

Review

The Role of Impaired Mitochondrial Transport in the Development of Neurodegenerative Diseases

Alexander Blagov^{1,*}, Evgeny Borisov², Andrey Grechko³, Mikhail Popov⁴,
Vasily Sukhorukov², Alexander Orekhov^{2,*}¹Laboratory of Angiopathology, Institute of General Pathology and Pathophysiology, 125315 Moscow, Russia²Petrovsky Scientific Center of Surgery, 119991 Moscow, Russia³Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, 109240 Moscow, Russia⁴Department of Cardiac Surgery, Moscow Regional Research and Clinical Institute (MONIKI), 129110 Moscow, Russia*Correspondence: al.blagov2014@gmail.com (Alexander Blagov); alexandernikolaevichorekhov@gmail.com (Alexander Orekhov)

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Abstract

The fight against neurodegenerative diseases is one of the key directions of modern medicine. Unfortunately, the difficulties in understanding the factors underlying the development of neurodegeneration hinder the development of breakthrough therapeutics that can stop or at least greatly slow down the progression of these diseases. In this review, it is considered the disruption of mitochondrial transport as one of the pathogenesis factors contributing to neurodegeneration using the examples of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. Here, the mechanism of mitochondrial transport under normal conditions and the mechanisms of disturbances for the indicated diseases will be considered.

Keywords: neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; mitochondrial transport; mitochondria

1. Introduction

Neurodegenerative diseases are a heavy burden for the global health system and pose a serious threat to health, especially for the elderly. Clinically, neurodegenerative diseases can manifest themselves both in the form of impaired motor functions and in the form of dementia. The main feature that unites this group of diseases is the progressive death of neurons, which determines the chronic nature of the diseases and the absence of effective methods of treatment, and also distinguishes neurodegenerative diseases from static neuronal damage caused by exposure to toxic compounds [1]. In addition to clinical manifestations, neurodegeneration also differs depending on the brain regions (frontotemporal lobes, extrapyramidal system of the brain, spinal nerve pathways of the spinal cord) where pathological processes occur [1]. However, the main classification of neurodegenerative diseases is related to the difference in abnormal structural modifications and the accumulation of the certain proteins in neurons, which are identified as the main causes of the disease progression. According to these anomalies, neurodegenerative diseases are classified into tauopathies (Alzheimer's disease), alpha-synucleinopathies (Parkinson's disease), amyloidosis, Fused in sarcoma gene (FUS/FET) proteinopathies, prion diseases, neuroserpinopathies, ferritinopathies, trinucleotide repeat expansion disorders and TAR DNA-binding protein 43 (TDP-43) proteinopathies [1]. The most common neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD). The clinical manifesta-

tion of AD is characterized by developing dementia, which is based on a neurodegenerative process, which is determined by two characteristic properties: the accumulation of plaques formed from amyloid-beta, which is a breakdown product of the amyloid precursor protein, and the formation of neurofibrillary tangles formed from hyperphosphorylated modifications of the tau protein, associated with microtubules [2]. The clinical manifestation of PD is associated with impaired motor functions, the main symptoms of such disorders are rigidity, bradykinesia, rest tremor and postural instability. The pathogenesis of PD is based on the degeneration of dopaminergic neurons of the substantia nigra, which is determined by the accumulation of Lewy bodies, consisting of fibrillar formations containing α -synuclein and ubiquitin [2]. Despite the common features of pathogenesis characteristic for all neurodegenerative diseases, there are still many unclear details that determine the initiation and progression of neuronal destruction, which baffle researchers and physicians and complicate the search for the new therapeutic targets for these diseases. An important issue is the changes that occur at the cellular level and determine the pathological process, in particular, the disruption of the functioning of the certain organelles inside the cell. For neurons, the proper functioning of mitochondria is of great importance, since the conduction of a nerve impulse is a highly energy-consuming process that requires the generation of high levels of adenosine triphosphate (ATP) [3]. It is known that central nerve system (CNS) cells have an extremely fast metabolism: they con-



