International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 7 Issue 6 Ver. I ǁ June 2018 ǁ PP.42-47

Mitochondrial Dynamics And Morphology In CNS: An Overview

Vivek Sharma, Harish Verma And Athar Javed
Government College of Pharmacy, Rohru, Distt. Shimla, Himachal Pradesh-171207, India
Corresponding Author:Dr. Vivek Sharma

ABSTRACT:*Mitochondria are rod-shaped intracellular organelles that can be considered the power generators of the cell, converting oxygen and other compounds in adenosine triphosphate (ATP), that meet the cell's metabolic activities and exchanges with adenosine diphosphate (ADP) in the cytosol. The main role of the mitochondria is the production of ATP, reduced nicotinamide adeninedinucleotide (NADH) and reduced flavin adenine dinucleotide (FADH). Mitochondria also control cell cycle, signalling, differentiation, growth, membrane potential, calcium (Ca2+) signalling, steroid synthesis and also cell death. Mitochondria, account for more than 90% of the cellular energetic production which assumes its crucial importance in the brain since neurons have a limited glycolytic capacity, have high energy demands which make them highly dependent on aerobic oxidative phosphorylation. Mitochondria continuously fragment and fuse in response to different physiological needs of the cell. Neurons are heavily dependent on mitochondria for neurotransmission and for regulation of sodium potassium ATPase pump, intracellular calcium concentration and exocytosis/recycling of synaptic vesicles. Thus mitochondrial dynamic processes like fusion, fission and their transport has decisive role in normal neuronal physiology and minor perturbations in these tightly regulated proceeses lead to disastrous consequences for neuronal functions.*

KEYWORDS: *Fission, Fusion, Mitochondria, Morphology, Neuron*

DateofSubmission:22-11-2018 Date of acceptance: 07-12-2018

I. INTRODUCTION

Mitochondria are organelles present in all eukaryotic cells which preside over a wide variety of crucial functions, including respiration, energy production (Trevisan et al., 2018) and ultimately have a critical influence on homeostasis. Beside carrying out ATP synthesis through oxidative phosphorylation, mitochondria are important for Ca^{2+} signaling, cell death, steroid synthesis, reactive oxygen species (ROS) production, neurotransmitter synthesis and inactivation (Flippo and Strack,2017). Mitochondria also regulate metabolite levels to provide precursors for the synthesis of amino acids, nucleotides and fatty acids and are also involved in the cellular response to stress. They also play an important role in regulation of cell proliferation, migration, neuronal morphology, neurogenesis and cell viability (Chandel, 2014).

Although brain having approximately 2% of the body weight, it consumes about 20% of the body's energy and having limited glycolytic capacity and extremely metabolically active nature, neurons in the brain are energetically demanding cells requiring the delicate maintenance of mitochondrial functions. In addition, highly polarized cells with complex cellular extensions i.e., dendrites and axons, neurons also need the timely and appropriate transport and distribution of mitochondria to serve as energy power source and source of internal Ca^{2+} storage pool for localized neuronal activities such as synaptic transmission, axonal and dendritic transport and synaptic vesicle recycling (Gao et al.,2017).

Mitochondria undergo continual fusion and fission events, which maintain their integrity and quantity and also help in all other functions. The widespread mitochondrial fragmentation, altered distribution in neuronal cell bodies is common in neurodegenerative diseases, suggesting that abnormal mitochondrial fusion, fission and trafficking dynamics may contribute to mitochondrial dysfunction and neurodegeneration (Gao et al., 2017).

Given the importance of processes where mitochondria are involved perturbations in mitochondrial physiology exert profound effects on neuronal development and function as these processes are dependent on mitochondrial localization, mitochondrial bioenergetics and mitochondrial biogenesis (Chan et al., 2012) which are strongly influenced by mitochondrial dynamics, which entails mitochondrial fission, fusion and transport (Flippo and Stefan Strack, 2017).

