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Review Article

Therapeutic approaches in alzheimer's disease: β-amyloid peptide inhibitors

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ABSTRACT

In 2015, around 44 million people throughout the world, Dementia caused due to Alzheimer's disease (AD) is associated with a progressive neurodegenerative disorder and this figure is estimated to double by the year 2050. Accumulation of β amyloid triggers the progression of AD through overproduction and aggregation which actively induce synaptic dysfunction leading to disease expression. The generation of Amyloid β-protein (Aβ), occurs through sequential cleavage of β- and γ-secretases while its removal is dependent on the proteolysis and lysosomal degradation system. The present review is focused on the treatments and strategies based on therapies being developed for treating AD which targets β- amyloid protein. These prospects include agents acting on (Aβ), blocking Tau oligomerization, acetylcholinesterase Inhibitors, N-Methyl-D-Aspartate Receptor (NMDA) antagonist. Targeting Amyloid β-protein (Aβ) (Anti-Amyloid Approach), targeting amyloid aggregation, amyloid based vaccination therapy, Inhibition of Tau Phosphorylation, targeting amyloid clearance and cholesterol lowering drug.

1. Introduction

Alzheimer's disease (AD) is the most common fatal neurodegenerative disease (ND), and it is the most common type of senile dementia. Neurodegeneration progresses that, destroys loss of mental and behavioural health which disrupts person's ability to function/learn independently. The World Health Organization (WHO) estimated that the prevalence of AD worldwide will quadruple to reach approximately 114 million by 2050 (Alzheimer's Association, 2017). Since the time of Dr Alois Alzheimer, neuropathologists have identified amyloid plaques and NFTs in the autopsied brains of people with AD (Figure 1), suggesting that these pathologies cause the disease.[1] These pathological changes gradually result in neuronal loss and eventual neuron death. The amyloid hypothesis proposes β-amyloid (Aβ) as the main cause of the disease and suggests that misfolding of the extracellular Aβ protein accumulated in senile plaques and the intracellular deposition of misfolded tau protein in neurofibrillary tangles cause memory loss and confusion and result in personality and cognitive decline over it. Accumulated (Aβ) peptide is the main component of senile plaques and derives from the proteolytic cleavage of a larger glycoprotein named amyloid precursor protein (APP). APP is a type 1 membrane glycoprotein that plays an important role in a range of biological activities, including neuronal development, signalling, intracellular transport, and other aspects of neuronal homeostasis.[2]

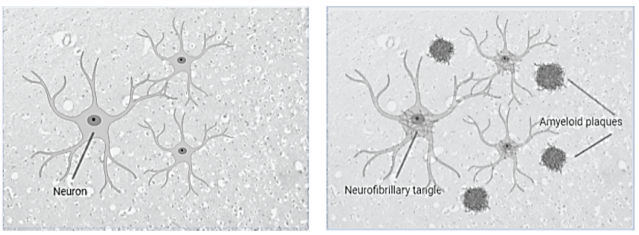

Fig. 1: (a) Normal brain; **(b)** Alzheimer's brain

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2. Signs and symptoms

Various signs associated with AD include mild cognitive impairment characterized by memory loss, poor judgment, mood swings, repetitive questions, and difficulty in doing mathematical calculations. The symptoms of moderate AD include the inability to learn new things, difficulty to recognized people, hallucinations, delusions, paranoia, and impulsive behaviour.[3]

2.1. The major neuropsychiatric and behavioural symptoms of AD

Alzheimer's dementia is the end result of multiple pathogenic processes including aberrant amyloid processing, changes in lipid metabolism due to apolipoprotein E (APOE) risk alleles, tau hyperphosphorylation, protein misfolding and endoplasmic reticulum (ER) stress, vascular dysfunction, oxidative stress and mitochondrial dysfunction, neurotrophic factor dysregulation, disrupted leptin signalling, fibrin clots, and processes mediated by a myriad of other AD-associated gene, and the pathogenic processes also occurred in major neuropsychiatric symptoms (Figure 2).[4]

