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The Essentials of Biochemistry of the Proteins as Related to Alzheimer's Disease: A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Amyloid plaques and Tau tangles, constitute the pathological hallmarks of the brains of the patients suffering from Alzheimer's disease. They are identified as far back as 1996 by Alois Alzheimer, a German psychiatrist and neuropathologist, but till this date, how they produce neuronal death remained an enigma. The amyloid cascade theory held its sway until recent times until the emphasis is shifted to the metabolites of amyloid Beta precursor protein (APP). Several metabolites of APP are formed depending on by which pathway, the APP is metabolized, either by the non - amyloidogenic pathway (forming α-C terminal fragment -CTFα / C83 and the N-terminal fragment sAPPα / P3 and the APP intracellular domain AICD). Or amyloidogenic pathways. (Forming extracellular Aβ and APP intracellular domain -AICD). The hyperphosphorylation is held responsible for the tau protein tangles. The over activity of the tau kinases or the failure of inhibition by the tau phosphatases is implicated, in tau tangle deposits. These biochemical aspects of AD assumed importance in connection with the interventional therapeutic strategies that are developed in the years bygone, as well as those still are in the developing stage. In keeping with this fact, it is attempted to review the essentials of the biochemical aspects of the involved proteins, as related to AD, in this article.

Keywords: Amyloid Precursor Protein (APP); amyloid beta; amyloid plaques; tau protein; amyloid cascade theory; amyloidogenic pathway; non-amyloidogenic pathway; secretases.

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1. INTRODUCTION

Alzheimer's disease is a progressive, irreversible, neurodegenerative disease, resulting in the death of neurons in areas concerned with the cognitive and behavioural functions of the brain. Review of statistics on the prevalence of AD is alarming. According to a 2017 report, AD affects an estimated 6.08 million people in the United States, and the projected figures by 2050 are 13.8 million. In 2016, the global prevalence is estimated to be 43·8 million. It is estimated that for every 3 seconds someone in the world is developing AD and every 66 seconds the same thing happens in the USA. The death rate from AD between 2000 to2016 increased by 145% we compared to deaths from heart disease w, the number one leading cause of death, decreased by 9%. Alzheimer disease, the leading cause of dementia, the world over, is characterised by deposition of Amyloid plaques extra neuronally and hyper-phosphorylated Tau protein, intra neuronally, resulting in neuronal death. There seems to be no halt to this relentless march of AD, as no cure for the disease is discernible, shortly. Nevertheless, great strides are made in the past, with no respite and so are the current strategies which as yet don't hold any promise .brief review of these strategies reveal the importance of the study of the biochemistry of these proteins. The biochemical interventional strategies against the ill effects of these proteins include the development of inhibitors to block APP expression or prevent its proteolytic cleavage into Aβps. Inhibitors of β- or γ-secretase, which of course failed during clinical trials, Chelation therapies, to disrupt interactions between Aβps and metal, which are also not successful, the only tau inhibitor molecule under clinical trials is phenothiazine methylene blue. Antibody therapies (immunotherapy) for AD failed due to the antibodies' inability to cross the BBB. Inhibition of Aβ Peptide Aggregation and Amyloid Formation. The small molecules that inhibit Aβ aggregation are found to be challenging for several reasons. The discovery of key regions in the Aβ peptide sequence i.e., N-terminus, hydrophobic core, hinge/turn region and C-terminus, responsible for Aβ plaque formation, are considered potential candidates. However, the review of ongoing research strategies is out of the scope of this article. For aforesaid reasons, the recapitulation of the essentials of the biochemistry of the involved peptides in AD is considered not out of place.

2. THE AMYLOID PLAQUES IN AD

2.1 Some Historical Perspectives

The presence of plaque deposits in the grey matter of the brain was reported by [1] Paul Blocq and Gheorghe, in 1892. The connection between plaques and dementia was discovered by Alois Alzheimer in 1906 [2]. Max Bielschowsky, a German neuropathologist proposed the amyloid-nature of plaque deposits in1911 [3]. 1985 beta amyloid formations were successfully identified through biochemical techniques.

3. DISCUSSION

3.1 Amyloid vs Amyloid-Beta (Aβ)

Amyloid is a physiological protein that the body produces normally. Physiological amyloids In humans are involved in pigmentation and release of endocrine secretions. Pathogenic amyloids mostly are aggregates of misfolded proteins, deposited in a variety of tissue causing a pathological condition called amyloidosis which also includes some neurodegenerative diseases. Infectious type of amyloids is called 'prions' which can act as a template to convert other non-infectious proteins into infectious forms. Amyloid-beta (Aβ) is a type 1 transmembrane glycoprotein, produced from the amyloid protein, post-transcriptionally. It is the main component of the amyloid plaques found in the brains of people with Alzheimer's disease. It is a type 1 membrane protein has single transmembrane span glycosylation, with its N terminus situated intracellularly and C terminus directed towards the ribosome. Aβ is a heterogeneous mixture of small peptides 37–43 amino acids in length that are generated by sequential cleavage of the amyloid precursor protein (APP) by β- and γ-secretase Lichtenthaler Haass, & Steiner, 2011 [4]. Aβ amyloid is produced from a precursor protein, (APP). In a healthy brain, Aβ protein fragments which are soluble, non-fibrillary and are dissolved in the fluid between the neural cells, which is flushed out of the brain. Deposits of Aβ peptides as amyloid plaques are mainly observed in the region of the hippocampus and the neocortex as well as in the cerebrovascular (CAA) [5]. Amyloid-beta deposited between neurons is believed to be toxic causing the death of neurons.

