Hypothyroidism affects about 3.7% of the general population in the United States [1], reaching levels of up to 8% in areas with high prevalence of iodine deficiency [2]. At first sight, treatment for hypothyroidism, regardless of its etiology, seems quite straightforward. According to current guidelines the standard of care is treatment based on hormonal replacement therapy with daily administration of levothyroxine, the pro-hormone produced exclusively by the thyroid gland [3]. The rationale is that the deiodinases, thioredoxin-fold containing selenoenzymes that metabolize thyroid hormone and are present in multiple extra thyroidal tissues, activate thyroxine (T4) and produce physiological amounts of the biologically active thyroid hormone, triiodothyronine (T3) [4]. The observation that circulating levels of T3 and TSH can be normalized in levothyroxine-treated hypothyroid patients reassures physicians that euthyroidism is achieved and probably contributed for the replacement of porcine thyroid preparations by the synthetic form of levothyroxine currently used [5, 6]. In fact, monitoring serum levels of TSH (and free T4 (FT4)) became an integral part of the routine to follow the therapeutic efficacy of thyroid hormone replacement. However, despite normalization of these biochemical parameters, about 15% of those treated with levothyroxine replacement therapy alone do not achieve clinical euthyroidism and experience some level of psychological impairment [7].

Abstract

Current guidelines recommend that hypothyroid patients should be treated with levothyroxine, which in the vast majority of the cases leads to resolution of the symptoms and normalization of serum free T4 (FT4), T3 and TSH levels. However, a small group of hypothyroid patients remain symptomatic for neurocognitive dysfunction despite normal serum FT4 and TSH, which could be explained by localized brain hypothyroidism. More than half of the T3 in the brain is produced locally via the action of the type II deiodinase (D2) and variability/defects in this pathway could explain the residual symptoms. If this rationale is correct, adding liothyronine to the replacement therapy could prove beneficial. However, with a few exceptions, several clinical trials failed to identify any beneficial effects of combined therapy. More recently, the results of a large clinical trial revealed a better neurocognitive outcome with combined therapy only in hypothyroid patients carrying a polymorphism in the DIO2 gene. This obviously needs to be confirmed by other groups but it is tempting to speculate that combined levothyroxine and liothyronine has a place in the treatment of hypothyroidism, for some.
The persistence of a relatively small number of clinically symptomatic patients has led to an explosion of alternative treatment strategies, including the reawakening of desiccated porcine thyroid and development of new ‘thyroid supplements’ that take advantage of regulatory loopholes to avoid governmental oversight. This has created greater awareness in the medical community, with concerns gravitating mostly around two areas, namely (i) defining what is missing in our understanding of thyroid hormone signaling (transport across cell membranes and metabolism) that prevents us from developing a treatment strategy that is effective for 100% of the patients, and (ii) preventing the widespread usage of ‘thyroid formulas’ that in many cases leads to long-term subclinical or clinical thyrotoxicosis and their well-known consequences.

**Basic Principles of Thyroid Hormone Transport, Metabolism and Action**

T₃ enters the target cells through a few specific thyroid hormone transporters, including monocarboxylate transporter (MCT) 8, MCT10, and organic anion-transporting polypeptide 1C1 (OATP) [8]. Once inside the cells, T₃ gains access to the cell nucleus where it interacts with two forms of nuclear receptors (TRα and TRβ); both TRs are unevenly distributed throughout the body, with virtually every cell expressing either one or both receptors. This modulates the expression of specific sets of T₃-responsive genes, thus producing T₃-dependent biological effects, e.g. positive cardiac chronotropism, bone resorption, acceleration of energy expenditure [9–11] (fig. 1).

In healthy adult individuals, about 80–90% of the extrathyroidal T₃ is produced by deiodination of T₄ via the type I (D₁) and type II (D₂) deiodinases [12, 13], which are widely expressed throughout extrathyroidal organs and tissues: D₁, in liver and kidney, and D₂, in the central nervous system, bone, skin, pituitary gland, brown adipose tissue and in minute amounts in skeletal muscle and heart [14, 15]. Thus, there are two sources of T₃ bound to tissue TR at any given time, i.e. (i) direct thyroid secretion or (ii) extrathyroidal deiodination of T₄ [14, 16]. There is also a third deiodinase, D₃, which can inactivate both T₄ and T₃ and is expressed mostly during embryonic life [17]; in healthy adults, D₃ expression remains only in a handful of tissues, including brain, skin, heart and pancreatic β-cells [14, 18]. However, during disease processes, D₃ expression can be enhanced severalfold or ectopically activated in most tissues, including liver, skeletal muscle and heart via signals such as ischemia and/or hypoxia [19, 20].

