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A REVIEW ON ALZHEIMER'S DISEASE: PATHOPHYSIOLOGY AND INVOLVING VARIOUS ALZHEIMER'S DISEASE ASSOCIATED RECEPTORS

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease. Alzheimer's disease, a multifaceted neurological ailment that progresses over time, is the most common cause of dementia in older people. Over the last few years, researchers have worked with humans and animals to uncover receptors linked in Alzheimer's disease, with the goal of better understanding the disease's processes and pathophysiological characteristics. Intracellular neurofibrillary tangles and extracellular amyloidal protein deposits are pathological features that contribute to senile plaques. Such receptors are important because blocking or activating them could improve or exacerbate AD symptoms, whether or not they are directly linked to current AD medication. Currently available therapies, such as acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate receptor antagonists (memantine), have a minor influence on the condition and are only used to treat late-stage symptoms. While the neuropathological symptoms of Alzheimer's disease are well-known, the mechanism's complexities remain unknown. This lack of understanding of the pathogenic process may be one of the main reasons for the lack of viable treatments to prevent illness start and progression.

Keyword: Alzheimer, Pathophysiology, Alzheimer’s disease-associated receptors, risk factors, treatment.

1. INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative disease, accounting for more than 80% of dementia cases in elderly individuals around the world. It is defined by a progressive decline in cognitive function that progresses from episodic memory impairments. It causes progressive mental, behavioural, and functional impairment, as well as a loss of learning ability1. The younger onset AD population is estimated to be around 200,000 people younger than 65 years old. In 2013, it was estimated that 44 million people worldwide were affected by dementia, with a rapid increase to 136 million predicted by 20502. There are currently no medicines that have been shown to have disease-modifying effects, and Alzheimer's disease remains the most unmet medical need in neurology. Changes in amyloid precursor protein metabolism, tau protein phosphorylation, oxidative stress, poor energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation, and neurotransmitter pathway disruption all play a role in the pathogenesis of Alzheimer's disease3. The majority of these clinical characteristics are linked to metabolic abnormalities, and it is now obvious that metabolic dysfunction is a major role in Alzheimer's disease. For example, impaired cerebral glucose uptake occurs decades before cognitive loss appears and is an unchanging hallmark of Alzheimer's disease. Deposition of amyloid-β (Aβ) plaques surrounding neurons, neurofibrillary tangles, cholinergic deficiency, and other neurotransmitter abnormalities are the key pathological hallmarks of Alzheimer's disease1.Oxidative stress, obesity, diabetes, hypertension, air pollution, smoking, and hypercholesterolemia are all risk factors. Physical activity and nutritional factors have been demonstrated to be protective and aid in the prevention of it4. We employ cerebrospinal fluid biomarkers and positron emission tomography to diagnose it. There are currently two standard pharmacotherapies available for AD which is approved by Food and Drug Administration (FDA) are respectively-acetylcholinesterase inhibitors- tacrine, donepezil, rivastigmine, galantamine and N-methyl-D-aspartate glutamate antagonist (NMDA)-memantine5.

1.1. Epidemiology of AD

In the United States and many other countries across the world, Alzheimer's disease is a major public health concern, posing a tremendous health, social, and economical burden on society. According to estimates, 35 million individuals worldwide suffer from Alzheimer's disease or other forms of dementia, with an additional 65 million projected by 2030. There is no single cause for Alzheimer's disease, and various modifiable and non modifiable risk factors have been linked to its development and progression. The most important risk factor for the development of Alzheimer's disease is age. The risk of having Alzheimer's disease rises exponentially with age, roughly doubling every 5 years after the age of 656The vast majority of people with Alzheimer's disease are 65 or older and have 'late-onset' or sporadic' disease (95 percent of all cases).Rare genetic mutations have been linked to the development of Alzheimer's disease (AD) before the age of 65, a condition known as 'early onset' or' familial' AD (which accounts for about 5% of

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all cases)7. Autosomal dominant mutations in one of the presenilin genes on chromosomes 1 and 14 or the amyloid precursor protein (APP) gene on chromosome 21 are seen in people with familial types of AD. Furthermore, those with Down's syndrome (trisomy 21) are more likely to have early-onset Alzheimer's disease. The genetics of sporadic Alzheimer's disease are more complicated and poorly understood. The epsilon fourallele of the apolipoprotein E (APOE) gene on chromosome 19 has been identified as a risk factor for the development of sporadic AD8. Females have a higher prevalence of Alzheimer's disease, which reflects their longer life expectancy9.Lower educational attainment has been linked to an increased likelihood of Alzheimer's disease dementia10, supporting the notion that education helps to strengthen a person's cognitive reserve and resilience to the disease10. A growing amount of research suggests that cerebrovascular risk factors play a key role in the onset and progression of Alzheimer's disease. Diabetes, hypertension, obesity, and smoking have all been linked to an increased risk of Alzheimer's disease11. A family history of Alzheimer's disease in first-degree relatives, as well as a history of a head injury resulting in loss of consciousness, are both risk factors for the onset of AD12.

