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Review

Mitochondrial changes associated with demyelination: Consequences for axonal integrity

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ABSTRACT

The loss of myelin sheath (demyelination) renders axons vulnerable to a variety of insults. Axonal degeneration is well recognised in inflammatory demyelinating disorders of the central nervous system (CNS) such as multiple sclerosis (MS) and also certain neurodegenerative diseases. Energy required for nerve impulse conduction and maintenance of structural integrity of axons is met by mitochondria. Based on the distribution of ion channels and the Na^+/K^+ ATPase, the energy requirements of demyelinated and dysmyelinated axons are likely to differ from myelinated axons. In this review we discuss the changes in mitochondrial presence within axons in relation to presence or absence of healthy myelin sheaths and propose the increase in mitochondrial presence following demyelination as an adaptive process. An energy deficit within demyelinated axons is likely to be more detrimental compared to myelinated axons, judging by the neuropathological findings in primary mitochondrial disorders due to mitochondrial and nuclear DNA mutations and the mitochondrial changes that follow demyelination. Agents that enhance and protect mitochondria, as potential therapy, need to be considered and investigated in earnest for demyelinating disorders of the CNS such as MS.

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1. Introduction

Axons are unique structures in the central nervous system with much of their cytoplasm found at great distances from the neuronal cell body. Myelination of axons is essential for fast conduction of action potentials and their metabolic efficiency (Yin et al., 2006). Axonal degeneration in demyelinating diseases such as multiple sclerosis (MS) indicate the importance of trophic support that myelin lends to axons also protecting from various extracellular insults. Axonal loss in MS is considered as the pathological substrate of

Abbreviations: β-APP, beta-amyloid precursor protein; CNS, central nervous system; KSS, Kearns–Sayre syndrome; LHON, Leber's hereditary optic neuritis; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibres; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy (MNGIE); MS, multiple sclerosis; mtDNA, mitochondrial DNA; Na_v, sodium channel; PLP, proteolipid protein; TMEV, Theiler's murine encephalomyelitis virus.

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irreversible decline in neurological function or disease progression. Mitochondria, the ubiquitous energy producing organelles, are found within axons. They are vastly dynamic and locate to areas in which they are most needed and, as we will discuss in this chapter, appear highly adaptable to energy changes within the axon. We review mitochondrial changes that follow demyelination and indicate the damaging consequences of mitochondrial failure for axons.

2. Mitochondria

Mitochondria are charged with supplying the vast amount of ATP required in eukaryotic cells. Other important roles in calcium buffering and apoptosis cannot be underestimated (DiMauro and Schon, 2003). The respiratory chain, which is responsible for the process of oxidative phosphorylation, ultimately resulting in the production of ATP from ADP, consists of complex I–complex IV and an additional ATP synthase. ATP synthase uses a proton gradient formed by the movement of protons from the matrix to the intermembrane space facilitated by complex I, complex III and complex IV to form ATP. The movement of protons across the inner mitochondrial membrane is coupled with the transfer of electrons which is aided by two electron carriers; ubiquinone and cytochrome *c*.

Mitochondria contain the only extra-nuclear DNA in the cell (mtDNA). The mitochondrial genome holds 13 protein encoding genes which incorporate into complex I, complex III, complex IV and ATP synthase. Complex II is the only complex with all subunits encoded by nuclear DNA, which, from an investigative point of view, is highly advantageous (Taylor et al., 2004; Taylor and Turnbull, 2005). MtDNA mutation (point mutations and deletions) led energy deficiency states frequently affect the central nervous system (CNS) in patients with primary mitochondrial diseases. mtDNA is also more prone to induced mutations than nuclear DNA due to its presence in a highly oxidative environment.

