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Mitochondrial dysfunction and neurological disorders: A narrative review and treatment overview

Eman E. Alshial [a], Muhammad Idris Abdulghaney [b], Al-Hassan Soliman Wadan [c], Mohamed Abdelfatah Abdellatif [d], Nada E. Ramadan [e], Aya Muhammed Suleiman [f], Nahla Waheed [g], Maha Abdellatif [h], Haitham S. Mohammed [i]

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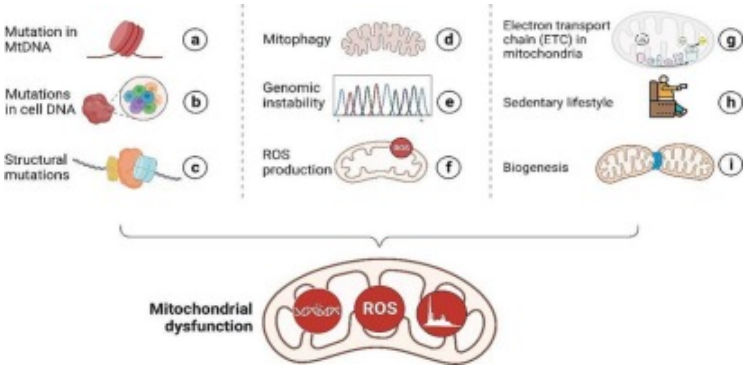
Abstract

Mitochondria play a vital role in the nervous system, as they are responsible for generating energy in the form of ATP and regulating cellular processes such as calcium (Ca^{2+}) signaling and apoptosis. However, mitochondrial dysfunction can lead to oxidative stress (OS), inflammation, and cell death, which have been implicated in the pathogenesis of various neurological disorders. In this article, we review the main functions of mitochondria in the nervous system and explore the mechanisms related to mitochondrial dysfunction. We discuss the role of mitochondrial dysfunction in the development and progression of some neurological disorders including Parkinson's disease (PD), multiple sclerosis (MS), Alzheimer's disease (AD), depression, and epilepsy. Finally, we provide an overview of various current treatment strategies that target mitochondrial dysfunction, including pharmacological treatments, phototherapy, gene therapy, and mitotherapy. This review emphasizes the importance of understanding the role of mitochondria in the nervous system and highlights the potential for mitochondrial-targeted therapies in the treatment of neurological disorders. Furthermore, it highlights some limitations and challenges encountered by the current therapeutic strategies and puts them in future perspective.

Graphical abstract



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Introduction

Mitochondria play a fundamental role in the normal functioning of neuronal cells. Besides being the main energy source that provides cells with the ATP molecules used for all cellular biochemical processes, these organelles are involved in several physiological and pathological pathways in living neurons. Some of these pathways are linked to the generation of oxidants, calcium (Ca^{2+}) homeostasis, and cell death [1]. The different aspects of mitochondrial function attain remarkable importance in neural tissue for several reasons. The brain is one of the high-energy-demanding organs in the body and it is substantially dependent on mitochondrial energy metabolism. Additionally, the nervous system is uniquely vulnerable to oxidants due to the large percentage of oxidizable lipids, the high oxygen consumption, and the low antioxidant capacity of other tissues [2]. Therefore, a large number of mitochondria necessary for the brain's bioenergetics could be a source of oxidants that damage neuronal cells when they go awry [3].

Mitochondrial dysfunction is currently considered a key step in the pathogenesis of neurological disorders [4]. Mitochondrial injury and abnormalities have been implicated in several neurological diseases such as Alzheimer's disease (AD) [5], Parkinson's disease (PD) [6], depression [7], multiple sclerosis (MS) [8], and epilepsy [9]. Mitochondrial dysfunction could originate from genetic (inherited) or acquired disorders which lead to attenuation or loss of mitochondrial efficiency to produce the high-energy molecules through their electron transport chain (ETC) [10]. The dysfunction of mitochondria leads to the accumulation of Ca^{2+} in the mitochondria's matrix and triggers the opening of the mitochondrial permeability transition pore (mPTP) which in turn results in leakage of cytochrome *c* (CC) into the cellular cytoplasm and induces apoptosis and mitophagy [11]. Additionally, mitochondrial injury leads to the accumulation of reactive oxygen species (ROS), which are responsible for oxidative stress (OS) and tissue damage, and an overall reduction in ATP production and depletion of cellular energy [12].

