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The Role of Mitochondria in the Development of Nervous System Diseases and Mental Disorders

Hala Deeb[1]; V. N. Perfilova[2]
[1].Private Al Hawash University, Homs, Syria
[2]Volgograd State Medical University, Vogograd, Russia
[2]Volgograd Medical Research Center, Vogograd, Russia

Abstract:- The review analyzed articles from the PubMed database mainly from the last 10 years, indicating the role of mitochondria in the development of diseases of the central nervous system and mental disorders. Mutations in mitochondrial/nuclear DNA genes, oxidative stress, impaired redox mechanisms, and regulation of mitochondrial dynamics have been found to cause mitochondrial dysfunction. At the same time, the permeability of mitochondrial membranes changes, the influx of calcium ions increases, as a result of which the membrane potential shifts, oxidation processes become more intense, a large number of reactive oxygen species are formed, oxidative phosphorylation is disrupted, and the process of neuronal apoptosis starts. Mitochondrial dysfunction is a common pathogenetic mechanism of Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, schizophrenia, etc.

Discoveries and advances in molecular genetics have increased our understanding of the early pathology of mitochondrial disorders, enabled disease modeling, and provided entirely new perspectives on molecular pathogenesis. It is necessary that this research continues and then, in the near future, it will help develop the search for possible ways to treat the diseases that people suffer from.

Keywords:- *Mitochondrial Dysfunction, Neurodegenerative And Mental Diseases, Mtdna Mutations, Oxidative Stress.*

I. INTRODUCTION

- *Acquired Mtochondrial Dsfunction and its Role in the Development of Neurodegenerative and Mental Diseases:*

Mitochondria play a key role in maintaining optimal function of neurons and synapses. As many studies show, their dysfunction underlies cognitive deficits in aging and is one of the most prominent features of diseases of the nervous system and mental disorders, as well as a promising target for new therapeutic strategies.

The review analyzed articles from the PubMed database mainly from the last 10 years, indicating the role of mitochondria in the development of diseases of the central nervous system and mental disorders. Mutations in mitochondrial/nuclear DNA genes, oxidative stress, impaired redox mechanisms, and regulation of mitochondrial dynamics have been found to cause mitochondrial dysfunction. At the same time, the permeability of mitochondrial membranes changes, the influx of calcium ions increases, as a result of which the membrane potential shifts, oxidation processes become more intense, a large number of reactive oxygen species are formed, oxidative phosphorylation is disrupted, and the process of neuronal apoptosis starts. Mitochondrial dysfunction is a common pathogenetic mechanism of Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, Huntington's chorea, epilepsy, schizophrenia, etc.

Discoveries and advances in molecular genetics have increased our understanding of the early pathology of mitochondrial disorders, enabled disease modeling, and provided entirely new aspects of molecular pathogenesis. It is necessary that this research continues and then, in the near future, it will help develop the search for possible ways to treat the diseases that people suffer from. Keywords: mitochondrial dysfunction, neurodegenerative and mental diseases, mtDNA mutations, oxidative stress

ADP - adenisine diphosphate, ATP - adenosine triphosphate, AF - Friedreich's ataxia, ROS - reactive oxygen species, AD - Alzheimer's disease, ALS - amyotrophic lateral sclerosis, BL - Lafora's disease, PD - Parkinson's disease, BD - bipolar disorder, HD - Huntington's disease, DA neurons – dopamine neurons, FTD – frontotemporal dementia, MERKV – myoclonic epilepsy and ragged red fiber syndrome, NONL – Leber optic neuropathy, LPO – lipid peroxidation, ASD – autism spectrum disorder, SOD – superoxide dismutase, CNS – central nervous system , TCA cycle - tricarboxylic acid cycle, ER - endoplasmic reticulum, MAM - endoplasmic reticulum membranes associated with mitochondria, MQC - mitochondrial quality control system, OXPHOS - oxidative phosphorylation

Mitochondria are intracellular organelles that have outer and inner membranes, between which there is an intermembrane space. The outer membrane is smooth, the inner one has folds - cristae, which are projected into the mitochondrial matrix, due to which the inner membrane has a large surface. The ultrastructure of cristae has a direct effect on oxidative phosphorylation, apoptosis, mitochondrial fusion/fission, and diseases associated with impaired energy metabolism [1]. An important component of the inner mitochondrial membrane is the phospholipid cardiolipin; it is

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necessary for the functioning of enzymes involved in ATP synthesis[1] .

It may also, by regulating the localization of cytochrome c in the inner membrane, modulate mitochondrial dynamics and the induction of apoptosis. The outer membrane of mitochondria contains integral proteins, porins, which ensure the permeability of substances with a molecular weight of up to 10 kDa. The inner membrane includes transport proteins and proteins of the oxidative phosphorylation system. The Ca2+ uniporter (mitochondrial calcium uniporter, MCU) is localized here, mediating the movement of Ca2+ into the matrix and the adenine nucleotide translocator (ANT), through which ADP is transported from the cytosol to the mitochondrion and ATP- from the mitochondrion to the cytosol[2]. The oxidative phosphorylation system consists of four electron transport chain complexes: I (NADH-ubiquinone oxidoreductase), II (succinate-ubiquinone oxidoreductase), III (ubiquinol-cytochrome c reductase) and IV (cytochrome c oxidase), electron transporters ubiquinone and cytochrome c and ATP synthase (complex V).

Each complex includes several subunits: I - 45, II - 4, III - 11, IV -13 and V - 16, respectively. The mitochondrial matrix is a gel-like structure containing proteins, mainly enzymes of the tricarboxylic acid cycle (TCA cycle), fatty acid oxidation, ribosome synthesis, RNA and DNA. Here, circular-shaped DNA (~ 16,600 base pairs) is localized, containing 37 genes (13 of them encode electron transport chain proteins, 2 -ribosomal RNAs and 22 -tRNAs). In addition, about 1,500 mitochondrial proteins are encoded in the nuclear genome, translated on endoplasmic reticulum (ER) ribosomes, and imported into mitochondria. Under physiological conditions, the DNA of all mitochondria has the same structure; this condition is called homoplasmy. When mutations occur in the mitochondrial genome and organelles with impaired function appear, heteroplasmy occurs and mitochondria with mutated and normal DNA are simultaneously present in the cell. In different types of cells, organelles differ from each other in number and shape[2].

Processes of oxidative phosphorylation - enzymatic oxidation of various substances occur in mitochondria, followed by the synthesis of energy in the form of adenosine triphosphate molecules - ATP. Redox reactions that promote ATP synthesis generate reactive oxygen species (ROS), which play important roles in cell signaling and homeostasis. High levels of ROS cause oxidative stress, destruction of proteins and lipids of cell membranes, DNA, and death of neurons in the central nervous system (CNS)[3].

Mitochondria synthesize membrane transport proteins and some structural components of the respiratory chain. The organelles play a key role in Ca2+ metabolism, which in turn can regulate ATP production and apoptosis. In particular, calcium is a positive allosteric regulator of three key dehydrogenases of the TCA cycle and increases the activity of the electron transport chain. However, prolonged overload of the organelle with it can lead to the opening of the mitochondrial permeability transition pore (mPTP) with a subsequent decrease in membrane potential (ΔΨmt), release of caspase cofactors into the cytoplasm and initiation of the apoptotic cascade [4]. Mitochondria modulate calcium levels at synaptic terminals, whereby they appear to be involved in the regulation of neurotransmission and some types of short-term synaptic plasticity[5].

In cells, mitochondria fuse, divide, branch, and change their size. This process, called mitochondrial network dynamics, ensures the normal functioning of the organelles. The mitochondrial network is controlled by the balance between mitochondrial fission and fusion, mitochondrial biogenesis, and the removal of defective organelles through mitophagy, processes that are critical to regulating the mitochondrial quality control system and maintaining cellular respiration. Fusion can be considered a compensatory process in which mitochondrial proteins and metabolic products are combined and mixed, while fission is a mechanism for eliminating morphologically and functionally altered organelles. Damaged or dysfunctional mitochondria divide and are captured by autophagosomes, which deliver them to lysosomes, where the process of mitophagy occurs. Mitochondrial dynamics can be linked to specific cellular functions and needs. A significant role in the functioning of mitochondria is played by their integration with other intracellular systems, such as the cytoskeleton, nucleus and endoplasmic reticulum[6].