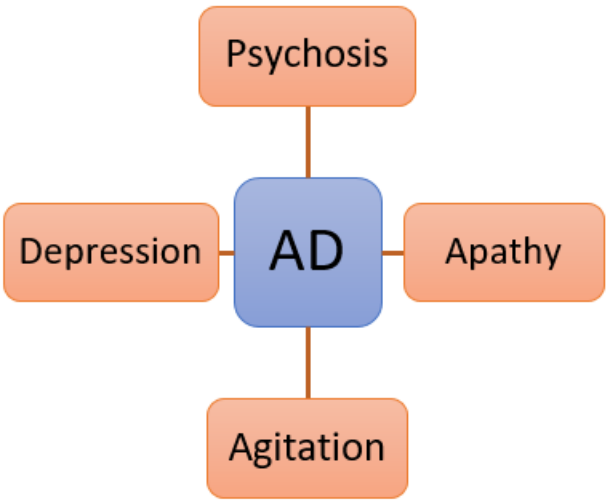

Fig. 2: Neuropsychiatric symptoms (NPS) with AD

2.1.1. Psychotic symptoms in AD

In AD, delusions occur more frequently than hallucinations. Persecutory delusions occur earlier in AD than misidentification delusions; both kinds increase with dementia severity.

2.1.2. Agitation in AD

Agitation occurs frequently in AD. The International Psychogeriatric Association consensus statement defines agitation as excessive motor activity, or verbal or physical aggression that associated with emotional distress: (1) severe enough to produce disability; (2) beyond what would be expected from cognitive impairment by itself; and (3) not solely attributable to another disorder, environmental conditions, or the physiological effects of a substance.[5]

2.1.3. Apathy in AD

Apathy is common in AD, characterized by lack of motivation, decreased initiative, akinesia, and emotional indifference, and a primary cause of caregiver distress.[6] In neuroimaging studies of preclinical or prodromal AD, apathy is associated with cortical dysfunction in the posterior cingulate or inferior temporal cortex as well as atrophy, hypometabolism, and hypoperfusion in these regions. Abnormalities in cholinergic, GABAergic, and dopaminergic function have also been associated with apathy, as well as high levels of tau and phospho-tau in the cerebrospinal fluid (CSF).[7]

2.1.4. Depression in AD

In patients with AD, severe neuropathology (tau, amyloid, and vascular disease) is seen. Accelerated cortical regression and white matter atrophy, particularly in frontal and temporal areas is associated with depression in AD. It may eventually damage regions involved in regulation of mood, a finding consistent with the high rates of depression in severe AD.[8]

3. Causes

Pathological characteristics of AD include the presence of neurofibrillary tangles, senile plaques, neuronal death, synapsis loss, astrogliosis in the entorhinal cortex, hippocampus, amygdala, and frontal, temporal, parietal, and occipital cortex.

3.1. Structural abnormalities

A cerebral cortex peppered with neurofibrillary tangles and senile plaques reveals the critical features of the disease when examine microscopically. AD can therefore be said to be the dementia associated with these histopathologic abnormalities.

3.2. Neurofibrillary tangles

Neurofibrillary tangles consist of aberrantly phosphorylated fibrillary proteins aggregated within the neuronal cytoplasm. However, it is an increased number and the architectonic distribution of the tangles that promote the cardinal pathology and define the stages of the disease, as described by Braak and Braak et al.,.[9] There are some groups of neurons which are preferentially affected by tangles in AD.

3.3. Senile plaques

Senile plaques (Figure 3) are more complex; they consist of extracellular deposits of amyloid material and are associated with swollen, distorted neuronal processes called dystrophic neurites. Like amyloid elsewhere in the body, complex sugar polymer components (glycosaminoglycans) are thought to be critical in the assembly of these deposits. Plaques start as innocuous deposits of nonaggregate, putatively non-neurotoxic β-amyloid (diffuse plaques). However, in some individuals they undergo an orderly sequential transformation into the mature senile neurotic's plaques that are associated with the development of AD[10] It is thought that the enzyme butyrylcholinesterase may play an essential role in this maturation process.[11]