Table 1. Potential physiological activities of Aβ

Activation of kinase enzymes.
protection against oxidative stress.
regulation of cholesterol transport.
functioning as a transcription factor.
and anti-microbial activity (potentially associated with Aβ pro-inflammatory activity)

3.2 How Amyloid Plaques are Formed?

M. Franke showed that a dementia disease is likely to occur when the number of senile plaques in the frontal cortex is more than 200/mm3. Amyloid plaques are also called 'senile' or 'neuritic plaques. Amyloid plaques are formed through different stages, starting from oligomers, monomers, protofibrils, Amyloid fibrils leading to amyloid plaque formation are hard, insoluble, sticky and fibrillary accumulations of beta-amyloid proteins that clump together between the neurons in the brains of Alzheimer's disease patients. Aβ- peptides are derived from the amyloid β-precursor protein (AβPP).

3.2.1 Structure of amyloid plaques

For a detailed description of the structure of amyloid plaque, the readers may refer to the review article by Chen GF, et al. [6].

"Aβ has peptides ranging in size from 37–49 residues. The three-dimensional solution structure of different fragments of the Aβ peptide was determined using nuclear magnetic resonance (NMR) spectroscopy, molecular dynamic (MD) techniques and X-ray crystallography. The structure of amyloid beta-peptide (1–28): It is the the major component of amyloid plaques in Alzheimer's disease. It has mostly alpha-helical structure convertible to a beta-sheet it's the structure in membrane-like media. Solution structure of amyloid beta-peptide (1–40): The C-terminal two-thirds of the peptide forms an alpha-helix between residues 15 and 36. There is a kink at 25–27. and a bend at residue 12, in aqueous sodium dodecyl sulfate micelles. Between residues 1 and 14. the peptide is unstructured and mainly polar. Amyloid beta-peptide (10–35): forms a collapsed coil structure. of loops, strands, and turns with no alpha-helical or beta-sheet structure. As revealed by the Solid-state NMR spectroscopy-derived models of the solution structure of Aβ peptide (10-35) in water29 van der Waals and electrostatic forces maintain its conformational stabilization.

Amyloid fibrils of Aβ form a parallel, in-register cross β-sheet structure. The accumulation of Aβ into long, unbranched fibrils is a hallmark of the disease, "

3.2.2 Newer insights into the structure of Aβ

3.2.2.1 Significance of the kink at amino acid 23 of the fibrils and the second zipper formation

(Biochemists discover new insights into what may go awry in brains of Alzheimer's patients. "Research organizations, Science News August 2019. University of California - Los Angeles. The journal Nature in 2005 reported that amyloid fibrils contain proteins that interlock like the teeth of a zipper)" With age, the 23rd amino acid can spontaneously form a kink, similar to one in a garden hose. This kinked form is known as isoAsp23. The normal version does not create the stronger second molecular zipper, but the kinked form does form harmful molecular zipper and leading to the death of neurons. The normal form of beta-amyloid has six water molecules that prevent the formation of a tight zipper, but the kink ejects these water molecules, allowing the zipper to form. Form initiates a dangerous cascade of events that we believe can result in Alzheimer's disease.

Once zipped, and once the formation of fibrils starts, it looks like you can&apost stop it. The kinks in this amino acid form throughout our lives, but we have a protein repair enzyme that fixes them. As we get older, maybe the repair enzyme misses the repair once or twice, "he said." The repair enzyme might be 99.9% effective, but over 60 years or more, the kinks eventually build up. If not repaired or if degraded in time, the kink can spread to virtually every neuron and can do tremendous damage.

3.2.2.2 Ultrastructure of the amyloid plaque it's cell surface interactions

Han, S., Kollmer, M., Markx, D. et al. reported the Amyloid plaque structure and cell surface interactions of β-amyloid fibrils revealed by electron tomography [7]. It is reported in the. Cited article by the author's that STEM (scanning transmission electron microscope) images taken

from the formed Aβ amyloid deposits revealed three main types of fibril network structures, termed amorphous meshwork, fibril bundle and amyloid star. All three were infiltrated by different types of lipid inclusions from small-sized exosome-like structures (50–100 nm diameter) to large-sized extracellular vesicles (up to 300 nm). The fibrils also presented strong interactions with the surrounding cells such that fibril bundles extended into tubular invaginations of the plasma membrane. Amyloid formation in the cell model was previously found to have an intracellular origin and the authors show that it functionally destroys the integrity of the intracellular membranes as it leads to lysosomal leakage. These data provide a mechanistic link to explain why intracellular fibril formation is toxic to the cell. For details, interested readers may refer to the original article.

3.2.2.3 Nanoscale structure of nonfibrillar AB plaques

Querol-Vilaseca, M., Colom-Cadena, [8] working on post-mortem studies of the brains of the AD patients, With Array Tomography (AT) and Stimulated Emission Depletion microscopy (STED), to characterize the nonfibrillar structure in amyloid plaques found that -"plaques are formed by a dense core of higher-order Aβ species (~0.022 μm3) and a peripheral halo of smaller Aβ structures (~0.003 μm3)" Further, the authors, using the aforesaid high power resolution of AT-STED, quantified a load of nonfibrillar structures in the AB plaques, between A DAD (autosomal dominant AD) and SAD (sporadic onset AD). They found that observed an increase in the number of Aβ structures for all sizes (small, medium and large) in the ADAD case compared with the SAD case ($p < 0.001$). The formation of membrane pores causing permeabilisation and inducing neuronal death

3.2.3 Amyloid Precursor Protein (APP)

APP is a large membrane protein that normally plays an essential role in neural growth and repair. However, pathologically, it could destroy nerve cells, leading to the loss of memory in Alzheimer's disease. It is a large membrane protein. It normally plays an essential role in neural growth and repair. A corrupted form can destroy nerve cells, leading to a cognitive defect in Alzheimer's disease. The amyloid precursor protein is cut by enzymes to create smaller fragments (peptides), some of which are released outside the cell. Two of these fragments are called soluble amyloid precursor protein (sAPP) and amyloid-beta (β) peptide. The detailed metabolism of APP is considered, vide infra.

