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REVIEW ARTICLE

BRIEF OVERVIEW ON ALZHEIMER`S DISEASE WITH RECENT TREATMENT

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Abstract:

The pathophysiology of Alzheimer Disease is very complexes, involving neurotransmitter system and processes. In this review number of diversity of aberrant mechanism increase the hope of finding and diverse therapeutic intervention for the treatment of AD. Hallmarks of AD neuritic plaque, loss of cholinergic cells, tau protein. It is the most common cause of dementia, leading to deterioration in vital cognitive process and behavioural changes. There are five drug approved for AD i.e. Acetylcholinesterase inhibitors (4), for the symptoms of mild to moderate AD and glutamate receptor antagonist (1),for the treatment of moderate to severe AD. Recent developments in the field confirm some important predictions of the hypothesis and shed new lights on potential mechanisms regarding how steady state may be achieved in severe or sporadic AD cases ,our opinion is that, strengthen the hypothesis & our studied with these drugs are focusing on longer effect or follow up.

KeyWords: Amyloid protein, neurofibrillary tangent, Acetylcholine, Alzheimer, APOE.

INTRODUCTION:

Alzheimer`s disease (AD) is a progressive neurodegenerative brain disorder i.e slow in onset but leads to dementia, unusual behavior, personality changes and ultimately death.[1] Alzheimer's disease is named after Dr. Alois Alzheimer, a German doctor, (1907) noticed changes in the brain tissue of a woman who had died of an unusual mental illness.[2] It is characterized by the presence of excessive amount of neuritic plaque containing amyloid β protein and abnormal tau protein filaments in the form of neurofibrillary tangle, loss of cholinergic cells, particularly in the basal forebrain is accompanied by loss of neurotransmitter acetylcholine.[3] There are two forms of the disease a genetics based early onset familial Alzheimer disease and a more prevalent age dependant form called Sporadic Alzheimer disease.[4]

Alzheimer`s disease also known as dementia, characterized into four stages namely, Pre-dementia, early dementia, Moderate dementia, and advanced dementia. Dementia is characterized by a decline in cognitive faculties and occurrence of behavioral abnormalities, which interfere with an individual's activities of daily living. Dementing disorders usually affect elderly individuals but may occur in individuals younger than 65 years (early-onset dementia or EOD).[5]

STAGE OF ALZHEIMER`S DISEASE-

In mild to moderate Alzheimer`s disease (AD), patient experience more prominent to memory loss (difficulty recalling well known names and confusion about familiar places), a decline in the ability to process complex thoughts (difficulty with balancing the checkbook and preparing a meal, mood and personality changes).[6]

At the chronic stages of AD progression, the cortex has atrophied in area that control speech, reasoning, sensory processing and conscious thoughts. As expected with this degree of brain atrophy, symptoms of severe AD increase in severity (i.e. impaired long term memory, seizure, incontinence, weight loss, no recognition of loved onces, inability to sit up groaning, moaning, grunting).[6]

Pathophysiology -

Alzheimer disease **(**AD**)** pathology can be characterized as the progressive loss of brain tissue. One of the easiest sign of AD is memory loss, particularly short term recall. The brain area involved in memory includes the cortex, especially the hippocampus. [7, 8,9]

The signature lesions in AD are neuritic plaques and neurofibrillary tangles (NFTs) located in the cortical areas and medial temporal lobe structures of the brain. [10]Along with these lesions,

degeneration of neurons and synapses as well as cortical atrophy, occurs. Plaques and NFTs may also be present in others disease, even in normal aging, but there is a much higher concentration of plaques and NFTs in patients with Alzheimer`s disease (AD). The circumstances in which these lesions lead to adverse symptoms of Alzheimer's disease is remain unclear. Several mechanisms have been proposed to explain these changes in the brain, including β-amyloid protein aggregation and deposition leading to the formation of plaques, hyperphosphorylation of tau protein leading to generation of NFT, inflammations, dysfunction of the neurovasculature, oxidative stress and mitochondrial dysfunction. [11]

