Hypoxic-like Aspects of MS

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Multiple sclerosis (MS), an inflammatory demyelinating disease, is a major cause of neurological disability in young adults in the developed world. Although the progressive neurological disability that most patients with MS eventually experience results from axonal degeneration, little is known about the mechanisms of axonal injury in MS. Accumulating evidence supports the concept that the increased energy demand of impulse conduction along excitable demyelinated axons and reduced axonal ATP production induce a chronic state of virtual hypoxia in chronically demyelinated axons. In response to such a state, key alterations that contribute to chronic necrosis of axons include mitochondrial dysfunction (due to defective oxidative phosphorylation or nitric oxide production), Na influx through voltage-gated Na channels and axonal AMPA receptors, release of toxic Ca from the axoplasmic reticulum, and activation of voltage-gated Ca channels, ultimately leading to excessive stimulation of Ca-dependent degradative pathways. The development of neuroprotective therapies that target these mechanisms constitute effective adjuncts to currently used immune modifying agents.