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Review Paper

Alzheimer's Disease: Role of Amyloid-β Peptide in the Pathogenesis of Neurodisorder

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Abstract:

Alzheimer's disease (AD) is a neurodegenerative disease distinguished by memory impairment and dementia. Amyloid beta (Aβ), a peptide, that recreates an influential role in neuronal damage by proliferation in the brain (plaque) and cerebral amyloid angiopathy (CAA).It is also caused by neurodegeneration due to the loss of acetylcholine). Aβ is produced via consecutive Amyloid-protein precursor (APP) divisions by the β and γ secretase, both found in lipid rafts. The modulation of these components is a critical element in Aβ generation during AD development. Aβ derived from Amyloid precursor protein (APP) is misfolded, and deposits as a plaque in the brain, thought to be a characteristic of AD. Aβ deposition in the brain originates from the brain itself. However, circulating Aβ can also cross the blood-brain barrier through the influence of both, contributing to AD-type pathologies. Aβ aggregation and clearance become an operational analysis area for healing and controlling AD. Therefore, this feature article intends to provide details of the aggregation mechanism and physiological role of Aβ peptide.

Keywords: Alzheimer's disease (AD), Amyloid beta, neurodegeneration, Amyloid-protein precursor, β and γ secretase

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder affecting brainthat resultsmemory impairment. Age is a significant risk factor for AD [1]. AD is characterized by intense accumulation of Aβ peptide in the brain (extracellular plaque)**(Figure 1)**. It also seems to be present in brain vessels, called cerebral amyloid angiopathy (CAA) [2]. Alzheimer's and other forms of dementia are growing among older people worldwide. It is estimated that in 2020 approximately 70% elderly population of developing countries, with an average of 14.2% in India [3]. As a result, the number of Alzheimer's patients, as well as those with hybrid types of dementia, will skyrocket during the subsequent decade. Around 80 million, sufferers will be there globally till year 2050 [4-8].

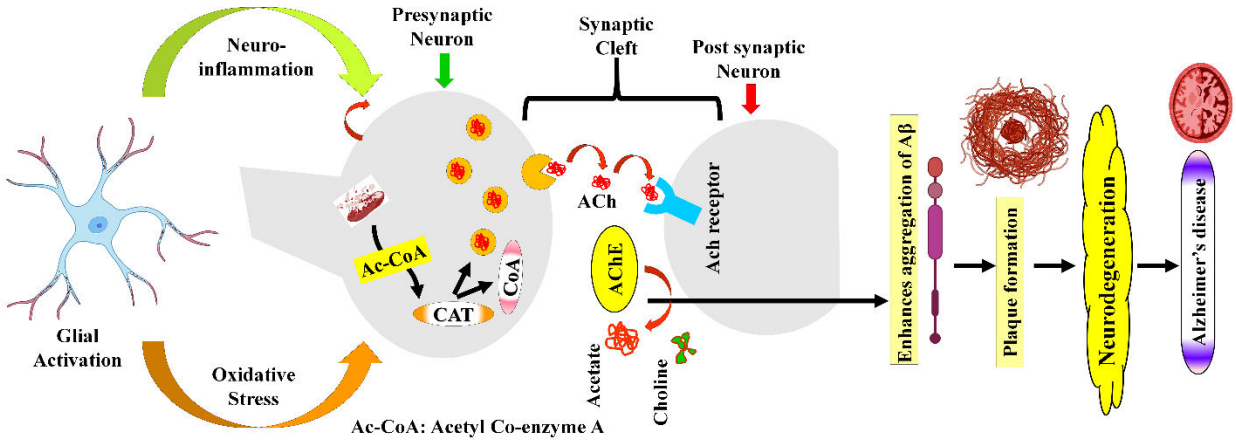

Figure 1: Neurodegeneration of neuron and development of Alzheimer's disease.

2. Aβ formation and lipid raft

The primary pathology of AD is beta-amyloid plaques. The Aβ protein and amyloid precursor protein (APP) causes illness and neurodeneragtion[9]. The integral membrane protein APP's external and intracellular C-terminal domains are significant. Three distinct APP isoforms have been known having sizes (695, 770, and 751 kDa) respectively. Specific enzymes, secretase, transform these APP isoforms into various-sized peptides and proteins [10].

