On commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues

E. Tjørve *, K.M.C. Tjørve, J.O. Olsen, R. Senum, H. Oftebro

Lillehammer University College, 2626 Lillehammer, Norway

Received 16 December 2006; accepted 10 January 2007

Summary Reduced sensitivity to thyroid hormone (TH) in peripheral tissues can occur as defects in TH transport into the cell, intracellular TH metabolism, cytosolic mechanisms, TH entry into the nucleus, thyroxin receptors (TRs) and receptor binding, transcription and post-transcriptional mechanisms. Current literature reveals an extensive list of mutations, drugs, toxins, metabolites and autoimmune antibodies that may impair TH action in the cell, but such impairment may not be picked up by assays of TH and TSH in blood plasma. Substances may induce tissue specific resistance to thyroid hormone (RTH), e.g. by affecting numbers of different TR isoforms. Recent literature also indicates mechanisms by which different conditions, for example, chronic fatigue syndrome (CFS), chronic renal failure (CRF) and nonthyroidal illness, can be accompanied by acquired RTH caused by inhibition of TH metabolism, cell uptake, TR binding and transcription. This prompts us to reassess commonness and rarity of congenital vs. acquired RTH. We hypothesise that observed clinical symptoms of hypothyroidism in chemically euthyroid patients are typically caused by changes in hormonal systems, autoimmune antibodies, metabolites or other substances in the body, leading to reduced sensitivity to TH in peripheral tissues. These changes may be a by-product of other processes and a reversible biological response in the body, and may also result in chronic acquired RTH. Antibodies may prove to be the most common cause of chronic reduction in TH sensitivity. It is argued that the acquired form of RTH, caused by endogenous and exogenous sources, may indeed be more common than the congenital, as in insulin resistance. If acquired RTH exists, then it may not be picked up by blood assays of TH and TSH. An appropriate test to assess TH action in peripheral tissues is therefore greatly desired.

Introduction Hypothyroidism is usually perceived as associated with lowered production of thyroid hormones (THs) (primary and central hypothyroidism), but impaired effect of THs in peripheral (adipose and muscle) tissues should also result in (or contribute to) clinical symptoms consistent with the hypothyroidism diagnosis. Ultimately, peripheral metabolism is governed by hormone concentration outside the cells, transport across the cell (plasma) membrane and efficiency of THs within the cell. In this paper we review factors affecting transport across the plasma membrane and impaired effect of THs in peripheral tissues.
within the cell, as the discovery of these may enforce a paradigm shift in our understanding of hypothyroidism. We are, in view of the recent literature, surprised that nobody has presented a revised hypothesis of commonness of reduced sensitivity to TH in peripheral tissues, often termed acquired resistance to TH.

In older literature, observed high rates of hypometabolism was interpreted as indication of resistance to TH being fairly common [1,2]. Today resistance to thyroid hormone (RTH), i.e., reduced responsiveness of target tissues to TH, is described as a relatively rare condition, with not many more than 1000 registered cases [3]. Practically all of these are attributed to what is termed congenital (or familial) RTH which is only found in a few families (see [4–6] for review). These patients are classified into generalised resistance (GRTH) and pituitary resistance (PRTH) (see [5,7]). It is usually believed that acquired RTH, also described as peripheral tissue resistance to TH (PTRTH) is even rarer, with only one commonly accepted case [8] described in the literature, and reports of other cases being seriously questioned [3]. This contrasts many other hormonal systems where congenital (i.e., genetic) hormone resistance is considered much rarer than acquired resistance. Genetic insulin resistance, for example, is listed as a rare disease compared to its acquired counterpart.

The number of molecular studies on TH action in the cell is rapidly increasing. Have recent advances in this field revealed mechanisms that should make us look for patients with reduced sensitivity to TH that is not congenital, but acquired (as in most cases of insulin resistance)? This study reviews newer literature and discusses evidence on the commonness and rarity of congenital and acquired RTH. The commonness of clinical indications of hypothyroidism in chemically euthyroid patients prompts us to hypothesise that RTH is, as was the interpretation more than 50 years ago, indeed a common condition, and that the acquired form is the dominating.

