World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

BIOCHEMISTRY OF ALZHEIMER'S DISEASE

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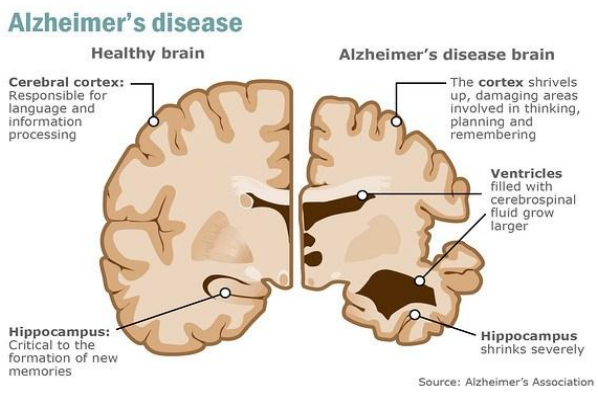
Article Received on 27/11/2017 **Article Revised on 18/12/2017** **Article Accepted on 08/01/2018**

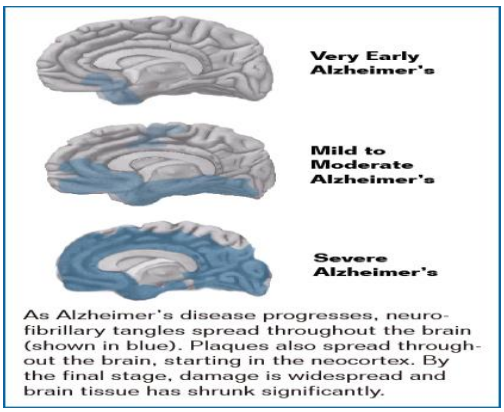
ABSTRACT

Alzheimer's disease, the cause of one of the most common types of dementia, is a brain disorder affecting the elderly and is characterized by the formation of two main protein aggregates: senile plaques and neurofibrillary tangles, which are involved in the process leading to progressive neuronal degeneration and death. Neurodegeneration in Alzheimer's disease is a pathologic condition of cells rather than an accelerated way of aging. The senile plaques are generated by a deposition in the human brain of fibrils of the beta-amyloid peptide (Abeta), a fragment derived from the proteolytic processing of the amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments (PHFs), which form a compact filamentous network described as neurofibrillary tangles (NFTs).[1] Experiments with hippocampal cells in culture have indicated a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. Furthermore, the degree of dementia is clearly associated more with the degree of neurofibrillary pathology than with the amyloid plaque burden. In general, amyloid formation may very well be at the end of a pathophysiological cascade, set in motion by many different triggers. This cascade could involve excessive apoptosis, followed by necrosis and inflammation.[2] The pathogenesis of AD is complicated, but further identification of the processes of neurodegeneration will also lead to identification of the factors that make specific neurons vulnerable and, hopefully, point the way to a means to prevent neuronal degeneration at an early stage.

KEYWORDS: Neurodegeneration, amyloid plaque, tau, proteolytic, Alzheimer's disease, hippocampal cells, neurons.

INTRODUCTION



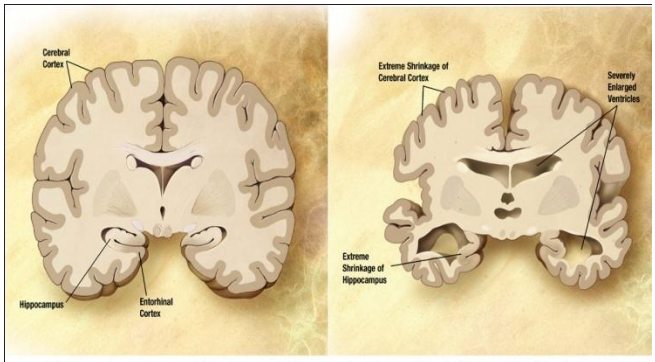


Alzheimer disease (AD)2 is a debilitating neurodegenerative disorder that directly affects millions of people and indirectly affects the lives of tens of millions. This devastating disorder, for which no cure is pathologically characterized by the presence in the brain of senile plaques containing amyloid - (A) and neurofibrillary tangles containing Tau. Only within the past decade have real advances been made in determining the molecular and biochemical basis of AD.[4] The first section starts with a discussion of the metabolism and function of the amyloid precursor protein (APP) and plaque formation in AD. The subsequent sections. Two main protein kinases have been shown to be involved in anomalous tau phosphorylation: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3beta. Cdk5 plays a

