Review Article

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Mitochondrial dysfunction and energy deprivation in the mechanism of neurodegeneration

Nörodejenerasyon mekanizmasında mitokondriyal fonksiyon bozukluğu ve enerji yoksunluğu

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Abstract: Energy-producing organelles mitochondria are involved in a number of cellular functions. Deregulation of mitochondrial function due to mutations or effects of mitochondrial toxins is proven to be a trigger for diverse pathologies, including neurodegenerative disorders. Despite the extensive research done in the last decades, the mechanisms by which mitochondrial dysfunction leads to neuronal deregulation and cell death have not yet been fully elucidated. Brain cells are specifically dependent on mitochondria due to their high energy demands to maintain neuronal ion gradients and signal transduction, and also, to mediate neuronal health through the processes of mitochondrial calcium homeostasis, mitophagy, mitochondrial reactive oxygen species production and mitochondrial dynamics. Some of these processes have been independently implicated in the mechanism of neuronal loss in neurodegeneration. Moreover, it is increasingly recognised that these processes are interdependent and interact within the mitochondria to ensure proper neuronal function and survival.

Keywords: Neuron; Mitochondria; Neurodegeneration; Energy deprivation; Astrocyte.

Öz: Enerji üreten organeller mitokondriler birçok hücresel fonksiyonda rol oynar. Mitokondriyal toksinlerin mutasyonlara veya etkilerine bağlı olarak mitokondriyal fonksiyonun düzensizleştirilmesinin, nörodejeneratif hastalıklar dahil olmak üzere çeşitli patolojiler için bir tetikleyici olduğu kanıtlanmıştır. Son yıllarda yapılan kapsamlı araştırmalara rağmen, mitokondriyal disfonksiyonun nöronal düzensizliğe ve hücre ölümüne yol açtığı mekanizmalar henüz tam olarak açıklanamamıştır. Beyin hücreleri, nöronal iyon gradyanlarını ve sinyal iletimini sürdürmek için yüksek enerji taleplerinden ve ayrıca mitokondriyal kalsiyum homeostazisi, mitofajisi, mitokondriyal reaktif oksijen türlerinin üretimi ve mitokondriyal dinamiği süreçleri yoluyla nöronal sağlığa aracılık etmek için yüksek enerji taleplerinden dolayı mitokondriye spesifik olarak bağımlıdır. Bu işlemlerin bazıları bağımsız olarak nörodejenerasyondaki nöronal kayıp mekanizmasında yer almıştır. Üstelik, giderek artan bir şekilde, uygun nöronal fonksiyon ve sağkalım sağlamak için bu işlemlerin birbirine bağımlı olduğu ve mitokondri içinde etkileşime girdiği kabul edilmektedir.

Anahtar Kelimeler: Nöron; Mitokondri; Nörodejenerasyon; Enerji yoksunluğu; Astrosit.

Introduction

The brain is an organ which consumes up to 10 times more oxygen and 20% of the total glucose than any other parts of the body. In regard to where most of the oxygen is used for mitochondrial respiration and for ATP production, neurons could be considered as the types of cells with high rate of energy production and the one with the highest rate of energy consumption. The majority of

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ATP in mammalian cells is produced in the processes of glycolysis and oxidative phosphorylation in mitochondria. Most of the mitochondrial reviews on brain pathology introduce these organelles as the "energy plants" of the cells. Clearly, mitochondrial dysfunction directly leads to a decrease in ATP level and consequently to brain cell death. As well, this should be expectable for brain cells that produce more than 90% of their ATP in the process of oxidative phosphorylation [1]. Further to that, the implication of glycolysis in ATP production for neurons has been suggested to be almost none. Despite some controversy regarding the absence of glycolysis in neurons, it is clear that dysfunction in mitochondrial respiration and oxidative phosphorylation should lead to changes in ATP level and, possibly, to energy deprivation and death in neurons.

Mitochondria are organelles with complex functionality that includes number of interdependent processes, loss of function of which can lead to cell death. The major function of mitochondria is ATP production in the F_0-F_1-ATP synthase. This enzyme uses the electrochemical transmembrane potential ($\Delta\Psi m$) generated by the electron transport chain, three of four complexes of which are working as a proton pump. All major mitochondrial processes are linked to the membrane potential such as: ATP production, mitochondrial Ca^{2+} uptake (Ca^{2+} is entering mitochondria via calcium uniporter via an electrogenic mechanism), reactive oxygen species production (ROS), and the initiation of the process of programmed cell death in response to loss of $\Delta\Psi m$. Importantly, fast drop in mitochondrial membrane potential caused by the opening of the permeability transition pore (PTP) could be triggered by mitochondrial calcium overload and ROS production [2]. This renders the deregulation of mitochondrial processes to be especially important in the mechanism of neuronal loss in neurodegeneration. Mitochondrial pathology has been associated with a wide range of neurodegenerative diseases. In primary mitochondrial diseases, diseases caused by mutations in mitochondrial DNA or nuclear DNA encoding mitochondrial proteins, perturbation in mitochondrial function alone is sufficient and necessary to trigger neuronal death [3]. It is less clear whether the mitochondrial dysfunction seen in the sporadic late onset neurodegenerative diseases is necessary for pathogenesis or a bystander effect of disease. In this review we explore the different mechanisms by which mitochondrial function leads to progressive neuronal death in different forms of neurodegeneration and study the evidence for its importance in causing neuronal death.

