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Systematic Review

Systematic assessment of pathophysiological mechanisms and their interrelation in progression of Alzheimer's disease

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ABSTRACT

Introduction: Alzheimer's disease (AD) consists of 60-80% of all dementia cases, thus is recognized as the commonest form of dementia. The current challenge to clinicians and researchers in the field of AD is development of treatment plans that can target the progression of pathology at molecular level as well newer diagnostic techniques for early detection and prevention of AD. This could be achieved by enhancing our understanding of the underlying pathophysiology of AD. This is systematic and concise review of various pathophysiological mechanisms contributing to AD.

Materials and Methods: Legitimate indexing portals and search websites were used to carry out the literature search for this article. A combination of MeSH terms and Boolean operators were used. Obtained research articles were carefully assessed first by reading title and abstract and finally by reading the whole text. A set of inclusion and exclusion criteria were used to select the reference articles.

Result: In our literature search 75 articles were obtained from PubMed, Google scholar and Cochrane Library after removing duplicate records. These were screened using titles and abstract. 23 articles were excluded from the study as per the exclusion criteria. Full text of 52 articles were read. 7 articles were excluded, 45 were studied thoughrouly and 30 were referenced during the writing of this review.

Conclusion: Various risk factors – old age, diabetes, smoking, mutation etc contribute to Aβ plaque accumulation due to cleavage of APP protein by α and Υ secretase. Aβ plaque further contributes to accumulation of neurofibrillary tangles, neuroinflammation and oxidative stress. This together with disturbance in Calcium homeostasis and excitotoxicity at glutamate receptors contribute to neurodegeneration and synaptic toxicity.

1. Introduction

On November 1906 at the 37^{th} meet of the Psychiatrists of South West Germany, Alois Alzheimer a well know German Neuro anatomist and Clinical Psychiatrist presented a case history of one of his patients Auguste D who suffered from long standing symptoms of progressive memory loss, emotional disturbances and sleep disorders until her death in April 1906.[1] Upon the histological examination of her brain Alzheimer noted the presence of unusual extracellular clumps consisting of a distinct material and intracellular thread like structures.[1] These unfamiliar findings led to the discovery of a new form neuro degenerative disease and few years later Alzheimer became a household name.[1] Alzheimer's disease (AD) is a "gradual onset disease causing an irreversible progressive

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neurodegeneration leading to progressive memory loss and other cognitive disabilities".[2] AD consists of 60-80% of all dementia cases, thus is recognized as the commonest form of dementia.[3] AD commonly affects the elderly population.[3] The frequency of AD doubles every 5 years after the age of 60 years (4). National Institute of Health of United States Alzheimer's Association (NIH-AA) have described other risk factors associated with AD to be – female gender, smoking (RR-1.59), diabetes mellitus (RR-1.46), depression(RR-1.65), physical and mental inactivity(RR-1.82), poor diet, low educational level(RR-1.59), obesity(RR-1.60) and hypertension(RR-1.61).[4] AD spans over a period of 8-10 years, the clinical phase usually occurs after a period of prodromal or pre clinical stage which usually span over a decade.[5] AD disease is characterised by multiple symptoms which vary depending upon the progression of the disease. The mild stage is characterised by memory loss and other cognitive deficits.[5] However, these deficits do not alter the abilities of the patient to carry out routine activites to a great extent. In the moderate phase patient's finds it difficult to perform their routine tasks and usually require assistance. Symptoms include memory loss, confusion, behavioural and personality changes including anxiety, depression and apathy, frequent mood changes, difficulty in planning and problem solving, poor judgement, language, visual disturbances and problems in understanding spatial relationships and withdrawal from work or social life.[5] Advanced clinical stage includes people requiring help in very basic activities including going to the bathroom etc. As the lesion progresses to higher up and effects the motor cortex, people find problems in movement and become bed ridden. Being bed bound makes the patient susceptible to skin infections, clots and sepsis. Sepsis may result in organ dysfunction. In advanced stages people may have difficulty in swallowing leading to aspiration of food causing aspirational pneumonia.[3]