The implementation of the functions of the central nervous system largely depends on the activity of mitochondria, which are the main producers of cellular energy, since brain tissue has a high demand for it and, therefore, mitochondria are critical for the functioning and survival of neurons, neuronal plasticity, carried out through the regulation of the production and inactivation of neurotransmitters, formation and maintenance of synapses, neurogenesis, interaction between cells [6].

Neurotoxins, mutations of mitochondrial DNA genes, oxidative stress, impaired redox mechanisms and regulation of mitochondrial dynamics, and mitophagy cause mitochondrial dysfunction, which plays a significant role in the pathobiology of neuropsychiatric disorders.

The review examines the molecular mechanisms of the pathogenesis of neurological diseases and mental disorders associated with mitochondrial dysfunction. A deep understanding of these mechanisms can help in the development of treatment strategies and the search for pharmacological correction of CNS diseases associated with mitochondrial dysfunction.

II. MITOCHONDRIAL GSFUNCTION CAUSED B MUTATIONS OF GENES ENCODING MITOCHONDRIAL PROTEINS AND DISORDERS ASSOCIATED WITH IT

Currently, more than 50 million people worldwide suffer from Alzheimer's disease (AD), and the number of patients is projected to quadruple by 2050 [7]. Its pathogenesis is not clear and is the subject of much research and debate.

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The most accepted hypothesis is the amyloid cascade, which causes the accumulation of amyloid plaques and intracellular neurofibrillary tangles, which play a fundamental role in the course and progression of the disease. The formed amyloid plaque contains a nucleus and surrounding degenerated neurons. The core consists of pathological hyperaggregated β-amyloid (Aβ), including 42 amino acids and other structures (apolipoprotein E, microglial remnants). The tangles within the neuron are tangles of hyperphosphorylated tau protein, which is normally associated with the microtubule system and maintains the internal structure of the neuron. In AD, excessive phosphorylation of tau protein causes its hyperaggregation, disruption of the transport of substances within the neuron and death of the latter [8]. It is believed that the formation of plaques and tangles provokes oxidative stress and progressive impairment of mitochondrial function[9,10].

Mitochondrial pathologies are the most common causes of hereditary metabolic diseases in adults and children, occurring at a frequency of ~1:2000 and affecting almost 400,000 people in Europe. Primary mitochondrial disorders are a group of more than 200 single gene defects arising from the nuclear and mitochondrial genomes leading to mitochondrial dysfunction and associated with heterogeneous phenotypes.

Most often, diseases arise in connection with a violation of oxidative phosphorylation due to mutations in genes encoding electron transport chain complexes, as well as defects in mitochondrial translation factors, mitochondrial fusion and fission proteins and other mechanisms.

Impairments in the synthesis of ND4, ND1, ND6 subunits of complex I of the respiratory chain are determined in Leber hereditary optic neuropathy (LHON), characterized by bilateral subacute loss of central vision due to the death of retinal ganglion cells, optic nerve atrophy and demyelination. In more than 95% of cases, they are the result of one of three point mutations in mitochondrial DNA (mtDNA) (11778 [G>A] 3460 [G>A] and 14484 [T>C]) [11].

Genetically It has been revealed that 80-90% of patients with myoclonus epilepsy with ragged-red fiber (MERRF) syndrome are caused by the A8344G mutation in the mtDNA tRNA (Lys) gene. The syndrome is a rare disorder characterized by myoclonus, mitochondrial myopathy, cerebellar ataxia, generalized epilepsy, cardiac conduction block and dementia[12,13]. Studies of skin fibroblasts have shown a positive correlation between the named mutation and a decrease in the activity of enzyme complexes I and IV of the mitochondrial respiratory chain. The disease is also associated with increased levels of ROS, manganese-dependent superoxide dismutase (SOD), and mitochondrial fragmentation [14].

A well-known mutation with the replacement of adenine by guanine in nucleotide 3243, which is part of the leucine transfer RNA codon (tRNALeu A>G) of mtDNA, causes mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes caused by impaired oxidative phosphorylation. More recently, 2 new mtDNA mutations associated with complex mitochondrial encephalopathy have been described. An A to G substitution at position 7495 (MT-TS1 (MT-tRNSer (UCN)) (heteroplasmy rate 83%) was identified in a 4-year-old child with ptosis, hypotension, seizures, and dilated cardiomyopathy. A 24-year-old woman was found to have homoplasmic mutation (C to T substitution at position 5577 (MT-TW (MT-tRNATrp)), which was associated with muscle weakness, hearing loss, seizures and cognitive impairment. In both cases, a significant decrease in the activity of complexes I and IV of the respiratory chain was found[14] .The mtDNA mutation m.8993T>G (or the more rare T>C) is accompanied by a deficiency of mitochondrial ATP synthase and leads to axonal, predominantly sensory polyneuropathy.

The development of Leigh syndrome, a hereditary neurodegenerative disease of subacute necrotizing encephalomyelopathy, is caused by gene mutations in both mitochondrial and nuclear DNA. These may be defects in the MTND1, MTND2 and MTND3 genes in mtDNA, encoding subunits of complex I of the respiratory chain, in the nuclear - COX10 and SCO1, located mainly on the 17th chromosome, causing damage to complex IV (cytochrome c oxidase) of the respiratory chain mitochondria, in the ATPAF2 gene, also localized on chromosome 17, leading to disruption of ATP synthase [15], in the SDHA and BCS1L genes, located on the 5th and 2nd chromosomes, respectively, which is accompanied by reduced expression of subunit A of succinate dehydrogenase complex (complex II) and the enzyme ubiquinone-cytochrome c reductase (complex III). Two variants of single nucleotide polymorphism were discovered in the NDUFV2 gene of nuclear DNA, encoding subunit I of the respiratory chain complex, associated with schizophrenia and bipolar disorder [16]. Genetic mutations that cause defects in the DNA-binding protein TAR 43 (TAR DNA Binding Protein, TARDBP, also known as TDP-43), lead to its accumulation in the mitochondria of neurons, the expression of the ND6 subunit of the respiratory chain complex is disrupted, and amyotrophic lateral sclerosis develops (ALS (amyotrophic lateral sclerosis, ALS). A defect in the ETHE1 gene, encoding mitochondrial sulfur dioxygenase involved in sulfide catabolism, is associated with the autosomal recessive fatal disorder ethylmalonic encephalopathy. When the enzyme is deficient, sulfides accumulate in the mitochondrial matrix to toxic levels and inhibit cytochrome c oxidase[17]. Mutations in the SURF1 gene, which encodes a protein (cytochrome c oxidase assembly factor) that ensures the correct assembly of complex IV of the mitochondrial respiratory chain and is important for oxidative phosphorylation, are associated with demyelinating/mixed sensorimotor polyneuropathy [18]. It was revealed that small mitochondrial proteins that form supercoils (structures of the coiled-coil-helix-coiled-coil-helix domain, CHCHD type) play an important role in the synthesis of components of the electron transport chain, regulation of organelle metabolism and modulation of cell apoptosis. Defects in the CHCHD10 gene are associated with ALS and/or frontotemporal dementia (FTD), late-stage spinal muscular atrophy, and autosomal dominant mitochondrial myopathy. Patients have abnormal mitochondrial cristae structure, deficiency of respiratory

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chain complexes, and multiple mtDNA deletions. CHCHD2 mutations are associated with autosomal dominant and sporadic forms of PD [19]. More than 95% of classic cases of Rett syndrome, a neurodegenerative disease that affects early childhood development, have been shown to be caused by mutations in the MBD2 gene, which encodes methyl-CpG-binding domain protein 2 (MECP2). It is currently known that MECP2 directly or indirectly regulates the expression of several nuclear DNA genes encoding mitochondrial factors (cytochrome c oxidase (complex IV), transcription regulator PGC-1α, uncoupling protein 3, cardiolipin synthase, NADH dehydrogenase subunit 2). Probably, its deficiency leads to changes in the structure and function of mitochondria, the development of oxidative stress, which is the cause of autistic behavior and regression of motor skills that appear in children after six months of life [21], secondary generalized convulsive, myoclonic, myatonic, tonic, versive, focal motor, atypical absence seizures, status epilepticus, generalized and focal epileptic seizures [22].

