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# Alzheimer's disease: risk factors, cellular and molecular basis of pathogenesis, analysis of pathogenetic mechanisms in comparison with amyotrophic lateral sclerosis

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## ABSTRACT

Alzheimer's disease is a neurodegenerative disease characterized by progressive neurocognitive dysfunction. Today, studying the pathogenesis of this disease remains an urgent problem. The review describes the pathogenetic basis of Alzheimer's disease, including not only extracellular deposition of amyloid plaques and intracellular hyperphosphorylation of tau protein with subsequent formation of neurofibrillary tangles, but also mitochondrial dysfunction, impaired autophagy, neuroinflammation, etc. Data are presented on the effect of hyperphosphorylated tau protein on the breakdown and enhancement of β-amyloid peptide synthesis. Oligomerized tau protein causes proteasomal dysfunction and oxidative stress. Mitochondrial dysfunction is closely related to oxidative stress, which can be both a cause and a consequence. Autophagy, namely mitophagy, in turn, also plays an important role in the development of mitochondrial dysfunction. It can be argued that neuroinflammation is associated with all of the listed links in pathogenesis. This review also examines the influence of intestinal dysbiosis on the development of the disease. The complex mutual influence of pathogenetic mechanisms forms a multicomponent network of pathological processes. Understanding the Alzheimer's disease pathogenesis is necessary in the search for methods for correcting impaired functioning mechanisms of the nervous system, which will help develop effective methods for treating this disease. In addition, to better understand the mechanisms of Alzheimer's disease development, it is necessary to search for common pathogenetic factors with other neurodegenerative diseases.

**Keywords**: Alzheimer's disease; β-amyloid peptide; tauopathy; mitochondrial dysfunction; neuroinflammation; intestinal dysbiosis.

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# Болезнь Альцгеймера: факторы риска, клеточно-молекулярные основы патогенеза, анализ патогенетических механизмов в сравнении с боковым амиотрофическим склерозом

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## АННОТАЦИЯ

Болезнь Альцгеймера — нейродегенеративное заболевание, характеризующееся прогрессирующей нейрокогнитивной дисфункцией. На сегодняшний день изучение патогенеза данного заболевания остаётся актуальной проблемой. В обзоре описаны патогенетические основы болезни Альцгеймера, включающие не только внеклеточное отложение амилоидных бляшек и внутриклеточное гиперфосфорилирование тау-белка с последующим образованием нейрофибриллярных клубков, но и митохондриальную дисфункцию, нарушенную аутофагию, нейровоспаление и др. Приведены данные о влиянии гиперфосфорилированного тау-белка на расщепление и усиление синтеза β-амилоидного пептида. Олигомеризованный тау-белок вызывает протеасомную дисфункцию и окислительный стресс. Дисфункция митохондрий тесно связана с окислительным стрессом, который может быть как причиной, так и её следствием. Аутофагия, а именно митофагия, в свою очередь, также играет важную роль в развитии митохондриальной дисфункции. Можно утверждать, что нейровоспаление связано со всеми перечисленными звеньями патогенеза. В представленном обзоре также рассмотрено влияние дисбиоза кишечника на развитие заболевания. Сложное взаимовлияние патогенетических механизмов образует многокомпонентную сеть патологических процессов. Понимание патогенеза болезни Альцгеймера необходимо в поиске методов коррекции нарушенных механизмов функционирования нервной системы, что поможет разработать эффективные способы терапии данного недуга. Кроме того, для лучшего понимания механизмов развития болезни Альцгеймера следует проводить поиск общих патогенетических факторов с другими нейродегенеративными заболеваниями.

**Ключевые слова**: болезнь Альцгеймера; β-амилоидный пептид; таупатия; митохондриальная дисфункция; нейровоспаление; дисбиоз кишечника.

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ЭКО•ВЕКТОР

## INTRODUCTION

Alzheimer's disease (AD), a neurodegenerative disease that constitutes the most prevalent form of dementia, accounts for 60%–80% of all cases. The global prevalence of this disease exceeds 50 million individuals,, with approximately 1.5–2 million dementia patients in Russia [2].

AD is classified based on the time of onset and origin. The disease may exhibit both sporadic and familial etiologies [3]. Late-onset (after 65 years of age) is linked to the sporadic form in about 95% of cases [3, 4]. An estimated 60% of cases of early-onset AD are caused by a familial factor. Patient age ranges from 30 to 60–65 years, with approximately 1%–6% of cases presenting with an early onset.

An estimated 60% of cases of early-onset AD are caused by a familial factor [4]. A complex combination of genetic and environmental factors is believed to be responsible for the sporadic form [5]. A significant proportion of the inherited risk of AD may be due to the Σ4 allele of the apolipoprotein E gene [5]. A mutation in the amyloid precursor protein (APP), PSEN1, or PSEN2 gene is characteristic of the familial form [6].

There are significant differences in the mechanisms of development between sporadic and familial forms. In cases where familial etiology is involved, such as in autosomal dominant inheritance, for example due to APP duplication, the pathology commences with the formation of β-amyloid peptide (Aβ), which subsequently increases the phosphorylation of tau protein. Conversely, in sporadic AD, the process is initiated by alterations in cell signaling that disrupt calcium regulation, leading to the phosphorylation of tau protein, which subsequently increases Aβ production [7].