3.2.3.1 APP is implicated in

1. Regulator of synaptic formation and repair [9].
2. Antimicrobial activity [10].
3. Anterograde neuronal transport [11].
4. and iron export [12].

3.2.3.2 The amyloid cascade hypothesis [13]

The amyloid hypothesis1,2,3 proposes β-amyloid (Aβ) as the main cause of the disease and suggests that misfolding of the extracellular Aβ protein accumulated in AD plaques, outside the neuronal cells and being toxic, causes the death of the neurons, held its sway for more than 25 years. Researchers started having second thoughts as to B-amyloid being toxic or causing neuronal death. It is also believed previously to be involved in the intra-cellular fibrillary tangles of the tau protein, causing neurodegeneration of AD. The change in the perspective, on the pathogenic role of amyloid plaques causing neurodegeneration in AD, is based on some of the following observations. These observations are considered as a blow to the amyloid plaque hypothesis, that held its sway till recently and has lead to the search of other metabolites of APP/ B amyloid.

3.2.4 Evidence cited in favour of the amyloid hypothesis

Down syndrome: The presence of an extra copy of gene 21 presumably causes increased production of AB (10), which precedes the onset of AD-like symptoms that occur. After the age of 40 years.

FAD (Familial autosomal dominant) an early-onset type of AD, exhibits increased production of AB peptide up to 6 fold, caused by mutations of PS 1 and PS2 genes (presenilin genes).

Val 717 mutations occurring in APP, in the vicinity of its carboxy-terminus terminal also cause increased AB production.

Transgenic mice exhibiting Val 717 mutations also exhibit AD-like symptoms.

3.2.5 Arguments against the amyloid hypothesis

1. “There are many normal patients with amyloid deposits, and also AD patients

with very few amyloid deposits" Edison et al. 2007 Li et al., 2008.

2. "In the brain of elderly non-demented patients, the distribution of senile plaques is sometimes as extensive as that of dementia patients" (Davis et al. 1999; Fagan et al., 2009; Price et al., 2009; Chewelah et al., 2013). This suggested that Aβ amyloid deposition is a phenomenon of ageing and has no direct relationship with the onset of AD.
3. "Various immunotherapies targeting Aβ in AD model mice were effective in decreasing Aβ deposition in the brains, but it did not lead to improvement of actual symptoms or accumulation of tau" (Ostrowitzki et al., 2012; Giacobini and Gold, 2013; Doody et al., 2014; Salloway et al., 2014).
4. Chewelah, 2013 summarises, basing on the evidence available that:

"Neurodegeneration/neuronal loss and amyloid deposition are independent, unrelated phenomena contrary to the amyloid hypothesis."

3.2.5.1 Beta-Amyloid Dysfunction hypothesis (BAD hypothesis) [14]

"In contrast to the "Beta-Amyloid Cascade hypothesis, this hypothesis" builds on the homeostasis of essential Aβ monomer in the synaptic vesicle cycle (SVC). Disease-relevant early pathology emerges through disturbance of the Aβ homeostasis by so far unknown factors leading to the formation of misfolded Aβ oligomers. These early species interfere with the synaptic physiological Aβ monomer regulation and exert their neurotoxicity via various receptors for sticky oligomer-type Aβ aggregates."

3.2.5.2 Arguments in favour of this hypothesis

1. The negative clinical results of Gamma-secretase and Beta-secretase (BACE) inhibitors.
2. As well as pan-Aβ isotype unselective immunotherapies.

3.2.5.3 APP metabolism

APP is located on chromosome 21q21.2. The APP gene has 18 exons. The region that encodes Aβ-sequence consists of exons 16 and 17. This region is extended. From the ectodomain into the transmembrane domain of the protein (vide infra).

3.2.5.4 Glycosylation of APP

APP is subject to N- and O-glycosylation and potential tyrosine sulfation, following protein synthesis. It is then thought to be cleaved in an intracellular secretory pathway. After or during these post-translational modifications, the mature form of APP (mAPP, N- and O-glycosylated form) is subject to successive cleavages by α- or β-, and γ-secretases in the late protein secretory pathway. and/or at the plasma membrane, while immature APP (imAPP, N-glycosylated form) locates in the early secretory pathway such as endoplasmic reticulum or cis-Golgi, in which imAPP is not subject to metabolic processing.

The mAPP is cleaved by alpha-, beta-, and gamma-secretases in step(s) during the transport of APP through Golgi complex, where O-glycosylation occurs, or in compartments after trans-Golgi of the APP secretory pathway.

3.2.6 Early and late secretory phases

APP is subjected to N-glycosylation (immature APP/imAPP) in the endoplasmic reticulum (ER) in the early protein secretory pathway, and further subject to O-glycosylation(m APP) in the late endosomes and Golgi compartment in the late secretory pathway.

Intracellular pathways: Aβ is generated by 2 pathways.

