Triumphs of the Thyroid Despite Lesser Conversion

Jessica A. Hall and Antonio C. Bianco

In a seemingly wasteful fashion, the thyroid gland focuses its effort into secreting an inactive version of thyroid hormone T₄. In fact, a hormone, from the Greek word for impulse, is a biologically active molecule, so in the case of thyroid hormone, the actual active hormone is that of the triply iodinated derivative, T₃. To successfully produce T₃, the human thyroid processes about 1000 nmol iodide daily, packaging the iodide into a very large molecule [thyrglobulin (Tg)] that is subsequently hydrolyzed. The resulting iodinated products are sequentially unleashed in a controlled manner so that, eventually, only 10 nmol of the highly potent T₃ are secreted. The bulk of T₃ production (40 nmol), however, occurs outside of the thyroid parenchyma through the conversion of T₄ to T₃ by the activating deiodinases, a group of selenoenzymes that can selectively remove iodine moieties from T₄ (reviewed in Ref 1). Given that only 10 nmol or less of T₃ are directly secreted from the thyroid, one would assume that an absence of the deiodinases should impair the overall daily production of T₃, leading to systemic hypothyroidism. In this issue of Endocrinology, Galton et al. (2) challenge the conventional paradigm of thyroid hormone homeostasis by showing that mice lacking both of the activating deiodinases maintain normal T₃ production, particularly in rodents (5). In fact, it is commonly accepted that D1 and D2 contribute equally to extrathyroidal T₃ production in mice and rats. This is unlike the situation in humans, where D2 is argued to play a greater role in the generation of plasma T₃ (1).

Despite these differences in T₃ production between humans and rodents, the generation of mice lacking specific deiodinase activity has allowed for in-depth study of the physiological roles played by D1 and D2 in thyroid hormone homeostasis (6). Remarkably, mice with targeted disruption of Dio1 [D1 knockout (D1KO)] or Dio2 (D2KO) have been found to exhibit a normal serum T₃ concentration (7, 8). Even the C3H/D2KO mouse that lacks D2 and expresses only residual D1 activity maintains euthyroid serum T₃ levels (9). All three of these mouse models have increased concentrations of serum T₄, and both the D2KO and C3H/D2KO have elevated TSH. These adjustments in T₄ and TSH indicate that keeping serum T₃ concentration within the normal range is the default hypothalamic primary directive for the TRH-TSH-thyroid axis, despite marked elevation in serum T₄ concentrations. This innate ability to avoid catastrophic hypothyroidism is fascinating and has only recently been appreciated as a result of these deiodinase-deficient mouse models.

To better appreciate the plasticity and adaptive capacity of the T₃-generating system, and to rule out the effect of possible compensation by D1 or D2 in the aforementioned mouse models, the present study by Galton et al. (2) evaluates mice lacking both D1 and D2 activity. As with the other mouse models, D1/D2KO mice sustain a normal serum concentration of T₃ at the expense of markedly altered thyroidal status. There is a 2-fold greater serum T₄ concentration and a 2.6-times higher TSH serum level when compared with wild-type mice. The elevated level of T₄ is higher than that seen in either the D1KO or D2KO, and the elevated TSH level is comparable to that measured in D2KO.
mice. These data indicate that thyroidal output of \(T_3\) must be enhanced in the D1/D2KO and that the elevated serum \(T_4\) is a byproduct of this compensatory mechanism due to the high \(T_2/T_3\) ratio in thyroid secretion. These data provide further evidence that \(T_4\) is a prohormone, given that the D1/D2KO mice are found to be systemically euthyroid and have elevated serum TSH despite a 2-fold elevation in serum \(T_3\).

Although it is likely to be the default condition, a serum \(T_3\) concentration within the normal range is not always observed. In many disease states or during caloric restriction, a marked drop in serum \(T_3\) levels takes place in a condition known as the low \(T_3\) syndrome or the euthyroid sick syndrome. Decreased extrathyroidal \(T_3\) production has been considered for many years as the predominant cause for this syndrome (10), but the results from this present study (2) counter and effectively reject this model. The fact that D1/D2KO mice have a normal serum \(T_3\) concentration indicates that a decrease in extrathyroidal \(T_3\) production \textit{per se} cannot be a predominant mechanism leading to low serum \(T_3\). Quite the contrary, the data support the concept that in healthy individuals, a reduction in serum \(T_3\) is automatically compensated by an increase in serum TSH, which then increases thyroidal \(T_3\) production. Others believe that low \(T_3\) syndrome is caused by reactivation of type 3 iodothyronine deiodinase (D3) expression, which inactivates thyroid hormone (11). However, D3KO mice can develop the euthyroid sick syndrome similarly to wild-type animals (12). Thus, in the euthyroid sick syndrome, it is likely that changes in extrathyroidal \(T_3\) production and/or catabolism do take place, but serum \(T_3\) is allowed to fall to levels that are essentially determined by the hypothalamus, the underlying mechanism being the inappropriately low serum TSH levels.

