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Analysis of significance of mitochondrial dysfunction in the pathogenesis of diseases of the central nervous system

Olena Petrivna Sokolik [1,*], Galina Olexandrivna Prozorova [2]

[1] Department of Pharmacology and Pharmacognosy, Odessa National Medical University, Odessa, Ukraine.
[2] Department of Pharmacy, Pylyp Orlyk International Classical University, Mykolayiv, Ukraine.
* Correspondence: sokolikep@gmail.com, Tel.: +380970594381

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ABSTRACT: One of the promising therapy areas for many diseases of the central nervous system is the search for agents of selective effect on mitochondria. Both the mitochondria themselves and the mitochondrial metabolism of the transformed cell of the central nervous system and activation of energy metabolism by reprogrammed mitochondria give impetus for the development of mitochondrial pharmacology to use the special properties of transformed cells mitochondria as targets for neuroprotective and neuroplastic effects. In this review, we analyse literary sources of domestic and foreign authors about the influence of mitochondrial dysfunction on various links in the pathogenesis of central nervous system diseases. Based on currently available data, scientists divided all signs of mitochondrial dysfunction in schizophrenia into three groups: morphological disorders of mitochondria, signs of a violation of the oxidative phosphorylation system and dysregulation of genes responsible for mitochondrial proteins. The therapeutic effect of drugs for central nervous system disorders should focus on reducing the accumulation of metabolic products and tissue breakdown, restoring mitochondrial functions and synaptic plasticity, and protecting mitochondria from toxic effects, thereby alleviating cognitive disorders with a neuroprotective effect.

Keywords: Mitochondrial dysfunction; central nervous system; bipolar affective disorder; major depression; schizophrenia; autism spectrum disorders; Alzheimer's disease; Parkinson's disease

1.0 INTRODUCTION

Mitochondrial dysfunction is one of the reasons for the development of many diseases of the central nervous system (CNS). Retrograde signalling initiated by dysfunctional mitochondria can cause global changes in gene expression that affect the morphology and function of cells and lead them to transformation. This is due to the disruption of important functions of mitochondria, leading to metabolic changes in the cell with energy deficiency. This dysfunction is not only the result of a defect within the mitochondria per se, but in particular, it is associated with defects in intermediate metabolism and regulatory interaction with them (Singh et al., 2019). Changes in the dynamics of mitochondria contribute to the restructuring of the bioenergetic and biosynthetic profile of CNS cells through the

transmission of signals from defective mitochondria to the nucleus, which leads to changes in transcription and/or gene activity. The heterogeneity of such changes suggests the existence of diverse metabolic patterns in cells in the same mass and the restructuring of their metabolic profile, primarily determined by the degree of mitochondrial dysfunction. In addition to these factors, mitochondria dynamics may play an important role in transmitting stress signals. Normal mitochondria are highly dynamic organelles whose size, shape, and network are controlled by cellular physiology. Defective mitochondrial dynamics and impaired function of these organelles have been reported in many CNS diseases (McAvoy & Kawamata, 2019).

One of the promising areas of therapy for many diseases of the CNS is the search for agents of selective effect on mitochondria, taking into account the specifics of rearrangement. Both the mitochondria themselves and the mitochondrial metabolism of the transformed cell of the CNS and activation of energy metabolism by reprogrammed mitochondria gives impetus for the development of mitochondrial pharmacology to use the special properties of transformed cells mitochondria as targets for neuroprotective and neuroplastic effects (Harland et al., 2020). This mini-review aims to analyse data from professional literature about patients with pathologies of the central nervous system, taking into account the influence of mitochondrial dysfunction on various links in the pathogenesis of the diseases.

2.0 MATERIAL AND METHODS

To analyse literary sources of domestic and foreign authors about the development of mitochondrial dysfunction in the pathogenesis of diseases of the CNS. Most analyses were based on human clinical studies (65%) and animal studies (35%) related to the bipolar affective disorder, major depression, schizophrenia, autism spectrum disorders, Alzheimer's disease and Parkinson's disease. Based on the time of publication of papers, most of the selected studies were published in the period 2017-2022, with an upward trend that intensified between 2019 and 2022. A summary of the selected research articles is given in **Table 1**.

