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Dysfunction of mitochondria as the basis of Parkinson's disease

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Abstract

Parkinson's disease is the second most common neurodegenerative disease, affecting about 0,15-0,3% of the world's population. Its characteristic feature is a loss of dopaminergic neurons in the substantia nigra. PD leads to dopamine deficiency and formation of intracellular inclusions called Lewy bodies, whose main ingredient is α-synuclein. Other types of nervous system cells are also affected by changes associated with that disease. The underlying molecular pathogenesis involves multiple pathways and mechanisms: mitochondrial function, oxidative stress, genetic factors, α-synuclein proteostasis, mitochondrial dynamic impairment, and disorders of the mitophagy process. This review summarizes the factors affecting the functioning of the mitochondria and their connection to the development of Parkinson's disease.

Running title: Mitochondrial dysfunction as Parkinson's basis

Keywords: mitochondria, dysfunction, Parkinson's, disease

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease [1]. It is diagnosed in 0,15-0,3% of the world's population, with the average age of onset of 58 years. It belongs to diseases of the central nervous and extrapyramidal system, with its main symptom being the occurrence of involuntary movements [2]. The characteristic feature of the disease is the death of dopaminergic (DA) neurons, mainly in substantia nigra pars compacta (SNpc), which leads to a dopamine deficiency in the basal ganglia [3]. PD progresses despite treatment. The average lifespan with the disease is about 15.8 years [2]. Accordingly, estimates predict an increasing number of PD patients due to our expanding human lifespan.

Based on clinical features, the disease can be divided into postural instability and gait difficulty (PIGD) type, characterized by instability of posture and difficulty in walking, with rapid progress. There are occasional occurrences of late-onset Parkinson disease (LOPD) subtype, which appears after 60 years of age. It can also be distinguished into the dominant tremor type, characterized by benign symptoms with slow progression, with the subtype of young-onset Parkinson disease (YOPD) manifesting itself between 20-40 years of age. The above phenotypes show the ability to overlap [4]. Depending on genetic traits, the disease is divided into a family form, usually inherited autosomal recessive with the YOPD phenotype and sporadic, inherited mostly autosomal dominant with the LOPD phenotype [5].

PD is a multifactorial disorder with unclear etiology [3]. The main causes of the disease are given genetic and environmental factors. A number of autosomal dominant or autosomal recessive mutations affect the development of the disease. Among environmental factors, age is distinguished as the largest development factor. The frequency of the first symptoms increases exponentially with age increase [6]. Sex also belongs to this group, as the incidence is more frequent in the case of men than women (3:2 ration). Environmental conditions such as exposure to pesticides also play a role in PD etiology [7].

Theories of molecular PD pathogenesis

The first theory states that the death of DA neurons in PD has source in mitochondrial dysfunction [8]. Genetic and environmental factors lead to production excessive amounts of ROS (reactive oxygen species) in mitochondria [9]. Accumulation of ROS leads to the formation of mitochondrial dysfunction, the effect of which is, among others, the decrease in the efficiency of the ubiquitin-proteasome system, causing disturbances in the removal of unnecessary cellular metabolites [7].

Another theory is the formation of Lewy Bodies (LB)- inclusions containing mostly defective forms of α-synuclein. LB disturbs many metabolic pathways and accumulation of them lead to cell death [4].

There is few different evidence showing mitochondrial dysfunction as a main factor leading to cause of Parkinson disease. It is possible to say that mitochondrial dysfunction and α-synuclein aggregation reinforce each other. This could explain why these symptoms are observed together in PD neurons [10].

The importance of mitochondria in maintaining neuron homeostasis

Nigral dopaminergic neurons are particularly vulnerable to metabolic and oxidative stress for several reasons. They have quite long (about 4.5 meters), unmyelinated axons, large ammount of synapses (about 1–2.4 million), and need a lot of energy to maintain homeostasis [11]. SN (substantia nigra) DA (dopaminergic) neurons have smaller mitochondria than other neurons. This may be correlated with higher risk of appearance of changes in mitochondrial function of these neurons [12].