The cause of Friedreich's ataxia (AF), a hereditary neurodegenerative disease, is the expansion of GAA triplet repeats in the FXN gene, which encodes the iron-binding protein frataxin, which is involved in the biogenesis of iron-sulfur groups, iron metabolism in mitochondria, and the protection of neurons from oxidative damage. A decrease in frataxin synthesis associated with a change in the gene leads to the accumulation of iron in them, organelle dysfunction, apoptosis, a decrease in ATP production, and disruption of the formation of iron-sulfur complexes and antioxidant defense mechanisms [22].

A significant role in the development of diseases of the nervous system is played by disruption of the processes of mitochondrial dynamics, changes in the morphology and distribution of mitochondria. Mutations in the nuclear DNA genes encoding mitochondrial fusion proteins mitofusin 2 (Mitofusin-2, Mfn2) and optic atrophy 1 (Opa1) cause Charcot-Marie-Tooth neuropathy type 2A and dominant optic atrophy, respectively [23]. Several mutations have been found in the DNM1L gene, which encodes the dynamin-related protein DRP 1, which plays a key role in mitochondrial fission, leading to severe encephalopathy, refractory epilepsy and, in some cases, death.

DRB 1 contains four domains, one of which plays an essential role in protein self-assembly. Mutations are localized in the region encoding this particular domain, which contributes to a decrease in oligomerization and protein recruitment. Recently, a new substitution R403C was identified, in which the disorders are less pronounced compared to previously known ones. A decrease in fission activity, elongation and changes in the cellular distribution of mitochondria were noted. Patients developed normally for several years before developing refractory epilepsy followed by rapid development of neurological deficits [21]. An association of ALS with a mutation in the OPTN gene encoding the optineurin protein (E50K substitution) has been shown. Axons associated with the glial plate in aged E50K-tg mice in vivo exhibit mitochondrial fission-mediated degradation. The E50K substitution leads to the activation of the proapoptotic protein Bax and the development of oxidative stress, and also causes mitochondrial degeneration and mitophagy in the soma of retinal ganglion cells (RGCs) in vitro [22]. Mutations in the gene encoding SOD 1 (G93A) cause mitochondrial clustering at the proximal side of the Schmidt-Lanterman notches in motor neuron axons and contribute to the appearance of aberrantly elongated mitochondria. Changes in somal organelles are characterized by the loss of the characteristic cylindrical, network-like morphology and the replacement of a less elongated, more spherical shape. Variations in the distribution and size of mitochondria are responsible for the development of ALS [23]. It was found that the expression of Miro1 (Mitochondrial Rho GTPase 1), a key regulator of mitochondrial movement connecting mitochondria and kinesin motor proteins, is significantly reduced in the spinal cord cells of patients with ALS and in transgenic mice expressing mutant SOD1 and TARDBP genes, which is accompanied by disturbances in mitochondrial dynamics [24]. Parkinson's disease (PD) is associated with mutations in the nuclear DNA genes Parkin, DJ-1, PINK1, HTRA2, Omi/HTR2a, which are associated with mitochondrial dysfunction. Parkin encodes a protein of the same name, which is an E3 ubiquitin ligase with an amino-terminal ubiquitin-like domain. The totality of experimental data suggests that parkin degrades defective forms of mitochondria and promotes the normal functioning of dopaminergic neurons; with its deficiency, changes in the ratio of various proteins of the mitochondrial electron transport chain and antioxidant defense are observed [25]. The PINK1 gene, encoding PTEN-inducible protein kinase 1, has 10 different missense and nonsense mutations, and homozygosity or compound heterozygosity for these mutations leads to early-onset PD and 2% of familial cases of early-onset disease. All these mutations cause dysfunction of mitochondria, which makes nerve cells more sensitive to oxidative stress and promotes the initiation of the process of apoptosis [26].

The DJ-1 (PARK7) gene, mapped to chromosome 1p36, contains seven exons, and about 10 different point mutations and deletions have been described in it, including L166P, A104T, M26I, D149A, E64D and L10P, causing the juvenile form of Parkinson's disease associated with focal dystonia. DJ-1 is a multifunctional protein that has the properties of a molecular chaperone that prevents protein misfolding and provides resistance to oxidative stress. It is assumed that, in complex with PINK1, it regulates the ubiquitin ligase activity of Parkin and promotes proteasomal degradation of misfolded proteins [25,26,27]. Omi/HTR2a (high temperature requirement protein A2) is a mitochondrial oligomeric serine protease localized in the intermembrane space of mitochondria and released in response to proapoptotic stimuli. The p.Gly399Ser mutation in the Omi/HTR2a gene in patients with PD causes an increase in the protease activity of the protein; in a stable transfected cell line, it significantly reduces the proteolytic activity of HTR2a, causes swelling and a decrease in the membrane potential of mitochondria [25].

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Genetically determined deficiency of mtDNA replication and repair enzymes can cause a diverse range of diseases. 180 pathogenic mutations in the POLG gene encoding polymerase γ have been described, demonstrating heterogeneous phenotypic manifestations and associated with Alpers-Huttenlocher syndrome, refractory occipital lobe epilepsy (OLE) and status epilepticus (SE); myoclonic epilepsy, myopathy, sensory ataxia (MEMSA); mitochondrial recessive ataxia syndrome (MIRAS). In addition, POLG mutations cause painful, axonal/mixed, predominantly sensory polyneuropathy and may be an etiological factor in PD [28].

It has been revealed that genetically determined disorders in the maturation of mitochondrial tRNAs can be the cause of the emergence and development of various pathological conditions. Mutations in the nuclear DNA HSD17B10 gene, encoding the SDR5C1 (short-chain dehydrogenase/reductase) protein, were found in a child with intractable epilepsy and general (global) developmental delay, static encephalopathy, optic nerve atrophy and blindness. SDR5C1 is a human mitochondrial RNase P enzyme that catalyzes tRNA processing as well as N(1)-methylation of purine bases at position 9, found in most mitochondrial tRNAs, and this modification is believed to stabilize their structure. The disease is associated with mitochondrial dysfunction caused by impairment of SDR5C1-dependent maturation of mitochondrial tRNAs [29]. In October 2018, at the international congress “International Parkinson and movement disorder society” in Hong Kong, scientists from Portugal Rosário M., Moldovan O., Reimão S. et al. A report was presented on the recently identified new heterozygous mutation in the HSD17B10 gene (c.340 T> A, p.F114I), associated with cognitive and behavioral impairment, progressive parkinsonism and psychosis [30]. It has also been shown that the tRNA(Gln) A8336G mutation may increase the risk of Alzheimer's disease (AD), Parkinson's disease and other neurodegenerative diseases.

Acquired mitochondrial dysfunction is a common pathogenetic mechanism of AD, PD, ALS, Huntington's disease (HD), schizophrenia, epilepsy, etc.

III. ALZHEIMER'S DISEASE

Mitochondria play a key role in maintaining optimal function of neurons and synapses. As many studies show, impairment of their function underlies cognitive deficits in aging and is one of the most prominent signs of diseases of the nervous system and mental disorders, as well as a promising target for new therapeutic strategies.

Animal experiments have shown that the induction of AD by a single injection of Aβ 30 ng into each hemisphere of the brain of Wistar rats causes memory impairment, as well as the development of oxidative stress and apoptosis in mitochondria. Depolarization of the mitochondrial membrane, swelling of mitochondria, release of cytochrome c, a significant decrease in the ATP/ADP ratio, and activation of caspase-3, the final mediator of apoptosis, were detected in animal brain homogenate[31,32].