AMYLOID HYPOTHESIS-

Neuritic plaques or amyloid plaques/ senile plaques are extracellular lesions found in the brain and cerebral vasculature. Plaques from Alzheimer`s disease (AD) brains largely consist of a protein called β amyloid protein. β-Amyloid protein is produced via processing of a larger protein, amyloid precursor protein (APP). Specific roles of APP are not entirely clear, however it has been reported that it contribute the normal neuronal function. [12] The amyloid cascade hypothesis proposed that altered APP processing drove β-Amyloid protein production, β-amyloid protein responsible for plaque formation, plaques induced neurodegeneration and this neuronal loss resulted in the clinical dementia syndrome typical of AD. [13] Specifically, mutations in two others genes, Preseniline-1 on chromosome 14 and preseniline -2 on chromosome 1, were also shown to cause variants of early onset, autosomal dominant AD. [14]

NEUROFIBRILLARY TANGLES HYPOTHESIS -

As β amyloid protein was being identified in plaques, it has been prooved that NFTs are commonly found in the cells of the hippocampus and cerebral cortex during AD and are composed of abnormally hyperphosphorylated tau protein. Tau protein provides structural support to microtubules, the cell`s transportation and skeletal support system.[15] When tau filaments undergo hyper phosphorylation at a specific site, they cannot bind effectively to microtubules, and the microtubules collapse.[16]

HYPOTHESIS OF INFLAMMATORY MEDIATORS-

Inflammatory or immunologic paradigms are often viewed as a corollary of the amyloid cascade hypothesis. Certainly, brain amyloid deposition associates with local inflammatory and immunologic alterations. Inflammation is relevant to Alzheimer`s disease (AD) neurodegeneration. [17] The inflammatory/ immunologic hypothesis argue that although β amyloid protein may have direct neurotoxicity, at least some of its toxicity might actually be an indirect consequence of a β amyloid protein proto fibril-induced microglia activation and astrocyte

recruitment. This inflammatory response may be for clear the deposited amyloid. However, it is also associated with release of cytokines, nitric oxide and other radical species and complement factors that damage the neurons and promote ongoing inflammation.[18] Indeed, levels of multiple cytokines and chemokines are elevated in AD brain and certain pro inflammatory gene polymorphisms are reported to be associated with AD. [18,19]

HYPOTHESIS OF CHOLINERGIC TRANSMITTER HYPOTHESIS-

Multiple neuronal pathways are destroyed in AD. Damage occurs in nerve cell population located in or traveling through plaque laden areas.[20] Widespread cell destruction results in a variety of neurotransmitter deficits with cholinergic abnormalities being the most prominent. Loss of cholinergic activity correlates with Alzheimer`s disease (AD) severity.[21] In late Alzheimer`s disease (AD), the number of cholinergic neurons is reduced and there is loss of nicotinic receptor in the hippocampus and cortex. Presynaptic nicotinic receptors control the release of acetylcholine as well as other neurotransmitters important for memory and mood including glutamate, serotonin and norepinephrine.[21] The discovery of vast cholinergic cell loss led to the development of a cholinergic hypothesis linked to the pathophysiology of Alzheimer`s disease (AD).[11]

GLUTAMATERGIC HYPOTHESIS-

Glutamate is a primary excitatory neurotransmitter in brain. In the central nervous system, it is virtually ubiquitous and is estimated to be involved in roughly 66% of all brain synapses. [17,22] Glutametargic neurons are also critical because they form projections to other areas of the brain, including cholinergic neurons thus influencing cognition. In Alzheimer`s disease (AD), the pathology associated with glutamatergic neuron is not with glutamate itself but with the levels of pre and post synaptic glutamate receptor. Out of the three types of post synaptic glutamate receptor, Alzheimer`s disease (AD) pathology has only been link to 1-type, the N-methyl-D-aspartate (NMDA receptor), which appears to undergo sustained low level activation in AD brain, causing low level neurotransmission. This dysregulation / continuous activation of NMDA receptor leads to chronic influx of calcium which interferes the normal signal transduction.[23] It also leads to increase production of APP; it is associated with higher rates of plaque development and hyperphosphorylation of tau protein followed by neuronal toxicity. [24,25]

LIPID PEROXIDATION (OXIDATIVE STRESS) HYPOTHESIS-

In Alzheimer`s disease (AD) brain, amyloid beta (Aβ) induces lipid peroxidation and generates reactive oxygen and nitrogen species, these are oxygen or nitrogen molecules containing an unpaired extra electron that reacts with other molecule to achieve a stable configuration.[26]