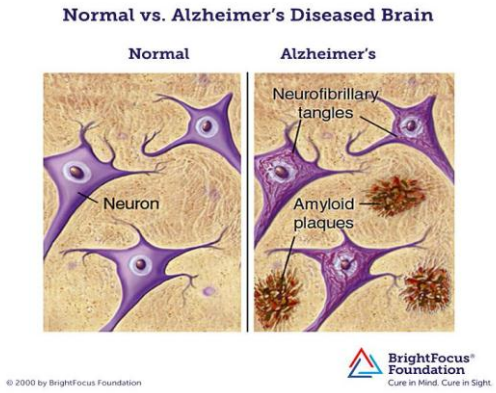
critical role in brain development and is associated with neurogenesis as revealed by studies in brain cells in culture and neuroblastoma cells. Deregulation of this protein kinase as induced by extracellular amyloid loading results in tau hyperphosphorylations, thus triggering a sequence of molecular events that lead to neuronal degeneration. Inhibitors of Cdk5 and GSK3beta and antisense oligonucleotides exert protection against neuronal death. On the other hand, there is cumulative evidence from studies in cultured brain cells and on brains that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells, leading to biochemical and structural abnormalities and neurodegeneration as related to the pathogenesis of Alzheimer's disease.[5] This review is focused on the main protein aggregates responsible for neuronal death in both sporadic and familial forms of Alzheimer's disease, as well as on the alterations in the normal signaling pathways of functional neurons directly involved in neurodegeneration. The analysis is extended to the action of neuroprotective factors including selective inhibitors of tau phosphorylating protein kinases, estrogens, and antioxidants among other molecules that apparently prevent neuronal degeneration.

Two main protein kinases have been shown to be involved in anomalous tau phosphorylation: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3beta. Cdk5 plays a critical role in brain development and is associated with neurogenesis as revealed by studies in brain cells in culture and neuroblastoma cells.[6] Deregulation of this protein kinase as induced by extracellular amyloid loading results in tau hyperphosphorylations, thus triggering a sequence of molecular events that lead to neuronal degeneration. Inhibitors of Cdk5 and GSK3beta and antisense oligonucleotides exert protection against neuronal death.[7] On the other hand, there is cumulative evidence from studies in cultured brain cells and on brains that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells, leading to biochemical and structural abnormalities and neurodegeneration as related to the pathogenesis of Alzheimer's disease.[8] This review is focused on the main protein aggregates responsible for neuronal death in both sporadic and familial forms of Alzheimer's disease, as well as on the alterations in the normal signaling pathways of functional neurons directly involved in neurodegeneration.

DISCUSSION



A representation of the normal human brain on the left, and the brain affected by Alzheimer's disease on the right.



