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Reviews

ANTIOXIDANT ROLE OF DJ-1 PROTEIN IN THE PATHOGENESIS OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease is a progressive age-related neurodegenerative disease, and oxidative stress is an important mediator in its pathogenesis. Loss of neurons in the midbrain region (Substantia nigra) causes dopamine deficiency and leads to the formation of intracellular inclusions containing α-synuclein aggregates. Both of these phenomena are considered neuropathological features of Parkinson's disease. Although the clinical diagnosis is based on the presence of bradykinesia and other major motor signs, Parkinson's disease is associated with many non-motor symptoms that contribute and complicate the disease. The underlying molecular pathogenesis involves several pathways and mechanisms: α-synuclein proteostasis, mitochondrial dysfunction, oxidative stress, disturbances in calcium homeostasis, and neuroinflammation.

Mutations in the *PARK7* gene resulting in loss of function of the encoded DJ-1 protein have been identified as the cause of one of several forms of the inherited form of Parkinson's disease. The DJ-1 protein is attributed the role of an antioxidant based on experiments in cellular model systems. The active site of DJ-1 contains a highly reactive cysteine residue (Cys106) which is oxidized under oxidative stress. It is assumed that Cys106 plays a critical role in the biological function of DJ-1, regulating antioxidant protection depending on the oxidation state of Cys106, i.e. acts as a sensor of oxidative stress. Thus, the level of oxidized DJ-1 (oxDJ-1) may serve as a possible biomarker of oxidative stress.

In this review, we tried to consider all sides of Parkinson's disease. Furthermore, functions and a role of Dj-1 protein in onset of early PD forms are characterized.

Key words: Parkinson's disease, DJ-1, *PARK7*, neurodegenerative diseases.

INTRODUCTION

Parkinson's disease (PD) is an age-related multifactorial neurodegenerative disorder [1], that affects up to 1% of people over 60 and up to 4% of people over 80 years of age. Still, people aged 18-50 years can also suffer from juvenile and early forms of parkinsonism, which include symptomatic parkinsonism resulting from brain damage (trauma, toxins, encephalitis, hypoxia) and parkinsonism that develops alongside other neurodegenerative diseases (Huntington's syndrome, dementia with Lewy bodies, multisystem atrophy). Clinical symptoms of PD include uncontrolled tremor at rest, rigidity, slowness of movement, and postural disturbances. In addition to disorders of motor function, PD is accompanied by disorders of the gastrointestinal tract, olfaction, sleep, and cognitive abilities. These symptoms are the result of loss of function and/or death of most midbrain dopaminergic (DA-ergic) neurons, followed by impaired DA-ergic neurotransmission in the dorsal striatum, where the presynaptic endings of neurons are located. [2, 3]. The pathological features of PD include selective loss of DA-ergic neurons in the «*Substantia nigra*» (SN) and deposition of α-synuclein (α-syn) in DA-ergic neurons. Since reactive oxygen species (ROS) are formed during enzymatic and non-enzymatic metabolism of dopamine, nigral DA-ergic neurons are saturated with ROS and are more vulnerable to oxidative stress compared to other neurons. Thus, dopamine production, on the one hand, is the main function of DA-ergic neurons, and, on the other hand, is the main cause of their death due to concomitant oxidative stress. The only treatment for PD is levodopa (DOPA), the metabolic precursor of dopamine (Fig. 1).

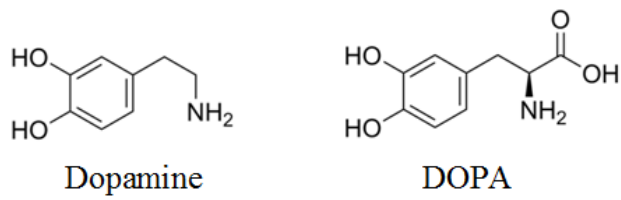

Figure 1 – Molecular structures of Dopamine and DOPA.

Sporadic PD accounts for about 90% of all cases of PD; familial PD with a monogenic mutation accounts for less than 10% of all cases of PD [4]. The sporadic form of PD is associated with various environmental factors including exposure to neurotoxins (MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), pesticides, and herbicides such as rotenone and paraquat [5].