1. Constitutive pathway.
2. Regulated secretory pathway.

Constitutive pathway: After leaving the Golgi apparatus, proteins following the constitutive secretion pathway merge with the cell membrane and release their cargo by a process called exocytosis in the constitutive pathway, the proteins are secreted from C M (cell membrane) continuously irrespective of external conditions or signals. This pathway subserved the nonamyloidogenic pathway. The N terminal of APP (extracellular domain) is fragmented by both alfa and Beta secretases. The soluble fragments are shed out no AB fragments are formed by this pathway. CM by a process, called exocytosis.

The secretory pathway: The secretory pathway refers to the endoplasmic reticulum, Golgi apparatus and the vesicles that travel in between them as well as the cell membrane and lysosomes. The C terminal fragments of APP after cleavage by both alfa and Beta secretases

are carried from the C M after internalization and by a process called "endocytosis", carried to Golgi apparatus where they are metabolized by the Gama secretase or to the lysosomes where they are degraded. The AB fragments are formed by the amyloidogenic pathway which uses this pathway. The products are secreted outside the CM and are insoluble, sticky and contribute to the amyloid plaque formation [15].

Intracellular regulation of MAPP: AD is a disease of the vesicular transport system [16]. Saito Y, Akiyama M, Araki Y, et al. [17] have shown that X11L (X11 -like) is a neural adaptor protein composed of a phosphotyrosine-binding (PTB) and two C-terminal PDZ domains. X11L suppresses amyloidogenic cleavage of mAPP by direct binding of X11L through its PTB domain, thereby generation of Aβ lowers. X11L expresses another function in the regulation of intracellular APP trafficking. It is suggested that LRP1 (low-density lipoprotein receptor) modulates APP trafficking along with early compartments of the secretory pathway.

ubiquitin-1 regulates APP: El Ayadi, Emily S. et al. [18] State that " Ubiquilin-1 inhibits the maturation of APP by sequestering it in the early secretory pathway, primarily within the Golgi apparatus. This sequestration significantly delayed the proteolytic processing of APP by secretases and the proteasome. These effects were mediated by ubiquilin-1–stimulated K63-linked polyubiquitination of lysine 688 in the APP intracellular domain." The authors opine that the results reveal the mechanistic basis by which ubiquilin-1 regulates APP maturation, with important consequences for the pathogenesis of late-onset AD.

The domains of APP: There are 3 domains:

A short cytosolic domain
A Transmembrane domain
An extracellular domain

Processing of APP: There are two main pathways by which APP is processed.

Non- amyloidogenic pathway
Amyloidogenic pathway.

Non-amyloidogenic pathway [19]: 90% of the APP processing is by non-amyloidogenic pathway, where as 10% is by the amyloidogenic pathway. Non-amyloidogenic processing of APP refers to the sequential processing of APP by membrane-bound α-secretases, which cleave within the Aβ domain to generate the membrane-tethered α-C terminal fragment CTFα (C83) and the N-terminal fragment sAPPα. CTFα is then cleaved by γ-secretases to generate extracellular P3 and the APP intracellular domain (AICD).

Amyloidogenic processing of APP is carried out by the sequential action of membrane-bound β- and γ-secretases. β-Secretase cleaves APP into the membrane-tethered C-terminal fragments β (CTFβ or C99) and N-terminal sAPPβ. CTFβ is subsequently cleaved by γ-secretases into the extracellular Aβ and APP intracellular domain (AICD).

The Secretase enzymes: A brief consideration of these enzymes is considered necessary due to their important role in the metabolism of the APP.

- **α-secretase:**

1. It is a membrane-bound metalloprotease in Alzheimer's
2. The alpha-secretase pathway is the predominant APP processing pathway.
3. It precludes amyloid-beta formation as alpha-secretase cleaves APP within the Abeta sequence.
4. It constitutes the non-amyloidogenic pathway in APP processing, in conjunction with game secretase.
5. Alpha secretases are members of the ADAM (a disintegrin and metalloprotease domain) family, which are expressed on the surfaces of cells and anchored in the cell membrane.
6. ADAM10, is such protein, possessing alpha-secretase activity.
7. It cleaves the extracellular ectodomain of APP
8. Upon cleavage, a fragment known as APPsα - is released into the extracellular environment.
9. This process is known as ectodomain shedding.
10. The APPsα being soluble in ECF is flushed out of the brain.
11. Alfa secretase inhibits B- secretase and inhibits amyloid genesis. Inhibition of alfa secretase increases the AB protein.

- **B - secretase:**

Beta-secretase, also known as BACE1 or memapsin-2, is a protease that makes specific cuts during the maturation of APP.

BACE1, is an aspartyl protease with an acid pH optimum for the cleavage of APP. The tail of the beta-secretase controls the location of the enzyme inside the cell. It binds to proteins that traffic proteins between the endoplasmic reticulum, Golgi, and cell surface, such as GGA. Together with Gama secretase it constitutes the amyloidogenic pathway for the processing of APP.

Though it is a minor pathway of APP processing, over expression of the enzymes can produce much A B protein.

The APP, not cleaved by alfa secretase is internalised and processed by beta-secretase, to generate CTFβ.

It is further cleaved by Gama secretase to produce 42 and 40 aa isoforms. These are fibrillar, sticky, insoluble and hence aggregate into amyloid plaques, implicated in neurotoxicity in AD.