Mitochondrial dysfunction, in turn, causes neuroinflammation, energy-intensive processes in neurons are suppressed, synaptic signal transmission is disrupted, and the plasticity of synaptic contacts is reduced. Reactive oxygen species can activate signaling pathways that mediate cell death in neurodegenerative diseases. When mitochondrial function is impaired, a decrease in ATP synthesis and an increase in ROS production contribute to the formation of large amounts of Aβ, which can have a toxic effect on mitochondria and aggravate neurodegenerative processes. These events lead to hyperphosphorylation of tau protein, synaptic dysfunction and apoptosis [33].

It has been shown that tau protein and Aβ act synergistically and cause disruption of oxidative phosphorylation processes. Aβ oligomers inhibit the activity of cytochrome c oxidase (complex IV) and ATP synthase, as well as the α-ketoglutarate dehydrogenase and pyruvate dehydrogenase complexes, thereby impairing ATP production [34, 35]. The interaction of Aβ with heme leads to damage to the heme-containing complex IV of the mitochondrial respiratory chain. The binding of Aβ and its precursor protein (APP) to the mitochondrial membrane contributes to a decrease in energy metabolism, suppression of the activity of translocases that transfer proteins from the cytosol to the mitochondrial matrix, as a result of which the entry of IV and Vb subunits of cytochrome oxidase into the mitochondria is hampered and the production of H2O2 increases [36]. Several transcription factors are capable of inducing APP expression, such as heat shock factor 1 (HSF-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which react to ROS. APP can form pores in mitochondrial membranes, which leads to disruption of intracellular ionic homeostasis and stimulates apoptotic processes. The result of oxidative damage-related changes in the structure of mitochondrial proteins during the development of AD is a decrease in the efficiency of electron transport along the respiratory chain and ATP synthesis, an increase in ROS levels and energy deficiency, especially in the hippocampus and cortex - areas closely associated with cognitive functions. Intensification of lipid peroxidation (LPO) processes causes disruption of the structure of the bilipid layer of membranes, excessive intake of calcium ions into the cell, activation of proteolytic enzymes and degradation of cytoskeletal proteins[37]. These events contribute to the initiation of apoptosis and a decrease in neuronal density. Disturbances in the processes of fission and fusion, degradation and elimination contribute to an increase in the number of functionally defective mitochondria in neurons, the energy supply of nerve cell processes and synaptic transmission deteriorate, which causes degeneration of synapses [38]. A significant decrease in the expression of all mtDNA OXPHOS genes and the main regulator of mitochondrial biogenesis PGC-1α (PPARGC1A) in the tissues of patients with AD was shown [39]. Thus, proteins involved in the development of AD may contribute to mitochondrial dysfunction through a variety of mechanisms. In turn, existing dysfunction can aggravate pathological processes, stimulating the appearance of defective proteins and thereby closing the vicious circle of disease development. With the aberrant accumulation of damaged or unfolded proteins in the mitochondrial matrix, there is an

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increase in the expression of key genes of the mtUPR stress response signaling pathway (mitochondrial unfolded protein response (mtUPR), which ensures adaptation of mitochondria. In sporadic and familial forms of AD, a significant increase in the expression levels of selective genes was detected, including including those encoding the mitochondrial chaperones dnaja3, hspd1 and hspe1, clpp and yme1l1, the thioredoxin family protein txn2, as well as proteins involved in ROS defense mechanisms, mitochondrial fission, and ubiquinone biosynthesis. Current observations suggest that this may be a physiologically important cellular response. chronically activated in AD, possibly as a compensatory neuroprotection against the accumulation of misfolded and damaged mitochondrial proteins. Although the physiological consequences of chronic activation of mtUPR in mitochondria remain unclear, they may be similar to processes occurring in the endoplasmic reticulum, where sustained activation of the UPR promotes the transition of protective mechanisms. to damaging [40]. It is necessary to study the processes occurring in the cell during this response, which will help explain the mechanism of neuronal vulnerability and endogenous compensatory mechanisms during the progression of AD, and determine the target for the effects of pharmacological drugs.

As mentioned above, neuronal degeneration in AD can be caused by disruption of mitophagy, a key process in maintaining cell homeostasis that promotes renewal and prevents the accumulation of dysfunctional mitochondria [41, 42]. A study by Fang et al. (2019) showed that the levels of mitophagy-associated proteins (Bcl2L13, PINK1 and BNIP3L/NIX) were reduced, and mitophagy initiation proteins (phospho-ULK1 (Ser555) and phospho-TBK1 (Ser172)) were inactivated in samples taken from patients with AD and in cultures of cortical neurons obtained from stem cells of patients with familial (APP/V717L) and sporadic (APOE4)/E4 forms of AD. In addition, the levels of FUNDC1 (hypoxia-induced mitophagy receptor), AMBRA1 (BECN1-regulated autophagy protein 1), and MUL1 (mitochondrial ubiquitin ligase activator NFKB-1) proteins were reduced in stem cell-derived cortical neurons, further confirming the disorder. mitophagy in AD. In addition to neurons, the intensity of this process decreases in microglia in the hippocampus of mice with AD, which affects its role in phagocytosis associated with the expenditure of large amounts of energy [34].

Recent studies indicate an important role of mitochondrial microRNAs in the pathogenesis of AD. It was found that microRNA-743a suppresses the activity of malate dehydrogenase, which increases in AD, and microRNA-23a/b inhibits glutaminase, resulting in disruption of the Krebs cycle. MicroRNAs 210, 338 and 34a inhibit the activity of enzymes involved in oxidative phosphorylation (OXPHOS), where most of the ATP for the functioning of neurons is synthesized. In this regard, suppression of the OXPHOS process prevents neurons from meeting their high energy demands, which leads to their death [43]. MicroRNAs 16-5p, 195 and 29b disrupt the integrity of the mitochondrial membrane and contribute to a decrease in membrane potential, which leads to a decrease in ATP synthesis and signal transmission between neurons. These disorders ultimately cause cognitive impairment similar to that in AD [44, 45]

MicroRNA-455-3p and 34a enhance synaptic activity and play a synaptoprotective role in AD [46], while a decrease in the expression level of microRNA-218 in AD suggests that it may have a protective effect against synaptotoxicity [47]. The work of Gowda et al. (2022) identified 24 mitochondrial miRNAs that are associated with AD. They regulate many mitochondrial functions, including bioenergetics, redox homeostasis, mitophagy, biogenesis, mitochondrial dynamics and apoptosis. Some of them play a significant role in synaptic activity, neurotransmission, neurotoxicity and synaptic plasticity [43]. Thus, mitochondrial dysfunction is closely related to the main pathological feature of AD: neuronal dysfunction. Targeting mitochondria and associated proteins may be a new strategy for developing disease-modifying therapies [48].

IV. PARKINSON'S DISEASE

Parkinson's disease (PD) is characterized by the loss of dopamine (DA) neurons and decreased dopamine synthesis in the substantia nigra (SN) in combination with Lewy bodies, the main component of which are aggregates of the protein α-synuclein (α-syn). The substantia nigra serves as a source of dopamine for the basal ganglia, which plays an essential role in initiating and facilitating movement. In this regard, tremor, bradykinesia, muscle rigidity, and decreased motor activity are observed in PD. In addition, there is a range of non-motor manifestations, including neuropsychiatric symptoms (depression, attention deficit, hallucinations, illusions, dementia), dysfunction of the autonomic nervous and sensory systems (nausea, constipation, pain), and sleep disturbances[49].