1.2. Pathophysiology of AD

Pathology of Alzheimer disease is not clearly understood yet because it is a polygenic and multifarious complex disease. Because Alzheimer disease is a polygenic and very complicated disease, its pathology is still unknown13,14. The accumulation of proteins over time, proteins that develop plagues around neurons, is the hallmark of Alzheimer's disease. hyperphosphorylation of tau proteins, which results in the formation of neurofibrillary tangles (NFTs), and a decrease in the level of the neurotransmitter ACh15. Acetylcholine is a neurotransmitter that is produced by cholinergic neurons in the brain. It aids in signal transmission and message delivery in the brain16. It demonstrates that it has a significant role in memory and learning17,18. The pathogenesis of Alzheimer's disease is associated with the formation of plaques and neurofibrillary tangles (NFTs) in the brain, which results in the degeneration of cholinergic neurons in the hippocampal and cortical areas of the brain, as well as a drop in acetylcholine levels19,20,21,22,23.Cholinergic dysfunction causes uncontrolled signal transmission in the cholinergic system, which is associated with Alzheimer's disease24. Cholinergic dysregulation originates in the basal forebrain and interacts with pathogenic elements of Alzheimer's disease, such as NFTs, inflammation, and oxidative stress, to impair cognition25.

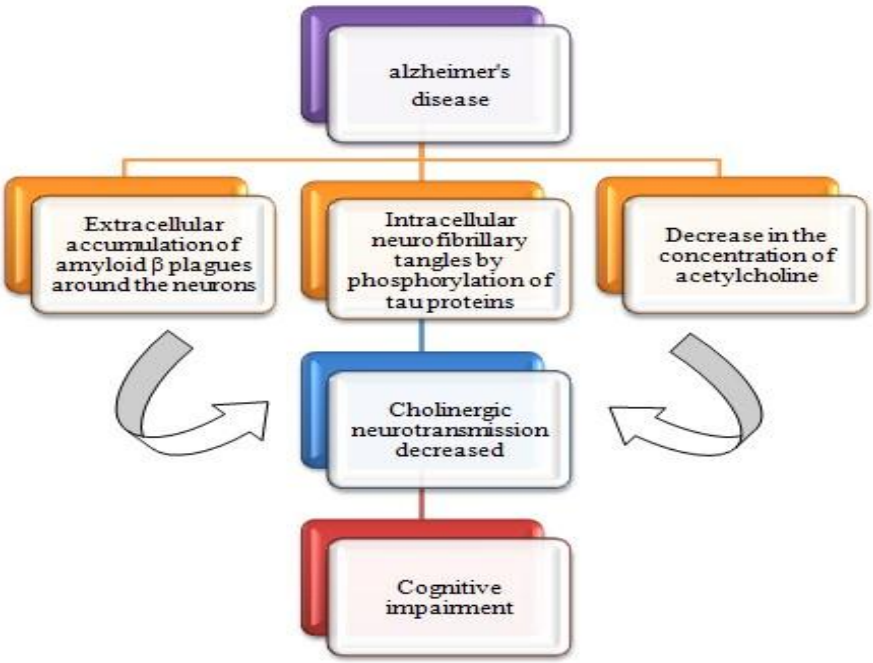

Figure1: Some important Alzheimer's pathologic conditions5.

2. ALZHEIMER'S DISEASE-ASSOCIATED RECEPTORS

2.1. N-methyl-d-aspartate receptors

N-methyl-d-aspartate receptors (NMDAR) have a role in CNS development and synaptic plasticity, both of which are necessary for learning and memory. Glutamatergic neurotransmission problems have been linked to cognitive symptoms such as learning and memory difficulties. Synaptic plasticity and neuron survival need excitatory glutaminergic neurotransmission via NMDAR. Excessive glutamate neurotransmitter activation induces cytotoxicity and leads in neuronal damage and death, implying a possible mechanism of neurodegeneration in Alzheimer's disease.

