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Commentary

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Cognitive function in hypothyroidism: what is that deiodinase again?

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Treatment of hypothyroidism involves the endogenous conversion of thyroxine (T4) to 3,5,3'-triiodothyronine (T3) and may not be optimal in some cases when based on T4 alone. In the current issue of the *JCI*, Jo et al. present results that explain the reduced enzymatic activity of a common genetic variant of the enzyme responsible for this conversion, type 2 deiodinase (DIO2). The authors further explore the functional consequences of this variant on brain T3 activity, endoplasmic reticulum stress in glial cells, and cognitive function. These findings have important implications for the clinical treatment of hypothyroidism and for susceptibility to other neurological and metabolic diseases.

Role of DIO2 in thyroid hormone therapy

Whether due to autoimmune thyroid disease or secondary to the removal of the thyroid gland, hypothyroidism is a highly prevalent condition that affects 5% to 10% of the adult population (1). Thyroid hormone therapy, which is based on the administration of thyroxine (T4, 3,3',5,5'-tetraiodothyronine), is used to help hypothyroid patients normalize their metabolism, cardiac function, mood, and cognition. However, to attain its full ability to regulate gene transcription in target cells, T4 must be converted to 3,5,3'-triiodothyronine (T3), the thyroid hormone that binds specific nuclear receptors with high affinity (2). This conversion process is largely accomplished by type 2 deiodinase (DIO2 or D2) (3).

Although this treatment is generally efficient, about 15% of patients are resistant and show persistent neurological symptoms, including deficits in memory and mood, even after T4 dosage is individually adjusted (4). Given the heavy reliance of this treatment on DIO2 function, investigators have explored DIO2 further and have been intrigued by the

presence of a SNP in the human *DIO2* gene (5). This SNP is present in up to a third of the human population and results in the change of a threonine (Thr) to an alanine (Ala) in amino acid 92 of the DIO2 polypeptide chain. The substitution affects a small and conserved domain of the protein involved in binding ubiquitin ligases (6), directing the enzyme for proteasomal degradation in a process that depends on the relative abundance and binding of its substrate, T4 (7).

Although initial assays on sonicates from transfected cells showed no deficits in the activity of Ala92-DIO2, studies in intact cells indicated reduced deiodination (8, 9), suggesting that the function of Ala-DIO2 is impaired in a physiological context. This notion was further supported by the clinical benefit that hypothyroid patients carrying this DIO2 SNP obtained from a combination therapy of T4 and T3 (10, 11).

Reduced functionality of Ala92-DIO2 explored

Why would Ala92-DIO2 not be fully functional *in vivo*? What would be the implications for brain thyroid hormone homeostasis

and neurological function? In a remarkable bedside-to-bench work published in this issue of the *JCI*, Sungro Jo and Tatiana Fonseca, together with colleagues from a multi-institutional team lead by Antonio Bianco, provide some critical answers to those questions and expand on the clinical implications of the Thr92Ala-DIO2 SNP (12).

In addition to confirming that intact transgenic cells expressing Ala-DIO2 exhibit a reduction in T3 production from T4, the authors observed that DIO2 is recycled between the ER and the Golgi using ER Golgi intermediary compartment (ERGIC) vesicles. They further showed (Figure 1) that the presence of this SNP causes ER stress and impairs ERGIC-mediated shuttling of Ala92-DIO2, which is then abnormally accumulated in the central Golgi, where it is enzymatically inactive.

If Ala92-DIO2 enzymatic activity is impaired *in vivo*, what are the functional consequences for the brain, a tissue highly dependent on T3 generated locally by DIO2 (13)? DIO2 is present in glial cells, where it also provides T3 for biological activity in neurons (14). This critical role has been further underscored by the abnormalities in behavior and brain gene expression observed in mice with astrocyte-specific DIO2 deficiency (15). Using “humanized” transgenic mice, Jo et al. showed that the subcellular abnormalities of Ala92-DIO2 were associated with decreased T3 action in the brain. Mice expressing the Ala92-DIO2 variant are euthyroid, based on serum parameters. However, areas of their brains exhibited decreased T3-dependent gene expression and abnormalities in the expression of genes related to ER stress and the ERGIC system. Furthermore, these mice exhibited impaired short-term memory, reduced levels of spontaneous physical activity, and increased sleep, characteristics that resemble those of clinical hypothyroidism.

