AWARENESS ABOUT MITOCHONDRIAL TOXICITY IN NBIA

Mitochondria are cytoplasmic organelles essential for life and death. Mitochondria play a pivotal role in a number of biochemical processes in the neuron including energy metabolism and ATP production, intracellular Ca^{2+} homeostasis and cell signalling which are all implicated in the regulation of neuronal excitability. For this reason, it is not surprising that alterations in mitochondrial function have emerged as a hallmark of neurodegenerative diseases (Cavallucci et al., 2013). Further, emerging evidence suggests that structural changes in mitochondria, including increased mitochondrial fragmentation and decreased mitochondrial fusion, are critical factors associated with mitochondrial dysfunction and cell death in neurodegeneration.

Mitochondrial involvement in Neurodegeneration with Brain Iron Accumulation (NBIA) pathogenesis has been demonstrated by several scientific reports. Thus, fibroblasts from PKAN patients displayed altered iron dependent oxidative status and mitochondrial iron homeostasis dysfunction, associated with mitochondrial membrane potential alteration and ROS accumulation (Santambrogio et al., 2015; Alvarez-Cordoba et al., 2018). Importantly, human-derived PKAN neurons displayed profound impairment of mitochondrial respiration and of electrophysiological properties, along with lipid peroxidation and alteration of oxidative status, mitochondrial iron-dependent biosynthetic pathway, and cytosolic iron homeostasis (Orellana et al., 2016; Alvarez-Cordoba et al., 2018). Furthermore, disturbances in mitochondrial potential and the changes in Ca^{2+} handling have been reported in animal models of PLA2G6-associated neurodegeneration (PLAN) (Strokin and Reiser, 2016).

Therefore, identifying potential mitochondrial toxic agents from medications to environmental factors is an essential part of managing the disease.

There are many reasons why certain substances may be toxic to the mitochondria. For instance, if the mitochondrial electron transport chain (ETC) is inhibited, patients in which mitochondria function is already compromised may be severely affected. Also, harmful free radicals can be formed from reactive oxygen species and aggravate mitochondrial dysfunction and, as a consequence, the progression of the disease.

In neurological diseases, clinicians use a variety of drugs that may help with the numerous symptoms of the disease or may be needed to treat co-morbidities (other diseases or conditions that the patient may have which may or may not be related to the neurological disease). Some of these drugs may actually be harmful to the mitochondria themselves therefore it is necessary (and critical) to always balance the medical need with potential harmful side effects to the mitochondria.

Information about potential harmful drugs for mitochondria is in

https://www.mitopatients.org/mitodisease/potentially-harmful-drugs

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