In this review, we have tried to cover all aspects of PD, including the etiology, developmental stages, and various consequences of this neurodegenerative disorder. In addition, the role of the DJ-1 protein and its possible molecular functions that prevent the onset of early forms of PD are considered.

DEVELOPMENT AND FORMS OF PD

The onset of Parkinson's disease most often occurs around the age of 60, but exceptions are possible. The generally accepted classification includes juvenile Parkinson's disease (age <20 years), early onset Parkinson's disease (age 20–50 years), and late onset Parkinson's disease (age >50 years).

In cases of diagnostic uncertainty, especially in the early stages of the disease, neuroimaging such as dopamine transporter single photon emission computed tomography (DAT-SPECT) or positron emission tomography (PET) with fluorodopa (FDOPA) may be used to more accurately diagnose DA-ergic deficiency [6]. Although these studies may confirm the presence of DA-ergic dysfunction, they cannot distinguish

Parkinson's disease from other degenerative forms of parkinsonism. DAT-SPECT is most often used to distinguish Parkinson's disease from benign tremor. It can also be used to confirm that a symptomatic person has a non-degenerative form of parkinsonism, such as DOPA-responsive dystonia. Laboratory or imaging studies such as brain MRI are only useful in ruling out alternative diagnoses such as infarction, tumor, or normal pressure hydrocephalus.

Usually, PD occurs in only one family member (simple case), although sometimes it occurs in several family members (for example, familial Parkinson's disease). It is estimated that 15% of people with Parkinson's disease have a positive family history of PD, while 5% to 10% of all Parkinson's diseases are associated with pathogenic variants of individual genes (monogenic Parkinson's disease). In addition to these variants, other genetic and environmental factors (known and unknown) may influence overall disease risk.

Monogenic Parkinson's disease

Monogenic Parkinson's disease can be inherited in an autosomal dominant, autosomal recessive, or, rarely, X-linked pattern [7, 8]. The patient's age at diagnosis can be helpful in differentiating autosomal dominant PD (usually >50 years of age) from autosomal recessive PD (usually <40 years of age), but age of onset can vary greatly between individuals with the same genetic background [9].

*Juvenile Parkinson's disease***.**

Variants in several genes have been associated with juvenile onset of Parkinson's disease (age of onset usually <20 years). Inheritance of juvenile PD is usually autosomal recessive, and the clinical picture often includes additional features such as dystonia and spasticity [10]. Patients with PD also show some non-motor symptoms such as sleep disturbances, dementia, sensory abnormalities, and autonomic dysfunctions [11].

OXIDATIVE STRESS AND ITS EFFECT ON THE DEVELOPMENT OF PD

Oxidative stress is critical to the etiology of many diseases associated with oxidative stress, especially neurodegenerative diseases and cancer. Inflammation induces the production of ROS and RNS (reactive nitrogen species) through respiratory processes and inflammatory cytokines, which can activate many oxidant-generating enzymes such as inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX2), myeloperoxidase (MPO), and eosinophilic peroxidase (EPO). Normal cellular mechanisms and reactions, including oxidative phosphorylation in mitochondria, generate free ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), and nitric oxide. And although ROS are important molecules for redox signaling and cellular functions, at the same time, ROS lead to oxidative damage, such as lipid peroxidation in cell and organelle membranes, fragmentation and oxidation of proteins by cross-linking them together, the formation of carbonyl groups and oxidation of DNA and RNA. The response to this is the activation of antioxidants, which reduce the level of these radicals. When essential endogenous antioxidants are deficient, as occurs in Parkinson's disease, uncontrolled ROS production can lead to excessive non-physiological and toxic levels of ROS, leading to oxidative stress [12].

Since the brain consumes a large amount of oxygen, a significant amount of oxygen is converted into ROS, which increases oxidative stress in patients with PD. There is evidence that dopamine metabolism, high levels of iron and calcium in SN, mitochondrial dysfunction, and neuroinflammation contribute to increased oxidative stress and death of DA-ergic neurons in the brains of PD patients [13].

