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Oligodendrocyte maturation and myelination: Implications of deficient thyroid hormone transport to the brain.

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Oligodendrocytes are glial cells that play a crucial role in the CNS. Their maturation and myelination are finely regulated processes that require key trophic signals important for growth and metabolism. Thyroid hormone (TH) is a potent signal that regulates oligodendrocyte maturation, oligodendroglial-synaptic interactions and myelination. TH transport across the blood-brain barrier and cellular membranes is mediated by a specific transmembrane transporter, the monocarboxylate transporter 8 (MCT8). Dysfunction of MCT8 leads to inherited hypomyelination and psychomotor disabilities in the X-linked Allan-Herndon-Dudley syndrome (AHDS) or MCT8-deficiency. Although impairments in myelination in AHDS patients represent one of the main hallmarks of the disease, there is no consensus on whether there is a permanent hypomyelination or a delay on myelination that is restored later in life.

To address this point, we made use of multiple techniques to study myelination processes in Mct8/Dio2 knockout mice (KO), an already validated model for AHDS, from postnatal to adult stages, to gain new insight into the pathophysiological mechanisms of AHDS and the effects of TH on myelination.

Myelination was studied histologically by assessing the content of myelin proteins and lipids. These studies revealed persistent myelination defects in the brain of Mct8/Dio2 KO mice, consistent with observations at the ultrastructural level showing severely decreased percentage of myelinated axons in the Mct8/Dio2 KO mice brain using transmission electron microscopy analyses. Myelination was also assessed by Magnetic Resonance Imaging, showing microstructural alterations in the white matter. These data obtained on myelination led to the study on oligodendroglial dynamics, showing altered proliferation and differentiation patterns from oligodendrocyte precursor cell stages.

Myelination and oligodendroglial dynamics in Mct8/Dio2 KO mice are altered from early developmental stages and these alterations persist throughout later stages. Altogether, these data provide new understanding on the pathophysiological mechanisms underlying MCT8 deficiency to design and evaluate possible future treatments.