

## Chapter 4

# Mitochondrial Dysfunction in Aging and Neurodegeneration

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### ABSTRACT

*Mitochondria are a dynamic organelle of the cell involved in the various biological processes. Mitochondria are the site of the adenosine triphosphate (ATP) production, electron transport chain (ETC), oxidation of fatty acids, tricarboxylic acid (TCA), and cellular apoptosis. Besides these, mitochondria are the site of production of reactive oxygen species (ROS), which further disrupts the normal functioning of this organelle also making mitochondria itself as an important target of oxidative stress. Thus, mitochondria serve as an important target in the process of neurodegeneration. In the present chapter, the authors describe mitochondria and its functioning, dynamics, and the mitochondrial dysfunction in aging and neurodegenerative disorders (NDs).*

### INTRODUCTION

Mitochondria are the main organelle of the cell which plays key role in the various processes including oxidative phosphorylation, calcium signaling (Rizzuto et al, 2012), stress responses (Pellegrino & Haynes, 2015) and cellular apoptosis (Bratic & Larsson, 2013). The primary role of mitochondria is the production of ATP by the process of oxidative phosphorylation. During this process some of the electrons eventually leaks and this results in the generation of free radicals or reactive oxygen species (ROS) (Payne & Chinnery, 2015). The production of ROS is known to cause the oxidative damage to various components of mitochondrial electron transport chain (ETC) resulting in the mitochondrial dysfunction. Mitochondria dysfunctional is further characterized by decreased activity of ETC complexes, decreased rate of electron transport in complex-I and IV, reduced capacity of oxidative phosphorylation, decreased ATP production, increased water permeability in brain mitochondria, decreased ATP-synthase activity, increased accumulation of oxidative products, decreased mitochondrial membrane potential, increased

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mitochondrial size and fragility. Further all these factors are the determining factors of brain aging (Navarro & Boveris, 2010). Further inactivation of complex-I has been recognized as characteristic of aging and neurodegeneration in brain. Mitochondrial dysfunction is more prominent in the areas of brain including hippocampus, frontal cortex and substantia nigra (Navarro & Boveris, 2010). In the present work author discuss different causes and features of mitochondrial dysfunction and demonstrate the role of mitochondrial dysfunction in the neurodegenerative pathologies.

## **BACKGROUND**

Mitochondria are the organelle linked with the production of ATP and dysfunction of this organelle thus led to ATP deficit. Besides the synthesis or production of ATP, mitochondria are the important site of various other physiological processes including sequestration of calcium within neurons (Trevelyan et al, 2010), misfolded/alterd/damaged protein clearance pathways (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; Rubinsztein et al, 2011), site of ROS production (Cui et al, 2012) and production of apoptogenic factors involved in the process of cellular apoptosis (Tsujimoto, 2000). The production of ROS increases with the increase in the age and aging is characterized by the increased generation of ROS which evokes oxidative stress and affects normal functioning of various cellular molecules (Gerschaman et al, 1954; Harman, 1956). Mitochondrial ROS production mediated damaged to cellular molecules led to the accumulation of oxidative and damaged products (Beckman & Ames, 1998; Harman, 2006; Vina et al, 2003). Further mitochondria derived from the brain of aged individual showed increased membrane permeability (Navarro & Boveris, 2004); reduced membrane potential and increased degradation (Beckman & Ames, 1998; Navarro & Boveris, 2004, 2007b) and decreased ATP-synthase activity (Lam et al, 2009). Dysfunctional mitochondria results in the prolonged elevation of intracellular calcium that results in the neuronal dysfunction observed in PD patients (Trevelyan et al, 2010). Reduced activities of mitochondrial protein clearance pathways including UPS system and autophagy (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; Rubinsztein et al, 2011) has been observed in the brain of the PD patients SN region (Bedford et al, 2008; McNaught et al, 2003; McNaught & Jenner, 2001). Also the activities of these pathways declines with the increase in the age (Emmanouilidou et al, 2010; Jana, 2012; Li & Li, 2011; McNaught et al, 2003; McNaught & Jenner, 2001; Rubinsztein et al, 2011) suggesting aging increased the risk of PD onset. Also it has been reported that the risk of developing PD increases after the age of 65 years and the PD generally affects the individuals in the later stages of life (de Lau & Breteler, 2006; Fearnley & Lees, 1991; Ma et al, 1999b; Nussbaum & Ellis, 2003; Wood-Kaczmar et al, 2006). The different events that evolved in context of mitochondrial dysfunction have been shown in Figure 1.

## **MITOCHONDRIA AND AGING**

Mitochondria consist of 2 membranes; outer membrane is porous while the inner membrane is impermeable. It is suggested that Bcl-2 class proteins (including proapoptotic proteins i.e. Bax, Bak, Bok, Bid, Bad, and Puma and antiapoptotic proteins i.e. Bcl-2, Bcl-x<sub>L</sub>, and Mcl-1) (Adams & Cory, 1998) maintains the integrity of the outer membrane of the mitochondria (Chipuk et al, 2010). The space between the 2 membranes is called inter membranous space in which cytochrome c (cyt-c) is present (Tait & Green,

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