As a result, inhibiting glutaminergic neurotransmission mediated by NMDAR receptors can reduce cytotoxicity, avoiding additional damage to neurons and cellular oxidative damage26. As a result, NMDAR antagonists have surfaced as possible medicines for Alzheimer's patients, as the receptor comprises numerous subunits and its versions have a variety of activities in the brain. For example, Conantokine is an NMDA receptor antagonist that aids in the understanding of the importance of NMDA receptor inhibition in the treatment of Alzheimer's disease. Moreover, Memantine, an NMDAR antagonist that specifically prevents NMDAR activity, may be used to block NMDAR activation. Extra synaptic NMDAR function is preserved, but normal neurotransmission is unaffected. However, memantine (and other current medications used to treat AD) only relieve the symptoms and do not alter the disease progression3.

2.2. Nicotinic acetylcholine receptor

In Alzheimer's disease, nicotinic acetylcholine receptors (nAChR) play a role in neuroprotection. Agonists and antagonists of the nAChR have also been demonstrated to improve memory performance. When in vitro and in vivo experiments have been undertaken, nAChR ligands such as cotinine and methyl cyclonite have been linked to brain protection. The muscarinic acetylcholine receptor family (mAChR) and nAChR are also acetylcholine targets in the brain. Because beta-amyloid peptides (A) can interact with these receptors, the nAChR family is compromised in Alzheimer's disease22.Acetylcholine (Ach) is an important component of the central nervous system. In the cytoplasm, the choline acetyltransferase enzyme is responsible for ACh production from acetyl-CoA and choline. In synaptic vesicles, the cholinergic vesicular transporter absorbs the neurotransmitter. Exocytosis allows ACh to enter the synaptic cleft after depolarization, where it can bind to its receptors. The acetylcholinesterase enzyme easily hydrolyzes ACh in the synaptic cleft, generating acetate and choline, which is recycled by the high-affinity choline transporter at the presynaptic nerve terminal. In Alzheimer's disease, cholinergic neurons in the basal forebrain, particularly those that make up Meynert's basal nucleus, are severely impaired. Memory and attention problems are caused by the loss of cholinergic neurons. As a result, medications that target the cholinergic system are a promising treatment option for Alzheimer's patients27.

2.3. Gamma-Aminobutyric Acid receptor

The Gamma-Aminobutyric Acid receptor controls GABA and glutamate release, inhibits Adenylyl Cyclase and the cAMP cascade, and affects learning, memory, and cognition. CGP35348 is a GABA receptor antagonist, and the hippocampus concentration of CGP35348 is critical for improving memory by lowering APP toxicity. Neuronal hyperexcitability in certain parts of the brain or spinal cord occurs in a variety of neurological and psychiatric illnesses, which is caused in part by the loss and/or malfunctioning of GABAergic inhibitory interneurons. Improvements in inhibitory neurotransmission in the affected brain regions may help to alleviate the impairments that come with these illnesses. This perception has changed sparked interest in employing preclinical models of neurological and psychiatric illnesses to investigate the efficiency of GABAergic interneuron transplantation in brain or spinal cord regions with hyperexcitability, GABAergic interneurons scarcity, or impaired inhibitory neurotransmission28. Cortical network hyperactivity and aberrant neuronal oscillations can be caused by faulty GABAergic neuronal activities, resulting in a negative shift in memory processes29. GABAergic cell treatment may help to reduce neurological impairments in preclinical AD models28. GABA levels in the brain and spinal cerebrospinal fluid (SCF) are low in Alzheimer's patients, and these changes are more severe in ApoE4 allele carriers. ApoE4 is linked to increased brain activity during rest and memory activities, which could indicate a problem with GABAergic inhibitory regulation. Furthermore, the strongest AD risk factor is the shift in GABA levels in human SCF with age. As a result, ApoE4 may have a role in the development of Alzheimer's disease, inducing age-related deterioration in GABAergic interneurons30.

2.4. G-protein-coupled receptor 40

The neurological system contains several polyunsaturated fatty acids, such as docosahexaenoic acid (DHA), an omega 3 carboxylic acid. The DHA binds to the G-protein-coupled receptor 40 (GPR40) in the neurological system and protects it. for example, GPR40 can boost synaptic plasticity, neuronal activity, and prevent cell death. GPR40 was proposed as a putative dementia target in this area31. The hippocampus, which is essential in learning and spatial memory, is one of the brain locations where the receptor is expressed. However, few research have looked at GPR40's functional role in the brain32. GPR40's functional significance in the AD mice model was investigated in one study. GPR40's functional significance in the AD mice model was investigated in one study. GPR40 treatment increased cognitive function significantly, while GPR40 agonist treatment improved learning and memory skills in multiple tests. GPR40 activation also raised neurotrophic factors levels in hippocampal neurons, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). These findings imply that GPR40 could be a promising therapeutic target for neurogenesis and neuroprotection in the

treatment and prevention of Alzheimer's disease32.GPR40 agonists have been shown to increase adult neurogenesis, block neuronal apoptosis, and protect nerves and reduce brain damage31.