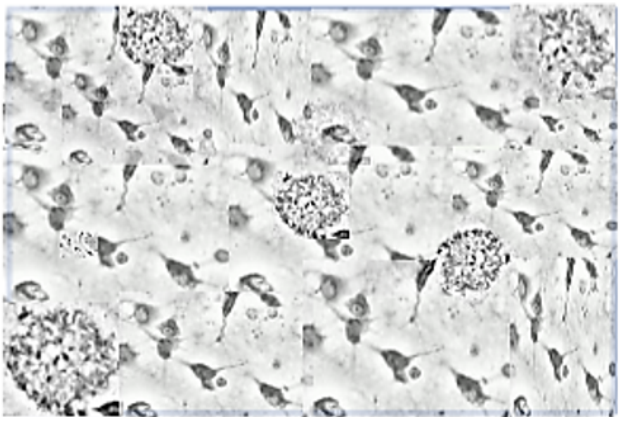

Fig. 3: Senile plaques

3.4. The role of genes

Several point mutations in the gene coding for β-APP on chromosome 21 are sufficient to cause early-onset autosomal dominant familial AD with complete penetrance; the clinical phenotype of these cases is entirely consistent with typical AD. Some mutations increase the production of β-amyloid, while others favour the formation of long (42 amino acid) forms of β-amyloid, which aggregate more readily than the short (40 amino acid) forms.[12]

3.5. Role of environmental factors

Environmental factors that may contribute the risk of development of AD. Toxic metals such as aluminium and lead have been linked with numerous neurodegenerative diseases including AD, causing toxicity to multiple organs of the human body. Other elements such as copper and arsenic have been associated in experimental model systems with the disruption of homeostasis of brain amyloid-β protein.[13]

4. Risk Factors

4.1. Non-Genetic Risk and Protective Factors

4.1.1. Cerebrovascular disease

Cerebrovascular changes such as haemorrhagic infarcts, small and large ischemic cortical infarcts, vasculopathies and white matter changes increase the risk of dementia but the specific underlying mechanisms remain unclear. Brain regions that are important in memory function, such as the thalamus and the thalamocortical projections may be directly damage due to infarcts or white matter hyperintensities. However, they may also increase the deposition of (Aβ), which in turn can lead to cognitive decline or could induce inflammatory responses impairing cognitive function.[14]

4.1.2. Blood pressure

Hypertension may increase the risk of AD through an effect on the vascular integrity of the blood–brain barrier (BBB), resulting in protein extravasation into brain tissue.[15] In turn, protein extravasation can lead to cell damage, a reduction in neuronal or synaptic function, apoptosis, and an increase in Aβ accumulation resulting in cognitive impairment.[16]

4.1.3. Body weight

Prospective studies have linked both low and high body weight to an increased risk of cognitive impairment in AD and suggesting a U-shaped relationship that is dependent on the age at which body weight is measured and seems to be driven by central obesity.[17]

4.1.4. Metabolic Syndrome

The relationship between metabolic syndrome as a whole and the risk of AD or cognitive decline has been assessed in various studies. Most of these investigations demonstrated a positive association between the presence of this syndrome and cognitive dysfunction.[18]

4.1.5. Traumatic brain injury

Individuals with a history of traumatic brain injury (TBI) had a higher risk of dementia than individuals with no history of such injury. The extent of Aβ pathology and tau pathology increases in brain tissue, cerebrospinal fluid (CSF) Aβ levels are elevated and APP is overproduced after human brain injury as suggested in evidences.[19]

5. Pathophysiology of AD

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdala, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also with subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the cholinergic basal nucleus. The deposition of tangles

follows a defined pattern, starting from the trans-entorhinal cortex; consequently, the entorhinal cortex, the CA1 region of the hippocampus and then the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques.

The accumulation of tau proteins correlates very closely with cognitive decline and brain atrophy, including hippocampal atrophy. In the neuropathology of Alzheimer's disease there is a loss of neurons and atrophy in temporofrontal cortex, which causes inflammation and deposit the amyloid plaques and an abnormal cluster of protein fragments and tangled bundles of fibres due to this there is an increase in the presence of monocytes and macrophages in cerebral cortex and it also activates the microglial cells in the parenchyma (Figure 4).[20]

5.1. Hyperphosphorylated tau protein and amyloid β-Hypothesis

One of the main pathological hallmarks of AD is the formation of senile plaques (SP), which is caused by amyloid beta (Aβ) deposition. Normally, Aβ are soluble small peptides, which are produced by the splitting of the precursor protein of amyloid (APP) by the action of α-secretase, β-secretase and γ-secretase. Various types of toxic oligomeric, namely protofibrils, fibrils and plaques depending upon the extent of oligomerization occurs due to imbalance between β-amyloid (Aβ) production and clearance.