The symptoms of AD are based upon the stage of the disease. Based on the extent of cognitive impairment, one of the existing classifications distinguishes between a preclinical or presymptomatic, moderate stage and a dementia stage [8].

These stages differ from the American Psychiatric Association's classification in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. The initial and most common symptom is episodic short-term memory loss, which occurs in most patients, with relative preservation of long-term memory [8]. Patients with AD develop multiple cognitive deficits, including memory impairment, aphasia, apraxia, agnosia, and executive dysfunction [9]. In mid- and late-stage disease, neuropsychiatric symptoms, including apathy, social withdrawal, disinhibition, agitation, and psychosis, are also prevalent [8].

## RISK FACTORS

The primary genetic risk factors for familial AD are mutations in three genes: APP, PSEN1, and PSEN2. Mutations in the APP gene most commonly impact the β-APP cleaving enzyme (BACE), the β-site APP cleaving enzyme, the γ-secretase cleavage site, and the middle domain region of Aβ. Mutations in this gene result in increased production of neurotoxic Aβ [10].

The presenilin genes are members of the γ-secretase family. The early onset of the autosomal dominant form of the disease is associated with 179 mutations in the PSEN1 gene and 14 mutations in the PSEN2 gene. These mutations, when combined with APP mutations, contribute to the generation of more toxic variants of Aβ [11].

Mutations in PSEN1 may also affect autophagy function. Mutations in this gene result in impaired acidification/proteolysis of lysosomes, which is a critical component of the autophagy process, as demonstrated in a study utilizing fibroblasts from Alzheimer's disease patients [5]. Mouse models that overexpress mutant APP also exhibit impaired autophagy. This may be due to the toxic effect of the C-terminal domain of APP being cleaved by β-secretase on lysosomes [5, 12].

The Σ4 allele of the apolipoprotein E gene is a glycoprotein that modulates lipoprotein clearance from plasma by acting as a ligand that binds to various cell surface receptors. In a study of 42 families (in late-onset cases), the risk of developing AD increased from 20% to 90% as the number of Σ4 alleles of the apolipoprotein E gene increased [13]. Furthermore, a whole genome association study has identified 11 genes associated with AD [10].

Age is one of the primary risk factors for AD [14]. Age-related changes affect cellular composition, body reactivity, and blood vessels, causing endothelial dysfunction or increased arterial wall stiffness. These alterations are considered when investigating AD pathogenesis, although the contribution of cardiovascular disease to the development of this pathology remains uncertain [14].

Research has demonstrated that both high and low blood pressure may be linked to AD development [10]. Additionally, patients with elevated cholesterol levels experience a more abrupt decline in cognitive function [10].

Anemia is one of the risk factors for AD. It has been suggested that hemoglobin production may be impaired in AD patients, following evidence of its association with the disease [15].

## MECHANISMS OF PATHOGENESIS

### β-Amyloid

One of the key AD pathohistological features is the extracellular accumulation of Aβ plaque aggregates. Aβ plaques initially develop in the basal, temporal, orbital, and frontal regions of the neocortex. In later stages, they progress throughout the neocortex, hippocampus, amygdala, midbrain, and basal ganglia [11].

Amyloid formation begins with the anomalous processing of APP, an integral protein at the plasma membrane, by β-secretases and γ-secretases to form Aβ fibrils, namely Aβ monomers (1–40) and Aβ monomers (1–42). The membrane-bound aspartic protease enzyme, β-secretase, catalyzes the initial proteolytic cleavage of APP and cleaves the β-site. This protease releases a secreted APP derivative and a membrane-bound protein fragment of 99 amino acids, the

so-called C-terminal domain, which is cleaved by β-secretase [10]. The released protein fragments subsequently oligomerize, diffuse into synaptic clefts, and polymerize into insoluble amyloid fibrils, thereby disrupting synaptic signaling. In AD, plaque aggregation is accompanied by the formation of neurofibrillary tangles. These two processes are accompanied by the activation of microglia, which begin to surround the plaques. This further contributes to the development of a local inflammatory response and neurotoxicity [11].

Despite the abundant evidence of Aβ toxicity to nerve tissue, only a weak correlation between the clinical manifestation of AD and plaque deposition in the sporadic form of the disease has been demonstrated [16]. This has led some to suggest that Aβ is not the primary factor contributing to the development of pathology. However, in the familial form, the disease pathogenesis is more clearly defined by the presence of Aβ deposits. This indicates that Aβ may cause neuronal loss without plaque colocalization and neurodegeneration [10].

The weak correlation between fibrillar Aβ and neuronal loss in the sporadic form may be attributed to the varying aggregation states of Aβ [10]. The severity of the disease was found to be correlated with the quantity of soluble forms of Aβ. Conversely, the level of insoluble Aβ does not exhibit such a correlation.

Two main types of Aβ polymers are directly involved in plaque formation and induce neurotoxicity: Aβ [1–40] and Aβ [1–42], which are composed of 40 and 42 amino acid residues, respectively.