Most APP is found in non-lipid rafts, with a small percentage in lipid rafts (LR)[11]. The LRis referred to a separate membrane domain. LR is empowered by high cholesterol levels[12]. The cholesterol-rich lipid raft domain appears to be involved in producing Aβ. Aβ, a hydrophobic peptide, composed of amino acids (units 40-43). Further, it is produced from the transmembrane- APP precursor. In addition, the peptide accumulates and results in neuronal toxicity. Moreover, APP precursor undergoes proteolytic cleavage.Furthermore, APP is first digested by the secretase at the beginning of this amyloidogenic route.This causes β-C-terminal fragment (β-CTF) to breakdown by γ-secretase, forming Aβ. Theamyloid precursor proteinas a digested protein referredas α-secretase. APP is then cleaving, and stops the formation of Aβ [13]. In recent years, the three secretases have been thoroughly defined [14,15].Further, due to Aβ-degrading peptidases, the peptide gets broken and removed from Aβ[16-18].

3. Enzymatic activities in the formation of Aβ

β-Secretase (β-site APP cleaving enzyme, BACE1 membrane protease) and γ-secretase (γ-site APP cleaving enzyme,BACE1 membrane protease) cleave APP sequentially in the amyloidogenicpathway, resulting in the production of Aβ. Further, the non-amyloidogenic path, caused α secretase to cleave within an Aβ sequence. Thus it prevents the Aβ formation[19].

3.1. β- Secretase

3.1.1. BACE1

It a transmembrane enzyme belongs to (aspartyl protease). It is located primarily on brain neurons. It cleaves the APP at the Aβ region's N-terminus. BACE1 processing of APP is most likely done in endosomes, which contain a low PH environment and are required for proteolytic action [20]. A minor proportion of BACE1 overexpressed in the lipid draft region. Any deviation in the integrity of the lipid raft by the depletion of cholesterol inhibits the β

cleavage.Furthermore, the BACE1 (transmembrane enzyme), shift to non-raft fraction from the raft fraction[21].

3.2. α- secretase

ADAM10 is a component of the ADAM (a disintegrin and metalloproteinase). Pro-protein convertase, a protease involved in the active shedding of type 1 transmembrane protein, cleaves off ADAM10's enzymatic activity[22]. Although ADAM10 is extensively localized on non-lipid raft membranes thus, cleavage by α secretase is done at those regions. The actuation of α secretase and its division takes placedue toinhibition of cholesterol. The cholesterol synthesis is inhibited by zaragozic acid present in neuroblastoma cells and statins (HMG-COA reductase).In addition, the α secretase cleavingoccurs in plasma membrane and depends on cholesterol formation[23].

3.3. γ-secretase

γ secretase (having elevated molecular mass) comprises complex presenilin1 or presenilin2, nicastrin. Presenilinhas a membrane-bound structure. It consists of nine (transmembrane domains)thatundergoesendoproteolysis. Theendoproteolysis occurs between (transmembrane domains 7 and 8) respectively. Further, it helps to generate stable C and N-terminal fragments [24]. The secretase substrate receptor is nicastrin, a type 1 transmembrane protein. Various family AD-related mutations in the presenilin1 and two genes have been shown to alter the amyloidogenic pathway, producing a significant quantity of Aβ42[25]. Several experiments also show that γ secretase is also associated with lipid draft. Oxidative stress appears to have a role in the etiology of AD. BACE1 and γ-secretase activity are affected by oxidative stress [26].

4. Pathophysiology of Alzheimer's diseases as a consequence of Aβ plaque formation

AD is a neurodegeneration disease that leads to the formation of Aβ plaque, and its consequences showed in **Figures 1 and 2**[27,28].