The current challenge to clinicians and researchers in the field of AD is development of treatment plans that can target the progression of pathology at molecular level as well newer diagnostic techniques for early detection and prevention of AD.[2] This could be achieved by enhancing our understanding of the underlying pathophysiology of AD. The pathology of AD usually starts with Entorhinal cortex and spreads to hippocampus.[6] Thus, memory loss is one of the earliest symptoms of AD. Furthermore, it spreads to posterior temporal lobe and parietal lobe areas AD is a multifactorial process involving brain cells.[6] A number of hypotheses have been formulated to explain the disease process. We have given a short and comprehensive details of each of these hypotheses in this article.

2. Materials and Methods

Legitimate indexing portals and search websites including PubMed, Google scholar and Cochrane Library were used to carry out the literature search for this article. A combination of MeSH terms and Boolean operators were used during search. MeSH terms such as Alzheimer's disease, pathophysiology, amyloid beta peptide, tau protein, presenile, neurofibrillary tangles, neuroinflammation, oxidative stress, Cholinesterase inhibitors and insulin were used during the search process. The literature search was carried out between September to November 2021. Furthermore, textbooks including Harrison's textbook of Medicine and Boron and Boulpaep, Textbook of Medical Physiology and website namely National institute of Health official web portal were referenced during the search process. Obtained research articles were carefully assessed first by reading title and abstract and finally by reading the whole text. A set of inclusion and exclusion criteria were used to select the reference articles. Narrative reviews, clinical trials and systematic review and meta-analysis describing pathophysiological mechanisms in AD and pharmaceutical research in AD published in indexed peer reviewed journals were included in the study. Articles published before year 2005, cross sectional studies, commentaries, opinions and case studies were excluded from the literature search. Finally, some of the articles cited in the selected studies were also referenced in the present study.

3. Results

In our literature search 75 articles were obtained from PubMed, Google scholar and Cochrane Library after removing duplicate records. These were screened using titles and abstract. 23 articles were excluded from the study as per the exclusion criteria. Full text of 52 articles were read. 7 articles were excluded for the following reasons- 2 studies were opinions and commentaries regarding different pathophysiological aspects of AD, 3 articles were written in language other than English and 2 articles were not published in peer reviewed journals. Finally, 45 were studied thoughrouly and 30 were referenced during the writing of this review.

4. Discussion

4.1. Aβ amyloid hypothesis

This is the most popular and widely researched hypothesis for AD pathogenesis.[7] The centrepiece of this hypothesis is a neuronal transmembrane protein called the Amyloid Precursor Protein (APP) (APP). Cleavage of this protein takes place through α, b and ϒ secretase enzymes. While cleavage with and a and ϒ Secretase produces soluble APP or s APP fragments that is non amyloidogenic, cleavage