Aβ (1–40) is more prevalent and less neurotoxic than Aβ (1–42), which is less abundant, completely insoluble, highly neurotoxic, and more prone to aggregation. It functions as a toxic building block of Aβ assembly [11]. Aβ (1–42) exhibits the ability to form Aβ oligomers, which are subsequently incorporated into the cell membrane and form channels that are highly permeable to $Ca^{2+}$. This causes disruption of calcium homeostasis, which in turn leads to synaptic degeneration [18]. Additionally, it has been suggested that Aβ (1–42) may induce neuronal apoptosis by activating caspase 3, thereby promoting mitochondrial cleavage and increasing the concentration of reactive oxygen species [10].

APP is an integral transmembrane protein with extracellular domains. It has been observed to be localized in the Golgi apparatus, endoplasmic reticulum, as well as on endosomal, lysosomal, and mitochondrial membranes [10]. In AD, APP generates amyloidogenic fragments through differential cleavage by its enzymes. APP encodes a type 1 transmembrane glycoprotein that is cleaved by either the non-amyloidogenic pathway (in the absence of pathology) or the amyloidogenic pathway (in the presence of pathology) [19].

In the absence of pathological processes, α-secretase cleaves and secretes the large soluble ectodomain of APPsα into the medium. The C-terminal domain (C83) is initially retained in the membrane and subsequently cleaved by γ-secretase at residue 711, releasing the soluble peptide P3. In the presence of a pathological process, an alternative pathway is activated, in which β-secretase initiates an aberrant cleavage event, releasing truncated secreted ectodomains of APPsβ and the C-terminal domain (C99). This latter fragment is also retained in the membrane and subsequently subjected to further γ-secretase-mediated cleavage. This procedure, in contrast to the conventional cleavage process, leads to the release of insoluble Aβ peptides. Cleavage of C83 or C99 by γ-secretase releases the intracellular APP domain into the cytoplasm. This soluble domain is subsequently transported to the nucleus for further function, specifically gene expression [11].

Loan Vaillant-Beuchot et al. (2020) suggest that the protein C-terminal domains of APP may be part of the trigger mechanism of AD pathogenesis. This mechanism probably occurs independently of Aβ [20].

BACE1 is a β-secretase that is essential for the synthesis of all monomeric forms of Aβ [21]. BACE1 cleaves APP at two sites: β-cleavage by aspartate and β-cleavage by glutamate in the Aβ domain [22]. The theory that BACE1 plays a significant role in the pathogenesis of AD is substantiated by the fact that the concentration and activity of this enzyme are elevated in the brain in AD. At the intracellular level, β-secretase is located in the plasma membrane, endosomes, and healthy synaptic terminals. The relationship between BACE1 gene mutations and AD pathogenesis remains to be determined [21].

Deoxyribonucleic acid (DNA) methylation regulates BACE1 expression. DNA hypomethylation may be another contributing factor to AD development. Such DNA hypomethylation in the APP promoter region elevates AD-related gene expression, including those of APP and PSEN1, leading to increased Aβ production [21, 23].

BACE1 is homologous to BACE2, another membrane-bound secretase [21]. Both enzymes are expressed in the same cell types in the brain; however, BACE2 is significantly less active. High levels of BACE2 expression and a strong correlation with BACE1 expression in the neurons and astrocytes of AD patients have been demonstrated in human post-mortem investigations [21].

This enzyme is not a true β-secretase. It serves as an antagonist of BACE1 and an alternative α-secretase. However, one study claims that BACE2 may function as a conditional β-secretase [22]. AD-associated mutations may trigger the β-secretase activity of BACE2 by damaging the juxtamembrane helix APP protein, which normally inhibits BACE2. Furthermore, clusterin, a cell aging marker that is activated in AD, stimulates BACE2-mediated β-splicing of wild-type APP by binding to the juxtamembrane helix. Although BACE1 is responsible for the main aberrant APP β-secretase cleavage, abnormally induced β-secretases may better correlate with AD [22].

Another study published in 2021 also indicates that BACE2 encodes an integral membrane glycoprotein that cleaves APP protein into Aβ, which becomes a critical step in AD development [24]. BACE2-mediated β-cleavage has been proposed as a potential marker for the progression of AD at specific phases or may characterize the progression of the disease at

certain stages. For example, this secretase is more active in the preclinical phase of AD [22].

Presenilin protein activates the γ-secretase enzyme, a membrane-embedded protease complex that comprises two transmembrane aspartates in its active site. It is also referred to as a membrane-bound proteasome, which performs the hydrolysis of substrates in the hydrophobic environment of the lipid bilayer. γ-Secretase is involved in the cleavage of the transmembrane domain of the APP, resulting in Aβ production [25]. In familial AD, mutations in the presenilin gene alter the Aβ formation process at the level of γ-secretase [25].