3.0 ANALYSIS OF THE LITERATURE

3.1 Bipolar affective disorder (BAD*)*

The clinical study results showed that about 20% of patients with mitochondrial diseases had concomitant bipolar disorder, while 0.38% of patients with bipolar disorder had DNA polymerase gamma (POLG) mutations that cause the development of mitochondrial diseases (Kato, 2017). BAD or manic-depressive psychosis, is a mental disorder characterised by alternating manic and depressive phases. The aetiology of BAD has been proposed as a model of monoaminergic systems dysregulation, as well as impaired calcium transfer. However, the interaction between these unrelated systems remained unclear (Harrison et al., 2018).

The adenine nucleotide translocator 1 (*ANT1*) L98P mutation was identified in a combined analysis of BAD and autosomal dominant chronic progressive external ophthalmoplegia. This has led to the assumption that mutations in the *ANT1* gene may increase the risk of developing bipolar disorder through a complex interaction between serotonin and mitochondrial functioning in the structures of the central nervous system. The authors studied the relationship between heterozygous loss of function of *ANT1* and BAD by generating a brain-specific *ANT1* conditional knockout mouse that showed heterozygous mice with diminished delay discounting (the choice of smaller but immediate reward than larger but delayed reward and an index of impulsivity) due to enhanced serotoninergic activity (Kato et al., 2018). Thus, a hypothesis was put forward about the involvement of two separate pathways in the formation of BAD. However, an association between levels of the neurotransmitter serotonin and mitochondrial dysfunction has not been established.

A study at the RIKEN Center for Brain Science found that mitochondrial dysfunction can affect the activity of serotonergic neurons in mice with *ANT1* mutations. Mitochondrial pathologies were established during neuroimaging and post-mortem morphological studies of brain tissues in about 20% of patients with BAD. In addition, the effectiveness of drug modulation of serotonin levels in individuals with bipolar disorder also indicates the involvement of this pathway in the pathogenesis of this affective pathology. Mitochondrial dysfunction may influence the activity of serotonergic neurons in the genesis of BAD (Kim et al., 2019).

When comparing laboratory mice with a missing *ANT1* gene in brain tissues to a control group, it was found that the intracellular calcium level was dysregulated due to a structural defect in the channels of animals with a genetic mutation. Also, in laboratory mice with a missing *ANT1* gene in brain tissues, lower impulsivity was observed in behavioural tests with higher rates of serotonin metabolism in the cerebral cortex, hippocampus and amygdala. Based on this, the researchers concluded that this hyperserotonergic state is likely the result of a cascade of changes starting with

the loss of the *ANT1* gene, which ultimately leads to mitochondrial dysfunction. Dysfunctional serotonergic activity can impair the functioning of mitochondria, forming a vicious circle of metabolic processes. In addition, it was found that dysfunctions of serotonergic neurons are observed in the region of the dorsal raphe nuclei, a structure that was also involved in the pathogenesis of Parkinson's disease, suggesting another possible relationship with mitochondrial dysfunctions (Pereira et al., 2018).

It was also revealed by magnetic resonance spectroscopy a decrease in intracellular pH and the level of phosphocreatine in the frontal lobe of the brain in patients with bipolar disorders, including those who did not receive treatment. Inefficient energy homeostasis in the brain, decreases in mitochondrial respiration and high-energy phosphates, decrease in intracellular pH, changes in mitochondrial morphology, increases in mitochondrial DNA polymorphisms, downregulation of nuclear mRNA molecules and proteins involved in mitochondrial respiration and decreased neuronal viability marker closely associated with mitochondrial dysfunction and BAD (Saxena et al., 2017). The same authors found a decreased level of phosphocreatine in the temporal lobe in patients resistant to lithium therapy. Other authors found a decrease in adenosine triphosphate (ATP) levels in the frontal lobe and basal ganglia of patients with major depression. Similar signs were observed in patients with some mitochondrial diseases, such as Leigh syndrome, myopathy encephalopathy, lactic acidosis, stroke-like episodes, Kearns-Sayre syndrome, and Leber hereditary optic neuropathy (Scaini et al., 2021).