High amount of calcium may be another determinant of selective sensibility of SN DA neurons. Their activity may lead to extrusion and oscillations of calcium trough calcium channels with the use of energy. This phenomenon increases with age and leads to sustained elevated cytoplasmic calcium levels, which may stimulate ROS production. An imbalance in calcium amount impairs ATP synthesis and ATP-dependent cellular processes [13,14].

Due to the functions performed by neurons, such as rapid reaction to stimuli, extremely high energy demand is observed in these cells. This requires increased metabolic activity of their mitochondria. Manufacturing enough energy triggers an intensive exposure of neurons to oxidative stress factors. This process requires high fidelity of mitochondrial control systems. Proper functioning of neurons is therefore critically dependent on the behavior of mitochondrial homeostasis [15].

Mitochondria are highly dynamic organelles, surrounded by a double protein-lipid membrane. There are involved, among others in: ATP generation process, regulation of cell metabolism, synthesis of fatty acids and amino acids, synthesis of hem, and calcium buffering. They are also a center for cell death signaling [16]. Mitochondria have individual genome, which only lets them produce several proteins of the respiratory chain [17]. It is known that these organelles are undergoing constant change, because of cycles of fusion and fission. This process allows to maintain morphological variability, which is necessary to maintain mitostasis [18].

Mitochondrial dysfunction

Mitochondrial dysfunction is a condition in which the mitochondria are unable to perform their

function properly. Such state leads to a reduction in the energy efficiency of the mitochondria and to the occurrence of disturbances in the processes in which they take part. Prolonged and intensifying dysfunction can lead to cell death and contribute to the development of various diseases. Due to this, dysfunctional mitochondria are constantly degraded in the process of mitophagy, which allows to reduce the oxidative load, and are replaced by new mitochondria. This process is particularly important in long-living, non-proliferating cells like SN DA neurons [19]. Aberrant mitochondrial function has been widely accepted as a central pathogenic mechanism underlying PD pathogenesis [20].

The mitochondrial dysfunction includes a wide spectrum of symptoms. One of them is the increase in production of ROS as result of many factors, such as ATP production shortages, which may lead to reduce the efficiency of metabolic processes. It is connected to a reduction of efficiency of the ubiquitin-proteasome system. This results in decreased efficiency in removal of protein directed for degradation, including proteins with incorrect conformation, and contributes to their accumulation. It leads to disturbances of many metabolic processes and translates into an additional increase in ROS production which, causing protein oxidation, additionally strains the proteasome. This process aggravates mitochondrial dysfunction [17,21,22].

ROS effect is also connected with deregulation of calcium economy, which is responsible for the maintenance of numerous neuronal functions, such as synaptic transmission or neural plasticity. [17]. It lead to an increase of intracellular calcium and iron levels [23,24]. Mitochondrial dysfunction and increased oxidative stress may cause lysosomal autophagy system (LAS) damage [25]. Moreover, mitochondrial defects induce release of proapoptotic proteins such as cytochrome C or apoptosis-inducting-factor (AIF) from intermembrane space of mitochondria to cytosol. Research suggested that mitochondrial apoptosis is a key factor in the loss of neurons in PD [17].

Oxidative stress as the cause of mitochondrial dysfunction

In properly functioning cells, a lot of oxidants are produced during cellular respiration. As a result of harmful factors, the production of ROS increases, which by reaction with nucleic acids, proteins, lipids or electron transport chain, leads to mitochondrial damage, increased ROS production, proteasome impairment, inclusions of defective proteins, and as a result may cause cell death [26]. Damaged mitochondria can produce ten times more hydrogen peroxide than undamaged ones [19]. Proposed mechanism of sporadic PD (95% of cases) is related to an excessive production of ROS that leads to oxidative stress [27]. In brain tissue from PD patients, oxidative damage to lipids, proteins and DNA is often found [28,29].

