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Mitochondrial diseases

Perspectives of drug-based neuroprotection targeting mitochondria

Perspectives de la neuroprotection mitochondriale par des approches pharmacologiques

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INFO ARTICLE

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ABSTRACT

Mitochondrial dysfunction has been reported in most neurodegenerative diseases. These anomalies include bioenergetic defect, respiratory chain-induced oxidative stress, defects of mitochondrial dynamics, increase sensitivity to apoptosis, and accumulation of damaged mitochondria with instable mitochondrial DNA. Significant progress has been made in our understanding of the pathophysiology of inherited mitochondrial disorders but most have no effective therapies. The development of new metabolic treatments will be useful not only for rare mitochondrial disorders but also for the wide spectrum of common age-related neurodegenerative diseases shown to be associated with mitochondrial dysfunction. A better understanding of the mitochondrial regulating pathways raised several promising perspectives of neuroprotection. This review focuses on the pharmacological approaches to modulate mitochondrial biogenesis, the removal of damaged mitochondria through mitophagy, scavenging free radicals and also dietary measures such as ketogenic diet.

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AD, Alzheimer's disease; AICAR, 5-aminoimidazole-4-carboxamide ribonucleoside; ALS, Amyotrophic lateral sclerosis; AMP, Adenosine monophosphate; ATP, Adenosine triphosphate; cAMP, Cyclic AMP; CCCP, Carbonylcyanide m-chlorophenylhydrazone; CNS, Central nervous system; ERR, Estrogen-related receptors; ETC, Electron transport chain; FAD/FADH, Flavin adenine nucleotide; GDAP1, Ganglioside-induced differentiation-associated protein 1; HD, Huntington disease; KTP, Kinetin triphosphate; LHON, Leber hereditary optic neuropathy; MAPK, Mitogen-activated protein kinases; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, Myoclonic epilepsy and ragged red fibers; MFN1/MFN2, Mitofusin; MnSOD, Manganese superoxide dismutase; mtDNA, Mitochondrial genome or DNA; mtPTP, Mitochondrial permeability transition pore; mTOR, Mammalian target of rapamycin; NAD/NADH, Nicotinamide adenine dinucleotide; NARP, Neurogenic muscle weakness, ataxia, and retinitis pigmentosa; nDNA, Nuclear genome or DNA; NMDA, Acide N-methyl-D-aspartic; NOS, Nitric oxide synthase; NRF1/NRF2, Nuclear respiratory factors; OPA1, Optic atrophy 1; OXPHOS, Oxidative phosphorylation; PARL, Presenilins-associated rhomboid-like protein; PD, Parkinson's disease; PGC-1-α, PPAR gamma coactivator 1-alpha; PINK1, PTEN-induced putative kinase1; PKA, Protein kinase A; PPAR, Peroxisome proliferators-activated receptors; PRC, PGC1-related coactivator; CoQ, Coenzyme Q; RC, Respiratory chain; ROS, Reactive oxygen species; RXR, Retinoid X receptors; SIRT, Sirtuins; TFAM, Mitochondrial transcription factor A; TFB2/TFB2, Transcription factors B1 and B2.

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RÉSUMÉ

Des dysfonctions mitochondriales ont été rapportées dans la plupart des maladies mitochondriales et neurodégénératives. Ces anomalies incluent des défauts énergétiques, une augmentation du stress oxydant lié au fonctionnement de la chaîne respiratoire, des défauts de la dynamique mitochondriale, une susceptibilité accrue à l'apoptose et une accumulation de mitochondries endommagées présentant un ADN mitochondrial instable. Des progrès importants ont été réalisés dans la compréhension de la pathophysiologie de ces maladies mitochondriales mais la très grande majorité de ces pathologies ne dispose pas de traitement. Le développement de nouvelles approches pharmacologiques est non seulement important pour ces maladies mais aussi pour l'éventail de pathologies neurodégénératives associant une dysfonction mitochondriale. La meilleure connaissance des voies de régulation mitochondriale a fait émerger des perspectives prometteuses de neuroprotection. Cette revue se focalise sur les possibilités pharmacologiques de moduler la biogenèse mitochondriale, la dégradation des mitochondries endommagées par mitophagie, la détoxification des radicaux libres ainsi que sur des aspects nutritionnels comme le régime cétogène.