The processing of APP is well studied. The initial endoproteolytic cleavage leads to the formation of 48- or 49-residue Aβ and corresponding fragments of the intracellular domain of APP. γ-secretase, which possesses the requisite carboxypeptidase activity, can process both varieties of Aβ and typically cleaves every three amino acids. Thus, the production of Aβ occurs via two pathways [25]:

1) Treatment of 49-residue Aβ with γ-secretase with sequential formation of 46-residue, 43-residue, and 40-residue Aβ;

2) Treatment of 48-residue Aβ with γ-secretase with sequential formation of 45-residue, 42-residue, and 38-residue Aβ.

## Tau protein

Tau protein is a phosphoprotein involved in maintaining microtubule stability and cytoskeletal organization in mature neurons. In AD, the protein's initial affinity for tubulin diminishes, resulting in its accumulation in the cytosol of somatodendritic compartments, where insoluble structures called neurofibrillary tubules are formed [26]. They are localized in the locus coeruleus as well as in the transentorhinal and entorhinal regions of the brain. The primary sensory and motor domains remain unaffected until the late stages of the disease, as tau protein spreads to the hippocampus and neocortex at the critical stage [11]. Tau pathology, involving the accumulation of neurofibrillary tangles in brain tissue, correlates well with progressive gray matter loss and cognitive impairment [10].

Neurofibrillary tangle formation occurs through the intracellular polymerization of tau protein. Hyperphosphorylated tau fibrils transform into paired helical filaments, which form neurofibrillary tangles, eventually damaging the neuron. The classical view maintains that tau protein hyperphosphorylation is triggered by the activation of kinases during Aβ monomer polymerization into insoluble amyloid fibrils [11].

Hyperphosphorylated tau protein can limit Aβ cleavage by trapping APP-containing endosomes in dendrites and forming endosomal plugs. Endosomal plugs promote Aβ synthesis by allowing APP to spend more time in endosomes, where it is cleaved to Aβ. Phosphorylated tau protein can also promote Aβ formation in axons by disrupting microtubules, which increases APP and BACE accumulation [7].

Numerous kinases, including glycogen synthase kinase 3β, extracellular Aβ-activated cyclin-dependent kinase 5, protein kinase C, protein kinase A, extracellular signal-regulated kinase 2, serine/threonine kinase, caspase 3, caspase 9, and others, phosphorylate tau protein [7, 11]. Among the various kinases and phosphatases, the anomalous hyperphosphorylation of tau protein is primarily attributed to protein kinase A and protein kinases 1 and 2A [27].

One of the critical processes is phosphorylation by protein kinase A at serine 214. Tau protein commences detachment from dendritic microtubules and further aggregates on them, as well as on smooth endoplasmic reticulum in dendrites, especially under glutamate synapses. The phosphorylation of tau protein by protein kinase A at serine 214 provides evidence of impaired calcium regulation by the endoplasmic reticulum at the same site. Tau protein is subsequently hyperphosphorylated [7].

These data suggest that cortical glutamate synapses, which increase in number during brain development, serve as a pathological engine that can generate the degenerative pattern characteristic of AD [28]. Transport of pathological tau protein occurs exclusively near excitatory synapses, but not inhibitory synapses. This is consistent with the fact that the tau protein affects glutamatergic but not GABAergic[1] neurons. A neuron can only be impacted by the translocated pathological tau protein if the intracellular environment is optimal for this process, such as a high calcium content in the cytosol [7].

The development of AD is significantly influenced by glycogen synthase kinase 3β and cyclin-dependent kinase 5, in addition to protein kinase A and protein phosphatases. The former regulates cleavage of the C-terminal domains of APP. Lithium and kenpaullone (two inhibitors of this enzyme) prevent the expression of glycogen synthase kinase 3β and contribute to the inhibition of Aβ formation. Thus, the formation of both Aβ plaques and neurofibrillary tangles in AD may be indirectly influenced by glycogen synthase kinase 3β. In addition, mitochondrial glycogen synthase kinase 3β activity has been associated with elevated oxidative stress.

Thus, this type of kinase is crucial in AD pathogenesis, contributing to Aβ synthesis and its mediation of neuronal death by increasing tau protein hyperphosphorylation. Furthermore, this phosphorylation is reported to be influenced by the interaction of Aβ with cyclin-dependent kinase 5. This interaction results in the cleavage of neighboring proteins, releasing cleaved peptides with lower solubility and longer half-lives, which may also phosphorylate the removed proteins [11].

Most tau proteins released into the extracellular fluid are truncated in the middle tau region and lack tail ends, leading to tau protein aggregation. The full-length tau protein, once inside exosomes, can spread by endocytosis or axonal transmission [27]. Tau protein transsynaptic transmission can be facilitated by exosomes. However, this process requires the preservation of exosome integrity [29].

Exosomes isolated from the blood of patients with AD or frontotemporal dementia were found to contain tau protein

[1] GABA, γ-aminobutyric acid.

in a 2015 study. Additionally, there was a significant increase in exosomal levels of total and phosphorylated tau protein, compared to controls [30].

Additionally, the tau protein study revealed that the concentration of abnormal pathological tau protein in exosomes secreted from the cerebrospinal fluid of patients with mild/severe stage AD (Braak stages 3–6) was significantly higher than that of patients with early-stage AD (Braak stages 0–2). This phenomenon implies that exosome-mediated secretion of pathological tau protein may play an important role in the abnormal increase of its concentration in cerebrospinal fluid during the early stages of AD [27].

