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Review Article

OXIDATIVE STRESS IN ALZHEIMER'S DISEASE–EVALUATING THE AMYLOID BETA HYPOTHESIS

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ABSTRACT

Dementia is defined by the debilitation of cognition and behavior of individuals more than 65 y. Alzheimer's disease (AD) is the most pervasive pervasive form of dementia, afflicting around 47 million individuals worldwide. Oxidative damage is a significant component in the pathophysiology of Alzheimer's disease (AD). Assessment of Alzheimer's disease mind has shown a lot of oxidative harm, related with both trademark pathologies (senile plaques and neurofibrillary tangles) just as in typical seeming pyramidal neurons. By the by, the process that eventually causes disruption of redox balance and furthermore the origin of the free radicals are as yet hazy. There is likewise the accessibility of proof that oxidative stress may enhance the conglomeration and production of Aβ and furthermore help the polymerization just as phosphorylation of tau, subsequently making a pernicious cycle that invigorates the development and even commencement of Alzheimer's. These neurotic trademarks have complex proportional collaborations with cholinergic abrasions. This review may give complemental data for understanding the relationship between oxidative stress, amyloid plaques, tau proteins and cholinergic system in processing of AD.

Keywords: Oxidative stress, Free radicals, Alzheimer's disease, Amyloid plaques, Tau proteins, Acetylcholine

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INTRODUCTION

Alzheimer's disease is a developing neurodegenerative disorder frequently connected with memory shortages and a decrease in cognition, although more uncommon clinical demonstrations are progressively recognized [1]. AD represents over 80% of dementia cases worldwide in old individuals. It results in the gradual decline of behavior, mental and capacity to learn [2]. The worldwide burden of AD is anticipated to speed up from 26.6 million cases in 2006 to 106.8 million by 2050. The complete expected overall expenses of dementia were US$ 604 billion of every 2010, identical to 1% of the world's Gross Domestic Product (GDP) [3]. Likewise, 20 to 30% of early AD patients show remarkable depressive manifestations and state of mind changes. Patients in leading phases of AD experience the ill effects of extreme cognitive decline, bewilderment, hallucinations and also lack of self-sufficiency [4].

AD involves several causes and it is considered as a complex disease, being a foremost reason for dementia among older individuals. Although old age is the most popular danger factor for AD, a few people may foster AD at more youthful age. Accordingly, based on the time of onset, AD can be grouped into two types: the first as Early-onset AD (EOAD), which normally occurs before the age 65 y, and the second as late-onset AD (LOAD) in those individuals who is more aged than 65 y. EOAD is brought about by uncommon and overwhelmingly genetic mutations in PSEN1, and PSEN2 and APP. LOAD has a strong hereditary segment, and it is additionally called sporadic [5]. As of now, the solvent protein components of insoluble neurotic lesions like neurofibrillary tangles and senile plaques are considered to be the predominant pathology. These uninvited depositions are malicious to the neural connections and result in the pathological course of the disease [6]. Oxidative equilibrium is arising as a significant issue in understanding the pathogenesis of AD. Assessment of Alzheimer's infected brain has shown a lot of oxidative harm, related with both trademark pathologies (decrepit plaques and neurofibrillary tangles) just as in typical seeming pyramidal neurons [7].

Oxidative stress

Hydrogen peroxide (H_2O_2), Superoxide radicals ($O_2^{\bullet -}$), singlet oxygen ($^1O_2$) and hydroxyl radicals (•OH) are often mentioned as reactive oxygen species (ROS); they are produced as metabolic derivative by biological systems. Production of profoundly Reactive Oxygen Species (ROS) is a necessary element of typical cellular function like mitochondrial respiratory chain, ovulation, arachidonic acid digestion, phagocytosis and fertilization [8]. At the point when the production of ROS enhances, they begin showing destructive impacts on significant cell structures like proteins, nucleic acids and lipids [9].

A free radical can be termed as a molecule or an atom consisting at least one unpaired electrons in a valence shell or external orbit and is equipped for independent presence [10]. Because of the presence of an unpaired free electron, these particles are profoundly reactive. They are significant intermediates in natural phenomenon engaged with cytotoxicity, neurotransmission and control of vascular tone [11].

