Triiodothyroacetic acid in health and disease

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Abstract

Thyroid hormone (TH) is crucial for development and metabolism of many tissues. The physiological relevance and therapeutic potential of TH analogs have gained attention in the field for many years. In particular, the relevance and use of 3,3′,5-triiodothyroacetic acid (Triac, TA$_3$) has been explored over the last decades. Although TA$_3$ closely resembles the bioactive hormone T$_3$, differences in transmembrane transport and receptor isoform-specific transcriptional activation potency exist. For these reasons, the application of TA$_3$ as a treatment for resistance to TH (RTH) syndromes, especially MCT8 deficiency, is topic of ongoing research. This review is a summary of all currently available literature about the formation, metabolism, action and therapeutic applications of TA$_3$.

Introduction

Thyroid hormone (TH) is crucial for the development and metabolism of many tissues. Thyroid stimulating hormone (TSH) controls the production and secretion of TH by the thyroid gland, which predominantly produces the prohormone thyroxine (T$_4$) and to a lesser extent the bioactive hormone 3,3′,5-triiodothyronine (T$_3$). T$_3$ mainly exerts its effects through binding to its nuclear receptors (TRs) at T$_3$ response elements (TREs), resulting in the transcriptional regulation of TH target genes (genomic effects). The TR$\alpha_1$, TR$\beta_1$ and TR$\beta_2$ isoforms are T3-binding TRs isoforms (Lazar 1993, Ortiga-Carvalho et al. 2004). In addition, several non-genomic effects have been ascribed to TH (Davis et al. 2011, Lin et al. 2012). To exert its biological function, TH has to cross the cell membrane, which requires membrane transporter proteins (Hennemann et al. 2001 and reviewed in Visser 2007 and Bernal et al. 2015). Monocarboxylate transporter 8 (MCT8) is the most specific TH transporter and the only TH transporter associated with human disease (Dumitrescu et al. 2004, Friesema et al. 2004).

The deiodinases (D1–3) importantly regulate the bioavailability of T3 in targets cells, while TH is also metabolized by glucuronidation and sulfation, which enhance biliary excretion (Engler & Burger 1984, Burger 1986, Visser 1996). Other modifications of iodothyronines include decarboxylation of the alanine side chain, resulting in iodothyronamines (Scanlan et al. 2004, Hoefig et al. 2015), and subsequent oxidative deamination resulting in the formation of iodothyroacetic acid derivatives (Wood et al. 2009). Recently, potential biological actions have been ascribed to 3-iodothyronamine (3-T$_1$AM) and thyronamine (T$_0$AM) (reviewed in Hoefig et al. 2016). The biological actions of 3,3′,5-triiodothyroacetic acid (Triac; TA$_3$) and 3,3′,5,5′-tetraiodothyroacetic acid (Tetrac, TA$_4$) have been more extensively described. The biological actions of TA$_3$ closely resemble those of T$_3$, although important differences in the cellular transport mechanism and TR-isoform-specific potency exist. For these reasons, TA$_3$ holds therapeutic potential in the treatment of...
patients with specific defects in TH signaling, such as patients harboring mutations in TRβ (resistance to thyroid hormone (RTH)-β). Likewise, the therapeutic use of TA₃ in patients lacking the MCT8 transporter (MCT8 deficiency or the Allan-Herndon-Dudley syndrome, AHDS) is subject of ongoing research.

In this review we summarize the literature from the 1950s until now regarding the biosynthesis, metabolism, action and putative therapeutic applications of TA₃.