### Reduced sensitivity to thyroid hormone

Dumitrescu and Refetoff [9] recently suggested reduced sensitivity to TH to be all defects that can interfere with the expression of the biological activity of THs in peripheral tissues. Steps of the TH action (based on Dumitrescu and Refetoff) that may be impaired or slowed include:

- TH transport into the cell,
- intracellular TH metabolism and distribution (including T4 to T3 conversion),
- cytosolic (nongenomic) mechanisms,
- TH entry into the nucleus,
- thyroxin receptors (TRs) and receptor binding and
- transcription and post-transcriptional mechanisms.

We review both mechanisms that cause congenital resistance to TH, and mechanisms that may

<table>
<thead>
<tr>
<th>Action</th>
<th>Congenital impairment</th>
<th>Acquired impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry into cell</td>
<td>Mutation to monocarboxylate transporter 8 (MCT8) gene</td>
<td>Unknown inhibitors linked to NTIS and caloric deprivation</td>
</tr>
<tr>
<td>TH metabolism (e.g. T4 to T3 conversion)</td>
<td>Mutation at the SBP2 locus</td>
<td>Selenium deficiency, toxins, drugs and metabolites inhibit TH metabolism</td>
</tr>
<tr>
<td>Cytosolic effects</td>
<td></td>
<td>TH and TH metabolites may regulate other mechanisms and gene expression, e.g. T1AM which inhibit TAR1</td>
</tr>
<tr>
<td>Entry into nucleus Receptor binding</td>
<td>Mutations to TRβ or the retinoid-X receptor gene</td>
<td>Carnitine is shown to inhibit TH uptake TR competition, repression or destruction by a wide array of antibodies, drugs, toxins and metabolites</td>
</tr>
<tr>
<td>Transcription</td>
<td></td>
<td>Toxins and metabolites as PCB, dioxins and uremic toxins block or weaken heterodimer binding to DNA. Coactivators and corepressors, as SRC-1, also affect transcription</td>
</tr>
</tbody>
</table>

---

Please cite this article in press as: Tjørve E, et al., On commonness and rarity of thyroid hormone resistance: A discussion based on mechanisms..., Med Hypotheses (2007), doi:10.1016/j.mehy.2006.12.056
cause acquired impairment, though emphasis is made on the latter. Possible mechanisms which impair or slow TH action in the cells could act at all levels mentioned above are summarized in Table 1.

**TH entry into the cell**

THs need to cross the plasma membrane into the cell. The transport of THs across the membrane is an active one and therefore an important mechanism. (There is on the other hand no active transport, only passive diffusion, of THs across the nuclear membrane into the nucleus where the majority of TRs are located.)

The transport across the plasma membrane has been shown to be a carrier-mediated process that is energy- and sodium-dependent [10–13] for review. This should hold true not only in hepatic tissue but also in cells of all peripheral tissues. Therefore impairment of this transport process, as mediated by MCT8, OATP-1 and System L amino acid transporters, will cause reduced action of T3 in the tissues. Congenital defects in MCT8 have recently been reported by several authors [14–17]. One may also expect the process to be susceptible to both deficiencies and substances acting as inhibitors (toxins and drugs). Inhibition of cell uptake has also been reported for substances such as amiodarone, phloretin, dansylcadaverine, phenylalanine, benzodiazepines and calcium channel blockers (see [18–20]).

It is believed that differences in tissue sensitivity to TH may arise because of tissue-specific regulation of expression of TH transporters [21,22]. The liver accounts for most of the T4 to T3 conversion. Therefore, decreased T4 uptake into hepatocytes will impair T4 to T3 conversion, as in nonthyroidal illness. This is partly caused by nonesterified fatty acids, and in patients with uremia, indoxyl sulfate and a furan fatty acid may inhibit T4 uptake to the liver [23]. Also caloric deprivation inhibits transport of T4 and T3 across membranes (see [24,25] for review). There are no in vivo studies that evaluate saturability and specificity of tissue uptake of THs [24], but studies on patients with nonthyroidal illness syndrome (NTIS) showed decreased transport of T4 into the liver which resulted in decreased serum T3/T4 ratio and normal TSH values [26,12].