5.2. Oxidative stress hypothesis

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in many normal and abnormal processes in humans, they play dual role as both have beneficial functions in cellular signalling pathways and venomous processes that can lead to damage of cellular structures (including cell membrane, lipid, protein, and DNA). In neurons, synapses have the highest concentration of long polyunsaturated fatty acids. It can interact with ROS, leading to the lipid peroxidation reaction and molecular apoptosis, in addition, less glutathione in neurons is also one of the causes of oxidative stress injury.[21]

5.3. Metal Ion hypothesis

A dysregulated metal homeostasis is associated with AD. Ionosphere and metal chelators are well known modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal-binding compounds are not the only drugs capable of targeting transition metal homeostasis. Their levels in the brain are found to be high in AD.[22]

5.4. Cholinergic hypothesis

Acetyl-cholinesterase inhibitors (AchEI) medications are the core of the treatment of AD, and apo-lipo-protein E genotype is the most important factor associated with AD. This lack of major effect of APOE is analysed with respect to the "Cholinergic Hypothesis" of AD. Cholinergic receptor binding is reduced in specific brain regions with mild to moderate AD and is related to neuropsychiatric symptoms. Cholinergic receptor binding in vivo may reveal links to other key brain changes associated with aging and AD and may provide a potential molecular treatment target. Clinically, decrease is related to an extensive loss of cholinergic neurons formed in the forebrain nuclei(medial) and a related decline in acetylcholine-mediated neurotransmission, drugs tending to regularize acetylcholine transmitter level, such as cholinesterase inhibitors (ChEIs) and donepezil, have for over 20 years served as the foundation of symptomatic therapy for AD.[23]

6. B-amyloid Peptide

Abnormal extracellular accumulation of amyloid and senile plaques observed in the brain of Alzheimer's disease patients consists principally of βamyloid peptide (BAP)' β amyloid peptide (BAP)' which is thought to be central to the pathogenesis and memory loss. The 39-42-amino acid (aa) BAP is derived by proteolytic cleavage from a larger amyloid precursor protein (APP), a transmembrane receptor-like glycoprotein which is expressed as three major isoforms containing either 695, 751, or 770 aa.[24]

Amyloid precursor protein, Aβ is generated through sequential cleavage of β- and γ-secretases while Aβ removal is dependent on the proteolysis and lysosomal degradation system.

6.1. The biogenesis of Aβ

The plaques and neurofibrillary tangles identified after histological examination of brains of patients with AD were subsequently shown to be composed largely of amyloid-β peptide and hyperphosphorylated tau, respectively. The discovery that AD could be inherited in an autosomal dominant fashion was a seminal event in AD research. The mutation that was described was in the gene coding for APP, the holoprotein from which the amyloid-β peptide is excised via sequential scission by the β-APP cleaving enzyme (BACE) and γ-secretase. These observations led to the articulation of the amyloid cascade hypothesis**.**

One prevailing proposal is the amyloid cascade hypothesis positing Aβ as the initiator of subsequent events that leads to AD: oxidative injury, microglial and astrocytic activity as well as kinase/phosphatase activity is induced or alters when Aβ peptides spontaneously aggregate and deposit into soluble oligomers, fibrils and SPs, eventually