Kinetic properties of TA₃ in humans

TA₃ is a naturally occurring TH metabolite, with reported serum levels between 2.6 and 15.2 ng/dL (42–244 pmol/L) in healthy human subjects (Nakamura et al. 1978, Burger et al. 1979, Gavin et al. 1980), whereas others reported TA₃ levels below the assay detection limit of ~4 ng/dL (64 pmol/L) (Menegay et al. 1989). The free fraction of TA₃ in plasma is relatively low compared to T₃, due its high affinity for plasma binding proteins, exceeding that of T₃ by 16-fold in rats (Ingbar 1960, Gosling et al. 1976). In humans, TA₃ particularly binds to transthyretin (TTR), whereas its binding to thyroxine binding globulin is negligible (Robbins & Rall 1955, Christensen 1960, Ingbar 1960). Nevertheless, the plasma clearance rate of TA₃ considerably exceeds the clearance rate of T₃ in humans (compiled data shown in Table 1). The clearance rate of TA₃ in rats is more similar to that of T₃ (Table 1; Gosling et al. 1976, Liang et al. 1997). In humans, the estimated plasma half-life of TA₃ is ~6 h and, thus, is markedly shorter than the half-life of T₃ (~24 h) (Table 1). Peak levels occur within 40 min after oral administration and higher peak levels are achieved upon intravenous administration (Menegay et al. 1989). The intestinal absorption efficiency amounts to 50–67% and the daily TA₃ production rate (PR) to 3.2–7.8 µg/day (Burger et al. 1979, Gavin et al. 1980, Siegrist-Kaiser et al. 1994). Gavin and coworkers (Gavin et al. 1980) found a slightly higher PR in athyroid subjects on 80 µg/day LT₃ substitution (10.1 ± 0.4 µg/day). A caveat in assessing circulating TA₃ concentrations is the interference of T₃ in the TA₃ radioimmunoassay (RIA) due to high antibody cross-reactivity (up to 50%). When preceded by proper serum extraction and column chromatography methods, this can be reduced to 1–6% (Burger et al. 1979, Gavin et al. 1980, Menegay et al. 1989). Since serum T₃ levels exceed those of TA₃ by about 50-fold, this leads to considerable overestimation of endogenous TA₃ levels.

Together, TA₃ is a naturally occurring TH metabolite, present in humans at ~50-fold lower concentrations than T₃ and is rapidly cleared from the circulation despite its high affinity for plasma binding proteins.

Biosynthesis of TA₃

The first evidence for in vivo TA₃ formation was provided by studies in thyroidectomized rats demonstrating the presence of ¹³¹I-TA₃ in kidney homogenates after injection of ¹³¹I-T₃ (Jouan et al. 1956). These findings were confirmed by incubation of rat kidney mitochondrial

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Kinetic properties of T₃ and TA₃ in humans and rats.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Species/substrate</td>
<td>Serum level (pmol/L)</td>
</tr>
<tr>
<td>TA₃</td>
<td>42–244</td>
</tr>
<tr>
<td>Rat T₃</td>
<td>768</td>
</tr>
<tr>
<td>TA₃</td>
<td>402</td>
</tr>
</tbody>
</table>

Overview of kinetic properties of T₃ and TA₃ in humans and rats. Data are compiled from indicated references. Peak levels have been determined after oral administration.

MCR, metabolic clearance rate; PR, production rate; t½, plasma half life time; TBG, thyroxine binding globulin, TTR, transthyretin.
extracts (Albright et al. 1956), and rat kidney (Tomita et al. 1957) or brain (Tata et al. 1957) homogenates with 131I-T4 and 131I-T3. More recent studies confirmed the in vivo formation of TA3 upon T3 injection in rats (Medina-Gomez et al. 2008). In vivo formation of TA3 and TA4 was demonstrated in humans after administration of 125I-LT4 (Braverman et al. 1970), whereas others detected TA3 after the administration of 125I-TA4 (Burger et al. 1979, Burger 1986). Based on these findings it was assumed that T3 and/or TA4 are intermediates in the conversion of T4 to TA3.

The mechanism by which iodothyronines are converted to iodothyroacetic acid metabolites has not been fully elucidated. A common hypothesis involves the decarboxylation and subsequent oxidative deamination of the alanine side chain of iodothyronines. Recently, purified human intestinal ornithine decarboxylase (ODC) was indeed demonstrated to facilitate the decarboxylation of 3,5-T2 to 3,5-diiodothyronamine (T2AM) and T4 to 3,3′,5′-tetraiodothyronamine (T4AM) (Hoefig et al. 2015). The involvement of aromatic l-amino acid decarboxylase (AADC, or l-DOPA decarboxylase), long regarded as the most likely candidate, has been disproven (Hoefig et al. 2012). It remains to be studied if other decarboxylases also possess this capacity. Although, recent studies have demonstrated the presence of decarboxylated (iodo)thyronine metabolites 3-T3AM and T3DAM in vivo (Scanlan et al. 2004), other iodothyronamines have not been detected in human serum thus far.