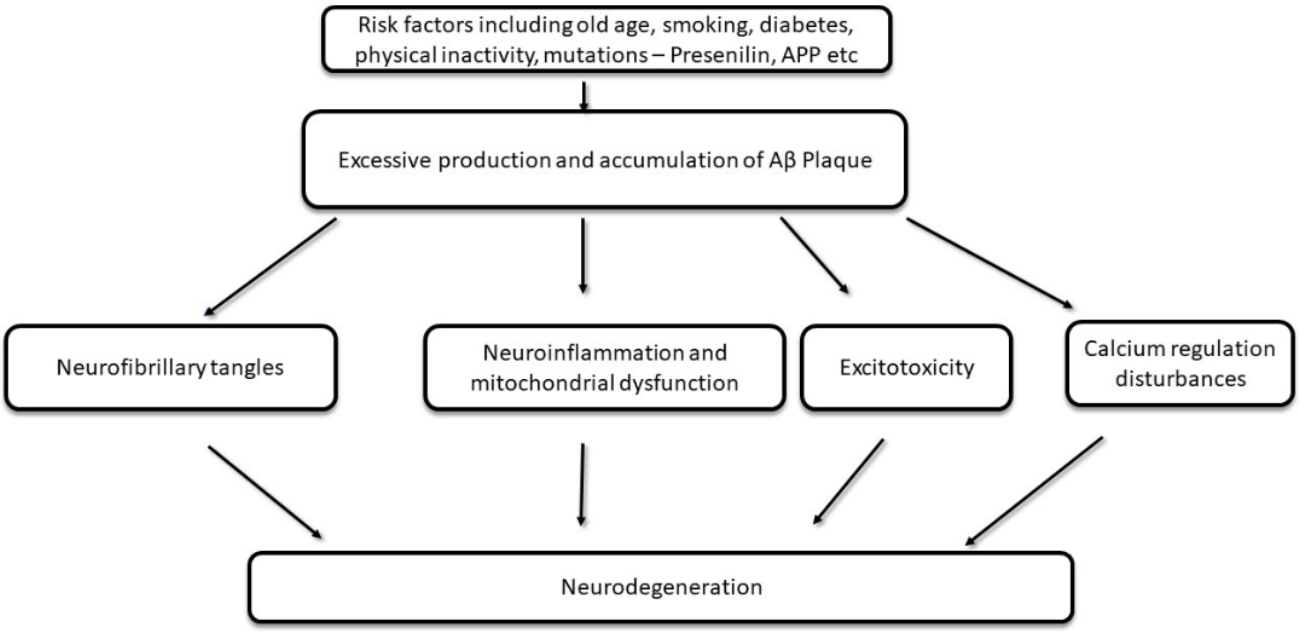

Fig. 1: Overview of different pathophysiological mechanisms in Alzheimer's disease.