Certain substances (metabolites and toxins) are present in higher concentrations in starving patients or patients with nonthyroidal illness. There is evidence that these limit the rate of T4 and T3 uptake (into tissue), and therefore the metabolism or effect of TH [24]. Already van der Heyden et al. [27] reported that caloric deprivation caused not only lowered T3 values, but also inhibited T4 and T3 cell uptake. Cell uptake in starving subjects is lowered not only in the liver, but also in other peripheral tissues [27]. For review of possible mechanisms of lowered cell uptake (see Ritchie et al. [13] and Hennemann and Visser [24]).

**TH metabolism in the cell**

Disturbance to TH metabolism in the cell may reduce T3 both by inhibition of the deiodination process and decrease of T3/rT3 ratio. Iodothyronine deiodinases (Ds) are enzymes that regulate TH metabolism in the cell, e.g. the conversion of T4 to T3/rT3. Ds are selenoproteins, and selenium deficiency (ingestion or uptake) causes impairment of T4 to T3 conversion [28]. SECIS-binding protein 2 (SBP2) seems to be important for the incorporation of selenocysteine into selenoproteins [29]. A congenital defect, a mutation at the SBP2 locus, has been shown to cause reduced levels of Ds in four children [9,30].

The list of inhibitors to Ds includes phloretin, beta blockers (as propranolol and alprenolol), amiodarone, propylthiouracil (PTU), methimazole, glucocorticoids and iodocontrast agents (contrast media) (see [20,23] for review). They typically inhibit T4 to T3 conversion in peripheral tissues and increase T3/rT3 ratio (see [20]).

Inhibition of T4 to T3 conversion (particularly in liver) and increased rT3 proportion are observed both with nonthyroidal illness [31] and starvation [32,33]. See also Sarne [20] and De Groot [25] for review.

**Nongenomic action of TH (Cytosolic effects)**

Recent findings show that nongenomic action of TH may affect metabolism, not via TRs, but via nongenomic cell signaling pathways that regulate neuronal activity [23,34]. Scanland [34] found that 3-iodothyronamine (T1AM), a naturally occurring TH metabolite, inhibits the trace amine receptor TAR1, and produces a rapid drop in body temperature and heart rate when injected. The discovery of the effect of such metabolic by-products shows that TH potency or resistance may depend not only on membrane crossing and thyroid receptor (TR) binding to TRs and gene transcription, but also a whole range of other pathways.
Furosamide is found to reduce T3 binding to cytosolic receptors, but a significant effect on TH action is not proven [20]. Extraneural nongenomic actions of TH are found to regulate gene expression of several loci, for example glucose in metabolism (see [35] for review). An interesting observation is that TH induction of glycolytic genes provides a possible contribution to the observed overlap between pre-diabetes (insulin resistance and hyperinsulinemia) and hypothyroidism. It is also recently found that TH analogs and derivates can bind not only to TRs but also to other proteins in a nongenomic signalling pathway, (see [23] for review).

TH entry into nucleus

TH entry into the nucleus is thought to be passive, but there is evidence that this is also partly active transport, or at least aided or suppressed by certain mechanisms (see [13] for review). For example, carnitine has been found to inhibit nuclear uptake of TH [36]. Carnitine, responsible for the transport of fatty acids from the cytosol into the mitochondria, is used as a nutritional supplement. It has also been proposed as a drug to treat hyperthyroidism (see [37]).