Oxidative stress is a phenomenon with a very wide spectrum of causes. One of them is the reduction of electron transport chain elements, leading to e.g. ATP production shortages [20,22]. There is demonstrated by diminished activity of electron transport chain complex I in the substantia nigra of PD patients [30,31]. The most common complex I inhibitors include pesticides or neurotoxins [32,33].

Functioning of dopamine neurons leads to formation of dopamine metabolites contributing to the ROS production. The reduction in the amount of antioxidants, such as glutathione, affects the reduction of protective mechanisms against ROS in SNpc neurons. This causes the particular vulnerability of DA neurons to ROS [17]. These observations have led to the conclusion that there is a "vicious circle" of oxidative stress and mitochondrial dysfunction that ultimately leads to a bioenergetic crisis and death of SNpc DA neurons [8].

Environmental Toxins as the reason of oxidative stress occurrence

Pesticides such as: rotenone, pyridaben, fenpyroximate, fenazaquin, tebufenpyrad are described as common inhibitors of electron transport chain complex I [33]. In rats, rotenon may induce neuropathological and behavioral changes, similar to human PD [34,35]. Neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is meperidine analog, is also responsible for complex I inhibition [36], able to easily enter the DA neurons. While there, it is transformed into the toxic MPP+ (1-methyl-4-phenylpyridinium) metabolite [34, 37]. MPP+ is absorbed into the DA neurons through dopamine transporter [38]. MPTP and rotenone impair oxidative phosphorylation by inhibiting complex I, leading to DA neuron loss [39, 40, 41, 42]. Epidemiological research showed that the prevalence of sporadic PD is higher among farming societies [43]. Exposure to pesticides increased risk of developing PD three to four times [44].

Others reason of oxidative stress occurrence

In SNca DA neurons higher levels of dopamine and its metabolites occur, which induces oxidative stress. Above substances are protected from oxidation by packing ROS into vesicles [45,46]. Disruption of packing process leads to the interaction of ROS with the intracellular environment [15].

ROS production is also connected with genetic implications, such as α-synuclein A53T mutation. This mutant protein may go into mitochondria and lead to inhibition of complex I activity [47,48]. It is summarized that expression of mutant genes such as: Parkin, PINK1, DJ-1, LRRK2 may lead to increased ROS in cells cultures [28,49].

ROS generation may also be caused by the phenomenon of nitrosative stress which includes reactive nitrogen species (RNS), occurring as an effect of superoxide and nitric oxide (NO) reaction. NO may inhibit complexes I and IV of the mitochondrial electron transport chain. It is suggested that NO and its metabolites are implicated in PD induction [50,51,52].

PD related genetic factors

5–10% of Parkinson's disease cases involve gene products, mainly those of monogenic mutations [53]. Most of them are connected with, but are not limited to, dysregulation of mitochondrial function. They may take a part in processes like dysregulation of mitochondrial dynamics, mitochondrial protein import, mitophagy and mitochondrial redox state [54].

The autosomal dominant inheritance mutations usually cause a phenotype of sporadic PD. Mutation of the SNCA gene (PARK1), encoding α-synuclein protein, contributes to early-onset PD, rapid progression with cognitive dysfunctions and to the formation of LB [8,55]. However, its occurrence is relatively rare [3]. Mutation of the UCHL1 gene (PARK5) contributes to the occurrence of cyclohydrolasis A defects [4]. Mutations of LRRK2 gene (PARK8), encoding leucine rich-repeat kinase 2, evoke dysfunctions in translocation of proteins to neurons. These mutations may cause errors in neurotransmission and lysosomal autophagy pathways, or damage to the structure of neurons [4,55]. They also lead to oxidative stress, mitochondrial dysfunction occurrence, and may cause mitochondrial fragmentation and reduction mitochondrial membrane potential, leading to decrease ATP production [56,57]. Nowadays there are over 50 variants of this gene's mutation found in PD patients [58]. G2019S mutant exhibits increase of the kinase activity of LRRK2, leading to rise of toxicity in DA neurons [59]. The above mutation is the most common cause of PD on a genetic basis, with phenotype similar to the sporadic form of PIGD [3,4]. Other mutations connected with autosomal dominant model of inheritance are located in GIGYF2 gene (PARK11), encoding GYF2 protein, or HTRA2 gene (PARK13), coding serine protease. Mutation in VPS35 gene (PARK17), coding vacuolar sorting protein, may interference with the transport of particles through membranes as well as disrupt the lysosomal autophagy pathway. Another mutation is found in the EIF4G1 gene (PARK18), coding eukaryotic translation initiation factor [4].