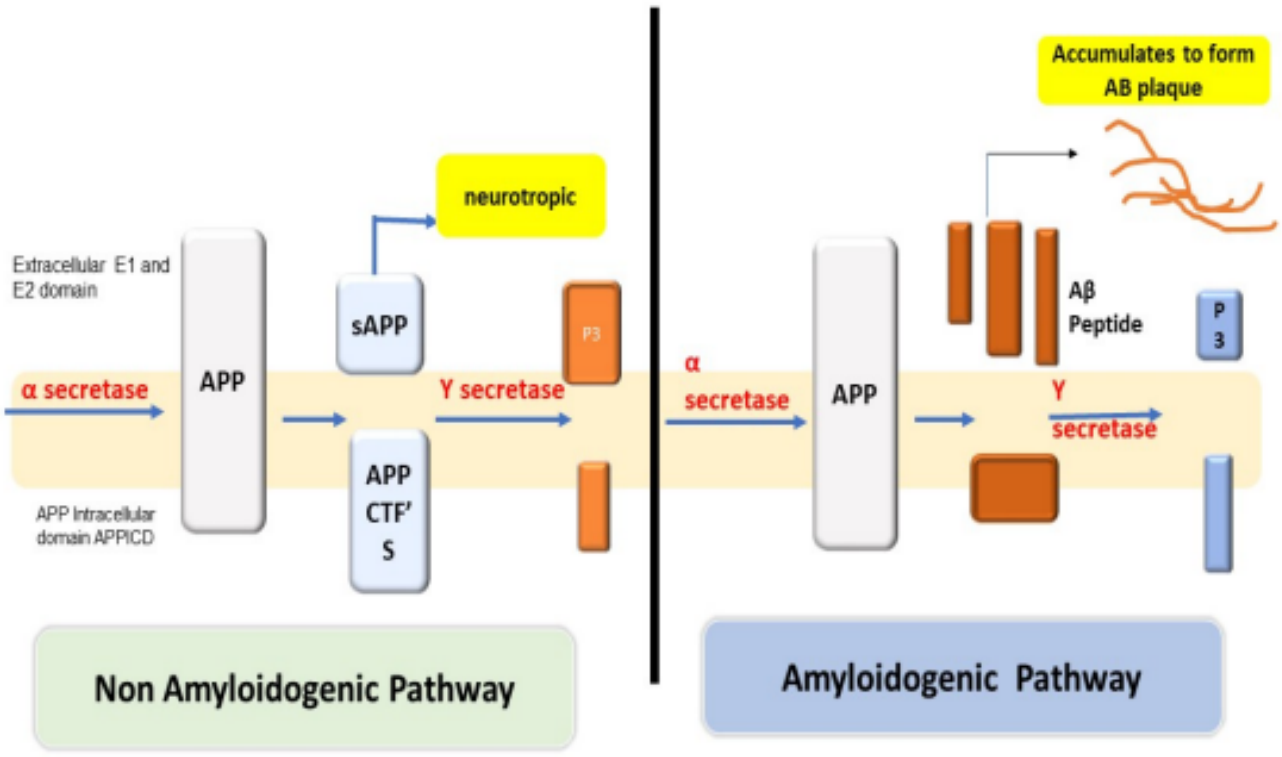

Fig. 2: Overview of amyloidogenic and non amyloidogenic pathways.

by β and ϒ secretase enzymes produces a sticky insoluble Aβ amyloid protein that accumulates between neurons and interferes in their communication. Accumulation of Aβ plaque is considered as a major pathophysiological mechanism of AD.[7]

4.1.1. Structure of APP

APP is a membrane protein with single transmembrane segment and huge N terminal extracellular domain.[8] It is a part of larger group of proteins including Amyloid Precursor like Protein APLP 1 & 2 in mammals.[8] APP & APLP are abundantly found in brain however they are also expressed in cells of other parts of body.[8] The gene for APP protein lies in chromosome 21. There are many isoforms of APP protein. APP isoforms containing 695,751 &770 amino acids produce Aβ segment. APP695 is the major source of APP in human brain.[8]

Even though APP is a single pass membrane protein it consists of many individual domains. These domains perform a variety of functions such as binding extracellular proteins, triggering cellular pathway, cell to cell adhesion etc.[9] The extracellular portion of APP consists of E1 and E2 regions. E1 region is made up of N terminal Growth factor like domain (GFLD) & Copper binding domain (CuBD). E2 region consists of Carbohydrate APP domain (CAPPD) which consists of two N glycosylation sites and juxta membrane domain. E1 and E2 domains are attached by an Acidic or linker domain. The juxta membrane domain continues into the trans membrane portion of protein which is followed by APP Intracellular domain (APPICD).[9]

4.1.2. Processing of APP

After its formation in RER APP enters the cell membrane through Constitutive secretory pathway.[9] APP is sequentially broken down into smaller fragments by three proteases α,β and ϒ proteases. There are two major pathways involved in breakdown, amyloidogenic and non-amyloidogenic pathways.[9]

4.1.2.1. Non amyloidogenic pathway. This is the predominant pathway for APP processing. The first step is cleavage by a secretase enzyme at the transmembrane segment. This results in release of entire ectodomain of APP from the membrane known as soluble or sAPPα and membrane attached carboxyl terminal fragments (APP CTFs).[9] APP CTFs are subsequently degraded by ϒ secretase enzyme leading to formation of two different segments- P3 segment and APPICD. sAPPα once released in extracellular environment is known to exert neurotropic effect. This pathway produces soluble proteins and that do not accumulate between cells.[9]

4.1.2.2. Amyloidogenic pathway. The first step of this pathway is mediated by b secretase enzyme. The most important β secretase enzyme is Beta-site Amyloid precursor protein Cleaving Enzyme 1 or BACE 1 enzyme which is an aspartate protease.[8] β secretase attacks the extracellular domain of the APP protein and cleaves it to form sAPP b and APP CTFb. CTF b is cleaved further by ϒ secretase to produce Aβ and APPICD.[8] Aβ is a non-soluble amyloidogenic protein that accumulates between neurons and blocks communication between neurons.[8]

