Amyotrophic Lateral Sclerosis; NFTs: Neurofibrillary Tangles

Introduction

Alzheimer’s disease (AD), Parkinson’s disease, and amyotrophic lateral sclerosis (ALS), such neurodegenerative diseases are characterized by the loss of neurons, cognitive decline and motor impairment. These diseases share the common assemblage of misfolded or aggregated intracellular or extracellular peptides or proteins, known as inclusion bodies. Senile plaques are extracellular deposits of amyloid-β-peptides (Aβ P) in the brain. According to the prevailing original “amyloid cascade hypothesis” [1], senile plaques are responsible for the pathology of AD; this hypothesis used to be accepted by the majority, but is not yet conclusively established. An alternative hypothesis is that some types of amyloid oligomers rather than senile plaques are responsible for the disease pathogenesis [2,3]. Recent evidence together with old ones, showed a need to put aluminum (Al) on the patho-physiology and patho-chemistry of AD.

Oligomers of Aβ P form neurotoxic channels

Aβ P is inclined to aggregate with Al to make various types of oligomers. Some oligomers of Aβ P are inserted into neural cell membranes to form amyloid-β channels that are neurotoxic [4-6]. These Aβ P deposits as senile plaque which are also a by-product of normal aging process. Aβ P (1-40) and Aβ P (1-42) also seem to feature highly different conformational states [7], with the C-terminus of Aβ P (1-42) being more structured than that of the 1-40 peptide fragment.

Aβ P may damage cells and finally do neurons to death. The mechanism starts by generating non-specific cation channels (like pores in the membrane). As a result, the amyloid-β channel promotes depolarization of the synaptic membrane, to cause excessive calcium influx through the channel, and mitochondrial impairment. Dissociated hippocampal and cerebral cortical neurons from embryonic brain form many functional synapses in culture. It appears that Al promoted the aggregation of Aβ P and enhanced its neurotoxicity in the cortical neurons, as well [8]. The abnormal aggregation of Aβ P and Al own neurotoxicity in neuronal cells is critical for the onset of Alzheimer’s disease. It was shown that toxic Aβ P (1-40) aggregates formed channels in GM1-ganglioside-containing membranes. Aβ P formed without membranes were thinner and much less toxic, because of weaker binding to cell membranes and a less surface hydrophobicity [9].

Increases in either total Aβ P levels or the relative concentration of both Aβ P (1-40) and Aβ P (1-42) [10] have been implicated in the pathogenesis of both familial and sporadic AD. Due to its more hydrophobic character, the Aβ P (1-42) is the most amyloid-like form of the peptide. Indeed, data indicated that, when in soluble intracellular form, the oligomers of Aβ P (1-42) (a toxic species of Aβ P), acutely inhibited synaptic functions, various types of patho-physiology that characterizes AD [11-13]. Genetically engineered mice to express oligomers but not plaques (APPE693Q) develop AD-like symptoms. On the other hand, mice engineered to convert oligomers

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into plaques (APPE693Q X PS1ΔE9), are no more cognitively impaired than the oligomer-only AD-like mice [14].

Accumulation of neurotoxic aluminum (Al) in AD brain

Although distributed environmentally abundant, aluminum is never essential for life, but is recognized as cell-toxic, especially as neurotoxic. Al inhibits thousands of biologically important functions and causes a lot of adverse effects in plants, animals, and, of course, in humans. The relationship between Al exposure and neurodegenerative diseases has been suggested, including dialysis-encephalopathy, AD [15] and ALS, and Parkinson-dementia complex in the Kii Peninsula of Japan and in Guam.

It was reported an accumulation of Al in neurofibrillary tangles (NFTs)-bearing neurons of AD brains [16]. An accumulation of Al in both senile plaques and NFTs has been reported in renal failure patients [17]. In 2004, Al accumulation was also analyzed in cerebrospinal fluid (CSF) of AD patients and Pick disease patients. Shoda et al. reported that Al concentration in CSF of AD patients were a 1.6 ± 0.4 time higher, and in Pick disease case 2.5 ± 1.0 times higher than normal people. Al concentration of CSF in cerebrovascular dementia patients is not significantly different from normal levels. Importantly, the more Al in CSF of dementia patients shows the less MMSE score, indicating Al may decrease recognition ability [18].