II. MITOCHONDRIAL DYNAMICS

Ranging from near spherical objects to interconnected networks, the morphology of mitochondrial network is influenced by the delicate balance between opposing fusion and fission events, which are regulated by several large dynamin-related GTPase proteins that utilize GTP hydrolysis in order to remodel the two

mitochondrial membranes. The enzyme responsible for fission of the outer mitochondrial membrane (OMM) is dynamin-related protein-1 (Drp1), whereas mitochondrial fusion requires coordination of three enzymes. Mitofusin 1 and 2 (Mfn1 and 2) promote fusion of the OMM, whereas optic atrophy 1 (Opa1) promotes fusion of the inner mitochondrial membrane (IMM) (Otera et al., 2013; Kasahara and Scorrano, 2014).

Fission

The key regulator in the mitochondria fission process is dynamin-related protein1 (Drp1 or DLP1), a large GTPase mainly localized in the cytosol [Smirnova2001]. During fission, cytosolic Drp1 is recruited to the mitochondrial outer membrane by several receptor proteins such as Mff, Fis1 and MiD48/51, followed by oligomerization into a ring-like structure to sever the mitochondrial membrane by self-assembly and GTP hydrolysis [Loson et al., 2013]. In addition to Drp1, Dyn2, an another dynamin-like protein also regulate the final step of membrane division after Drp1 recruitment and polymerization [Lee et al.,2016].

The molecular mechanisms for initiation of mitochondrial fission remain largely unknown but endoplasmic reticulum (ER), together with actin filaments, plays a critical role in the establishment of constriction sites before mitochondrial Drp1 recruitment [Korobova2013]. After the fission process is completed, Drp1 complex remains on one of the daughter mitochondrion [Chan et al., 2006]. Recent studies indicated that the Drp1 oligomeric complex on mitochondria could not sever mitochondria and become inactive or even inhibitory [Merrill, 2011]. The key component of retromer recognition complex VPS35 can preferentially interact with Drp1 oligomeric complex and direct their trafficking from mitochondria to lysosome for degradation [Wanget al., 2016].

Fusion

Mitochondrial fusion involves the fusion of both the outer and inner membrane and is regulated by three other large GTPase proteins, i.e., Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2) for mitochondrial outer membrane fusion and optic atrophy protein 1 (OPA1) for mitochondrial inner membrane fusion [Santel 2001]. Mitochondrial outer membrane fusion is mediated through interactions of the coiled-coil domains of Mfn1 and Mfn2 to form either homo-oligomeric or hetero-oligomeric complexes to tether membranes together [Ishihara2004]. The outer and inner mitochondrial membrane contains different phospholipids and the proper phospholipid composition is important for the regulation of mitochondrial fusion [Frohman2015].

Mfn2 plays an important role in regulating the association between the endoplasmic reticulum (ER) and mitochondria, and can localize to both the ER and to mitochondria and this, ER-mitochondrial contact is necessary for ER-mitochondrial Ca^{2+} signaling and mitochondrial fission (Lee and Yoon, 2014).

Mitochondrial Transport

Mitochondria utilize microtubules and associated motor proteins dynamin and kinesin to disperse within the cell. The positioning of mitochondria at specific cellular locations is regulated mainly by bidirectional (anterograde and retrograde) movements along microtubules for fast movement and along actin filaments for slow movement via different motor-adaptor complexes [Frederick, 2007]. The core of the motor-adaptor complex consists of kinesin-1 (kinesin heavy chain or Kif5), dynein (cytoskeletal motor proteins), Miro1 and 2 (RhoT1 and RhoT2) and Milton1 and 2 (TRAK1 and TRAK2) [Sheng, 2014]. The anterograde motor kinesin-1 and the retrograde motor dynein/dynactin complex directly interact with Milton and Miro on mitochondria to drive their movement along the microtubules [Glater2006]. In addition actin filaments are also involved in mitochondria movement [Hatch et al., 2014]. Actin motors, such as Myo2 and Myo19, are associated with mitochondria to facilitate the short-distant movement along the filaments. In addition to trafficking, mitochondrial distribution and positioning may be influenced by mitochondrial morphological dynamics. For instance, mitochondrial fission and fusion regulators such as Drp1 and Mfn2 have been reported to regulate mitochondrial axonal transport [Fukumitsu et al., 2016], therefore suggesting the close interplay between mitochondrial morphological dynamics and trafficking (Gao et al., 2017).