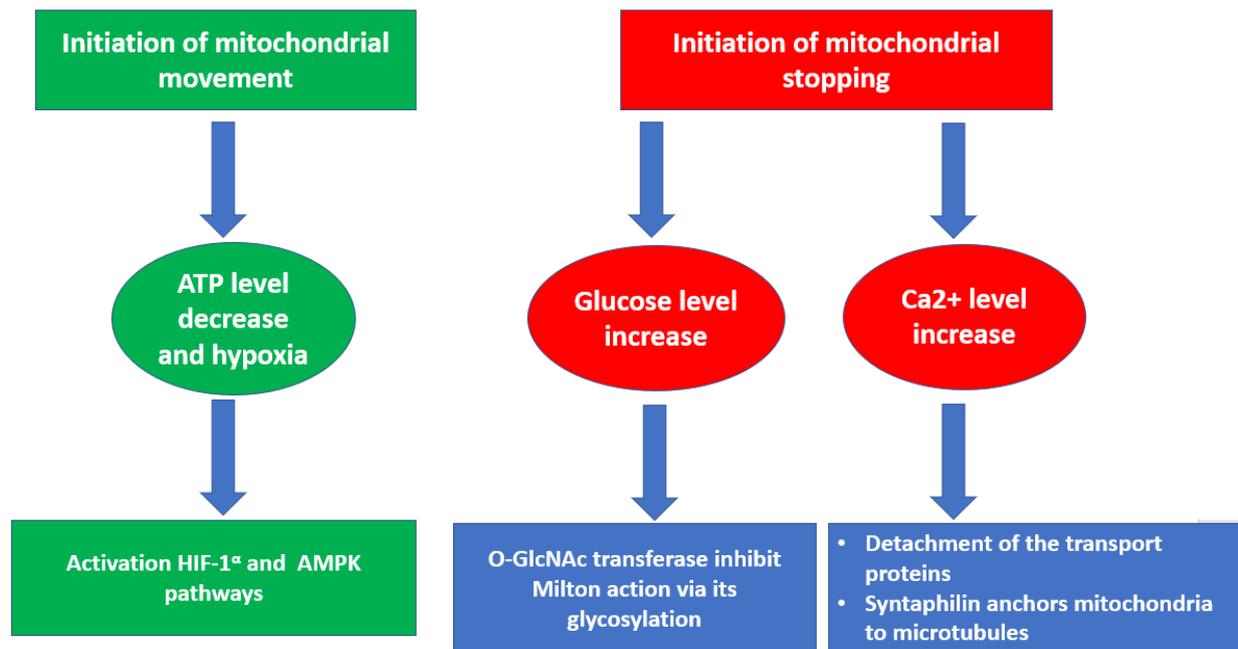


Fig. 1. General scheme of regulation of mitochondrial transport.

sume 20% of the inhaled oxygen at rest, while their share is no more than 2% of the body weight [4]. In addition to their role in providing energy, mitochondria are necessary for neurons to synthesize neurotransmitters, some of which are products of the metabolic pathways in mitochondria [5]. The high dependence of the work of neurons on the state of mitochondria determines that the occurrence of mitochondrial dysfunction is a proven phenomenon observed for a number of neurodegenerative diseases, including AD and PD [6,7]. The highly elongated branched polarized structure of neurons requires the maintenance of dynamic processes in the cell at a high level [8]. So, in synapses which are the places of a nerve impulse generation, the greatest synthesis of ATP, the supply of neurotransmitters and the operation of ion channels are required, which determine the need for high localization of mitochondria in this place. This statement means that the system of delivery, synthesis of new and removal of old mitochondria must work flawlessly in neurons to fully meet the energy needs of neurons [8]. This system is determined by the processes of mitochondrial dynamics, which include the regulation of the number of mitochondria (mitochondrial division and mitochondrial fusion), the creation of new mitochondria (mitochondrial synthesis), the destruction of old mitochondria (mitophagy) and intracellular movement of mitochondria (mitochondrial transport). In this review, we will focus on mitochondrial transport, as one of the key processes necessary for the maintaining of neurons vitality, and disruptions of which lead to the development of pathologies associated with neurodegenerative disorders. As an example, for analysis and comparison with each other, we will consider how the transport of mitochondria in neurons changes in such

neurodegenerative diseases as: AD, PD, as well as Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS).