As regards molecular genetic data, it should be noted that the results of a number of studies (Giménez-Palomo et al., 2021; Moya et al., 2021) indicate the absence of evidence for the involvement of mitochondrial deoxyribonucleic acid (mtDNA) deletions in the development of mood disorders. The study of mtDNA polymorphisms and haplotype differences between patients with bipolar disorders and the control group revealed some mutations in positions 5178 and 10398 of mtDNA – both positions are located in the zone of complex I genes (Kato, 2019).

There are some reports about mutations in the genes of complex I, not only in mitochondrial but also in nuclear ones (Xie et al., 2022; Spohr et al., 2022). Thus, in cultures of lymphoblastoid cells obtained from patients with bipolar disorders, a mutation was found in the *NDUFV2* gene locus on chromosome 18 (18p11) that encodes for one of the complex I subunits. MtDNA sequencing of patients with bipolar disorders revealed a mutation at position 3644 of the *ND1* subunit gene, which also belongs to complex I. An increase in the translation level (but not transcription) was found in some subunits of complex I in the visual cortex of patients with bipolar disorders (Sigitova et al., 2017). Among other reports, the genes of the respiratory chain were studied, and genetic abnormalities were found in the prefrontal cortex and hippocampus of patients with bipolar disorders. In one work in patients with major depression, a number of mitochondrial enzyme aberrations and decreased ATP production in the musculoskeletal tissue were revealed. There was a significant correlation between decreased ATP production and the clinical manifestations of the mental disorder. Declining skeletal muscle mitochondrial function in older adults may be associated with clinically depressive symptoms at follow-up, supporting the hypothesis that mitochondrial dysfunction can be a critical pathophysiological mechanism in adults with late-life depression (Brown et al., 2019).

3.2 Schizophrenia

Based on currently available data, scientists divided all mitochondrial pathologies in schizophrenia into three groups: morphological aberration of mitochondria, dysfunctional oxidative phosphorylation system and dysregulation of gene expression for mitochondrial proteins. This division can be supported by examples from many works (Ni & Chung, 2020; Creed et al., 2021; Ben-Shachar, 2017).

Autopsy of the brain tissue of patients with schizophrenia revealed a decrease in the number of mitochondria in the frontal cortex, caudate nucleus, and putamen. At the same time, it was noted that it was less pronounced in patients treated with antipsychotics, and therefore the authors considered it possible to talk about the normalisation of mitochondrial processes in the brain under the influence of antipsychotic therapy. This gives reason to mention mitochondrial hyperplasia in presynaptic axon terminals in the area of substantia nigra in schizophrenia. Other scientists examining the autopsy brain material of schizophrenic patients revealed a decrease in the activity of complex IV of the respiratory chain in the caudate nucleus (Roberts, 2021).

These results suggested a primary or secondary role of mitochondrial dysfunction in the pathogenesis of schizophrenia. However, the autopsy material studied was related to patients treated with antipsychotics;

naturally, mitochondrial pathologies were associated with drug exposure. Such assumptions, often not unfounded, accompany the history of mitochondrial changes discovered in various organs and systems for different diseases. Concerning the possible influence of neuroleptics, it should be reminded that the tendency to lactic acidosis in patients with schizophrenia was discovered before neuroleptics appeared (Wu et al., 2019).

A decrease in the activity of various components of the respiratory chain was found in the frontal and temporal cortex, as well as in the basal ganglia of the brain and other tissue elements – platelets and lymphocytes in patients with schizophrenia. This made it possible to speak about the multisystem nature of the mitochondrial deficiency. It was shown that the activity of complex IV decreases in the frontal cortex and that of complexes I, III, and IV in the temporal cortex; in the basal ganglia – I and III complexes, no changes were found in the cerebellum (Ben-Shachar, 2017). It should be noted that the activity of the intramitochondrial enzyme, citrate synthase, corresponded to the control values in all the studied regions, which gave grounds to speak about the specificity of the obtained results for schizophrenia.

Other authors found no signs of changes in the activity of complex I, but the activity of complex IV was reduced in the caudate nucleus. At the same time, the activities of complex II and IV were increased in the shell and the nucleus accumbens. Moreover, an increase in the activity of complex IV in the shell significantly correlated with the severity of emotional and cognitive dysfunction but not with the degree of motor disorders (Kanellopoulos et al., 2020).

