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MOLECULAR MECHANISMS OF NEURODEGENERATIVE DISEASES

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Abstract: Neurodegenerative diseases are progressive and irreversible disorders of the central nervous system characterized by neuronal death and functional dysfunction. According to the World Health Organization (WHO), in 2023, neurodegenerative diseases affected more than 55 million people worldwide and are among the leading causes of disability and death. Alzheimer's disease alone accounts for over 50 million cases (WHO, 2023). This article analyzes the molecular mechanisms of major neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and Amyotrophic Lateral Sclerosis (ALS). The main molecular bases of these diseases include protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and genetic factors. The article provides an extensive overview of each mechanism supported by scientific data and statistical indicators, aiming to enhance the understanding of neurodegenerative processes. Research indicates that these mechanisms are interrelated and co-occur in approximately 80–90% of cases (Alzheimer's Association, 2022).

Keywords: Neurodegeneration, protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, genetic factors, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, beta-amyloid, alpha-synuclein, tau protein, free radicals, microglia.

Neurodegenerative diseases are characterized by the progressive loss of neurons in the central nervous system. These disorders are among the leading causes of disability and death worldwide. According to WHO data, the number of patients is expected to reach 139 million by 2050, primarily due to population aging and urbanization (WHO, 2023). Although no definitive cure has been found yet, early diagnosis and preventive measures can help alleviate symptoms. The death and dysfunction of nerve cells lead to the emergence of clinical symptoms and encompass several complex disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic Lateral Sclerosis (ALS) (Przedborski et al., 2003). For instance, Alzheimer's disease affects 10–15% of individuals over 60 years old globally, while Parkinson's disease affects more than 1 million Americans (Parkinson's Foundation, 2023). A deep understanding of molecular mechanisms enables the development of effective therapeutic strategies. Recent studies have shown that 20–30% of neurodegenerative cases are linked to genetic factors, whereas the remaining are influenced by environmental and lifestyle factors (Labbé et al., 2016).

Protein Aggregation and Anomalies

In most neurodegenerative diseases, abnormal accumulation of misfolded proteins occurs within neurons. This process, known as protein misfolding and aggregation, leads to the death of approximately 70–80% of affected neurons (Ross & Poirier, 2017). Protein aggregation arises

due to the impairment of the cellular proteasome system, resulting in the formation of toxic oligomers that disrupt mitochondrial and lysosomal function. For example:

In Alzheimer's disease, the accumulation of beta-amyloid peptides forming extracellular plaques and tau proteins forming neurofibrillary tangles are characteristic features. Statistical data show that beta-amyloid plaques are present in 90% of AD cases and cause up to 50% neuronal loss (Selkoe, 2001; Alzheimer's Association, 2022). This process is associated with mutations in the APP gene and disrupts synaptic communication in the cerebral cortex.

In Parkinson's disease, the aggregation of alpha-synuclein proteins occurs in the form of Lewy bodies.

Protein Aggregation and Toxicity

In 85% of Parkinson's disease (PD) cases, Lewy bodies are found in the substantia nigra region, leading to the loss of 60–80% of dopaminergic neurons and resulting in motor dysfunctions (Spillantini et al., 1997; Parkinson's Foundation, 2023).

In Huntington's disease (HD), aggregation of the mutated huntingtin protein with long polyglutamine chains is observed. All HD cases (100%) are genetic in origin, and the disease develops when CAG repeat expansions exceed 36, resulting in a 40% reduction of the brain's striatum volume (Ross & Tabrizi, 2011).

In Amyotrophic Lateral Sclerosis (ALS), aggregation of TDP-43 and SOD1 proteins causes the death of motor neurons. About 5–10% of ALS cases are familial, and in 90% of these, TDP-43 aggregates are detected, reducing the average patient lifespan by 2–5 years (Neumann et al., 2006).

These protein aggregates exert toxic effects within neurons, leading to cellular dysfunction and the activation of apoptotic and necrotic pathways. Studies indicate that pharmacological agents designed to prevent aggregation—such as anti-amyloid antibodies—have shown 20–30% efficacy in clinical trials (Cummings et al., 2021).

Oxidative Stress

Oxidative stress refers to cellular damage caused by an imbalance between free radicals—reactive oxygen species (ROS)—and antioxidants (Halliwell, 2006). Neurons are particularly vulnerable to oxidative stress because they have high metabolic demands and relatively weak antioxidant defenses. Free radicals induce lipid peroxidation and damage proteins and DNA, constituting a primary mechanism in 60–70% of neurodegenerative disease cases (Lin & Beal, 2006).

For instance, in Alzheimer's disease (AD), ROS levels in brain tissue increase by two to three times, leading to the death of approximately 40% of neurons (Markesbery, 1997). In Parkinson's disease, oxidative stress in the substantia nigraenhances dopamine oxidation, causing up to 50% neuronal loss (Halliwell, 2006). This process is further amplified by mitochondrial dysfunction, ultimately leading to neuronal death.