In a study involving mouse models of AD, taupathy was revealed to be exacerbated by the activation of the complement system and microglia, although the mechanisms of this process are unknown [31]. Furthermore,the study implicated microglia in the intercellular spread of tau protein throughout the brain, possibly mediated by microglial uptake and exosomal release of tau [31].

It has been postulated that neurofibrillary bundles may cause injury to the neurons and glial cells by displacing cytoplasmic organelles to the periphery, inhibiting proteasome activity, or disrupting microtubule assembly [10].

The proteasome system is essential for the maintenance of intracellular protein homeostasis by facilitating the clearance of misfolded proteins. Reduced proteasomal activity can lead to abnormal protein accumulation and initiate a cascade of events that culminate in neuronal death. Compared to controls, proteasome activity is diminished in the AD group, which is associated with increased neurofibrillary tangles [32].

Tau protein is a proteasome substrate, both *in vitro* and *in vivo*. Neurofibrillary tangle formation may be influenced by proteasome dysfunction. This study concluded that moderate phosphorylation of tau protein activates proteasomes, but additional phosphorylation/accumulation of tau protein inhibits enzyme activity. It follows that proteasome dysfunction may be a consequence of tau protein hyperphosphorylation during AD development [32].

Further, oligomerization of tau proteins induces oxidative stress and energy depletion, which reduces the level of mitochondrial respiratory complex I activity, resulting in neurodegeneration [10]. However, mitochondrial oxidative stress itself is thought to be a factor that causes hyperphosphorylation of tau protein [33].

## Mitochondrial dysfunction

Mitochondria are the cell's powerhouse, synthesizing most of the adenosine triphosphate (ATP) it requires. Mitochondrial dysfunction is highly characteristic of neurodegenerative diseases, especially AD [5]. One of the key questions in the study of this dysfunction is the timing of its occurrence: is it a result of Aβ and pathological tau protein accumulation, or does it itself act as a stimulating factor for the aggregation of senile plaques and neurofibrillary tangles, thereby being one of the initial steps in AD pathogenesis [5]. Some recent studies continue to maintain that mitochondrial dysfunction occurs during the initial stages of AD development [5, 34].

Over time, Aβ accumulates in mitochondria and leads to impaired mitochondrial function, as confirmed by immunogold staining of postmortem brain sections. This study indicates that intramitochondrial accumulation of Aβ begins prior to its extracellular deposition. Presumably, intramitochondrial Aβ accumulation may be a provocative or early factor of Aβ-mediated neuronal dysfunction [35].

Mitochondrial dysfunction involves low levels of ATP production, impaired oxidative phosphorylation activity, impaired mitochondrial membrane potential, and high levels of reactive oxygen species [36]. Mitochondrial dysfunction may play a distinct role in the brain's increased susceptibility to AD development. The aging brain is characterized by a reduction in energy consumption, which encompasses a decrease in glucose consumption and cellular respiratory activity.

The respiratory electron transfer chain is composed of enzymatic complexes that facilitate oxygen-dependent ATP synthesis through a process known as oxidative phosphorylation. Proteomics has demonstrated the deficient expression of proteins of the oxidative phosphorylation pathway and has identified this process as one of the most significantly impacted in AD, including in the cortex of patients [37].

Mitochondrial dysfunction leads to the loss or dysfunction of specific respiratory electron transport chain enzymes: cytochrome c oxidase, the pyruvate dehydrogenase complex, and the ketoglutarate dehydrogenase complex of the Krebs cycle. The expression of these enzymes encoded by mitochondrial DNA can be influenced by DNA damage. This damage can occur in two mechanisms: maternally inherited or acquired through mutagenesis. Currently, there is no consensus on the issue, since several studies support both theories [37].

In the context of bioenergetic dysfunction, AD is associated with a reduction in glucose metabolism, which serves as the primary energy substrate for the brain [10]. This hypometabolism in the frontal, temporal, and parietal cortex in AD patients correlates closely with diminished levels of blood thiamine diphosphate, the critical coenzyme pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in the Krebs cycle, and transketolase in the pentose phosphate pathway [38]. In AD patients, the cerebral cortex exhibits reduced levels of glucose transporters type 1 and 3, which may lead to hypometabolism and delayed glucose transport. Reduced glucose levels lower mitochondrial ATP [10].

Aβ significantly contributes to the pathogenesis of mitochondrial dysfunction. Aβ oligomers cause intracellular calcium imbalance, thereby increasing mitochondrial dysfunction. The mitochondrial $Ca^{2+}$-dependent pore is one of the therapeutic targets for AD, as it modulates the permeability of the mitochondrial membrane.

In addition to Aβ exposure, cyclophyllin D levels are significantly elevated in neurons affected in AD. Cyclophyllin D is also linked to pore dysfunction. Cyclophylline D-deficient neurons have been demonstrated to be resistant to impaired

mitochondrial Aβ function. Increased synthesis of reactive oxygen species with concomitant impaired mitochondrial function leads to neuronal injury and mitochondrial $Ca^{2+}$-dependent pore dysregulation, altering mitochondrial membrane permeability [39].