Pathologies induced by ATP deprivation

Changes in mitochondrial bioenergetics due to damage to the respiratory chain may be caused by mitochondrial DNA mutations or by mutations in nuclear genes encoding proteins of the Electron Transport Chain (ETC) of mitochondria. Mutations in the mtDNA encoding complex I leads to Leber's hereditary optic neuropathy. Mutations in nuclear genes encoding complex I or complex II result in Leigh's syndrome. Complex V mutations cause ataxia and retinitis pigmentosa. Mutations in tRNA genes result in MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), or MERRF (myoclonic epilepsy with ragged red fibers). Mitochondrial diseases manifest themselves with wide ranging neurological symptoms such as loss of vision, deafness, ataxia, seizures, external ophthalmoplegia, and cognitive impairment, but also muscle weakness [4, 5]. However, mutations directly affecting mitochondrial energy production (mostly mtDNA mutations) comprise a relatively small number of neurodegenerative diseases. Moreover, some human neurons with mitochondrial mutations have a higher $\Delta\Psi m$ due to consumption of ATP in F_0-F_1-ATPase to compensate lack of activity ETC by glycolysis [6]. However, despite the high glycolytic activity, stimulation of the cells with these mutations with higher functional activity induces energy deprivation [7].

Mitochondrial uncoupling (transfer of the protons from one site of membrane to another not through F_0-F_1-ATP without ATP synthesis) is important process which helps to maintain thermoregulation in mammalian [8]. It acts through specific family of mitochondrial uncoupling proteins (UCP). However, upregulation of UCP or UCP deregulation could lead to a lower ATP level and further to the development of pathology [9, 10]. In the cells with familial forms of neurodegenerative disorders, such as motoneuron disease (VCP) or parkinsonism (HTRA2 deficiency) profound mitochondrial uncoupling lead to the lack of ATP and neuronal loss [11, 12]. Importantly, uncoupling could be induced by abnormal function of the mitochondrial proteins – F_0-F_1-ATP or ATP/ADP exchanger [11–13].

Oxidative damage and energy deprivation

Mitochondria produce reactive oxygen species (ROS) as a byproduct of ETC and also in some enzymes of TCA cycle or Monoamine oxidase [14]. It makes this organelle the

major candidate for a trigger but also a target of oxidative stress. Oxidation of the proteins, DNA, lipid peroxidation can be a stimulus for cellular dysfunction and induction of cell death by itself [14, 15]. One of the important features of mitochondrial ROS or free radicals from different sources is the fact that they are one of the major triggers for opening of the permeability transition pore (PTP), [16]. Enhanced level of ROS in combination with calcium overload shown to be involved in cell death in Parkinson's disease [17, 18], Alzheimer's disease [19–21], and number of other neurodegenerative disorders [22, 23] (Figure 1).

However, ROS production and oxidative stress can have direct and indirect effects on mitochondrial metabolism that cause energy deprivation in cells. Thus, oxidation of DNA activates the DNA-repairing enzyme Poly-(ADP-ribose) polymerase (PARP) and the consumption of NAD, respectively. It reduces mitochondrial NADH followed by the decrease in ATP production and as result neuronal loss is triggered (Figure 1). This mechanism was shown for Alzheimer's disease [24, 25], Parkinson's disease [26] and excitotoxicity [27, 28].

Oxidative stress in Parkinson's disease could be the reason for inhibition of the glucose transporter that leads to NADH deprivation and inhibition of mitochondrial respiration and further to ATP deprivation [29–31]. In familial form of frontotemporal dementia inhibition of the TCA cycle limits the NADH-a substrate availability for the electron transport chain, inhibits mitochondrial respiration, utilization of ATP in glycolysis for the maintenance of $\Delta\Psi m$ and overproduces ROS [23]. It is interesting that in another form of tauopathy-progressive supranuclear palsy (PSP), the mechanism of mitochondrial pathology is similar, but the most important is that ROS overproduction and ATP depletion in mesenchymal stem cells with this pathology lead to a reduced ability of this type of cells for differentiation [32].