The size of mitochondria is determined by the equilibrium between fission and fusion which in turn affect mitochondrial transport as the extreme mitochondrial fission or fusion stalls mitochondrial transport in neurons (Sheng, 2014). Neurons are especially sensitive to perturbations in mitochondrial transport given the length and complexity of their axons and dendrites so inefficient mitochondrial transport result in deficits in ATP production, which is important for neurotransmitter synthesis, vesicular recycling and maintenance of the membrane potential (Birsa et al., 2013).

Importance

The mitochondrial fusion allows the exchange of lipid membrane and intramitochondrial contents between different mitochondria to enable mtDNA repair and equally distribute metabolites to maintain a healthy

population of mitochondria [Chen, H2007]. Due to the high levels of ROS produced and the lack of efficient DNA repair systems, mitochondria are relatively vulnerable to deleterious damage and the defective mitochondria need to be cleared and mitochondrial fission has been shown to participate in the elimination of damaged mitochondria by autophagy [Twig, 2008]. Considering the critical dependence of neuronal function and structure on mitochondrial function, it could be expected that, as highly polarized cells, neurons are particularly sensitive to alterations in mitochondrial dynamics. For instance, neurons are vulnerable to the ablation of mitochondrial dynamic regulators such as Drp1, Mfn2, and Miro1 [Ishihara 2009; Nguyen2014]. The deficiency of almost all mitochondrial fusion and fission regulators such as Drp1, OPA1, Mfn1, Mfn2 and Fis1 or the expression of dominant negative mutants of mitochondrial fusion and fission regulators such as Drp1 K38A and OPA1 K301A impairs mitochondrial movement and proper localization, leading to mitochondrial depletion in neurites and synapses and eventually to dendritic spine and synaptic loss [MacAskill, 2009; Gao et al., 2017]

Further, neurons, being excitable cells require maintaining of large ionic gradients across the plasma membrane which is accomplished through the activity of the plasmalemma Na+/ K+-ATPase and requires the sustained production of high levels of ATP, which in neurons is provided almost exclusively through oxidative phosphorylation at the IMM. Mitochondrial fission and fusion shape ATP supply in neurons in multiple ways. Mitochondrial fusion increases the mitochondrial membrane potential in neurons (Dickey and Strack, 2011) and the ability to maintain ATP levels in response to hypoxia (Schrepfer and Scorrano, 2016) this is a result of improved efficiency of oxidative phosphorylation (Westermann, 2012). Conversely, enhancing mitochondrial fission in neurons depolarizes mitochondria (Dickey and Strack, 2011) and has been associated with decreased levels of cellular ATP (Ju et al., 2007). Mitochondrial Ca^{2+} uptake is an electrophoretic process and, thus, requires a negative mitochondrial membrane potential while also being regulated by the mitochondrial Ca^{2+} uniporter (MCU). Interestingly, mitochondrial Ca^{2+} uptake can enhance ATP production by stimulating mitochondrial dehydrogenases and transporters that fuel the Krebs cycle. Furthermore, Ca^{2+}-mediated regulation of mitochondrial transport and bioenergetics has been suggested to position mitochondria in an activity-dependent manner, matching ATP production with demand. Mitochondrial Ca^{2+} uptake further boosts ATP synthesis, necessary for high-frequency neurotransmitter release (Stephen et al., 2015; Flippo and Stark, 2017).
In the process of supplying ATP, mitochondria – through the electron transport chain – generate reactive oxygen species (ROS), which mediate oxidative stress and also been shown to act as a homeostatic signaling molecule in various physiological processes, including synaptic transmission (Shadel and Horvath, 2015) and regulate the strength of synaptic transmission. Specifically, it was shown that mitochondria-derived ROS selectively recruit α3 subunit-containing GABAA receptors to inhibitory synapses in order to increase the frequency and amplitude of inhibitory postsynaptic currents (IPSCs) in cerebellar stellate neurons (Accardi et al., 2014). Although mitochondrial dynamics serve important physiological roles in providing ATP and regulating Ca^{2+} and ROS signaling in neurons, there is also a strong body of evidence suggesting that aberrant mitochondrial dynamics contribute to neurological disease through these processes as well (Flippo and Stefan Strack2017).

