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Mitochondrial biogenesis: pharmacological approaches.

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Abstract

Organelle biogenesis is concomitant to organelle inheritance during cell division. It is necessary that organelles double their size and divide to give rise to two identical daughter cells. Mitochondrial biogenesis occurs by growth and division of pre-existing organelles and is temporally coordinated with cell cycle events [1]. However, mitochondrial biogenesis is not only produced in association with cell division. It can be produced in response to an oxidative stimulus, to an increase in the energy requirements of the cells, to exercise training, to electrical stimulation, to hormones, during development, in certain mitochondrial diseases, etc. [2]. Mitochondrial biogenesis is therefore defined as the process via which cells increase their individual mitochondrial mass [3]. Recent discoveries have raised attention to mitochondrial biogenesis as a potential target to treat diseases which up to date do not have an efficient cure. Mitochondria, as the major ROS producer and the major antioxidant producer exert a crucial role within the cell mediating processes such as apoptosis, detoxification, Ca2+ buffering, etc. This pivotal role makes mitochondria a potential target to treat a great variety of diseases. Mitochondrial biogenesis can be pharmacologically manipulated. This issue tries to cover a number of approaches to treat several diseases through triggering mitochondrial biogenesis. It contains recent discoveries in this novel field, focusing on advanced mitochondrial therapies to chronic and degenerative diseases, mitochondrial diseases, lifespan extension, mitohormesis, intracellular signaling, new pharmacological targets and natural therapies. It contributes to the field by covering and gathering the scarcely reported pharmacological approaches in the novel and promising field of mitochondrial biogenesis. There are several diseases that have a mitochondrial origin such as chronic progressive external ophthalmoplegia (CPEO) and the Kearns- Sayre syndrome (KSS), myoclonic epilepsy with ragged-red fibers (MERRF), mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes (MELAS), Leber's hereditary optic neuropathy (LHON), the syndrome of neurogenic muscle

weakness, ataxia and retinitis pigmentosa (NARP), and Leigh's syndrome. Likewise, other diseases in which mitochondrial dysfunction plays a very important role include neurodegenerative diseases, diabetes or cancer. Generally, in mitochondrial diseases a mutation in the mitochondrial DNA leads to a loss of functionality of the OXPHOS system and thus to a depletion of ATP and overproduction of ROS, which can, in turn, induce further mtDNA mutations. The work by Yu-Ting Wu, Shi-Bei Wu, and Yau-Huei Wei (Department of Biochemistry and Molecular Biology, National Yang-Ming University, Taiwan) [4] focuses on the aforementioned mitochondrial diseases with special attention to the compensatory mechanisms that prompt mitochondria to produce more energy even under mitochondrial defect-conditions. These compensatory mechanisms include the overexpression of antioxidant enzymes, mitochondrial biogenesis and overexpression of respiratory complex subunits, as well as metabolic shift to glycolysis. The pathways observed to be related to mitochondrial biogenesis as a compensatory adaptation to the energetic deficits in mitochondrial diseases are described (PGC- 1, Sirtuins, AMPK). Several pharmacological strategies to trigger these signaling cascades, according to these authors, are the use of bezafibrate to activate the PPAR-PGC-1α axis, the activation of AMPK by resveratrol and the use of Sirt1 agonists such as quercetin or resveratrol. Other strategies currently used include the addition of antioxidant supplements to the diet (dietary supplementation with antioxidants) such as L-carnitine, coenzyme Q10,MitoQ10 and other mitochondria-targeted antioxidants,N-acetylcysteine (NAC), vitamin C, vitamin E vitamin K1, vitamin B, sodium pyruvate or -lipoic acid. As aforementioned, other diseases do not have exclusively a mitochondrial origin but they might have an important mitochondrial component both on their onset and on their development. This is the case of type 2 diabetes or neurodegenerative diseases. Type 2 diabetes is characterized by a peripheral insulin resistance accompanied by an increased secretion of insulin as a compensatory system. Among the explanations about the origin of insulin resistance Mónica Zamora and Josep A. Villena (Department of Experimental and Health Sciences, Universitat Pompeu Fabra / Laboratory of Metabolism and Obesity, Universitat Autònoma de Barcelona, Spain) [5] consider the hypothesis that mitochondrial dysfunction, e.g. impaired (mitochondrial) oxidative capacity of the cell or tissue, is one of the main underlying causes of insulin resistance and type 2 diabetes. Although this hypothesis is not free of controversy due to the uncertainty on the sequence of events during type 2 diabetes onset, e.g. whether mitochondrial dysfunction is the cause or the consequence of insulin resistance, it has been widely observed that improving mitochondrial function also improves insulin sensitivity and prevents type 2 diabetes. Thus restoring oxidative capacity by increasing mitochondrial mass appears as a suitable strategy to treat insulin resistance. The effort made by