It should be noted that production of GSH upon increased oxidative stress in the cell is also occurring at an energy cost (in the form of NADPH) and it could also be a substrate limiting factor for the mitochondrial ATP production and thus induces neurodegeneration [33, 34] (Figure 1).

Cellular quality control

Autophagy is a process whereby cellular components are degraded by merging into the autophagosomes. Autophagosomes fuse with lysosomes, which contain hydrolytic enzymes that break down cellular components.

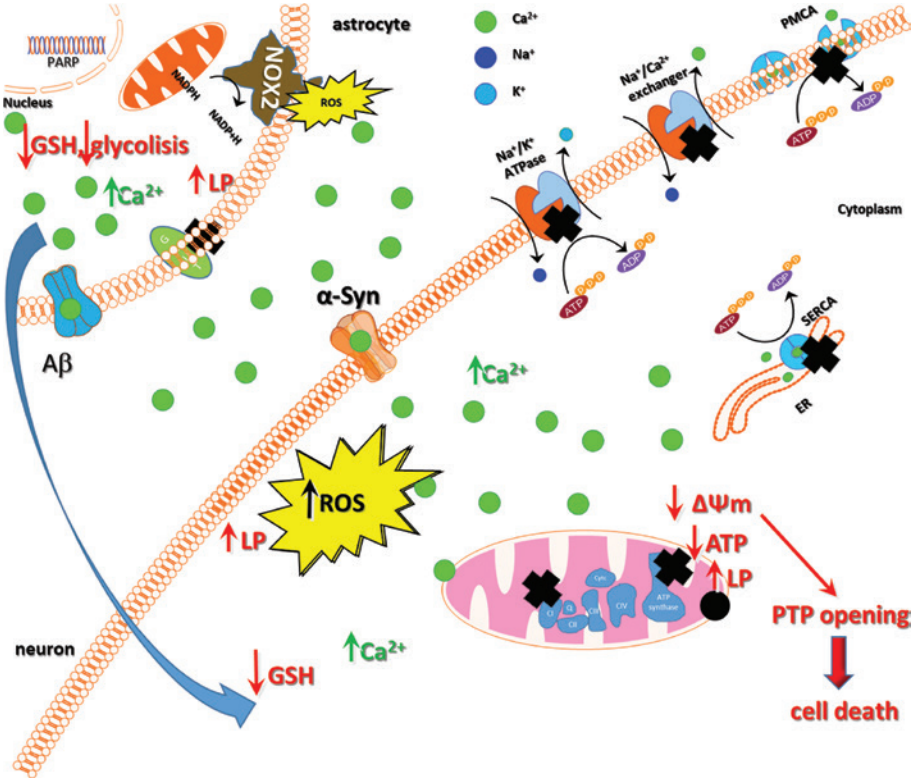

Figure 1: The role of mitochondria in cellular mechanism of neurodegeneration. Mitochondria interact with various cellular processes and lead to cell death.

Selective autophagic degradation of mitochondria, termed mitophagy, is necessary for the sustained turnover of mitochondria, the adjustment of mitochondrion numbers to changing metabolic demands, or the removal of damaged mitochondria [35].

Functional mitochondrial alterations, such as loss of mitochondrial potential or permeabilization of the outer mitochondria membrane (OMM), trigger mitophagy, probably in an attempt to limit potential deleterious effects associated with damaged mitochondria such as excessive ROS production or enhanced release of mitochondrial pro-apoptotic factors [36].