Oxidative stress is a process that reviews an unevenness between the generations of reactive oxygen species, thus called oxidants and their eradication by defensive systems [12]. Oxidative stress is faced by cells after bacterial disease and in a condition of inflammation furthermore, is indeed essential for the primary innate immune defense of the body, including likewise the prominent oxidative explosion of macrophages and monocytes [13]. Oxidative stress is likewise generated by Reactive Nitrogen Species (RNS), which incorporates nitrite, nitrate, nitric oxide, nitric dioxide and peroxynitrite [14]. RNS like nitrogen dioxide, peroxynitrite and nitrosoperoxycarbonate are among the most harming species available in biological systems because of their capacity to cause alterations of key biomolecular frameworks through nitration, oxidation and nitrosylation [15].

Reactive species or free radicals incorporate reactive oxygen and nitrogen species together and so-called reactive oxygen-nitrogen species (RONS). RONS are profoundly reactive because of the availability of unpaired valence shell electrons or non-static bonds, and their appropriate regulations are crucial for an effective immune reaction and for restricting tissue harm [16]. Oxidative stress is firmly associated with nitrosative stress. In general, the uncontrolled generation of ROS or the losses of cell evacuation of these species or both are answerable for enhanced oxidative pressure. When ROS levels are upgraded, responses among ROS and RNS happen and results in nitrosative stress [17].

ROS are created through various cell pathways including protein tyrosine kinase, calcium dependant pathway, protein tyrosine phosphatase, mitogen enacted protein kinase, a serine-threonine kinase, G–Protein-coupled receptor, phospholipase, NF κB, ion channel receptor, cytokines receptors, epidermal growth factor and growth receptor [18]. The primary provenance of ROS is in the electron transport chain (ETC) at the mitochondrial internal membrane, where energy is created as ATP [19]. The superoxide radicals are delivered at two significant locales in the electron transport chain, to be specific, complex I i. e NADH dehydrogenase and complex III (ubiquinone cytochrome c reductase). The exchange of electrons from complex I or II to coenzyme Q or ubiquinone (Q) brings about the development of the decreased type of coenzyme Q (QH2). The reduced structure QH2 recovers coenzyme Q by means of an unsteady intermediary semiquinone anion (·Q-) in the Q-cycle. The assembled ·Q-quickly moves electrons to molecular oxygen prompting the arrangement of superoxide extremist. The production of superoxide is non-enzymatic and thusly the higher the metabolic rate, the more prominent is the generation of the ROS.

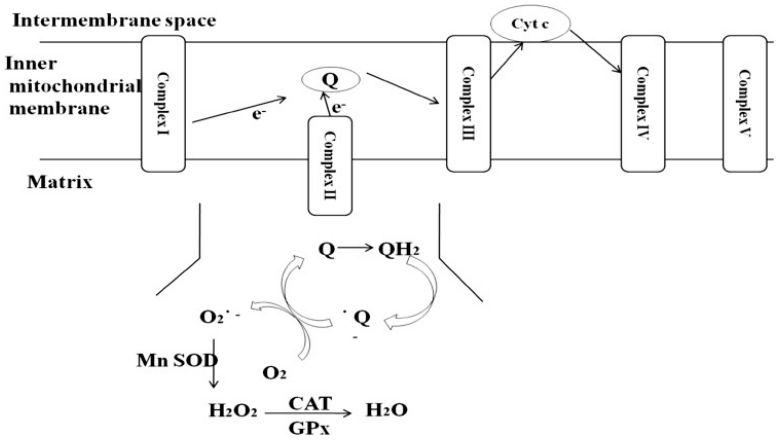

Fig. 1: Mitochondrial ROS production [10]

The mitochondria ETC contains various redox pivots that exudes electrons to oxygen and consists the fundamental sources of O2•- in most of the tissues. In this manner, the major enzymatic derivations of O2•- are NADPH oxidases situated in different cell layer, including macrophages, polymorphonuclear and endothelial cells, just as cytochrome P450and H2O2 -dependent oxygenases. Another enzymatic derivation of O2•- as a wellspring of OH• is the proteolytic transformation of xanthine dehydrogenase to xanthine oxidase [20].

The O2. extremists can likewise react with mitochondria determined Nitric Oxide to produce harmful peroxynitrite radicals. Superoxide radical production in detached mitochondria basically relies upon accessible local oxygen level, the levels of diminished redox proteins and the second-order rate constants of the responses among oxygen and the redox proteins. It is necessary to understand that the consistent state level of ROS will rely on the harmony between the rate of ROS creation and ROS generation and mitochondria indeed can scavange H2O2 at a higher rate.