III. NERVOUS SYSTEM AND MITOCHONDRIAL DYNAMICS

Mitochondria populate the cytoplasm of mammalian cells, including neurons, which rely on mitochondrial energy production for survival. These organelles contain their own genome—the mitochondrial DNA (mtDNA)—which encodes essential subunits of the respiratory chain where electrons are combined with oxygen to enable the flow of energy through mitochondria. Energized mitochondria can then synthesize ATP that fuels energy- dependent intracellular reactions (such as endocytosis, ion transport and neurotransmitter biosynthesis) and sustain other critical mitochondrial functions [Ca^{2+} handling, reactive oxygen species (ROS) production etc.), contributing to intracellular signaling (Wallace DC (2010).

In developing neurons, mitochondria are concentrated near growth cones, where they satisfy their high metabolic requirements (Morris and Hollenbeck, 1993). Besides providing ATP, mitochondria also regulate intracellular Ca^{2+} dynamics, which, in turn, influences growth cone extension and collapse (Kaczmareket al., 2012). Mitochondrial fission/fusion influences the decision making of growth cones with regard to their directionality. Thus, mitochondrial dynamics has important role in local signaling responses to growth factors that, in turn, influence growth cone development and synapse formation. In addition to exerting important roles in presynaptic development, mitochondrial dynamics also contribute to the development of postsynaptic dendritic spines. Activity-dependent transport of mitochondria to dendrites is required for the maintenance of dendritic spines in cultured hippocampal neurons (Li et al., 2004). Furthermore, increasing mitochondrial fragmentation by over expression of Drp1 enhances synapse formation, whereas dominant-negative inhibition of Drp1 has the opposite effect in cultured hippocampal neurons, indicating a prominent role for mitochondrial dynamics in synaptogenesis (Dickey and Strack, 2011; Li et al., 2004).

During development of CNS, neural stem cells proliferate and differentiate during neurogenesis. The newborn neurons then grow an axon and dendrites and eventually form synapses (Mattson et al., 2008). Adult

neurogenesis occurs in the hippocampal region of most mammals including humans which play a critical role in hippocampus-dependent memory formation. Adult neurogenesis involves a multistep process of lineage progression starting with neural stem cells (NSCs), which give rise to intermediate progenitor cells (IPCs), which in turn produce neuroblasts, which mature into neurons (Ming and Song, 2005). For example, NSCs are glycolytic, but mature neurons require mitochondrial respiration for ATP generation. Indeed, cellular mitochondria are essential for the differentiation of NSCs into mature neurons (Puri, 2017).

Changes in mitochondrial energy metabolism occur in brain cells during embryonic and early postnatal development with a shift from the use of fatty acids as fuels during early development to the use of glucose later on (Erecinska et al., 2004), suggesting roles for mitochondria in supporting the different bioenergetic requirements of highly proliferative neural stem cells and postmitotic neurons. During neuronal differentiation too, the number of mitochondria per cell increases, but the velocity at which individual mitochondria move decreases as neurite outgrowth slows and synaptogenesis occurs (Chang and Reynolds, 2006).

Soon after differentiating from stem cells, neurons extend several neurites, one of which begins to grow rapidly and acquires the molecular, structural and functional characteristics of the axon, while the other neurites become dendrites. Shortly before axogenesis occurs mitochondria congregate at the base of the neurite that is destined to become the axon (Mattson and Partin,1999) and during axogenesis there is increased entry of mitochondria into the nascent axon while the mitochondrial density in the remaining short processes (dendrites) decreases (Rutheland Hollenbeck, 200) .