3. Electrogenic machinery and a question of energy for axons

The vast energy requirement of axons is highlighted by the location of the sodium potassium ATPase (Na^+/K^+ ATPase) which extends along myelinated segments of the axons (internodes) (Young et al., 2008). The Na^+/K^+ ATPase facilitates the rapid extrusion of sodium for extracellular potassium, through the process of active transport and is thus a major consumer of energy in the CNS (Waxman, 2008a,b). Sodium channels play an important role in axons and their clustering at the nodes of Ranvier facilitate the fast propagation of action potentials or 'saltatory conduction', and allow influx of sodium into the axon. Different isoforms exist but the accepted forms known to exist in neurons are $Na_v1.1$, $Na_v1.2$ and $Na_v1.6$. Those expressed on axonal membranes are predominantly $Na_v1.2$ and $Na_v1.6$ (Kaplan et al., 2001). The importance of the persistent sodium influx allowed for by $Na_v1.6$ is highlighted by the redistribution of the channel along unmyelinated axons to maintain action potentials (Black et al., 2002). During development in the pre-myelination state, $Na_v1.2$ channels support action potentials (Waxman et al., 1989) which are soon replaced following myelination with $Na_v1.6$ channels, identified to allow a persistent current of sodium. Myelin also induces the clustering of sodium channels at nodes of Ranvier (Shrager, 1989). In the CNS, mitochondria were presumed to reside in the unmyelinated segments, nodes of Ranvier, based on findings in PNS, however recent evidence suggests that mitochondria preferentially locate in the internodes (Edgar et al., 2008), at least in small diameter axons, which would fit with the energy demand hypothesis. Evidence for the need of precise location of mitochondria within axons is observed in growth cones. An elegant study by Morris and Hollenbeck in 1993 showed that the presence of mitochondria in neurons is co-ordinated with axonal outgrowth. They showed that by blocking the growth of a number of axons and then visualising the mitochondrial content, the preferential location of the mitochondria was in the outgrowing axons, particularly in the terminal ends (Morris and Hollenbeck, 1993). Whilst ATP can readily diffuse into the cytosol it appears the precise location of mitochondria is important.

Axons, both myelinated and unmyelinated, are an excellent forum to understand the relationship between mitochondria and the differing energy demands of the CNS, given the difference in ion channel expression in these axons (Waxman, 2006). Lessons can be learnt from those areas of the CNS that are unmyelinated. The lamina cribrosa is a region of the optic nerve that is unmyelinated with myelination of fibres occurring at the posterior border. This represents a unique opportunity to study the distribution of mitochondria and activity in myelinated and unmyelinated segments of the same axons. Complex IV activity was assessed in fibres of the lamina cribrosa. Complex IV is the terminal complex in the electron transport chain and consists of three catalytic subunits encoded by mitochondrial DNA and accessory subunits, encoded by nuclear DNA (Taylor and Turnbull, 2005). The complex consumes 90% of cellular oxygen (DiMauro and Schon, 2003) and is involved in proton pumping across the inner mitochondrial membrane. Perhaps importantly, numerous inhibitors of complex IV exist including nitric oxide, a competitive inhibitor (Brown and Cooper, 1994), whilst its more toxic derivative, peroxynitrite, can irreversibly inhibit both complex I and complex IV (Clementi et al., 1998). Complex IV activity was found to be vastly increased in the unmyelinated segment compared to the myelinated segment, which corresponded with an increase in complex IV subunit II level (Bristow et al., 2002; Balaratnasingam et al., 2009). The distribution of complex IV activity correlated with certain isoforms of sodium channels. Both $Na_v1.1$ and $Na_v1.6$ were found to increase in intensity with lack of myelin whilst there was little predilection for $Na_v1.2$ in either region (Barron et al., 2004). These findings within unmyelinated fibres in control subjects suggest that the increase in mitochondrial content within axons may not necessarily be a pathogenic process.

4. Demyelination associated mitochondrial changes in experimental systems

Several groups have predicted metabolic changes within axons based on changes in ion channel distribution following demyelination and dysmyelination (Mutsaers and Carroll, 1998; Andrews et al., 2006; Hogan et al., 2009). There have been a number of studies with animal models in which genes for myelin proteins have been knocked out or toxic insults to myelin have been introduced (Figs. 1 and 2).

In a mouse model of hypomyelination caused by gene knockout encoding the myelin basic protein gene, complex IV activity was found to be increased associated with an increase in mitochondrial density suggestive of adaptive changes to the disturbance in myelin (Andrews et al., 2006). Furthermore in a proteolipid protein (PLP) overexpressing mouse model, dysmyelination at 1 month followed by complete demyelination at 4 months was associated with an increase in mitochondrial density and complex IV activity compared to wildtype (Hogan et al., 2009). In a hemizygous PLP overexpressing mouse model predisposing to only partial demyelination, whilst mitochondrial density increased, complex IV activity remained similar to wildtype. Electron microscopy revealed the presence of degenerating axons suggesting a lack of compensation from complex IV predisposed to the phenotype. These animal models show the relationship between disruptions to myelin and changing energy demands compensated for by amendments in mitochondria.

In one particular model in which antiserum to galactocerebroside was used to selectively demyelinate cat optic nerve a significant increase in mitochondrial number was observed which reached a peak at seven days post injection (Mutsaers and Carroll, 1998). The fact that this coincided with a change from conduction block to slowed conduction (Carroll et al., 1985) suggests a physiological response of mitochondria to demyelination in order to resume conduction. In a demyelination model induced by Theiler's murine encephalomyelitis virus (TMEV),

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