4.1.3. Accumulation of insoluble Aβ plaque

In diseased state, after the cleavage by β and ϒ secretase enzymes, the insoluble Aβ plaque accumulates in the intercellular clefts between neurons. The aggregation of Aβ monomer takes place in different forms namely protofibrils, oligomers and amyloid fibrils. Insoluble amyloid fibrils further aggregate to form amyloid plaques.[10] Aβ plaques start appearing in the neocortex of the brain during the initial stage of AD and further spreads to Hippocampus, amygdala and basal ganglia.[7] In later stages of the disease Aβ plaque can be seen in hind brain regions including cerebellar cortex and brain stem. The accumulated Aβ plaque not only interferes with intraneuronal communication but interacts with several receptors leading to neurotoxicity.[10] This binding takes place with proteoglycans, lipids and proteins and can lead to massive calcium influx, mitochondrial dysfunction and oxidative stress. Such receptors include p75 neurotrophin receptor (P75NRT), the low-density lipoprotein receptor-related protein (LRP), cellular prion protein (PrPc), metabotropic glutamate receptors (mGluR5) etc. Some of such receptors bind with Aβ to internalise it in cell triggering cellular defects.[11]

There are two form of Aβ polymers that accumulate in the disease process. Aβ 40/Aβ42. Aβ40 is more abundant and less toxic as compared to Aβ42. Aβ40/Aβ42 accumulation blocks neuronal communication and causes mitochondrial dysfunction, oxidative stress, increased calcium influx,

diminished energy metabolism and glucose regulation, which leads to neuronal degeneration.[10]

In early onset forms of AD (familial forms of AD), the underlying disease process occurs due to increased accumulation of Aβ plaque while in late onset AD underlying defect is due to failure of clearance of accumulated Aβ plaque due to insufficient working of mechanisms such as defects in proteolytic enzymes such as neprilypsin etc.[10]

4.2. The Tau (τ) Protein hypothesis

Tau is a microtubule associated protein usually found within the neurons. Tau is most prominently found in the axon of neurons followed by somatodendritic compartment and glial cells.[12] Tau proteins are mostly associated with microtubules in cytoplasm but also occur in association with ribosomes. Tau proteins in association with microtubules contribute to providing structural framework for the cell.[12]

However recent research point towards that the major function of Tau proteins is regulating vesicular transport along the microtubules in association with dynein and kinesin. In 1980's it was discovered that Tau protein was an important component of the intracellular neurofibrillary tangles (NFT) associated with AD. Later it was proposed that Tau proteins in NFT were abnormally phosphorylated. Phosphorylation at certain sites may cause Tau to dissociate itself from the microtubule, initiating formation of NFT. Aβ plaque meets several receptors to activate kinases, these enzymes when comes in contact with tau protein, cause its hyperphosphorylation. After hyperphosphorylation tau proteins oligomerise and loses affinity to microtubules as a result of which the tubules loses its continuum and divides into big chunks of tubular subunits which along with tau proteins form Tau filaments. Tau filaments accumulate to form NFT. Accumulation of these fibrillary and insoluble NFT in cytoplasm causes abnormal signal processing and initiation of apoptotic pathways.[13] Glycogen Synthase kinase 3 (GSK3β) and cyclin-dependent kinase 5 (CDK5) activated by Aβ plaque are some of the kinases that are involved in the regulation of tau phosphorylation.[13] As it is one of the kinases that is central to may pathological pathways related to AD many pharmaceutical researches were carried out to find chemical blocker for GSK3β. Lithium has been known to block the effect of the enzyme and is also known as the mood stabiliser as it has been used in bipolar disorders.[14]

GSK3β enzyme has been known to play an important role in oxidative stress and contributes to Aβ plaque formation. It further leads to neurotoxicity by stimulating tau hyperphosphorylation. Tau hyperphosphorylation is also stimulated by interaction of CDK5 with Aβ plaque. Other enzymes that have been implicated to stimulate tau phosphorylation include Mitogen activated kinase (MAP Kinase), ERK1 and -2, microtubule affinity-regulating kinase (MARK) etc.[15]

