**Advances in Bioresearch**
Adv. Biores., Vol 12 (1) January 2021: 234-244

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.12.1.234244

Advances in Bioresearch

## REVIEW ARTICLE

# The Importance of Mitochondrial Function in Neurons: Focus on Therapeutic Targets in Neurodegeneration

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**ABSTRACT**
*The integrity of the mitochondrial function is important in cell life. Mitochondria are very coordinated, interconnected organelle that stimulate cellular activities and contribute to programme death by initiating regulated apoptotic cascades. The mitochondrial turmoil in the system can therefore correlate with cell disruption or even death. Approximately one-fifth of the body's energy consumption is responsible for brain energy masses to carry out neurotransmission and other developmental processes. Approximately one-fifth of the body's energy consumption is responsible for brain energy masses to carry out neurotransmission and other developmental processes. Mitochondrium is the key intercellular organelle that controls neuronal energy and survival. This review aims to connect our understanding of structural-functional integrity to healthy neurons. Clarify mitochondrial dynamics disturbances which lead to neurodegenerative diseases. This analysis also seeks to explain the key facets of mitochondrial biology as a critical step in our understanding of the neuronal health contribution of mitochondria. Influence of cell signaling and the control of mitochondrial activity, mitochondrial calcium intake, while over-accumulation of mitochondrial calcium has a significant effect on neuronal production and activity. Again mitochondria are the key reservoirs and the primary targets of free radical species. Various pharmacological techniques were investigated to deal with various cellular complex mitochondrial dysfunctions. Eventually, debate is expanded to consider the significance of nutrition in enhancing the mitochondrial functions coordinated with neuronal health.*
**Keywords:** Mitochondrial dynamics, neuronal health, synapse, neurodegenerative disease, nutrition

Received 29.11.2020 Revised 28.12.2020 Accepted 04.01.2021

**How to cite this article:**
S P. Badole, N L. Wankhede, P L. Tiwari, M D. Umare, B G. Taksande, A B. Upaganlawar, M J. Umekar, M B. Kale. The Importance of Mitochondrial Function in Neurons: Focus on Therapeutic Targets in Neurodegeneration . Adv. Biores., Vol 12 (1) January 2021: 234-244

## INTRODUCTION

In various metabolic processes, mitochondria are penetrative and multifunctional organelle, particularly energy generation and bimolecular synthesis. Intracellular $Ca^{2+}$ homeostasis, steroid synthesis, free radical generation and apoptotic cell deaths are also centralized by mitochondria. Consequently, mitochondrial dysfunction has a detrimental impact on cell integrity, and can be objectively associated with ageing, metabolic and degenerative disease in higher-species and humans[1]. Highly dynamic organelles fuse, split, transmit and replicate in most mitochondria cells, and are typically associated with a small life span shorter than that of host cells [2]. In addition to harboring initiative enzymes which catalyze synthesis of essential byproducts (e.g., heme and urea), mitochondria successfully lead to cell signaling and maintaining redox cellular condition and homeostasis of energy with concomitant thermogenesis [3]. The current review aims to summarize neuronal health associated with mitochondrial function. We expect in most ways that the basic functional properties of mitochondria in neurons mimic those in other types of cells. Nonetheless, the challenges posed by having to move organelles across extreme distances, and also preserving cellular homeostasis in very large and highly active cells, are

peculiar to neurons, rendering mitochondrial function of special interest in these cells. Neuronal mitochondrial dynamics is a simple but highly nuanced process with broad ramifications for normal and abnormal cellular and mitochondrial activity [2]. Trafficking in mitochondria is very important in neurons and particularly in their axons and dendrites. [4].

Survival requires cells to make organized economic use of their resources. In this link mitochondria is similar to high-energy subcellular sites. The central nervous system requires mitochondria; despite just 2 % of total body weight, the human brain absorbs 20% of the remaining metabolism resources [5]. The key part of the central nervous system is the production, distribution and transmission of impulses. The primary ions, Na+, K+ and Ca2+ in the neuronal plasma membrane can only be done if they have an electromagnetic imbalance that requires constant energy consumption. That's why 50%-60% of the total brain-produced adenosine triphosphate (ATP) is used for ion movements [6]. Indeed, neuronal processes have greatest demand for mitochondrial energy. Most of the studies have shown a lack of uniform energy demand in the human brain and are predicted to increase in cortical grey matter ( GM) compared to white matter (WM), based upon the fundamental assumption that GM tissue associated with large synapsis populations and intensive neuroactivity needs more energy compared to WM. In addition, quantitative imaging research showed that 4.7 billion ATP molecules per second are absorbed by a resting cortical neuron [7]. Since the oxidative metabolism of most neuronal ATPs depends critically on mitochondrial function and oxygen supply [8]. Conversely, neuronal activity and the survival of mitochondrial dysfunction are very sensitive [9]. To proceed with complex organ operations, considerable amount of energy is required and mitochondrial dysfunction interrupts energy flow to the detriment of biochemical operations in complex biological processes. This affects the cell cycle and contributes to increased apoptosis (ageing) and cancer development. With this mitochondrial malfunction, several human diseases such as diabetes, atherosclerosis, heart failure, myocardial infarction, stroke, neurodegenerative and multi-organ failure trauma also grow [3].

In order to understand neuronal physiology and pathophysiology in particular neurological disorders, it is important to provide detailed explication of interplay between mitochondrial control, energy metabolism and neuronal activation. In this review we discussed normal mitochondrial and neuronal physiology and attempts to link plethora of information on role of mitochondria in neuronal health. Furthermore, mitochondrial dysfunction relates with neuronal health and associated neurodegenerative diseases. Finally, the nutritional function of healthy mitochondria is being addressed with healthy neurons.

## MITOCHONDRIA: THE HUB OF ENERGY / DYNAMIC CELL ORGANELLE

Mitochondria are the most critical sources of cellular energy and do so with high efficiency. By connecting electron transportation with proton gradients generation for oxidative phosphorylation, Mitochondrion generates approximately 15 times more ATP in glycolytic cells via the glycolytic pathway [10]. Mitochondria consist of two independent and functionally distinct outer membrane (OM) and inner membrane (IM) that encapsulate the compartments of the intermembrane space (IMS) and matrix [11]. The inner mitochondrium membrane typically consists of many infoldings that form structures containing a variety of membrane-bound mitochondrial enzymes. The cristae arrangement tends to vary greatly between different tissues, and the functionality of these structural variations is quite uncertain [12].

