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Modern Approaches in Mitigation and Curing of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a critical neurodegenerative illness characterized by memory loss and diminished performance, language, and visuospatial skills, insidious onset of memory and cognition impairment, the emergence of psychiatric symptoms and behavioral disorder, and impairment of activities of daily living. There were about 26.6 million cases of AD in the world in 2006 and, predictably, the worldwide dominance of AD will grow fourfold to 106.8 million by the year 2050. Among several hypotheses, the β- amyloid (Aβ) cascade and the tau hyperphosphorylation are the theories that have widely been accepted. Thus, the disease-modifying therapies focus mainly on the agents that will decrease Aβ content and tau hyperphosphorylation. Here we review the potential disease-modifying therapies and some compounds that are currently undergoing preclinical and clinical evaluations.

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INTRODUCTION:

In the field of neuromuscular disorder, Alzheimer's disease is a household name to the clinicians which is characterized by memory loss and diminished performance. On account of epidemiological study, it can be said that the occurrence of this disease is related to age and doubles every five years after a person reaches his/her 65 summers. This disease is solely associated with intracellular neurofibrillary tangle as well as extracellular senile plaque, Aβ which is generated utilizing proteolytic degradation of amyloid precursor protein[1].

Pathophysiology:

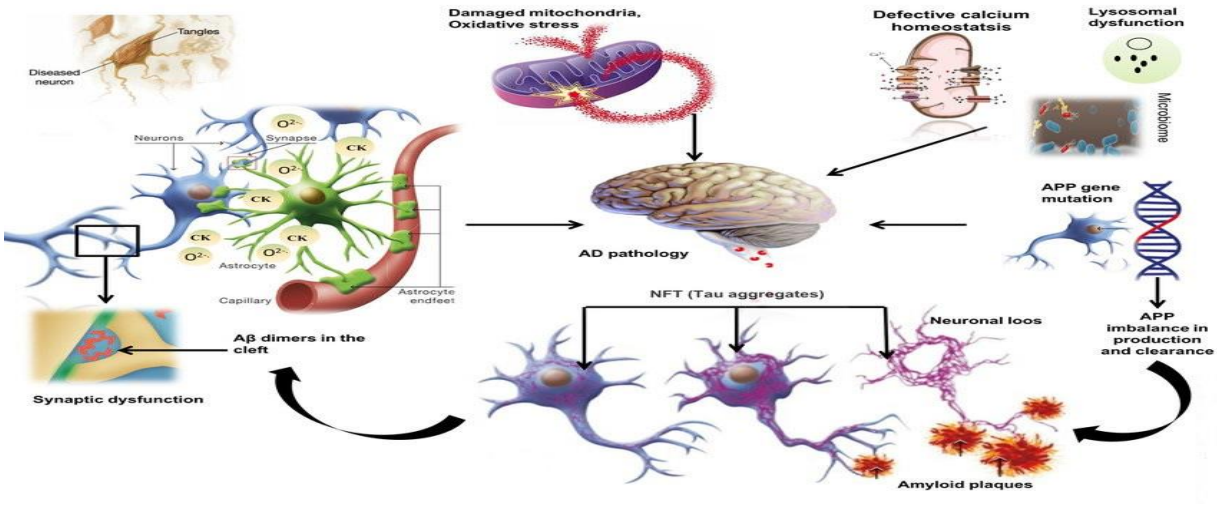

Figure No 1: Pathophysiology of Alzheimer's disease

Aβ plaque formation is regulated as the pathological hallmarks of Alzheimer's disease which can be overproduced by the virtue of mutation and subsequently accelerate the intracellular neurofibrillary entanglement. Thus, these facts cause neuromuscular functional impairment and cell loss. Post-translational modification of 'Tau' like proteolysis and phosphorylation can increase the proportion of aggregation. Moreover, it is scientifically observed that the solubility of Aβ oligomers dimers is more highly pathogenic.

Diagnosis:

Generally, two types of dementia are diagnosed. Diagnosis of AD can be differentiated into three subsequent steps including:

a) Pre-clinical: Amyloid cause the hypothesis stated that preclinical stage of AD typically begins many years even decades before the onset of AD. Thus, preclinical phase is associated with asymptomatic cerebral amyloidosis. Leaving its reservoir in CSF monomeric Aβ aggregate and finally begins to accumulate on the neuronal surface and synapses[2,3]. During the second stage of the preclinical phase increased CSF tau, hypometabolism in posterorcingulation and cortical thinning become detectable, where the patients, still don't display any dementia type syndrome. In the last stage of the preclinical phase the patients begin to detect subtle symptoms and biomarkers, here are, continue to increase. The cognitive behaviors are detected in Montreal cognitive assessment and mini-mental status examination.

