The brake on neurodegeneration

Increased mitochondrial metabolism in the injured MS spinal cord

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In this issue of *Neurology*®, Ciccarelli et al.[1] present an intriguing study assessing 14 patients with multiple sclerosis (MS) at the time of an acute relapse related to a lesion at the spinal C1–C3 level. The authors performed magnetic resonance spectroscopy (MRS) and atrophy measurements on spinal cords of these 14 patients with MS and 13 age- and gender-matched healthy controls. Spinal *N*-acetylaspartate (NAA) concentrations were calculated at baseline and followed for 1, 3, and 6 months, as was spinal cord cross-sectional area. The investigators found that after an initial decrease in the first month, NAA levels recovered partially in the months after the inflammatory demyelinating event, and that patients who recovered showed a greater increase in NAA after 1 month. Spinal cord cross-sectional area gradually decreased over time and was independent of NAA recovery and, interestingly, of clinical outcome. The authors report that longer disease duration at baseline predicted less NAA recovery over time, suggesting that repair processes become "burnt-out" (i.e., less effective) with progressing disease.

NAA is abundantly present in the human CNS, especially in neurons, and decreased levels of NAA, as measured with MRS, are therefore used as a marker for neuronal loss or dysfunction. Although the exact function of the metabolite is still debated, it is known that it is synthesized in neuronal mitochondria, and changes in NAA levels thus point to abnormal mitochondrial metabolism, which in turn may lead to neurodegeneration. Ciccarelli et al. point out that the initial decrease in NAA (during the first month of their study) is in line with decreased mitochondrial activity, which is probably related to the interaction of axons with microglia and other immune modulators.[2] The subsequent NAA increase may reflect increased mitochondrial numbers or activity or both, all in an attempt to maintain axonal electrical conduction. Increased numbers of mitochondria and enhanced activity of mitochondrial complex IV were indeed found in histopathologic studies investigating demyelinated axons in actively demyelinating and chronic MS lesions,[2,3] and may be considered as an endogenous protective mechanism of the CNS to repair damage after an inflammatory demyelinating insult.

However, whether increased mitochondrial activity is to be considered beneficial in the long run is a question worth delving into further. Mitochondria are an important source of reactive oxygen species (ROS); hence, it is conceivable that prolonged mitochondrial overactivity might contribute to the formation of highly toxic oxygen radicals and concomitant oxidative tissue injury. Increased ROS production and enhanced expression and activity of nitric oxide synthase inhibits the mitochondrial electron transport chain, which, in turn, leads to increased mitochondrial ROS production, adenosine triphosphate depletion, and disturbed Ca^{2+} homeostasis due to reversed Na^{+}/Ca^{2+} transporter activity. Together, these detrimental changes impair mitochondrial function and subsequent energy production, ultimately resulting in axonal death.[4] We previously showed that mitochondria in MS lesions are subjected to oxidative stress as indicated by enhanced expression of the mitochondrial heat shock protein 70.[3] In addition, several reports have demonstrated the occurrence of ongoing oxidative damage in MS brain tissue.[5]

The findings by Ciccarelli et al.[1] in combination with the above discussed histopathology studies[2,3] emphasize that mitochondrial dysfunction is an important pathologic hallmark in MS and that strategies aimed at improving mitochondrial function may limit disease progression. Previously, NAA recovery in MS was reported to occur after treatment with interferon beta-1b and glatiramer acetate,[6,7] which suggests that currently available medication might already be of use in treating and partially reversing axonal damage related to mitochondrial dysfunction. However, more targeted therapies that boost endogenous levels of mitochondria-specific antioxidant enzymes, such as superoxide dismutase 2,[8] or administration of antioxidant compounds

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that selectively accumulate in mitochondria, e.g., mitoquinone (MitoQ),[9] may be even more effective. MitoQ represents a novel class of powerful antioxidants that, because of their positive charge, specifically accumulate within mitochondria. Recently, it has been shown that MitoQ has therapeutic potential in vivo, because it blocked mitochondrial oxidative damage and greatly reduced tissue damage in a cardiac ischemia-reperfusion model.[10] Currently, phase 2 trials are ongoing to explore the efficacy of MitoQ in a human setting. Future explorative clinical trials using mitochondrial antioxidants could rely on the MRS approach adopted by Ciccarelli et al. to monitor NAA recovery over time, in relation to tissue atrophy.

It has been repeatedly demonstrated that in response to tissue damage in MS, repair processes occur throughout the entire CNS. Aside from the increases in mitochondrial number and function already discussed, and the redistribution of axonal sodium channels in an attempt to maintain axonal function upon demyelination, remyelination and extensive use of the reserve capacity of the brain were found.[11,12] Unfortunately, however, all these compensatory changes are finite, and relentless neurodegeneration will eventually set in. In the study by Ciccarelli et al., longer disease duration predicted less NAA recovery, which underlines the limits of compensatory changes over time. This might explain why the rate of gray matter atrophy suddenly starts accelerating around the conversion point from relapsing-remitting to secondary progressive disease[13]: the brake on neurodegeneration is released.

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DISCLOSURE

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