Statistical data show that antioxidant therapies—such as treatment with vitamin E—can alleviate PD symptoms by 15–20%, although long-term efficacy rarely exceeds 30% (Fahn & Sulzer, 2004). Lifestyle modifications, including regular exercise and dietary regulation, can reduce the risk of oxidative stress–related neurodegeneration by up to 25% (Saeed et al., 2016).

Mitochondrial Dysfunction

Mitochondria are the energy-producing centers of the cell, playing a crucial role in ATP synthesis. In neurodegenerative diseases, mitochondrial dysfunction results in energy deficiency and impaired cellular metabolism (Lin & Beal, 2006). In PD, mitochondrial complex I activity decreases by 30–50% in 90% of cases, which doubles ROS production (Schapira et al., 1990). In Alzheimer's disease, mitochondrial DNA mutations cause a 60% energy deficit in neurons, exacerbating cognitive impairment (Reddy & Beal, 2008).

Moreover, mitochondrial dysfunction disrupts intracellular calcium homeostasis, triggering apoptotic cascades. In ALS, SOD1 mutations impair mitochondrial transport, leading to the death of approximately 70% of motor neurons (Shi et al., 2010). In Huntington's disease, mitochondrial energy production decreases by 40%, increasing neuronal sensitivity to glutamate excitotoxicity (Bossy-Wetzel et al., 2008). Recent studies report that mitochondrial-protective agents such as Coenzyme Q10 (CoQ10) demonstrate 20–25% clinical efficacy (Matthews et al., 1998).

Neuroinflammation

Recent evidence highlights the crucial role of inflammation—specifically, neuroinflammation—in neurodegenerative diseases. Activation of microglial and astroglial cells, along with the overproduction of inflammatory mediators such as cytokines and chemokines, directly contributes to neuronal damage (Glass et al., 2010).

Alzheimer's disease drug development pipeline: 2021. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 7(1), e12179. https://doi.org/10.1002/trc2.12179

Neuroinflammation

According to statistical data, microglial activation in Alzheimer's disease (AD) increases 3–5 fold around amyloid plaques in 80% of cases, accelerating neuronal death by 50% (Heneka et al., 2015). In Parkinson's disease, cytokines IL-1β and TNF-α double in concentration within the substantia nigra, causing the loss of approximately 60% of dopaminergic neurons (McGeer & McGeer, 2008). In Amyotrophic Lateral Sclerosis (ALS), neuroinflammation contributes to the degeneration of 70% of motor neurons, reducing average patient lifespan by about 20% (Philips & Robberecht, 2011). In Huntington's disease, inflammatory mediators cause a 40% reduction in striatal volume (Roos, 2010).

This inflammatory response accelerates disease progression and exacerbates neuronal loss. Anti-inflammatory drugs (e.g., NSAIDs) have been shown to reduce the risk of AD by 15–20%, although their long-term effectiveness rarely exceeds 10% (in 't Veld et al., 2001).

Genetic and Epigenetic Factors

Numerous genetic mutations have been identified in neurodegenerative diseases. According to statistics, approximately 10–20% of neurodegenerative diseases are familial, while the rest are sporadic (Labbé et al., 2016). For instance, Huntington's disease follows an autosomal dominant inheritance pattern and is caused by HTT gene mutations involving CAG repeat expansions. These mutations account for 100% of HD cases, with disease onset typically occurring between 30 and 50 years of age (MacDonald et al., 1993).

In Alzheimer's disease, mutations in the PSEN1/2 (presenilin-1/2) and APOE ε4 genes are recognized as major genetic risk factors. The APOE ε4 allele increases AD risk by 3–15 fold and is found in 20–25% of cases (Corder et al., 1993). In Parkinson's disease, LRRK2 and SNCA gene mutations represent 5–10% of PD cases and enhance alpha-synuclein aggregation (Klein & Westenberger, 2012). In ALS, SOD1 and C9orf72 mutations occur in about 20% of familial forms of the disease (Renton et al., 2011).

Epigenetic changes—such as DNA methylation and histone modifications—also influence neuronal function and contribute to disease pathogenesis. For example, in AD, methylation of the ANK1 gene in brain tissue changes by approximately 30%, accelerating disease progression by 40% (De Jager et al., 2014). Epigenetic factors, in combination with environmental exposures (e.g., toxins), may increase disease risk by 25–30% (Qureshi & Mehler, 2014).

Conclusion

The molecular mechanisms of neurodegenerative diseases are complex and multifactorial. Protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and genetic factors are interrelated processes that play central roles in disease development. According to

WHO projections, by 2030, the global health burden of these diseases is expected to double, highlighting the urgent need for early diagnosis and molecular-level therapeutic interventions (WHO, 2023).

A deeper understanding of these mechanisms is essential for improving early detection, prevention, and the development of innovative therapeutic approaches—such as gene therapy and anti-aggregation drugs. Future molecular research, including the application of CRISPR technology, holds great potential for preventing and mitigating neurodegeneration.

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