Autosomal recessive inheritance mutations usually show a phenotype of YOPD. One of them occurs in PARKIN gene (PARK2), which belong to the RING (Really Interesting New Gene) family. It encodes the E3 ubiquitin ligase and is responsible for mediating poly-ubiquitination of substrates for proteasomal degradation. Loss of activity results in mitochondrial disfunction, deregulation of mitophagy process and functioning of the ubiquitin-proteasome system, leading to neurotoxicity of substrates or mitophagic impairment [60,61,62,63]. It is the most common mutation in YOPD patients [4]. PINK1 gene (PARK6), coding serine/threonine-protein kinase induced by phosphatase and tensin homologue (PTEN), mutation results in disorders associated with phosphorylation of its substrates [64]. Mutations result in defects of complex I activity, as well as alterations in the mitochondrial function and morphology, also leading to mitophagy perturbation [65,66]. The phenotype caused by the above mutation is accompanied by the occurrence of psychiatric disorders [4,8]. PINK1/Parkin cooperation is involved in the direction of mitochondrial quality control, leading to the elimination of damaged ones. Because of that, mutation in one of them, may be reason for mitophagy disturbances [67]. DJ-1 gene (PARK7) encodes one of the proteins from the C56 family. It is a cytoprotective protein under conditions related to oxidative stress, thanks for the modification of cysteine to cysteine-sulfinic and cysteine-sulfonic acids [68]. Mutation in above gene causes disorders in the system protecting the mitochondria from oxidative stress and is linked with mitochondrial fragmentation and mitochondrial structural damage [55,69]. Mutations in the ATP13A2 gene (PARK9), encoding a lysosomal 5-type ATPase, are related to alterations in mitochondrial and lysosome functions, affecting disorders of the lysosomal autophagy pathway and divalent cation regulation [55]. Mutations of PLA2G6 gene (PARK14), coding phospholipase A2, or mutation of FBXO7 gene (PARK15), coding F-BOX 7 protein, cause disorders of ubiquitin-proteasome system[4]. Mutation in a SLC41A1 gene (PARK16) was also found.

It is worth noting that few proteins of PD-related genes, like α-synuclein, PINK1 and Parkin can interact with subunits of the TOM complex (main entry portal for most mitochondrial proteins that are synthesized in cytoplasm), disturbing mitochondrial protein import. Mutants of α-synuclein are able to suppress TOM40-dependent import pathways. They may also enter mitochondria through the TOM complex and attach to the inner membrane [70]. In PD samples, there is a noted correlation between TOM40 and α-synuclein levels. Overexpression of wild-type α-synuclein or A53T mutant results in the loss of TOM40. TOM40 overexpression counters these damages [70].