Most mitophagy studies in mammalian cells have focused on PTEN-induced putative kinase protein 1 (PINK1)/Parkin-dependent mitochondrial degradation by autophagy. Parkin and PINK1 are encoded by the PARK2 and PARK6 genes, respectively; both are responsible for familial Parkinson's disease (PD) and have been reported to be associated with mitophagy [37, 38]. PINK1 is expressed in the cytoplasm and constitutively translocates into the mitochondrial inner membrane (IMM) where it is promptly degraded by the mitochondrial inner membrane rhomboid protease presenilin-associated rhomboid-like protein (PARL) [30, 38–40]. When mitochondria lose their membrane potential, PINK1 can target to the mitochondria, but cannot translocate across the mitochondrial outer membrane; therefore, it accumulates there. Accordingly, only depolarized mitochondria are marked by PINK1 accumulation. Parkin translocates to mitochondria in a PINK1-dependent manner [37, 38, 41, 42]. Further, Parkin triggers the ubiquitination of many mitochondrial proteins such as mitochondrial assembly regulatory factor (MARF) in flies or mitofusin 1, mitofusin 2, and voltage-dependent anion channel 1 (VDAC1) in mammalian cells [43–45]. In PD, overall autophagic degradation, including mitophagy, seems to be impaired. Indeed, in experimental PD models and *post mortem* PD brain samples, abnormal mitochondria readily accumulate in the cytosol of affected neurons [46, 47], indicating that it cannot be efficiently degraded through mitophagy. Accumulation of dysfunctional mitochondria may contribute to dopaminergic cell death by an increased production of ROS and an enhanced release of mitochondrial apoptogenic factors [48–51]. Defective autophagy in PD originates, at least in part [51], from a pathogenic reduction in the amount of functional lysosomes [46, 52, 53]. Lysosomal breakdown in PD appears secondary to the abnormal permeabilization of lysosomal membranes by mitochondrially driven oxidative attack [46], leading to a vicious cycle in which increased ROS production from dysfunctional mitochondria contributes to defective autophagy by oxidatively damaging lysosomal membranes, thereby resulting in a further accumulation of altered mitochondria which cannot be degraded through mitophagy. Supporting a pathogenic role for decreased autophagy/mitophagy in PD, pharmacological restoration of lysosomal-mediated degradation by rapamycin is able to reduce the cytosolic accumulation of undegraded autophagosomes (which contain abnormal mitochondria) and attenuate dopaminergic neurodegeneration in MPTP-treated mice [46, 54]. Besides a general impairment of autophagic degradation, specific defects in mitophagy may also occur in PD.

For instance, PD-linked mutations in PINK1 and Parkin have been shown to disrupt the coordinated normal regulatory role of these molecules at promoting autophagic degradation of dysfunctional mitochondria, thereby leading to defective mitophagy [38, 44, 55].

Parkin has been reported to be recruited to mitochondria, which is followed by a stimulation of mitochondrial autophagy. Relocation of Parkin to mitochondria induced by a collapse of $\Delta\Psi m$ relies on PINK1 expression and that overexpression of WT but not of mutated PINK1 causes Parkin translocation to mitochondria, even in cells with normal $\Delta\Psi m$. Co-overexpression of Parkin and PINK1 collapses the normal tubular mitochondrial network into mitochondrial aggregates and/or large perinuclear clusters, many of which are surrounded by autophagic vacuoles [55].

It should be noted that some specific pathways of mitophagy and autophagy could be corrected by other ones. Thus, acidification of the cytosol induces autophagy and PINK1-dependent and independent mitophagy which potentially can activate mitophagy in PINK1 or PARKIN form of pathology [56].

However, pathological mutation in p62 – one of the pathways of autophagy lead to motoneuron disease. It induces mitochondrial dysfunction due to substrate deprivation and ATP level decrease. Importantly, it can be restored by the use of Nrf2 activator [57]. Because Nrf2 controls production of mitochondrial substrates, one could assume that it also could be cell protective in PINK1 model of Parkinson's disease [58–60]. It should be noted that changes in autophagy or mitophagy are less likely to be the initial trigger of neurodegeneration, but mitochondrial dysfunction of non-removed damaged mitochondria or misfolded proteins could induce pathological cascades which are usually described for neurodegenerative disorders [61].

Mitochondrial Ca^{2+} and neurodegeneration

Mitochondrial calcium overload is one of the major triggers for cell death in neurodegeneration and many other

pathologies [62]. Pathology in mitochondrial transport, and, specifically in enzyme responsible for calcium efflux from mitochondria could lead to neurodegeneration in Parkinson's disease [29, 63]. These conditions could potentially be corrected by the limitation but not by the complete inhibition of calcium uptake by mitochondria with pharmacological compounds [64]. However, neurons spend ~80–90% of their total ATP for the maintenance of calcium homeostasis. Consider this, any activation of calcium signal in the cells with mitochondrial dysfunction or inhibition of mitochondria with environmental toxins may lead to a cell collapse due to ATP deprivation [7, 65, 66] (Figure 1).

The role of mitochondria is central to the viability and vitality of the organism. Proper functioning of these organelles is essential for the compatibility to life of every cell and any dysfunction of these organelles will result in the reduction in the efficiency of mitochondria to produce ATP. Neurons are heavily dependent on the OXPHOS for the production of their ATP and any disturbance in this process, both ways, would have detrimental effects for the cell, as OXPHOS plays a central role as well in other processes as calcium buffering, ROS production, signaling and programmed cell death. Thus, any unbalances in the process of OXPHOS would render neurons extremely susceptible to the development of a disease condition, e.g. neurodegeneration. Therefore, substances, able to balance out this process hold a high therapeutic potential in the field of brain diseases.

Conflict of interest: Authors have no conflict of interest.

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