Free Radical Biology and Medicine 102 (2017) 203–216

Contents lists available at ScienceDirect

Free Radical Biology and Medicine

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

Review Article

Adaptive responses of neuronal mitochondria to bioenergetic challenges: Roles in neuroplasticity and disease resistance

Sophia M. Raefsky[a], Mark P. Mattson[a,b,*]

[a] Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD 21224, United States
[b] Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States

ARTICLE INFO

Keywords:
3-hydroxybutyrate
Aerobic exercise
Autophagy
CREB
Hormesis
Intermittent fasting
Mitochondrial biogenesis
PGC-1α

ABSTRACT

An important concept in neurobiology is "neurons that fire together, wire together" which means that the formation and maintenance of synapses is promoted by activation of those synapses. Very similar to the effects of the stress of exercise on muscle cells, emerging findings suggest that neurons respond to activity by activating signaling pathways (e.g., Ca^{2+}, CREB, PGC-1α, NF-κB) that stimulate mitochondrial biogenesis and cellular stress resistance. These pathways are also activated by aerobic exercise and food deprivation, two bioenergetic challenges of fundamental importance in the evolution of the brains of all mammals, including humans. The metabolic 'switch' in fuel source from liver glycogen store-derived glucose to adipose cell-derived fatty acids and their ketone metabolites during fasting and sustained exercise, appears to be a pivotal trigger of both brain-intrinsic and peripheral organ-derived signals that enhance learning and memory and underlying synaptic plasticity and neurogenesis. Brain-intrinsic extracellular signals include the excitatory neurotransmitter glutamate and the neurotrophic factor BDNF, and peripheral signals may include the liver-derived ketone 3-hydroxybutyrate and the muscle cell-derived protein irisin. Emerging findings suggest that fasting, exercise and an intellectually challenging lifestyle can protect neurons against the dysfunction and degeneration that they would otherwise suffer in acute brain injuries (stroke and head trauma) and neurodegenerative disorders including Alzheimer's, Parkinson's and Huntington's disease. Among the prominent intracellular responses of neurons to these bioenergetic challenges are up-regulation of antioxidant defenses, autophagy/mitophagy and DNA repair. A better understanding of such fundamental hormesis-based adaptive neuronal response mechanisms is expected to result in the development and implementation of novel interventions to promote optimal brain function and healthy brain aging.

1. Bioenergetic challenges as fundamental 'Drivers' of brain evolution

In order to survive and reproduce, organisms must obtain sufficient energy from their environment. Be they herbivores, carnivores or omnivores, mammals have evolved to be highly efficient in obtaining food and storing the molecular energy substrates in the food in forms that are readily mobilized to sustain high levels of physical and mental exertion. In the case of carnivorous predators living in environments where prey are limited, it is intuitively obvious and an established fact that the brain and body must function well when the animal has not eaten for extended time periods of many days to weeks or even months [1,2]. For example, the availability of food for gray wolves varies considerably within and between years such that the wolves may locate and kill a prey species only once every 10–20 days [3]. In the case of herbivores, there are very large seasonal fluctuations in food availability such that, similar to many carnivores, the animals must endure extended periods of food deprivation. For example, the deer that live in regions of the Northern hemisphere with harsh winters experience a drastic reduction in food availability and lose considerable weight during the winter months [4]. The success of any individual in obtaining the energy (calories) required to survive and reproduce depends critically upon their cognitive abilities, which for many species involves cooperation with other members of their species. Thus, by hunting in 'packs' wolves can surround and collectively kill animals, such as buffalo, that could not be killed by an individual wolf. Our human ancestors responded to limited food resources by evolving the extraordinary abilities of imagination and creativity [5] to: invent tools to kill prey at a distance (spears, bow and arrows, firearms); domesticate large animals solely for the purpose of their consumption; develop machines and agricultural processes for large-scale production of grains, fruits and vegetables; and create methods for the processing

* Corresponding author at: Laboratory of Neurosciences, National Institute on Aging, Baltimore, MD 21224, United States.
E-mail address: mark.mattson@nih.gov (M.P. Mattson).

http://dx.doi.org/10.1016/j.freeradbiomed.2016.11.045
Received 22 October 2016; Accepted 27 November 2016
Available online 29 November 2016
0891-5849/ Published by Elsevier Inc.

of foodstuffs into inexpensive high energy-density products such as high-fructose corn syrup, and saturated and trans fats [2].

As with other species, human brain evolution was influenced greatly by the 'pressure' of limited food resources. The brain regions that expanded most during the evolution of non-human primates and the different species of their human descendants play fundamental roles in the processing of visual and auditory patterns (occipital and parietal lobes) and decision making (prefrontal cortex) [5]. Neuronal networks in these and associated brain regions (e.g., hippocampus, frontal cortex) mediate the mental 'fabrication' of new patterns (images and sounds) in the processes of imagination and creativity. The flexibility of mental 'manipulation' of patterns is the basis all aspects of the advanced capabilities of the human brain including: spoken and written languages; the invention of tools, machines, drugs, etc.; efficient decision-making; and the ability to understand the world and universe using the tools of science [5]. A major expansion of the prefrontal cortex occurred in arboreal primates who were foragers that subsisted on the fruits and nuts in the canopy; individuals that were able to make accurate decisions as to where and when those foods were available (mediated by the prefrontal cortex) were selected for [6]. The archeological record suggests that during an extended time period during early evolution of bipedal ground-dwelling human species, the only tools developed were for the purpose of obtaining food [7]. The invention of methods for the cultivation of crops and animal husbandry led to a rapid decrease in hunter-gatherer lifestyles and fostered the evolution of large societies (cities, states and countries) of individuals who then devoted their time and energy to learning and teaching specialized skills, and to the development of new technologies.