Dopamine is synthesized by tyrosine hydroxylases using molecular oxygen to hydroxylate the aromatic ring, hydrogen peroxide being one of the products of this reaction. In addition, DA is capable of self-oxidation with the formation of dopamine quinones and free radicals, which can contribute to neurodegeneration in PD. Cyclization of dopamine quinones leads to the formation of aminochrome, which generates superoxide and inhibits the antioxidant nicotinamide adenine dinucleotide phosphate (NADPH) [14]. Metabolism of DA by monoamine oxidase-B (MAO-B) leads to the formation of 3,4-dihydroxyphenylacetaldehyde, ammonia and H_2O_2 [15]. H_2O_2 in DA-ergic neurons reacts with Fe^{2+} to form a hydroxyl radical. MAO-B induction in astrocytes leads to selective death of DA-ergic neurons in SN, which has been experimentally shown in mice [16].

Transportation and storage of DA also increase the production of ROS. DA storage requires transport through vesicular monoamine transporter 2 (VMAT2) [17]. Excess production of VMAT2 provides protection against toxicity caused by MPTP. DA-ergic neurons with inhibited VMAT2 are more vulnerable to oxidative stress. On the other hand, dopamine transporters (DAT) are required for DA reuptake [18]. Inhibition of DAT increases the level of extracellular DA, which is prone to autooxidation. SNCA and DJ-1 mutations in PD patients are associated with impaired dopamine reuptake or storage, suggesting a role for DAT in neuronal susceptibility to oxidative stress [19].

It has been shown that high iron levels in SN are observed in patients with PD. Iron is an essential metal for tyrosine hydroxylase, which is required for DA synthesis [16, 20]. Iron ions Fe^{3+} and Fe^{2+} react with superoxide and H_2O_2 to form free hydroxyl radicals, which can be toxic to neurons. Iron exposure in mice causes loss of neurons in the SN and loss of DA in the striatum (*Corpus striatum*, SS), develops a parkinsonian phenotype, and becomes more vulnerable to MPTP [21]. Stereotactic infusion of iron into the SN of rats leads to an increase in the level of iron hydroxyl radicals in the SS. Administration of an iron chelator to mice reduces brain iron levels and demonstrates a neuroprotective effect against iron- or MPTP-induced neurotoxicity. These results suggest that elevated SN iron levels contribute to oxidative stress and neurodegeneration in PD [13].

Regulation of intracellular Ca^{2+} ions requires ATP-dependent pumps in mitochondria, which consequently increases ROS generation, [22]. In primary cultures of mouse mesencephalic DAergic neurons, the opening of L-type Ca2+ channels can enhance oxidative stress, while α-synuclein aggregates potentiate this excess in production of ROS in mitochondria. L-type calcium channel Cav1.3 predominates in DA-ergic SN neurons [23]. This distribution in calcium channels may explain why DA-ergic neurons in the SN are more susceptible to oxidative stress or excitotoxicity (damage and death of nerve cells by neurotransmitters). Isradip-

ine, an L-type calcium channel blocker, shows a protective effect against α-synuclein, 6-hydroxydopamine (6-OHDA), or MPTP-induced neurotoxicity in DA-ergic neurons, suggesting a link between calcium influx through L-type Ca^{2+} channels and pathogenesis of PD [24].

Mitochondria are the main sites of ROS production. Premature leakage of electrons to oxygen in complex I (nicotinamide adenine dinucleotide dehydrogenase) and complex III (cytochrome bc1) leads to the formation of O^{2-} in mitochondria [25]. Mitochondrial dysfunction leads to further increase in production of ROS. On the other hand, ROS are also harmful to the electron transport chain itself [26]. The association between mitochondrial dysfunction and PD is demonstrated by MPTP-induced parkinsonism in drug abusers. In the brain, MPTP is metabolized to 1-methyl-4-phenylpyridine (MPP+), which enters DA-ergic neurons via DAT. MPP+ selectively inhibits complex I and leads to death of DA-ergic neurons in SN [27]. Of note, activity of complex I in SN is also reduced in patients with PD, [28]. Genes encoding mitochondrial proteins are also downregulated in DA-ergic neurons in PD patients. Mitochondrial dysfunction in PD includes mitochondrial biogenesis, fusion/breakdown, and mitophagy [29].