A correlation has been revealed between dysfunction of complex I of the mitochondrial respiratory chain and degeneration of dopaminergic neurons in the pars compacta of the substantia nigra [49]. Previous studies have shown that complex I inhibitors cause PD in animals and possibly in humans[50]. In brain tissues taken at autopsy from deceased patients with PD accompanied by dementia, a decrease in the activity of complex I in the prefrontal cortex (Brodmann area 9, BA) was found by 27% and in the amount of mtDNA by 18%. In the somatosensory cortex (BA 1, 2 and 3), the indicators decreased by an average of 50 and 41%, respectively [51]. More recent work has also shown that respiratory chain complex I dysfunction alone is sufficient to cause progressive parkinsonism, in which loss of dopamine release from nigral neurons is a critical contributor to motor and fine motor deficits [52].

Mitochondrial dysfunction leads to the accumulation and oligomerization of α-synuclein, and elevated levels cause mitochondrial disorders. It has been shown that some post-translationally modified protein species have a high affinity for the outer mitochondrial membrane translocase TOM20, hindering the import of mitochondrial proteins, which causes a decrease in respiration, mitochondrial membrane potential and an increase in ROS production in PD.

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Transgenic mice overexpressing α-synuclein exhibit reduced electron transport chain complex IV activity and enlarged and abnormal mitochondria. α-synuclein knockout mice demonstrate resistance to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced dopamine neuron degeneration, which is due to the inability of the toxin to inhibit complex I in the absence of the protein and indicates the role of the latter in modulating mitochondrial toxicity and oxidative stress. At the same time, α-synuclein does not affect mitochondrial function under physiological conditions [53]. Some α-synuclein is associated with mitochondria in DA neurons, for example, it is present in the membrane of organelles or associated with complex I of the respiratory chain[54].

When increased in expression in cultured cells and in Caenorhabditis elegans, α-synuclein binds to mitochondria and leads to their fission. Age-related fragmentation of C. elegans intensifies and manifests itself at an earlier time [55]. Mitochondrial fission is ultimately accompanied by respiratory depression and cell death. Disrupted mitochondrial dynamics lead to changes in their morphology and intracellular transport[55,56]. It has been shown that wild-type α-synuclein from human and mouse cell lines and brain tissue is present in endoplasmic reticulum (ER) membranes associated with mitochondria (mitochondria-associated ER membranes (MAM)) and point mutations in the gene encoding it lead to decreased association with MAM and increased mitochondrial fragmentation compared to the wild type. The accumulation of large amounts of α-synuclein affects the ability of mitochondria to regulate Ca2+ homeostasis. The lack of efficient transfer of Ca2+ from the ER to mitochondria leads to the activation of autophagy, which can disrupt the processes of cellular bioenergetics[56].

In addition, in cells with overexpression of α-synunlein, a decrease in the number of contact sites between the ER and mitochondria was detected due to disruption of the GRP75-IP3R (glucose regulated protein 75-inositol 1,4,5-trisphosphate receptor) interaction and a decrease in Ca2+ buffering by mitochondria, the excess of which can lead to the formation of toxic clusters characteristic of PD [57].

Activation of mitophagy in primary cortical neurons that overexpress mutant α-synuclein A53T leads to massive destruction and loss of mitochondria, which is associated with ATP deficiency and neuronal degeneration. Thus, the removal of excessive mitochondria in this case may be one of the factors causing PD [58].

Cells have “quality control” mechanisms by which damaged components are removed and new ones are synthesized. The mitochondrial quality control (MQC) system is necessary for their normal functioning. Mammalian mitochondrial rhomboid protease (parsenilins-associated rhomboid-like protein, PARL) and pyruvate dehydrogenase kinase isoform 2 (PDK2) exhibit defects in mitochondrial bioenergetics, regulate PINK1/PARKIN-mediated mitophagy, and mediate MQC. MQC dysfunction may become a key mechanism in the pathogenesis of various diseases, including PD [59, 60]. It has been shown that mitophagy and mitochondrial biogenesis are impaired in human DA neurons lacking PARKIN, and that these impairments are an important driving force behind the decline in mitochondrial function and loss of DA neurons in PD due to PARKIN deficiency [61]. The mechanisms by which PARKIN protects the adult brain from PD are not fully understood. Perhaps the cysteines of this protein are involved in redox reactions, which is reflected in its post-translational modifications. In postmortem human brain, including the substantia nigra, it was found that PARKIN becomes largely insoluble after 40 years of age, due to its oxidation, for example, at residues Cys95 and Cys253. Similarly, in an experiment in mice, oxidative stress causes post-translational modifications of the cysteines of this protein, as a result of which its solubility in vivo decreases. Oxidation of recombinant PARKIN with hydrogen peroxide (H2O2) renders it insoluble, forming aggregates, and H2O2 is reduced. In the case of precise mutations, for example, p.C431F and p.G328E, this ability is lost [62].

V. HUNTINGTON'S DISEASE

HD is caused by multiplication of the CAG (PolyQ) codon in the HTT gene, which encodes the huntingtin protein. Wild-type genes in different people do not include the same number of CAG repeats, and when their number exceeds 36, the disease develops. The length of PolyQ determines the onset and severity of the disease, with more repeats causing an earlier onset. The disease is associated with progressive motor impairment, cognitive decline, and mental distress [63]. Accumulation of mutant huntingtin (mtHtt) during disease may cause mitochondrial dysfunction, which plays a role in the pathogenesis of HD (Figure 1). In patients with this pathology, there is an abnormal morphology of organelles in the cells of the cerebral cortex, a decrease in the activity of complex II of the electron transport chain in the caudate nucleus and in the cerebral cortex, complex III in the caudate nucleus and putamen, complex IV in the putamen [64], striatum and cerebral cortex of R6/2 mice, fragmentation of mitochondria in peripheral cells [65] increased expression of mitochondrial fission regulator proteins (DRB1 and Fis1) and decreased expression of mitofusin fusion proteins (Mfn 1 and 2) in the brain of patients with HD [66]. A certain contribution to the pathogenesis of HD is made by peroxisome proliferator-activated receptor-γ coactivator 1α, PGC1α, a key factor in the biogenesis and regulation of mitochondrial functions, the levels and activity of which are reduced in the brain and muscles of patients with HD and transgenic animals, which is associated with abnormalities of myelination and oligodendrocyte differentiation [67].

Extended polyglutamine repeats mtHtt, which selectively bind to mitochondrial glyceraldehyde 3-phosphate dehydrogenase (GAPDH), inhibit its mediated uptake of damaged mitochondria by the lysosomal system, which leads to their accumulation, increased ROS levels, and cell death [68]. mtHtt was found to change mitochondrial morphology in photoreceptor neurons to an abnormal ring-shaped one and block mitophagy in Drosophila. There is evidence that mitophagy deficiency is one of the main fac-

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tors contributing to neuronal death in neurodegenerative diseases, including HD. Accurate and proper degradation of dysfunctional mitochondria is necessary to maintain control over the quality and quantity of mitochondria in neurons[67].

Recent work has shown that expression of high levels of mutHtt fragments can affect mitochondrial network dynamics and mitophagy, leading to pathogenic mtDNA mutations [69].