1. Introduction

Mitochondrial diseases are often associated with clinical neurological features and are usually seen by a neurologist. Moreover, most of the common neurodegenerative disorders such as Alzheimer's (AD) and Parkinson's diseases (PD), Friedreich's ataxia (FA), Huntington's Disease (HD) or Amyotrophic Lateral Sclerosis (ALS) have also been linked to a mitochondrial dysfunction [1].

In the last decade, spectacular progress has been made in our understanding of the pathophysiology of inherited mitochondrial disorders. However, the lack of a cure and efficient therapies impair our potential to treat these mitochondrial disorders and special efforts have to be made to validate therapies of mitochondrial disorders. Our ability to treat these disorders is extremely limited by their rarity but more importantly by the heterogeneity of these diseases [2,3]. A limited number of clinical trials have been conducted on putative mitochondrial therapies. Recently, the Cochrane study on mitochondrial disorders judged only twelve clinical trials to be methodologically valid, using a variety of compounds such as coenzyme Q10, creatine monohydrate, dichloroacetate and dimethyglycine [4]. So far, there have been very few randomized, prospective, double-blind, placebo-controlled trials performed in adults or children with mitochondrial diseases but a large number of open-labeled studies with limited probative value [4]. Moreover, several drugs or cofactors have been given in an uncontrolled manner making difficult to assess the efficacy and safety of these drugs. Most of the time these drugs have been used in combination as a ''cocktail'' and then difficult to assess the efficacy. Following these observations, it was suggested that treatments may have to be tailored for each patient based specifically on their molecular defects and mutation pathophysiology. The development of new metabolic and mitochondrial therapeutics will be useful not only for rare inherited mitochondrial syndromes but also for the wide spectrum of common age-related neurodegenerative diseases shown to be associated with mitochondrial dysfunction.

2. Mitochondria: powerhouse of the cell

Mitochondria are organelles producing the energy required for cellular functions. The mitochondrial respiratory chain or Oxidative Phosphorylation (OXPHOS) is composed of five, multi-enzymatic complexes. Complexes I, II, III, and IV make up the electron transport chain (ETC), while complex V or ATP synthase produces ATP for energy cell requirements (Fig. 1). As a toxic by-product of OXPHOS, the mitochondria generate much of the endogenous cellular reactive oxygen species (ROS). These organelles also contain the mitochondrial permeability transition pore (mtPTP) which initiates cell death through the opening of mtPTP, when mitochondrial energy function declines [5]. Hence, mitochondrial dysfunctions which inhibit OXPHOS and generate ROS production increase the tendency of the cell to undergo apoptosis.

Mitochondrial respiratory chain (RC) deficiencies represent one of the major causes of metabolic disorders with an estimated prevalence of 1 in 5000 of the general population [6]. However, these disorders represent a heterogeneous group of genetic diseases, mitochondrial diseases can be caused by genetic defects in mitochondrial DNA (mtDNA) [7] or nuclear DNA (nDNA) genes encoding mitochondrial proteins [8]. The large majority of the mitochondrial proteins is encoded by the nuclear genome, synthesized in the cytoplasm, and then imported into the mitochondria. Hundreds of nuclear genes are required for the synthesis, import and assembly of the respiratory chain complexes, as well as for the maintenance and expression of the mtDNA. In the last few years, the number of identified mutations in nuclear genes responsible for mitochondrial or neurodegenerative diseases has exponentially increased [8].

3. Mitochondrial genome

The mtDNA is a circular molecule of 16.5 kb that encodes 13 polypeptides, which are essential components of OXPHOS, 12S