During the years 1983–1985, efforts independent of those of Glenner were made in several laboratories to isolate and sequence the amyloid in senile plaque cores. from AD brains.[8] These efforts began before the identification of the vascular Aβ peptide by Glenner and Wong, but they were greatly facilitated by it. In 1983, Allsop, Landon, and Kidd reported a method for isolating intact neuritic plaque cores from postmortem AD brain and found them to be insoluble in various denaturants (Allsop et al. 1983). They published an amino acid composition which did not resemble any previously described amyloid protein. There are authors describing bacteria, leading to concerns about the accuracy of this composition. Masters and Beyreuther pointed out that the molecular mass, amino acid composition and amino-terminal sequence of the protein they isolated from cores were essentially identical to those described for vascular Aβ by Glenner, although their analyses showed considerable amino-terminal "raggedness" in the plaque-derived protein.[9] They concluded that the shared 4 kDa subunit indicated a common origin for the plaque and vascular amyloid in AD. Masters and Beyreuther was striking, in that only 12% of the sequenced protein began at Asp1, with 64% starting at Phe4 and the remainder at downstream residues, perhaps deriving in part from their use of pepsin digestion during plaque purification. Other types of amino acid modifications of plaque Aβ, such as racemization and isomerization of its aspartates (e.g., D-aspartate and L- and D-isoaspartates) or formylation of serines during formic acid solubilization, have been reported. The former changes may occur during the prolonged aging of the deposited amyloid proteins in vivo, whereas the latter is an artifact of an in vitro method of solubilization. Recent work has shown that glutaminyl cyclase, an enzyme in brain and other tissues which cyclizes exposed glutamates, can do so with high efficiency at Glu3 (Seifert et al. 2009) after removal of

the first two residues by aminopeptidases (Schlenzig et al. 2009; Sevalle et al. 2009). As mentioned above, the peptide isolated from fibrillar amyloid plaques shows substantial heterogeneity at both its amino and carboxyl termini. Its biochemical properties vary significantly depending on its terminal residues, particularly at the hydrophobic carboxyl terminus.[10] This heterogeneity arises secondary to the initial ε-cleavage of APP by the presenilin/γ-secretase complex at the membrane/cytoplasmic interface, namely at Leu49-Val50 (Weidemann et al. 2002), followed by processive intramembrane processing by this protease in an amino-terminal direction. The ultimate goal of studying the biochemistry of Aβ is to understand its nature and biological properties as it accumulates in the human brain.[11,12,13] Early studies detected SDS-stable low-n oligomers on western blots of AD brain extracts (e.g., Masters et al. 1985; Roher et al. 1993), although their biological activities were not studied at that juncture. Turning now to studies of human brain tissue, soluble (aqueously extractable and nonpelletable) forms of Aβ in postmortem AD cortex, which include monomers and various oligomers, have become recognized as stronger quantitative correlates of degree of cognitive impairment shortly before death than are amyloid plaques Early compositional analyses performed on isolated amyloid plaque cores suggested that Aβ, although clearly the major component, was not the sole protein constituent.[14] Moreover, nonproteinaceous components were also identified to varying degrees in enriched—albeit not fully purified—plaque core preparations. It has been difficult to determine on a biochemical basis alone which of these additional constituents are important and integral components of the amyloid plaques and which might become adventitiously associated with Aβ during plaque purification from homogenized brain tissue. Positive results suggest that a particular protein is indeed associated with the amyloid deposits, although not an integral component of the amyloid fibrils because, like other tissue amyloids, the fibrils should be composed solely of the specific subunit protein. Indeed, the ability to reconstitute amyloid fibrils with an ultrastructure closely resembling the fibrils seen in situ from synthetic Aβ peptides alone has strongly suggested that the sole component of the amyloid filaments in vivo is Aβ.[15] In short, mature amyloid (neuritic) plaques are heterogeneous mixtures of proteinaceous and nonproteinaceous constituents, and the temporal sequence of accrual of these elements onto the presumed initial Aβ polymer has been difficult to determine.[16] A recently completed interact me of APP disclosed more than 200 different entities which interact with different domains of APP (128 validated, 74 putative), including a significant proportion interacting with the Aβ region (Perreau et al. 2010). One of the earliest to be identified was the enzyme acetylcholinesterase (AChE; Friede 1965), At the level of grey matter homogenates, there is no agreement that any particular metal ion is specifically elevated or lowered in AD brain.[17] Most techniques have detected elevations in Cu, Zn, or Fe in AD amyloid plaques. The concept of therapeutic chelation needs to be qualified by the relative affinities each metal ion has for its target protein. Thus, metal "chaperone" is a preferred concept when discussing the reversible interactions divalent cations can have with Aβ, regardless of which oligomeric or fibrillar assembly is being considered.[18]