**The First Question: Can Plasma and Tissue T₃ Concentrations Be Normalized in Levothyroxine-Treated Hypothyroid Individuals?**

Serum T₃ concentrations are expected to be normal in levothyroxine-treated hypothyroid individuals [21–23]. This would indicate that the deiodinase pathways are sufficient to normalize T₃ levels in the plasma, provided that enough T₄ is available. However, a recent large-scale cross-sectional study involving about 3,900 euthyroid volunteers and about 1,800 athyreotic patients kept on replacement therapy with levothyroxine indicates that serum T₃ is consistently lower in the hypothyroid patients, although within the normal range [24]. Furthermore, in approximately 15% of these hypothyroid patients, serum T₃ is not normalized despite normal serum TSH [24]. In addition, it seems that further increases in the dose of levothyroxine would not result in normalization of serum T₃ without bringing serum TSH below the normal range.

Of note, when all individuals are stratified as a function of their serum TSH, it is clear that for any given serum TSH, the levothyroxine-treated hypothyroid patients exhibit significantly lower serum T₃ [24].

One additional point to keep in mind is that, as opposed to T₄, T₃ is mostly an intracellular hormone [14, 25]. Yes, it is true that plasma and tissue T₃ are at equilibrium at all times, but the sizes of both pools are not the same [14] and both T₃ production and T₃ degradation are intracellular events [26, 27]. Deiodinase-mediated T₃ production takes place inside the T₃-target cells and thus in any given cell there is a chance that the TR-bound T₃ was produced locally (within that very same cell) and found its way to the cell nucleus before exiting the cell or reaching the plasma (fig. 2). The odds of this happening vary from tissue to tissue and depend among other things on the local activity of the deiodinases. At the same time, D₂-mediated T₂ inactivation also takes place inside the cells and thus some of the T₃ produced intracellularly might be degraded before reaching the plasma [27].

Thus, plasma T₃ level is a poor predictor of tissue T₃ concentration because it does not account for the intracellular production/inactivation of T₃ via the deiodinase pathways. As a consequence, a normal serum T₃ does not mean that the T₃ content in all tissues is normal. In fact, a mouse with targeted inactivation of D₂ (D₂KO) has nor-
mal serum T₃ levels, but its brain has only half as much T₃ when compared to a normal mouse [28, 29]. Even the mouse with combined D₁/D₂ inactivation exhibits normal serum T₃, revealing a remarkable ability of the murine thyroid to upregulate T₃ secretion when extrathyroidal T₃ production is abolished [30, 31]. A similar compensatory mechanism is expected to exist in humans, even though the human thyroid contributes much less to the daily T₃ production. Thus, based on the mouse studies, it is very unlikely that patients with a ‘defect’ in the activating deiodinase pathway would be identified by a low serum T₃. Remarkably, each of these animals has a normal serum T₃ concentration and an increased serum T₄ concentration. The elevations in serum T₄ concentration may result from increased thyroidal secretion and/or decreased clearance, but in either case it is fascinating that the hypothalamic-pituitary-thyroid axis could be wired such that adjustments in serum T₄ concentrations are made in order to maintain serum T₃ concentrations [32]. Thus, it is tempting to speculate that serum T₃ plays a critical role for some cells/tissues, perhaps the ones that do not exhibit significant deiodinase expression.