It should be noted that most of the works cited above explain the signs of energy metabolism disorders by the influence of neuroleptics. A decrease in the activity of mitochondrial enzymes and ATP production was found in 6 out of 8 patients who did not receive antipsychotics, whereas, in patients on antipsychotic therapy, there was an increase in ATP production (Valiente-Pallejà et al., 2020).

The next cohort of scientists studied the activity of complex I of the respiratory chain in the platelets of 113 patients with schizophrenia in comparison with 37 healthy ones (Shivakumar et al., 2020). The patients were divided into groups: (1) with an acute psychotic episode, (2) with a chronic active form, and (3) with residual schizophrenia. The results showed that the activity of complex I was significantly increased compared to the controls in groups 1 and 2 and decreased in patients of group 3. Moreover, a significant correlation was found between the obtained biochemical parameters and the severity of clinical symptoms of the disease. Similar changes were obtained in studying flavoprotein subunits of complex I in the same RNA and protein materials. The results of this study not only confirmed the high likelihood of multisystem mitochondrial failure in schizophrenia but also allowed the authors to recommend appropriate laboratory methods for disease monitoring (Amiri et al., 2021).

Another author published exciting data on the effect of dopamine (a neurotransmitter that plays a significant role in the pathogenesis of schizophrenia) on the respiratory chain of mitochondria. It was found that dopamine can inhibit complex I activity and ATP production, and at the same time, the activity of IV and V complexes does not change. It turned out that, unlike dopamine, norepinephrine and serotonin do not affect ATP production (Toriumi et al., 2021).

The emphasis in the reviewed works is noteworthy on the dysfunction of complex I of the mitochondrial respiratory chain. This kind of change may reflect relatively moderate disturbances in mitochondrial activity, which are more significant in the functional regulation of energy metabolism than gross (close to lethal for the cell) drops in cytochrome oxidase activity (Gonçalves et al., 2018).

A group of scientists found that the frequency of a common deletion of mtDNA (the most common deletion of 4977 base pairs, affecting the genes of subunits I, IV, and V complexes and underlying several severe mitochondrial diseases, such as Kearns–Sayre syndrome) does not differ significantly in the autopsy material of the schizophrenic patients' brain, does not accumulate with age, and does not correlate with altered cytochrome oxidase activity (Fernandez et al., 2019). However, this group revealed a cytochrome b gene polymorphism in patients with schizophrenia that was different from the controls by sequencing the mitochondrial genome.

A group of scientists studied the expression of nuclear and mitochondrial RNA in the frontal cortex in cases of schizophrenia and found significantly increased expression of the mitochondrial gene of the 2nd subunit of cytochrome oxidase. Four other genes were related

to mitochondrial ribosomal RNA (Srivastava et al., 2021).

Japanese researchers examined 300 cases of schizophrenia and did not find the 3243A/G variant (causing a disorder in complex I in Mitochondrial Encephalopathy, Lactic Acidosis or MELAS syndrome and Stroke-like episodes) (E Silva et al., 2019). In the following work, no increased mutation frequency was found in the mitochondrial genes of the 2nd subunit of complex I, cytochrome b, and mitochondrial ribosomes in schizophrenia. However, a variant in mtDNA at position 12027 (the gene of the 4th subunit of complex I) was found present in male patients with schizophrenia but not in females.

Characterisation of three nuclear genes of complex I was studied in the prefrontal and visual cortex of patients with schizophrenia. They found that the transcription and translation of some subunits were reduced in the prefrontal cortex and increased in the visual cortex (the authors interpreted these data following the concept of hypofrontality in schizophrenia). No changes were found in the study of gene variants of mitochondrial proteins in the hippocampal tissue of patients with schizophrenia treated with antipsychotics (Schulmann et al., 2019).

Japanese researchers studied changes in the genes responsible for hereditary information for mitochondrial proteins in the prefrontal cortex in schizophrenia patients treated with antipsychotics. They obtained evidence in favour of drug effects on cellular energy metabolism. Data from the intravital investigation can supplement the above results. When studying the distribution of the 31^{p} phosphorus isotope using magnetic resonance spectroscopy, a decrease in ATP synthesis in the basal ganglia and the temporal lobe of the brain of patients with schizophrenia was revealed (Glausier et al., 2020).