Aβ oligomers also facilitate the activation of dynamin-related protein 1, a fundamental component of the mitochondrial fission machinery, causing elevated mitochondrial fragmentation and subsequent cell death in AD patients [5].

Reactive oxygen species (ROS) are the inevitable by-products of electron transport during mitochondrial aerobic respiration. Estimates suggest that mitochondria contribute approximately 90% of cellular ROS. Despite performing vital signaling functions, when present in excess, ROS can induce oxidative stress and significant damage. Mitochondria are vulnerable to oxidative stress despite the presence of an antioxidant system. Damaged mitochondria become less effective ATP producers and more efficient ROS producers. Consequently, increased oxidative stress may be both a cause and a consequence of mitochondrial dysfunction [38].

Mitochondrial superoxide radicals form primarily at two conjugation sites: in complexes I and III of the respiratory chain. In AD, both complexes are the principal sources of ROS generation, whereas under normal metabolic conditions, only complex III performs this function [40].

The mitochondrial macromolecules, which include DNA, proteins, and lipids, can be damaged by the highly reactive hydroxyl radical. Damaged mitochondrial DNA can elevate oxidative stress by decreasing the expression of critical proteins required for electron transport, leading to a vicious cycle of ROS and organelle dysregulation, eventually triggering apoptosis [40].

Oxidative stress impacts mitochondrial membrane permeability. Mitochondrial phospholipid peroxidation increases the proton permeability of the inner mitochondrial membrane, alters the mitochondrial membrane properties, and impairs the biochemical functions of various transporters and respiratory enzymes in the inner and outer membranes [10]. By altering the permeability of the mitochondrial membrane, active oxygen species can contribute to the disruption of the normal function of the pore. Additionally, damage to the pore itself causes their increased production [40]. Thus, an increase in oxidative stress could be caused by mitochondrial malfunction or be an effect of it [38].

Several studies of brain samples from AD patients have validated the accumulation of damaged mitochondria in neurons of affected brain regions [41, 42]. This may be attributed to the impaired clearance of damaged mitochondria (e.g., by mitophagy) in AD. Tau protein is known to impede mitophagy. Mitochondrial dysfunction and classical pathological changes in AD may form a vicious cycle [5].

## Autophagy and neurodegeneration

The term "autophagy" is derived from the Greek "to eat oneself," which implies that the main purpose of this process is the destruction of internal components of the cell [5]. There are three distinct types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy, which result in the proteolytic degradation of cytosolic components in the lysosome. When examining AD pathogenesis, it is crucial to comprehend the mechanism of macroautophagy (hereafter referred to as "autophagy").

The process commences with the insulating membrane, also referred to as the phagophore. It expands to engulf intracellular components, including protein aggregates, organelles, and ribosomes, thereby insulating them with a double membrane to form an autophagosome. The autophagosome fuses with the lysosome, facilitating degradation of the autophagosomal contents by lysosomal proteases.

Autophagy is critical for eliminating non-functional cellular components and increasing ATP production, which is necessary for damage control. It performs several functions: selective or non-selective removal of specific damaged organelles (mitochondria, peroxisomes, and endoplasmic reticulum), ribosomes, and protein aggregates; promotion of cell aging and cell surface antigen presentation; protection against genome instability; and prevention of necrosis [43]. However, in neurons, autophagy serves to facilitate axonal guidance, synaptic transmission, the maintenance of communication between neurons, and neural stem cell development. In general, there is evidence that brain dysfunction in neurodegeneration is significantly influenced by impaired autophagy [5].

This perspective is due to an understanding of the peculiarities of neuronal structure and function. The vital activity of neurons is significantly reliant on the external supply of nutrients and, consequently, on active membrane transport that connects the distant cell body with dendrites and axons. Neuronal sensitivity to intracellular imbalances causes an absence of tolerance to the accumulation of aggregated or damaged cytosolic compounds or membranes, which occurs due to impaired autophagy mechanisms. Autophagy is an important homeostatic mechanism in healthy neuronal cells and a cytoprotective response in chronic neurodegenerative diseases [3].

The number of mitochondria decreases with autophagy; hence, autophagy and mitochondrial dysfunction are evidently connected in AD [3, 5]. AD impairs mitophagy (a selective form of autophagy), causing the accumulation of damaged mitochondria in neurons [5]. The translocation of misfolded proteins into the mitochondrial membrane impairs oxidative phosphorylation and activates autophagy. Lysosomal degradation of damaged mitochondria is a critical factor in the regulation of mitochondrial quality in the absence of pathology. A defective mitophagy mechanism reduces the efficiency of this control, which leads to the oligomerization of Aβ and α-synuclein in the mitochondrial membrane, an increase in its permeability, and the release of cytochrome c. This may initiate a caspase cascade, causing massive cell death and neurodegeneration [3].

Research on mitophagy is currently focused on identifying genetic causes of dysfunction in the mechanism of degradation of damaged mitochondria [5]. An unusual accumulation of mitochondrial DNA mutations has been found in the brains of AD patients. This disease results in the suppression of DNA repair pathways, including double-strand break repair and excision base excision repair. However, the exact relationship between impaired DNA repair and mitophagy/autophagy is still unclear.