2.5. 5-Hydroxytryptamine 6 receptor

The serotoninergic neurotransmitter system has been linked to the development of Alzheimer's disease. Furthermore, because 5HTR6 affects pyramidal neuron migration during corticogenesis As a result, 5HTR6 is engaged in a variety of functions, including cognition, anxiety, memory, and affective state. it may be added to presently approved "Food and Drug Administration" medicines such as cholinesterase inhibitors and NMDA receptor antagonists. 5HTR6 is also a TOR signalling activator that controls GABAergic, glutamatergic, and cholinergic activities. The 5-hydroxytryptamine 6 receptor (5HTR6) is found in parts of the brain involved in cognitive processes and has been studied as a potential treatment target for Alzheimer's disease symptoms33. With specific 5HTR6 antagonists, a variety of studies have been undertaken. Glutamate and GABA levels are modulated by these antagonists. As a result, dopamine, Ach and norepinephrine concentrations in the brain rise, which are all compromised in Alzheimer's disease. Furthermore, 5HTR6 agonists have been demonstrated to offer cognitive benefits. Cognitive effects from partial or inverse agonists could be promising33,34. Furthermore, 5HTR6 gene variations can be a genetic risk factor for late-onset AD, and 5HTR6 polymorphisms, such as the C267T polymorphism, may play a role in AD susceptibility33. However, there are few genetic research that look into the link between Alzheimer's disease and serotonergic system gene polymorphisms.

3. RISK FACTORS

Diabetes, oxidative stress, hypertension, air pollution, hypercholesterolemia, atrial fibrillation, alcohol, smoking, and other genetic, environmental, and dietary risk factors for Alzheimer's disease exist. These risk factors have influenced the development of Alzheimer's disease prevention strategies35.

3.1. Diabetes

Insulin-degrading enzyme acts as an amyloid and insulin cleavage enzyme. Because insulin signalling is reduced in type 2 diabetes, the production of insulin degrading enzyme is reduced, resulting in A buildup and hyperinsulinemia36. It was also shown that insulin and amyloid competed for an insulin-degrading enzyme, lowering A clearance37. Insulin is also thought to influence tau protein phosphorylation, and they all have a role in the aetiology of Alzheimer's disease38.

3.2. Hypertension

Hypertension is a risk factor for a variety of pathological illnesses, including myocardial infarctions, strokes, ischemic white matter lesions, atherosclerosis, and cardiovascular diseases, among others. All of these are linked to Alzheimer's disease39.According to a study, higher midlife systolic blood pressure (160 mmHg) is linked to a higher number of senile plaques and lower brain weight in the hippocampus and neocortex, while higher late-life diastolic blood pressure (95 mmHg) is linked to a higher number of neurofibrillary tangles in the hippocampus40.

3.3. Obesity

According to studies, increased cholesterol and saturated fats increase the risk of Alzheimer's disease41. Obesity is characterised by a continuous mild systemic inflammation that leads to a brain inflammatory process marked by increased cytokine release at first42,43. It is a pro-inflammatory factor in which the cytokines tumour necrosis factor alpha (TNF), interleukin-1beta (IL-1), chemokine, and interleukin-6 (IL-6) play a key role44.

3.4. Oxidative Stress

According to multiplen research, oxidative stress appears to have a negative impact on the development of Alzheimer's disease45,46.Reactive oxygen species such as superoxide, hydrogen peroxide, hydroxyl radicals, nitric oxide radicals, and others are produced in an infinite amount during oxidative stress15.It is linked to the oxidation of nucleic acids, proteins, lipids, and carbohydrates, which causes oxidative damage to these components47,48. Endogenous sources such as mitochondria, cytochrome P450, peroxisomes, etc., antioxidant defences such as vitamins (A, C, and E), glutathione peroxidase, catalase, glutathione, and exogenous sources such as UV, ionising radiations, inflammatory cytokines, and so on are all involved in the production of reactive oxygen species (ROS)48. Endogenous sources such as mitochondria, cytochrome P450, peroxisomes, etc., antioxidant defences such as vitamins (A, C, and E), glutathione peroxidase, catalase, glutathione, and exogenous sources such as UV, ionising radiations, inflammatory cytokines, and so on are all involved in the production of reactive oxygen species (ROS)48.