However, mitochondrial transmembrane electrochemical gradient, NADH/NAD+ratio, QH_2/Q ratio and local concentration of oxygen are important determinants of *in vivo* ROS production in mitochondria [21].

The proof to date for oxidative pressure in Parkinson's disease, AD and other neurodegenerative diseases is strongly effective. Clinical investigations show that various events related with Alzheimer's are fit for reviving the generation of free radicals and depletion of antioxidant levels [8].

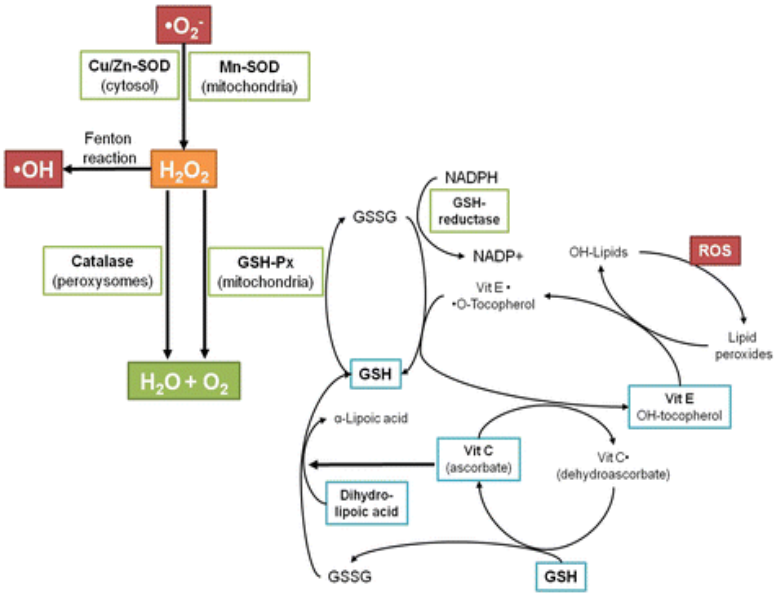

Fig. 2: Antioxidant defenses in the organism [23]

Antioxidant is a substance adequately stable to give an electron to a rampaging free radical and counteract it, hence lessening its ability to harm. These antioxidants defer or hinder cell harm essentially through their free radical scavenging property. These low-atomic antioxidant agents can securely collaborate with free radicals and end the chain reaction before essential particles are damaged [22].

The antioxidants can be endogenous or got exogenously as a portion of a diet or as dietary enhancements [23]. Endogenous compounds in cells can be grouped as non-enzymatic antioxidants and enzymatic antioxidants. The significant antioxidant enzymes straightforwardly engaged with the balance of ROS and RNS are: catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GRx) and glutathione peroxidase (GPx). The non-enzymatic antioxidants are likewise isolated into metabolic antioxidants and nutrient antioxidants. Metabolic antioxidants be included in endogenous antioxidants, are formed by digestion in the body, like glutathione, lipoid acid, L-ariginine, coenzyme Q10uric acid, melatonin, bilirubin, transferrin, metal-chelating proteins and so on. While nutrient antioxidants be included in exogenous antioxidants, are compounds which can't be generated in the body and should be given through food sources or enhancements, like vitamin C, vitamin E, carotenoids, flavonoids,trace metals (selenium, manganese, zinc),omega-6 and omega-3 unsaturated fats, and so on [24].

Oxidative stress and ad

A number of proof exhibits that oxidative stress makes destruction to cell actions with aging and is associated with various age-related issues including atherosclerosis, joint pain, and neurodegenerative problems. The neurodegenerative disease getting the most consideration has been AD, in which a rise happens in the oxidation of brain lipids, proteins, carbohydrates and DNA. Since the brain is generally made out of simply oxidized lipids, has a high oxygen utilization rate, and dearth of antioxidant protection, it is very defenseless against oxidative injury [25].

The neurotoxic Aβ peptide, which is the neuropathological analytic model of the disease, along with τ protein, form intermediary of neurodegeneration, which is among the principle causative elements of disabled synaptic versatility, neuroinflammation, part of vascular reactivity destruction, cholinergic denervation, synapse disproportion, loss of neurons, dendritic changes and generous synaptic loss through oxidative stress [23].