During this process, the reactive species forms a molecular bond with another molecule, while a high energy electron (termed ``free radicals``) is thrown off. The reaction is permanent, thus structurally and functionally altering the molecule to which the reactive species is attached. The free radical is left to cause cellular and molecular damage. This oxidative damage can occur in virtually all types of neuronal macromolecules (e.g., lipids, carbohydrates, proteins and nucleic acids) .[27] The brain is especially vulnerable to damage from oxidative stress because of its high oxygen consumption rate, abundant lipid content and relative paucity of antioxidant enzymes compared to other organs. In neurons, oxidation can result in numerous problems, including upregulation of proinflammatory cytokines and irreversible DNA damage.[28] Oxidative stress is thought to be important early in AD progression because it is temporally linked to the development of plaques and NFTs.[29]

CHOLESTROL HYPOTHESIS-

The brain contains the higher amount of cholesterol of any human organ. Although the CNS accounts for 2% body mass, it contains almost 25% of the body's unesterified cholesterol.[30] Cholesterol is now also implicated in Alzheimer`s disease (AD) pathogenesis. In vivo and in vitro data suggest that elevates cholesterol levels increase amyloid beta (Aβ) production, whereas administration of hypocholesterolemic drugs is noted to reduce Aβ levels. Cholesterol reduction may also reduce the risk or severity of dementia through protection from vascular risk factors, which often coexist in patient with AD. The APOE-ε (apolipoprotein-E) 4 allele is associated with high cholesterol levels is a dose dependant risk factor for AD and correlates with an increase in Aβ pathology. [31,32]

TWO HIT HYPOTHESIS-It has been proved oxidative stress and aberrant mitotic signalling both play early roles in the pathogenesis of AD, but their temporal relationship to each other is unclear. Based on the studies of oxidative stress signalling and mitotic signalling pathways in vulnerable neuronal populations in AD, Importantly, there are two major assumptions:

(1) The presence of a steady state: after the process being initiated by one of these two hits, neurons recruit permanent adaptive changes and enter a new steady state that can last for decades where they still function normally or at worse, in a slightly compromised fashion;

(2) The depletion of neuronal compensatory potential: the new steady state requires great compensatory adaptations which likely deplete much of the neuronal compensatory potential to fight against insult (i.e., first hit), therefore, neurons at new steady state are uniquely vulnerable to secondary insults that requires additional compensatory changes in other pathways.[33,34]

TABLE 1. APPROVED DRUG FOR ALZHEIMER DISEASE –

S.n	Generic name	Brand Name	Action	Dose	Symptoms
1.	Donepezil	Aricept™ & Aricept™ RDT	cholinesterase inhibitors	5 mg or 10 mg per day	Mild, Moderate & Advanced Alzheimer
2.	Ebixa	MEMANTINE HYDROCHLORIDE	NMDA receptor antagonist	20 mg per day	Moderate to severe Alzheimer
3.	REMINYL™ ER	EXTENDED RELEASE GALANTAMINE HYDROBROMIDE	cholinesterase inhibitors	8mg once a day in the morning with food	Mild to moderate Alzheimer
4.	RIVASTIGMINE	EXELON™ and NOVO- or TEVA-RIVASTIGMINE)	cholinesterase inhibitors	6 mg twice a day	Mild to moderate Alzheimer
5.	Tacrine	Cognex	cholinesterase inhibitors	------	Mild to moderate

Tacrine (cognex), the first cholinesterase inhibitor was approved in 1993 but it is rarely prescribed today because of associated side effects i.e. possible liver damage.[35,36]

Conclusion- As we learn more of the details involved in the pathophysiology of AD, we gain insight into potential therapeutic target. The long held hallmark s of AD namely Amyloid plague and NFT are certainly major factors amongst the neurodegenerative processes. More interesting fact is that these changes in neuronal function and neurotransmitter and they appear to correlate to greater or lesser hallmark symptoms of AD. Optimal treatment approaches will need to focus on the pathophysiology changes in AD and address with multiple mechanisms because of the complex nature of devastating disease.

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