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A COMPREHENSIVE REVIEW ON THE PATHOPHYSIOLOGY, EXPERIMENTAL MODEL OF ALZHEIMER DISEASE

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ABSTRACT: Alzheimer's disease is a progressive neurological disorder and the main cause of dementia worldwide. It imposes a substantial socioeconomic and healthcare burden, especially as people age. This article discusses the complex pathophysiology of Alzheimer's disease, including the β-amyloid cascade, tau hyperphosphorylation, cholinergic dysfunction, excitotoxicity, oxidative stress, chronic neuroinflammation, and neurotransmitter deficits. Genetic variables such as mutations in APP, PSEN1, PSEN2, and the APOE4 allele are reviewed, as well as environmental and metabolic aspects that contribute to both early- and late-onset illnesses. The article summarizes preclinical models used to investigate Alzheimer's disease, including chemically induced genetically modified and non-genetic models. Each model is useful for assessing treatments and targets distinct disease pathways. A brief overview is also given of recent advancements in gnostic biomarkers and disease-modifying treatments. The article's overall message highlights the intricacy of Alzheimer disease pathogenesis and the value of a variety of study models in promoting early detection, treatment approaches, and preventative initiatives.

INTRODUCTION: The primary cause of Alzheimer's disease is rapidly rising to the top of the list of this century's most costly, deadly, and debilitating illnesses. One The understanding of the underlying pathology, the identification of several protective and causative genes, the discovery of new blood-based and imaging biomarkers, and the first tentative indications of the beneficial effects of disease-modifying therapies and lifestyle changes have all advanced significantly since the Seminar was published in 2016. This new seminar's goal is to give the reader current information about Alzheimer's illness [1-2].

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Prevalence: Clinically diagnosed with dementia has a high prevalence and is predicted to increase over time in tandem with population aging. A variety of estimates from several research indicate that 3–4% of persons in their late working or retirement years have dementia. Regional variations or variations in the study design (e.g., different ages of study participants, diagnostic criteria for dementia) may be reflected in these estimations. As people age, the prevalence of AD with a clinical diagnosis increase.

According to a comprehensive analysis conducted in 2010, the frequency in China rose with age, rising from 0.2% among those aged 55–59 to 48.2% among those aged 95–99. Dementia is also more common in women than in men, according to a meta-analysis that found that Alzheimer disease affected 7.13% (95% CI 6.56, 7.72) of women and 3.31% (95% CI 2.85, 3.80) of men. A systematic review that included prevalence in both men and

women found that the prevalence was higher in women. Women were more than twice as likely to have Alzheimer disease. According to a different study done in China. dementia than men after adjustment for age, period of study [3].