The amyloid precursor protein/amyloid β metabolism

The amyloid precursor protein (APP) is one individual from a group of related proteins that incorporates the amyloid precursor-like proteins (APLP1 and APLP2) in mammals and the amyloid precursor protein-like (APPL) in Drosophila [26]. APP is made out of a huge ectodomain, an intramembranous segment and a short intracellular tail [27]. The APP gene is situated on chromosome 21 in humans with three significant isoforms emerging from alternative joining. These are APP695, APP751 and APP770 (consisting 695, 751, and 770 amino acids, respectively) [28]. APP is related with the development of neurons, an outgrowth of neurites, and the transport of axons [29].

APP is alternatively metabolized by two distinct routes, i.e., the non-amyloidogenic and the amyloidogenic pathways [30]. In the non-amyloidogenic one (overwhelming), APP is first separated by α-secretase and afterward by γ-secretase to form shortened Aβ17–40/42 (P3) peptides or by β-secretase to prompt the arrangement of the shortened Aβ1–16 peptide.

In the amyloidogenic one, which happens to a minor extent, APP is divided continuously by β-and γ-secretases prompting the arrangement of full-length Aβ peptides (mostly Aβ1–40/42). Both pathways likewise lead first to the arrangement of amino-terminal portions (discharged APP (sAPP) α or β) and carboxy-terminal portions (CTF83 or CTF99) and afterward to the development of the amino-terminal APP intracellular domain (AICD). Depending upon the specific area of the cleavage by γ-secretase, a few lengths of peptide can be produced, from Aβ1–38 to Aβ1–43. Notwithstanding, the most generous species formed in the brain are Aβ1–40 and less significantly Aβ1–42 [31].

Single atoms of β-amyloid-42 have a characteristic affinity to match up with one another to frame a dimer or a trimer or agglomerate of a lot more β-amyloid molecules leading to amyloid plaques.

In mammals also, the development of β-amyloid monomers, dimers, trimers, and multimers happens before the demise of neurons and before the accumulation of amyloid plaques in transgenic mice that buildup more APPs [32].

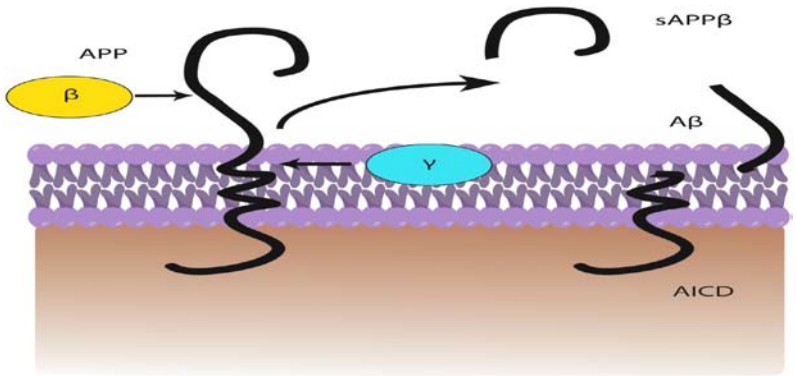

Fig. 3: A general depiction of amyloidogenic processing. Amyloid precursor protein (APP) is cleaved by β-secretase followed by γ-secretase within the bilayer to produce a fragment of amyloid-beta peptide (Aβ), sAPPβ, and AICD [33]

However, during amyloidogenic processing, APP is sequentially cleaved by BACE [membrane-tethered protease also called as beta amyloid cleaving enzymes], or β-and γ-secretases to mainly generate $Aβ_{38}$, $Aβ_{40}$, and $Aβ_{42}$ fragments. Insoluble $Aβ_{42}$, showing higher rate concentration in AD patients, is more inclined to agglomerate. In a physiological condition, over 90% of Aβ is as Aβ40 while below 5% is created as the longer type of Aβ42. As of now, in excess of 30 coding transformations in the APP gene have been found [34-37].

Moreover, investigation of Aβ40 generation *in vitro* and *in vivo* upon pharmacological or hereditary restraint of mitochondrial ETC, either by focusing on complex I and additionally complex III, has exhibited that upgraded production of ROS by mitochondria builds BACE1 activity and thusly advances amyloidogenic processing of APP and overproduction of Aβ [38]. Additionally, both presenilin 1 (PSEN1) and 2 (PSEN2) manage the proteolytic capacity of γ-secretase, and transformations in these proteins can change the activity of γ-secretase and increment the proportion of Aβ in early-onset types of AD [39].

