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Review

Mitochondrial specific therapeutic targets following brain injury

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ABSTRACT

Traumatic brain injury is a complicated disease to treat due to the complex multi-factorial secondary injury cascade that is initiated following the initial impact. This secondary injury cascade causes nonmechanical tissue damage, which is where therapeutic interventions may be efficacious for intervention. One therapeutic target that has shown much promise following brain injury are mitochondria. Mitochondria are complex organelles found within the cell. At a superficial level, mitochondria are known to produce the energy substrate used within the cell called ATP. However, their importance to overall cellular homeostasis is even larger than their production of ATP. These organelles are necessary for calcium cycling, ROS production and play a role in the initiation of cell death pathways. When mitochondria become dysfunctional, they can become dysregulated leading to a loss of cellular homeostasis and eventual cell death. Within this review there will be a deep discussion into mitochondrial bioenergetics followed by a brief discussion into traumatic brain injury and how mitochondria play an integral role in the neuropathological sequelae following an injury. The review will conclude with a discussion pertaining to the therapeutic approaches currently being studied to ameliorate mitochondrial dysfunction following brain injury.

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Contents

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1. Introduction

Cellular homeostasis requires an intricate orchestration of many complicated processes. These processes would not occur without proper energetics. Mitochondria, known as the "Power Plant" of the cell, provide a vast majority of the energetic substrates necessary for these processes to occur. In addition to a source of energy, the study of mitochondria have also been implicated in cellular homeostasis as well as regulatory mechanisms such as cell death pathways and have an importance in calcium buffering. Because of this, the study of these microscopic organelles has revealed fundamental insights into many cellular processes. Being an important mediator of the cell fate and the only source of aerobic respiration in higher eukaryotes, they have also been linked to various neurological disorders like Parkinson's Disease, Alzheimer's Disease, traumatic brain injury and stroke. For these reasons, mitochondria occupy a central position in the field of cell biology and neurobiology.

Mitochondrial bioenergetics play an important role in maintaining neuronal homeostasis and proper neuronal function. Similar to a power plant, mitochondria provide the energy necessary for cells in the brain to function properly (Chance et al., 1973, 1979, 1955; Chance and Smith, 1955; Chance and Williams, 1955a, 1955b, 1955c, 1955d; Chancey and Zatz, 1955). However once mitochondria become dysfunctional, cellular dysfunction soon follows which can lead to cell death. Therefore, scientists have used these organelles as targets for novel therapeutic interventions and several of these pharmacological treatments have shown positive outcomes in disease states related to tissue of the central nervous system. Traumatic brain injury, TBI, is one of these diseases.

Within this review, the history of mitochondria, insight into mitochondrial bioenergetics and how these bioenergetics provide proper brain function will all be discussed. Additionally, mitochondrial mediated cell death pathways, specifically related to an injury to the CNS, will be reviewed as well. This will be followed by a number of important findings from the literature that have shown mitochondrial targeting interventions are able to improve histological and functional outcomes following injury.

2. Mitochondria bioenergetics

Mitochondria have a very rich history in the scientific literature. They have been argued as the organelle involved in the most Nobel Prizes which helps to further demonstrate their importance to the contribution to overall cellular homeostasis. The first known documentation regarding the existence of mitochondria dates back to the 1840s when a researcher by the name of Jakob Henle observed the unknown intracellular structures during his research in the musculature of insects. At this time, these structures were described with words such as "chondros", "Korn" and "grain'. Then, in 1898, with the development of improved staining techniques, the Greek term "mitos" was adopted which lead to the new term: "mitochondria" [Lehninger (1965) and Scheffler (2008)]. It was around this same time that Altman, in the 1890s, who first described these intracellular granules as autonomous, forming bacterial-like colonies within their host cells and describing them as "bioplasts" (Scheffler, 2008). According to the Symbiogenesis, or the endosymbiotic theory, which is the evolutionary theory that prokaryotic and eukaryotic symbiosis formed billions of years ago, this was indeed a very astute observation (Wallace, 1992, 2010, 2007).

Since their discovery, at least 4 Nobel prizes have been directly linked to mitochondrial function. The first was awarded to Otto Warburg who identified co-enzymes and described what is now known as the Electron transport chain rendering him a Nobel Prize in 1931. Otto Warburg is also well known for his work in glycolysis leading to identification of the Warburg Effect, which is the glycolysis mediated cellular respiration exhibited by cancer cells. The next Nobel Prize linked to mitochondrial function was awarded in 1937 to Hans Krebs and Fritz Lipmann for the discovery of Krebs Cycle. As known today, this metabolic cycle forms the center of the intracellular metabolism and is necessary to produce the electron rich NADH and FADH molecules necessary for functioning of the electron transport chain. In 1978, Peter Mitchell was awarded the Nobel Prize for the Chemiosmotic Coupling Hypothesis which describes a membrane potential generated by ions separated across a membrane, specifically protons, to provide the proper energy to phosphorylate ADP, generating ATP. Lastly, and in 1997, Paul Boyer and John Walker were awarded the Nobel Prize for their work and further understanding of the structure and function of ATP Synthase.

Mitochondria are crucial considering 95% of the ATP made in the cell is produced through mitochondrial mediated oxidative phosphorylation. These energy generating organelles are structured to shift and maintain the ratio of ATP to ADP in the direction of ATP. Structurally, they have a dual (inner and outer) membrane, each responsible for specific functions. The outer membrane (OM) contains transporter proteins such as Voltage Dependent Anion Channel/Porin (VDAC) as well as Translocase of the Outer Membrane Channel which have a function of importing and exporting many ions and proteins necessary to maintain mitochondrial function (Nicholls and Ferguson, 2002). The inner membrane (IM) is separated from the OM by the inner mitochondrial space. Within this membrane, inner mitochondrial membrane proteins can be found such as Complex I, Complex