2. Mechanism of Mitochondrial Transport

Due to the dependence of local ATP concentrations on the subcellular location of mitochondria, the regulation of their distribution is an extremely important mechanism responsible for the bioenergetic state of the cell. In neurons, mitochondria are in a balance of movement and stationary state: new mitochondria move from the neuron body along the axon towards synaptic endings to ensure high-energy processes, such as the recycling of synaptic vesicles; old mitochondria move in the opposite direction to the neuron body, where they are degraded by mitophagy [9]. Mitochondrial transport occurs as a result of the movement of motor proteins that carry out their activity mainly along microtubules. Kinesin motor proteins promote mitochondrial transport in the anterograde direction, i.e., from the neuron body to synapses, while dynein motor proteins ensure retrograde transport, which runs in the opposite direction [10]. Motor proteins bind to mitochondria as a result of interaction with receptor and adapter proteins. Mammalian receptor proteins are the Miro1 and Miro2 proteins, which are localized on the outer mitochondrial membrane [11]. Adapter proteins act as anchors between the receptor and motor proteins. These proteins are known as Milton proteins or Trak1 and Trak2 [12]. Together, the complex of these proteins ensures the movement of mitochondria along microtubules and, accordingly, their movement into various cellular compartments. The regulation of mitochondrial transport is of great importance for the vital activity of neurons. The implementation of the transport of mito-

chondria within the axon is a complex process that requires maintaining a balance between movement and stopping of mitochondria in the process of their movement. One of the signals to stop mitochondrial movement in the axon is an excess level of calcium, which is necessary for concentrating mitochondria in areas that require the most energy supply. The Miro protein is able to bind calcium, which provides a determination of the calcium concentration in the environment of mitochondria. There are several hypotheses for the stopping of the mitochondrial movement. According to the first of them, excess calcium triggers the detachment of the complex of motor-adapter and receptor proteins from microtubules [13]. According to another hypothesis, a high concentration of calcium leads to the dissociation of the motor protein from the Milton/Miro complex, which causes detachment of mitochondria from microtubules [14]. According to the third hypothesis, mitochondrial arrest is mediated by the activity of the syntaphilin protein, which anchors mitochondria to microtubules [15]. In addition, the energy state of the cell directly regulates the transport of mitochondria. Thus, it is quite obvious that the lack of ATP and the state of hypoxia favor the anterograde movement of mitochondria. This regulation is based on the activation of the 5' Adenosine monophosphate-activated protein kinase (AMPK) or Hypoxia-inducible factor 1-alpha (HIF-1 α) molecular pathways [16]. In addition, mitochondrial transport is directly affected by the metabolite concentrations. Thus, the Milton protein is able to interact with the enzyme O-linked N-acetylglucosaminyltransferase (O-GlcNAc transferase), which carries out glycosylation of this adapter protein. At high glucose concentrations, Milton glycosylation blocks the progression of mitochondria. This regulatory mechanism contributes to the concentration of mitochondria in places with a high concentration of nutrient compounds, which increases the productivity of the ATP synthesis [17]. The general scheme of regulation of mitochondrial transport is shown in Fig. 1.

Modulation of mitochondrial transport can occur in response to a number of stimuluses, including changes in the concentration of calcium ions and metabolites, in the energy state of the cell as well as the development of hypoxia. In response to these stimuluses, either inhibition or activation of motor proteins of mitochondrial transport occurs, which in turn either enhances or weakens the movement of mitochondria.

3. Mitochondrial Transport in Alzheimer's Disease

It is noted that in AD, the occurrence of abnormalities in mitochondrial transport is a closely related event in the relation to the formation of aggregates of the toxic proteins and is directly related to the synaptic dysfunction and a decrease in the integrity of axons [18]. The exact mechanisms of the development of mitochondrial transport disorders in AD in neurons are not fully known, however,