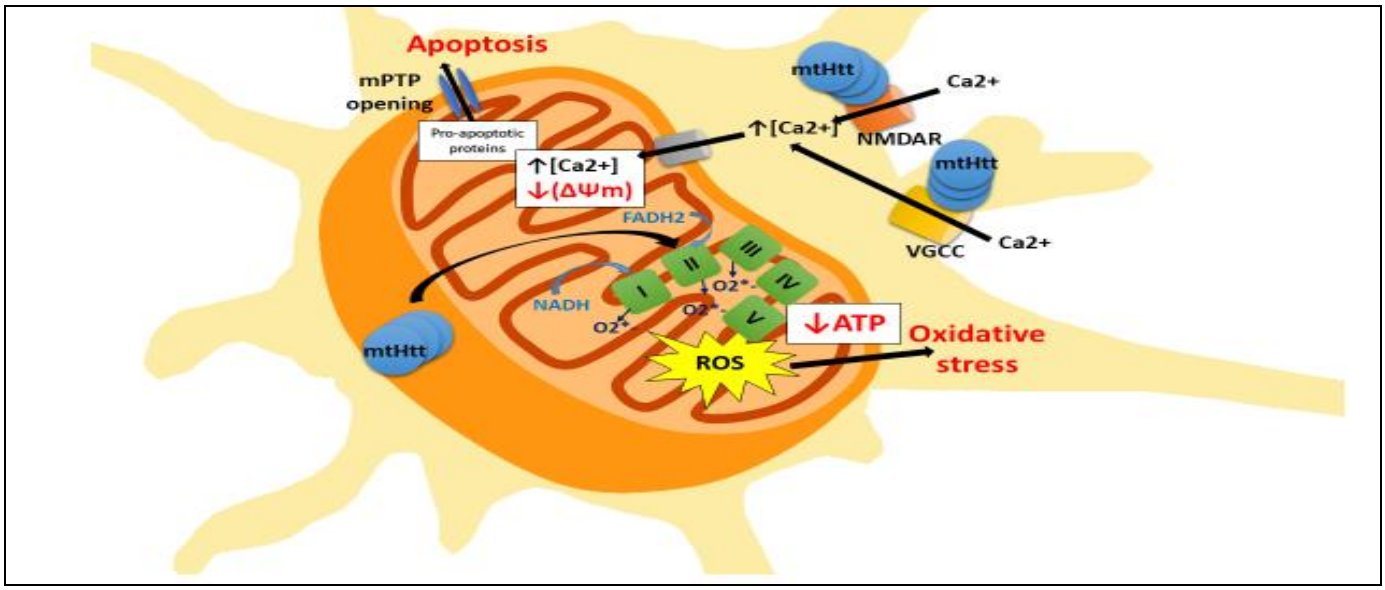

Fig 1: The Role of Mitochondria in the Pathogenesis of Huntington's Disease

Designations: mPTP – mitochondrial pore; VGCC - voltage-gated calcium channels NMDAR - glutamate receptors; ROS – reactive oxygen species; mtHtt - mutant huntingtin protein; ΔΨm - electrical potential gradient on the inner mitochondrial membrane, mPTP – mitochondrial permeability transition pore; VGCC - voltage-gated calcium channels NMDAR - glutamate receptors; ROS – reactive oxygen species; mtHtt - mutant huntingtin; ΔΨm - mitochondrial membrane potential Degradation of an antiapoptotic protein of the mitochondrial membrane belonging to the Bcl-2 family - MCL1 (multidomain antiapoptotic protein of the Bcl2) was detected in patients with HD in the presence of mtHtt. Reduced MCL1 levels are associated with mitochondrial and cellular damage. Apoptosis of neurons in HD is also caused by impaired calcium metabolism, as a result of which the mitochondrial pore (MP) opens and MP-dependent cell death is initiated [70].

A significant increase in the proportion of heteroplasmies of pathogenic mtDNA mutations in the lymphoblasts of 1549 patients with HD compared with the lymphoblasts of 182 healthy individuals was revealed and a correlation with the progression of the stage and increasing severity of the disease, measured by motor and cognitive functions, as well as functional capabilities [71], which indicates participation of mitochondria in the development of HD.

VI. NEUROMUSCULAR DISORDERS

ALS is characterized by degeneration of upper (frontal motor cortex) and lower (spinal and brainstem) motor neurons, leading to progressive paralysis and death, usually due to respiratory failure. Motor neurons and neuromuscular junctions contain large numbers of mitochondria. Disturbances in their structure, dynamics, bioenergetics and calcium metabolism are widespread in patients with ALS and play a significant role in the pathogenesis of the disease.

A decrease in the activity of complex IV of the respiratory chain was found in gray matter cells in the cervical and lumbar spinal cord of patients with ALS, a significant increase in mitochondrial density and their abnormal distribution in motor neurons[72]. In peripheral blood platelets there was also a decrease in the activity of complex IV, and in mononuclear cells - I of the electron transport chain complex, while the number of mitochondria gradually increased, which, obviously, can be considered a compensatory mechanism [73]. Mutations in the SQSTM1 gene, which encodes the protein p62 (also known as sequestoma 1, is a scaffold or adapter protein involved in a variety of cellular functions) have been identified in patients with frontotemporal dementia and ALS. p62 deficiency is accompanied by inhibition of complex I of the respiratory chain due to impaired NADH delivery and a decrease in mitochondrial membrane potential [74]. Studies in cellular models have shown that p62 is involved in mitophagy, which is impaired in pathological conditions.

An in vivo model of sporadic amyotrophic lateral sclerosis caused by intrathecal injection of cerebrospinal fluid from patients to the offspring of rats revealed an increase in the level of ROS, mitochondrial dysfunction and a decrease in the amount of 35 mitochondrial and 4 lysosomal proteins, which contributes to disruption of the electron transport chain and organelle morphology. In addition, this model demonstrates overexpression of a proapoptotic mitochondrial protein (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like), encoded by BNIP3L [75].

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Increased levels of mitochondrial ROS were also found in living skeletal muscle fibers obtained from SOD1G93A transgenic mice with ALS. In addition, disease stage-dependent impairments in mitochondrial functions associated with the opening of the mitochondrial pore (mPTP) in skeletal muscle in ALS have been identified. Future studies are needed to explore the molecular mechanism of the major effect of this mutation on mitochondria through the regulation of the expression and function of CypD, a regulatory component of the mitochondrial pore, and other possible signaling pathways involved in the process[76]. Damage to mitochondria and death of neurons in patients with ALS are observed as a result of impaired calcium metabolism between this organelle and the ER, which is caused by mutations in the SIGMAR1 gene (c.304 G>C). This gene encodes the sigma-1 receptor (Sig-1R), a transmembrane ER protein that stabilizes calcium signaling between the reticulum and the mitochondrion [77]. (***Fig. 2***).