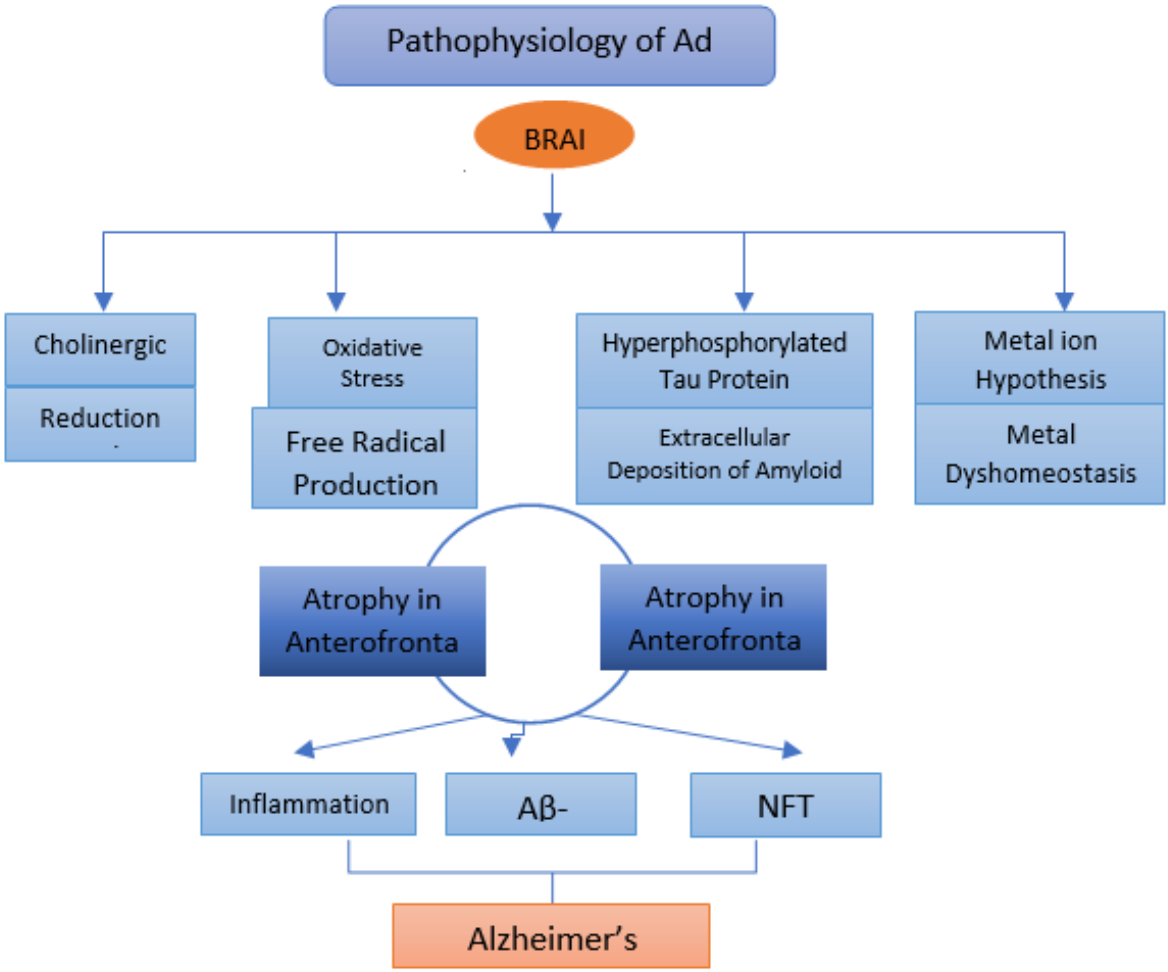

Fig. 4: Pathophysiology of Alzheimer's disease

leading to the neuronal death. However, whether Aβ acts on tau aggregation is still debated. A variety of biophysical states is exhibited by Aβ, a small protein composed of 39–43 amino acids. There are two major isoforms of Aβ, soluble Aβ40 and insoluble Aβ42, the latter peptide showing higher percentage concentration in AD patients is more prone to aggregate.[25]

7. Therapeutic Approaches for the Treatment of Alzheimer's Disease

Total of five drugs developed to improve the symptoms of Alzheimer's disease have been approved by the FDA. It is important to note that a new drug, Namzaric (donepezil and memantine) was approved in 2014. The five drugs function by two different mechanisms. One is cholinesterase inhibition, which delays Alzheimer's disease by blocking hydrolysis of the critical neurotransmitter acetylcholine. This category of drugs includes donepezil (Aricept)rivastigmine (Exelon)and galantamine (Razadyne). The other one is memantine (Namenda), a non-competitive N-methyl-D-aspartate (NMDA) channel blocker that reduces the activity of the neurotransmitter glutamate, which plays an important role in learning and memory by binding to the NMDA receptor (Figure 5).