4. PROTECTIVE FACTORS

4.1. Physical Exercise

Several studies have shown that regular aerobic exercise improves cognitive ability49, It is regarded as a useful preventive method for the treatment of various stages of Alzheimer's disease50. Physical activity has been shown to increase the amount of neurotrophic factors such as brain-derived neurotrophic factor (BNDF), and their neuroprotective function improves cognition in Alzheimer's disease51. Exercise can also help to reduce oxidative stress and inflammation. It protects against neurodegeneration and Alzheimer's disease by lowering the damage caused by reactive oxygen species (ROS)52,53. Physical activity also lowers levels of tumour necrosis factor alpha (TNF-) and interleukin-1 alpha (IL-1), which reduces amyloid-induced neuroinflammation in the brain and has a protective effect on cognition or dementia54. It also raises the level of nitric oxide in the brain by increasing endothelial nitric oxide synthase activity, which improves neuronal blood flow and reduces brain damage55. The cleavage enzymes neprilysin (NEP) and insulin degrading enzymes (IDE) regulate and determine the quantity of amyloid accumulation and protect neurons from amyloid toxicity56,56,57. Physical activity activates IDE and NEP, preventing A build up, which is thought to be the most critical factor in Alzheimer's disease pathogenesis.

4.2. Nutritional Factor

Nutrition appears to be a key preventive factor against Alzheimer's disease58. It has been found that a diet high in cholesterol, carbs, and lipids has a negative impact on Alzheimer's disease59. It has been discovered that consuming dietary vitamin E without taking additional vitamin E supplements is linked to a lower risk of Alzheimer's disease60. Inadequate levels of folate, vitamin B6, and vitamin B12 result in a rise in homocysteine level and concentration, which is linked to AD as a neurotoxic61.

5. PHARMACOTHERAPY

There are two types of conventional pharmacotherapy for Alzheimer's disease that have been licenced by the Food and Drug Administration (FDA).

- Acetylcholinesterase inhibitors - tacrine, donepezil, rivastigmine, galantamine
- N-methyl-D-aspartate glutamate antagonist (NMDA antagonist)- memantine

5.1. Acetylcholinesterase Inhibitors

According to the cholinergic theory, cognitive dysfunction arises in Alzheimer's patients as a result of significant cholinergic neuron loss, enzymatic failure for ACh generation and degradation, and an inability to transmit neurologic impulses across cholinergic synapses62,63. AChEIs have been hypothesised to improve cholinergic transmission by delaying the breakdown of ACh between synapses18. They also work by lowering levels of the precursor protein for amyloid, as well as amyloid synthesis and accumulation64. To date, the FDA has approved four AChEIs (tacrine, donepezil, rivastigmine, and galantamine) for the treatment of various stages of Alzheimer's disease.

5.2. N-methyl -D- aspartate Glutamate Antagonist (NMDA Antagonist)

NMDA receptors appear to be a promising target for preventing neurodegeneration in Alzheimer's disease65. Overactivation of the N-methyl-D-aspartate glutamate (NMDA) receptor allows for excessive Ca2+ influx, causing excitotoxicity and resulting in damage and loss of number of neurons66As a result, NMDA antagonist has been a new hope for the treatment of Alzheimer's disease in recent years. Memantine is the first NMDA receptor blocker to receive FDA approval for the treatment of moderate to severe Alzheimer's disease67.

6. CONCLUSION AND FUTURE ASPECTS

Alzheimer's disease is a chronic neurodegenerative disease that is rapidly spreading around the world. Because of its complex pathology, variable symptoms, and lack of a specific diagnosis, current therapies such as acetylcholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and glutamate antagonists (memantine) provide only symptomatic relief and have limited efficacy, there is currently no cure. Because there has been a rapid increase in knowledge about AD etiology and its underlying pathophysiological process in recent years, research in this field has a very broad scope, and a cure for it is still a long way off. Nowadays lots of studies were performed to find the cure for AD. In recent years, several interesting studies have been conducted with some novel options, including as medicines that target amyloid- in various ways. Some current ongoing research approaches for AD are like α secretase promotors, γ-secretase inhibitors, β secretase inhibitors, immunotherapy (anti-amyloid antibodies), etc. So, with so many big advances in the book in the future years, We will be able to deliver more complete and unique pharmacotherapy for Alzheimer's disease thanks to therapeutic agents.

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