Only direct measurements of tissue T₃ can answer the first question. Human tissues have been processed for T₃ content largely in the context of embryonic development or non-thyroidal illnesses [33–35], and not to address the ‘first’ question. Only studies in rats have addressed this point and the answer is a resonant ‘no’, i.e. extrathyroidal

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**Fig. 1.** Major aspects of thyroid hormone economy in healthy human subjects. The human thyroid produces approximately 90 μg of T₄ and 5 μg of T₃ daily; deiodinases (D₁ and D₂) in extrathyroidal tissues are responsible for the production of approximately 25 μg daily. Plasma T₃ enters thyroid hormone target cells and binds to TRs, changing the expression of T₃-responsive genes. The subsequent changes in specific mRNA levels underlie the biological effects of thyroid hormone in various tissues during development, growth, metabolism and neurocognition.
metabolism of T₄ does not normalize T₃ content in most tissues [36]. However, prudence should be exercised while extrapolating rodent data to humans given that in rats the thyroidal contribution to T₃ production is much larger than in humans, about 40% [14].

Nonetheless, when thyroidectomized rats were given a range of T₄ doses (0.2–8.0 μg/100 g b.w./day), no single dose of T₄ was able to restore normal serum TSH, T₄ and T₃, as well as T₄ and T₃ in all tissues, or at least to restore T₃ simultaneously in plasma and all tissues, except for the brain [36]. Indeed, central to our discussion is the fact that T₃ content in the cerebral cortex and cerebellum was indeed normalized over a wide range of T₄ doses, even by doses that were not sufficient to normalize serum TSH [36] (fig. 3). Thus, the normal rat brain (and probably the human brain as well) contains a highly efficient D₂-mediated mechanism that maintains its T₃ concentration based on circulating T₄. This agrees with the undeniable observation that about 85–90% of all patients with hypothyroidism on levothyroxine therapy alone are clinically and biochemically euthyroid, living normal healthy lives.

The Second Question: Can a Variability/Defect in Thyroid Hormone Metabolism and/or Transport Affect Tissue T₃ and Be Clinically Relevant?

The fascinating aspect of the thyroid hormone transport across cell membranes combined with the deiodinase-mediated control of thyroid hormone action is that thyroid hormone signaling can be customized in a cell- and time-specific fashion, independently of serum T₃ lev-
els [8, 11, 16]. In fact, in healthy adult individuals, serum levels of T_{4} and T_{3} are remarkably constant throughout life [37], unlike the T_{3} tissue content that can change rapidly in response to a number of developmental, metabolic and environmental cues [38]. Thus, it is logical to suppose that those patients who still experience neurocognitive impairment despite normalization of serum TSH, T_{4} and T_{3} concentrations lack sufficient T_{3} in discrete brain areas due to a variability/defect in D_{2} and/or D_{3} pathways or thyroid hormone transport in the brain.

**Deiodinase Pathways**

Loss-of-function mutations have not been reported in any of the deiodinase genes. However, there is a report of a single index in which 3 affected individuals exhibited transient growth retardation as a result of a broad deficiency in selenoprotein synthesis [39]. This is an extremely rare syndrome that affects the synthesis of the three deiodinases. No data are available on whether such individuals exhibit alterations in tissue T_{3} content. However, because it is so rare, it is unlikely to impact significantly the present discussion.

A D_{1}-deficient mouse (D_{1}KO) exhibits elevated serum levels of T_{4} and rT_{3}, whereas serum TSH and T_{3} as well as several indices of peripheral thyroid status are unaffected [40, 41]. However, D_{1} deficiency results in increased fecal excretion of endogenous iodothyronines suggesting that D_{1} may play a major role in limiting the impact of iodine deficiency [41]. At the same time, in humans a single nucleotide polymorphism rs2235544 of DIO1 gene has been identified [42] in association with an increase in free T_{3} and a decrease in FT_{4} and rT_{3}, with no effect on serum T_{3} levels. Similarly, carriers of the D_{1b} G/T (rs12095080) allele in elderly individuals had higher serum T_{3} and T_{3}/rT_{3} [43]. On the other hand, D_{1a} C/T (rs11206244) carriers had higher serum FT_{4} and rT_{3}, lower T_{3}, and lower T_{3}/rT_{3} [43]. Despite biochemical differences in thyroid hormone serum levels, no data are available regarding tissue T_{3} levels and, more importantly, no clinical syndrome has been identified in carriers of these polymorphisms.