An element that confers the brain with the capacity to learn and adapt is the plasticity of its synaptic connections. Synapses that are very active become potentiated, resulting in long-term increase in the size and functional ‘‘strength’’ of those synapses, which are forms of synaptic plasticity implicated in learning and memory (Harms et al., 2008). Mitochondria play active roles in synaptic plasticity. During synaptogenesis the movement of mitochondria into dendritic protrusions correlates with the morphological plasticity of developing spines; impairment of the dynamin-like GTPasesDrp1 and OPA1 reduces dendritic mitochondria content and causes a loss of synapses and dendritic spines, whereas increasing dendritic mitochondrial content enhances the number and plasticity of spines and synapses (Li et al., 2004).

Mitochondrial Shape

Mitochondrial dynamics can be affected by changes in bioenergetic status in response to physiological or environmental alterations and impact all aspects of mitochondrial functions. In neurodegenerative disorders like Alzheimer’s disease (AD) there are ultrastructural alterations in mitochondrial morphology such as reduced number, increased size and broken internal membrane cristae [Hirai K et al.,2001). These alteration in mitochondrial dynamics leads to severe consequences in the cell such as structural changes in the cristae formation and assembly of electron transport complex compromising bioenergetics and causing calcium dyshomeostasis, increased oxidative stress, mtDNA damage, and synaptic dysfunction [Zhu et al., 2013].

Mitochondria dynamically undergo shape changes through regulated processes of fusion and fission (making longer or shorter organelles, respectively) and actively traffic between cell compartments such as the soma, axon and presynaptic boutons (Chan DC (2012).

There has been demonstration of relationship between mitochondrial shape and age-related cognitive function (Hara et al., 2014). The spheroid to elongated tubule mitochondria is thought to be normal while donut-shaped (i.e., toroid) mitochondria are a hallmark of mitochondrial stress, inducible in controlled conditions (in vitro) by respiratory chain poisons and involving oxidative stress (Liu X 2011; Ahmad T, et al. (2013)

The presence of donut mitochondria was associated with diminished synapses, as indicated by smaller active zone sizes. Furthermore, donut-containing presynaptic terminals had fewer total docked vesicles, representing fewer readily releasable neurotransmitter containing synaptic vesicles. Given that mitochondrial volume density (i.e., content) within synaptosomes strongly correlates with total synaptic vesicle content and release (Ivannikov2013), this suggest that the morphological and thus functional state of mitochondria at the synapse influence brain function, possibly by modulating synaptic strength (Hara et al.,2014; Picarda2014).

There is an emerging appreciation that mitochondrial morphology is a dynamic parameter that may be associated with cell injury. In several different models of apoptosis it has been reported that the normal mitochondrial reticulum becomes fragmented after the application of apoptotic stimuli (Frank et al., 2001). Fragmentation of mitochondria may be a consequence of the association of proteins such as DRP1 with mitochondria. Overexpression of this protein causes fragmentation (Filiano et al., 2002), whereas a dominant-negative form of DRP1 decreases sensitivity to mitochondrially mediated apoptosis (Frank et al., 2001). It is not clear whether such mechanisms are activated by calcium, or even whether DRP1 is normally present in neurons. A different family of proteins appears to mediate fusion of mitochondria (Santel and Fuller, 2001). It is also possible that an inhibition of an ongoing fusion reaction could result in an apparent fragmentation or rounding. Alterations in mitochondrial morphology in both neuronsand astrocytes in response to calcium loading has also been reported by Dubinsky and colleagues (Kristal and Dubinsky, 1997; Dubinsky and Levi, 1998), who found

that mitochondria changed from a rod-like to spherical morphology when challenged. In these studies the authors concluded that the shape change was caused by mitochondrial permeability transition (Rintoul, 2003**;** Trevisan et al., 2018**).**

IV. CONCLUSION

Mitochondria may be regarded as a super specialized and organized organ that have multifaceted role in central nervous system. The delicate balanced state of mitochondrial dynamics (Fission, Fusion and transport) is required for normal neuronal physiology and minor perturbations and changes may have diverse implications.