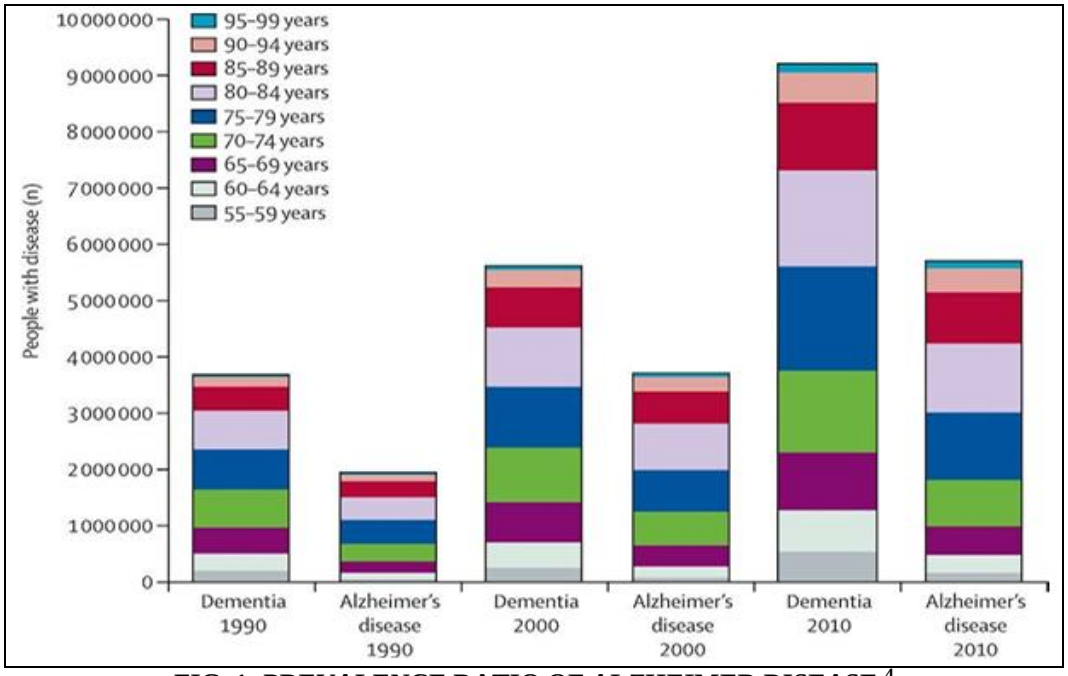

FIG. 1: PREVALENCE RATIO OF ALZHEIMER DISEASE [4]

Pathophysiology:

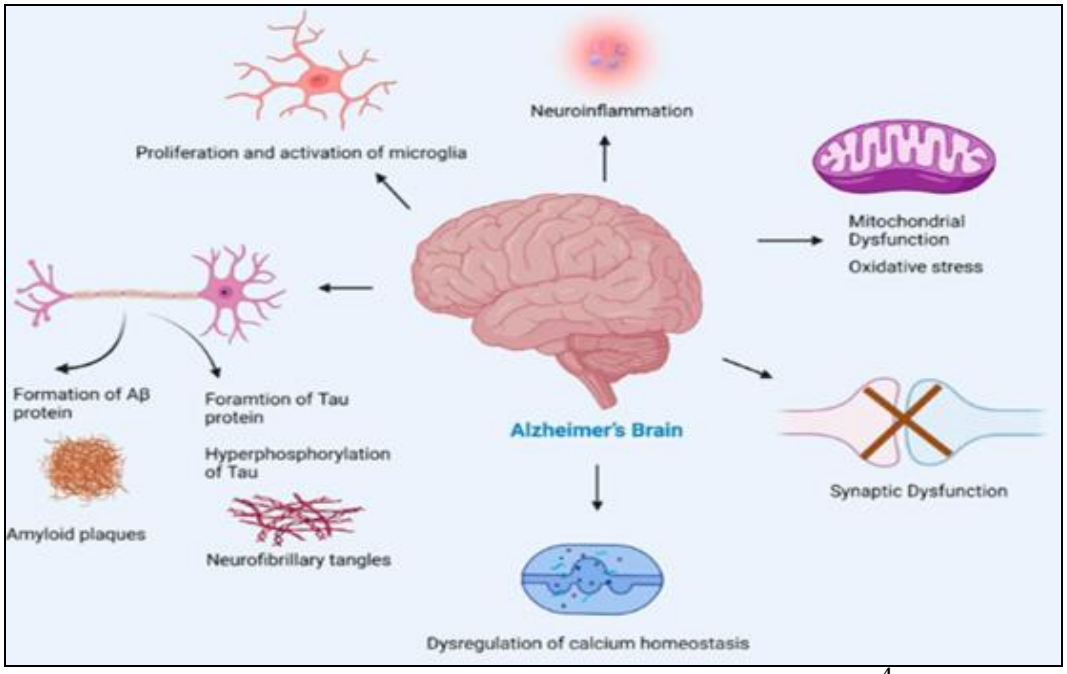

FIG. 2: PATHOPHYSIOLOGY OF ALZHEIMER DISEASE [4]

The β-Amyloid Hypothesis: Clumps of insoluble peptides known as β-amyloid plaques are caused by aberrant cleavage of amyloid precursor protein, the precise function of which is uncertain. Enzymes called βsecretase, γ-secretase, and α-secretase typically cleave APP. After being cleaved by β-secretase and then γ-secretase, a soluble forty amino acid peptide is produced. One When APP is cleaved at the wrong location by a mutant version of the γ-secretase in Alzheimer disease, a 42 amino acid peptide known as Aβ42 or Aβ is produced. This peptide is insoluble and forms recognizable