### Mitochondrial Dynamics

Mitochondria, which can rapidly alter form and function to satisfy physiological requiring of the cell, are tightly regulated and multi-faceted organelles. These processes are known collectively as mitochondrial dynamics because they are necessary to understand many biological processes such as preserving mitochondrial functions, apoptosis and ageing. In a cell i.e. fission and fusion, two dominant factors mainly control changes in the amount and size of mitochondria [12]. Overall, fission and fusion processes regulated by various protein component (Figure 1).

 

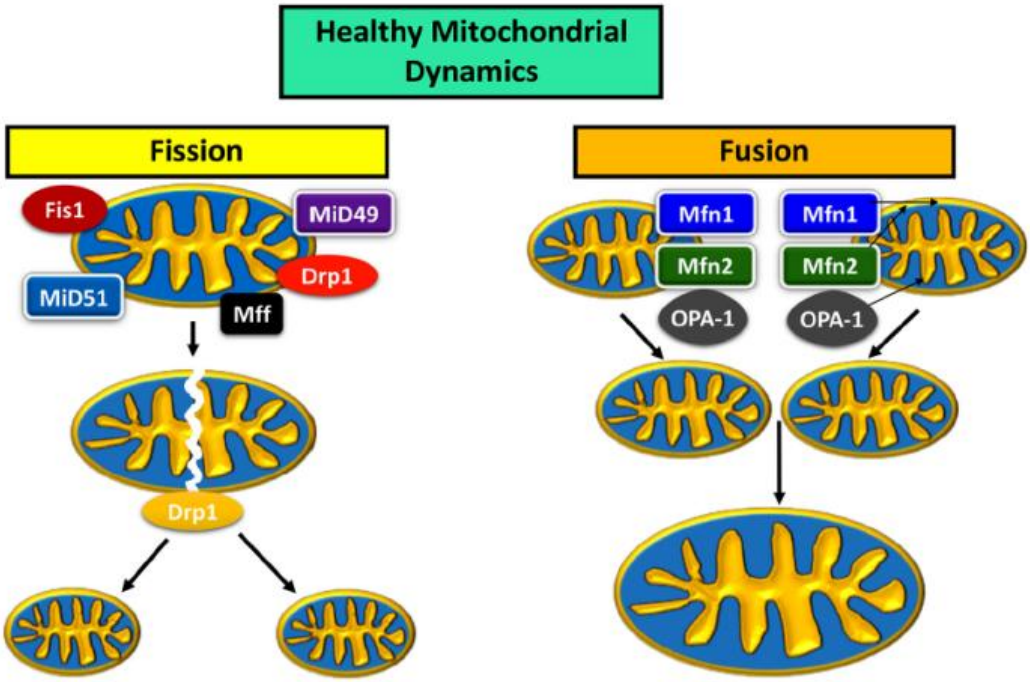


**Figure 1.** Mitochondrial dynamics
Fis1- Mitochondrial fission 1, MiD51-Mitochondrial Dynamic Protein 51, MiD 49- Mitochondrial Dynamic Protein 49, Drp1- Dynamin-related protein 1, Mff-Mitochondrial fission factor, Mfn 1-Mitofusion 1, Mfn 2- Mitofusion 2, OPA-1- Optic Atrophy 1, OPA-2- Optic Atrophy 2

The plasma membrane is wrapped in the components in the cell during endocytosis and then sprayed to create a vesicle through which the cytosol is transferred. This membrane scission is done by dynamin superfamily members which are versatile broad GTPases (guanosinetriphosphatases) that mediate different processes of membrane remodeling in eukaryotic cells. Dynamine, a mechanical enzyme that narrows and then cleaves vesicles to the neck and separates membranes. Dynamin-related protein 1 (Drp1) mainly present in cytosol of mammalian cells and Dnm1 in yeast cells are the key mediators of mitochondrial division in most eukaryotic organisms and yeast cells respectively. These are soluble protein that includes an N-terminal GTPase, a middle domain and an effector C-terminal GTPase domain active in self-assembly [13].
The process for recruiting Drp1 for spiral development and mitochondrial fission into the mitochondria remains unknown [14]. The role of mitochondrial fission is better understood in yeast [13]. Initially, dynamin is recruited to the OMM with the help of adaptor proteins mitochondrial fission 1 (Fis1) and mitochondrial division protein 1 (Mdv1). Fis1 is a tiny protein in the outer membrane. Its N-terminal domain faces the cytosol, forming a six-helix bundle with repeat tandem tetratricopeptide (TPR) motifs which provides an interface for interaction of Mdv1 protein. Mdv1 includes a Fis1 binding N-terminal segment, a heptad repeat area that mediates homo-oligomeric interactions, and a dynamin-interacting with WD40 C-terminal repeat domain [15]. Drp1 and the related division proteins establish pressure for division at the target position creating a depression in the mitochondrial membrane. Depression rises until the membranes fuse with each other on either side of the region, allowing the mitochondrion to become two mitochondria [16]. Hence, a mutation in any of these proteins leads to blocking of mitochondrial division.
Mitochondrial fusion and fission are interdependent processes. Membrane fusion is fundamental process which are part of various activities in eukaryotic cells like fusion of transport vesicles with cell organelles, gametes fusion during fertilization etc. [14]. In mammals, the process of mitochondrial fusion is regulated by three GTPase in dynamin superfamily i.e. Mfn1, Mfn2 (Mitofusion 1 and 2) and OPA1 (Optic atrophy 1). Cell-free fusion assays indicate that Mfn1 and 2 mediate fusion of OMM while OPA1 mediates fusion of the inner mitochondrial membranes. OPA1 is situated on the mitochondrial membrane inside, towards intermembranespace. OPA1 is also responsible for the preservation of mtDNA, as well as IMM cristae structural integrity. Around their OMM, the two mitochondria first attach, and Mfn1 and 2 function

 

to connect the OMM, in which OPA1 works to link the IMM. The merger of two mitochondria raises the amount of mtDNA copies and rejuvenates the organelle components [16].

