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Commentary

Can Thyroid Hormone Analogues Be Used to Overcome Hypomyelination and Demyelination of the Central Nervous System?

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Thyroid hormone (TH) regulates the development of many tissues, including the brain (Calza et al., 2015). It is synthesized by follicular cells in the thyroid gland, and secreted as a prohormone (T4) that is deiodinated to bioactive T3 in the target cells (Gereben et al., 2008). While the concentration of T3 within neural cells, and therefore the biological influence of TH in the brain, is determined by the synthesis of T4 and the activity of type 2 diodionases, it is also highly dependent on the appropriate functioning of TH transporters, which are critical for the movement of TH across the blood–brain barrier and across the plasma membrane of the target neural cells (Groeneweg et al., 2017). A variety of TH transporters have been identified that regulate TH uptake into different tissues, but monocarboxylate transporter 8 (MCT8) and the organic anionic transporter polypeptide 1C1 (OATP1C1), are the key regulators of TH uptake into the brain (Groeneweg et al., 2017). Mutations in the gene encoding MCT8 (*SLC16A2*) lead to the development of Allan-Herndon-Dudley syndrome (AHDS) - an X-linked inherited psychomotor retardation and hypomyelination disorder (Schwartz et al., 2005). As TH promotes oligodendrocyte differentiation and central nervous system (CNS) myelination (Calza et al., 2015), it is likely that the hypomyelination phenotype observed in children with AHDS could be overcome by promoting TH signaling in cells of the oligodendrocyte lineage.

Using a human embryonic cell culture system, Lee et al. (2017) demonstrate that MCT8 is expressed by cells of the oligodendrocyte lineage, ranging from oligodendrocyte progenitor cells through to differentiated oligodendrocytes. Of particularly relevance to AHDS, they show that the loss of MCT8 function, achieved pharmacologically or by gene knockdown, impairs the survival of human oligodendrocytes. While T3 was unable to influence the behavior of MCT8 deficient cells, di-iodothyropropionic acid (DITPA), a thyroid hormone analogue that can enter the CNS and cells without requiring transport by MCT8, regulated TH-responsive genes to overcome this effect. DITPA was found to promote progenitor cell cycle exit, oligodendrocyte differentiation and survival, and could increase the proportion of axons myelinated when the human cells were co-cultured with rat retinal ganglion neurons (Lee et al., 2017). These data suggest that DITPA treatment could overcome some of the developmental consequences of AHDS, if mutations in *SLC16A2* were detected early by genetic screening.

The ability of DITPA to promote oligodendrocyte survival and enhance myelination, also has important implications for the treatment of other dys/demyelinating disease, particularly the adult-onset demyelinating disease, multiple sclerosis (MS). In people with MS, oligodendrocytes die, leading to the formation of lesions in which axons are demyelinated and no longer have the essential metabolic support provided by the associated oligodendrocytes. In some cases, remyelination occurs naturally, with new oligodendrocytes being generated from local oligodendrocyte progenitor cells, but in other cases, oligodendrocyte progenitor cells develop "differentiation block", where they fail to mature. A significant effort has been made in recent years to better understand and overcome this process (Franklin and Ffrench-Constant, 2008). As Lee et al. (2017) have shown that DITPA triggers the maturation of human oligodendrocytes and ultimately promotes their myelination, it is conceivable that DITPA administration to people with MS, could expedite oligodendrocyte generation and myelin repair, to critically guard against neuron loss and disability accrual.

Disclosure

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