3.3 Autism spectrum disorders (ASD)

American scientists have clarified the link between impaired mitochondrial function and the development of ASD. Certain types of mitochondrial DNA mutations have been found to increase the risk of these diseases. Several recent studies have shown a possible link between ASD (autism and related conditions) and mitochondrial dysfunction. Colleagues at Cornell and Columbia Universities analysed the mitochondrial genome of children with ASD, their mothers, and one sibling who did not have similar disorders. In total, 903 such triplets took part in the study. It turned out that participants with ASD, on average, are 53% more likely to have heteroplasmic mutations (the presence of normal and mutant mtDNA in one cell) affecting non-polymorphic (having a stable structure) regions of the mitochondrial genome. Mutations in these regions are more likely to produce a pathogenic effect than changes in polymorphic regions (Rose et al., 2018).

Consistent with this, children with ASD had 1.5 times more non-synonymous mutations (resulting in an amino acid substitution in the encoded protein) and 2.2 times more predicted pathogenic mutations than their healthy siblings (Frye, 2020). Both non-synonymous and predicted pathogenic mutations, which were observed only in participants with ASD, but not in their relatives, were associated with an increased risk of these disorders (by 87% and 155%, respectively). Moreover, this relationship was most pronounced in children with ASD who have a reduced IQ or impaired social behaviour compared with brothers or sisters.

Further analysis showed that the inheritance of mtDNA heteroplasmy with high pathogenic potential from the mother differs between children with ASD and their healthy brothers or sisters, which means that they can be both inherited and acquired in the process of individual (including intrauterine) development, the researchers write. The obtained results confirm the relationship between the development of ASD and mitochondrial dysfunction, although the direct molecular mechanisms of the influence of mtDNA mutations on the occurrence and course of these disorders remain to be elucidated. Moreover, the identification of mutations in the mitochondrial genome in high-risk families can improve the diagnosis and treatment of ASD (Gevezova et al., 2020).

3.4 Alzheimer's disease (AD)

AD is the most common neurodegenerative disease that leads to brain atrophy and dementia. Its incidence increases with increasing life expectancy and the ageing of the population; there are no effective methods for preventing and treating this disease due to incomplete knowledge of pathogenesis. According to the dominant hypothesis of the amyloid cascade, the accumulation of neurotoxic forms of the amyloid-beta (Aβ) peptide becomes the central event in the pathogenesis of AD, leading to the formation of amyloid plaques, hyperphosphorylation of the tau protein and the formation of neurofibrillary tangles, synaptic failure, neuronal cell death, inflammation, mitochondrial dysfunction and oxidative stress. However, it gradually became apparent that this hypothesis is justified only

for the early, hereditary form of AD (~5% of cases). In the late, sporadic form of the disease, which accounts for ~95% of cases, the hyperproduction of Aβ becomes a secondary event. Mitochondrial dysfunction is a crucial factor initiating the development of sporadic AD (Shoshan-Barmatz et al., 2018). According to the mitochondrial cascade hypothesis, a decrease in ATP synthesis and oxidative stress lead to excessive production of Aβ, which has a toxic effect on mitochondria, aggravating neurodegenerative processes.

The idea that mitochondria play a crucial role in ageing and the development of related diseases was first formulated by D. Harman. It formed the basis of the mitochondrial free radical theory of ageing caused by the accumulation of damage due to the formation of reactive oxygen species (ROS). However, it has become evident in recent years that increased ROS generation is neither the initiator nor the main cause of ageing. Moreover, episodic enhancement of ROS generation by mitochondria, which play an important regulatory role, causes changes that can increase the lifespan of an organism. The origin of the damage is common (uncontrolled ROS release by different origins, diminished energy production and extensive oxidative stress to life-important biomolecules such as mtDNA and chrDNA), with individual outcomes differing significantly and representing a spectrum of associated pathologies including but not restricted to neurodegeneration, cardiovascular diseases and cancers (Koklesova et al., 2021). It also turned out that mitochondrial dysfunction can contribute to ageing, regardless of the formation of ROS – so, not only their metabolic dysfunction but also disturbances in mitochondrial dynamics and communication with other organelles, in particular, with the endoplasmic reticulum, also contribute to ageing (Perez Ortiz & Swerdlow, 2019). Thus, there is no doubt that the pathogenesis of AD is associated with mitochondrial dysfunction, but its contribution to the transition from healthy ageing to the development of this disease remains unclear. This is mainly due to the infeasibility of studying the processes in humans and the lack of adequate biological models of AD, most of which reproduce rare hereditary forms of the disease associated with mutations in the *PSEN1*, *PSEN2*, and *APP* genes (Kim, 2018).