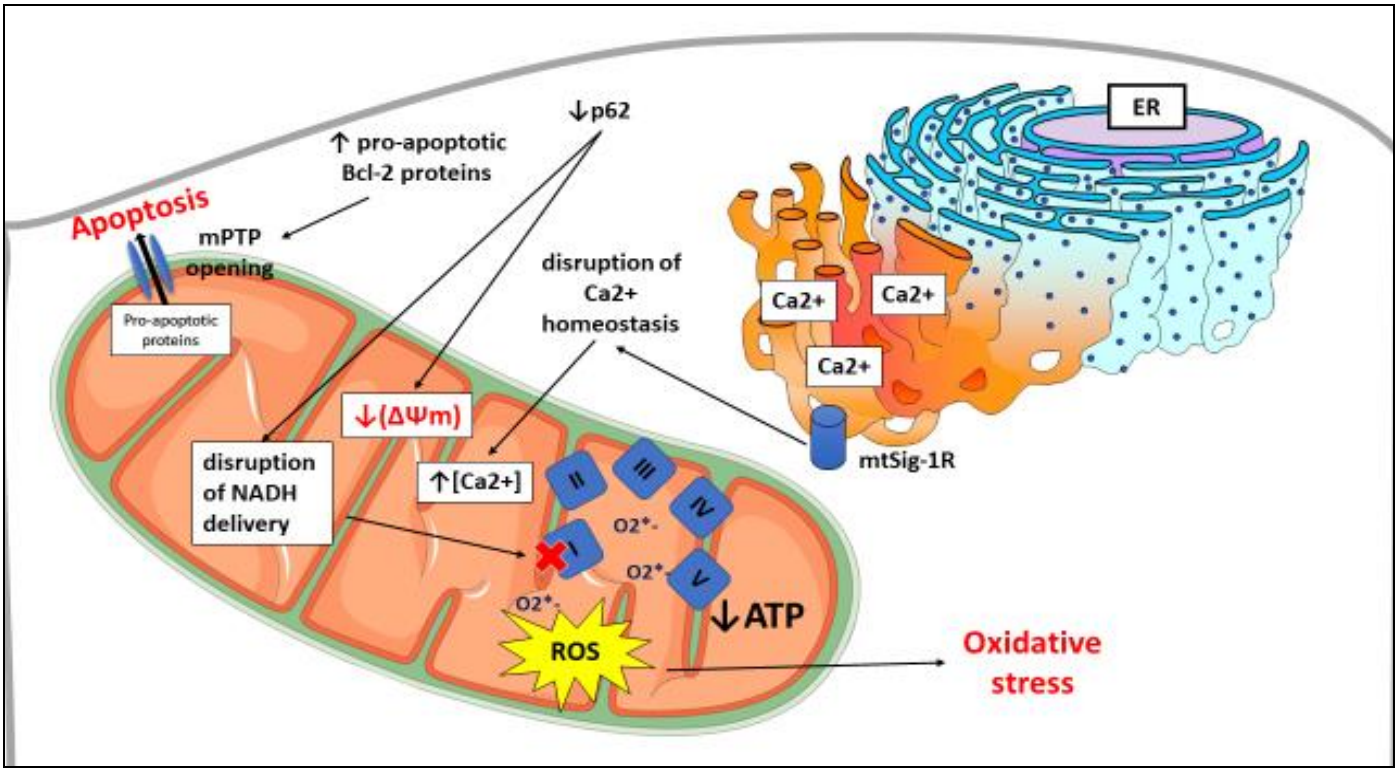

Fig 2: Mitochondrial Damage and ALS

Mitochondrial damage and ALS mPTP – mitochondrial permeability transition pore; Sig-1R - sigma-1 receptor - transmembrane protein of the ER; p62 protein, also known as sequestoma 1, is a scaffold or adapter protein involved in a variety of cellular functions; ROS – reactive oxygen species; ΔΨm -mitochondrial membrane potential; ATP - adenose-triphosphoric acid (ATP), plays a major role in energy metabolism in the cells of living organisms; ER-endoplasmic reticulum

Designations: mPTP – mitochondrial pore; Sig-1R - sigma-1 receptor - transmembrane protein of the ER; p62 protein, also known as sequestoma 1, is a scaffold or adapter protein involved in a variety of cellular functions; ROS – reactive oxygen species; ΔΨm - electrical potential gradient on the inner mitochondrial membrane; ATP - adenosine triphosphoric acid (ATP), plays a major role in energy metabolism in the cells of living organisms; ER-endoplasmic reticulum

VII. MENTAL ILLNESS

Bipolar disorder (BD) is a severe mental illness characterized by phasic mood swings and may be associated with progressive structural changes in the brain and cognitive decline. Mitochondria play a significant role in the development of the disease, as evidenced by their smaller size in patients with pathology compared to healthy people [78], changes in the expression of genes (NDUFV1, NDUFV2, NDUFS1 and NDUFS7) encoding subunit I of the electron transport chain complex, and the activity of this complex [79], which may be associated with energy deficiency and negatively affect the processes of plasticity, stability and survival of neurons. Decreased levels of anti-apoptotic proteins Bcl-xL, survivin and Bcl-xL/Bak dimer, and increased caspase-3 in patients with BD, decreased expression of genes encoding proteins mitofusin 2 and Opa1 associated with mitochondrial fusion, increased gene expression and protein levels Fis1 fission in peripheral blood mononuclear cells indicates a positive correlation between changes in mitochondrial dynamics and activation of the cell death pathway in patients with BD, as well as a link between mitochondrial dysfunction and disease pathophysiology[80].

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Mitochondrial dysfunction is thought to be associated with schizophrenia. An autopsy of brain tissue from patients with this pathology revealed a decrease in the number of organelles in the frontal cortex, caudate nucleus, putamen, and activity of complex IV of the respiratory chain in the caudate nucleus. At the same time, in the putamen and in the nucleus accumbens, the activity of complexes II and IV was increased. The activity of complex IV in the putamen was negatively correlated with the severity of emotional and cognitive dysfunction. A schizophrenia-specific anatomical pattern was identified in complex I subunits of post-traumatic prefrontal cortex and striatum samples. A significant decrease in the expression of subunits II and IV-I of the electron transport chain complexes in the rostro-caudal region of the substantia nigra/ventral tegmental area (SN/VTA) was shown in schizophrenia; mitochondrial hyperplasia was detected in the presynaptic terminals of axons in the nigra region substances [81]. In postmortem brain samples from patients diagnosed with schizophrenia, the activity of complex IV was significantly reduced in the frontal and temporal cortex, and complexes I + III in the temporal cortex and basal ganglia.

It has been suggested that oxidative/nitrosative stress responses caused by mitochondrial dysfunction may activate immunoinflammatory pathways and subsequently lead to neuroprogressive changes in schizophrenia. An experiment on a model of schizophrenia induced by ketamine in Wistar rats showed hyperproduction of ROS, a drop in mitochondrial membrane potential, swelling of organelles, and release of cytochrome c [82]. Patients were found to have lower mtDNA content, decreased mitochondrial enzyme activity, and decreased oxygen consumption compared to healthy controls[83].

Schizophrenia may be caused by impaired mitochondrial transport, which is inextricably linked with the dynamics of fission/fusion processes. For example, it has recently been demonstrated that overexpression of a mutant of DISC-1 (disrupted in schizophrenia 1), a protein disrupted in schizophrenia-1, can form aggregates that interfere with mitochondrial trafficking [84, 85.]

A meta-analysis found that mitochondrial dysfunction is associated with autism spectrum disorder (ASD). Patients with ASD were more likely to have abnormal values for biomarkers of mitochondrial dysfunction compared to controls, some of which correlated with the severity of disease symptoms. Neuroimaging and in vitro postmortem brain studies have also shown impaired mitochondrial function [86]. Patients aged 4 to 10 years had significantly lower levels of complexes III and V in the cerebellum, I in the frontal cortex, and II, III and V in the temporal cortex compared to the control group. Significant increases in lipid hydroperoxide levels, a marker of oxidative stress, were also observed in the cerebellum and temporal cortex of children with autism [87]. In the postmortem temporal cortex in the BA21 area of patients with ASD, a decrease in the activity of complexes I and IV of the respiratory chain, the level of the antioxidant enzyme SOD2, oxidative DNA damage, an increase in the concentration of mitochondrial membrane proteins Tom20, Tim23 and porin, mitochondrial fission proteins (Fis1 and DRB1) and a decrease in level of fusion proteins (Mfn1, Mfn2 and Opa1), which indicates a significant role of mitochondrial dysfunction in the pathogenesis of the disease [88].

Two cases of autism with a mutation in chromosome 15, in the 15q11-q13 region, have been described. In both cases, the pathology is manifested by a decrease in the activity of complex III of the electron transport chain and mitochondrial hyperproliferation in muscle fibers, delayed motor development, lethargy, severe hypotension. It is assumed that the biosynthesis and proliferation of mitochondria is a response to the insufficiency of their functioning to meet the metabolic needs of cells [89]. There is evidence that mitochondrial dysfunction in various brain regions is associated with depression. New ideas about the pathophysiology of depression are associated with impaired neuroplasticity. Mitochondria take part in many intracellular processes associated with synaptic plasticity and cellular resistance, so their dysfunction plays a significant role in the pathogenesis of the disease. Research suggests that impaired mitochondrial function and oxidative stress may contribute to the death of neurons and glial cells in major depressive disorder (MDD), a mental disorder characterized primarily by decreased mood, motor retardation, and cognitive impairment[90].

VIII. EPILEPSY

Mitochondrial dysfunction is one of the potential causes of epileptic seizures; it affects the excitability of neurons and synaptic transmission, causing their death, which causes treatment-resistant epilepsy. Energy deficiency has been postulated as a cause of acquired epilepsy, but on the other hand, not all patients with mitochondrial diseases experience seizures. There are other mechanisms underlying mitochondrial epilepsy, including oxidative stress, disturbance of calcium homeostasis, deficiency of vitamins, cofactors, reducing equivalents and other metabolites. Different mechanisms may predominate during mitochondrial dysfunction in different types of neurons and astrocytes in different brain regions [91, 92] (***Fig. 3***).