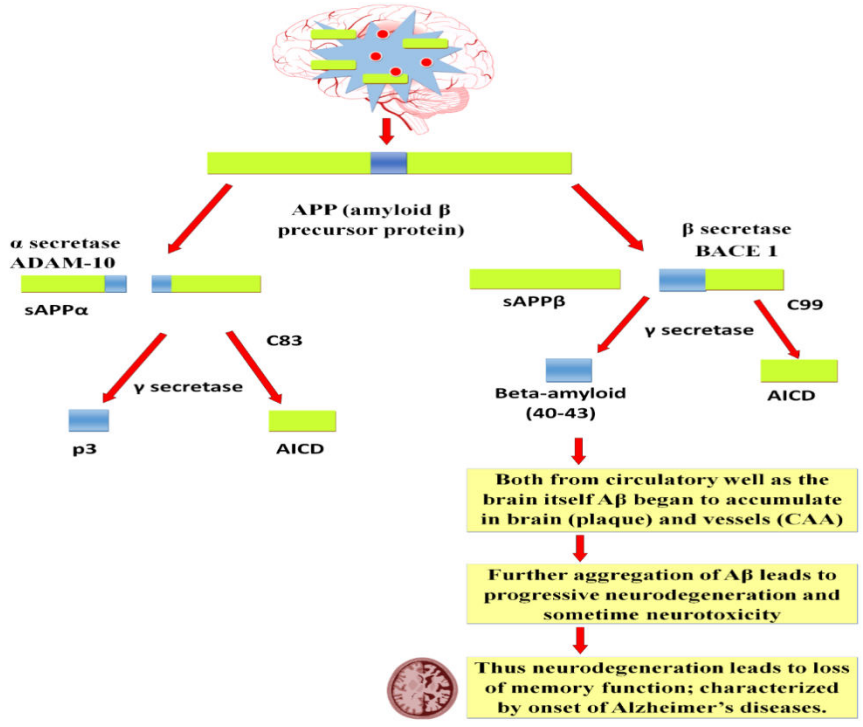

Figure 2: Pathophysiology of Alzheimer's diseases. [APP (amyloid protein precursor) is found in the plasma membrane and platelet granules. Secreted APP and C83 fragments are produced when APP is processed by α-secretase (non-amyloidogenic pathway). Secreted APPα and C99 components are produced when APPβ is processed by β-secretase (amyloidogenic path). Further, cleavage of such fragments by γ secretase leads to the biogenesis of beta-amyloid peptides. It mainly produces 40-43 amino acid peptides. γ additional extracting in the company of secretase has smaller AICD and p3 fragments.]

4.1. Aβ formation with active involvement of platelets

Platelets, essential components of blood cells, also contain APP, which seems to be inserted in the plasma membrane as a granule [27,28]. Total APP residing in blood plasma contributes to around 7mg/ml (70pM)[29]. The bulk of peripheral Aβ (90%) is secreted into the bloodstream by platelets, with A1-40 peptide being the most common[30]. Platelets contain all three secretases isoforms and can cleave APP and produce Aβ [31]. CAA occurs and results in Aβ accumulation in the vessel. Furthermore, the various vascular hazards cause brain hyper-perfusion. In addition, results in formation of toxic molecules thatenters the brain from blood[32] .Blood components, particularly platelets, are thought to have a role in the production of CAA because they actively assist in artery injury repair and also contain a substantial quantity of APP, which generates Aβ 40 [33,34].

4.2. Aβ functions

A few research conducted over the last several decades indicate that in addition to its involvement in neuron toxicity, cadmium is actively engaged in concentration-dependent nervous system regulation[35]. Aβ actively engage in neurogenesis, andresults in neurons development and differentiation. Further,the Aβ40 involves in neurogenesis and forms neutrotrophins (nerve growth factor) [36]. In addition, the synaptic plasticity results in boosting and diminishing of synapses in relation with neurotransmitter [37].This involve in learning process and memory formation; it also enhances long term potentiation (LTP) neuronal transmission [38].Hippocampus an important region in brain mainly involve in memory formation, as a result of the injection of a pico-molar dose of A, memory formation is improved[39].Antioxidant activity; metals such as copper, zinc, and iron may participate in redox reactions in biochemical and create reactive oxygen species (ROS). When present in low concentrations, Aβ works as a scavenger for ROS [40].

4.3. Aβ catabolism

After the formation of Aβ the remaining proteins are have to be cleared through various pathway, Aβ can be degraded enzymatically by peptidase or it can also be cleared by cerebral vessels via special drainage system. Aβ clearance also mediated by microglial phagocytosis [16].The thiol-zinc metallopeptidase IDE (insulin-degrading enzyme) is engaged mostly in hydrolysis of several peptides,including Aβ. In neuroblastoma cells, it is largely cytosolic, although it is also linked to the plasma membrane lipid raft fraction[41]. The bonding between IDE and lipid raft are mediated by brain cholesterol level [42].

ECE (Endothelil-converting enzyme, ECE1 & ECE2). They are the member of M13 zinc binding metalloprotease family having type II membrane structure. In addition, ECE also

contributes in Aβ catabolism [43].ECE1 regulates both extracellular as well as intracellular peptide pool whereas ECE2 regulates only intracellular peptide pool which is a marker of endosomal-lysosomal pathway [44].BACE2 which are localized in intracellular compartment also actively involved in Aβ degradation [45].