More signs of the early association of the oxidative pressure in AD pathogenesis come from the information showing that markers of oxidative stress in the APP23 mice, conveying APP KM670/671NL transformation, and triple transgenic mice, holding onto APP

KM670/671NL, PS1 M146V, and Tau P301L changes, are available generally right on time, before the development of amyloid aggregates. Aβ production in the oxidative conditions may be additionally influenced by changes in the function of the PSEN1/γ-secretase complex. Injection of 4-hydroxy-2-nonenal (4-HNE) or 4,4-dithiodipyridine (DTDP) into the mouse brain has been accounted for to instigate pathogenic change in the course of action of PS1 subdomains inside the γ-secretase complex, bringing about upgraded production of longer, more subjective to agglomeration of Aβ species (Aβ42), comparative with the shorter types (Aβ40).

Significantly, it has been accounted for that ROS can tweak Aβ generation/discharge yet additionally, Aβ can equally advance unrestricted ROS production in a dangerous process. The impeding role of APP/Aβ in the elicitation of oxidative stress has been additionally announced in several *in vivo* examines. For instance, a transgenic AD mouse model, holding onto APP KM670/671NL and APP V717F changes, has been accounted for to introduce raised levels of protein and lipid oxidation markers, like protein carbonyls, 3-nitrotyrosine (3-NT), and 4-HNE. In addition, intracranial imaging of APP KM670/671NL, PS1dE9 mouse brains have shown that senile deposits are straightforwardly answerable for the generation of ROS [38].

ROS action has for quite some time been perceived to influence DNA transcription through its oxidation of DNA and related proteins. Epigenetics alludes to the progressions in the expression of gene through chemical activities, like histone alteration and DNA methylation, without the interruption of the sequence of DNA. As of late, investigations of the epigenetic regulation process present a new knowledge into OS and its connection to AD. A few investigations have uncovered the epigenetic control of Aβ generation in the development of AD. Sung *et al.* also, Chouliaras *et al.* have reported that not exclusively is there a worldwide decline of DNA methylation in the hippocampus of postmortem AD patients, yet additionally, APP-related changes cause an epigenetic shift in an AD model cell line [40].

Tau protein

Oxidative stress is found to be a noticeable early event in the pathogenesis of AD, adding to tau phosphorylation and the development of neurofibrillary tangles [NFTs]. Notwithstanding, the relationship and fundamental tool between oxidative stress and tau hyperphosphorylation stay shifty. Unsaturated fat oxidative products give an immediate connection between the systems of how oxidative stress prompts the development of NFTs in AD [41]. Tau is a microtubule-related protein and upholds microtubules by configuring congregations of tubulin subunits. Tau is a phosphoprotein and its level of phosphorylation directs microtubule polymerizing action [42]. As per current AD speculations, (a) tau turns out to be strangely phosphorylated, (b) separates from microtubules, and (c) agglomerates into NFTs [43].

Audrey *et al.* found in neuron culture assays, exposed to oxidative pressure, an amassing of dephosphorylated tau in the nuclei. Utilizing immunoprecipitation tests, the capacity of tau to collaborate with neuronal DNA under thermal stress was demonstrated. Additionally, in cells overexpressing tau, comet examines uncovered that tau applied DNA defensive impacts against free radical initiated destruction. These discoveries have pertinent ramifications on understanding the pathology of AD since oxidative stress and DNA damage assume a critical part in this disease. A few models to consider the conduct of tau at cellular levels have been depicted, including mouse skin fibroblasts and recombinant cell lines. In humans, fibroblast lines have additionally been utilized to examine Aβ and tau agglomeration [44].

Tau overexpressed cells manifest enhanced liability to OS. Moreover, mice (P301S and P301L) with AD exhibited dysfunction of mitochondria, which is related with enhanced ROS. Conversely, Aβ level is enhanced upon the induction of OS yet reduces with time. These processes show that ROS alters Aβ generation, yet additionally, Aβ produces enormous ROS in instances of AD. Moreover, rodent cortical neurons from shortened tau expressing transgenic rodents showed an enhanced level of ROS. This proof proposes that OS straightforwardly advances tau agglomeration, and conversely, noxious tau species invigorate OS conditions in tauopathies [45].