Neuroinflammation, mainly caused by microglia, is now well recognized as a characteristic pathological feature and a potential source of oxidative stress in PD [30]. Microglia consist of highly mobile phagocytes that make up 10% to 15% of all brain cells. Microglia can be activated and acquires phagocytic capacity under the action of α-synuclein. Activated microglia is an important source of oxidative stress and can produce glutamate and pro-inflammatory factors, including tumor necrosis factor (TNF)-α, interleukins (IL)-1β and IL-6 [31]. In patients with PD, microglial activation in the SN is detected along with an increase in pro-inflammatory factors in the brain and cerebrospinal fluid. Microglial activation is observed in cellular and animal models induced by MPTP, rotenone, 6-OHDA and lipopolysaccharide (LPS) as well as by oxidized lipids, proteins, and DNA released by dead neurons. Because the midbrain contains large amounts of microglia, its activation can be extremely toxic to DA-ergic neurons in the midbrain. Interestingly, genetic studies are finding an association between PD and single nucleotide polymorphisms in the human leukocyte antigen (HLA)-DRA, DRB1, DRB5, and DQB1 regions. [13].

MAIN PROTEINS ASSOCIATED WITH PD

In recent years, genetic research has revolutionized the understanding and classification of neurodegenerative conditions, including PD. Currently, *PARK* loci with autosomal dominant genes such as *SNCA* and *LRRK2* have been described; the most common are autosomal recessive genes such as *PRKN*, *PARK7* and *PINK1*. Information on these *PARK* loci/genes is presented in Table 1.

Autosomal dominant (AD) forms of PD

PARK1–4/SNCA

The first locus of autosomal dominant PD was mapped on chromosome 4q21-q23 in 1996 in an Italian-American family. A year later, a point mutation was identified in the SNCA gene encoding α-synuclein, which leads to the replacement of the amino acid A53T [33]. Since then, two additional point mutations in α-synuclein have been found: A30P in a German family [34] and E46K in several Basque families [35]. Point mutations in the *SNCA* gene usually cause early parkinsonism and often lead to dementia. Genomic multiplications of the entire *SNCA* gene, both duplications and triplications, are also associated with familial Parkinson's disease, which manifests itself at an early stage in the development of dementia and autonomic dysfunctions.

Point mutations or multiplications of the *SNCA* gene can cause Parkinson's disease by enhancing the mechanisms of toxic function suggested by their dominant mode of inheritance. α-synuclein, when mutated or multiplied, tends to develop a beta-sheet structure that can polymerize into oligomers and fibrils, which are the main components of Lewy bodies (LB) [32]. α-synuclein is a small protein (14 kDa) that is abundant in presynaptic terminals and has regulatory activity in membrane and vesicular dynamics [36]. The physiological function of α-synuclein is to regulate neurotransmitter release, synaptic function, and plasticity of DA-ergic neurons.

PARK8/LRRK2

Table 1 - General information on PARK loci/genes

Disease	Gene	loci	Inheritance	Clinical phenotype	Pathology
PARK1/4	*SNCA*	4q21	AD	P, D	ND, LB (point mutation), LB
PARK2	*PRKN*	6q25.2–q27	AR	DLB	Pure ND (a single case with LB)
PARK3	-	2p13	AD	EOP	LB
PARK5	*UCHL1*	4p14	AD	P, D	Unknown
PARK6	*PINK1*	1p36	AR	P, D	Unknown
PARK7	*DJ1*	1p36	AR	EOP, Dy, Py	Unknown
PARK8	*LRRK2*	12q12	AD	EOP	ND, LB (rarely, tau pathology)
PARK9	*ATP13A2*	1p36	AR	P	Unknown
PARK10	-	1p32	AD	EOP, D, O, S, Py, Psy	Unknown
PARK11	*GIGYF2*	2q37.1	AD	P	Unknown
PARK12	-	Xq21-q25	X-linked	P	Unknown
PARK13	*Omi/HtrA2*	2p12	AD	–	Unknown
PARK14	*PLA2G6*	22q13.1	AR	P	LB, tau pathology
PARK15	*FBXO7*	22q12-q13	AR	EOP, D, O, S, Dy, Py	Unknown
PARK16	-	1q32	–	EOP, S	Unknown

Note: A- Ataxia; AD- autosomal dominant; AR- autosomal recessive; D- Dementia; DLB – Dementia with Lewy bodies; Dy- Dystonia; EOP - Parkinsonism with early development; LB – Lewy bodies; ND – Nigral degeneration; O - Oculomotor dysfunction; P- parkinsonism; Psy - Psychiatric syndrome; Py - pyramid signs; S – Spasticity [32].