REFERENCES

[1]. Trevisan T, Pendin D, Montagna A, Bova S, Ghelli AM, Daga A. 2018. Manipulation of Mitochondria Dynamics Reveals Separate Roles for Form and Function in Mitochondria Distribution. Cell Rep 23(6):1742-1753

[2]. Kyle HF and Stefan S.2017. Mitochondrial dynamics in neuronal injury, development and plasticity, Journal of Cell Science 130: 671-681

[3]. Chandel NS. 2014. Mitochondria as signaling organelles. BMC Biol 12

[4]. Gao J, Luwen W, Jingyi L, Fei X, Bo S and Xinglong W.2017. Abnormalities of Mitochondrial Dynamics in Neurodegenerative Diseases, Antioxidants 6: 25

[5]. Chan DC.2012. Fusion and fission: Interlinked processes critical for mitochondrial health. Annu Rev Genet 46:265–287.

[6]. Otera H, Ishihara N and Mihara K. 2013. New insights into the function and regulation of mitochondrial fission, Biochim. Biophys. Acta 1833: 1256-1268.

[7]. Kasahara A and Scorrano L. 2014. Mitochondria: from cell death executioners to regulators of cell differentiation. Trends Cell Biol 24: 761-770.

[8]. Smirnova E, Griparic L, Shurland DL, van der B. 2001. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol. Biol. Cell 12: 2245–2256.

[9]. Loson OC, Song Z, Chen H, Chan DC.2013. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol. Biol. Cell 24: 659–667.

[10]. Lee JE, Westrate LM, Wu H, Page C, Voeltz GK. 2016. Multiple dynamin family members collaborate to drive mitochondrial division, Nature 540: 139–143.

[11]. Korobova F, Ramabhadran V, Higgs HN.2013. An actin-dependent step in mitochondrial fission mediated bythe ER-associated formin INF2. Science 339: 464–467.

[12]. Chan DC.2006. Mitochondrial fusion and fission in mammals, Annu. Rev. Cell Dev. Biol 22: 79–9

[13]. Merrill RA, Dagda RK, Dickey AS, Cribbs, JT, Green SH, Usachev YM, Strack S.2011. Mechanism of neuroprotective mitochondrial remodeling by PKA/AKAP1. PLoS Biol 9:10

[14]. Wang W, Wang X, Fujioka H, Hoppel C, Whone AL, Caldwell MA, Cullen PJ, Liu J, Zhu X.2016. Parkinson's disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. Nat. Med 22: 54–63.

[15]. Santel A, Fuller MT. 2001. Control of mitochondrial morphology by a human mitofusin. J. Cell Sci 114: 867–874.

[16]. Ishihara N, Eura Y, Mihara K. 2004. Mitofusin 1 and 2 play distinct roles in mitochondrial fusion reactions via GTPase activity. J. Cell Sci 117: 6535–654

[17]. Frohman MA. 2015. Role of mitochondrial lipids in guiding fission and fusion. J. Mol. Med. Berl 93: 263–269.

[18]. Lee H and Yoon Y. 2014. Mitochondrial fission: regulation and ER connection. Mol. Cells 37: 89-94.

[19]. Frederick RL, Shaw JM. 2007. Moving mitochondria: Establishing distribution of an essential organelle. Traffic 8: 1668–1675.

[20]. Sheng ZH. 2014. Mitochondrial trafficking and anchoring in neurons: New insight and implications, J. Cell Biol 204: 1087–1098.

[21]. Glater EE, Megeath LJ, Stowers RS, Schwarz TL. 2006. Axonal transport of mitochondria requires Milton to recruit kinesin heavy chain and is light chain independent, J. Cell Biol 173: 545–557.

[22]. Hatch AL, Gurel PS, Higgs HN. 2014. Novel roles for actin in mitochondrial fission, J. Cell Sci 127:4549–4560.

[23]. Fukumits, K, Hatsukano T, Yoshimura A, Heuser J, Fujishima K, Kengaku M. 2016. Mitochondrial fission protein Drp1 regulates mitochondrial transport and dendritic arborization in cerebellar Purkinje cells, Mol. Cell Neurosci 71: 56–65.