**Mitophagy**

Autophagy is the catabolism process of cellular components, such as cytosols, organels and protein aggregates, through their encapsulation with a double-membrane structure known as the autophagosome[17]. Mitochondrial autophagy also known as "mitophagy" refers to the destruction of mitochondria via autophagy is thus considered to be the core mechanism of both mitochondrial quality and quantity control [18]. Some developmental processes involve removal of non-damaged mitochondria which are essential for tissue and organ development. Paternal mitochondria in fertilized oocytes and during erythrocyte differentiation mitophagy eliminate healthy mitochondria in programmed fashion [19]. Recent findings indicate that mitophagy is triggered by stable aggregation of putative kinase protein 1 (PINK1) induced by PTEN on the surface of impaired mitochondria, accompanied by Parkin recruitment from the cytosol to the mitochondria. Parkin, an E3 ubiquitin ligase, then ubiquitinates a variety of mitochondrial OM proteins and stimulates the ubiquitin proteasome network that acts to degrade mitochondrial OM proteins along with the AAA ATPase p97. This leads to formation of autophagosome which engulf damaged mitochondria [15]. This pathway has been suggested to be important to mitophagy in response to acute mitochondrial stresses.There are some other identified pathways as well. The mitochondrial OM protein, the BCL-2 homology 3 (BH3)-containing NIP3-like protein X (NIX, also named BNIP3L), has been shown to play an important role in erythrocyte removal of mitochondria [20]. NIX comprises an amino terminal LC3-interacting region (LIR) that attaches to LC3 on the isolation membranes [21]. This helps NIX to function as a selective mitophagy receptor that binds the autophagy system physically with the mitochondrial surface of erythroid cells. The mitochondrial OM protein suggested as a mitophagy receptor is FUN14 domain containing 1 (FUNDC1), which controls mitochondrial autophagy degradation in reaction to hypoxia. FUNDC1 has the required LIR for LC3 recruitment [22]. Under hypoxic circumstances, the mitochondrial phosphatase phosphoglyceratemutase family member 5 (PGAM5) dephosphorylated this LIR, thereby increasing its physical interaction with LC3 and facilitating mitophagy (Figure 2)[23].

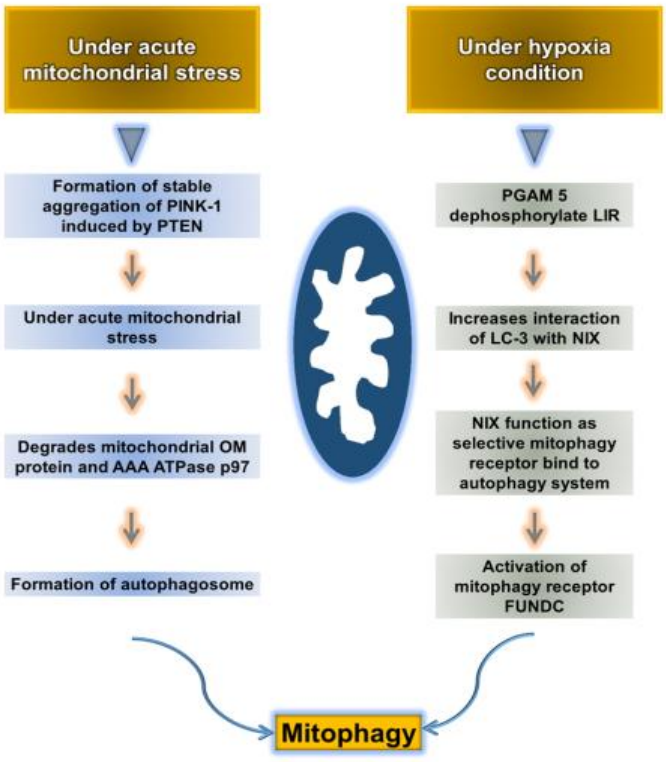


**Figure 2.** Schematic view of factor inducing mitophagy

PINK1- Putative Kinase Protein 1, PTEN- Phosphatase and Tensin Homolog, OM-Outer Membrane, PGAM5- PhosphoglycerateMutase Family Member 5, LIR- LC3-interacting region, FUNDC- FUN14 Domain Containing

 

Mitophagy actively destroys mitochondria that are damaged by a laser irradiation in hepatocytes. Studies of pancreatic b-cells and COS7 cells indicate that mitochondrial fission, with one depolarized daughter mitochondrion and one hyperpolarized mitochondrion, will create unequal items. These depolarized mitochondria are much less likely to fuse, have decreased OPA1 protein amounts, and ultimately autophagocytised. Such mitophagy is based on fusion depletion and fission involvement, as OPA1-overexpression, Fis1 RNAi, and Drp1 dominant-negative expression both minimize mitophagy rates. Through this way, oxidized proteins accumulate as mitophagy is disrupted, and cell respiration and insulin secretion decline. It should be noted that while mitochondrial fragmentation is permissive for mitophagy, but it is not an adequate signal for mitophagy[24].

**Mitochondria in Neurons**

Neurons are polarized cells that contain relatively small cell body, dendrites and a slender axon that, in some peripheral nerves, can extend up to one meter long. These are extremely developed cells that interact with one another at synapses by electrical and chemical processes. At chemical synapses, synaptic vesicles carrying a neurotransmitter are quickly expelled into the synaptic cleft in response to an accumulation of $Ca^{2+}$ ions through voltage-gated $Ca^{2+}$ channels, activated by action potentials [23].

Mitochondria apart from production of ATP also participate in synaptic plasticity for the short term and regulate neurotransmission by buffering presynaptic $Ca^{2+}$. The depletion of mitochondria from axonal terminals is also likely to impede synaptic transmission due to inadequate ATP supply or decreased $Ca^{2+}$ buffer ability. Neurons are post mitotic cells which live during the lifetime of organism. If a mitochondrion is old or damaged, it must be disabled. Mitochondria often change their motility and distribution under such stress situations or compromise their integrity. Therefore, efficient control of mitochondrial trafficking and anchoring is necessary to hire and redistribute mitochondria to meet instructed metabolic needs and to eliminate aged and weakened mitochondria and rejuvenate healthy mitochondria at distal terminals [25](Figure 3).