Mutations at the *PARK8* locus on chromosome 12q12 have been identified in the Japanese Sagamihara Kindred family. Subsequently, the association of mutations R1441G, R1441C, Y1699C and I2020T with Parkinson's disease was also confirmed in families of European origin [37]. Patients with PD who carry mutations in the *LRRK2* gene most often suffer from parkinsonism with clinical manifestations indistinguishable from late-onset sporadic PD. Seven *LRRK2* point mutations that result in a protein change have been classified as pathogenic: N1437H, R1441C, R1441G, R1441H, Y1699C, G2019S, and I2020T. Two mutations (R1628P and G2385R) have been associated with an increased risk of PD in the Asian population. In most cases, the pathology of carriers of the *LRRK2* gene is associated with LB, but the presence of tauopathy and a defect in the TDP-43 gene have also been observed. *LRRK2* encodes a large protein (285 kDa) with seven different domains [32], containing several motifs that provide protein interactions, dual enzymatic activity domains for GTPases and protein kinases [38]. Possible mechanisms by which a mutant form of *LRRK2* leads to cellular dysfunction are related to its hyperfunction or increased abnormal function. Because of the similarities between *LRRK2* defect-related parkinsonism and idiopathic PD, understanding *LRRK2* gene mutations is essential for understanding the fundamental mechanisms of PD pathogenesis and for developing new therapeutic agents [32].

VPS35 (Vacuolar protein sorting ortholog 35)

VPS35 is an important component of the target retromer recognition complex involved in the recycling of membrane proteins between endosomes and the trans-Golgi network. The discovery of VPS35 mutations indicates the dysfunction of the retromer in neurodegenerative processes [32] and confirmed that the D620N substitution in VPS35 is a causative autosomal dominant mutation in PD [38].

GBA (Glucocerebrosidase)

A dominantly inherited heterozygous mutation in the glucocerebrosidase (*GBA*) gene is an important risk factor for PD [39]. Pathogenic mutations in the GBA are also associated with PD, although with a slightly earlier onset. The most common finding is an asymmetric resting tremor, although postural instability and difficulty walking are also relatively common. The presence of mutations in *GBA* has a significant impact on the natural course of Parkinson's disease: patients with mutations in *GBA* develop earlier onset of symptoms and severe motor impairment [40]. There is a high prevalence of dementia and a distinct pattern of cognitive deficits characterized by greater impairment of memory, executive function, and visuospatial abilities [41]. Other non-motor clinical signs are also common, the most common of which are anosmia and dysautonomia, REM sleep disorder, depression, anxiety, and hallucinatory psychotic manifestations [42].

Autosomal recessive (AR) PD genes

Autosomal recessive homozygous or compound heterozygous loss-of-function mutations have been identified in three genes using traditional gene mapping approaches: *PARK2* (RBR E3 ubiquitin protein ligase, commonly known as *Parkin*), *PINK1* (PTEN-induced kinase 1) and *PARK7* (Parkinson-associated protein 7, commonly known as DJ-1) [38]. Although mutations in these genes are relatively rare in the general PD population, they seem to be responsible for a significant proportion of the early manifestations of PD (mean age of homozygous mutation carriers for *PARKIN*, *PINK1* and *PARK7* ~ 39 years) [43]. The most frequently mutated autosomal recessive PD gene is *Parkin*, which accounts for 8.6% of early onset PD (<50 years), followed by *PINK1* (3.7%) [44].