The D_{2}KO mouse exhibits a rich phenotype based on alterations of tissue T_{3}. The BAT [44–46], brain and pituitary gland [31, 47], skeleton [48], skeletal muscle [49, 50] and lungs [51] have all been extensively studied with major phenotypes attributed to deficient local generation of T_{3} via the D_{2} pathway. This of course opens the door for the existence of individuals with clinical syndromes caused by potential variability/defects in the D_{2} pathway. This is particularly true for the brain, where T_{3} content is dramatically affected by the D_{2} pathway [31, 52]. D_{2} is responsible for more than half of the T_{3} present in the murine brain [52]. Accordingly, D_{2}KO animals have half as much brain T_{3} content as their wild-type siblings [31], greatly supporting the idea that any interference in the D_{2} pathway could affect brain function and/or result in intellectual or cognitive symptoms.

A potentially relevant polymorphism in the DIO2 gene (Thr92AlaD_{2}) has been described in about 15% of normal individuals [53] (fig. 4a, b). This was originally associated with insulin resistance and increased BMI [53], and subsequently with type 2 diabetes mellitus [54]. A recent case-control study with 1,057 type 2 diabetes patients and 516 non-diabetic subjects indicated that the frequencies of D_{2} Ala92Ala homozygosity were 16.4% (n = 173) versus 12.0% (n = 62) in diabetic versus controls,
respectively, resulting in an adjusted odds ratio of 1.41 (CI 95% 1.03–1.94, p = 0.03) [55]. These data indicate that the homozygosity for D2 Thr92Ala polymorphism is associated with increased risk for type 2 diabetes, a conclusion that was supported by a meta-analysis including 11,033 individuals [55]. Today there is a much broader spectrum of diseases and conditions that have been associated with the Thr92AlaD2 polymorphism, including mental retardation [56], hypertension [57], osteoarthritis [58], bipolar disorder [59], clinical course and myocardial remodeling [60], accelerated bone turnover [61], response to lung injury [51, 62], indicating that indeed this locus (and the Thr92AlaD2 polymorphism) is clinically relevant (table 1).

Within the context of this discussion, the logical assumption is that the Thr92AlaD2 polymorphism results in decreased D2 activity and thus localized tissue T3 deficiency and hypothyroidism. However, different groups have failed to detect differences in enzyme kinetics (Km (T4) and Vmax) of the Thr92AlaD2 protein when transiently expressed in cultured cells [54, 63]. A single study in tissue samples of individuals with the Thr92AlaD2 polymorphism revealed decreased Vmax in biopsies of skeletal muscle and thyroid gland [54]. However, the data in skeletal muscle have since lost relevance given the subsequent discovery that special technical considerations are needed to correctly assay skeletal muscle D2 activity [15, 64], which were not considered in the said study [54]. Nevertheless, the reported decrease in thyroidal Thr92AlaD2 Vmax remains unchallenged, albeit not yet reproduced by other groups. Two studies in patients indirectly support the view that Thr92AlaD2 is a catalytically less active enzyme: (i) higher doses of levothyroxine were needed to achieve target TSH levels in 191 thyroid-

Table 1. Clinical features associated with the Thr92AlaD2 polymorphism

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T3 and T4 need to move across the blood-brain barrier, in to establish a transcriptional footprint in the brain, both

The D3 KO mouse has central hypothyroidism (as a result

including problems with survival and maturation of cone
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TR-containing neighboring neurons to finally trigger its

at the same time, it is important to highlight that the

literature about the Thr92AlaD2 polymorphism is con-
troversial, with poor reproducibility amongst different

studies [67–72]. This suggests that additional unidentified

linkage factors such as ethnic background could play

a significant role in the physiological and clinical rele-
vance of the Thr92AlaD2 polymorphism [71, 73]. If future

studies by other groups identify and isolate such factors

and confirm the observation that Thr92AlaD2 polymor-

phism limits D2’s ability to produce T3, then ‘yes’ a vari-

ability/defect in the deiodination pathway that controls
tissue T3 could be clinically relevant based on the multi-

ple phenotypes associated with said polymorphism. At

the time of this writing, other DIO2 polymorphisms have

been reported, but their clinical relevance is even less well

established [74].