there is a clear relationship between inhibition of mitochondrial movement and such pathological processes associated with AD, such as an imbalance in the division and fusion of mitochondria, an increase in the concentration of A β and pTau proteins, and the development of oxidative stress [19]. In a model of mouse (Tg2576 mouse line) neurons that produced a mutant human Amyloid precursor protein (APP) protein, a strong decrease in anterograde mitochondrial transport was shown, as well as an increase in mitochondrial fission and a decrease in mitochondrial fusion, the presence of abnormal synaptic and mitochondrial proteins, and existing mitochondrial dysfunction [18]. At the same time, the introduction of the Szeto-Schiller 31 (SS31) peptide with antioxidant properties led to the restoration of the efficiency of mitochondrial transport and the resumption of the synaptic transmission [18]. Several studies have shown a direct correlation between the concentration of toxic A β peptides and the mitochondrial mobility in neurons, with A β peptides having a greater ability to aggregate, and fibrils formed from A β having the highest inhibitory activity which can possibly act as blocking elements for the mitochondrial moving. One of the key events in this case is the binding of A β to the plasma membrane of the neurons, which is sufficient to initiate inhibition [19,20]. It should be noted that impaired mitochondrial transport in these studies was not associated with a decrease in an ATP production and other cellular parameters of bioenergetics, which indicate a different time interval in the pathogenesis of AD for the onset of mitochondrial dysfunction and the development of the impaired mitochondrial movement. In addition to the effect of A β on the inhibition of mitochondrial transport, increased phosphorylation and production of the Tau protein also impair the mitochondrial movement, as has been shown in AD models [21]. This revealed the molecular mechanism underlying this inhibition. An important role in this process is played by the glycogen synthase kinase 3 enzyme, which causes disruption of mitochondrial transport in AD as a result of phosphorylation of motor proteins, which leads to their deactivation which manifests itself in the inability to bind to mitochondrial transport proteins. At the same time, this enzyme phosphorylates Tau at the AT8 site (S202 and Th 205), which, in addition to the development of fibrillar structures of this protein, causes a sharp decrease in microtubule stability, which leads to the inhibition of mitochondrial transport [22]. Thus, the long-characterized pathological A β and pTau proteins are involved in the inhibition of mitochondrial transport in AD, and if the inhibition mechanism for pTau is sufficiently characterized, then for A β it requires additional study. A possible role in the disruption of mitochondrial transport in AD is connected with some other proteins, which are also involved in the pathogenesis of AD. Thus, Apolipoprotein E4 (ApoE4) affects the binding of mitochondrial membranes and endoplasmic reticulum (ER), which is indirectly associated with the organization of mitochondrial transport [23]. Another possi-

ble mediated participant in the disruption of mitochondrial transport may be another predictor of AD, the Translocase Of Outer Mitochondrial Membrane 40 (TOMM40) protein, which has been shown to develop mitochondrial dysfunction in AD [24].

4. Mitochondrial Transport in Parkinson's Disease

As noted above, due to the high energy requirements of neurons for the transmission of a nerve impulse, mitochondria are actively recruited to cellular compartments which are remoted from the neuron body, such as axonal and dendritic endings. The target neurons that are affected in PD, called dopaminergic neurons, have long and relatively thin axons and minimal or no myelination. This characteristic makes this population of neurons more sensitive to possible changes in mitochondrial transport due to increased vulnerability to the supply of ATP for the nerve impulse conduction due to the weak axon myelination and the long path that mitochondria have to travel to get from the neuron body to the axon endings [25]. Thus, it has been shown that dopaminergic neurons, unlike other types of neurons, have a smaller number of mitochondria, which also have smaller sizes, and, moreover, mitochondrial transport is much slower [26]. There is evidence that proteins whose mutant forms are genetic risk factors for the development of PD, such as Leucine rich repeat kinase 2 (LRRK2), Parkin, PTEN-induced kinase 1 (PINK1), and α -synuclein, can interfere with the processes of cellular transport associated with the participation of microtubules and disrupt them [26]. Thus, for α -Syn, this intervention was demonstrated in the zebrafish model [27] and human neurons [28]. Two possible ways of inhibiting mitochondrial transport in axons could be direct interaction of α -synuclein with mitochondrial transport proteins or mediated through the induction of the mutations in these proteins. The first option has been proven in several studies, according to the results of which it turned out that α -synuclein was able to interfere with axonal transport as a result of the impaired binding of the motor protein kinesin to microtubules [29,30]. It was determined that the speed of the microtubules movement during the movement of cell cargo with the participation of kinesin is significantly reduced in the presence of α -synuclein molecules [29]. Additional evidence is the increased accumulation of mitochondria and other transported cellular components in axons at sites with the positive α -synuclein staining in the samples taken from patients with sporadic PD [31]. This situation leads to an abnormal distribution of mitochondria, which, in turn, leads to a decrease in a mitochondrial clearance, which is observed in the development of PD. At the same time, the mechanism of action of other pathogenic proteins mentioned above in PD on mitochondrial transport disorders remains to be studied.