PTEN- induced kinase 1 (PINK1)

Mutations in PTEN-induced kinase 1 (*PINK1*) are associated with recessive parkinsonism. *PINK1* is a neuroprotective kinase found primarily in mitochondria and cytosolic compartments and plays a role in neuronal differentiation. Increased expression of *PINK1* induces neurite outgrowth in SH-Sy5y cells and increases dendritic length in DA-ergic neurons [45]. *PINK1* is rapidly degraded in normal mitochondria but accumulates in damaged mitochondria, triggering autophagy to protect cells. In addition, studies have shown that *PINK1* mutants exhibit degeneration of DA-ergic neurons along with motor defects [29]. *PINK1* mutations are either missense or nonsense mutations, and rarely include entire exon deletions [46]. More than 61 different missense and nonsense mutations have been identified, affecting all 8 exons of *PINK1* with almost the same frequency. *PINK1* is a 581 amino acid ubiquitously expressed protein kinase. Two-thirds of reported mutations in *PINK1* are loss-of-function mutations affecting the kinase domain, demonstrating the importance of *PINK1* enzymatic activity in the pathogenesis of PD.

PARKIN

PARKIN is a ubiquitin ligase that plays an important role in proteasome degradation; destructive mutations in *PARKIN* lead to the loss of its function [36]. In patients with mutated *parkin* gene, the disease begins in the third or fourth decade of life, usually slowly progressing with a marked response to levodopa. PD has been reported even in childhood, with homozygous mutations in *PARKIN* being the most common cause of juvenile PD. *PARKIN* mutations are the best known causes of precocious PD: 77% of familial cases with onset < 30 years and 10-20% of patients with precocious PD overall. In the human genome, *PARKIN* is the second largest gene, and the product of this gene functions as an E3 ubiquitin ligase involved in the ubiquitinylation process [38]. Since ubiquitinylation is the main way of labeling defective mitochondria for subsequent destruction by autophagy, the molecular function is easy to interpret in the pathogenesis of PD: defective mitochondria produce a large amount of ROS, which leads to a cascade of damage in the cell and ends with its death.

DJ-1/ PARK7

Human DJ-1 (encoded by the gene *PARK*7) is mapped to chromosome 1 at position 1p36.23 while the mouse homologue is found on chromosome 4E. *PARK7*, contains 17 different gt-ag introns and 7 exons, is 23.86 kb long. Due to the presence of alternative promoters and alternative splicing, 17 different variants of the gene have been described. Among them, 15 transcripts have the potential to encode a protein and 2 variants of transcripts encode the same protein. [47]. Human DJ-1 consists of 189 amino acid residues and is a small (20 kDa) protein belonging to the large DJ-1/ThiJ/PfpI superfamily that is ubiquitously expressed in more than 22 human tissues, including the pancreas, kidneys, and skeletal muscle, liver, testicles and heart. Over the years, the DJ-1/ThiJ/

PfpI protein family has been found in various organisms from bacteria to humans [48]. While human DJ-1 is a homodimer, the DJ-1 monomer adopts a flavodoxine-like helix-bend-helix folding pattern with 11 β-sheets (β1–β11) and 8 α-helices (αA–αH) [49, 50].

Combined analysis based on 3D structures and nucleotide sequence helps to identify the features of members of the DJ-1 family that appear to be key to their functions in the source. For example, the nucleophilic region between the α-helix and β-sheet contains a highly conserved cysteine result (Cys106 in humans). This residue is reactive in most family members and readily oxidized in human DJ-1. This mechanism is necessary for the activity of DJ-1 as a redox sensor [51]. Three-dimensional structures of reduced and oxidized DJ-1 showed detailed interactions between the oxidized cysteine and its surrounding conserved residues. In addition, structural studies have shown how certain pathogenic mutations associated with parkinsonism cause a loss of function due to destabilization of DJ-1. Destabilization appears to be the most common mechanism by which parkinsonian mutations reduce the protective function of DJ-1. Overall, the current understanding about the functions of the DJ-1 family is largely based on the abundance of currently available structural information, which is used to both form and test hypotheses about the function of these proteins [52].