The oxidative deamination of T1AM and T4AM to their thyroacetic acid counterparts has been demonstrated in HepG2 cells and human thyroid tissue and was reduced by iproniazide, an inhibitor of monoamine oxidase (MAO) and semicarbazide-sensitive amine oxidase (SSAO) (Wood et al. 2009). It was suggested that at least one of these enzymes converts 3-T3AM and T4AM to their aldehyde intermediates, which may be substrates for the abundantly expressed aldehyde dehydrogenase (ALDH), resulting in the formation of 3-iodothyroacetic acid (3-TA′) and TA′, respectively (Wood et al. 2009). Of interest, TA3 modulates the activity of ALDH (McCarthy et al. 1968, Márđh et al. 1987, Zhou & Weiner 1997). Conversion of T4AM to TA4 has not been demonstrated thus far. Although iodothyronamines are efficiently deiodinated, neither D1 nor D2 catalyzes the conversion of T4AM to TA4 (Piehl et al. 2008). This indicates that conversion of T4AM to T3AM is not an intermediate step in the conversion of T4 to TA3 (Fig. 1). Together, these studies support the hypothesis that at least some iodothyronines can be converted to their acetic acid metabolites via a thyroacetic acid intermediate. An alternative route for the metabolism of the alanine side chain of iodothyronines involves its conversion by aminotransferase(s) to pyruvic acid, followed by decarboxylation to acetaldehyde and oxidation to acetic acid (e.g. Wilkinson 1957). However, the enzymes catalyzing these reactions remain to be identified.

**Metabolism of TA3**

TA4 has been shown to be metabolized via similar pathways as T3, i.e. stepwise deiodination, and conjugation with glucuronic acid and sulfate.

**Deiodination**

Early studies found that TA3 inhibits inner ring deiodination (IRD) of T3 in rat brain microsomes (Kaplan et al. 1983) and monkey hepatocellular carcinoma cells (Sorimachi & Yasumura 1981). Later studies demonstrated that TA3 is efficiently deiodinated to 3,3′-diiodothyroacetic acid (3,3′-TA2) by D1 and D3 (Rutgers et al. 1989a,
Horn et al. 2013). TA₃ is even a better substrate for D1 than T₂, illustrated by a 16-fold higher Vmax/Km ratio (Rutgers et al. 1989a). Similar to T₂, TA₃ induced the expression and activity of D1 in rat liver and kidney (Medina-Gómez et al. 2008). Moreover, outer ring deiodination by Dio1 and Dio2 mediates the conversion of TA₂ to TA₃ (Burger et al. 1975, Köhrle et al. 1986, Horn et al. 2013).

In humans, up to 60% of the administrated ¹³¹I-TA₃ dose appears in urine as inorganic ¹³¹I within 24 h (Green & Ingbar 1961), suggesting that deiodination of (conjugated) TA₃ comprises an important metabolic pathway in vivo. In contrast, Flock and coworkers (Flock et al. 1962) found that only 20% of ¹³¹I-TA₃ administered to dogs appeared as inorganic ¹³¹I in urine within 24 h, while 3,3'-TA₂ sulfate was also detected in serum. A similar fraction of ¹³¹I-TA₃ was excreted in urine as inorganic ¹³¹I in rats (Wilkinson et al. 1959, Juge-Aubry et al. 1995).

Deiodination of TA₃ ultimately results in the formation of thyroacetic acid (TA₃h), which is excruted in urine in humans (Chopra et al. 1988). Given that the estimated PRs of TA₄ and TA₃ together amount to ~10 µg/day (Pittman et al. 1980, Siegrist-Kaiser & Burger 1994), the urinary TA₄ levels (up to ~15 µg/L) cannot be derived from deiodination of endogenous TA₄ and TA₃ alone. Based on the studies of Hoefig and coworkers (Hoefig et al. 2015) and Wood and coworkers (Wood et al. 2009), the metabolism of (iodo)thyronines such as 3,5-T₂, 3-T₁ and T₀ via thyronamine intermediates to their thyroacetic acid derivatives also contributes to urinary TA₄ excretion.

Conjugation

In addition to deiodination, conjugation of TA₃ to its glucuronide (TA₃G) and sulfate (TA₃S) constitutes an important part of TA₃ metabolism. Incubation of rat hepatocytes with ¹³¹I-⁴-I₃ results in almost complete metabolism of TA₃ within 3 h, mainly to TA₃G (50%), ¹³¹I- (40%) and TA₃S (<10%) (Rutgers et al. 1989b). The formation of TA₃G and TA₃S increases to 60% and 16%, respectively, by blocking Dio1 with propylthiouracil (PTU), and TA₃G levels even further increase to 80% by simultaneous inhibition of sulfation, without affecting total TA₃ metabolism (Rutgers et al. 1989b).