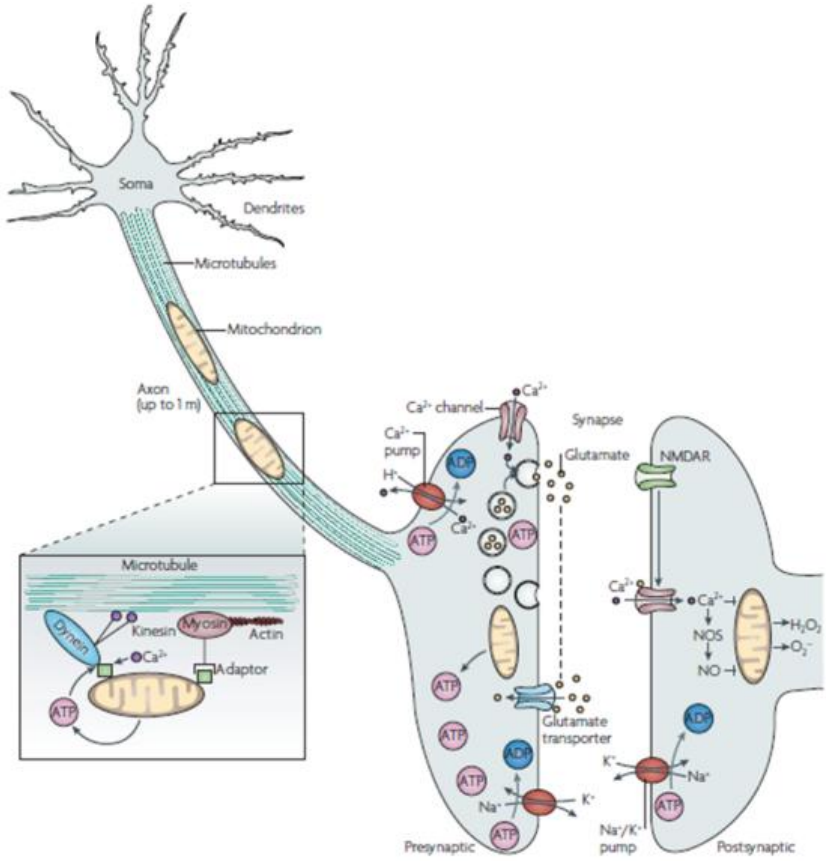


Figure 3. Mitochondria in neuron

Ca2+ - Calcium, H+- Proton, K+- Potassium, Na+- Potassium, Na+/ K+ - Sodium Potassium Pump, O2- - Superoxide, H2O2 - Hydrogen Peroxide, NOS - Nitric Oxide Synthase, NO – Nitric Oxide, NMDAR - N-methyl-D-aspartate Receptor, ADP – Adenosine Diphosphate, ATP – Adenosine Triphosphate

**Role of Mitochondria in Neuronal Development**

Mammalian neurogenesis begins at the prenatal stage and continues to the postnatal stage. Neural stem cells (NSCs) called radial glial cells (RGCs) live in the ventricular region in early fetal development, and contain neurons that form the neocortex[26]. Diverse molecular pathways modulate Neurogenesis. A representative mechanism regulating neurogenesis is the regulation of transcriptional genes [27,28]. Transcription factors contribute during neuronal development to a change in the cell transcriptome profile. Extrinsic influences including signaling molecules can have an impact on other neurogenesis steps. Interest in studying the neurogenesis mechanisms has recently expanded to lipid metabolism. Fatty acid oxidation is important for the conservation and proliferation of neural progenitor cells (NPCs) in adult hippocampal neurogenesis, and lipogenesis is critical for neuronal differentiation [29,30]. Furthermore, neurons display a complex morphology, highly compartmentalized according to their cell type and brain region in long neuronal segments, thus demanding a proper network of mitochondrial trafficking. In addition, synapses, which are mostly found at cell extremities, need the maximum ATP levels. Hence, several processes of neural development depend on mitochondrial control, including self-regeneration and NSC differentiation, neurogenesis, axonal and dendritic expansion, and synaptic formation and reorganization [31].

Most of findings have documented morphological differences in mitochondria as NSCs in the developing brain and adult brain are separated. The separated neuronal mitochondria show an elongated morphology in the infant brain and a broader and strongly elongated morphology in the adult hippocampus. Morphological changes in mitochondria throughout neurogenesis demonstrate mitochondrial maturation and indicate the metabolic shift of cells from glycolysis to oxidative phosphorylation in order to increase bioenergetics [32].

**Mitochondrial Apoptosis and Neurons**

Many triggers that causes intracellular damage, like damage to DNA, calcium overload, and cytotoxic drugs can prompt the mitochondrial apoptosis, known as the intrinsic apoptosis pathway. This contributes to the activation of the Bcl-2 family's pro-apoptotic proteins, which would then cause mitochondrial destabilization and start the reaction chain [33]. Besides becoming an important member of the apoptotic system, and the "cell superpower" by regulating anabolic / catabolic processes, mitochondria could also have additional regulatory roles in other cellular contexts. In addition, it has been shown that mitochondria controls proliferation and differentiation, as well as stem cell metabolic flipping, and ageing. It has also been shown that productive neuronal differentiation and development rely on integrity of mtDNA and the change from glycolysis to aerobic respiration [34,35]. Ironically, it has been shown that selected members of the Bcl-2 family, the main players of apoptosis machinery, also function as coordinators of mitochondria-to-nucleus. In addition, these family members are known to toggle between mitochondria, cytosol and nucleus, having pivotal roles in the regulation of mitochondrial activity / integrity and cell cycle status through ROS [36]. Particularly, an optimized mitochondrial specialization often tends to synchronize the cellular interaction of a specific lineage. The Bcl-2 family member, Bcl-XL, influences immortalized human neuronal growth, thus supporting the proliferation ability of neuronal progenitors and enabling neuronal maturation rather than glial generation [37].

**Mitochondrial ROS and Neurons**

While other ROS processing sites, including cytosol, peroxisomes and endoplasmic reticulum, have been established in recent years, the mitochondria electron transport chain (ETC) still represents the main pathway for ROS generation under physiological conditions [31]. Curiously, an increasing evidence points to an interrelationship between ROS production and signaling, self-renewal and differentiation of neural stem and progenitor cells in the CNS. Throughout, emerging neurons exhibit higher levels of ROS and mitochondrial respiratory chain components in comparison to undifferentiated cells, without exposing oxidative stress features [38]. Moreover, early stem cells and NSCs present higher antioxidant capacity than more differentiated progenitors, and offer more protection from oxidative pressure interceded cell demise [39]. Moreover, the neurogenic basic helix – loop – helix (bHLH) key transcription NeuroD6 plays a major role in ROS equilibrium, results in activation of associate degree anti-oxidant response [40].Interestingly, it has been shown that ROS affects the selection among neuronal and astroglial differentiation. The induction of mild oxidative stress triggers Sirt1 activation and next Hes1-mediated transcriptional inhibition of Mash1, main to elevated astrogliogenesis. At the other hand, p53 reduces mitochondrial ROS and interferes with neural differentiation ability by promoting neuronal rather than astroglial conversion [41]. Over the last few years, it has been made clear that NSC's fate regulation is reliant on a very nuanced and context-dependent process mediated by ROS. In this manner, a strong consensus remains to be reached on the amount of ROS needed by the stem cells for successful neuronal, astroglial or oligodendrocyte production and function [31].