Receptor binding and transcription

For hormone action, T3 binds to nuclear receptors, which participate in the activation of the messenger RNA production. Possible causes and mechanisms for inhibition of TH action in the cell nucleus has been offered by several authors (see [20,38–43]). Such possible inhibitions are associated with

- competition at receptor level,
- impaired or destroyed receptors,
- change in corepressors and coactivators,
- blocking of TR-heterodimer complex binding to DNA and
- impaired DNA transcription (after binding).

Most cases of congenital RTH are believed to be caused by mutations that impairs or destroy receptors or impair transcription. Congenital RTH comprises generalized resistance to TH (GRTH) and pituitary resistance to TH (PRTH), both caused by TRβ mutations (see [3,5,6] for review). Cases reported where no mutation has been found in the TRβ gene [44] are usually attributed to possible mutations that affect the retinoid-X receptor (RXR) or to coactivators.

Both naturally occurring anti-TR antibodies and other antibodies may compete for or block TR sites or transcription. For example anti-thyroglobulin (anti-Tg), has been suggested to be able to block TRs in the cells, causing peripheral hormone resistance [45]. Many inhibitors (toxins, drugs, metabolites and antibodies) are shown to or expected to compete with THs for TR binding or to destroy or impair TRs. Substances found to or expected to reduce TH binding to TRs, include iodocontrast agents [46], amiarodone [47] and phloretin [18]. Lithium is found to cause tissue specific reduction or increase of different types of TRs [48]. Several drugs have been developed which repress TH action in certain tissues by binding to specific TRs [49].

It is proposed that chronic fatigue syndrome (CFS) patients suffer from type I interferon induced repression or destruction of TRs [50]. This is caused by interferon promoting 2-5OASL proteins, which in turn either repress thyroid receptor activity or target the TRs for destruction by proteasomes. Interferons not only have effect on TRs, but also on both TH synthesis, release and metabolism (see [51] for review). It has been postulated that interferon can also induce autoimmune reactions, resulting in anti-thyroid and anti-thyrotropin (anti-TPO) receptor antibodies [52].

The work of Santos et al. [43] shows that chronic renal failure (CRF) can lower the T3 activity in the cell by impairing TRs (specifically TRβ1) function. They found that dialyzable uremic toxins seen in CRF patients appear to cause TR resistance in peripheral cell tissues by blocking hormone receptors in the cells. The results suggest that T3 transcriptional activity is debilitated by blocking the binding of TR and VDR heterodimers (TRβ1-RXRα and VDR—RXR) to DNA. Santos et al. [43] argue that vitamin D3 (VD3) resistance, as seen in CRF patients [53], arise from the same inhibitory mechanism as the one inhibiting T3. (The debilitating toxins were not identified, only that the effect recedes after haemodialysis.) Also starvation seems to reduce the TH binding to TRs [54], caused by a decrease in the binding capacity of TRs [55].

Exposure to PCB and other dioxin-like compounds (DLCs) produce the same symptoms of hypothyroidism and neurobiological abnormalities as RTH [4]. Some of these substances are very similar in structure to T3 and T4. Hauser et al. [4] proposed that polychlorinated biphenyl (PCB) and other dioxin-like compounds (DLCs) may bind to TRs. The work of Iwasaki et al. [56], and Miyazaki et al. [57] later showed that PCBs do not compete directly with TRs for receptor binding, but affect transcription by causing the TR/receptor heterodimer complex to partly dissociate from the TR-re-
sponse element (TRE). They also bind to transthyretin and probably other carrier proteins [58] in competition with THs, decreasing hormone concentrations (see [4] for review).

A growing number of corepressors (CoRs) and coactivators (CoAs) have been shown to inhibit or enhance the transcriptional activation of T3-regulated genes (see [38–42,59]). It has, for example, been found that knockout mice lacking coactivator SRC-1 show TR resistance [60]. All factors that affect the concentrations of these substances in the body may influence TH potency or resistance.