Similar to sulfated iodothyronines, TA₃S is rapidly degraded through IRD (Rutgers et al. 1989a). The aryl sulfotransferase Sult1a1 (or phenol sulfotransferase 1 (PST1)) mediates the sulfation of TA₃ at the 4'-hydroxyl group in rats (Sekura et al. 1981) and the ubiquitously expressed (human) SULT1A1 is the most likely candidate in humans (Visser 1994). In rats, stable ether glucuronides are formed at the phenolic hydroxyl group of TA₃h, whereas mainly labile ester glucuronides at the carboxyl group are formed in humans (Burger 1986, Moreno et al. 1994).

Although deiodination of TA₃S appears to be the principal metabolic route of TA₃ in humans, TA₃G is the major TA₃ metabolite excreted in bile (Roche et al. 1956, Green & Ingbar 1961). Up to 50% of ¹³¹I-⁴-I₃ administered to rats is excreted within 4 h as TA₃G in bile (Rutgers et al. 1989b), suggesting that glucuronidation is also the main route of TA₃ metabolism in rats. Interestingly, serum TA₃S and biliary TA₃G and TA₃S excretion are increased by blocking deiodination with PTU, without affecting the TA₃ clearance rate. Flock and coworkers (Flock et al. 1965) obtained similar results using another D1 inhibitor, butyl 4-hydroxy-3,5-diiodobenzoate (BHDB). Bilirubin glucuronosyltransferase-deficient Gunn rats show a reduction in biliary excretion of TA₃G, accompanied by a compensatory increase of non-specific metabolites in urine (Flock et al. 1965). Moreover, newborn sheep reveal a rapid decrease of TA₃G plasma levels which coincides with the maturation of glucuronosyltransferase (and deiodinase) expression (Wang et al. 1986, Wu et al. 2008).

Lastly, hepatectomized dogs show complete abolishment of TA₃G formation and a concomitant increase in sulfate conjugates in plasma and urine, most predominantly 3'-TA₃S and 3,3'-TA₃S (Flock et al. 1962).

Together, these studies suggest that deiodination and conjugation are responsible for a stable TA₃ clearance, even in case one of these pathways is not properly functioning. Importantly, since the relative contribution of these pathways differs across species, metabolic and kinetic studies in animal models should be extrapolated to different models with caution.

Cellular transport of TA₃

As for TH, the cellular entry of TA₃ is supposed to be transporter-mediated. Studies using rat anterior pituitary cells and cardiomyocytes have shown a similar time course of ¹²⁵I-⁴-I₃ and ¹²⁵I-T₃ uptake (Everts et al. 1994, Verhoeven et al. 2002). Based on free hormone levels, the transport rate of TA₃ even exceeds that of T₃ (Everts et al. 1994, Verhoeven et al. 2002). Moreover, TA₃ competes with TH uptake in rat anterior pituitary cells and isolated hepatocytes, but not in rat cardiomyocytes (Blondeau et al. 1988, Everts et al. 1994, Neves et al. 2002, Verhoeven et al. 2002). These findings suggest that tissue-specific transporters facilitate the cellular entry...
of TA3, some of which may work in an ATP and sodium independent manner (Everts et al. 1994).

TA3 transporters have not been identified yet. MCT8, MCT10 and Organic Anion Transporting Polypeptide (OATP)1C1 do not appear relevant for transport of TA3 (Horn et al. 2013, Groeneweg et al. 2014, Kersseboom et al. 2014). Studies in rodents suggest that the TA3 transporter(s) are widely expressed, given the increase in TA3 levels in many tissues after injection of TA3 (Medina-Gomez et al. 2008, Kersseboom et al. 2014). However, the transporter(s) involved remain to be identified.