7.1. Acetylcholinesterase inhibitors

It is well known that acetylcholine (ACh) plays a crucial role in mediating learning and memory. The effective treatment for AD is achieved with cholinesterase inhibitors, which corresponds well to Davies and Maloney's early cholinergic deficit hypothesis (1976) explaining AD pathophysiology. Various drugs have been developed and studied for the treatment of AD includes Tacrine, rivastigmine, galantamine, para-aminobenzoic acid, coumarin, flavonoid, and pyrroloisoxazole analogues. Rivastigmine, donepezil, and galantamine are the approved drugs that promote higher ACh levels and improve the brain's cholinergic function by

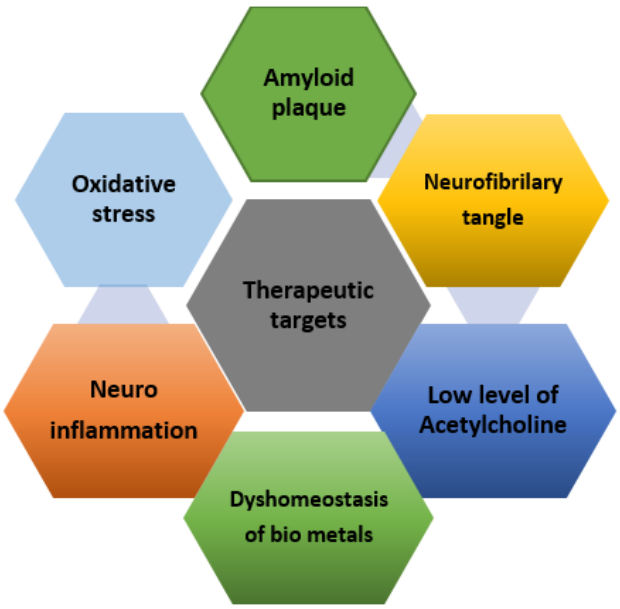

Fig. 5: Therapeutic targets for the management of AD

inhibiting the enzyme acetylcholinesterase which degrades the neurotransmitter.

7.2. N-Methyl-D-aspartate receptor (NMDA) antagonist

Glutamate-mediated excitotoxicity is known to result in calcium overload and mitochondrial dysfunction, with increased nitric oxide generation, which can be detrimental to cells, forming high levels of oxidants and eliciting neuronal apoptosis. This overstimulation can be blocked by NMDA receptor antagonists such as memantine, which was approved in 2003 by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe AD, with a marginal beneficial effect on cognition in mild-to-moderate AD. Memantine can protect neurons by attenuating tau phosphorylation through a decrease in glycogen synthase kinase 3β (GSK-3β) activity. This non-competitive glutamatergic NMDA receptor antagonist can be administered alone or in combination with an acetylcholinesterase inhibitor, although there may be few significant favourable changes in the combination therapy.[26]

7.3. Targeting Ab protein (Anti-amyloid approach)

The anti-amyloid therapeutics targets several aspects of APP metabolism. Targeting amyloid transport, it is reported that with age, LRP expression decreases, impairing Ab oligomers efflux contributing to prolonged there stay in the brain. Antibodies against LRP reduce Ab oligomers efflux from the brain so, this can be targeted as a potential treatment strategy in AD.

Tramiprosate, a glycosaminoglycan, binds to monomeric Ab and preventing its oligomerization and aggregation. oligomerization properties as this compound effectively decreased insoluble Ab oligomers and reversed cognitive decline in transgenic mice. Colostrinin (CLN) or proline rich polypeptide complex. It has strong immunoregulatory properties besides which it affects learning, memory and cognitive functioning. Colostrinin prominently inhibit the aggregation of Ab peptides and dissolve pre-formed fibrils.[27]

7.4. Targeting amyloid clearance

In AD the levels of Ab oligomers degrading enzymes decline which may confer to Ab accumulation. Experimental evidence suggests that inhibitors of plasminogen activator inhibitor 1 decrease the plasma and brain Ab oligomers levels in transgenic animals.[28] Previous studies have shown that the peptide hormone somatostatin regulates Ab oligomers clearance through activation of neprilysin.[29]

7.5. Amyloid based vaccination therapy

Amyloid based immunotherapy means vaccination of the individuals with Ab oligomers which in turn induces an immune response that causes inhibition of Ab oligomers aggregation and its clearance from the body.[30] In 2001 first clinical trial was started sponsored by Elan and Wyeth with active immunization, consisting of aggregated synthetic Ab42 peptide delivered in QS21 adjuvant.[31] From these studies it has been reported that treatment with Ab42 peptide generated anti-Ab antibodies, reducing cerebrospinal levels of tau and reported a slower cognitive decline.[32]

