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Review

Mitochondrial respiration as a target for neuroprotection and cognitive enhancement

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ABSTRACT

This paper focuses on brain mitochondrial respiration as a therapeutic target for neuroprotection and cognitive enhancement. We propose that improving brain mitochondrial respiration is an important future direction in research and treatment of Alzheimer's disease (AD) and other conditions associated with cognitive impairment and neurodegeneration. The central thesis is that supporting and improving brain mitochondrial respiration constitutes a promising neurotherapeutic principle, with potential applications in AD as well as in a wide variety of neuropsychological conditions. We propose three different interventional approaches to improve brain mitochondrial respiration based on (a) pharmacology, (b) photobiomodulation and (c) nutrition interventions, and provide detailed examples for each type of intervention. First, low-dose USP methylene blue is described as a pharmacological intervention that can successfully increase mitochondrial respiration and result in memory enhancement and neuroprotection. Second, transcranial low-level light/laser therapy with near-infrared light is used to illustrate a photobiomodulation intervention with similar neurometabolic mechanisms of action as low-dose methylene blue. Finally, a nutrition intervention to improve mitochondrial respiration is proposed by increasing ketone bodies in the diet. The evidence discussed for each intervention supports a fundamental neurotherapeutic strategy based on improving oxidative energy metabolism while at the same time reducing the pro-oxidant tendencies of the nervous system. Targeting brain mitochondrial respiration with these three types of interventions is proposed as part of a holistic neurotherapeutic approach to improve brain energy metabolism and antioxidant defenses. This strategy represents a promising new bioenergetics direction for treatment of AD and other neuropsychological disorders featuring cognitive impairment and neurodegeneration.

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1. Introduction

Brain oxidative energy metabolism is a target to which attention has only indirectly been devoted in neurotherapeutic interventions, but it is suspected to have a large potential for the implementation of effective treatments of brain diseases and for enhancing normal cognitive functions. The paucity of neurotherapeutic strategies targeting brain energy metabolism may be explained not only by a lack of technology and pharmaceutical resources to specifically enhance brain oxidative metabolism, but also by failure to identify energy metabolism as one of the most important processes in neuronal physiology. The brain has one of the highest rates of energy demand in the body. Neurons have a unique oxidative potential and heavily rely on an adequate supply of oxygen and glucose to survive and maintain normal function. Of all neuronal functions, active transport of ions against their concentration and electrical gradients is by far the largest energy consuming function of neurons [1]. Active ion transport restores the plasma membrane potential after depolarization by activation of the Na + K + ATPase pump [2]. In consequence, neuronal activity and energy metabolism are tightly coupled [3]. In other words, highly active neurons display high energy consumption and formation. To achieve this, the intracellular metabolic machinery that supports the generation of energy from oxygen and glucose is abundantly expressed. The core of this metabolic machinery resides in mitochondria, and within it, key components for energy demand/production coupling are those in the electron transport chain in the inner mitochondrial membrane, including cytochrome oxidase. Mitochondria are central organelles in neuronal physiology. They coherently integrate cell respiration, energy metabolism, and calcium ion balance to support cell survival. Remarkably, a single neuron is not metabolically homogeneous, but the neuronal metabolic capacity, represented by mitochondrial content, is highest in dendrites, intermediate in cell bodies and lowest in axon trunks [3]. This subcellular compartmentalization of energy reflects an adaptation to maximize efficiency in energy utilization, so that energy is generated only when and where energy is needed.