It has been proven that a line of prematurely ageing OXYS rats is a unique model of the sporadic form of AD, in which all the key signs of the disease develop: destructive changes in neurons and their death, synaptic insufficiency, mitochondrial dysfunction, hyperphosphorylation of tau protein, increased accumulation of A01-42 peptide and the formation of amyloid plaques in the brain, behavioural disorders, and learn and memory deficits. Mitochondrial dysfunction is the most likely cause of premature ageing in rats. It has recently been shown that the progression of AD signs in OXYS rats is closely related to structural and functional changes in mitochondria. The development of early disorders of mitochondrial function in OXYS rats is indirectly indicated by a significant increase in the period of early ontogenesis of the level of an extended deletion (4834 base pairs) of mitochondrial DNA, which can potentially lead to an energy deficit in cells (Swerdlow, 2018). As a result, the question of the contribution of structural and functional changes in mitochondria to the initiation and development of pathological molecular AD cascades in OXYS rats remains open. It seems relevant to assess the structural changes in the mitochondria of OXYS rats and their functional activity during the development of AD signs when energy deficiency plays a significant role and can be the main event that leads to the manifestation of clinical symptoms. One of the approaches to studying the mechanisms of disease development is to study the effect on it of drugs that can affect this process, an example of which is the mitochondrial antioxidant plastoquinonyl-decyl-triphenylphosphonium (SkQ1), the previously proven neuroprotective properties (Macdonald et al., 2018).

3.5 Parkinson's disease (PD)

PD is a complex, destructive neurodegenerative disease diagnosed annually in 1% of the world's population over 65 years old (Rocha et al., 2018). The neuropathology of PD is characterised by a progressive deterioration in the control and regulation of motor functions, clinically manifested as pronounced motor fluctuations, such as tremor of the arms and legs at rest, muscle stiffness (rigidity), dyskinesia or slowness of movement (bradykinesia, akinesia), instability of body positions and impaired balance. Motor disorders arise due to the selective death of neuromelanin-containing dopaminergic neurons located in the substantia nigra pars compacta region and the limitation of dopaminergic neurotransmission in the striatum (corpus striatum), where the endings of dopaminergic neurons are located. In the remaining damaged cells, protein inclusions are found, consisting of accumulations of the fibrillar protein α-synuclein, called Lewy bodies, which is a histopathological marker of PD (Nguyen et al., 2019).

It has been established that suppression of the activity of complex I (NAD-ubiquinone oxidoreductase) in the mitochondrial respiratory chain can cause degeneration of dopaminergic neurons and thus contribute to developing PD pathology. Based on this, the suppression of the activity of complex I by specific inhibitors has become one of the approaches for creating experimental models and studying the mechanisms of the onset and development of PD (González-Rodríguez et al., 2021).

A 25-35% inhibition of the activity of the respiratory chain component of complex I was found in the substantia nigra and then in the peripheral tissues of patients with PD. At the same time, the action of the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which causes chronic parkinsonism in humans and experimental animals, leads to a deficiency in the activity of complex I (Malpartida et al., 2021). In glial cells, MPTP is converted by monoamine oxidase B (MAO B) into the active neurotoxin MPP+ (N-methyl-4-phenylpyridinium ion), which, via the dopamine transporter, enters dopaminergic neurons, where it accumulates in mitochondria, inhibiting complex I. The latter leads to inhibition of ATP synthesis, accumulation of free radicals, and cell death. Animal model experiments have shown that chronic systemic exposure to another complex I inhibitor, the pesticide rotenone, causes the death of dopaminergic neurons in the substantia nigra, damage to the proteasome system, DJ-1 protein, and α-synuclein and behavioural symptoms (bradykinesia, muscle rigidity, impaired posture, stiffness of movements characteristic of PD). Complex I inhibitors and other neurotoxins, such as paraquat, maneb, 6-hydroxydopamine (which also inhibits mitochondrial complex IV and monoamine oxidase), cause signs of PD in humans and experimental animals. The discovery of the relationship between a decrease in the activity of complex I and symptoms of PD left the question of the role of functional insufficiency of complex I in the pathogenesis of parkinsonism (Jankovic & Tan, 2020).

