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Review

Heterogeneity of nervous system mitochondria: Location, location, location!

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ABSTRACT

Mitochondrial impairments have been associated with many neurological disorders, from inborn errors of metabolism or genetic disorders to age and environmentally linked diseases of aging (DiMauro S., Schon E.A. 2008. Mitochondrial disorders in the nervous system. Annu. Rev., Neurosci. 31, 91–123.). In these disorders, specific nervous system components or brain regions appear to be initially more susceptible to the triggering event or pathological process. Such regional variation in susceptibility to multiple types of stressors raises the possibility that inherent differences in mitochondrial function may mediate some aspect of pathogenesis. Regional differences in the distribution or number of mitochondria, mitochondrial enzyme activities, enzyme expression levels, mitochondrial genes or availability of necessary metabolites become attractive explanations for selective vulnerability of a nervous system structure. While regionally selective mitochondrial vulnerability has been documented, regional variations in other cellular and tissue characteristics may also contribute to metabolic impairment. Such environmental variables include high tonic firing rates, neurotransmitter phenotype, location of mitochondria within a neuron, or the varied tissue perfusion pressure of different cerebral arterial branches. These contextual variables exert regionally distinct regulatory influences on mitochondria to tune their energy production to local demands. Thus to understand variations in mitochondrial functioning and consequent selective vulnerability to injury, the organelle must be placed within the context of its cellular, functional, developmental and neuroanatomical environment.

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Introduction

Many elements contribute to the perception of compartmentalization of metabolic and mitochondrial function within the nervous system. From a historical perspective, this question has been

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approached using biochemical, histological, anatomical, genomic, proteomic and functional imaging techniques. This review will combine these diverse approaches to address emerging issues in the underlying biochemistry and how these translate into functional differences in basal, stimulated and stressed states. The majority of this information relates to CNS mitochondria. Because metabolic impairment can result in peripheral neuronal injury and because mitochondria in peripheral nervous tissues are more accessible for some techniques, information from the PNS will be included where pertinent.

Regional variations in metabolism comprise key measurements for understanding basic functional neuroanatomy. The underlying assumption is that high neuronal activity requires increased metabolism to fuel pumps, maintain membrane gradients and support synaptic activity (Sokoloff et al., 1977). Activation of a functional circuit will be reflected in the increased metabolic activity measured in the corresponding brain regions. From histology to contemporary in vivo imaging techniques, understanding differences in metabolism and substrate utilization across CNS structures associated with different behaviors has yielded insights into CNS circuitry (Raichle, 2008). In the absence of localized techniques to examine the electrophysiological behavior of large groups of neurons simultaneously, histological examination of ^{14}C 2-deoxyglucose uptake and cytochrome oxidase activity linked the concept of ocular dominance columns to activity generated metabolic demand (Kennedy et al., 1976; Hubel et al., 1977; Wong-Riley, 1979). By carefully manipulating behaviors, patterns of glucose uptake using ^{14}C 2-deoxyglucose uncovered functionally linked anatomical circuits (Sokoloff et al., 1977; Kennedy et al., 1980). 2-Deoxyglucose uptake studies identified regions and neurons with high glucose uptake capacity that correlated with dark cytochrome oxidase histochemical reactivity indicating comparably high oxidative metabolism in regions with high glucose metabolism (Humphrey and Hendrickson, 1983). In monocularly deprived cats, the absence of activity decreases the size of presynaptic nerve terminals in striate cortex and the number of mitochondria they contain (Tieman, 1985). PET and fMRI imaging techniques are regularly employed to link brain activity to physiological behaviors and mental activity in the field known as brain mapping (Raichle, 2008). Human ocular dominance columns can now be mapped non-invasively with high field fMRI, a technique based upon blood oxygen level-dependent contrast and hemodynamics (Yacoub et al., 2008). Brain activity levels in rats, manipulated by anesthetic levels and measured by EEG, have been correlated to measurements of the reaction rate for ATP synthesis using ^{31}P magnetic resonance spectroscopy combined with magnetization transfer (Du et al., 2008). From cortical columns to mapping of brain regions involved in complex and cognitive behaviors, visualizing patterns of metabolic activity links brain regions into functional circuits.