Biochemical indications

Traditionally, before modern biochemical assays took over, basal metabolic rate (BMR) was used to assess the overall metabolic effect of TH in the body [61–63]. The use of biochemical indications in the diagnosis of hypothyroidism postulates that TH concentration in the cells of peripheral tissues and TH action in the cells can be estimated from levels of FT4, FT3 and TSH in blood serum. The underlying assumption in this statement is that every step in the mechanism functions perfectly; TH transport into the cells, TH metabolism, receptor binding, transcription and post-transcriptional mechanisms.

Patients with congenital RTH can be clinically euthyroid, but often show increased levels of FT4 and FT3 with nonsuppressed TSH (see [5]). We have found little information on correlation between TH and TSH levels in blood and reduced sensitivity to TH caused by drugs and by toxins, antibodies and metabolites from endogenous or exogenous sources. Though reduced TH transport into the cell and altered TH metabolism, as caused by for example NTIS, may result in low FT3 values (and sometimes high rT3) (e.g. [25]).

Already in 1989, Escobar del Rey et al. [64] reported that TH levels in blood may not reflect cellular TH status (finding T3 deficiency in tissues of rat, despite normal plasma T3), although no possible mechanisms were discussed. One should expect mechanisms that reduce sensitivity to TH may cause hypothyroidism even with blood values within the normal range. In addition tests of FT4, FT3 and TSH can be compromised by the presence of certain substances in the blood. Difficulties measuring FT3 and FT4 values have been reported particularly for nonthyroidal illness syndrome (NTIS) (most often resulting in overestimation, with possibly FT4 even more so than FT3) (see [25,65] for review). Estimation may be affected by inhibitors, drugs, metabolites and free fatty acids. The presence of TH antibodies (anti-T3 and anti-T4) and abnormal carrier (albumin/transthyretin) forms may also cause FT3 and FT4 to be overestimated [7]. In addition anti-TSH antibodies is reported to lead to an underestimation of TSH levels (and rarely to overestimation) [7,66–68].

One should therefore be cautious when diagnosing patients with symptoms of hypothyroidism, but with no biochemical findings, as it may be difficult to discern reduced TR action from compromised blood tests or other confounding factors.

Differential resistance between tissues

Patients can sometimes show clinical symptoms of both hypothyroidism and hyperthyroidism, possibly caused by differential resistance between tissues. This can potentially be caused by both differences in carrier mechanisms and the differences in TR isoforms in different organs and tissues. Four isoforms, TRα1, TRβ1, TRβ2 and TRβ3, are found to bind T3 and activate transcription in the nucleus [69]. These isoforms are expressed at different levels in different tissues (see [5]).

Congenital hypothyroidism is typically caused by mutations to the TRβ locus. Mutations affecting the TRβ2 locus, for example, may be expected to cause PRTH, as this isoform is mostly restricted to the pituitary. Lithium has been found to alter proportions of isoforms in rat brain [48]. One should expect different substances or antibodies to affect TR isoforms differently, causing differential resistance to TH between tissues. In addition, several TH analogs have been described that have either specific affinity for TR isoforms found in different tissues or they have different tissue-specific uptake rate (see [23,70] for review). Such compounds have been developed as potential treatment for conditions such as obesity, heart failure and hypercholesterolemia. There are thus several ways in which differential effect on TR isoforms in different tissues may induce tissue-specific TH resistance.

Commonness and rarity of RTH

TH resistances is usually thought to be caused by genetic mutations of hormone receptor proteins or proteins involved in signal transduction (e.g. [7]). We have however, failed to find a reference to substantiate this type of statement. Little direct evidence has, on the other hand, been presented
for the existence of acquired RTH other than the large number of patients with clinical symptoms of hypothyroidism, but no chemical findings in blood samples (i.e., normal FT4, FT3 and THS). The recent developments reviewed in this paper have made it possible to discuss the existence of acquired RTH, possible commonness and mechanisms behind. This emerging literature indicates how impaired transport into or within the cell, TH metabolism, TR nuclear binding and transcription may decrease TR action.