- **Y -secretase:**

It is an intramembrane protease. The components of the γ-secretase complex are presenilin (PS), nicastrin (NCT), presenilin enhance 2 (Pen-2) and anterior pharynx-defective 1 (Aph-1). It cleaves CTFβ to 4 kDa Aβ and CTFα to a smaller 3 kDa fragment named P3 or Aα. It is a final common pathway for both the non- amyloidogenic and amyloidogenic pathways. γ-secretase which appears to reside within multiple locations including the Golgi apparatus and the cell surface.

- **η-secretase:**

A new physiological APP processing pathway is described, by M Willem et al. (2015). According to them, Proteolytic fragments generated by this pathway are capable of inhibiting neuronal activity within the hippocampus.it is a higher molecular mass carboxy-terminal (CTFs) fragment of APP, termed CTF-η, They suggest that the CTF-η generation is mediated by membrane-bound matrix metalloproteinases such as MT5-MMP, referred to as η-secretase activity. η-Secretase cleaves APP releasing a truncated ectodomain. N, CTF-η is further processed by ADAM10 and BACE1 to release long and short Aη peptides (termed Aη-α and Aη-β). η-secretase produced CTF is rich in dystrophic neurites of AD.

APP degradation pathways: Cell membrane-bound APP is internalised via receptor-mediated endocytosis and degraded within lysosomes. These organelles contain acid proteases (such as cathepsins B, H, L and D) and acid hydrolases (such as phosphatases, nucleases, proteases and glycosidases. Material tagged for degradation is first surrounded by a phagophore-formation and then wrapped into double-membrane vesicles called autophagosomes, which then can fuse with late endosomes to form an amphisome. Some cytosolic proteins are degraded after being engulfed in autophagic vacuoles that fuse with lysosomes for removal [20,21,22]. It has been reported that autophagy directly affects the levels of both intracellular and extra cellar Aβ and that intracellular Aβ severely affects memory function.

Clearance of Aβ from the brain:

Mechanisms include

1. Enzymatic pathways.
2. non-enzymatic pathway:

The non-enzymatic clearance is by 1) the bulk flow of the interstitial fluid (ISF) into the CSF followed by ISF drainage pathway through perivascular basement membranes, 2) The uptake by microglial or astrocytic phagocytosis. 3) The transport across the blood vessel walls into the blood vessel which is mediated by a series of clearance receptors such as low-density lipoprotein receptor-related protein 1 (LRP1), very low-density lipoprotein receptor (VLDLR) and P-glycoprotein localized predominantly on the abluminal side of the cerebral endothelium (Shibata et al., 2000; Deane et al., 2004).

The enzymatic clearance involves several proteases:

1. Neprilysin (NEP): It is observed that the decline in NEP in the brain of AD patients, in vulnerable regions such as the hippocampus and the mid-temporal gyrus, is associated with an increase in deposition of Aβ
2. Nsulin-degrading enzyme (IDE): Using Western blotting and in-situ hybridization, it was reported that there was an inverse relationship between IDE expression and age, suggesting that loss of this activity may play a role in the development of AD pathology [23]

3. Matrix metalloproteinase (MMP)- MMPs, like MMP-2, MMP-3, and MMP-9 have been implicated in Aβ degradation.

The peripheral sink hypothesis [24] postulates that clearance of Aß from the brain accelerated by the removal of Aß from the plasma via the liver and kidneys. Peripheral sink hypothesised that there is some form of equilibrium for the Aβ in the brain and the periphery such that Aβ can be transported across the blood-brain barrier. By modulating the periphery Aβ levels, it is predicted that the brain Aβ levels will undergo concomitant changes, forming the basis of the "sink hypothesis.

ApoE isoforms may influence CNS Aß degradation through indirect mechanisms such as regulation of cellular cholesterol - enhancing endocytosis and lysosomal degradation of Aß.

The present focus: Researcher's current focus is on the APP metabolites/isoforms to explain the toxicity and pathogenicity of amyloid-beta, which are considered in detail below.

APP super Family: In addition to APP, there are two APP LIKE proteins in the super Family. They are

APLP 1
APLP 2

APP and the APP-like proteins (APLPs) are transmembrane glycoproteins with a similar modular domain structure.APLP2 more closely resembles the isoform APP770 in domain composition whereas APLP1 is more similar to APP695.

Isoforms and metabolite of APP: The three major isoforms of APP are APP695, APP751/ 751, APP770.

They are generated by alternative splicing of exons 7 and 8.

APP 695 is principally neuronal and is expressed at relatively high levels compared with the other two isoforms in human cortex.

APP751/751 and 770 isoforms contain an additional Kunitz-type protease inhibitor (KPI) domain. APP-KPI may be more amyloidogenic than other APP. The 770 isoform also contains a 19-amino acid, OX-2 domain.

There is no functional difference between the isoforms but for the presence of KPI activity. But APP695 appears to be involved in the gene control.

Successive γ-secretase cleavages of CTFβ, produce various Aβ species. Endoproteiolytic cut at the ε site of APP, releases AICD and generates Aβ48 or Aβ49, they undergo C-terminal trimming by γ-secretase, every three residues at the ζ and then γ sites to produce the shorter and secreted forms of Aβ. Two product lines exist depending on the initial ε site of cleavage 1) a primary line produces Aβ49 and subsequent trimming generates Aβ46→43→40,2) A minor line with ε cleavage first generating Aβ48 and leading to Aβ45→42→38.

AB 40: Formed Constitutes 90% were as only 10% is AB 42 type. But despite this large production of AB 40, it is the AB 42 that is a predominant constituent in the amyloid plaque and is considered, the chief culprit, in the pathogenesis of AD.