4.4. Aβ aggregation and neuronal toxicity

Under certain conditions, Aβ an unfolded protein tends to clump together. It further creates a heterogeneous combination of soluble fibrils, protofibrils, and oligomers. The various experiments showed that soluble oligomer is key pathogenic structure responsible for AD. Aβ oligomer binds with neurons causing neurotoxicity and synapse deformations. Recent research suggests that lipid rafts serve as a pathogenic signalling platform for Aβ receptors such glutamase, nerve growth factor, and insulin receptors [46]. The binding of Aβ oligomer to these receptors causes abnormal receptor localization. Furthermore, it also has a negative impact on their physiological long-term synaptic potentiation. In addition, the LTP act as electrophysiological predictor. It helps in acquisition and remembering. The formation of lipid rafts is essential for the propagation and amplification of A oligomer-mediated neurotoxicity responsible for Alzheimer's disease[47].

Accumulation to Aβ peptide to great extent leads to interfere in various biochemical reactions on accounts of redox mediated ROS and metals thus hypothesized to create an environment of oxidative stress [48].Copper ions that are redox active accumulate in plaque and form the Cu-Aβ complex, which catalyzes the generation of ROS[49].Synaptic loss is more closely linked to cognitive impairment in Alzheimer's disease than the number of Aβ plaques. Synaptic transmission disturbances arise long before the establishment of the signature a deposits[50].

4.5. Aβ clearance

Human brain should maintain a balance between Aβ synthesis and elimination in order to sustain adequate Aβ levels. The three secretases, and Aβ-degrading peptidases, are primary therapeutic targets for AD. Furthermore, inhibiting or modulating γ- and β- secretases, activating α-secretase and Aβ-degrading peptidases are used as therapeutic treatments for AD.Aβ clearance by extracellular chaperones: Albumin, antichymotrypsin (ACT), and complement protein binds to Aβ that is present in cerebral spinal fluid (CSF) and plasma[16,51,52].

4.5.1. Pinocytosis

Fluid phase pinocytosis with extensive production and internalization of pinosomes can rapidly remove soluble Aβ via microglia. However, Aβ (1-42) can cause self-uptake and pinocytosis[53].

4.5.2. Phagocytosis

Microglia are found here. Astrocytes may phagocytose fibrillary Aβ and endocytose monomeric and oligomeric Aβ via actin regulation[54].Receptor mediated endocytosis: Through a variety of receptors, oligomeric and fibrilic Aβ are normally ingested by receptor mediated endocytosis.Furthermore, the Scavenger receptors (SR) such as types A (SR-A), B1 (SR-B1), CD36, and CD40 can adhere to oligomeric, fibrillar Aβ and easily penetrates into the cell [55].

5. Conclusion

The majority of APP is found in nonlipid rafts, with lipid rafts accounting for only a small percentage. In lipid raft fractions, BACE1 is only partly localized.Furthermore, BACE1 raft

association has little effect on APP-cleavage or Aβ production. Alzheimer's patients have an identical type Aβ aggregate throughout the brain, whereas in vitro aggregates have variations. This demonstrates that Aβ aggregate is a highly sophisticated procedure with a mechanism that varies from what has been found in vitro. Besides its function in neurogenesis at higher concentration it tends to damage neuron and also reduce synapse plasticity which further cause the loss of neurotransmitter generally acetylcholine and neurodegeneration occur. Aβ malfunction as a plaque in brain and also in vessel in forms of cerebral amyloidangiopathy which retard the LTP and reduces the neuronal transmission so that fictional loss of memory can be observe in Alzheimer's diseases, dementia an associated part of AD may also be accounts for overproduction and deposition of Aβthrough neural cells.

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List of Abbreviations

AD: Alzheimer's disease; CAA: Cerebral amyloid angiopathy; AChE: Acetyl choline esterase, APP: Amyloid precursor protein; Aβ: Amyloid-β; LR: Lipid rafts; β-CTF: β-C-terminal fragment; ADAM: A disintegrin and metalloproteinase; LTP: Long term potentiation; ROS: Reactive oxygen species; ECE: Endothelil-converting enzyme; IDE: Insulin-degrading enzyme; ACT: Antichymotrypsin; CSF: Cerebral spinal fluid; SR: Scavenger receptors.

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