α-synuclein as a factor of mitochondrial disfunction

α-synuclein is a protein containing about 140 amino acids [71]. It is present in the cytosol and has a role in synaptic vesicle dynamics, mitochondrial function and intracellular trafficking [72]. A30P and A53T mutations lead to the creation of pathogenic pore-like annular and tubular protofibrils which inhibit the activity of complex I and induce mitochon-

drial fragmentation, causing mitochondrial dysfunction [48,73]. It was found that correct function of ubiquitin–proteasome system may be disturbed by oligomeric form of *α*-synuclein (the most toxic form) [74]. The lysosomal autophagy system (LAS), macroautophagy and chaperone-mediated autophagy are important for maintenance of α-synuclein homeostasis [75,76]. Rise of α-synuclein quantity leads to cytochrome c release, as well as increased calcium and ROS levels, resulting in dopaminergic neuron death [77]. Mutations and proteostasis impairment lead to formation of inclusions consisting of incorrect, insoluble α-synuclein forms, such as oligomers and fibrils [73,74,78].They are major components of LB inclusions, which also contain tau, huntingtin and superoxide dismutase proteins. LBs were found in neurons of PD patients [79]. LBs disturb metabolic pathways, with their accumulation leading to cell death [4].

α-synuclein prion hypothesis states that α-synuclein aggregates are capable of trans-synaptic penetration between neuronal cells [4]. They may be transported intra-axonally to other brain regions, released into the extracellular space. At last, they may be taken in by healthy neurons and cause start of aggregation process inside of them [76].

Mitochondrial DNA mutations in PD

Human mitochondrial DNA (mtDNA) is a circular molecule of 16,569 base pairs [31], coding 13 subunits of respiratory chain proteins: seven components of complex I, one complex III subunit, three elements of complex IV, and two complex V subunits [18]. Environment of mtDNA is characterized by high ROS content, which may increase the likelihood of mutations resulting in respiratory chain dysfunction [17]. It was found that the amount of mtDNA deletions was higher in neurons with reduced cytochrome oxidase activity [70]. Research indicates that mutations in the human mtDNA polymerase subunit γ (POLG) gene lead to the occurrence of PD with multiple mtDNA deletions [27]. It is said that mitochondria contribute to aging through the accumulation of mtDNA mutations and net production of ROS. Correlation between mtDNA mutations and age increase is observed [32]. These findings support a mitochondrial genetic contribution towards PD.

Mitochondrial dynamics impairment in PD

Mitochondria create dynamic, tubular net which is reshaped through opposite processes of fusion and fission [80]. The balance between the above processes was described, being responsible for the proper function of the mitochondria. Fusion is important for interactions and communication between mitochondria. Fission allows for the segregation of mitochondria into daughter cells and strengthens mitochondrial renewal and distribution along cytoskeletal tracks. These processes lead to the exchange and mixing of the mitochondrial components. Moreover, they allow for the control of morphology, subcellular location and function of mitochondria [81]. Both of them are controlled by GTPases.

Fusion is regulated by mitofusin-1 (MFN1), overexpression of which prevents neurotoxin induced mitochondrial fission and neuronal cell death, as well as by mitofusin-2 (MFN2), overexpression of which leads to reduction of mitochondrial network [82]. Optic atrophy 1 (OPA1) also serves in fusion regulation, with its overexpression also reducing mitochondrial network [83].

Fission is regulated by dynamin-1-related protein (Drp1) [84]. It is found in cytosol and is able to translocate to the mitochondrial surface and induce fission through GTPase activity. Drp1 inhibition obviates neurotoxin induced mitochondrial fission [82]. Reduction of Drp1 leads to mitochondrial network depletion [83]. Drp1 is also important for directing the mitochondria towards the dopaminergic neurons synapses [85].

Defects of fusion and fission cause limits in mobility, energy production, and rise of ROS. All those lead to mitophagy, cell dysfunction and cell death [86]. Role of mitochondrial fission and fusion in the pathogenesis of PD is supported by toxin induced PD models. Fusion and fission balance disorders might contribute to the pathogenesis of PD.