clusters known as β-amyloid plaques. One since it cleaves APP at a location that inhibits the generation of Amyloidβ, α-secretase has a protective role. Genetic study supports the role of β-secretase and γ-amyloid plaques in the disease's etiology. Genetic study on Alzheimer disease supports the role of β-secretase and γ-amyloid plaques in the disease's etiology. Aβ is known to be produced by all three genes that have been connected to familial APP, PS1 and PS2. (A normal font displays the protein that is derived from a gene, whereas italics identify a gene). The gene APP, which produces the protein, is found on the chromosome. Remarkably, people with Down syndrome eventually develop Alzheimer disease earlier than the general population. The catalytic component of γ-secretase, presenilin, is encoded by the genes PS1 and PS2. There are at least 140 reported mutations in PS1, roughly in PS2, and at least one known mutation in APP. Immunization against Aβ is being researched as a potential treatment for both people and animals. After histologic staining, neurofibrillary tangles appear as dead or dying neurons. When tau, the protein that supports neuronal microtubules, is altered, it destroys the microtubules, resulting in NFTs. One Crucial elements of neuronal cell structure, microtubules serve as channels for the delivery of nutrients and the propagation of neural transmission in the neuronal axon. The hyperphosphorylation of tau proteins during Alzheimer disease pathogenesis causes them to break their links with microtubules, causing the microtubule structure to collapse and the transport and communication system of the neuron to be destroyed. The result is the death of neurons. Tau hyperphosphorylation is believed to follow plaque development, while the exact cause is unknown [4-5].

The Cholinergic Hypothesis: Cholinergic neuron loss is another well-known Alzheimer disease pathophysiology. Cholinergic neurons are drastically diminished by late-stage Alzheimer disease; in certain regions of the brain, this loss exceeds 75%. In parts of the brain related to memory, acetylcholine is a crucial neurotransmitter, and certain elements of cognitive impairment are associated with a decrease in cholinergic activity. The most noticeable neurotransmitter alterations are cholinergic abnormalities. Muscarinic and nicotinic postsynaptic receptors are the two types of receptors that acetylcholine binds to. The neurotransmitters acetylcholine, glutamate, serotonin, and norepinephrine all of which have been linked to Alzheimer disease pathology are released in response to presynaptic nicotinic receptors [6].

The Glutamatergic/Excitotoxicity Hypothesis: The brain's main excitatory neurotransmitter is glutamate. It is thought to be involved in about 66% of all brain synapses and is almost universal in the central nervous system. Additionally, glutamatergic neurons are important because they influence cognition by projecting to other parts of the brain, such as cholinergic neurons. Glutamate itself does not cause the disease linked to glutamatergic neurons in rather, pre- and postsynaptic glutamate receptor levels do. The N-methyl-D-aspartate (NMDA) receptor is the only one of the three types of postsynaptic glutamate receptors that have been connected to pathology of Alzheimer disease. It seems to experience persistent low-level activation in brains, which results in persistently low-level neurotransmission. It is believed that this dysregulation at the glutamate NMDA receptor feeds a vicious cycle of neuronal injury, whereby persistent receptor activation causes a persistent calcium influx inside the neuron that disrupts regular signal transmission. Additionally, it causes APP production to rise, which is linked to increased rates of plaque growth and tau protein hyperphosphorylation (hence NFT formation), which are followed by neuronal toxicity, as mentioned earlier in this article. Reuptake into the terminal nerve and adjacent glial cells remove glutamate from the synapse [7-8].

The Oxidative Stress Hypothesis: Reactive oxygen and nitrogen species, which are molecules of oxygen or nitrogen with an unpaired extra electron (referred to as species) that react with other molecules to form a stable configuration, are produced in Alzheimers disease brains by Aβ-induced lipid peroxidation. In the process, a high-energy electron known as a "free radical" is ejected as the reactive species creates a chemical link with another molecule. The molecule to which the reactive species is bound undergoes structural and functional changes because of the irreversible reaction. The free radical is allowed to harm

molecules and cells. Almost every kind of neuronal macromolecule, including lipids, carbohydrates, proteins, and nucleic acids, is susceptible to this oxidative damage. Because of its rapid rate of oxygen consumption, high lipid content, and relative lack of antioxidant enzymes in comparison to other organs, the brain is particularly susceptible to oxidative stress-induced damage. Oxidation in neurons can lead to a variety of issues, such as irreversible DNA damage and an increase in proinflammatory cytokines. Because oxidative stress is temporally associated with the development of plagues and NFTs, it is believed to be significant early in the progression of Alzheimer disease [9-10].