[24]. Sheng ZH.2014. Mitochondrial trafficking and anchoring in neurons: new insight and implications. J. Cell Biol 204: 1087-1098.

[25]. Birsa N, Norkett R, Higgs N, Lopez DG, Kittler J T. 2013. Mitochondrial trafficking in neurons and the role of the Miro family of GTPase proteins. Biochem. Soc. Trans 41:1525-1531.

[26]. Chen H, McCaffery JM, Chan DC. 2007. Mitochondrial fusion protects against neurodegeneration in the cerebellum. Cell 130: 548–562.

[27]. Twig G, Elorza A, Molina AJ, Mohamed H, Wikstrom JD, Walzer G, Stiles L, Haigh SE, Katz S, Las G et al. 2008. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J 27: 433–446

[28]. Ishihara N, Nomura M, Jofuku A, Kato H, Suzuki SO, Masuda K, Otera H, Nakanishi Y, Nonaka I, Goto YI.2009. Mitochondrial fission factor Drp1 is essential for embryonic development and synapseformation in mice. Nat. Cell Biol 11: 958–966.

[29]. Nguyen TT, Oh SS, Weaver D, Lewandowska A, Maxfield D, Schuler MH, Smith NK et al. 2014. Loss of Miro1-directed mitochondrial movement results in a novel murine model for neuron disease. Proc. Natl. Acad. Sci. USA 111:3631–3640.

[30]. MacAskill AF, Brickley K, Stephenson FA, Kittler JT.2009. GTPase dependent recruitment of Grif-1 by Miro1 regulates mitochondrial trafficking in hippocampal neurons. Mol. Cell Neuroscibjhmjk 40: 301–3.

[31]. Dickey AS and Strack S. 2011. PKA/AKAP1 and PP2A/Bbeta2 regulateneuronal morphogenesis via Drp1 phosphorylation and mitochondrial bioenergetics. J. Neurosci 31: 15716-15726.

[32]. Schrepfer E and Scorrano L. 2016. Mitofusins, from Mitochondria to Metabolism. Mol. Cell 61: 683-694.

[33]. Westermann B. 2012. Bioenergetic role of mitochondrial fusion and fission. Biochim. Biophys. Acta 1817: 1833-1838.

[34]. Ju WK, Liu Q, Kim KY, Crowston JG, Lindsey JD, Agarwal N et al.2007. Elevated hydrostatic pressure triggers mitochondrial fission and decreases cellular ATP in differentiated RGC-5 cells, Invest. Ophthalmol. Vis. Sci 48: 2145-2151

[35]. Stephen TL, Higgs NF, Sheehan DF, Al Awabdh S, Lopez-Domenech G, Arancibia-Carcamo IL, Kittler JT. 2015. Miro1 Regulates Activity- Driven Positioning of Mitochondria within Astrocytic Processes Apposed to Synapses to Regulate Intracellular Calcium Signaling. J. Neurosci 35: 15996-16011.

[36]. Shadel GS, Horvath TL.2015. Mitochondrial ROS signaling in organismal homeostasis. Cell 163: 560-569

[37]. Accardi MV, Daniels BA, Brown PM, Fritschy JM, Tyagarajan SK, Bowie D. 2014. Mitochondrial reactive oxygen species regulate the strength of inhibitory GABA-mediated synaptic transmission. Nat. Commun 5: 3168.