researchers trying to understand the signaling pathways mediating mitochondrial biogenesis has uncovered new potential pharmacological targets and opens the perspectives for the design of suitable treatments for insulin resistance. In addition some of the current used strategies could be used to treat insulin resistance such as lifestyle interventions (caloric restriction and endurance exercise) and pharmacological interventions (thiazolidinediones and other PPAR agonists, resveratrol and other calorie restriction mimetics, AMPK activators, ERR activators). Mitochondrial biogenesis is of special importance in modern neurochemistry because of the broad spectrum of human diseases arising from defects in mitochondrial ion and ROS homeostasis, energy production and morphology [1]. Parkinson´s Disease (PD) is a very good example of this important mitochondrial component on neurodegenerative diseases. Anuradha Yadav, Swati Agrawal, Shashi Kant Tiwari, and Rajnish K. Chaturvedi (CSIR-Indian Institute of Toxicology Research / Academy of Scientific and Innovative Research, India) [6] remark in their review the role of mitochondrial dysfunction in PD with special focus on the role of oxidative stress and bioenergetic deficits. These alterations may have their origin on pathogenic gene mutations in important genes such as DJ-1, -syn, parkin, PINK1 or LRRK2. These mutations, in turn, may cause defects in mitochondrial dynamics (key events like fission/fusion, biogenesis, trafficking in retrograde and anterograde directions, and mitophagy). This work reviews different strategies to enhance mitochondrial bioenergetics in order to ameliorate the neurodegenerative process, with an emphasis on clinical trials reports that indicate their potential. Among them creatine, Coenzyme Q10 and mitochondrial targeted antioxidants/peptides are reported to have the most remarkable effects in clinical trials. They highlight a dual effect of PGC-1α expression on PD prognosis. Whereas a modest expression of this transcriptional co-activator results in positive effects, a moderate to substantial overexpession may have deleterious consequences. As strategies to induce PGC-1α activation, these authors remark the possibility to activate Sirt1 with resveratrol, to use PPAR agonists such as pioglitazone, rosiglitazone, fenofibrate and bezafibrate. Other strategies include the triggering of Nrf2/antioxidant response element (ARE) pathway by triterpenoids (derivatives of oleanolic acid) or by Bacopa monniera, the enhancement of ATP production by carnitine and -lipoic acid. Mitochondrial dysfunctions are the prime source of neurodegenerative diseases and neurodevelopmental disorders. In the context of neural differentiation, Martine Uittenbogaard and Anne Chiaramello (Department of Anatomy and Regenerative Biology, George Washington University School of Medicine and Health Sciences, USA) [7] thoroughly describe the implication of mitochondrial biogenesis on neuronal differentiation, its timing, its regulation by specific signaling pathways and new potential therapeutic strategies. The maintenance of

mitochondrial homeostasis is crucial for neuronal development. A mitochondrial dynamic balance is necessary between mitochondrial fusion, fission and quality control systems and mitochondrial biogenesis. Concerning the signaling pathways leading to mitochondrial biogenesis this review highlights the implication of different regulators such as AMPK, SIRT1, PGC-1α, NRF1, NRF2, Tfam, etc. on the specific case of neuronal development, providing examples of diseases in which these pathways are altered and transgenic mouse models lacking these regulators. A common hallmark of several neurodegenerative diseases (Huntington´s Disease, Alzheimer´s Disease and Parkinson´s Disease) is the impaired function or expression of PGC-1α, the master regulator of mitochondrial biogenesis. Among the promising strategies to ameliorate mitochondrial-based diseases these authors highlight the induction of PGC-1α via activation of PPAR receptors (rosiglitazone, bezafibrate) or modulating its activity by AMPK (AICAR, metformin, resveratrol) or SIRT1 (SRT1720 and several isoflavone-derived compounds). This article also presents a review of the current animal and cellular models useful to study mitochondriogenesis. Although it is known that many neurodegenerative and neurodevelopmental diseases are originated in mitochondria, the regulation of mitochondrial biogenesis has never been extensively studied. (ABSTRACT TRUNCATED).

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