Recent progress in our understanding of brain oxidative metabolism has revealed discrete potential mitochondrial molecular targets that may be used for neurotherapeutic purposes. Effective cognitive enhancement and neuroprotection are two clinical desirable outcomes that may be achievable by targeting brain energy metabolism. Both seem a crucial unmet need in the treatment, for example, of neurodegenerative diseases. Neurodegenerative disorders are heterogeneous, but they all feature progressive neuronal atrophy and loss. The etiology of neurodegeneration in most cases is unknown, but it has been hypothesized to be multifactorial, with both genetic and environmental contributing factors. Whereas differential regional vulnerability and distinct types and patterns of protein aggregation seem to distinguish between neurodegenerative entities, universal features of neurodegeneration include chronic and progressive cell loss, atrophy and loss of function in specific brain systems. In addition, mitochondrial failure has gained attention as a major pathogenic event common to the broad spectrum of neurodegenerative disorders. Leber's hereditary optic neuropathy (LHON) appears as a model neurodegenerative disease caused by mitochondrial failure. This relatively rare condition is produced by specific mutations in NADH dehydrogenase, the entry enzyme of the respiratory chain in mitochondria. As it is classical of mitochondrial disorders, LHON follows a particular inheritance pattern, affecting mainly young adult males. Nevertheless, its expressivity is variable and its onset can occur during childhood or in elder individuals [4]. On the other extreme of the neurodegeneration spectrum, Alzheimer's disease (AD) appears as the most common neurodegenerative disorder. It is mostly sporadic, and associated with advanced age and β-amyloid and tau accumulation in the brain. In contrast to LOHN, in which the role of mitochondrial dysfunction is widely acknowledged, the mainstream hypothesis on the cause of AD puts little emphasis on the potential role of mitochondrial dysfunction. While many believe that the amyloid/tau pathogenic hypothesis will further our ability to understand and treat AD, this view is not universal and alternate pathogenic hypotheses exist.

A major alternate hypothesis supported by us [5] and others [6–8] proposes mitochondrial dysfunction as a key pathogenic step, not only in AD but also in other neurodegenerative conditions. The mitochondrial hypothesis of neurodegeneration derives from the observed relationship between mitochondrial durability (*e.g.* efficiency, accumulation of mitochondrial DNA mutations) and aging, which is believed by some groups to be causal [9]. Hence, whereas the baseline mitochondrial function is determined by gene inheritance, exposure to environmental factors, in turn proportional to age, determine the rate of mitochondrial decline [10]. The mitochondrial hypothesis of neurodegeneration also predicts that mitochondrial failure precedes synaptic dysfunction, protein aggregation, atrophy and loss of function. Mitochondrial failure has been linked to known major pathogenic aspects of neuronal dysfunction associated with neurodegeneration, including excitotoxicity [11], abnormal protein aggregation [12], neuroinflammation [13] and oxidative stress [14]. Specific evidence supporting the primordial role of mitochondrial dysfunction in AD include (1) decreased ATP, reduced basal oxygen consumption, decreased NAD+/NADH ratios, increased oxidative stress, pervasive mitochondrial depolarization, altered calcium homeostasis and increased β-amyloid production in cell cultures after AD and mild cognitive impairment (MCI) subject mitochondrial transfer [15]; (2) reduced cytochrome oxidase activity in AD subject platelets and brains [16,17]; (3) correlation between disease duration and cytochrome oxidase activity in the posterior cingulate cortex, a region showing hypometabolic changes in preclinical stages of dementia [18]; and (4) consistent early selective brain hypometabolism that precedes cognitive decline in AD, underlies synaptic dysfunction and occurs in brain regions with higher synaptic activity, including multimodal cortical network hubs [19]. Defects in energy metabolism are a constant in the pre-clinical stages of dementia. For example, cognitively normal individuals with a family history of late onset AD, in particular individuals with a maternal history of AD, have a progressive reduction in glucose metabolism on FDG-PET in the posterior cingulate, parieto-temporal, and medial temporal regions. These regions are affected in patients with clinical AD and such changes are more significant than those seen in individuals with a paternal or negative family history of AD [20]. Notably, this evidence has led to a recent revision of a popular pathogenic model for AD to now include energy metabolic failure as one of the earliest steps in the natural history of the disease [21]. Similarly, early metabolic changes preceding neuronal atrophy have been observed in patients with parkinsonism [22,23] and Huntington's disease [24]. Since mitochondrial bioenergetics plays a central role in neuronal function and survival, it can be hypothesized that the putative heterogeneous etiologic factors of neurodegeneration may find in mitochondria points of vulnerability for structural and functional neuronal integrity.

Based on a growing body of data discussed below, targeted manipulations of mitochondrial respiratory function seem to be the next logical step in attempts to design effective therapeutic interventions against neurodegeneration, including AD. Nevertheless, as more is learned about the metabolism of the nervous system, it becomes evident that the oxidative bioenergetics' particularities of the brain would demand consideration of so far non-conventional strategies of neuroprotection and cognitive

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