Progress in Neurobiology 157 (2017) 273–291

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

Alternative mitochondrial electron transfer for the treatment of neurodegenerative diseases and cancers: Methylene blue connects the dots

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 10 September 2015
Accepted 20 October 2015
Available online 18 November 2015

Keywords:
Mitochondria electron transport chain
Methylene blue
Neurodegeneration
Cancer
Metabolism

ABSTRACT

Brain has exceptional high requirement for energy metabolism with glucose as the exclusive energy source. Decrease of brain energy metabolism and glucose uptake has been found in patients of Alzheimer's, Parkinson's and other neurodegenerative diseases, providing a clear link between neurodegenerative disorders and energy metabolism. On the other hand, cancers, including glioblastoma, have increased glucose uptake and rely on aerobic glycolysis for energy metabolism. The switch of high efficient oxidative phosphorylation to low efficient aerobic glycolysis pathway (Warburg effect) provides macromolecule for biosynthesis and proliferation. Current research indicates that methylene blue, a century old drug, can receive electron from NADH in the presence of complex I and donates it to cytochrome c, providing an alternative electron transfer pathway. Methylene blue increases oxygen consumption, decrease glycolysis, and increases glucose uptake *in vitro*. Methylene blue enhances glucose uptake and regional cerebral blood flow in rats upon acute treatment. In addition, methylene blue provides protective effect in neuron and astrocyte against various insults *in vitro* and in rodent models of Alzheimer's, Parkinson's, and Huntington's disease. In glioblastoma cells, methylene blue reverses Warburg effect by enhancing mitochondrial oxidative phosphorylation, arrests glioma cell cycle at s-phase, and inhibits glioma cell proliferation. Accordingly, methylene blue activates AMP-activated protein kinase, inhibits downstream acetyl-coA carboxylase and cyclin-dependent kinases. In summary, there is accumulating evidence providing a proof of concept that enhancement of mitochondrial oxidative phosphorylation *via* alternative mitochondrial electron transfer may offer protective action against neurodegenerative diseases and inhibit cancers proliferation.

Contents

Abbreviations: MB, methylene blue; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; CBF, cerebral blood flow; GLUT, glucose transporter; TCA, tricarboxylic acid; ETC, electron transfer chain; NADH, dihydronicotinamide adenine dinucleotide; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; MCT, monocarboxylate transporter; AMPK, AMP-activated protein kinase; ACC, acetyl-CoA carboxylase; CaMKKβ, calcium/calmodulin-dependent protein kinase kinase β; APOE, apolipoprotein E; MPTP, 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine; FRDA, Friedreich's ataxia; FXN, frataxin; mTORC1, mammalian target of rapamycin complex I.

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http://dx.doi.org/10.1016/j.pneurobio.2015.10.005
0301-0082/

1. Introduction

Cancer and neurodegeneration are often believed to be two distinct pathological disorders of opposite etiology and therapeutic intervention. While cancers are characterized by the enhanced resistance to cell death, neurodegenerative diseases are featured by the progressive premature neuron death (Plun-Favreau et al., 2010). Indeed, neurodegenerative diseases such as Alzheimer's disease (AD) have been found to be inversely associated with cancers (Bajaj et al., 2010; Driver et al., 2012). On the other hand, there is increasing evidence that cancers and neurodegenerative diseases might share common etiologic mechanisms and therapeutic targets. Age is the single most important risk factor for both neurodegeneration and cancers (Niccoli and Partridge, 2012). Dietary restriction has been found to be one of the most effective interventions to extend lifespan and retard age-related diseases including cancers and neurodegenerative diseases (Hursting et al., 2010, 2013; Graff et al., 2013; Prolla and Mattson, 2001). There are many drugs that may be effective for the treatment of both cancers and neurodegenerative diseases. For example, Bexarotene, a retinoid X receptor agonist for the treatment of T cell lymphoma, has been shown to reduce Aβ plaques and attenuates cognitive deficits in murine models of AD (Aicardi, 2013; Cramer et al., 2012; Tai et al., 2014).

From the discoveries of Krebs cycle (Krebs and Johnson, 1937) to mitochondrial oxidative phosphorylation (Boyer et al., 1973; Gresser et al., 1982), biology has experienced great advance of our knowledge in cellular metabolism from 1920s to 1980s. For the past 3 decades, molecular biology approaches have been dominating biological research without paying much attention to the metabolic state of cells. Despite the dramatic advantage of molecular biology and modern medicine, neurodegenerative disorders and cancers remain the most devastating diseases and effective therapeutic interventions are desperately needed. Recently, it is beginning to be accepted that transcription participates in dictating cellular metabolism (McKnight, 2010). The integrative molecular, cellular, and metabolic approaches might provide a better understanding of neurodegenerative disorders and cancers, thus, leads to discover novel therapeutics for those incurables.

Abnormal metabolism is the key feature of many disorders. Neurodegenerative diseases are a heterogeneous group of disorders which presume to primarily affect different subset of neurons at the CNS, mainly including AD, Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Despite the heterogeneity, both experimental and clinical studies have indicated that many neurodegenerative disorders often coexist metabolic dysfunction (Cai et al., 2012). Similarly, cancer cells are genetically and phenotypically heterogeneous given the different origination and the inter-tumor genomic instability (Burrell et al., 2013). Nonetheless, cancer cells have long been known to have characteristic alterations in their metabolism since 1920s (Warburg, 1956a, b). Reprogramming of energy metabolism has recently been proposed as an emerging cancer hallmark (Hanahan and Weinberg, 2011). Accordingly, novel therapeutic targets on metabolic pathway have been exploring for the treatment of cancers and neurodegeneration. In this review, we recapitulate the findings that highlight the metabolic alteration in neurodegenerative diseases and cancers, summarize the novel function of methylene blue, a century old drug, as an alternative mitochondrial electron transfer carrier, and propose that alternative mitochondrial electron transfer as a common therapeutic mechanism for the treatment of both neurodegenerative diseases and cancers.

2. Brain energy metabolism

2.1. Brain bioenergetics

Einstein's famous equation, $E = MC^2$, simplifies the relationship of two fundamental physics entities, energy and mass, and linked them with the speed of light. Thus, mass and energy, used to be thought as separate entities, are known to be interchangeable. The significance of Einstein's formula is even beyond physics. In biology, energy is an attribute of all living organisms from bacteria to human being. The conversion between mass and energy are fundamental to the biological processes defined as metabolism by which living organisms cycle energy through different mechanisms to produce the necessary molecules and perform the essential functions of life. Through anabolism, complex compounds are biosynthesized from simpler molecules with the energy expense provided by ATP hydrolysis. Through catabolism, complex nutrients are broken down to simpler oxidized molecules with an energy releasing process coupled to ATP production. Life is the interplay between energy and structure (Wallace, 2005). As the metabolism goes on, the life goes on (Fig. 1).

Mammalian brain is characterized by high metabolic activity with fine regulatory mechanisms to ensure adequate energy substrates supply in register with neuronal activity. The human brain constitutes only 2% of the body weight, but receives 15% of cardiac output, accounts for almost 20% of the total oxygen consumption, and consumes approximately 25% of total body glucose utilization. The human brain is by far the most expensive