Aβ 42: It is considered the major toxic Aβ in causing Alzheimer's disease. Insoluble Aβ42 is deposited which aggregates to form the core of neuritic plaques in the brain of AD patients. Aß peptides vary in length from 39 to 43 amino acids with the predominant species being Aß40 and Aß42.

Increase either bulk Aß levels or the ratio of Aß42:Aß40 production whether absolute or ratiometric, is critical to the aetiology of familial EOAD

Role of AICD:

1. AICD, is mainly produced via the amyloidogenic pathway (34) [25]. AICD is derived from α-secretase-derived C83 or C83 derived from C99 by a secondary α-secretase cleavage. Equimolar amounts of the Aβ peptides and the C-terminal fragment AICD are derived from the β-C-terminal fragment C99 [26].
2. It has potential activity in transcriptional regulation [27]. Its detection in brain tissue (8) immediately suggested that it has transcriptional activity, like the Notch intracellular domain (NICD).
3. AICD generation could be blocked by β- and γ-secretase inhibitors [28,29]. AICD undergoes rapid inactivation by the cytosolic and endosomal insulin-degrading enzyme,[30] and by caspases to yield a fragment called C31. [31]

Role of soluble peptides: Whilst neuronal loss and neurofibrillary tangle count strongly predict cognitive status in LOAD patients, total Aß plaque load correlates weakly with cognitive impairment [32]. The prevalent explanation for this disparity is that it is diffusible Aß oligomers, rather than Aß plaques, that represent the toxic species. The E693Δ APP mutation, for example, causes Alzheimer's-type dementia through the toxicity of non-fibrillar, intracellular Aß oligomers [33].

Michal Arbel-Ornath, Eloise Hudry, Josiah R Boivin, et al. 2017 have shown that calcium dyshomeostasis by the Soluble oligomeric amyloid-β precedes synaptic loss in mouse brain.

There is growing evidence that soluble Aβ species are more toxic than fibrillar Aβ in causing neuronal loss and synaptic dysfunction [34,35, 36,37]. The oligomers are toxic to nerve cells.

Aβ oligomers can induce neuronal and synaptic damage through different mechanisms, such as

1. Inhibition of hippocampal long-term potentiation.
2. Inhibition of exocytosis by impairing SNARE complex formation.
3. Deregulation of NMDA-mediated calcium influx triggering the synaptic collapse.

sAPP-α: For a detailed consideration, the readers are directed to the article by Ahsan Habib, 2017 [38].

sAPP-α-auto-regulating role of APP metabolism and Therapeutic role in AD:

A) Autoregulation of APP:

1. sAPP-α decreases Aβ generation by directly associating BACE1, thereby modulating APP processing.
2. Specifically targeting sAPP-α using antibodies enhances Aβ production; in transgenic mice with AD-like pathology,
3. sAPP-α overexpression decreases β-amyloid plaques and soluble Aβ. In support, immunoneutralization of sAPP-α increases APP amyloidogenic processing in these mice.
4. Several risk factors for sporadic AD serve to lower levels of sAPP-α in brains of AD patients, inadequate sAPP-α levels may be sufficient to polarize APP processing towards the amyloidogenic, Aβ-producing route.
5. Furthermore, α-secretase mutations have been associated with familial late-onset AD31. These data, in combination with previous data implying that sAPP-α has a role in the autoregulation of APP processing.

Therapeutic role of sAPP-α: sAPP-α is largely considered to have significant therapeutic potential.

1. sAPP-α is found to have neurotrophic and neuroprotective properties15.
2. sAPP-α can enhance long-term potentiation16.

Therefore, restoration of sAPP-α or enhancement of its association with BACE may be viable strategies to ameliorate imbalances in APP processing that can lead to AD pathogenesis.

The ion channel hypothesis: In 1993 introduced the possibility of an ion-channel-forming oligomer of soluble, non-fibrillar Aβ as the cytotoxic species allowing unregulated calcium influx into neurons in AD. [39] Neurons are particularly vulnerable to channel-forming toxins because of their reliance on the maintenance of strict Na+, K+, and Ca2+ concentration gradients and membrane potential for proper functioning and action potential propagation [40]. Leakage caused by insertion of an ion channel such as Aβ rapidly alters intracellular ionic concentrations, resulting in energetic stress, failure of signalling, and cell death. Ionic leakage alone has been demonstrated to be sufficient to rapidly disrupt cellular homeostasis and induce cell necrosis [41].

Aβ channels may also trigger apoptosis through insertion in mitochondrial membranes.

η-secretase cleavage products: As already seen above two products that result from this cleavage are - Aη-α and Aη-β.

Aη-α:

1. BACE inhibition increases the Aη-α fragment in vitro and in vivo,
2. Aη-α impairs hippocampal LTP and reduces neuronal activity.

Aη-β: It is shorter than Aη-α at the C-terminus by only 16 amino acids. It does not appear to have negative effects on LTP or neuronal activity.

N terminally extended (NTE) Aβs: They begin 40 amino acids before the β-secretase site and run to the γ-secretase site. Through human V717F mutant APP, they overproduce Aβ42. Like Aη, the NTE Aβ fragments impaired synaptic plasticity in hippocampal slices and their levels increased in cell culture after BACE inhibition

Role of Apolipoprotein E and Therapeutic applicability of ApoE antibody: Apo lipoprotein E (ApoE) transports cholesterol in the central nervous system (CNS). It is synthesised in astrocytes [42]. There are 3 ApoE alleles APOE2, APOE3, and APOE4 which encode the three isoforms apoE2, apoE3 andapoE4). The APOE4 allele, found in 15% of the population, remains the most significant genetic risk factor for LOAD [43].

