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Neurophysiological mechanisms 0f Alzheimer's disease comprehensive review

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Abstract: Alzheimer's disease is an incurable brain disease describe by a gradual and advanced decline in brain function in older adults.The disease process begins years before symptoms appear, which can make most treatments less effective. Alzheimer's disease (AD) biomarkers that are currently recognised and used primarily reflect the molecular and structural alterations in the brain that are linked to AD. They can be change in healthy people and frequently do not accurately reflect the degree of cognitive and functional deficits in influenced subjects, despite the fact that they are essential for identefying disease specific neuropathology and have no strong correlation with the way dementia manifests clinically. When clearance mechanisms fail, Amyloid-beta is generated when the amyloid protein (APP) is cleaved by (β , γ) secretase enzymes, leading to the buildup 0f insoluble peptide aggregates in the extracellular space. These clusters create amyloid plaques, which have direct neurotoxic effects, interfere with synaptic transmission, and cause neuroinflammation. At the same time, neurones experience pathological hyperphosphorylation of the microtubule-associated protein tau, which causes it to separate from microtubules and then aggregate into intracellular neurofibrillary tangles. Axonal transport is hampered by this process, which also destabilises the cytoskeletal structure. Amyloid-beta extracellular toxicity and tau pathology-induced intracellular dysfunction work together to cause progressive neuronal degeneration, which eventually results in Alzheimer's disease symptoms. Damaged mitochondria interfere with nerve cell communication and increase the buildup of tau and amyloid-beta proteins, two important characteristics of Alzheimer's disaese. This review's objective is to better diagnose Alzheimer's disease (AD), comprehend its aetiology and natural course, and conduct research.

Key points: AD, neurophysiology, Aβ, tau protein, synaptic dysfunction.

Introduction

(AD) is a neurodegenerative disease responsible for 60 to 80 percent of all cases of dementia worldwide. Neuroinflammation, extracellular amyloid (Aβ) peptide deposition, intracellular neurofibrillary entanglement, characterized by tau protein degradation, neuronal loss, and progressive cognitive decline [1; 2]. In the field of insanity research, (AD) becomes a prominent topic, illuminating the complex relationship between neurophysiological abnormalities and cognitive dysfunction [3]. Numerous intracellular signalling and cellular/molecular pathways are dysregulated, and genetic and epigenetic factors interact to cause (AD), a multifactorial and heterogeneous trouble [4]. Intraneuronal neurofibrillary ravel (NFTs), which consist of aggregated hyperphosphorylated (tau protein), along with extracellular plaques formed from aggregated amyloid-beta (Aβ) peptides, represent the key neuropathological features of (AD). [5;6]. (AD) is a neur0logical dis0rder characterized by gradual memory impairment and cognitive decline, and it has become a major global public health concern due to the complexity of its pathophysiological mechanisms. [7;8]. Amyloid plaques (also known as senile plaques) and neurofebrillary tangles (NFTs) are the primary neuropathological features of (AD), along with an inflammatory process, microglia and astrocyte activation, and eventually synaptic and neuronal loss [9]. Ageing is the main factor influencing the prevalence of AD worldwide, but more cases have been found thanks to

improvements in diagnostic technology. Lifestyle modifications, poor eating habits, inactivity, environmental variables, and genetic susceptibility can all raise the risk. Furthermore, a higher risk of AD is linked to long-term conditions like obesity, diabetes, and cardiovascular disease. WHO reports confirm that the number of people suffering from dementia worldwide exceeds fifty-five million, and also indicate that by 2030 it may reach seventy-eight million and perhaps exceed one hundred and seventy million by 2050, a very large number [10;11]. By 2050, 152 million people worldwide are predicted to have Alzheimer's disease (AD) [12]. 8.2 million Americans are predicted to receive an AD diagnosis by 2030, and by 2060, that figure is predicted to rise to 14 million [13;14]. The amyloid cascade hypothesis, the cholinergic mechanism, and the protein misfolding theory are among the most important hypotheses explaining Alzheimer's diseas [15]. Extracellular dep0sition of (Aβ) peptide as amyloid plaques, the formati0n of intracellular neur0fibrillary tangles caused by hyperphosphorylation of tau protein in the cerebral cortex, amygdala, and hipp0campus—together with neuronal loss, neuroinflammation, and oxidative stress—constitutes the hallmark pathological features of AD [16]. About twenty years after the premier structural alterations in the brain, the first clinical signs of AD usually manifest[17;18] . Modifiable factors (including metabolic syndrome, level 0f education, physical activity, rest, diet, sm0king, and alc0hol consumption) and n0n-modifiable factors such as (age, sex, and genetic predisposition) are considered among the determinants influencing the disease [19]. Aimed to improve the diagnosis of Alzheimer's disease, understand its pathogenesis and natural progression, and investigate.