5. Mitochondrial Transport in Amyotrophic Lateral Sclerosis

ALS is the most common neurodegenerative disease affecting motor neurons, including both upper and lower motor neurons. As a result of the dysfunction of motor neurons, muscle denervation occurs, which ultimately leads to respiratory failure, paralysis and death, which occurs within five years from the onset of the disease [2]. To date, there are no effective ways to completely cure ALS: there are only two drugs approved by the Food and Drug Administration (FDA) for use in the treatment of ALS, but they only slightly increase life expectancy [2]. This circumstance makes the search for new therapeutic targets in the pathogenesis of ALS a potentially promising direction. It is noted that one of the most frequent pathological events that occur in ALS are mitochondrial abnormalities. These abnormalities include disturbances in mitochondrial dynamics such as mitochondrial fission, fusion, and transport. The resulting disturbances in these processes lead to an increase in the number of dysfunctional mitochondria and a defective distribution of mitochondria in a neuron [32]. Since motor neurons are CNS cells with a highly elongated axoplasm, the disruption of mitochondrial function at sites that require more energy, such as muscle-bound synapses, can lead to the detrimental consequences, resulting in muscle denervation. Some evidence indicates a correlation between defects in the axonal transport and the development of the motor neuron degeneration in ALS [33]. Impaired axonal mitochondrial transport has been shown in mouse models of ALS [34,35]. Based on the results of these studies, it was concluded that impaired transport of mitochondria in motor neurons was a process preceding degeneration. To date, the reasons underlying the development of impaired mitochondrial transport in motor neurons in ALS are not yet sufficiently understood. One of the mechanisms in this case is a direct effect on the motor proteins. Thus, in studies [36,37], it was hypothesized that the mutant form of the antioxidant enzyme superoxide dismutase type 1 (SOD1) interacted with the complex of motor proteins dynein and dynactin, which led to the formation of aggregates and blocking of axonal transport. According to another hypothesis, mutant forms of proteins in ALS, including SOD1, form aggregates that damage mitochondria, which causes a disruption of energy metabolism and, accordingly, the production of ATP, which is also necessary for mitochondrial transport [38]. At the same time, it was shown that ATP concentrations affected the initiation of the mitochondrial movement [39]. This hypothesis directly links mitochondrial dysfunction to impaired mitochondrial dynamics in ALS. Mitochondrial transport over long distances is based on the interaction of the transport proteins with microtubules, while the movement of mitochondria over short distances is carried out with the help of the actin filaments [40]. At the same time, the actin cytoskeleton is a highly vulnerable cellular component in the diseases associated with the dysfunction

of motor neurons [41]. The mutant form of the profilin 1 protein associated with the development of ALS causes a disruption in the structure of the actin cytoskeleton in motor neurons, with a decrease in the level of fibrillar actin [42,43]. At the same time, it has been shown that the induced cytoskeletal disorders have an effect on mitochondria, which may be associated with the inhibition of their transport [42].