Recently, Yumoto et al. analyzed Al using energy-dispersive X-ray spectroscopy with transmission electron microscopy. Their detailed careful analysis demonstrated that Al was present in cores of senile plaques [19]. In 2012, sporadic AD brains suggested that a diagnosis of AD could be predicted by a combination of Aβ P pathology and ratio of brain concentration of Al to copper [20]. Very recently Exley's group published new paper, stating that "the first ever measurements of Al in brain tissue from 12 donors diagnosed with familial AD. The concentrations of Al were extremely high, for example, there were values in excess of 10 μg/g tissue dry wt. in 5 of the 12 individuals. Overall, the concentrations were higher than all previous measurements of brain Al except cases of known Al-induced encephalopathy" [21].

Effect of Al on the forming oligomers of Aβ P

Many studies on biochemistry, cell biology, toxicology, and genetics have favored a hypothesis, namely, that the oligomerization of Aβ P and its neurotoxicity play a central role in the pathogenesis of AD [22].

Genetic studies of familial AD indicated that APP mutations and Aβ P metabolism are associated with AD [23]. The first 40 amino acid residues of Aβ P (1-40) caused the cell-death of cultured rat hippocampal neurons or neurodegeneration in the brains [24].

Aβ P is a hydrophobic peptide with a tendency to self-assemble and form SDS-stable oligomers in aqueous solution. The monomeric form of Aβ P has a random coiled structure. Oligomeric Aβ Ps have β-pleated sheet structures and form amyloid channels in cell membranes, but in the normal aging process finally form insoluble aggregates, mainly termed senile plaques. Using size-exclusion chromatography, gel electrophoresis, and atomic force microscopy, it is demonstrated that the soluble oligomers are neurotoxic and impair synaptic plasticity [25].

Aβ P is secreted in the CSF of young normal individuals as well as in aged or dementia patients. Factors to accelerate or inhibit the oligomerization can have fundamental roles in the pathogenesis of AD [26].

Intriguingly, rodent Aβ P showed the less tendency to oligomerize than human Aβ P *in vitro* [27] and deposits of Aβ P are rarely observed in the brains of rodents as compared to humans. The amino acid sequences of rodent Aβ P differ from human with 3 amino acids, namely Arg5, Tyr10, and His13. All three amino acids have the strong ability to bind metals. Therefore, trace metals, especially Al^{3+}, are particularly of interest as potential accelerators and may play important roles in the accumulation of Aβ P in the human brain.

Exley et al. demonstrated by CD spectroscopy that Al^{3+} induces a conformational change in Aβ P (1-40) [28]. We have demonstrated that Al enhances polymerization of Aβ P (1-40) and forms SDS-stable oligomers *in vitro* [29]. Oligomerization induced by Al^{3+} is stronger than that induced by other metals. Furthermore, Al-aggregated Aβ P binds tightly to the surface of cultured neurons of rat cerebral cortex and forms fibrillar deposits [30]. Secreted Aβ P is usually degraded by various proteases such as neprilysin within a short time. Down regulation of neprilysin induced by Al^{3+} can cause the accumulation of Aβ P [31]. Indeed, Al^{3+} has been shown to inhibit degradation of Aβ P as a result of conformational changes [32]. More interestingly, Aβ P combined with Al is more toxic than normal Aβ P, and may easily form amyloid channels, causing membrane disruption and interruption of neural Ca^{2+} homeostasis and mitochondrial functions [33,34].

Rat orally administered Al^{3+} caused a marked increase in the amount of Aβ P both in its secreted and accumulated forms, and increased deposition of senile plaques in AD-model mice genetically transfected with the human *APP* gene (Tg 2576) [35]. These results are consistent of other studies demonstrating that oral Al^{3+} exposure causes the accumulation of Aβ P and impairs spatial learning memory in AD-model mice [36]. Very recently, it was reported that only Aβ P (1-42) oligomers, but not significantly Aβ P (1-40) oligomers, appeared to form 3 types of amyloid channels in neuronal cells [37].From the standpoint of "Amyloid-β channel-Al hypotheses", the results seem to be quite possible, because so little Al3+exsist in the medium under the *in vitro* experimental condition, compare to considerable amounts of Al^{3+} exist *in vivo* human CSF [18] to form a stable and convenient chemical structure for the channel formation in the membrane.

Conclusion

The etiology of AD seems to be dependent on the interaction of two neurotoxic substances, Aβ P and Al^{3+} ions. A new "Amyloid-β channel-Al hypothesis" will follow. Aβ P oligomers with Al^{3+} are readily incorporated into cell membranes, resulting in the formation of Ca^{2+}-permeable amyloid channels. A following influx of Ca^{2+} through these amyloid channels leads to the phosphorylation of tau, depletion of neurotrophic factors and the formation of free radicals, and so on, with final neuronal death. Al^{3+} neurotoxity also blocks various Ca^{2+} channels and influences Ca^{2+} homeostasis.

Further research is necessary to understand fully about AD.

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