Methodology:

This review synthesizes evidence from clinical trials and meta-analyses conducted among middle-aged and 0lder adults, including those with a confirmed diagnosis or those identified as being at increased risk of developing the condition. A number of databases such as PubMed, MEDLINE, ScienceDirect, and Google Scholar, were used to perform an extensive literature search (last accessed on April 20, 2026). Certain keywords, including Alzheimer's disease, neurophysiology, amyloid beta, tau protein, and synaptic dysfunction, were used in the search. The search was further narrowed to only look for human and English-language research. This review's main goal is to assess the most recent research on the neurophysiological causes of Alzheimer's disease.

Neurophysiological mechanisms:

The term Neurophysiology refers to the study of how the nervous system functions, that is, how nerve signals are generated, transmitted, and interpreted within the brain and nerves. It is still unclear what pathophysiological processes underlie both normal ageing and neurodegenerative conditions like Alzheimer's disease (AD) [20]. The study of the electrical and chemical properties of nerve cells, or neurones, and how they interact to shape behaviour and perception is known as neurophysiology [21]. The biological and functional processes that control the nervous system's activity are referred to as neurophysiological mechanisms. To put it simply, they are the methods by which the brain, spinal cord, and neurones produce and interpret chemical and electrical signals in order to perform motor, emotional, and sensory functions [22]. The production and transmission of electrical signals, or action potentials, are among the most significant components of nerve cell electrical activity. An electrical impulse that travels along the axon is produced when a stimulus reaches a nerve cell, changing the distribution of ions across the cell membrane. All brain functions, including thought and movement, are based on these impulses [23]. Chemical transport across synapses, Neurones exchange signals chemically across synapses. Neurotransmitters are released when the impulse reaches the end of the axon; these substances travel across the synapse and impact the subsequent cell. This serves as the foundation for memory, learning, and motor control and permits intricate communication between millions of neurons [24].

Result and Discussion

Classical Pathological Mechanisms:

Alzheimer's disease is a pr0gressive neurodegenerative dis0rder, and its causes are explained by several interrelated pathological mechanisms, the most important of which are:

1- Beta-amyloid deposits (Amyloid Plaques) : The physiological mechanisms underlying (AD) are still n0t well underst00d, in contrast to autosomal dominant genetic disorders, whose occurrence is directly associated with abnormalities in the amyloid-β protein [25]. The accumulation various aberrant pr0teins, such as Aβ in plaques and hyperphosph0rylated tau in neur0fibrillary tangles, is one of the neuropathological characteristics of Alzheimer's disease. This causes a significant lack of synapses, dendrites, and eventually neurons [25]. The recognised pathophysiological characteristics (1) extracellular amyloid beta (Aβ) deposition; (2) intracellular tau protein aggregates, eventually known as neurafibrillary tangles (NFT); and (3) neurodegineration has been incorporated into research diagnostic criteria [26]. Microglia cluster around plaques in experimental models of Alzheimer's disease, likely via chemotactic signals, and may participate in responses to Aβ [27]. In addition, abnormal protein clumps in the brain may be initiated or exacerbated by impaired microglial function, including dystrophic microglia, acting either as a contributing trigger, an aggravating factor, or both [28].

2-Tau protein: Numerous studies have examined the mechanisms underlying exercise's impact on AD, with a particular emphasis on the reduction of tau pr0tein tangles and Aβ plaques. Research investigating the causes and mechanisms underlying the progression of Alzheimer's disease has found that a reduction in cerebral glucose metabolism, resulting from impaired energy production, is one of the contributing factors to the development of the disease [29]. Mitochondria play an important role in supplying the energy required through the oxidation of glucose, thereby providing the brain with the necessary energy to perform its functions. They also serve as a key site for the interaction of (Aβ) proteins and tau protein. Therefore, any dysfunction in mitochondrial activity can contribute to Alzheimer's disease, as indicated by previous studies [30]. The lack of cholinargic neurones and cortical cholinergic innervations is intricately linked to the primary pathophysiological features of AD, such as brain Aβ deposition and tau protein hyperphosphorylation [31].

Chemical structures of Tau protein:

The tau protein's binding characteristics and structure (Figure 1) It can be found in it: (A) [18F] PM-PBB3 b0und t0 straight filaments by AD seen from the side. (B) Cryo-EM images of double helical and direct filaments in AD [34]. (C) The f0ur high-affinity binding sites f0r tau tracers are represented by the chemical structure 0f a tau prot0fibril, S2 displays the surface site, while S1, S3, and S4 display the c0re sites [35].

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