The D2KO mouse exhibits the richest phenotype of all
deoiodase KO animals, which stems from elevated tissue
T3 during developmental and post-natal life [18, 75–77].
The D2KO mouse has central hypothyroidism (as a result
of enhanced T3 signaling in the hypothalamus), growth
delay and a major central nervous system phenotype in-
cluding problems with survival and maturation of cone
photoreceptors [77] and in cochlear development and au-
ditory function [78], as well as aggressiveness and infer-

tility [75, 76, 79]. However, despite the potential for mul-
tiple clinical symptoms in humans, no relevant DIO3
mutations or polymorphisms or mutations have been de-
scribed in humans that are relevant for the ‘second’ ques-
tion.

Thyroid Hormone Transport Pathways

It is clear that localized thyroid hormone deficiency in
the brain could result from a variability/defect in thyroid
transport across cell membranes as well. In order for T3
to establish a transcriptional footprint in the brain, both
T3 and T4 need to move across the blood-brain barrier, in
and out of cells. T4 is taken up by D2-containing astro-
cytes and tanyctyes and the resulting locally generated
T3 must then exit these D2-containing cells and enter
TR-containing neighboring neurons to finally trigger its
transcriptional effects [80, 81]. A variability/defect in any
of these steps could affect intracellular T3 content and
lead to localized brain hypothyroidism. This is illustrated

in patients with the Allan-Herndon-Dudley syndrome,
carriers of an inactivating mutation in the X-linked
MCT8 gene, a member of the MCT family that preferen-
tially transports T3 across cell membranes and is highly
expressed in several organs including the brain. Patients
with this syndrome exhibit psychomotor retardation and
neurological impairment, indicating brain-specific hy-
pothyroidism during development [82, 83].

Other thyroid hormone transporters have been ident-
tified, including the blood-brain barrier-specific anion
transporter OATP1C1, mainly expressed in capillaries
throughout the brain for which T4 has a high affinity and
specificity [8, 11]. In rats, OATP1C1 mRNA and protein
are up- or downregulated depending on the T4 serum lev-

els, suggesting that this transporter plays a role in pre-

serving physiologic concentrations of T4 (and thus T3)
in the brain [84]. Interestingly, a clinical analysis of 141
hypothyroid participants of a randomized clinical trial
revealed that OATP1C1 polymorphisms are associated
with fatigue and depression but were not linked to neu-

rocognitive dysfunction [85].

The Third Question: Can a Deficiency in Brain
T3 Be Restored by Treatment with Combined
Levothyroxine and Liothyronine Therapy?

There is circumstantial evidence supporting the para-
digm that a variability/defect in thyroid hormone trans-
port and/or metabolism could lead to insufficient T3 in
discrete brain areas of levothyroxine-treated patients ex-
plaining their residual neurocognitive impairment de-
spite normalization of serum TSH, T4 and T3 concen-
trations. However, what makes this issue particularly
challenging is that such a variability/defect(s) would be
silenced by a functional thyroid gland, only to become
clinically relevant after the onset of hypothyroidism and
treatment with levothyroxine. This could be an indica-
tion that the small amounts of T3 contained in thyroid
secretion would be sufficient to compensate for such a
variability/defect, making it unlikely that levothyroxine
alone would restore brain T3 in such individuals. In fact,
even when the transport/metabolism pathways in the rat
brain are fully functional, brain T3 did not increase (and
remained fairly stable) in hypothyroid rats receiving a
wide range (20-fold) of T4 doses [36]. In contrast, brain T3
increased progressively in hypothyroid rats treated with
a much narrower range (8-fold) of T3 doses [86].

Thus, it is conceivable that administration of liothy-
ronine could restore brain euthyroid
individuals that remain clinically symptomatic on levothyroxine therapy. For example, if a variability/loss of function mutation in the D₂ pathway or in one of the thyroid hormone transporter genes is behind the persistent psychological impairment, such patients would benefit clinically from taking liothyronine, bypassing the variability/defect. However, even if successful, such a strategy has the obvious caveat that not only the brain but all tissues would be exposed to the additional T₃, thus essentially creating a state of systemic thyrotoxicosis for life [87].