b) Mild cognitive impairment: It is the phase of AD in which cognitive function gets reduced, although the patient is found an autonomous and functional member of society. MC 1 cannot be diagnosed by laboratory tests. But PEI imaging and CSE analysis are viable methods of differentiating dementia symptoms. Ethnopharmacological factors viz deficiencies in vitamin B12, TSH, folate, glucose, calcium, complete blood cell count, renal and liver function abnormalities are observed in MC1[4]. However, serological tests for micro bacterium like syphilis, borrella, and most importantly HIV must be performed on patients with MC1 reveals scores in the range 1- 1.5. Positive Aβ biomarkers, as well as positive biomarkers of neuronal impairment, suggest MC1 is associated with AD. But negative biomarkers assure that AD pathology is not the cause of MC1 symptoms.

c) Alzheimer's disease dementia: When performing post-mortem neuropathological studies, it is confirmed that; criteria for an AD diagnosis have demonstrated a reasonably high sensitivity of 81% and specificity of 70%.AD can be successfully different from other dementia. It causes dementia that occurs late in the disease process. A diagnosis of dementia is performed following a thorough history and cognitive function tests like MoCA and MMSE. In AD it is shown that amnesic symptoms performed before nonamnesic prevention such as language and visuospatial deficit[5]. Besides clinical history, cognitive testing like MMSE and MoCA biomarkers (CSF Aβ levels MoCA and PET scan) may yield additional etiology of the dementia symptoms.

Risk factor: The number of factors that regulate AD pathophysiology, among those some of them are stated here –

1. **Vascular factors:**

a) Smoking: It causes oxidative stress, inflammation, and atherosclerosis which further promote augmentedβ secretase cleavage of APP and abnormal tau phosphorylation.

b) Alcohol: Light to adequate alcohol intake causes brain atrophy and volume loss, in heavy consumers of alcohol cause injury in the brain.

c) Obesity- It has been shown that obese people contribute to dementia and cerebral decay.

d) Diabetes mellitus- Activation of insulin receptor substrate -1 by insulin or insulin growth factor (IGF-1), stimulate two signal pathways-

I) R13k pathway: It involves preservation of synaptic plasticity and memory consolidation,$A\beta$ induced memory loss, synthesis of NOS[6].

II) MAPK cascade: It causes induction of several genes essential for neural and synapse development conservation and helps in the process.

III) Genetic factor: Onset of disease progression can be differentiated into early-onset and late-onset AD. In the first case i.e. early-onset AD, an autosomal dominant variant of preseline 1 and preseline 2 encode amyloid precursor protein (APP), whereas in the case of late-onset AD as the number of apoE4 allele increases[7], the greater the possibility of AD and lesser the age of onset.

IV) Nutritional factors: Antioxidants can decrease the oxidative stress as well as accumulation of amyloid -protein, hence consumption of vitamin likes vitamin E, C that are beneficial in redressing AD[8]. Apart from the polyphenol like resveratrol, polyunsaturated fatty acid(DHA, EPA), fish, fruit, vegetable(*Curcuma longa*), tea are useful in redressing the chance of AD. On the other hand, cholesterol, whole fat, saturated fatty acid, unsaturated fatty acids, carbohydrates, are harmful to AD.

V) Psychosocial factors: Psychosocial factors and a vigorous lifestyle are regarded to decline the risk of dementia.