Three significant pathways have been proposed to represent the connection among Aβ and tau pathology. To start with, the actuation of tau kinases by Aβ initiates NFT development through tau hyperphosphorylation. Second, Aβ diminishes tau deterioration by the advancement of dysfunction of proteasome and at last, Aβ initiates caspase-3, which causes the tau truncation and modified tau conglomeration that prompts NFT development. Since immunotherapy with anti-Aβ antibodies in a triple transgenic mouse model of AD diminished Aβ deposition and eased back the development of NFT, it appears to be that Aβ is additionally engaged with the development of NFTs. This deduces is upheld by the way that during AD advancement, NFTs steadily deposit in limbic regions and in the isocortex after Aβ agglomeration and cause dementia and dysfunction of cognition.

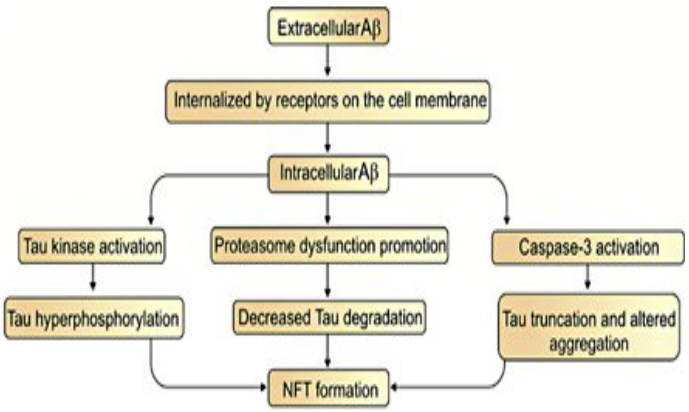

Fig. 4: Interrelationship between Aβ and NFT formation [46]

Lewis and Gotz showed that Aβ enhanced the recurrence of NFT in explicit cortical areas, as demonstrated by Gallyas-positive NFT. In spite of the fact that Gallyas staining is a typical method to examine NFT pathology, it's anything but a particular method to find out whether-pleated structures exist in NFT, which is the trademark highlight of amyloids [47].

A few prospects exist; including that Aβ may instigate tau changes through explicit binding receptors (or nonspecific restricting to lipid layers). Another chance is that Aβ is connected to tau by implication through changes in microglial or astrocytic action, which thusly actuates tau pathology. Another chance is that Aβ agglomerates can cross-seed with tau proteins to spread tau accumulation [48]. Nevertheless, with the development of AD and the ensuing

increment of reactive species, proficient evacuation of A-β metal system and hyperphosphorylated tau would be overwhelmed by their excessive-high production, bringing about a wild development of plaques and NFTs and, subsequently, an enhancement in reactive species production [49].

Cholinergic system

Acetylcholine [ACh] was first recognized by Dale for its activities on heart tissue. It was subsequently perceived as a neurotransmitter by Loewi, who at first named it "Vagusstoff" in light of the fact that it was delivered from the vagus nerve. From that point forward, the complex operations of ACh synthesis and synaptic interaction have been recognized [50]. Choline Acetyltransferase (ChAT) is answerable for the biosynthesis of ACh. This enzyme is synthesized in the perikaryon of cholinergic neurons and is heavily influenced by different regulatory components [51]. It was shown that ACh can likewise be generated by the catalyst carnitine acetyltransferase (CarAT) in few non-neuronal cells, for example, skeletal muscle cells and the urothelium [52]. Craig proposed a changed cholinergic theory by recommending that the diminution of the ACh neurotransmitter decreases the capacity of the brain to make up for secondary outcomes that accompany the aging cycle [53]

Acetylcholinesterase[AChE] is a serine hydrolase basically found at neuromuscular intersections and synapses of the cholinergic brain. Its vital biological function is end of transmission of impulse at cholinergic neural connections by fast hydrolysis of the neurotransmitter ACh to acetate and choline [54].