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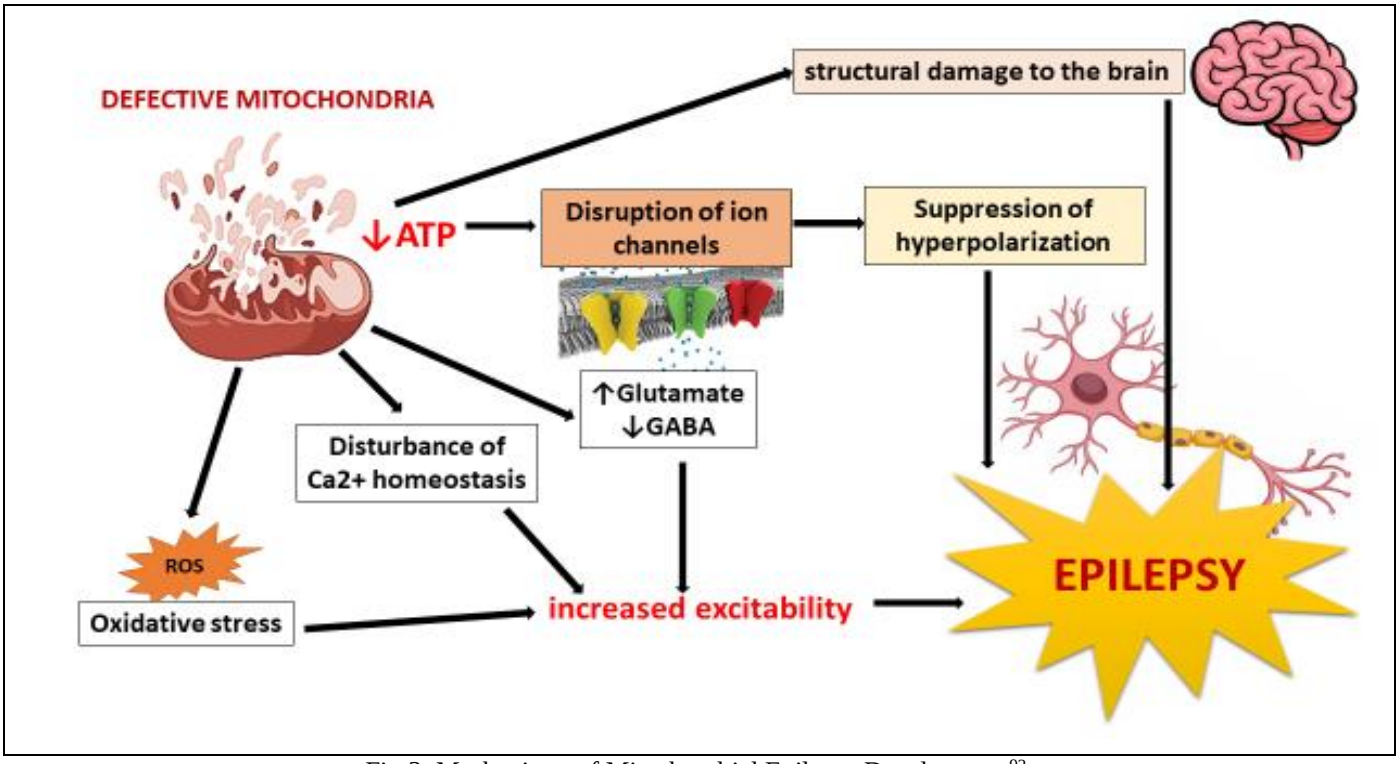

Fig 3: Mechanisms of Mitochondrial Epilepsy Development[92].

Oxidative stress results from mitochondrial dysfunction that progressively disrupts intracellular Ca2+ homeostasis, which modulates neuronal excitability and synaptic transmission, making cells more vulnerable to additional stress and leading to energy deficiency and neuronal loss in epilepsy. Various animal models of this pathology have shown that seizures are accompanied by an increase in the level of mitochondrial hydrogen peroxide, damage to mtDNA, a decrease in the expression of repair enzymes Ogg1 (8-Oxoguanine glycosylase) and γ DNA polymerase, and a decrease in the efficiency of mtDNA repair. It has been found that oxidative stress promotes post-translational modification of complex I of the electron transport chain of mitochondria, a decrease in its activity, and the development of epileptogenesis [93]. With a brain stroke, activation of lipid peroxidation processes, reactive gliosis, degeneration of hippocampal neurons, reorganization of neural networks and hypersynchrony are observed. These factors predispose the brain to spontaneous recurrent seizures, which ultimately cause temporal lobe epilepsy (TLE) [94]. Patients with this disease show deficiency of complex I of the mitochondrial respiratory chain in the CA3 region of the hippocampus [95], dysfunction of complex IV and ultrastructural damage to mitochondria [96].

Aberrant accumulation of damaged mitochondria has been noted, especially in the hippocampus of patients with refractory temporal lobe epilepsy (rTLE) and hippocampal sclerosis, which may be a consequence of impaired mitophagy and the cause of epileptogenesis [97]. Mitochondrial dysfunction is involved in the development of status epilepticus (SE), the maximum expression of epilepsy with high morbidity and mortality. Seizures gradually become resistant to drugs (benzodiazepines), as a result of which, through excessive activation of the NMDA receptor, calcium accumulates in the mitochondria, which leads to a decrease in ATP production and the opening of MP. Together, these changes lead to SE-dependent neuronal death. Using two animal models of status epilepticus induced by substances with different mechanisms of action (DL-homocysteine acid and 4-aminopyridine), a pronounced inhibition of mitochondrial complex I in the brain was demonstrated during the acute phase and during epileptogenesis[98].

Recently, it was discovered that defects in the EPM2A and/or NHLRC1 genes, encoding laforin phosphatase and malin E3 ubiquitin ligase, respectively (malin is a subunit of E3 ubiquitin ligase, its RING domain is required for ubiquitination), are the cause of Lafora disease (LD), a myoclonic epilepsy that characterized by the deposition of polysaccharide substances in various tissues, primarily in cerebral structures. The clinical picture is dominated by myoclonic paroxysms, generalized epileptic seizures, progressive dementia, mental disorders and visual impairments. Autophagic defects, large lysosomes, neurofibrillary tangles, amyloid beta deposits, and abnormal mitochondria are observed. Neurodegenerative changes may result from the loss of laforin/malin, which is accompanied by an increase in the level of DRP1 and, as a consequence, division of organelles, the appearance of a large number of fragmented mitochondria, and an increase in calcium concentration in them [99, 100].

Despite numerous studies, the above indicates that whether mitochondrial dysfunction is a cause or consequence of epilepsy is controversial; the two may be interrelated and create a vicious cycle.

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IX. CONCLUSION

Thus, nervous and mental diseases caused by mitochondrial dysfunction may be due to mutations in mitochondrial/nuclear DNA genes, or associated with other causes. With increasing knowledge about pathogenetic mechanisms, the number of treatable mitochondrial disorders is growing, but most of them remain uncured. The reason for this condition is the heterogeneity of clinical manifestations of genetically determined mitochondrial disorders, insufficient knowledge of the connections between intermediate metabolism and mitochondrial function, and the molecular mechanisms of interaction between mitochondria, the cellular and extracellular environment in different tissues. All this makes it difficult to identify similar pathogenic pathways underlying progressive diseases and the search for therapeutic approaches to treatment. In addition, the most severe forms of mitochondrial dysfunction occur in the neonatal period, making this group of patients the most difficult to target for therapy. Another factor complicating the study of neurodegenerative diseases is the inability to separate the effects of normal aging from disease-related changes in mitochondria, such as in PD, where these changes are clearly important but not always particularly different.

Discoveries and advances in molecular genetics have increased our understanding of the early pathology of mitochondrial disorders, enabled disease modeling, and provided entirely new perspectives on molecular pathogenesis. It is necessary that this research continues and then, in the near future, it will help develop the search for possible ways to treat the diseases that people suffer from.

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