The premise that glycolytic and oxidative metabolic activity reflects circuit activation is based upon the assumption that the biochemical pathways of glycolysis and oxidative phosphorylation operate similarly in all nervous system structures. Expression levels, activities, and fluxes may vary but the basic biochemistry of energy production in nervous system mitochondria utilizes glycolysis, TCA cycle and oxidative phosphorylation pathways, with a smaller component from beta oxidation, which will not be discussed here. While the delivery of oxygen and glucose to the brain is complicated by the dynamics of blood flow, the underlying mitochondrial biochemistry utilizing the delivered glucose and oxygen to generate ATP remain essentially the same as in liver (Maker et al., 1976). In the cytosol, glucose is processed to pyruvate through glycolysis. After transport into mitochondria, pyruvate is converted to acetyl CoA which enters the TCA cycle to produce GTP, $FADH_2$, CO_2, H_2 and NADH. Electrons from NADH and $FADH_2$ enter the electron transport chain (ETC) to produce ATP through oxidative phosphorylation. The idea that the capacity of these pathways may be limited by regionally specific regulatory mechanisms in their ability to respond to functional demands forms the basis for many hypotheses of selective neuronal vulnerability.

The concept that neurons and astrocytes interact to form a single functional metabolic unit is supported by extensive experimental evidence (Kasischke et al., 2004; Magistretti, 2006; DiMauro and Schon, 2008). The proposed metabolic coupling operates with astrocytes processing glucose through glycolysis and exporting lactate to neighboring neurons. In neurons, reverse operation of lactate dehydrogenase converts the lactate to pyruvate and generates ATP through the TCA cycle. While this may account for glucose utilization following activation, both cell types contain both sets of enzymes and can operate both aerobic and anaerobic pathways. Determining the conditions conducive for proportional use of each pathway remains an experimental challenge (Hertz, 2004; Bonvento et al., 2005; Fillenz, 2005; DiMauro and Schon, 2008). Glutamate–glutamine cycling represents another example of metabolic handshaking between neurons and astrocytes (Bak et al., 2006; Hyder et al., 2006; Hertz et al., 2007). Synaptically released glutamate is taken up by astrocytes where glutamine synthase converts it to glutamine with subsequent export to the extracellular space. Neuronal uptake of glutamine provides a substrate for glutamate synthesis via phosphate-activated glutaminase. An additional illustration of metabolic cooperation among the different nervous system cell types is the production of N-acetyl aspartate (NAA), one of the unique amino acids found in the CNS (Maker et al., 1976). Neuronal mitochondria and to a much smaller extent microsomes synthesize NAA via the enzyme aspartyl-N-acyltransferase (reviewed in Satrustegui et al., 2007). NAA is subsequently shuttled via axon-to-myelin transfer to oligodendroglia which contain the enzyme aspartoacylase II that cleaves NAA to produce the acetate needed for myelin formation.

Nervous system cells vary metabolically in their oxygen consumption. Photoreceptors, which are depolarized in the dark and continuously release neurotransmitter, consume oxygen at rates two to three times higher than other retinal neurons in order to maintain their ionic gradients (Kageyama and Wong-Riley, 1984; Yu and Cringle, 2005). Structures in auditory pathways have the highest 2-deoxyglucose uptake of all CNS regions (Sokoloff, 1993). Stimulation of the sciatic nerve activates dorsal horn metabolism in a frequency dependent manner but metabolism in the DRG is unaltered (Sokoloff, 1993). Although oligodendroctyes rank second to neurons in oxygen demand by cell type (Maker et al., 1976), oxygen consumption and 2-deoxyglucose uptake in white matter are two to four times less than that of gray matter (Heller and Elliot, 1955; Sokoloff et al., 1977). Within peripheral nerves, however, Schwann cells consume two thirds of the energy and axons only a third (Stewart et al., 1965). Heterogeneity of enzyme expression occurs even within neuronal mitochondria from the same neurotransmitter phenotype in the same region. Phosphate-activated glutaminase activity within parallel and climbing fibers is only 20% that of mossy fibers (Laake et al., 1999), an observation that correlates with firing frequency rather than neurotransmitter phenotype. The common theme among these areas with high oxidative capacity is the need to sustain ionic gradients underlying high frequency spiking or chronic neurotransmitter release for long periods of time. Those areas involved in low frequency activity consume proportionately less oxygen (Sokoloff, 1993).

Nonuniformities can also occur in different regions of the same neuron (Wong-Riley, 1989). Mitochondrial density varies from dendrites and somas to axons and nerve terminals. For projection neurons, axonal volume far exceeds that of somas and dendrites yet estimates of mitochondrial numbers and energy demand are less for the axonal compartment than for the soma-dendritic compartment (Attwell and Laughlin, 2001). Unmyelinated axons require more energy than myelinated axons (Carelli et al., 2004). Metabolic activity is higher in the terminal fields of axons than at the sites of neuronal somas (Sokoloff, 1993). Mitochondrial density is so high in