A series of clinical trials indicate that a relative elevation in serum T₃ can be achieved by switching patients from monotherapy with levothyroxine to a combined therapy with levothyroxine and liothyronine [87–91]. The elevation in serum T₃ is variable, depending on the dose of liothyronine used. Multiple combination regimens exist, with levothyroxine:liothyronine ratios being applied at 10:1 to 5:1 [87]. A recent meta-analysis of ten such randomized controlled studies confirmed that serum TSH did not vary significantly between the monotherapy and combined therapy groups, but serum FT₄ levels decreased and total serum T₃ increased significantly in the patients switching to combined therapy [92]. In other regimens, relatively less T₃ is used and the switch to combined therapy does not elevate serum T₃ levels [93]. However, given the relatively short T₃ half-life of about 12 h in humans, a normal serum T₃ in the morning actually indicates that during the preceding 24 h the integrated serum T₃ fluctuated at higher levels in the patients receiving combined therapy. In fact, the 24-hour profile of individuals placed on such mild combined therapies indicates that serum free T₃ levels increased significantly, by about 40%, within the first 4-hour post-dose, with an integrated area under the curve for serum free T₃ significantly higher by about 10% [94]. In contrast, there is only a modest 16% rise in serum FT₄ with no change in serum free T₃ in the first 4-hour post-levothyroxine dose [94].

Despite the logic of this rationale, most randomized clinical trials (with three exceptions [88, 89, 95]) comparing monotherapy versus combined therapy failed to reveal a statistically significant difference in clinical outcomes [96]. The meta-analysis of eleven studies, in which 1,216 patients were randomized, found no difference in the effectiveness of monotherapy versus combined therapy symptoms such as bodily pain, depression, anxiety, fatigue, quality of life, body weight, total serum cholesterol, triglyceride levels, low-density lipoprotein, and high-density lipoprotein [96]. Yet, even when the objective methods used to assess the well-being of the patients did not uncover a meaningful change, patients did seem to prefer combined therapy [97].

The discovery of polymorphisms in the genes of the deiodinases and thyroid hormone transporters led to the obvious hypothesis that subgroups of hypothyroid patients respond differently to monotherapy versus combined therapy depending on their genetic makeup. This hypothesis was tested and the results seem encouraging, particularly in the light of a relatively large analysis of 552 individuals in the WATTS study, suggesting that the combined therapy is associated with a favorable clinical outcome in patients exhibiting the Thr92AlaD₂ polymorphism [98]. In the WATTS study, the thyroid hormone formulation used included the simultaneous reduction in the dose of levothyroxine by 50 μg/day and the introduction of 10 μg/day of liothyronine [98].

Notably, not all studies involving the Thr92AlaD₂ polymorphism resulted in such clear-cut results [97]. However, given that this D₂ polymorphism is present in a relatively small proportion of the population on levothyroxine, previous studies are likely to have been underpowered to see this effect [97]. Likewise, no differences in appreciation for the combined therapy were observed in a relatively small sample of patients carrying OATP1C1 polymorphisms [85].

Conclusions

The vast majority of the hypothyroid patients achieve biochemical and clinical euthyroidism on thyroid hormone replacement therapy with levothyroxine alone. A small group of hypothyroid patients on monotherapy with levothyroxine remain clinically symptomatic with impaired neurocognitive functions despite normalization of serum TSH, T₄ and T₃ levels. This could be attributed to localized brain hypothyroidism due to a variability/defect in thyroid hormone transport and/or metabolism. Addition of liothyronine to the treatment regimen could theoretically restore brain euthyroidism and, in fact, depending on the dose of liothyronine used, patients who switched from monotherapy to combined therapy exhibited elevation in serum T₃. However, a large number of clinical trials did not find improved outcomes with combined therapy. Only recently a polymorphism in the DIO2 gene, which could result in decreased D₂ activity, was taken into consideration. In the WATTS trial, the largest so far, only hypothyroid patients carrying the Thr92AlaD₂ polymorphism exhibited favorable outcomes on combined therapy, indicat-
ing that personalized medicine is catching up with thyroid disease. More studies are needed to further evaluate this question, but in the meantime the report of a slow-release liothyronine preparation seems to offer a more stable T3 level over time [99, 100], opening the doors to an appealing new approach to mildly and steadily elevate serum T3 in some hypothyroid patients to offset variability/defects in thyroid hormone signaling in the brain.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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