Aβ may have more than one Cu^{2+}-binding site (Behbehani and Mirzaie 2009; Jun et al. 2009; Sarell et al. 2009). Depending on the stoichiometry, Cu^{2+}–Aβ interactions can cause synthetic Aβ to aggregate in vitro principally via an oligomer-forming pathway or a fibrillogenic pathway (Brzyska et al. 2009; Whether the metal-modified Aβ is capable of pro- or anti-oxidant activity is also uncertain (Baruch-Suchodolsky and Fischer 2009), but it is an important question that needs to be resolved in terms of understanding the toxicity of Aβ oligomers. Reducing intracellular Cu^{2+}bioavailability has an inhibitory effect on Aβ oligomer formation (Crouch et al. 2009a).[19] The Zn^{2+}-induced formation of cytotoxic Aβ oligomers in proximity to excitatory glutamatergic synapses is believed to be a mechanism contributing to synaptic degeneration in AD (Deshpande et al. 2009). Zn–Aβ complexes also become more resistant to proteolytic degradation in in vitro experiments (Crouch et al. 2009b). Potentially allowing metal-bound Aβ fibrils to accumulate in the extracellular space. Studies of Fe^{3+}/Fe^{2+} complexes with Aβ indicate a potential pro-aggregating role for this abundant metal (Jiang et al. 2009a; Uranga et al. 2010), especially if evidence that Aβ has significantly higher affinity for Fe^{2+} than does transferrin (Jiang et al. 2009a) is confirmed.[20] These types of bonding apply also to Aβ interactions with the lipoprotein particles formed with ApoE, ApoA, and ApoJ, as well as with other membrane-associated macromolecular complexes in the vicinity of synapses such as NMDA, AMPA, insulin, and nicotinic ACh receptors. The role of negatively charged phospholipid head groups, sphingolipids, sialic acid, etc. in affecting the binding and oligomerization of Aβ is being increasingly examined. Over the past 30 years, many other proteins have been described as being associated with Aβ extracellular deposits, using a variety of immunohistochemical or biochemical approaches. Among these, two broad categories of proteins stand out: extracellular matrix factors and inflammatory/stress response factors. The latter include members of the complement cascade, cytokines, immunoglobulins, acute phase proteins, components of the inflammosome, etc. The serine protease inhibitor, α1-antichymotrypsin, is an acute phase protein that may be tightly associated with amyloid plaque cores (Abraham et al. 1988).[21]

CONCLUSION

Even the wealth of details and accompanying references that we have discussed above cannot do the subject of Aβ biochemistry justice. Since Glenner and Wong's seminal paper in 1984,[23] innumerable studies of this small, hydrophobic, and potentially lethal protein have

been published. Indeed, several important aspects of its biology, including its mechanisms of formation (Haass et al. 2011) and clearance (Saido and Leissring 2011) and its measurement by brain imaging (Johnson et al. 2011) and in biological fluids (Blennow et al. 2011),[24] are covered extensively in other parts of this volume.[22] The genetics of dominantly inherited AD and the pathobiology of the apolipoprotein ε4 allele in AD have combined to give Aβ an apparent initiating role in at least some forms of the AD syndrome.[22] Because these familial forms are largely indistinguishable from "sporadic" late-onset AD, parsimony suggests that an imbalance between Aβ production and clearance—an Aβ dyshomeostasis—is a driving force for many or all cases of AD as we define this eponymic syndrome. And yet, precisely why Aβ accumulates and what upstream events can lead to this accumulation remains unknown for the majority of cases of the disease. Perhaps only through the results of clinical trials of agents that must be working solely on Aβ (e.g., highly specific anti-Aβ antibodies) can we adequately test the theory that Aβ accumulation is a central pathogenic event in AD. For the sake of our patients and their families, one can only hope that the answer to this provocative question lies not too far in the future.

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