Thus, it seems pretty clear that very powerful redundant mechanisms are in place to maintain serum \(T_3\) levels within the normal range, except when it is not meant to be in that range, \textit{i.e.} euthyroid sick syndrome. In the latter, all compensatory mechanisms are shut down, and serum \(T_3\) drops to levels that might reach the undetectable range. However, the fact that serum \(T_3\) is normal in the D1/D2KO mouse does not mean that deiodinases are unimportant in maintaining serum \(T_3\). It indicates that adaptive mechanisms are triggered to maintain serum \(T_3\), despite deiodinase impairment or absence. Deiodinases are a part of these redundant mechanisms that exhibit remarkable plasticity and could be necessary during times when thyroid hormone homeostasis is stressed by additional/coexisting challenges, \textit{e.g.} iodine availability, supposedly the single most important evolutionary pressure that shaped development of thyroid hormone homeostatic mechanisms in the first place. Although the work by Galton \textit{et al.} (2) solidifies a major role played by the thyroid gland in thyroid hormone homeostasis, it is important to stress that the deiodinases do play essential roles that go beyond their contribution to systemic \(T_3\) maintenance. For example, \(T_4\) inhibition of TSH expression and secretion is only possible thanks to D2 in the thyrotrophs (13), the absence of which results in elevated serum \(T_4\), as documented previously (8). At the same time, the deiodinases modulate thyroid hormone signaling in a tissue-specific manner despite a relatively constant level of thyroid hormone in plasma (reviewed in Ref. 14). The critical nature of this control is exemplified in the D2KO mouse, which suffers from tissue-specific hypothyroidism despite normal serum \(T_3\). In fact, lacking D2 activity results in impaired brown adipose tissue thermogenesis, leaving mice unable to maintain core temperature when exposed to cold (15). Although these effects are dramatic, nowhere are the effects of the deiodinases in controlling thyroid hormone signaling more important than during development. For example, D2KO mice are deaf due to a disruption in cochlear development (16). Also, as we learn more about these animals, a complex brain phenotype is being unraveled. Such is the case with the current findings of Galton \textit{et al.} (2), which suggest impaired learning and memory in the euthyroid D1/D2KO mouse.

Although the plasticity of the mouse TRH-TSH-thyroid axis is notable, caution must be taken before extrapolating the present results to humans, with the caveat being that humans rely on extrathyroidal conversion of \(T_4\) to \(T_3\) to a greater extent than rodents do (80 vs. 60% in rodents). In fact, the ability of the human thyroid to compensate for a lack of D1 and/or D2 may not be adequate to the same degree as it has been shown in the present article for mice. Furthermore, iodine deficiency, a condition that afflicts about 200 million people worldwide, could also potentially limit the adaptive capacity of the thyroid to increase \(T_3\) output. In this regard, a lack of deiodinases could worsen iodine deficiency, because deiodinases generate iodide that may be taken up by the thyroid and reused in the synthesis of thyroid hormone (7). As discussed by Galton \textit{et al.} (2), a scavenger role has been attributed to D1, given that the D1KO and the D1/D2KO mice lose increased amounts of iodothyronines in the feces, which minimizes reuse of iodide (2, 7).

In conclusion, this novel animal model supports the interesting concept that maintenance of serum \(T_3\) within normal limits is a major driving factor in thyroid hormone homeostasis. However, there is more to the story; the thyroid may ultimately dominate the battle when it comes to serum \(T_3\) maintenance and, clearly, low \(T_3\) syndrome, but in the realms of thyroid hormone signaling during development and energy homeostasis, the deiodinases come to the foreground.

**Acknowledgments**

Address all correspondence and requests for reprints to: Antonio C. Bianco, Suite 816 Dominion Tower, 1400 Northwest 10th Avenue, Miami, Florida 33136.

Disclosure Summary: The authors have nothing to disclose.

**References**


2. Galton VA, Schneider M, Clark AS, Germain DL 2009 Life without thyroxine to 3,5,3'-triiodothyronine conversion: studies in mice devoid of the 5'-deiodinases. Endocrinology 150:2957–2963


7. Schneider MJ, Fiering SN, Thai B, Wu SY, St Germain E, Parlow AF, St Germain DL, Galton VA 2006 Targeted disruption of the type 1 selenodeiodinase gene (dio1) results in marked changes in thyroid hormone economy in mice. Endocrinology 147: 580–589