In this Perspective Article we posit that, via evolutionarily conserved cellular and molecular signaling mechanisms that converge on brain cell mitochondria, fasting and vigorous exercise enhance cognitive performance and increase resistance of neurons to injury, aging and disease. It has been known for decades that, in response to the bioenergetic challenge of intermittent vigorous exercise, signaling pathways are activated in muscle cells that result in an increase in the number of healthy mitochondria (mitochondrial biogenesis) and so increase resistance of muscle cells to fatigue [8,9]. Moderate energy restriction/intermittent fasting can also improve skeletal and cardiac muscle health and stress resistance [10]. Elevated ketone levels, such as occurs during fasting, may enhance endurance exercise performance [11]. Emerging evidence suggests that, similar to the effects of exercise on muscle cells, exercise and energy restriction activate signaling pathways in neurons that bolster mitochondrial function and cellular stress resistance. Moreover, by brain autonomous and non-autonomous mechanisms described below, mitochondrial responses to bioenergetics challenges can enhance synaptic plasticity, learning and memory and neurogenesis. Because both exercise and intermittent fasting have robust neuroprotective and neuroplasticity-promoting effects in animal models of many different brain disorders in which mitochondrial dysfunction is implicated [12,13], we will also consider how bioenergetic challenge-based improvements in mitochondrial health could be applied to the prevention and treatment of a range of human brain disorders.

2. Overview of mitochondrial functions and dynamics in neurons

Mitochondria are essential for cell viability and proper cell function, including their prominent roles in the production of ATP, metabolism of reactive oxygen species, regulation of Ca^{2+} dynamics, and apoptosis [13,14]. In neurons, mitochondria are critical for maintenance of membrane ion (Na^+ and Ca^{2+}) gradients, and for neurotransmission and synaptic plasticity [15].

Most of the ATP produced in neurons is generated by the mitochondrial membrane-associated ATP synthase which is the final enzyme complex in the electron transport chain. Neurons have a limited glycolytic capacity such that only approximately 10% of their ATP is produced by glycolysis [16]. Therefore, mitochondrial bioenergetics is pivotal for the many different ATP-dependent processes that enable neurons to function and respond adaptively to environmental challenges. Examples include fueling of: membrane ion-motive ATPases; kinases involved in the intracellular transduction of extracellular signals including neurotransmitters and neurotrophic factors; proteins involved in cytoskeletal remodeling; the movement of organelles within the neuron; and the release and recycling of neurotransmitters [13,17–21].

Neuronal mitochondria are especially susceptible to oxidative stress because their electron transport chain is very active in these excitable cells and therefore generates large amounts of superoxide anion radical [13]. The mitochondrial antioxidant enzyme superoxide dismutase 2 (SOD2), and proteins such as sirtuin 3 (SIRT3) that increase SOD2 activity, are very important in the removal of superoxide [22]. Another feature of mitochondria is that they contain high amounts of polyunsaturated fatty acids which are especially vulnerable to reactive oxygen species (ROS) [23]. When polyunsaturated fatty acids are oxidized, one of the byproducts is the aldehyde 4-hydroxynonenal (HNE), which, through the non-enzymatic process of Michael addition, can covalently modify cysteine, lysine, and histidine residues of proteins, which can impair the function of the proteins [24]. Some of the proteins that are modified by HNE are mitochondrial electron transport chain proteins, ion and nutrient transporters, growth factor and neurotransmitter receptors, protein chaperones, proteasomal proteins, and cytoskeletal proteins [24–26]. Mitochondrial DNA is particularly susceptible to oxidative stress because of its proximity to the respiratory chain and absence of protective histones [21]. Because the mitochondrial DNA encodes 13 protein components of the electron transport chain, oxidative damage to DNA can impair ATP production and elicit a destructive cycle in which ROS damage DNA resulting in increased ROS generation [24].

The numbers of mitochondria in a cell and the size of individual mitochondria are malleable, and are regulated by the processes of mitochondrial fission and fusion. Fission plays a role in mitochondrial biogenesis, and is also fundamental to the elimination of dysfunctional mitochondria in a process called mitophagy [14,27–30]. Proteins that mediate mitochondrial fission include dynamin-related protein 1 (Drp 1) and fission 1 (Fis1), and proteins involved in mitochondrial fusion include mitofusins 1 and 2 (Mfn1/2) and optic atrophy type 1 (Opa1) [31,32]. The processes of fission and fusion are associated with the movement of mitochondria to specific subcellular locations, and can also influence the ability of the cell to repair damaged mitochondrial DNA [21]. The process of mitochondrial biogenesis involves not only the fission of mitochondria, but also an increase in the size of mitochondria prior to and after fission. The protein peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a transcriptional regulator that promotes the expression or transcriptional activity of proteins critical for mitochondrial biogenesis including transcription factor A of mitochondria (TFAM) and nuclear respiratory factors 1 and 2 [33]. PGC-1α can be induced by metabolic challenges such as exercise, by ROS and by cyclic AMP response element binding protein (CREB).

Mitophagy is a term used to describe the process by which mitochondria are chaperoned through an autophagy pathway that ends in destruction of the mitochondrial components in lysosomes. Mitophagy is an ongoing process in healthy cells that selectively removes damaged or dysfunctional mitochondria that could harm the cell by generating excessive amounts of ROS and by the release of pro-apoptotic signals such as cytochrome C [34]. Mitophagy can be stimulated by moderate levels of metabolic and oxidative stress and by inhibition of the mTOR (mammalian target of rapamycin) pathway. Dietary energy restriction and exercise, which are known to improve brain function and increase resistance of neurons to oxidative, metabolic and excitatory stress, inhibit the mTOR pathway and stimulate both mitophagy and mitochondrial biogenesis [35,36].