Mutants of a few genes, such as: PINK1, Parkin, LRRK2 and DJ-1, are related to mitochondrial dynamics. It is stated that PINK1 or Parkin mutations lead to mitochondrial fusion [87]. Samples from PD patients with mutations in the above genes showed dysfunctional and more fragmented mitochondrial network. G2019S mutant of LRRK2 gene may interact with Drp1 and lead to mitochondrial fission [88,89]. The above results suggest that the impairment of mitochondrial dynamics might contribute to the pathogenesis and progression of PD.

Mitophagy and autophagy Impairment in PD

Process of component degradation by autophagosomes fused with lysosomes is known as autophagy [90]. Autophagosomes are able to degrade protein aggregates or impaired mitochondria in the mitophagy process. This process involves receptors responsible for binding ubiquitinated mitochondria and the autophagosome protein light chain 3 (LC3), which plays crucial roles in biogenesis of the autophagosome membrane [91]. Evidence suggests a significant role of impaired autophagy/mitophagy in PD associated neurodegeneration [92].

PINK1-depenent activation of Parkin is a major pathway of mitophagy. Accumulation of PINK1 on mitochondria is a key signal in mitophagy transduction [89]. This process is crucial to recruit Parkin to injured mitochondria. PINK1 interaction with the TOM complex allows the recruitment and activation

of Parkin, leading to degradation of mitochondrial outer membrane protein, which leads to mitophagy [93]. Failure in cooperation of PINK1/Parkin leads to accumulation of damaged mitochondria, causes raising concentrations of ROS, and leads to neuron death [94]. Lower amount of DJ-1 leads to lowered mitochondrial membrane potential, increased ROS and autophagy dysfunction [95].

It was found that overexpression of LRRK2, particularly mutant variants, seems to suppress autophagy in PD patients [96]. On the other hand, it is shown, that LRRK2 may induce autophagy through an ERK1/2-dependent pathway [97]. It is known that LRRK2 may lead to lysosome-related calcium storage and, hence, autophagy disorders [98,99]. It seems that common signal for mitochondrial degradation through mitophagy is the loss of mitochondrial membrane potential, associated with mitochondrial dysfunction.

Conclusion

High susceptibility of SNca DA neurons to damage may result from fact that DA and its metabolites are toxic. Disorders in vesicle storage of these substances lead to an increase of ROS, causing mitochondrial dysfunction and, in perspective, cell death. Moreover, lower amount of antioxidants, such as glutathione, leads to reduction of protective mechanisms against ROS, causing decreased resistance of DA neurons to oxidative stress. Another phenomenon causing higher vulnerability of these neurons may be the increase of calcium concentration, which may lead to calcium metabolism disorders, further leading to increase in ROS production and impairment of ATP-dependent pathways. However, none of the present hypotheses can explain the selective vulnerability of the above mentioned cells. This points to combination of the phenomena described above as well as some yet unknown factors bearing responsibility for this neuronal property.

Nowadays, we are able to say that molecular pathogenesis includes multiple pathways and mechanisms. The observed causes include: disorders of oxidative economy, α-synuclein proteostasis, mitochondrial dynamics impairment, disorders of the mitophagy process, and occurrence of some gene mutations. The above factors contribute to the occurrence of mitochondrial dysfunction, which ultimately leads to the death of neurons.

Outcomes of mitochondrial dysfunction, seem to share common pathways despite the differences of PD phenotypes induced by neurotoxin or associated with mutations. The above examples support the hypothesis that mitochondrial abnormalities and dysfunction may have a crucial impact on degeneration of SN dopaminergic neurons in wide spectrum of PD. Deregulation of mitochondrial oxidation economy and mitophagy pathways is highly implicated in the neuropathology of PD. Cited evidence confirms the hypothesis that mitochondrial dysfunction might be a critical reason leading to the development of PD. This information allows for potential design of therapies focused on counteracting mitochondrial dysfunction, used to treat various PD phenotypes. To improve the ability of effective Parkinson's disease treatment and counteract the increasing incidence, further, more insightful research into the factors involved in its pathogenesis needs to be conducted.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest statement
The authors declare they have no conflict of interest.

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