Certain endogenous mechanisms exist to maintain mitochondrial healthy functions. Mitochondrial fusion and fission are considered part of mitochondrial dynamics and serve as compensatory mechanisms for damaged organelles, facilitating the process of mitophagy [13]. Mitochondrial fusion and fission balance two opposing forces: damage compensation by fusion and damage removal by fission [14]. The balance between these two processes determines how mitochondria look and how well they work, and disruptions in these processes are associated with several

diseases, including mainly neurological disorders. Inactivation of the key regulators of mitochondrial fusion and fission dynamics is linked to abnormalities in neuronal development, plasticity, and function, both in vitro and in vivo [15]. Surprisingly, modulation of mitochondrial fusion or fission can improve the symptoms of the neurodegeneration in various disease models [16]. Therefore, mitochondrial fusion and fission are critical processes for preserving mitochondrial health and preventing neurodegenerative diseases, and understanding their work in neurodegenerative diseases is important for developing new treatments [17]. Furthermore, the cellular antioxidant system protects the cells against the damaging effects of free radicals generated during metabolism [18]. Neurological disorders may be manifested due to the inability of these innate mechanisms to maintain the required balance for the healthy function of neuronal tissue and cells.

Several treatment strategies have targeted mitochondrial dysfunction as a key contributor to neurological disorders. Pharmacological treatments [19], mitochondrial transplantation/transfer (mitotherapy) [20], photobiomodulation (PBM) (Phototherapy) [21], and gene therapy [22] are among the main emerging therapeutic strategies that target mitochondrial dysfunction (Fig. 1). The present review provides an update on the mechanisms underlying mitochondrial dysfunction in some neurological disorders and focuses on the recent treatment strategies implemented in mitigating mitochondrial dysfunction linked to these neurological diseases (Table 1). Some clinical treatments are provided (Table 2). The main challenges and treatment limitations will be addressed, and future perspectives will be provided.

Section snippets

Main functions of mitochondria in the nervous system

Mitochondria are essential to cell organelles because they produce energy and regulate a variety of functions, including signaling and cell death [12]. The synthesis of phospholipids and heme, Ca^{2+} homeostasis, apoptosis activation, and cell death are all part of the eukaryotic organisms' energy-producing processes [23]. The distribution of mitochondria in cells from various tissues depends on the amount of energy required. Although myocytes have a higher density of mitochondria than neurons, …

Mitochondrial dysfunction

Attenuation in ETC efficiency, reduction in ATP synthesis, and loss of transmembrane electrical and chemical potential are the main parameters that characterize mitochondrial dysfunction. This dysfunction has been linked to several chronic diseases including neurodegenerative diseases [4], cardiovascular diseases [45], autoimmune diseases [46], psychiatric diseases [47], and

musculoskeletal diseases [48]. Common cellular consequences of mitochondrial dysfunction are OS, inflammation, and …

PD

PD is the second-most common neurodegenerative disorder and is characterized by bradykinesia, rigidity, postural instability, and resting tremor. It is primarily caused by the gradual loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), which is thought to be the site of dopamine production [57]. Since mitochondrial complex 1 insufficiency was initially discovered in PD brains by Schapira and colleagues, mitochondrial dysfunction is considered one of the …

Pharmacological treatment

The mechanism of PD pathology related to mitochondrial dysfunction has motivated mitochondria targets to be used in familial PD patients [160]. Although the mechanisms of PD are not fully understood in terms of mitochondrial dysfunction, several drugs have been studied in several experimental models of PD for mitochondrial dysfunction [161]. The following strategies could be used to mitigate mitochondrial dysfunction and its consequences in PD [160]. Antioxidants are one of the pathways …

Challenges and limitations

Despite significant progress made in the field of mitochondrial medicine during the last two decades, we still don't fully understand how mitochondria work at the molecular level. In addition, the development of mitochondrial-based therapeutics for neurological disorders is hindered by a number of translational challenges, including the genetic complexity of these disorders, the complexity of mitochondrial biology itself, the heterogeneous clinical presentations of patients, and the lack of …

Concluding remarks

In conclusion, this review underscores the critical role of mitochondria in the nervous system, serving as essential energy generators and regulators of cellular processes. The implications of dysfunctional mitochondria are far-reaching, leading to OS, inflammation, and cell death, all of which contribute to the development and progression of neurological disorders. By delving into the mechanisms of mitochondrial dysfunction, this review sheds light on its involvement in conditions such as PD, …

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Declaration of competing interest

The authors of this manuscript have no conflicts of interest to disclose. …

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