The autopsy brain preparations were taken from patients with long-term PD and treated with various drugs, such as levodopa. In the striatum, no deficiency of complex I activity was shown, which could be expected based on model experiments on levodopa toxicity in rats. Moreover, in patients with multiple systemic atrophy who took levodopa for the same time and in the same amounts as patients with PD, no mitochondrial insufficiency was found in the substantia nigra. There is no evidence that other drugs, including dopamine agonists and MAO B inhibitors, inhibit the activity of complex I (de la Fuente et al., 2017). Following the report of complex I deficiency in the substantia nigra of PD patients, respiratory chain abnormalities have been found in the skeletal muscle mitochondria of patients with parkinsonism, although the results obtained by different researchers did not agree with each other. Then, a decrease in the activity of complex I was also found in the mitochondria of platelets from patients with PD. In this case, the results of different laboratories coincide and indicate a decrease in the activity of complex I by 20-25%. Unfortunately, such a decrease in the activity of complex I do not warrant it to be used as a PD biomarker (Park et al., 2018).

In addition, energy metabolism disorders in PD may be associated with a decrease in the activity of the mitochondrial polyenzyme ketoglutarate dehydrogenase complex (CGD), which catalyses one of the vital metabolic reactions. Inactivation of CGD in PD may be caused by the action of free radicals or due to genetic aberrations. The fact that MPTP and MPP+ inhibit CGD *in vitro* stimulated the study of the activity of this multienzyme complex in the brains of patients with PD. A decrease in CGD activity in the substantia nigra of patients with PD and a decrease in immunostaining for CGD content was shown in proportion to the severity of the disease. Genetic studies also support the role of CGD in the aetiology of PD. Biallelic polymorphism of the gene of the E2 component of the a-ketoglutarate dehydrogenase complex is expressed in a single nucleotide substitution of adenine (allele 2) for guanine (allele 1), which does not affect the amino acid sequence enzyme. However, in the group of patients with PD, the frequency of the genotype of people carrying allele 2 is significantly higher than in the control group, which indicates that this mutation belongs to risk factors for PD (Burbulla et al., 2017). *In vitro* experiments have shown the sensitivity of lipoamide dehydrogenase, the E3 component of the pyruvate dehydrogenase, α-ketoglutarate dehydrogenase complexes, and the branched-chain α-keto acid dehydrogenase complex to MPTP and MPP+. As part of multienzyme complexes, E3 is involved in the oxidation of pyruvate, a-ketoglutarate, and a-keto acids branched chain. Being located on the inner surface of the inner mitochondrial membrane, lipoamide dehydrogenase in the presence of zinc ions and NADH can convert the coenzyme Q component of the mitochondrial respiratory chain (ubiquinone) into ubiquinol. This reduced form of ubiquinone (QH2), which is low in tissue compared to the oxidised form,

Table 1: Summary of key mechanisms of mitochondria features for neurological diseases and disorders.