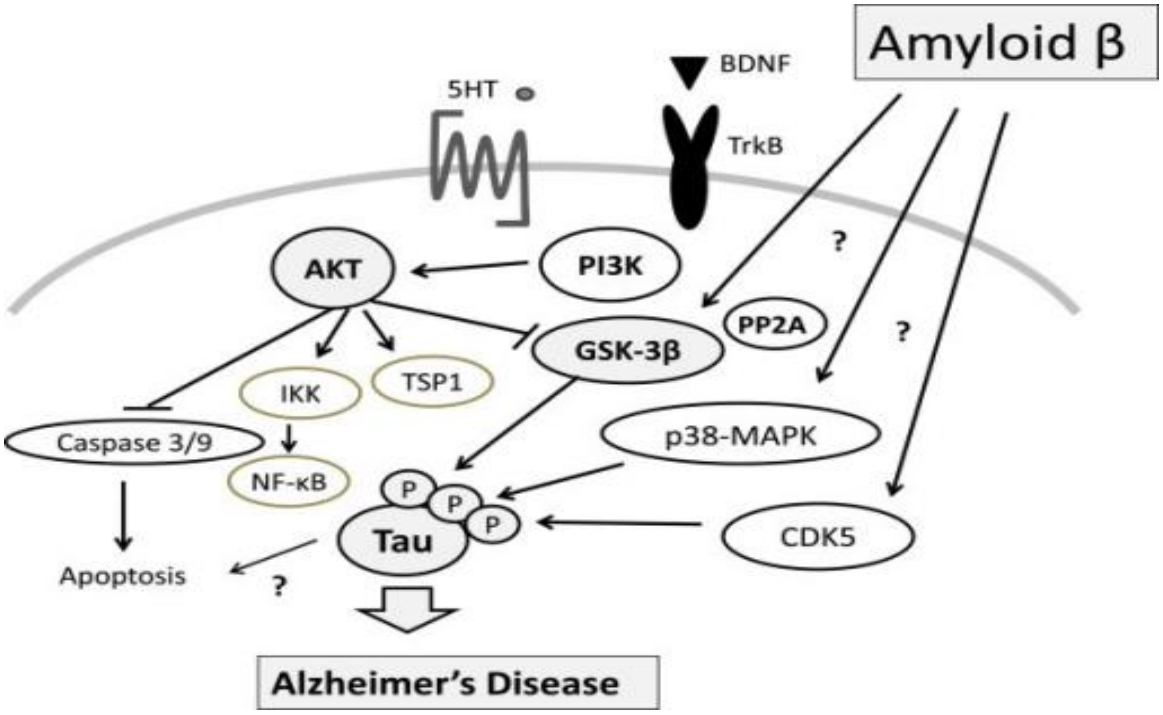

Figure no 2: Several diagnostic approaches of AD

Treatment

1) Cholinesterase inhibitors- According to post-modern studies loss of cholinergic neurons as well as the release of acetylcholine and its uptake get prohibited in Alzheimer's disease. Donepezil, rivastigmine, tacrine and galantamine, these are four FDA approved drug used in the treatment of AD since 1993. Tacrine has been withdrawn from the market due to its poor oral bioavailability, GIT disturbance, and hepatotoxicity[9-11].

Another drug huperzine A, extracted from a Chinese herd is regarded as a selective reversible inhibitor of acetylcholinesterase. Antialzheimer drugs are now day's administered through a transdermal patch, to avoid nausea and vomiting.

2) Immunotherapy-Active and passive immunization come under consideration treatment of Alzheimer's disease. Active immunization by the virtue of AN 1792/ Gs-21 against Aβ resulted in decreasing in plaque and improve cognitive function in transgenic mice[12-15]. This phenomenon is detected by Moris Water maze trials. A novel peptide carrier protein using an amino-terminal fragment of Aβ has been developed to avoid harmful T cell response observed in meningoencephalitis, however, LY2062430 are also being instigated.

3) N methyl D aspartate (MMDA) antagonist: Memantine is approved not only as an NMDA antagonist but also to restore damaged nerve cell function and reduced abnormal excitatory signals. The drug is thought to block selectively the effects associated with abnormal transmission of glutamate, which is found associated with learning and memory[16-19]. Although memantine itself is enough to manage AD in the case of outpatient study, the synergistic combination of donepezil and memantine results in significant improvement in cognitive, functional, and global outcomes compared with placebo.

4) Treatment based on tau pathology: Alzheimer's disease is strictly associated with tau phosphorylation. Phosphorylation of tau is regulated by several kinase and phosphatase, for example, mitogen-activated protein kinase (MAPK), Cyclin-dependent protein kinase (CDK5), Glycogen synthase kinase Cyclin-dependent protein kinase (CDK5), (GSk3B) are responsible for phosphorylation of tau[20-22], on the other hand, Protein phosphate PP-2A may increase dephosphorylation of tau. When P25 is administered it is shown that inhibition of CDK5 may suppress tau phosphorylation and prevent tangle formation.

5) Treatment based on Aβ pathology: The presence of senile plaque in the hippocampus is one of the hallmarks of AD, which are primarily formed from the extracellular deposition of Aβ. Aβ polypeptides are further derived from Amyloid precursor protein(APP) utilizing β and γ secretase which cleave the peptide from the N and C terminus respectively[23-24]. Degradation of APP thus yields Aβ as well as SAPPα(a soluble protein). Secretase decreases the amount of APP and subsequently Aβ protein. Several pharmacological studies put forward the adamalysin family of proteins like ADAM2, 10, 17 that fulfill the criteria required for α secretase. Previous studies however showed that protein kinase activators increase the activity of αsecretase. On the contrary, βsecretase inhibitors like kMI 429, GSK 188909, PMS 777, and γ secretase inhibitors likes BMW 298897, MRK 560 can come under the consideration of AD treatment[25].

CONCLUSION:

AD has a complex pathophysiology, covering both environmental and genetic factors. Apart from the investigation of novel inhibitors for BACE, kinase, and γSecretase, the role of a key protein, oxidative damage, mitochondrial dysfunction, and cholinergic hypothesis is assumed

to contribute to AD pathogenesis. There are fields for advanced research to delay the onset of disease and modify the progression of Alzheimer's Disease.

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