 

**Role of Mitochondria in Synaptic Communication**

Regulation of events at the presynaptic terminal of am synapse is important for determining whether a neuronal pathway will become reinforced during such processes as learning and the making of new memories. Alternatively, biochemical synapse events may trigger synapse to fail during neurodegeneration, such as AD, or in acute injury, like brain ischemia [42].

Synapses allow neurons to interact with each other and are therefore a necessity for normal brain function. Presynaptically, this contact involves energy and causes large variations in calcium concentrations. The balance of electrochemical gradients and the release and recycling of synaptic vesicles are both energy-intensive processes. Neurons therefore need a mechanism by which local energy use can be spatially matched to the output of energy and the buffer of $Ca^{2+.}$ Mitochondria are best suited to accommodate this spatial variation in metabolic demand and $Ca^{2+}$ buffering as they produce ATP (through oxidative phosphorylation) and carry $Ca^{2+}$ into the mitochondrial matrix [43]. Mitochondria at synapse may undergo functional and structural specialization. Synaptic mitochondria are morphologically distinct from mitochondria elsewhere, are smaller and have enhanced motility and have a higher proportion of cristae to outer membrane surface area associated with higher metabolic demand. Synaptic mitochondria also has a peculiar metabolic profile: they are more prone to complex 1 inhibition and $Ca^{2+}$ overload than nonsynaptic mitochondria, likely due to its relative isolation, older age and cumulative exposure to oxidative damage, rendering them vulnerable to elimination [44–46].

To order for neuronal circuits to operate properly, neuronal connections need to be formed and renovate correctly to response to rising demands. Local protein synthesis is progressively recognized as playing a crucial role in the formation and redecorating of synapses mitochondria are excellent candidates for energy supply to power these processes [47]. Glycolysis is capable of releasing cellular energy directly from glucose breakdown, and some neuronal features have a preference for this fuel generation method. For example, the rapid axonal transport of vesicles depends heavily on glycolysis and the vesicles are equipped with their own set of glycolytic enzymes. During growth, however, neurons (from rodents at least) use ketone bodies as their primary energy source, requiring mitochondria for metabolism and eventual release of ATP. In addition, induced pluripotent stem cells shift from glycolysis to oxidative phosphorylation as they differentiate into neurons [48,49].

**Mitochondrial Defects: A Window to Neurodegeneration**

The central nervous system (CNS) has an extremely high demand for oxygen, and its excess of phospholipids makes it particularly susceptible to lipid peroxidation. These qualities collectively make it more sensitive to mitochondrial oxidative stress, particularly since the blood-brain barrier restricts the eviction of ROS and antioxidants into systemic circulation. The intimate relationship between oxidative stress and neurodegeneration in AD is clearly demonstrated by the presence of oxidative stress markers in affected brains [50–52]. This oxidative stress, which goes hand in hand with the downregulation of the mitochondrial antioxidant superoxidant dismutase, is exacerbated by the activation of the microglia amyloid-β (Aβ) protein fragment, which produces ROS. Although activated microglia can clear Aβ, the generated ROS induce mitochondrial dysfunction, which decreases antiapoptoticBcl-xL activity and activates caspase-3 [53]. In PD, mitochondrial dysfunction is associated with reduced activity of the mitochondrial complex I, which promotes synuclein aggregation and development of disease. The removal of this aggregate restores normal mitochondrial metabolism, indicating essential cellular processes that unplug and decay protein aggregates constantly [54,55]. PINK 1 is especially suggested as a major molecular checkpoint for preserving function and integrity of the mitochondria. In addition to those PD-related proteins, a novel interacting parkin substrate (PARIS) has recently been reported. PARIS negatively regulated PGC-1α and NRF-1 expression and PARIS overexpression increased selective cell death of dopaminergic neuronal cells [56,57]. Considering the functional interaction of certain proteins could enlighten the molecular mechanism of mitochondrial driven neurodegeneration. In addition, disrupted mitochondrial fusion resulting from OPA1 mutations causes optic atrophy [58], and impairments from mutations in Mfn2 can induce Charcot–Marie–Tooth disease type 2A (a familial neuropathy) (Figure 4) [59].

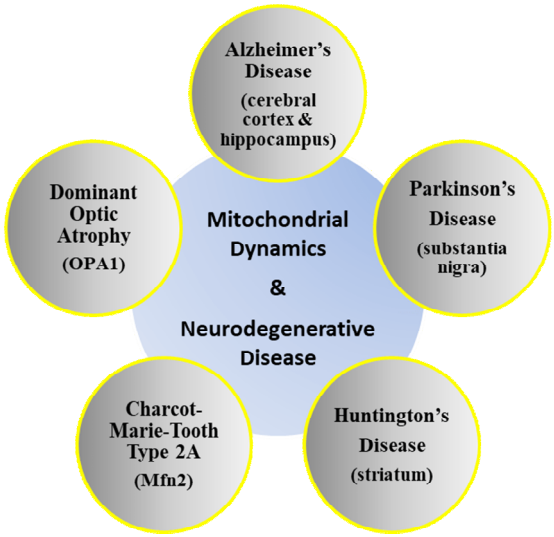


**Figure 4.** Mitochondrial dynamics and associated neurodegenerative disease
OPA1 – Optic Atrophy 1, Mfn2 - Mitofusion 2

**Mitochondrial Therapeutics in Neurodegenration**

The restoration of mitochondrial function by pharmacological approach is a potentially effective way to treat a wide range of conditions that include mitochondrial dysfunction. The neurodegenerative disease associated with mitochondrial malfunction requires repairing and restoring mitochondrial function. A couple of strategies are already being devised that open up ways of controlling mitochondrial functions and may facilitate selective neuronal shield in neurodegenerative disease care.

a) rhTFAM

A recent study suggested that the human mitochondrial genome can be engineered from outside the cell to alter the expression and increase the production of mitochondrial energy. Mitochondrial transcription factor A (TFAM), a protein that occurs naturally, can be engineered to easily move through cell membranes and enter mitochondria. rhTFAM has been shown to function on cultured cells with both a mitochondrial DNA disorder and laboratory mice. rhTFAM reaches and energizes the mitochondrial mice's DNA allowing these mice to run twice as long on their spinning rods compare to control group cohort [60].

b) MitoQ

MitoQ is a mitochondrially targeted form of coenzyme Q10 (a key part of the mitochondrial electron transport chain and an antioxidant) which has been shown to have positive effects in animal neurodegeneration models, with amplification of neuropathology and synaptic shortfalls in AD and Huntington disease transgenic mouse models [61].