Substances and antibodies which disrupt thyroid systems may have either endogenous or exogenous origin, the first generated by accompanying conditions and trauma, the second by exposure to drugs, toxins or environment. A range of conditions, such as metabolic syndrome, chronic fatigue syndrome, diabetes, fibromyalgia, depression, immune failure, rheumatoid arthritis, polycystic ovary syndrome, nonalcoholic fatty liver disease and chronic renal failure are often accompanied by clinical symptoms similar to those described for hypothyroidism (see [71]). This leads us to believe that clinical symptoms of hypothyroidism in chemically euthyroid patients may be caused by changes in hormonal systems, autoimmune antibodies, metabolites or other substances in the body, leading to reduced sensitivity to TH. This may be caused by either a by-product or a biological response to the condition in question.

Inhibition of T4 to T3 transformation and TH cell uptake in nonthyroidal illness and caloric deprivation are suggested to be a normal biological response (see [13,24]), whereas the effect of uremic toxins blocking heterodimer binding to DNA in CRF is clearly an “unintentional” by-product of the condition. Whether proposed interferon induced repression or destruction of TRs in CFS [50] is a by-product or a biological response has not been discussed. Regardless, this indicates that different conditions can be accompanied by acquired RTH caused by inhibition of TH metabolism, cell uptake, TR binding and/or transcription.

Autoimmunity

The triggering of autoimmune response in an individual may result in a cascade of various antibodies, leading to the expression of various autoimmune manifestations and diseases. There is a large amount of literature on the connection or overlap between different autoimmune conditions, as recently described by several authors (e.g., [72–80]). Autoimmune illnesses comprise more than 80 different conditions, including celiac disease, chronic fatigue, colitis, Crohn’s disease, fibromyalgia, lupus, multiple sclerosis, rheumatoid arthritis, Sjogren’s syndrome, hypothyroidism and type 1 diabetes. Autoimmune antibodies may also well prove to be a main cause of chronic reduction of sensitivity to thyroid hormone. One may expect such TH-resistance to be caused not only by oblige anti-TR antibodies, but also by other types of antibodies, for example anti-Tg, that may reduce TH sensitivity in cell tissue by impairing or destroying TRs (though not by thyroid hormone antibodies which seem to be a rarer phenomenon [81]).

Conclusions

The commonness of acquired insulin resistance is well accepted, despite the mechanisms not being well known, whereas acquired RTH has by most been regarded as nonexistent. The rapidly accumulating knowledge forces us to rethink and reconsider our perception of the commonness and rarity of acquired vs. congenital RTH. The recent literature reviewed here inclines us to hypothesise that acquired RTH may be the commoner of the two. We infer that reduced TR binding and transcription inhibition may occur as a by-product of other processes or a reversible biological response in the body, but may also result in chronic acquired RTH.

If acquired RTH indeed exists, then chemical indications may not reveal this condition, as it is not possible to detect all types of reduced sensitivity to TH. A much needed tool would be a test that assesses TH action in peripheral tissues. BMR may be used, and has been so even after the method disappeared as a preferred diagnostic tool, (e.g. by Alemzadeh et al. [82]) who looked at BMR to reveal hypometabolism in chemically euthyroid infants. Urinary cortisol metabolites have been proposed in assessment of peripheral TH action [83,84]. There has long been an expressed need for better tools to determine thyroid status at a peripheral level (see [85]). The rapidly expanding knowledge of the molecular basis of TH action may hopefully soon provide us the appropriate test of peripheral sensitivity.

References

On commonness and rarity of thyroid hormone resistance


[35] Moeller LC, Cao X, Dimitrescu AM, Seo H, Refetoff S. Thyroid hormone mediated changes in gene expression can be initiated by cotosomal action of the thyroid hormone receptor b through the phosphatidlyinositol 3-kinase pathway. Nuclear Receptor Signaling (<www.nursa.org>) 2006;4 DOI:10/nrs.04020. p. 4.


[37] Benvena S, Ruggeri RM, Russo A, et al. Usefulness of l-carnitine, a naturally occurring peripheral antagonist


doi:10.1186/1478-1336-3-1