In vitro studies have demonstrated that apoE4 interacts directly with Aß, [44] enhancing Aß fibrillation [45].

Role of ApoE antibody: Researchers focused on antibodies that recognize and bind to APOE Once antibodies attach themselves to their APOE target, they attract the attention of roving immune cells, which carry both antibodies and target off to be destroyed. The researchers reasoned that nearby amyloid might be cleared away along with APOE. One antibody -- called HAE-4 - cut the level of plaques by half. The fact that it involves only the brain ApoE, but not blood ApoE has come as a boon as the later involvement can lead to side effects. This preferential action of this antibody is explained by the fact that the HAE-4 antibody recognises only the ApoE of the brain but not that of the blood. Thus the ApoE antibody is looked upon as a possible therapeutic target in the management of AD. (Source: Washington University School of Medicine. Date: March 26, 2018 "Antibody removes Alzheimer's plaques, in mice Potential therapy removes APOE and plaques from the brain, Science News from research organizations.)"Antibody removes Alzheimer's plaques, in mice. Potential therapy removes APOE and plaques from the brain": March 26, 2018, Washington University School of Medicine).

The Tau proteins: The tau proteins were identified in 1975 as heat-stable proteins is done by this clipping [46,47]. Tau protein is a highly soluble microtubule-associated protein tau (MAPT), found mostly in neurons. Au build-up is caused by increased activity of enzymes that act on tau called tau kinases, which causes the tau protein to misfold and clump, forming neuro-fibrillary tangles. The pathological hallmark of AD. It is active primarily in the distal portions of axons where it provides microtubule stabilization but also flexibility as needed expressed at very low levels in CNS astrocytes and oligoden-drocyte [48]. It is not present in dendrites.

Neurofibrillary tangles (NFT): Are hyperphos-phorylated tau into insoluble aggregates. These aggregates are known also as PHF, (paired helical filaments). NFT are the pathological hallmarks of AD, though, it is also seen in other tauopathies (see below).

NFT maturation stages: Immunostaining with anti-tau antibody revealed that NFT is formed through the following stages. Stage 0: Normal pyramidal cells showing fine granular cytoplasmic staining

Stage 1: Delicate elongate inclusions, the early tangles, is seen in.

Stage 2: Classic NFT are seen.

Stage 3: Ghost tangles i.e. tangles outside of dead neurons are seen. These are characterized by a reduced anti-tau but marked anti-ubiquitin immunostaining [49].

Locations of NFT, as seen in the brains of AD patients: NFTs are generally limited to all cortical/limbic regions of the brain with limited progression to the neocortex but a greater density in the all cortical/hippocampal region. Plaques are generally absent [50].

Braak staging: The degree of NFT involvement in AD is defined by Braak staging. Braak stages I and II: Are used when NFT involvement is confined mainly to the trans-entorhinal region of the brain. Stages III and IV are indicated when there is the involvement of limbic regions such as the hippocampus, and V and VI when there is extensive neocortical involvement. This should not be confused with the degree of senile plaque involvement, which progresses differently [51].

Normal functions of tau protein:

1. Stabilization, assembly and polymerization of the microtubules (1). This contrasts with MAP6 (STOP) proteins in the proximal portions of axons, which, lock down the

microtubules and MAP2 that stabilizes microtubules.
2. Intracellular transport [52,53].
3. Synaptic plasticity/function (reviewed in [54].
4. Nucleic acid protection [55,56].
5. MAPTs have also been found to recruit signalling proteins and regulation of microtubule-mediated transport [57].
6. Tau proteins interact with tubulin to stabilize microtubules and promote tubulin assembly into microtubules [58].

The tau hypothesis:

Tau proteins are implicated in the pathogenesis of the primary tauopathies. The tau hypothesis states that excessive or abnormal phosphorylation of tau results in the transformation of normal adult tau into PHF-tau (paired helical filament) and NFTs. Tau protein is a highly soluble microtubule-associated protein (MAP). Hyperphosphorylated tau disassembles microtubules and sequesters normal tau, MAP 1(microtubule-associated protein1), MAP 2, and ubiquitin into tangles of PHFs. This insoluble structure damages cytoplasmic functions and interferes with axonal transport, which can lead to cell death [59].

The primary tauopathies: These are neurodegenerative diseases where tau aggregates into neurofibrillary tangles (NFTs). They include Alzheimer's disease (AD), progressive supranuclear palsy (PSP), cortical basal degeneration (CBD), Pick's disease (PiD) and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP. In AD, all the isoforms of tau are expressed, whereas in others an or more isoforms are expressed.

Phosphorylation of tau protein:

When PKN is activated, it phosphorylates tau, resulting in disruption of microtubule organization [60]. The phosphatase 1 and dephosphorylates the phosphorylated Tau. The balance between these two causes the regulation of tau phosphorylation (Wendy Noble et al. 2013). Tangles are clumps of tau protein that stick together and block essential nutrients that need to be distributed to cells in the brain, causing the cells to die [61]. For details of physiological and pathological consequences of Tau phosphorylation, the readers may refer to the article in Biochimica et Biophysica Acta (BBA), the article titled "- Molecular Basis of Disease").