Neurological disorders	*Key mitochondria features*	*Source of study in human*	*Source of study in animal (rats)*
Bipolar affective disorder (BAD)	- changes in mitochondrial morphology - decreases in mitochondrial respiration - downregulation of nuclear mRNA molecules and proteins - decreases in high-energy phosphates - increases in mitochondrial DNA polymorphisms - mitochondrial enzymes disorders	- DNA polymerase gamma (POLG) mutations (Kato, 2017) - dysregulation of monoaminergic systems (Harrison et al., 2018; Kim et al., 2019; Pereira et al., 2018) - impaired calcium transfer (Harrison et al., 2018) - decrease in intracellular pH (Saxena et al., 2017) - decrease in intracellular phosphocreatine (Saxena et al., 2017; Scaini et al., 2021) - decreased neuronal viability (Saxena et al., 2017) - mutations in the genes of complex I (Kato, 2019; Xie et al., 2022; Spohr et al., 2022; Sigitova et al., 2017; Brown et al., 2019)	- adenine nucleotide translocator 1 (ANT1) mutation (Kato et al., 2018)
Schizophrenia	- morphological disorders of mitochondria - signs of a violation of the oxidative phosphorylation system - disturbances in the expression of genes responsible for mitochondrial proteins	- decrease in the activity of complex IV of the respiratory chain (Roberts, 2021) - tendency to lactic acidosis (Wu et al., 2019) - decrease in the activity of complex I, III, and IV of the respiratory chain (Ben-Shachar, 2017) - decrease in the activity of complex IV of the respiratory chain and increase decrease in the activity of complex II (Kanellopoulos et al., 2020) - activity of complex I significantly increased (Shivakumar et al., 2020; Amiri et al., 2021) - dopamine inhibits complex I activity and ATP production (Toriumi et al., 2021) - cytochrome b gene polymorphism (Fernandez et al., 2019) - mutation in mitDNA in male patients (E Silva et al., 2019)	
Autism spectrum disorders (ASD)	- increases in mitochondrial DNA polymorphisms	- mitochondrial DNA mutations (Rose et al., 2018; Frye, 2020; Gevezova et al., 2020)	

Alzheimer's disease (AD)	- decrease in ATP synthesis, energy deficiency - disturbances in mitochondrial dynamics and communication with other organelles	- oxidative stress, formation of reactive oxygen species (Koklesova et al., 2021; Perez Ortiz & Swerdlow, 2019) - excessive production of neurotoxic forms of the amyloid-beta peptide (Ab) (Koklesova et al., 2021; Perez Ortiz & Swerdlow, 2019) - mutations in the PSEN1, PSEN2, and APP genes (Kim, 2018)	- structural and functional changes in mitochondria (Swerdlow, 2018; Macdonald et al., 2018) - mitochondrial DNA mutations (Swerdlow, 2018; Macdonald et al., 2018)
Parkinson's disease (PD)	- respiratory chain abnormalities - inhibition of ATP synthesis	- suppression of the activity of complex I (Malpartida et al., 2021; de la Fuente et al., 2017; Park et al., 2018) - decrease in the activity of the mitochondrial polyenzyme ketoglutarate dehydrogenase complex (CGD) (Burbulla et al., 2017)	- suppression of the activity of complex I (González-Rodríguez et al., 2021; Malpartida et al., 2021; Jankovic & Tan, 2020) - inhibition of lipoamide dehydrogenase, the E3 component of the pyruvate dehydrogenase, α-ketoglutarate dehydrogenase complexes, and the branched-chain α-keto acid dehydrogenase complex (Rani & Mondal, 2020)

has even greater antioxidant properties and thus performs a neuroprotective function. Therefore, inhibiting lipoamide dehydrogenase will decrease the concentration of ubiquinol, which prevents the formation of toxic radicals, which can cause oxidative stress (Rani & Mondal, 2020).

4.0 CONCLUSIONS

Mitochondrial dysfunction plays an important role in the development of CNS diseases and can be considered a therapeutic target in treating clinical symptoms of several diseases. Mitochondrial dysfunction is noted in the early preclinical stages of most diseases, and pharmacological intervention occurs later. Therefore, more research is needed in the early stages before the clinical progression of the disease. It is assumed that the therapeutic effect of drugs should reduce the accumulation of metabolic products and tissue breakdown, restore mitochondrial functions and synaptic plasticity, and protect mitochondria from toxic effects, thereby weakening cognitive disorders with a neuroprotective effect. At the moment, a large number of researchers in the world agree that the disturbances in mitochondrial dynamics and communication with other organelles, oxidative stress as a result of the formation of reactive oxygen species, increases in mitochondrial DNA polymorphisms, decrease in the activity of complex I, III, and IV of the respiratory chain and calcium homeostasis is one of the early manifestations of neurodegeneration and precedes the appearance of cognitive impairment in patients. Therefore, drugs aimed at correcting mitochondrial functions and calcium homeostasis can be considered promising approaches for early therapy of those neurodegenerative diseases for which ageing is one of the main risk factors.

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