The Chronic Inflammation Hypothesis: Inflammation may be triggered by injured neurons, NFTs, and β-amyloid deposits as a normal reaction to cell damage. One of the four types of brain cells along with neurons, astrocytes, and oligodendrocytes microglia play a role in the immunological and inflammatory reactions to infection or injury in the brain. Proinflammatory cytokines, reactive oxygen species, proteinases, and complement proteins are among the potentially deadly substances released by activated microglia during pathogenesis. This is typical reaction to cellular damage that seems to go unchecked in Alzheimer disease, doing more harm than good. Cytokines trigger inflammatory reactions that may cause myelin injury and encourage oligodendrocyte and neuronal apoptosis, or programmed cell death. Increased prostaglandins, which are generated by the cyclooxygenases COX-1 and COX-2, have been identified as a sign of inflammation in the Alzheimer disease brain. It's interesting to note that, like the other forms of cellular damage associated the inflammation in Alzheimer is persistent and restricted to certain regions of the brain [11].

Other Neurotransmitter Deficiencies: Acetylcholine, serotonin, and norepinephrine-rich brain regions undergo changes during the process, impacting large swaths of the cerebral cortex. Depression is a common comorbidity with serotonin and is known to play a role in affective illnesses (such as anxiety and depression). In brains, there are less serotonin receptors and transporters, which correlates with a decrease in cognitive tests and anxiety. Additionally, it causes a decrease in norepinephrine levels as well as the loss of norepinephrine neurons. In addition to memory loss, norepinephrine may be a significant factor in various behavioral and psychological symptoms of dementia, such as aggression, agitation, and psychosis [12-13].

Preclinical Models Of Alzheimer's disease [14-31]: Chemically Induced Central Administration:

ICV-STZ-Induced Model: A complex condition, sporadic Alzheimer's disease is brought on by a combination of metabolic, environmental, genetic, and epigenetic variables. Among metabolic variables, poor energy utilization and glucose metabolism are seen early in the course of the disease. Potential treatment strategies have been developed because of significant advancements achieved in this area by animal models revealing the molecular pathways implicated in the pathophysiology of Alzheimer disease. The infusion of intracerebroventricular streptozotocin (STZ) to induce insulin signaling dysfunction is one such often used animal paradigm [2]. Insulin receptors are abundant in the cortex, hippocampus, hypothalamus, olfactory bulb, and other parts of the brain. Clinical findings have shown that mediated insulin resistance causes downregulation of insulin, insulin receptors, and insulin receptor substrates. Therefore, these traits linked to the neuropathology of the ICV-STZ model have the potential to cause memory loss and cognitive disability, which is a compelling argument for the validation of the sporadic model [14-15].

Amyloid-Induced Model: Amyloid-42, amyloid-40, and it can be given intracerebroventricularly or intrahippocampally in place of (ICV STZ). These amyloids have been divided into several groups according to how many amino acids they contain. Additionally, they exhibit varying degrees of pathogenicity with amyloid-42 being the most harmful. It has been demonstrated that the ICV- Aβ injection causes neurodegeneration and memory and learning impairment. Normalizing oxidative and nitrosative factors could produce this result. Amyloid-β has caused an overabundance of reactive oxygen species (ROS) to be produced. Additionally, in an Aβ-42 model of Alzheimer disease, APP processing is improved, leading to an increase in senile plaque deposition.

In an amyloid-induced model, nicotinic acetylcholine receptors are downregulated. Cholinergic dysfunction results from this downregulation. Transgenic mouse models also involve amyloids. Furthermore, tau-related tangles are formed because of central administration. Additionally, oxidative stress pathways may cause mitochondrial malfunction. One of the primary pathological features of is amyloid, which has been addressed by the most recent research for a treatment, aducanumab, a monoclonal antibody, which has been given accelerated approval by the FDA [16].

Chemically Induced Oral Administration [17-18]:

Colchicine-Induced Model: Colchicine, which comes naturally from a plant species (Colchicum autumnal), has been utilized in clinical settings to treat gout. Its ability to attach to microtubule-associated tubulin protein is special. Microtubule destabilization is the result of its administration, which is often done orally. However, cognitive impairment is produced by a dose of 15 μg in a 5 μL vehicle, like pure water in rats. When administered intracerebroventricularly, the resulting cognitive impairment is quite similar to that of sporadic AD. Colchicine exacerbates the neuroinflammatory pathways that cause synaptic dysfunction and neurodegeneration, as well as destroying oxidative equilibrium and cholinergic pathways. Prostaglandin E2 (PGE2), interleukin-β (IL-1β), cyclooxygenase-2 (COX-2), and tumor necrosis factor-α (TNF-α) may oversee the inflammatory response in the colchicine-induced paradigm. Moreover, neuronal death is facilitated by the substantial degradation of microtubules, the primary structural component of the axonal and neuronal cytoskeleton [19].