c) Mitochondrial division inhibitor 1

The modification of the mitochondrial fission-fusion equilibrium may also be used therapeutically. For example, in a mouse model of AD, genetic depletion of Drp1 reduces mitochondrial dysfunction and improves synaptic function. Mitochondrial division inhibitor 1 (Mdivi1), commonly known as an inhibitor of Drp1, balances PINK1 mediated mitochondrial dysfunction and ameliorates mitochondrial dysfunction, synaptic impairment and cognitive deficits in an AD mouse model. Mdivi1 has also recently been shown to be a complex I inhibitor [62].

d) Resveratrol

Resveratrol polyphenol stilbene molecule has recently gained significant attention and interest as a novel antioxidant drug. Specific enhancement of mitochondrial biogenesis and oxidative ability can be accomplished with resveratrol, which promotes sirtuin 1 activity and thereby imitating calorie restriction which improves longevity in a variety of organisms [63,64]. Resveratrol has also shown promise in a recent small clinical trial of AD, minimizing cognitive loss and the inflammatory indicators of the cerebrospinal fluid [65].

e) Dimebon

Dimebon was initially used as an anti-histaminergic drug. Recent findings confirms its neuroprotective role. It has been shown that dimebon can inhibit mitochondrial transition pore permeability and defend neuronal mitochondria from mutant proteins such as Aβ, Huntingtin mutant, and other toxic mitochondrial insults [66].

 

## CONCLUSION

Impairment of mitochondrial function is obviously one of the main pathogenic factors in a spectrum of neurodegenerative disorders. Mitochondrial function and actions are fundamental to human physiology, and thus mitochondrial impairment has been identified in a wide variety of diseases that include all areas of medicine. Neurodegenerative disorders are currently a significant cause of worry in health care professions. Of course there are more. The basic pathophysiological mechanisms in most of the neuronal diseases remain skeptical, but in all, mitochondrial abnormalities have been implicated at some stage of the pathogenic cycle. Among the many factors that control synaptic, neuronal, and network behavior, the location and role among mitochondria's has a significant effect. The nuanced and often confounding reciprocal relations between mitochondrial and neuronal dynamics explored in this review allow for the derivation of certain general principles.

## REFERENCES


1. Kann O. &Kovács R. (2007). – Mitochondria and neuronal activity. Am. J. Physiol. - Cell Physiol.https://doi.org/10.1152/ajpcell.00222.2006.
2. Warda M., Kim H.K., Kim N., Ko K.S., Rhee B.D. & Han J. (2013). – A matter of life, death and diseases: Mitochondria from a proteomic perspective. Expert Rev. Proteomics. https://doi.org/10.1586/epr.12.69.
3. Chang D.T.W. & Reynolds I.J. (2006). – Mitochondrial trafficking and morphology in healthy and injured neurons. Prog. Neurobiol. doi:10.1016/j.pneurobio.2006.09.003.
4. Schwarz T.L. (2013). Mitochondrial trafficking in neurons. Cold Spring Harb. Perspect. Biol. https://doi.org/10.1101 /cshperspect.a011304.
5. Hudetz A.G. &Bruley D.F., eds. (1998). – Oxygen Transport to Tissue XX. Springer US, Boston, MA. https://doi.org/10.1007/978-1-4615-4863-8.
6. Erecińska M. & Silver I.A. (1994). – Ions and energy in mammalian brain. Prog. Neurobiol. https://doi.org/10.1016/0301-0082(94)90015-9.
7. Zhu X.H., Qiao H., Du F., Xiong Q., Liu X., Zhang X., Ugurbil K. & Chen W. (2012). – Quantitative imaging of energy expenditure in human brain. Neuroimage. https://doi.org/10.1016/j.neuroimage.2012.02.013.
8. Erecinska M., Cherian S. & Silver I.A. (2004). – Energy metabolism in mammalian brain during development. Prog. Neurobiol. https://doi.org/10.1016/j.pneurobio.2004.06.003.
9. Fiskum G., Murphy A.N. & Beal M.F. (1999). – Mitochondria in neurodegeneration: Acute ischemia and chronic neurodegenerative diseases. J. Cereb. Blood Flow Metab. https://doi.org/10.1097/00004647-199904000-00001.
10. Rube D.A. &Bliek A.M. van der (2004). – Mitochondrial morphology is dynamic and varied. Mol. Cell. Biochem. https://doi.org/10.1023/b:mcbi.0000009879.01256.f6.
11. Nunnari J. &Suomalainen A. (2012). – Mitochondria: In sickness and in health. Cell, 148 (6), 1145–1159. https://doi.org/10.1016/j.cell.2012.02.035.
12. Lee H. & Yoon Y. (2016).Mitochondrial fission and fusion. Biochem. Soc. Trans., 44 (6), 1725–1735. https://doi.org/10.1042/BST20160129.
13. Westermann B. (2010). – Mitochondrial fusion and fission in cell life and death. Nat. Rev. Mol. Cell Biol. https://doi.org/10.1038/nrm3013.
14. Suen D.F., Norris K.L. &Youle R.J. (2008). Mitochondrial dynamics and apoptosis. Genes Dev. https://doi.org/10.1101/gad.1658508.
15. Cai Q. &Tammineni P. (2016). Alterations in mitochondrial quality control in alzheimer's disease. Front. Cell. Neurosci. https://doi.org/10.3389/fncel.2016.00024.
16. Oliver D. & Reddy P.H. (2019). – Dynamics of Dynamin-Related Protein 1 in Alzheimer's Disease and Other Neurodegenerative Diseases. Cells. https://doi.org/10.3390/cells8090961.
17. Youle R.J. &Narendra D.P. (2011). – Mechanisms of mitophagy. Nat. Rev. Mol. Cell Biol. https://doi.org/10.1038/nrm3028.
18. Wei H., Liu L. & Chen Q. (2015). – Selective removal of mitochondria via mitophagy: Distinct pathways for different mitochondrial stresses. Biochim. Biophys. Acta - Mol. Cell Res. https://doi.org/10.1016/j.bbamcr.2015.03.013.
19. Palikaras K. &Tavernarakis N. (2012). – Mitophagy in neurodegeneration and aging. Front. Genet. https://doi.org/10.3389/fgene.2012.00297.
20. Sandoval H., Thiagarajan P., Dasgupta S.K., Schumacher A., Prchal J.T., Chen M. & Wang J. (2008). – Essential role for Nix in autophagic maturation of erythroid cells. Nature. https://doi.org/10.1038/nature07006.
21. Novak I., Kirkin V., McEwan D.G., Zhang J., Wild P., Rozenknop A., Rogov V., Löhr F., Popovic D., Occhipinti A., Reichert A.S., Terzic J., Dötsch V., Ney P.A. &Dikic I. (2010). – Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep. https://doi.org/10.1038/embor.2009.256.
22. Liu L., Feng D., Chen G., Chen M., Zheng Q., Song P., Ma Q., Zhu C., Wang R., Qi W., Huang L., Xue P., Li B., Wang X., Jin H., Wang J., Yang F., Liu P., Zhu Y., Sui S. & Chen Q. (2012). – Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat. Cell Biol. https://doi.org/10.1038/ncb2422.
23. Chen G., Han Z., Feng D., Chen Y., Chen L., Wu H., Huang L., Zhou C., Cai X., Fu C., Duan L., Wang X., Liu L., Liu X., Shen Y., Zhu Y. & Chen Q. (2014). – A regulatory signaling loop comprising the PGAM5 phosphatase and CK2