4.3. Cholinergic hypothesis

Acetyl choline (Ach) is the major excitatory neurotransmitter in brain. 30-40% of neurons distributed in brain are Cholinergic neurons. Cholinergic fibres from reticular area in brain stem diffusely innervate areas of neocortex, hippocampus and entorhinal cortex via thalamus.[16] These cholinergic fibres help in maintaining background neuronal activity and plays an important role in awareness, attention, memory and cognition.[16] In AD early loss of cholinergic neurons are observed in hippocampal area leading to decline in memory.[17] These changes are attributed to deposition of Aβ plaque and formation of neurofibrillary tangles. FMRI and other neuroimaging techniques have found cerebellar atrophy starting from medial temporal lobe and spreading to temporal, frontal and parietal neocortex along with ventricular dilation in AD.[18] This can lead to disruption in neuronal connections causing memory and cognitive loss. It has been seen in animal experiments that lesions which disrupts the connection of cholinergic fibres from hindbrain to neocortex and hippocampal areas in rats impairs their performances in memory-based tests.[17] Similar results have been observed in rats given Atropine, centrally acting nicotinic-cholinergic antagonists such as mecamylamine and muscarinic M1 blockers. Physostigmine has been clinically given AD which is Acetylcholine esterase enzyme inhibitor and is currently one of the therapies of choice in AD.[17]

4.4. Excitotoxicity hypothesis

Glutamate is leading excitatory transmitter in CNS. There are two types of receptors for glutamate distributed in brain. One is metabotropic that is responsible for mediating synaptic plasticity in regions of hippocampus and cerebellum contributing to learning and motor activity and other is inotropic receptors which are of three kinds-AMPA, NMDA and kainate receptors.[19] NMDA receptors are involved in the process of long-term potentiation that is important for converting short term memory to long term memory.[19] Glutamate is produced from glutamine in the cytoplasm of neurons by glutaminase enzyme. Glutamine is transported into the cell from interstitial fluid.[20] Inside neurons glutamate is stored in vesicles. Receptors VGLUT 1 and VGLUT 2 maintain the levels of glutamate inside the vesicles. Neurons release glutamate into synaptic cleft in response to a neuronal signal. Astrocytes re uptakes the glutamate released into the synaptic cleft through receptors EAAT 1 and 2. This glutamate is converted into glutamine by enzyme glutamine synthase and released into extracellular space where it is again taken by neurons.[20] This Glutamate cycle is disturbed during AD. Aβ peptides accumulated in AD in intercellular space producing the following – 1. Inhibition of reuptake of glutamate by astrocytes 2. Inhibition of glutamate receptor activity 3. Increase in glutamate release. All these effects are known to produce glutamate excitotoxicity in AD.[20] Increased Glutamate at Glutaminergic synapse can produce prolonged activation of NMDA receptors in post synaptic membrane leading to increased calcium influx which can cause excitotoxic cell death through a number of pathways such as activation of calpain, depolarization of mitochondrial membrane and release of cytochrome C and release of reactive oxygen species finally leading to activation of apoptotic pathways.[21]

4.5. Calcium homeostasis in AD

Calcium is a major intracellular messenger and generates concentration gradients across membranes.[16] Calcium homeostasis is important to maintain major cellular pathways and is vital to cell survival. Calcium is

continuously regulated across Endoplasmic reticulum (ER) where Calcuim ATpase pump helps in maintaining Ca concentrations inside ER. Calcium is also present inside mitochondria.[16] AD effects the movement of Ca across the cell membrane as well as its compartmentalisation in different organelles this happens as a result of various processes such as glutamic excitotoxicity, oxidative stress and mitochondrial cascade, disruption in function of membrane Ca channels and compromised calcium buffering mechanisms.[22] Increased accumulation of intracellular Ca in AD causes cleavage of intracellular proteins, enhanced accumulation of Aβ peptide and formation of neurofibrillary tangles, increased formation of ROS, reduced cellular metabolism and activation of apoptotic pathways.[23]