7.6. Targeting tau protein

Tau protein normally synthesized by neuronal cells in order to stabilize the microtubules for proper functioning of the neurons, particularly axonal morphology, growth, and polarity. So, targeting tau protein may prove to be better therapeutic intervention.[33]

7.7. Inhibition of tau phosphorylation

Glycogen synthase kinase 3 (GSK3), one of the primary enzymes involved in tau phosphorylation, is targeted. It is reported experimentally that lithium and valproate have inhibitory actions on GSK3 and when administered they reduce tau pathology.[34]

7.8. Targeting microtubule stabilization

Microtubule stabilizer paclitaxel is known to improve fast axonal transport, microtubule density and motor function in experimental model of AD. Epothilone D a microtubule stabilizing compound known for its blood brain barrier

clearance has been reported to show significant amelioration in microtubule pathology.[35]

7.9. Blocking tau oligomerization

Astemizole, lansoprazole show a strong affinity for tau protein, therefore, indirectly reduce tau–tau interaction. The dye methylene blue (methylthioninium chloride) has also known to prevent tau interactions, it also inhibiting Ab aggregation, improving electron transport, decreasing oxidative stress, prevent mitochondrial damage, regulate autophagy and inhibition of AChEs.[36]

7.10. Enhancing tau degradation

Heat shock protein 90 (Hsp 90), a chaperone involved in folding the denatured proteins, seems to play a role in preventing tau degradation. Curcumin with wide varieties of action has also known to inhibit Hsp 90.[37] It has been investigated that curcumin treatment decreases the tau pathology in tau transgenic mice by suppressing tangle formation as well as promoting dissolution of already formed tangles.[38]

7.11. Tau based vaccination therapy

Tau-based immunotherapy to promote immunological clearance of tau tangles.[39] Active immunization studies have recently raised the possibility of modulating tau pathology by activating the immune system. JNPL3 mouse P301S tauopathy model for passive immunotherapy is effective at preventing the intracellular tau pathology and associated symptoms, although the exact mechanism remains uncertain.[40]

7.12. Targeting intracellular signalling cascades

Modulation of intracellular signalling cascades can also be targeted as a therapeutic intervention in AD. As Ab oligomers activate various intracellular pathways, so drugs that interrupt these signalling pathways could be useful in AD.[41] It has been reported that inhibitors of phosphodiesterase (PDE) provides significant benefit in experimental models. Recently reported that, rolipram is a PDE-4 selective inhibitor that effectively reversed memory and cognitive deficits in Ab treated mice; sildenafil, a PDE-5 inhibitor also produced similar results.[42]

7.13. Cholesterol-Lowering drugs

The $\varepsilon 4$ allele of the apolipoprotein E gene (APOE), which is involved in the CNS distribution of cholesterol among neurons and represents the most common lipoprotein expressed in the brain, is also the main genetic risk factor for sporadic AD. APOE $\varepsilon 4$ is associated with a slight increase of serum cholesterol and might have a direct role in the deposition of amyloid fibrils and Aβ aggregation. In 1994, Sparks and co-workers reported that animals fed a cholesterol-rich diet have increased Aβ immunoreactivity in the brain; more recently Refolo et al.[43] have shown that diet-induced hypercholesterolaemia speeds up amyloid pathology in a transgenic mouse model of AD. Furthermore, Puglielli and co-workers recently studied the roles of free cholesterol and cholesteryl esters in Aβ secretion by use of inhibitors of acyl-coenzyme A-cholesterol acyltransferase (ACAT), which catalyses the synthesis of cholesteryl esters. Aβ production seems to be related to concentrations of cholesteryl esters, and ACAT inhibitors modulate Aβ production, which changes the balance between cholesteryl esters and free cholesterol. Chronic use of statins is associated with a significant decreased risk of developing AD.[44]

8. Conclusion

In the present review paper deals with the disease progression of AD and the potential therapeutic targets. Currently available drugs (AChEIs and memantine) only target the symptoms and not the cause of the disease. With the advent of novel therapies, to stop the progressive accumulation of Aβ has increased. Targeting Aβ production via inhibition of β-secretase, seems to be a promising approach. Another enzyme involved in Aβ oligomers production i.e. γ -secretase can also be target for treatment of AD. We have also tried to elucidated different approaches to overcome amyloid burden by using therapeutic drugs.

9. Source of Funding

None.

10. Conflict of Interest

None.

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