controls receptor-mediated mitophagy. Mol. Cell. https://doi.org/10.1016/j.molcel.2014.02.034.
24. Chen H. & Chan D.C. (2009). – Mitochondrial dynamics-fusion, fission, movement, and mitophagy-in neurodegenerative diseases. Hum. Mol. Genet. https://doi.org/10.1093/hmg/ddp326.
25. Sheng Z.H. (2014). – Mitochondrial trafficking and anchoring in neurons: New insight and implications. J. Cell Biol. https://doi.org/10.1083/jcb.201312123.
26. Son G. & Han J. (2018). –Roles of mitochondria in neuronal development. BMB Rep. https://doi.org/10.5483/BMBRep.2018.51.11.226.
27. Beckervordersandforth R., Zhang C.L. & Lie D.C. (2015). – Transcription-factor-dependent control of adult hippocampal neurogenesis. Cold Spring Harb. Perspect. Biol. https://doi.org/10.1101/cshperspect.a018879.
28. Martynoga B., Drechsel D. & Guillemot F. (2012). – Molecular control of neurogenesis: A view from the mammalian cerebral cortex. Cold Spring Harb. Perspect. Biol. https://doi.org/10.1101/cshperspect.a008359.
29. Knobloch M., Braun S.M.G., Zurkirchen L., Schoultz C. Von, Zamboni N., Araúzo-Bravo M.J., Kovacs W.J., Karalay Ö., Suter U., MacHado R.A.C., Roccio M., Lutolf M.P., Semenkovich C.F. &Jessberger S. (2013). – Metabolic control of adult neural stem cell activity by Fasn-dependent lipogenesis. Nature. https://doi.org/10.1038/nature11689.
30. Knobloch M., Pilz G.A., Ghesquière B., Kovacs W.J., Wegleiter T., Moore D.L., Hruzova M., Zamboni N., Carmeliet P. &Jessberger S. (2017). – A Fatty Acid Oxidation-Dependent Metabolic Shift Regulates Adult Neural Stem Cell Activity. Cell Rep. https://doi.org/10.1016/j.celrep.2017.08.029.
31. Xavier J.M., Rodrigues C.M.P. &Solá S. (2016). – Mitochondria: Major Regulators of Neural Development. Neuroscientist. https://doi.org/10.1177/1073858415585472.
32. Son G. & Han J. (2018). – Roles of mitochondria in neuronal development. BMB Rep., 51 (11), 549–556. https://doi.org/10.5483/BMBRep.2018.51.11.226.
33. Kroemer G., Galluzzi L. & Brenner C. (2007). – Mitochondrial membrane permeabilization in cell death. Physiol. Rev. https://doi.org/10.1152/physrev.00013.2006.
34. Wang W., Esbensen Y., Kunke D., Suganthan R., Rachek L., Bjørås M. &Eide L. (2011). – Mitochondrial DNA damage level determines neural stem cell differentiation fate. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.0852-11.2011.
35. Fornazari M., Nascimento I.C., Nery A.A., Caldeira Da Silva C.C., Kowaltowski A.J. & Ulrich H. (2011). – Neuronal differentiation involves a shift from glucose oxidation to fermentation. J. Bioenerg. Biomembr. https://doi.org/10.1007/s10863-011-9374-3.
36. Maryanovich M. & Gross A. (2013). – A ROS rheostat for cell fate regulation. Trends Cell Biol. https://doi.org/10.1016/j.tcb.2012.09.007.
37. Liste I., García-García E., Bueno C. &Martínez-Serrano A. (2007). – Bcl-XL modulates the differentiation of immortalized human neural stem cells. Cell Death Differ. https://doi.org/10.1038/sj.cdd.4402205.
38. Tsatmali M., Walcott E.C. &Crossin K.L. (2005). – Newborn neurons acquire high levels of reactive oxygen species and increased mitochondrial proteins upon differentiation from progenitors. Brain Res. https://doi.org/10.1016/j.brainres.2005.01.087.
39. Madhavan L., Ourednik V. &Ourednik J. (2006). – Increased "Vigilance" of Antioxidant Mechanisms in Neural Stem Cells Potentiates Their Capability to Resist Oxidative Stress. Stem Cells. https://doi.org/10.1634/stemcells.2006-0018.
40. Uittenbogaard M., Baxter K.K. &Chiaramello A. (2010). – The neurogenic basic helix-loop-helix transcription factor NeuroD6 confers tolerance to oxidative stress by triggering an antioxidant response and sustaining the mitochondrial biomass. ASN Neuro. https://doi.org/10.1042/AN20100005.
41. Rharass T., Lemcke H., Lantow M., Kuznetsov S.A., Weiss D.G. &Panáková D. (2014). – Ca 2+ -mediated Mitochondrial Reactive Oxygen Species Metabolism Augments Wnt/β-Catenin Pathway Activation to Facilitate Cell Differentiation . J. Biol. Chem., 289 (40), 27937–27951. https://doi.org/10.1074/jbc.m114.573519.
42. Jonas E. (2004). – Regulation of synaptic transmission by mitochondrial ion channels. . In Journal of Bioenergetics and Biomembranes https://doi.org/10.1023/B:JOBB.0000041768.11006.90.
43. Devine M.J. & Kittler J.T. (2018). – Mitochondria at the neuronal presynapse in health and disease. Nat. Rev. Neurosci. https://doi.org/10.1038/nrn.2017.170.
44. Chang D.T.W., Honick A.S. & Reynolds I.J. (2006). – Mitochondrial trafficking to synapses in cultured primary cortical neurons. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.1012-06.2006.
45. Davey G.P., Peuchen S. & Clark J.B. (1998). – Energy thresholds in brain mitochondria: Potential involvement in neurodegeneration. J. Biol. Chem. https://doi.org/10.1074/jbc.273.21.12753.
46. Brown M.R., Sullivan P.G. & Geddes J.W. (2006). – Synaptic mitochondria are more susceptible to Ca2+ overload than nonsynaptic mitochondria. J. Biol. Chem. https://doi.org/10.1074/jbc.M510303200.
47. Rangaraju V., tom Dieck S. & Schuman E.M. (2017). – Local translation in neuronal compartments: how local is local? EMBO Rep., 18 (5), 693–711. https://doi.org/10.15252/embr.201744045.
48. Hall C.N., Klein-Flügge M.C., Howarth C. &Attwell D. (2012). – Oxidative phosphorylation, not glycolysis, powers presynaptic and postsynaptic mechanisms underlying brain information processing. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.0026-12.2012.
49. Harris J.J., Jolivet R. &Attwell D. (2012). – Synaptic Energy Use and Supply. Neuron. https://doi.org/10.1016/j.neuron.2012.08.019.
50. Olanow C.W. &Tatton W.G. (1999). – Etiology and pathogenesis of Parkinson's disease. Annu. Rev. Neurosci. https://doi.org/10.1146/annurev.neuro.22.1.123.