SIRT1 and SIRT3, two genes with neuroprotective properties, exhibit diminished activity in neurodegenerative diseases, including AD. SIRT1 exerts its neuroprotective function by inducing autophagy/mitophagy, while SIRT3 is an activator of FOXO3, an essential protein for autophagy in neurons. Consequently, SIRT1 and SIRT3 dysfunction suppresses mitophagy and causes the subsequent accumulation of damaged mitochondria in neurons.

Neuronal NAD+[2] deficiency may also impair mitophagy in AD. Numerous studies have linked autophagy to neuroinflammation. Initially, proinflammatory cytokines released in AD activate autophagy. Research suggests that prolonged Aβ exposure can impair microglial autophagy in AD. Thus, disruption of autophagy mechanisms exacerbates neuroinflammation and promotes AD progression [5, 44, 45].

## Neuroinflammation

Neuroinflammation denotes an inflammatory response in the central nervous system accompanied by the aggregation of microglia and astrocytes [46]. Neurodegeneration is exacerbated by mediators of inflammation, which in turn contributes to neuropathology. Neuroinflammation plays an important role in AD pathogenesis, as it commences at the earliest phases of the disease [5].

Postmortem brain sections from patients with mid- and late-stage AD showed large quantities of microglial cells [10]. Microglia are a collection of resident phagocytes in the central nervous system [5]. Microglial cells, which are true phagocytes, perform all the functions inherent to phagocytes. In the absence of neurodegenerative pathology, microglia inhibit neuroinflammation, as they have pronounced anti-inflammatory properties [47].

The phenomenon of activated microglia is a critical concept for understanding AD pathogenesis. This indicates a loss of homeostasis that was previously maintained by microglia. It entails the triggering of microglia polarization by the proinflammatory phenotype M1 [31, 48].

Initially, microglia play a protective role; however, in AD, the continuous accumulation of amyloid leads to microglia-induced chronic inflammation. Even though microglia phagocytize amyloid and protect neurons from its toxicity, they also release proinflammatory mediators that cause neuronal damage [49]. Additionally, Aβ can bind to several receptors expressed on microglia, thereby stimulating the production of cytokines (e.g., tumor necrosis factor α) and ROS [10].

Inflammasomes play a key role in this process. These are multiprotein complexes that trigger inflammation within cells by stimulating cleaving caspase-1 and releasing inflammatory cytokines such as interleukin-1β and -18. Phagocytosis of Aβ by microglia has been demonstrated to induce lysosomal damage and leakage of cathepsin B into the cytosol, resulting in inflammasome activation. The brain tissue is severely damaged by cytokines and chemokines. Many factors contribute to excessive microglial activation. One of them is complement receptor activation, which exacerbates the neuroinflammation process. This microglial activation in AD is linked to the activation of the nuclear factor κB pathway [5].

## Intestinal dysbiosis

The intestinal microbiota refers to a group of microorganisms that reside in the gastrointestinal tract [50]. Animal models have demonstrated the existence of a two-way communication pathway between the stomach and the brain. This interaction is depicted as the microbiota —intestine—brain axis [51]. This axis denotes a complex network of interactions involving both cellular and humoral modes of communication [52]. Intestinal metabolites that influence brain function include short-chain fatty acids, serotonin, acetylcholine, GABA, tryptophan, dopamine, norepinephrine, endotoxins, and histamine [53].

Common elements of the modern lifestyle can disrupt the intestinal microbiota and stimulate dysbiosis [50]. Alterations in the intestinal microbiota can increase the permeability of the intestinal wall and the blood-brain barrier, contributing to the accumulation of intestinal microbiota metabolites in the brain with a subsequent transition from a homeostatic state to a proinflammatory state. As a result, resident central nervous system macrophages, specifically microglia, are activated because of the influence of intestinal dysbiosis on neuroinflammation.

Microbiota alterations also increase circulating levels of humoral (e.g., proinflammatory cytokines) or cellular (e.g., monocytes) effectors of peripheral immunity. The ability of the microbiota to modulate both peripheral and central immune responses is being increasingly recognized [52]. Dysbiosis of the microbiota may lead to a systemic inflammatory response, thereby affecting the microglial immune response [50].

A potential mechanism by which Aβ gains access to the enteric nervous system for further translocation to the central nervous system via vagus nerve axons has been hypothesized. AD and neuroinflammation may be substantially influenced by the translocation of Aβ oligomers from the intestine to the brain [53]. Furthermore, microbiota-induced cytokine synthesis is involved in regulating vagus nerve function [52].

[2] NAD, nicotinamidadenine dinucleotide.

Another mechanism affecting immune response enhancement is related to the ability of certain bacteria, such as *Streptococcus, Staphylococcus, Salmonella, Mycobacteria, Klebsiella, Citrobacter,* and *Bacillus,* to produce functional extracellular amyloid proteins. The appearance of this amyloid in the intestine may trigger an immune response, resulting in neuroinflammation with endogenous amyloid formation in the brain [54].