Hyper phosphorylated Tau protein: The accumulation of hyper phosphorylated tau in neurons leads to the neuro fibrillary degeneration [62]. A 68 protein is found to be hyper phosphorylated in Alzheimer's disease [63]. The tau protein has multiple phosphorylation sites. When all these sites are phosphorylated, hyper phosphorylation results. (For details of phosphorylation of different tau sites during the progression of Alzheimer's disease" readers are suggested to refer to the article by Joerg Neddens, Magdalena Temmel, Birgit Hutter-Paier") [64]. It is this hyper phosphorylated tau that is the culprit in the pathogenesis of AD. The microtubules binding site of tau is positively charged and attracts the negatively charged microtubule site. Thus it is in bound functional form. But when hyper phosphorylated, the positive charge of the binding site of tau is lost. hyperphosphorylation may disengage tau from microtubules, thereby increasing the pool of unbound tau, which may be more resistant to degradation and more prone to aggregation than microtubule-bound tau.

Transiently hyperphosphorylated tau: During development, during anaesthesia and hypothermia a transient form of hyperphosphorylation Which is different from what is seen in AD, occurs. The hyperphosphorylated tau in AD brain differs from the transiently hyper phosphorylated tau by its ability (1) to sequester normal tau, MAP1 and MAP2 and disrupt microtubules, (2) can self-assemble into PHF/SF.

Hyper phosphorylated tau, How it wrecks the damage: Normal adult human brain tau contains 2–3 moles phosphate/mole of tau protein. In AD brain, tau is ~three to four-fold more. The tau protein has multiple phosphorylation sites. When all these sites are phosphorylated, hyper phosphorylation results. It is this hyperphosphorylated tau that is the culprit in the pathogenesis of AD. The microtubules binding site of tau is positively charged and attracts the negatively charged microtubule site. Thus it is inbound functional form. But when hyper phosphorylated, the positive charge of the binding site of tau is lost. hyperphosphorylation may disengage tau from microtubules, thereby increasing the pool of unbound tau, which may be more resistant to degradation and more prone to aggregation than microtubule-bound tau.

How does Tau protein spread through the brain: Tau has been proposed to spread through

the brain from neuron to neuron by a “prion-like” mechanism Clavaguera et al., 2015 [65].

Carol Huseby, Jeff Kuret and Ralf Bundschuh, [66] explains how the tangles grow and reach various lengths. This problem remained an enigma, hitherto. Scientists have previously described fibrils as "the tangles untangled. “It is now accepted that at first, the protein is broken into short fibrils and in the second step, the short fibres are attached forming the longer fibrils, which is the hallmark of the pathology of AD. It is held that the shorter fibrils are soluble and hence diffuse out of cells and reach the inside of the other neuronal cell where they are synthesised into longer fibrils, the aggregation of which forms the tau tangles.

Tau Aggregation, in AD: Tau dissociates from microtubules, leading to their destabilization. It then aggregates into oligomers, paired helical filaments, and ultimately neurofibrillary tangles. lysine acetylation and other PTMs impair tau function and promote aggregation [67].

Tau protein- genetic aspects: The MAPT gene is located on chromosome 17q21. It has16 exons [68]. The major tau protein in the human brain is encoded by 11 exons nucleotide sequence on chromosome 17q21.3, has one non-coding- and 14 coding exons (7–9). Normally, tau protein exists as six major isoforms. They produced by the alternative splicing of exons 2, 3 and 10. The alternative splicing of exon 10 produces tau isoforms with either three MT-binding repeats (3R-tau) due to the exclusion of exon 10 or four repeats (4R-tau) due to exon 10 inclusion. Aberrant splicing of exon 10, causing imbalances in the 3R-tau: 4R-tau ratios is now considered to be the cause of several tauopathies. Exons 4A, 7 and 8 are absent in the CNS. Exons 2 and 3 code for N-terminal inserts, alternative splicing leads to tau isoforms with 2, 1 or no N-terminal inserts (2N, 1N or 0N). FTDP-17 missense and silent mutations and deletions are indicated with numbering relating to the longest 441 residue 2N,4R isoform. Alternative splicing of Exons 2, 3 and 10 leads to the formation of the six tau isoform [69]. The six isoforms have a range of 352-441 amino acids.

The tau -Isoforms: Are distinguished by their number of binding domains distinguish the Three isoforms have three binding domains and the other three have four binding domains. The binding domains are located in the carboxy-terminus of the protein and are positively charged allowing it to bind to the negatively charged microtubule. The isoforms with four binding domains are better at stabilizing microtubules than those with three binding domains. Tau proteins have six isoforms. They range from 352 to 441 amino acids. The longest isoform has four repeats designated as, R1, R2, R3, and R4 and two inserts. The shortest isoform has three repeats (R1, R3, and R4) and no insert. All of the six tau isoforms are present in an often hyperphosphorylated state in paired helical filaments from AD. Mutations in the function of the isoforms lead to hyperphos-phorylation of the tau.

The tau haplo groups: The MAPT gene has two haplogroups, H1 and H2, the haplotype H2 is associated with increased risk of AD. The tau protein is belied to exert its toxicity through PAR-1 kinase. This enzyme stimulates phos-phorylation of serine 262 and 356, which in turn leads to activation of other kinases like GSK-3 and Cdk5 that cause disease-associated phos-phoepitopes the other possible mechanism is the phosphorylation of Tau protein.

4. CONCLUSION

Great strides are made in the field of biochemistry of the amyloid-beta and hyper-phosphorylated tau protein which are the pathological hallmark of Alzheimer’s disease. The metabolism of these proteins holds key to both the pathogenesis of AD and the search for a remedy for the same. This article has reviewed both the old and recent developments in the biochemistry of these proteins.

COMPETING INTERESTS

Author haS declared that no competing interests exist.

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