[38]. Wallace DC. 2010. Colloquium paper: Bioenergetics, the origins ofcomplexity, and the ascent of man. Proc Natl Acad Sci USA 107(2):8947–8953.
[39]. Morris R L, Hollenbeck PJ. 1993. The regulation of bidirectionalmitochondrial transport is coordinated with axonal outgrowth. J. Cell Sci 104: 917-927.
[40]. Kaczmarek JS, Riccio A, Clapham D E.2012. Calpain cleaves and activates the TRPC5 channel to participate in semaphorin 3A-induced neuronal growth cone collapse. Proc. Natl. Acad. Sci. USA 109: 7888-7892.
[41]. Li Z, Okamoto KI, Hayashi Y and Sheng M.2004. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses, Cell 119: 873–887.
[42]. Mark P, Mattson MG, Aiwu C. 2008. Mitochondria in Neuroplasticity and Neurological Disorders Neuron 60:748-765
[43]. Ming GL, Song H. 2005. Adult neurogenesis in the mammalian central nervous system. AnnuRev Neurosci. 28:223–250
[44]. Puri R. 2017. Protecting Mitochondrial Health: A Unifying Mechanism in Adult Neurogenesis. Mitochondria shape and implications. The Journal of Neuroscience 37(28):6603– 6605
[45]. Erecinska M, Cherian S, Silver IA. 2004. Energy metabolism in mammalian brain during development. Prog. Neurobiol 73: 397–445.
[46]. Chang DT, Reynolds IJ. 2006. Differences in mitochondrial movementand morphology in young and mature primary cortical neurons in culture. Neuroscience 141: 727–736.
[47]. Mattson MP, Partin J.1999. Evidence for mitochondrial control of neuronal polarity. J. Neurosci. Res 56: 8–20.
[48]. Ruthel G and Hollenbeck PJ. 2003. Response of mitochondrial traffic toaxon determination and differential branch growth. J. Neurosci 23: 8618– 8624.
[49]. Harms KJ, Rioult-Pedott, MS, Carter DR, Dunaevsky A. 2008. Transient spine expansion and learning-induced plasticity in layer 1 primarymotor cortex. J. Neurosci 28: 5686–5690.
[50]. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, VintersHV, Tabaton M, Shimohama S, Cash AD, SiedlakSL, Harris PL, Jones PK, Petersen RB, PerryG and Smith MA.2001. Mitochondrial abnormalities in Alzheimer's disease, J Neurosci 21:3017-3023.
[51]. Zhu X, Perry G, Smith MA et al. 2013. Abnormal mitochondrial dynamics in the pathogenesis of Alzheimer's disease. Journal of Alzheimer's disease 33(1): S253–S262, 2013.
[52]. Hara Y, Yuk F, Puri R, Janssen WGM, Rapp PR, Morrison JH. 2014. Presynaptic mitochondrial morphology in monkey prefrontal cortex correlates with working memory and is improved with estrogen treatment. Proc Natl Acad Sci USA.111:486–491.
[53]. Liu X, Hajnóczky G. 2011. Altered fusion dynamics underlie unique morphological changes in mitochondria during hypoxiareoxygenation stress. Cell Death Differ. 18(10):1561–1572.
[54]. Ahmad T, et al. 2013. Computational classification of mitochondrial shapes reflects stress and redox state. Cell Death Dis 4:461.
[55]. Martin P, Bruce SM. 2014. Mitochondria impact brain function and cognition, PNAS 111(1): 7–8.
[56]. Frank S, Gaume B, Bergmann-Leitner ES, Leitner WW, Robert EG, Catez F,Smith CL, Youle RJ. 2001. The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis. Dev Cell 1:515–525.
[57]. Filiano AJ, Rintoul GL, Brocard JB, Votyakova TV, Reynolds IJ. 2002. Mitochondrial homeostasis and neuronal injury in primary cortical cultures. Soc Neurosci Abstr 32:297.2.
[58]. Gordon LR, Anthony JF, Jacques BB, Geraldine JK, Ian JR. 2003. Glutamate Decreases Mitochondrial Size and Movement in Primary Forebrain Neurons; The Journal of Neuroscience 23(21):7881–7888
[59]. Tatiana T, Diana P, Aldo M, Sergio B, Anna MG, and Andrea D. 2018. Manipulation of Mitochondria Dynamics Reveals Separate Roles for Form and Function in Mitochondria Distribution, Cell Reports 23: 1742–1753

Dr. Vivek Sharma "Mitochondrial Dynamics And Morphology In CNS: An Overview "International Journal of Pharmaceutical Science Invention(IJPSI), vol. 07, no. 06, 2018, pp. 42-47