Thus, it can be contended that the nervous system's functionality is significantly influenced by the microbiota-intestine-brain axis. There is increasing evidence that intestinal dysbiosis may exacerbate Aβ aggregation and neuroinflammation in AD [51, 55].

## COMMON PATHOGENETIC MECHANISMS IN VARIOUS NEURODEGENERATIVE DISEASES

Neurodegeneration is characterized by progressive neuronal death. This process combines multiple nervous system pathologies into a group of neurodegenerative diseases, including AD, amyotrophic lateral sclerosis (ALS), and Parkinson's disease [56]. The development of neurodegenerative diseases is characterized by numerous pathogenetic processes, which presents an opportunity to investigate the shared mechanisms of their development. In this review, we have explored this relationship using the example of the similarity of pathogenetic factors in AD and ALS.

ALS belongs to the clinical and pathological spectrum of motor neuron diseases. It is characterized by moderate and progressive dysfunction and loss of motor neurons [56]. Presently, the most prevalent hypothesis is that the accumulation of oligomers of key proteins is the primary cause of a number of neurodegenerative diseases, such as AD and ALS [57]. For example, AD is characterized by extracellular accumulation of Aβ plaque aggregates, whereas the pathogenesis of ALS is frequently linked to aggregates of pathological superoxide dismutase 1, FUS, or TAR DNA-binding protein 43 in motor neurons and oligodendrocytes [56].

There is evidence of the presence of analogous neuroinflammation mechanisms, despite the differences in the primary factors of AD and ALS pathogenesis [56]. The processes of microglia, astrocyte and inflammatory activation, oxidative stress, production of neurotoxic mediators, mitochondrial dysfunction, and autophagy defects may also be characteristic of neuroinflammation in both AD and ALS patients.

Neuroinflammation in ALS is initially provoked by microglial activation and proliferation, infiltration of the central nervous system by lymphocytes and macrophages, and the presence of reactive astrocytes in the anatomical areas where motor neuron injury occurs [56, 58]. The release of misfolded proteins from damaged motor neurons and astrocytes has been shown to influence microglial activation in ALS. These activate microglia via CD14, Toll-like receptors 2, 4, and scavenger receptor-dependent pathways [59].

In addition to activated microglia, factors that contribute to neuroinflammation in ALS and AD include unregulated and excessive inflammasome activation [58]. In ALS, inflammasome components include interleukin-18, cryopyrin, apoptosis-associated speck-like protein, and caspase-1. In comparison, interleukin-18 and -1β, NLRP1, apoptosis-associated speck-like protein, and cryopyrin have been identified as inflammasome components in AD [58]. The production of neurotoxic mediators, such as cytokines and interleukins, is considered a critical factor in neuronal death.

The primary source of ROS is microglial cells; consequently, neuroinflammation is closely associated with oxidative stress. Oxidative stress in ALS is associated not only with microglial activation [60], but also with the loss of function of superoxide dismutase 1, which plays an important role in scavenging ROS. However, other proteins associated with ALS, such as mutant TAR DNA-binding protein 43 and other as-yet unknown factors in sporadic ALS, may also contribute to oxidative stress in motor neurons [59].

It is not feasible to discuss neurodegenerative diseases without addressing the violation of autophagy and mitophagy mechanisms. As mechanisms that contribute to the development of neuroinflammation, these pathogenic factors can be regarded as a distinct link in the disease's progression. Lysosomal dysfunction results from genetic mutations or toxic effects in ALS [61].

Lysosomal deficiency leads to an abnormal accumulation of autophagic vacuoles that engulf damaged mitochondria in the axons of motor neurons in mice with superoxide dismutase 1 mutations. Therefore, lysosomal proteolysis defects are linked to mitochondrial pathology and defective mitophagy in ALS [62].

Disruption of autophagy and mitophagy in motor neurons can result in the accumulation of misfolded proteins and damaged mitochondria, respectively, leading to cell death [59, 63]. The mitochondria of ALS patients exhibit elevated levels of ROS and impaired Ca2+ homeostasis. Further, ALS results in metabolic alterations in neurons due to the impaired axonal transport of mitochondria along microtubules [59]. Autophagy and mitophagy are also impaired in AD.

## CONCLUSIONS

Multiple factors contribute to the development of AD, including genetic mutations, age-related changes in physiological processes, as well as external and internal risk factors. The study of the interaction between pathological accumulation of Aβ and hyperphosphorylation of tau protein illuminates novel mechanisms that contribute to the disease's pathogenesis.

In the absence of AD, the dysfunction of intracellular mechanisms that maintain homeostasis in neurons is highlighted. Mitochondrial dysfunction and impaired autophagy mechanisms, complex interrelated processes leading to neuroinflammation and synaptic loss, are important steps in AD

pathogenesis. Neuroinflammation may result from intestinal dysbiosis. The relationship between the intestinal microbiome and the brain is emerging as the most promising area of research in AD pathogenesis.

## ADDITIONAL INFORMATION

**Authors' contributions**. L.A.A. — writing — original draft, investigation, resources; K.K.N. — investigation; A.L.Z. — writing — review and editing; M.A.M. — conceptualization, validation, writing — review and editing, supervision, project administration, funding acquisition.
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