The gene expression changes in the Ala92-DIO2 brains may seem too modest to cause a neurological phenotype. How-

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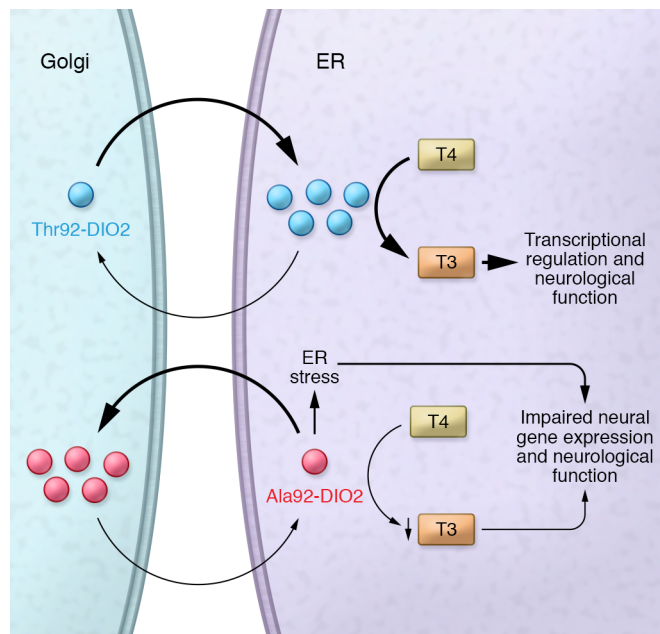


Figure 1. Pathological basis of Ala92-DIO2. Thr92-DIO2 localizes in the ER where, with the support of appropriate cofactors, it is able to convert T4 into T3 for transcriptional regulation in the nucleus. DIO2 is recycled through the Golgi. Ala92-DIO2 causes ER stress and impairs the recycling of DIO2, which aberrantly accumulates in the Golgi, where it is not active. ER stress and decreased T3 production exert biological effects on glial cells and neurons, affecting neurological function.

ever, the brain is notorious for its strict and spatial-specific regulation of thyroid hormone levels. In fact, when Ala92-DIO2 mice were treated with T3, their levels of physical activity were normalized, demonstrating that at least some of their neurological deficits were actually caused by local T3 deficiency. Furthermore, the authors examined neurological function after rendering the mice hypothyroid with antithyroid drugs, a model that recapitulates the clinical condition of many hypothyroid patients and eliminates the biological contribution of the T3 secreted by the thyroid gland. When hypothyroid, both Thr92-DIO2 and Ala92-DIO2 mice showed neurological deficits affecting memory, sleep, and locomotor activity. However, after T4 administration, this phenotype was rescued only in Thr92-DIO2 mice and not in Ala92-DIO2 mice. In the latter, neurological function was normalized only when the mice were treated with a combination of T4 and T3. These findings again highlight the deficit in brain T3 associated with Ala92-DIO2, a situation that could become even more critical in the context of hypothyroidism secondary to thyroid disease, as seen in human patients.

Broader implications of the study

There are additional and highly intriguing aspects of this work. As mentioned above, in intact Ala92-DIO2 mice, T3 treatment rescues only one of the neurological phenotypes examined. However, normalizing protein homeostasis with an ER stress inhibitor fully restores the neurological functions. This observation suggests that, at least under serum euthyroid conditions, part of the neurological pathophysiology of Ala92-DIO2 mice is primarily due to ER stress. In this scenario, ER stress can potentially lead, not only to mislocalization of DIO2 and reduced T3 generation, but also to glial cell dysfunction, potentially influencing neuronal physiology. This possibility is consistent with epidemiological studies showing increased prevalence of bipolar disorder and Alzheimer's disease in individuals carrying the Ala92-DIO2 polymorphism (16). It would be interesting to determine whether Ala92-DIO2 contributes to age-related cognitive decline and neurodegeneration, especially in the context of the natural changes in thyroid function associated with age.

It is also conceivable that other neurological abnormalities of Ala92-DIO2 mice not identified in this work could partly

originate during development, either as a consequence of ER stress alone or combined with reduced local T3 generation. DIO2 expression in most rodent brain regions peaks during neonatal stages, when T3 action and responsiveness are highest in the central nervous system (17). It is then possible that impaired T3 generation in Ala92-DIO2 carriers may influence brain development and explain the increased incidence of mental retardation associated with this DIO2 variant (16).

The extent to which hypothyroid patients with T4-resistant neurological symptoms coincide with those carrying Ala92-DIO2 is not yet clear. Even if this is only partially the case, the presence of Ala92-DIO2 appears as an important risk factor for suboptimal treatment of hypothyroidism, and the present work is a substantial advance in understanding the cellular and molecular basis of this risk.

Clinical implications of Ala92-DIO2 SNP pathology

The high prevalence of hypothyroidism, the relatively high abundance of the Ala92-DIO2 variant in the human population, and the presence of DIO2 in many areas of the central nervous system and other tissues confer broad clinical relevance to the present work and strongly warrant additional studies. Work examining the interacting proteins responsible for the altered subcellular homeostasis of Ala92-DIO2 and defining the thyroid status in which these interactions are most critical to pathophysiology could yield important mechanistic insights. Research defining the pathological contributions of ER stress and T3 deficiency or focusing on specific brain regions and additional neurological functions is also warranted. Finally, given the associations of this SNP with increased metabolic abnormalities, it is also possible that disease susceptibility in Ala92-DIO2 carriers is partly the result of thyroid hormone alterations in nonneural, DIO2-expressing tissues. Our understanding of the pathological basis of the Ala92-DIO2 SNP has just begun, and clinical implications may extend well beyond the treatment of hypothyroidism.

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