4.6. Role of oxidative stress and mitochondrial cascade in AD pathogenesis

Oxidative stress is characterised by imbalance between production of reactive oxidative species and levels of anti-oxidants required to counter them. ROS chemically destroys several sub cellular elements such proteins, lipids and nucleic acid. In addition to Aβ plaque and NFT, OS has been considered an important feature of AD.[24] ROS has bidirectional relationship with AB plaque accumulation. Reaction of metal ion such as zinc or copper with Aβ plaque can produce ROS and Oxidation of Aβ peptide chains can produce a Aβ plaque that is hard to remove.[24] GSK3β enzyme whose production increases with Aβ accumulation, can further oxidative stress by changing mitochondrial membrane permeability. Mitochondrial permeability changes due to the downstream effect of GSK3β on mPTP protein in the inner mitochondrial membrane. Opening of this protein causes entry of any material less than 1500 Da in mitochondrial matrix producing its swelling and mitochondrial dysfunction.[25] It has been proposed that oxidative stress produces mitochondrial abnormalities including such as alteration of membrane potential, reduced antioxidant enzymes and energy production which further increases oxidative stress. This vicious cycle promotes caspase activation causing cell death. Oxidative stress further promotes hyperphosphorylation of tau proteins leading to formation of NFT.[25]

4.7. Neuroinflammation in AD

There are few reasons as to why the Amyloid cascade hypothesis and Tau protein hypothesis alone cannot explain the pathogenesis of AD. Firstly, Aβ plaque has been histologically found in autopsies of normal elderly without AD and secondly, it has been shown in many animal and human models that therapies that target Aβ plaque formation alone do not stop the advancement of the disease process. Chronic inflammation has been found to be histologically a hallmark of AD.[26] Although acute inflammatory reaction protects the brain tissues against harmful Aβ plaque accumulation inflammation, when continued for a longer period of time damages the neural tissues.[26] Aβ plaque promotes inflammatory process by interacting and activating a number of pro inflammatory receptors on microglia. Chronic inflammation produces a disbalance between pro-inflammatory cytokines and anti-inflammatory molecules, pro-inflammatory cytokines activate CDK's which are known to promote hyperphosphorylation of Tau protein and accumulation of Aβ plaque, these cytokines also induces the production of NO synthase protein by the microglial cells, NO synthase accumulate in intracellular spaces inhibiting synaptic plasticity and lastly these molecules inhibit the ability of microglial cells to clear Aβ plaque.[27] A number of cytokines are released by activation of immune cells such as IL Iβ and IL 18 while other cells such as endothelial cells can also release inflammatory cytokines such as IL 6 and CCL2.[27] Recent evidences reflect towards a role of systemic inflammation in progression of AD.[15]

4.8. AD as type 3 diabetes mellitus

GLUT 1 and 3 are major transporters of glucose in brain neurons which are not dependent on insulin for their action, hence majority of glucose transport in brain occur independent of insulin and brain has been considered insulin-independent organ for a long time.[28] However, research in the area of neuro endocrinology reveals that insulin acts as a major neuropeptide in brain regulating feeding behaviour. In a study chronic delivery of intra nasal insulin reduces food intake in men and eating of food post prandially by women.[29] The intake of Insulin in brain is mediated through BBB via insulin receptors.[29] These receptors are not uniformly distributed across BBB and is more densely present in regions concerned with memory and learning like hippocampus, entorhinal cortex and frontal cortex. Clinically there seems an important link between Type 2 DM and AD. In a community-based study, with 9 years of follow up the risk of AD in people with Type 2 DM was 65% much higher than normoglycemic population.[30] This could be due to linkage between insulin resistance and cognitive decline.[30]

5. Conclusion

AD is the most common cause of dementia in elderly population. Inspite of many pharmaceutical and molecular research, there is dire need to fill in the gaps in our understanding of the disease's progression and the interconnection of various pathophysiological mechanisms. This work presents a systematic and concise presentation of various pathophysiological mechanisms in AD. This will provide a comprehensive tool to clinicians and

researchers seeking to enhance their understanding of various pathophysiological mechanisms of AD. Various risk factors – old age, diabetes, smoking, mutation etc contribute to Aβ plaque accumulation due to cleavage of APP protein by α and Υ secretase. Aβ plaque further contributes to accumulation of neurofibrillary tangles, neuroinflammation and oxidative stress. This together with disturbance in Calcium homeostasis and excitotoxicity at glutamate receptors contribute to neurodegeneration and synaptic toxicity.

6. Conflict of Interest

The authors declare no relevant conflicts of interest.

7. Source of Funding

None.

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