DJ-1 acts as an antioxidant through a variety of mechanisms, including removing ROS in a manner dependent on three redox cysteine residues at positions 46, 53, and 106 [53]. Under physiological conditions, DJ-1 is predominantly present in the cytoplasm and, to a lesser extent, in the nucleus and mitochondria, including the outer membrane, matrix, and intermembrane space of mitochondria [54]. However, under oxidative stress, cytoplasmic DJ-1 translocates to mitochondria and then to the nucleus, while mitochondrial-localized DJ-1 shows stronger cytoprotective effects against oxidative stress than either cytosolic or nuclear DJ-1. The ability of DJ-1 to immediately redistribute according to changes in the microenvironment is critical for the regulation of mitochondrial homeostasis and function, coinciding with cytoprotective activity [55]. Studies have shown that the loss of DJ-1 leads to mitochondrial dysfunction, including decreased respiratory control ratio, mitochondrial membrane potential, ATP levels, and impaired dynamics *in vitro* and *in vivo*. Mitochondrial DJ-1 translocation likely mediated by chaperones (Hsp70) in response to oxidative stress [56].

DJ-1 plays a key role in the regulation of oxidative stress-induced apoptosis, in particular by preventing ASK1 activation through multiple mechanisms. DJ-1 can stabilize the Trx1-ASK1 inhibitory complex. Under normal conditions, ASK1 binds to Trx1 equally with or without overexpression of DJ-1. However, under oxidative stress, Trx1 releases ASK1, a process that suppresses overexpression of DJ-1 [57]. In addition, DJ-1 can upregulate *Trx1* expression through Nrf2, thereby increasing intracellular Trx1 levels and downregulating ASK1 activation. Also, DJ-1 can disrupt ASK1 homodimerization through physical interaction, resulting in inhibition of the ASK1 signaling pathway [58].

Along with a large number of publications related to the possible role of DJ-1 as an oxidative stress sensor, evidence has recently been published on the importance of the enzymatic function of DJ-1 [2]. DJ-1 has methylglyoxalase activity [59], which for some time was misinterpreted as deglycase activity [60]. The most compelling evidence for the importance of the enzymatic function of DJ-1 is the recently published data on the accumulation of proteins with lysine modifications by glyceric and phosphoglyceric acids in cells and tissues lacking DJ-1. Evidence has been obtained for the effectiveness of DJ-1 as a cyclic ester hydrolase spontaneously formed from 1,3-bisphosphoglycerate. This highly reactive ester spontaneously reacts with various molecules in the cell converting them into phosphoglyceric acid adducts resulting in loss of biological function [61]. Thus, DJ-1 possibly protects neurons from the stress associated with increased utilization of proteins damaged by the by-product of glycolysis.

CONCLUSION

Neurodegenerative diseases place a heavy burden on the health of not only affected patients, but also their families and communities. The sporadic development of PD is the norm in the general practice of neurodegenerative diseases, however, early onset PD remains a major problem among young populations around the world. Although several mechanisms have been postulated for the pathogenesis of neurodegenerative diseases, oxidative stress and mitochondrial dysfunction have been identified as the main mechanisms.

Research indicates a link between oxidative stress, DJ-1 oxidation, and the onset and progression of PD. The importance of preventing oxidative stress in PD has been recognized. DJ-1 binds to various transcription factors and regulates their transcriptional activity, resulting in different effects on dopamine synthesis, oxidative stress response, and signaling pathways. DJ-1 may play an important role in antioxidant defense by acting as a sensor of oxidative stress, determining the redox status of cells through Cys-106 oxidation, and altering the activity of signaling mediators and expression levels of genes involved in antioxidant defense. Overall, oxidized DJ-1 has important biological significance, and oxidized DJ-1 may be a promising biomarker candidate for oxidative stress, including that associated with Parkinson's disease. At the same time, studies on the molecular function of DJ-1 are not yet complete, especially since Cys106 oxidation may only be a consequence of oxidative stress and reactivity associated with catalytic function, and not a signal that is recognized by the cell under stress conditions. Therefore, studies of the possible enzymatic function of DJ-1 have intensified recently, and important experimental data have already been obtained on the presence of the unique enzymatic activity of DJ-1, which allows inactivation of toxic secondary metabolites of glycolysis.