Chemically Induced Intraperitoneal Administration [20-21]:

Aluminium Chloride-Induced Model: Scopolamine-Induced Model. Also referred to as hyoscine, scopolamine is a tropane alkaloid. It comes from Hyoscyamus Niger and is a strong anticholinergic medication. It is typically used to monitor nausea and vomiting following surgery and to prevent motion sickness before travel. As a competitive inhibitor of muscarinic receptors, it helps with a variety of cholinergic side effects and discomforts, including increased bowel movements, perspiration, lacrimation, and salivation. Since acetylcholine strengthens synaptic connections and is one of the most important neurotransmitters in memory processing, scopolamine-mediated inhibition of cholinergic innervation is frequently utilized as an animal model. By increasing acetylcholinesterase (AChE) activity, scopolamine facilitates the breakdown of acetylcholine. For an model, scopolamine is administered intraperitoneally at a dose of around 2 mg/kg. Scopolamine interferes with the connectivity of many brain regions, including the functional network and spatial memory mapping, during this process. One benefit of the scopolamine induced model is that it eliminates the need for intricate surgical procedures, unlike an ICV model. Additionally, scopolamine-induced memory impairment has been shown to be reversed by cholinergic medications such as donepezil and rivastigmine and antioxidants such as melatonin indicating the additional involvement of the oxidative stress pathway. Consequently, this paradigm is mostly favored for developing preventive alternatives in the treatment [22-23].

Atropine-Induced Model: Atropa belladonna is the source of atropine, another alkaloidal medicine that has been used as an anticholinergic medication to treat myopia and low heart rate. Like scopolamine, atropine disrupts the cholinergic pathway, which lessens the hypofunction of the muscarinic Ach receptor. Additionally, it somewhat inhibits nicotine. Amyloid plaques, a histological characteristic. Were produced after taking atropine intraperitoneally (i.p) at a dose of 5 mg/kg for 21 days. This mechanism may be the consequence of a connection between amyloid genesis and the cholinergic pathway. Additionally, it was noted that Aβ caused a decreased release of acetylcholine and vice versa [24-25].

Chemically Induced Subcutaneous Administration [26]:

D-Galactose-Induced Model: D-Galactose-Induced Model. Dairy products, avocados, sugar beets, and other foods include D-galactose, monosaccharide (for example, milk has 7.12 mg of galactose per 100 g, an avocado has 0.66 g of sugar (which comprises glucose, fructose, sucrose, and galactose), and sugar beets have 0.65% galactose). ROS are produced during the metabolism of D-

galactose. The subcutaneous administration of 50, 100, and 200 mg/kg of galactose resulted in a dose-dependent increase in escape latency in the Morris water maze (MWM) and a decrease in the discrimination index in the new object recognition (NOR) test. This increase demonstrates poor recognition and spatial memory. Additionally, it causes the hippocampus to experience more oxidative stress. It has been reported that when galactose is taken, the immune system becomes weaker and resembles an aging brain. Additionally, it disturbs calcium homeostasis in the cortex and hippocampus, stops neurogenesis in the hippocampus and dentate gyrus regions of the brain, and produces excitotoxicity conditions akin to those seen in dementia cases. Since D-galactose is a sugar that creates a state like insulin resistance, this model can be applied to cases of Alzheimer disease linked to insulin resistance [27].

Genetically Manipulated Model Triple Transgenic Model [28]:

Triple Transgenic Model: The triple transgenic model, so named because it involves mutations on three genes APP on the chromosome, presenilin 1 on the chromosome, and p-tau in mice is a model of an inherited family form of Alzheimer disease. Because AAP and tau are associated with amyloid plaques and NFT, respectively, and presenilin 1 is the proteolytic subunit of γ-secretase mutations in these genes may contribute to the pathophysiology. Transgenes encoding the ones are microinjected into mice to produce the model. Knocking in tau-P301L, PS1-M146 V, and APP-Swe can result in the mutations. Alzheimer model may also be produced by crossing the mutant mice. Furthermore, the formation of tau paired helical filaments and amyloid oligomers was investigated. Cognitive decline and memory impairment result from this transgenic model's inability to repair neurons in the prefrontal cortex, hippocampus, and dentate gyrus, as well as brain atrophy, synaptic disruption, and neuronal death. Transgenic mice were shown to have poor spatial and recognition memory. Mutated mice have also been shown to exhibit phenotypic changes in addition to cognitive impairment. It is also possible to produce a transgenic mouse with characteristics that are closely akin to FAD, either with mutations at APP and presenilin on chromosome or just at APP. Although mice models for immunotherapies and APPG F for BACE1 inhibitors (BACE1 is beta-site -cleaving enzyme 1 that breaks down APP) have been found, they are not appropriate for the more common sporadic [29].