6. Mitochondrial Transport in Huntington's Disease

HD has a clearly identified etiology associated with a mutation of the gene encoding the huntingtin protein, which has an unknown function in the norm condition. This mutation is a multiple expansion of cytosine, adenine, and guanine (CAG) repeats in the first exon of the gene. HD is typical for the middle-aged people, its frequent symptoms are uncontrolled movements, the development of dementia and the rapid onset of death after the onset of the disease. The pathogenesis of HD is characterized by degeneration of neurons, which are predominantly represented by striatal neurons; however, in the later stages of the disease, neurodegeneration also affects other areas of the brain [44]. At the same time, it has been shown in animal models that degeneration of striatal neurons can be caused by the introduction of compounds toxic to mitochondria, which is a prerequisite for the hypothesis of a significant role of mitochondrial dysfunction in the development of HD [45]. Mitochondrial dysfunction in HD was confirmed on the basis of the activity analysis for the number of enzymes of the tricarboxylic acid cycle and oxidative phosphorylation, which was carried out from the brain tissues of deceased patients with HD [46]. According to the results of the analysis, a decrease in the concentration of detectable enzymes in the striatum of the brain was found. At the same time, it was confirmed that the mutant huntingtin protein directly had a negative effect on the metabolism of neurons. It is known from its properties that it is able to penetrate into the cell nucleus, where it can interact with transcription factors, thus acting as a regulator of gene transcription. In particular, it was found that the mutant form of huntingtin is able to change the transcriptional activity of p53 and PGC-1 α , which are nuclear factors that indirectly affect mitochondrial function [47,48]. In cell models, it was found that huntingtin could cause disturbances in the maintenance of the mitochondrial membrane potential and mitochondrial-mediated calcium traffic [49,50]. At the same time, several studies on various animal models have shown that huntingtin is able to inhibit mitochondrial transport in axons [51,52]. The mechanism of this inhibition can be explained by the close interaction of huntingtin with the Huntingtin Associated Protein 1 (HAP1) protein, which, in turn, interacts with the motor proteins dynactin and kinesin [53,54]. Thus, the complex of huntingtin and HAP1 probably forms some kind of competing object with respect to mitochon-

drial transport proteins for the binding to the microtubule motor proteins. Additionally, it was shown that huntingtin was able to independently bind to transporter proteins and, thus, modulated axonal transport [55]. Another option for the inhibition of mitochondrial transport by huntingtin may be a physical blockade of the transfer within the neuron, caused by the formation of large aggregates of the mutant protein. Huntingtin is the large cytoplasmic protein, which makes it a convenient target for cellular proteases. Cleavage of mutant huntingtin by proteases leads to the formation of N-terminal peptide fragments that easily aggregate with each other in different parts of the neuron [56]. In addition, in support of the previous hypothesis, it was shown that the N-terminal peptide fragments of huntingtin were able to inhibit mitochondrial transport in neurons by interfering with the binding of mitochondria to the microtubule motor proteins [57]. The disruption of mitochondrial transport leads to a decrease in the level of ATP produced in synaptic endings, which also negatively affects the transport of mitochondria along axons.

7. Interrelation of Mitochondrial Transport with other Processes of Mitochondrial Dynamics in Neurons

As indicated above, mitochondria are highly dynamic organelles, and all processes of mitochondrial dynamics must function properly not only separately, but also in interconnection with each other, which makes it possible to effectively satisfy the energy needs of cells. Neurons obtain the established system of distribution, quality control and quantity of mitochondria because they have a high vulnerability associated with disturbances in the processes of mitochondrial dynamics. The fusion of mitochondria is necessary for the exchange of molecular components between the connecting mitochondria, which allows mitochondria with morphological or functional disorders to restore their function as the result of the receiving components from healthy mitochondria. The fission of mitochondria allows the damaged mitochondria to retain functioning components in one of the daughter mitochondria, and to concentrate dysfunctional elements in the other, which will undergo mitophagy, which, thus, contributes to the preservation of the functional components of mitochondria. The subtle interaction between these processes and the high dependence of neurons on their conduction means that even seemingly minor disturbances can lead to the development of the serious neurodegenerative disorders.

Since the size of the mitochondria directly affects its mobility, the disturbances that occur during mitochondrial division also affect mitochondrial transport. One of the key regulatory proteins of mitochondrial division is Dynamin-related protein (DRP1). In a culture of hippocampal neurons, it was shown that induced disturbances in DRP1-mediated mitochondrial division led to abnormal mitochondrial distribution associated with an increase in the number