51. Varadarajan S., Yatin S., Aksenova M. & Butterfield D.A. (2000). – Review: Alzheimer's amyloid β-peptide-associated free radical oxidative stress and neurotoxicity. J. Struct. Biol. https://doi.org/10.1006/jsbi.2000.4274.
52. Flint Beal M. (2000). – Oxidative metabolism. . In Annals of the New York Academy of Sciences, New York Academy of Sciences. pp 164–169 https://doi.org/10.1111/j.1749-6632.2000.tb05575.x.
53. Zhu Y., Hou H., Rezai-Zadeh K., Giunta B., Ruscin A., Gemma C., Jin J.J., Dragicevic N., Bradshaw P., Rasool S., Glabe C.G., Ehrhart J., Bickford P., Mori T., Obregon D., Town T. & Tan J. (2011). – CD45 deficiency drives amyloid-β peptide oligomers and neuronal loss in alzheimer's disease mice. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.3268-10.2011.
54. Blin O., Desnuelle C., Rascol O., Borg M., Paul H.P. Saint, Azulay J.P., Billé F., Figarella D., Coulom F., Pellissier J.F., Montastruc J.L., Chatel M. &Serratrice G. (1994). – Mitochondrial respiratory failure in skeletal muscle from patients with Parkinson's disease and multiple system atrophy. J. Neurol. Sci. https://doi.org/10.1016/0022-510X(94)90248-8.
55. Lee H.J., Shin S.Y., Choi C., Lee Y.H. & Lee S.J. (2002). – Formation and removal of α-synuclein aggregates in cells exposed to mitochondrial inhibitors. J. Biol. Chem. https://doi.org/10.1074/jbc.M105326200.
56. Koh H. & Chung J. (2012). – PINK1 as a molecular checkpoint in the maintenance of mitochondrial function and integrity. Mol. Cells. https://doi.org/10.1007/s10059-012-0100-8.
57. Shin J.H., Ko H.S., Kang H., Lee Y., Lee Y. Il, Pletinkova O., Troconso J.C., Dawson V.L. & Dawson T.M. (2011). – PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in parkinson's disease. Cell. https://doi.org/10.1016/j.cell.2011.02.010.
58. Sarzi E., Seveno M., Angebault C., Milea D., Rönnbäck C., Quilès M., Adrian M., Grenier J., Caignard A., Lacroux A., Lavergne C., Reynier P., Larsen M., Hamel C.P., Lenaers G. & Müller A. (2016). – Increased steroidogenesis promotes early-onset and severe vision loss in females with OPA1 dominant optic atrophy. Hum. Mol. Genet. https://doi.org/10.1093/hmg/ddw117.
59. Sandoval H., Yao C.K., Chen K., Jaiswal M., Donti T., Lin Y.Q., Bayat V., Xiong B., Zhang K., David G., Charng W.L., Yamamoto S., Duraine L., Graham B.H. &Bellen H.J. (2014). – Mitochondrial fusion but not fission regulates larval growth and synaptic development through steroid hormone production. Elife. https://doi.org/ 10.7554/eLife.03558.
60. Onyango I.G., Lu J., Rodova M., Lezi E., Crafter A.B. &Swerdlow R.H. (2010). – Regulation of neuron mitochondrial biogenesis and relevance to brain health. Biochim. Biophys. Acta - Mol. Basis Dis. https://doi.org/10.1016/j.bbadis.2009.07.014.
61. Mcmanus M.J., Murphy M.P. & Franklin J.L. (2011). – The mitochondria-targeted antioxidant mitoq prevents loss of spatial memory retention and early neuropathology in a transgenic mouse model of Alzheimer's disease. J. Neurosci. https://doi.org/10.1523/JNEUROSCI.0552-11.2011.
62. Ruiz A., Alberdi E. &Matute C. (2018). – Mitochondrial division inhibitor 1 (Mdivi-1) protects neurons against excitotoxicity through the modulation of mitochondrial function and intracellular Ca2+ signaling. Front. Mol. Neurosci. https://doi.org/10.3389/fnmol.2018.00003.
63. S. Mohar D. (2012). – The Sirtuin System: The Holy Grail of Resveratrol? J. Clin. Exp. Cardiolog., 03 (11). https://doi.org/10.4172/2155-9880.1000216.
64. Gertz M., Nguyen G.T.T., Fischer F., Suenkel B., Schlicker C., Fränzel B., Tomaschewski J., Aladini F., Becker C., Wolters D. &Steegborn C. (2012). – A Molecular Mechanism for Direct Sirtuin Activation by Resveratrol. PLoS One. https://doi.org/10.1371/journal.pone.0049761.
65. Moussa C., Hebron M., Huang X., Ahn J., Rissman R.A., Aisen P.S. & Turner R.S. (2017). – Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J. Neuroinflammation. https://doi.org/10.1186/s12974-016-0779-0.
66. Ustyugov A., Shevtsova E., Ashraf G.M., Tarasov V. V., Bachurin S.O. &Aliev G. (2016). – New Therapeutic Property of Dimebon as a Neuroprotective Agent. Curr. Med. Chem. https://doi.org/10.2174/ 0929867 323666160804122746.