5XAD Model: Another transgenic mouse model that shows mutations in five different genes is called 5XAD. uses the mutant genes S-K670N, S-M671L, F-I716 V, and L-V717I to express APP695. Mice that express these genes have APP mutations. pathogenesis is caused by mutations in these genes. Because of these alterations, proteins produce senile plaques in excess. Additionally, this model depicts neuronal death, synaptic disruption, and gliosis. Although phosphorylated tau pathology is less common than amyloid plaques in this animal, the hallmarks of Alzheimer are depicted earlier than in previous transgenic models.

Additionally, proinflammatory cytokines and immunological markers have been documented through microglial and caspase3 activation in the cortex and hippocampus, indicating neuroinflammation and eventual neurodegeneration caused by apoptosis [30].

Animal Models without Chemical Induction or Genetic:

Aged Rat Model: The hippocampus, temporal lobe, and neocortex of older rats have naturally occurred damage that impairs learning and memory as compared to younger rats. Because of its noninvasive influence and ability to replicate late-onset/aged sporadic clinical signs, this model is favored above other chemically generated models. Rats between the ages of 15 and 20 months could be employed in this model. Considering the clinical features of the illness, this model is more pertinent.

Additionally, neuroinflammatory cytokines, oxidative stress, insulin resistance, and mitochondrial dysfunction have been described in aging-induced dementia. These conditions are brought on by age-related factors such as energy and glucose metabolism, obesity, physical inactivity, etc. Like other models this model also exhibits tau pathology and amyloid genesis. It has been demonstrated that exercise, intermittent fasting, and a number of other antiaging strategies can reverse these negative aspects of improving memory formation and synaptic [31].

High-Fat Diet-Induced Model: A high-fat diet is frequently used to imitate diabetes mellitus, obesity, and insulin resistance. However, it has also been suggested that it be classified as a model of cognitive failure in several recent research publications. Apart from the peripheral distortion of insulin sensitivity, giving rats or mice meals high in fat for roughly 10 14 weeks instead of a normal diet may also partially cause cerebral insulin resistance. 25% fat, 20% protein, and 50% carbohydrates make up the fat diet. It has long been known that Alzheimer's disease and dementia are characterized by abnormal insulin signaling in the brain. Insulin resistance is a fundamental component of this paradigm that is pertinent to memory assessment and enhancing treatment interventions.

Additionally, obesity brought on by a high fat diet impairs appropriate blood flow to the brain's various areas, lowering the availability of oxygen and glucose and leading to vascular dementia. Furthermore, high dietary fat intake has also been linked to cognitive deterioration brought on by diabetes and hypertension. Because fat-associated cholesterol upregulates APP, which is responsible for neuronal death, it contributes to the development of senile plaques. Glucose- transport interference and lipid profile imbalance may potentially be contributing factors to memory loss. By reducing antioxidant enzymes and raising proinflammatory cytokines, the high-fat diet Alzheimer disease model also makes oxidative stress and neuroinflammation worse [31].

CONCLUSION: Alzheimer’s disease is a slowly progressive neurodegenerative disorder with a multifactorial origin involving genetic, metabolic, and environmental influences. Recent advances in research have improved understanding of its underlying mechanisms, particularly in relation to disease pathology, genetic susceptibility, and the development of experimental models. Early disease progression is largely attributed to cellular disturbances, including dysfunction of neurons, microglia, and astrocytes. Abnormal processing of amyloid-β and tau proteins, along with genetic variations in APP, PSEN1/2, APOE, and TREM2, plays a crucial role in initiating and accelerating neurodegeneration. To better mimic humans and investigate cognitive impairment, both chemically induced and genetically modified animal models are widely used. Commonly employed models such as intracerebroventricular streptozotocin, amyloid-β administration, scopolamine, colchicine, and high-fat diet models reproduce different aspects of Alzheimer disease.

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