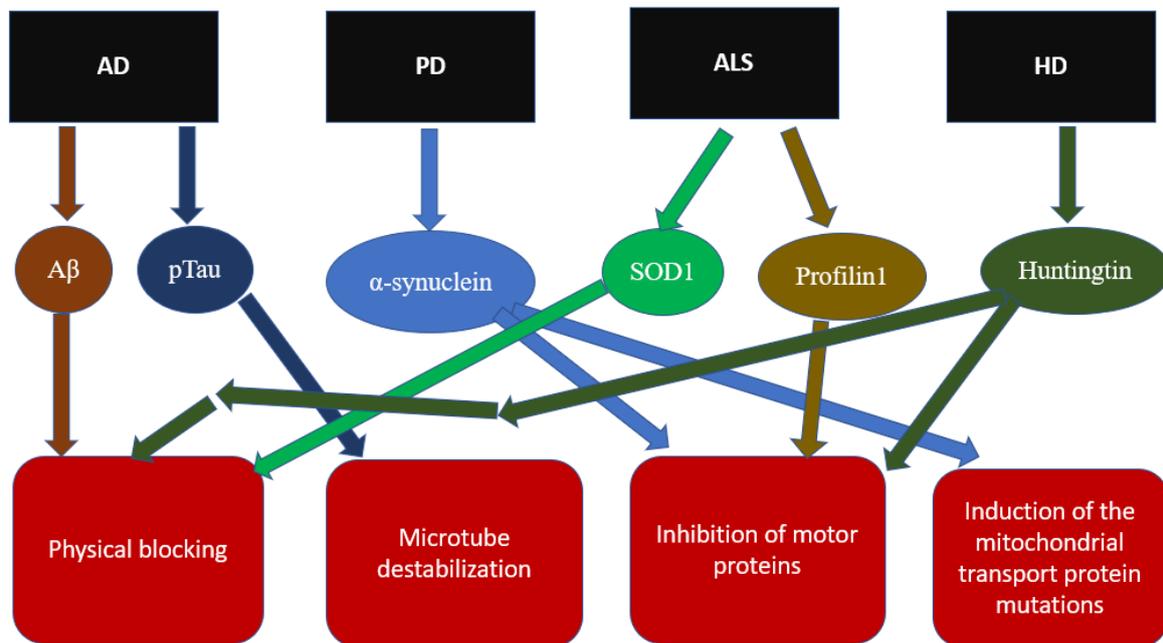


Fig. 2. Mechanisms of impaired mitochondrial transport in the neurodegenerative diseases.

of mitochondria in the neuron body and a decrease in their number in dendritic endings [58]. This indicates that the deficiency of division leads to a decrease in the efficiency of mitochondrial transport to the distal regions of neurons. In turn, dysfunction of the mitochondrial transport protein Miro1, in addition to inhibition of mitochondrial transport, causes enhanced mitochondrial fission, and its overexpression has the opposite effect [59].

Fusion initiation requires the convergence of neighboring mitochondria, so mitochondrial transport is essential for mitochondrial fusion to occur. In turn, the fusion of mitochondria also affects their movement. It has been shown that in neurons with a mutation of the gene encoding the main regulatory fusion protein Mitofusin 2 (MFN2), the overall mitochondrial mobility decreases, which leads to disruption of both retrograde and anterograde mitochondrial transport [60]. In a study [61], it was demonstrated that the interaction of MFN2 with the Miro-Milton protein complex was required for the axonal transport of mitochondria.

A direct relationship between the processes of mitophagy and mitochondrial transport has not yet been fully established. At the same time, the mitophagy regulatory enzyme PINK1 is known to be able to bind to the Miro-Milton complex [62]. Also, in a study on a culture of neurons, it was shown that at the early stage of mitophagy, degradation of proteins of the outer mitochondrial membrane developed, among which the transport proteins Miro1 and Miro2 were also present [63]. This circumstance shows that in the course of mitophagy, suppression of mitochondrial transport occurs. As a result, the movement of mitochondria stops due to the detachment of the motor proteins from mi-

tochondria. The roles of the pathological proteins of the described neurodegenerative diseases in the disruption of mitochondrial transport are shown in Fig. 2.

8. Discussion

Despite differences in the type of affected neurons, the variants of initiating pathological factors, and other features that characterize neurodegenerative diseases, there are some common patterns that are characteristic of progressive neuronal damage. In this review, we described the most well-known and common examples of neurodegenerative diseases, and for each of them data have been shown which indicating the occurrence of the mitochondrial transport disorders in neurons, which characterize this pathology as a rule rather than an exception in the pathogenesis of neurodegenerative disorders. Despite the differences, there are also common signs in the mitochondrial transport disorders for the different diseases. First of all, defects in mitochondrial transport are most often initiated by the main characterized mutant proteins associated with the progression of the disease under consideration: A β and tau in AD, huntingtin in HD, α -synuclein in Parkinson's disease, SOD1 in ALS at the same time, one of the general mechanisms of inhibition of mitochondrial transport is the formation of insoluble aggregates from these pathological neurons, which prevent the movement of mitochondria between the neuron's compartments. Another common mechanism of the inhibition of mitochondrial transport is the competitive interaction of mutant proteins with a complex of motor and mitochondrial transport proteins, which leads to detachment of mitochondria from microtubules. That is, mutant proteins can directly inhibit the movement of mitochondria, which

Table 1. The mechanisms of the inhibition of mitochondrial transport in neurodegenerative diseases.