It has been noticed that abnormal AChE articulation in the AD brain happens in relationship with the two trademark highlights of the AD pathology, the amyloid plaques and the NFT. Aβ peptides impact AChE levels; in this manner Aβ might be answerable for enhanced AChE around plaques. Notwithstanding, the enhancement in AChE related with NFT has remained generally neglected [55]. Postmortem investigations of cognitively typical old-aged individuals have revealed that diminished choline acetyltransferase action was essentially connected with enhanced convergence of Aβ. Additionally, enhanced Aβ levels were related with rapid loss of cholinergic filaments in the inferior temporal gyrus and entorhinal cortex [56].

Abe *et al.* found that the intraparenchymal organization of Aβ into the basal forebrain of grown-up rats diminishes the production of acetylcholine from the hippocampus. Utilizing a comparative methodology Harkany and collaborators found that Aβ1-42 manifests toxic impacts towards cholinergic neurons as demonstrated by a lessening in ChAT immunoreactive neurons inside the basal forebrain and by a decrease in ChAT immunoreactive axons in the cerebral cortex. Additional considers have shown that infusion of Aβ into the parallel ventricles of grown-up rats brings about impeded execution on learning and memory activities which are associated with shortfalls in cholinergic transmission. Later investigations have shown that low Aβ concentrations can impede both acetylcholine generation and delivery in cultured cells and brain tissue arrangements [57].

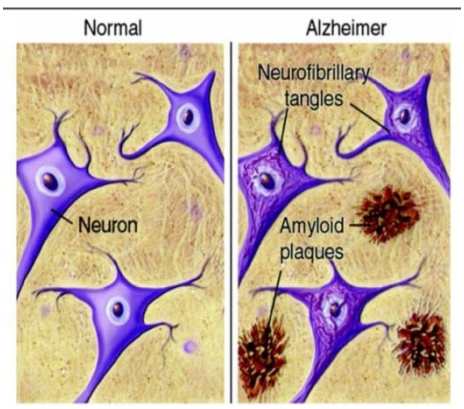

Fig. 5: A representation of the basic histology of Alzheimer's Disease, consisting of intracellular neurofibrillary tangles composed of hyperphosphorylated tau and extracellular collections of misfolded Aβ peptide forming amyloid plaques [58]

Oxidatively-stressed on aged cortex is less receptive to ACh and may make up for this by requiring upgraded contribution from basal forebrain neurons consequently causing enhanced neuron terminating rates and additionally changes, for example, enhanced articulation of genes that are engaged with energy. Raised metabolic activity may likewise go before enhanced ROS-RNS levels and, alongside pathology, for example, enhanced Aβ levels, may intercede their specific vulnerability. Note that basal forebrain cholinergic neurons are subject to areas with Aβ aggregates, while pontine cholinergic neurons don't. Of note in any case, cholinergic neurons are additionally necessary in the advancement of amyloid-based pathology as they can manage the processing of APP and thus, Aβ can diminish. It is realized that cholinergic neurochemical activity is influenced straight by Aβ in a way that isn't identified with neuron degeneration, yet it isn't known how much these impacts are because of the oxidant stress involved in by enhancing Aβ [59].

In addition, apparent neuronal degeneration doesn't happen in any transgenic mouse model of AD evolved to date, regardless of diminshed function of memory. Curiously, of all the neurochemical records modified in AD brain, ChAT action has been accounted for to give the best biochemical connect of the seriousness of dementia in this issue These results focuses on the significance of concluding the connections between enhanced generation of Aβ, accumulation of Aβ, oxidative pressure and the cholinergic deficiencies of AD brain [57].

CONCLUSION

Certainly, oxidative stress is a critical component in AD pathogenesis. Furthermore, few evidence recommends that it is probably the most punctual indication of the disease. Perhaps, absence of defense against ROS generation in the maturing brain could be one setting off the reason for AD and a main thrust in disease development Oxidative stress, which mediates the neurotoxicity induced by abnormal accumulation of Abeta and tau proteins, may augment Abeta production and aggregation as well as facilitate tau phosphorylation and polymerization, further enhancing a variety of neurotoxic events including ROS production, thus forming a vicious cycle that promotes the initiation and progression of AD. The cholinergic system assumes a significant part in memory and consideration and the deficiency of cholinergic neurons from the nucleus basalis that happens in the AD patient's brain has all the earmarks of being a vital factor adding to AD memory loss. Thus this review article focuses on the significance of concluding the connections between enhanced generation of Aβ, accumulation of Aβ, oxidative pressure and the cholinergic deficiencies of AD brain.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise

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