ANTIOXIDANTS HALT AXONAL DEGENERATION AND DISABILITY IN A MOUSE MODEL OF THE NEUROMETABOLIC DISEASE ADRENOLEUKODYSTROPHY

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\textbf{Introduction:} Adrenoleukodystrophy (X-ALD) is a neurodegenerative disease caused by loss of function of the ABCD1 peroxisomal transporter of very long-chain fatty acids (VLCFA). The mouse model for X-ALD exhibits a late-onset neurological phenotype with locomotor disability and axonal degeneration in spinal cords. Axonal degeneration is a main contributor to disability in progressive neurodegenerative diseases in which oxidative stress is often associated as pathogenic factor. Recently, we have identified oxidative damage as an early event in life, and the excess of VLCFA as a generator of radical oxygen species (ROS) and oxidative damage to proteins in X-ALD.

\textbf{Aims:} To demonstrate that antioxidants are able to improve axonal degeneration and locomotor deficits in the X-ALD mouse model.

\textbf{Methods and results:} Here, we prove the capability of the antioxidants N-acetyl-cysteine, a-lipoic acid and a-tocopherol to scavenge VLCFA-dependent ROS generation \textit{in vitro}. Further, in a preclinical setting, the cocktail of the three compounds reversed:

i) oxidative stress and lesions to proteins,

ii) immunohistological signs of axonal degeneration and

iii) locomotor impairment in bar cross and treadmill tests.

\textbf{Conclusions:} We have established a direct link between oxidative stress and axonal damage in a mouse model of neurodegenerative disease. This conceptual proof of oxidative stress as a major disease-driving factor in X-ALD provides warrants translation into clinical trials, and invites assessment of antioxidant strategies in axonopathies in which oxidative damage might be a contributing factor.