Disease	Inhibitor	Inhibition mechanisms
AD	A β	Possible physical blocking of transport during the formation of A β fibrils
AD	pTau	Glycogen synthase kinase 3 phosphorylates Tau at the AT8 site, leading to Tau fibril formation and microtubule destabilization
PD	α -synuclein	(1) Impaired binding of kinesin to microtubules (2) Possible induction of mutations in the genes of mitochondrial transport proteins
ALS	SOD1	(1) Formation of protein aggregates blocking mitochondrial transport (2) It is possible that aggregates damage mitochondria, which leads to their dysfunction and a lack of ATP for transport
ALS	Profilin1	Disruption of actin cytoskeleton structure
HD	Huntingtin	(1) Formation of protein aggregates blocking mitochondrial transport (2) N-terminal peptide fragments block the binding of mitochondria to motor proteins

AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; SOD1, superoxide dismutase type 1; ATP, adenosine triphosphate.

leads to the understanding that the disruption of mitochondrial transport in neurons is indeed an important pathological event in neurodegenerative diseases. The mechanisms of the inhibition of mitochondrial transport in neurodegenerative diseases are summarized in Table 1.

As noted in the previous section, mitochondrial transport is not an isolated process of mitochondrial dynamics, but works in close relationship with mitochondrial fission and fusion, as well as mitophagy. Accordingly, disorders that directly affect mitochondrial transport in neurons also potentially lead to changes in mitochondrial fusion and fission, and vice versa. These indirect mechanisms of influence may be important for understanding the pathogenesis of neurodegenerative diseases, but require further study. Also of great importance is the accumulation of a large amount of data on impaired axonal movement of mitochondria during the course of the disease in patients with neurodegenerative disorders, since it is still not completely known at what stages of the disease these disorders occur and how they are associated with the clinical manifestations of diseases. The other step in this direction is the study of the modulation of internal apoptosis regulated by the mitochondrial proteins. In connection with the disruption of mitochondrial function, the regulation of internal apoptosis is also disturbed, which leads to the spread of neurodegeneration. To a certain extent, this is facilitated by the main pathological proteins of neurodegenerative diseases: A β , α -synuclein, huntingtin protein, directly or indirectly causing increased apoptosis [64]. It is also pay attention to research the possible impaired mitochondrial transport for other neurodegenerative diseases, which can give a more complete picture of the role of this disorder in pathological processes. Thus, in brain injury, this disorder is based on calcium flux dysregulation caused by the activation of the calpain protein, increased mitochondrial fission, and destruction of the microtubule structure [65].

9. Conclusions

The greater vulnerability of neurons to mitochondrial function identifies mitochondria as one of the key targets of neurodegenerative diseases. At the same time, an important component of the work of mitochondria, especially in neurons, is the correct implementation of mitochondrial transport, which contributes to the required distribution of mitochondria in neuron compartments depending on energy needs. Impaired mitochondrial transport is one of the important events in the pathogenesis of neurodegenerative diseases. At the same time, mutant proteins, which are pathological factors of these diseases, play a key role in the initiation of this disorder. The main mechanisms of inhibition of mitochondrial axonal movement are physical blocking of transport caused by the formation of protein aggregates and competitive binding of mutant proteins to microtubule motor proteins. The development of drugs that inhibit the spread of pathological protein complexes in neurons or their binding to microtubules may be a promising direction for the therapy of neurodegenerative diseases because of the restoration of the energy state of neurons and further decline in neurodegeneration.

Author Contributions

AO, EB and VS designed the review plan and wrote the manuscript. AB, AG and MP aquized, analyzed and interpreted the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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