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АНТИОКСИДАНТНАЯ РОЛЬ БЕЛКА DJ-1 В ПАТОГЕНЕЗЕ БОЛЕЗНИ ПАРКИНСОНА

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АННОТАЦИЯ

Болезнь Паркинсона представляет собой прогрессирующее возрастное нейродегенеративное заболевание, а окислительный стресс является важным медиатором в его патогенезе. Потеря нейронов в области среднего мозга (*Substantia nigra*), вызывает дефицит дофамина и приводит к формированию внутриклеточных включений, содержащих агрегаты α-синуклеина. Оба этих явления считаются нейропатологическими признаками болезни Паркинсона. Хотя клинический диагноз основывается на наличии брадикинезии и других основных двигательных признаков, болезнь Паркинсона связана со многими немоторными симптомами, которые усиливают общую картину недуга. Лежащий в основе молекулярный патогенез включает несколько путей и механизмов: протеостаз α-синуклеина, митохондриальная дисфункция, окислительный стресс, нарушения в гомеостазе кальция, и нейровоспаление.

Мутации в гене *PARK7* приводящие к потере функции кодируемого белка DJ-1 были идентифицированы как причина одной из нескольких форм наследственной формы болезни Паркинсона. Белку DJ-1 приписывается роль антиоксиданта на основе экспериментов в клеточных модельных системах. Активный центр DJ-1 содержит высокореакционноспособный остаток цистеина (Cys106) который окисляется при окислительном стрессе. Предполагается, что Cys106 играет критическую роль в биологической функции DJ-1, регулируя антиоксидантную защиту в зависимости от степени окисления Cys106, т.е. действует как датчик окислительного стресса. Таким образом, уровень окисленного DJ-1 (oxDJ-1) может быть возможным биомаркером окислительного стресса.

Ключевые слова: болезнь Паркинсона, DJ-1, *PARK7*, нейродегенеративные заболевания.

ПАРКИНСОН АУРУЫНЫҢ ПАТОГЕНЕЗІНДЕГІ DJ-1 АҚУЫЗЫНЫҢ АНТИОКСИДАНТТЫҚ РӨЛІ

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ТҮЙІН

Паркинсон ауруы – жасына байланысты үдемелі нейродегенеративті ауру, ал тотығу стрессі оның патогенезінде маңызды медиатор болып табылады. Ортаңғы ми аймағындағы нейрондардың жоғалуы (Substantia nigra) дофамин тапшылығын тудырады және құрамында α-синуклеин агрегаттары бар жасушаішілік қосындылардың пайда болуына әкеледі. Бұл құбылыстардың екеуі де Паркинсон ауруының невропатологиялық ерекшеліктері болып саналады. Клиникалық диагноз брадикинезияның және басқа да негізгі моторлық белгілердің болуына негізделгенімен, Паркинсон ауруы аурудың жалпы көрінісін толықтыратын көптеген моторлық емес белгілермен байланысты. Негізгі молекулярлық патогенез бірнеше жолдар мен механизмдерді қамтиды: α-синуклеин протеостазы, митохондриялық дисфункция, тотығу стрессі, кальций гомеостазының бұзылуы және нейроинфламация.

Кодталған DJ-1 протеинінің функциясын жоғалтуға әкелетін *PARK7* геніндегі мутациялар Паркинсон ауруының тұқым қуалайтын түрінің бірнеше түрлерінің біреуінің себебі ретінде анықталды. DJ-1 протеині жасушалық модельдік жүйелердегі эксперименттерге негізделген антиоксидант рөліне жатады. DJ-1 белсенді сайтында тотығу стрессінде тотығатын жоғары реактивті цистеин қалдығы (Cys106) бар. Cys106 тотығу күйіне байланысты антиоксиданттық қорғанысты реттейтін DJ-1-ң биологиялық қызметінде шешуші рөл атқарады деп болжанады, яғни. тотығу стрессінің сенсоры ретінде қызмет етеді. Осылайша, тотыққан DJ-1 (oxDJ-1) деңгейі тотығу стрессінің ықтимал биомаркері болуы мүмкін.

Түін сөздер: Паркинсон ауруы, DJ-1, PARK7, нейродегенеративті аурулар.