Molecular basis of TA3 action

TA3 binds efficiently to nuclear TRs (Oppenheimer et al. 1973, Smith et al. 1980, Evans et al. 1983, Bres et al. 1986, Luo et al. 1986), i.e. with a similar affinity as T3 to TRα1 and a 3- to 6-fold higher affinity than T3 to TRβ1 and TRβ2 (Schueler et al. 1990, Takeda et al. 1995, Messier & Langlois 2000, Martinez et al. 2009), which may indicate relative TRβ-selective binding and action of TA3. This is supported by a 2- to 3-fold lower EC50 value for TRβ1 compared to TRα1 mediated transcriptional activation by TA3 (Martinez et al. 2009). The preferential binding of TA3 to TRβ is supported by X-ray crystallography (Martinez et al. 2009). Although TA3 shows a better fit in the TRα1 ligand binding cavity, its binding to TRβ is more energetically favorable. This is mainly caused by a single amino acid difference between TRα1 (Ser277) and TRβ1 (Asn331) at the ligand binding domain (LBD), leading to a relative displacement of the β-hairpin of the TRβ LBD which potentiates direct substrate contacts (Wagner et al. 2001, Martinez et al. 2009). Of clinical importance is the relatively high affinity of TA3 for several TRβ mutants identified in patients with RTH-β which display reduced T3 binding (Takeda et al. 1995, Messier et al. 2001).

Importantly, despite its higher affinity for TRβ than T3, controversy exists to what extent this leads to higher transcriptional activation levels. Messier and Langlois (2000) did not observe differences in TRβ-mediated transcriptional activation potency between T3 and TA3 in case of the direct repeat (DR4), the most prevalent TRE configuration in humans (Yen 2001), whereas TA3 was 1.5- to 2-fold more potent than T3 in case of palindromic and inverted palindromic TREs. In contrast, Martinez and coworkers (Martinez et al. 2009) found that TA3 was also 6-fold more potent than T3 in activating TRβ-mediated transcription in case of DR4. Although not studied in detail, differences in the potency of TA3 and T3 to dissociate or recruit co-factors may exist. It was found that TA3 has a lower efficacy than T3 in recruiting the steroid receptor co-activator (SRC-1) to TRα1 (Koury et al. 2009). Of note, most of these studies have been carried out in the absence of retinoid X receptor (RXR), which has been shown to exert a central role in modulating the sensitivity of TH-responsive genes to different TR ligands (Bogazzi et al. 1997).

The non-genomic effects of TA3 have been scarcely studied (Lin et al. 1998, D’Arezzo et al. 2004). TA3 was found to exert a stimulatory effect on the plasma membrane integrin αvβ3 receptor, although less potently compared to T3 (D’Arezzo et al. 2004). Taken together, TA3 has somewhat higher affinity and transcriptional activation potency for TRβ than TRα and, thus, may exert stronger thyromimetic effects in TRβ-expressing tissues. However, it should be realized that intracellular TA3 levels are governed by tissue-specific transporters, deiodinases and conjugating enzymes which also impact the tissue-specific biological actions of TA3.

Regulation and role of TA3

TA3 is an important bioactive hormone in marine invertebrates. Interestingly, the TR of Branchiostoma floridae (amphioxus) is selectively activated by TA3 and not by T3 (Paris et al. 2008, Wang et al. 2009). Nevertheless, administration of T3 to the developing amphioxus stimulates its metamorphosis (Paris et al. 2010), suggesting that T3 is a precursor of the bioactive hormone TA3. Indeed, TA3 is present in amphioxus and its administration promotes metamorphosis to a similar extent as administration of T3 (Paris et al. 2008, 2010). In addition, the non-selenodeiodinase bDy from B. floridae specifically catalyzes the IRD of TA3 and TA3 but not of T4 and T3 (Klootwijk et al. 2011). Also in other species, TR activation by TA3 may differ from the human situation (Oka et al. 2013).

Although TA3 is a naturally occurring bioactive TH metabolite in humans, its exact biological role is unknown. In addition, little is known about factors that affect its serum and tissue concentrations. Several studies found up to 3-fold increased serum TA3 and TA3 levels during fasting and non-thyroidal illness (Burger et al. 1976, Pittman et al. 1980, Dlott et al. 1992, LoPresti & Dlott 1992). It was suggested that the reduction in D1 and increase in D3 activity during these ‘low T3 states’, favor the formation of rT3 and other TH metabolites such as...
TA$_3$ (Carlin & Carlin 1993, Farwell 2013). Indeed, urinary excretion of TA$_3$(S) is increased during fasting and iopanoic acid (IOP) treatment (LoPresti et al. 1993, Kaiser-Siegrist & Burger 1994). The molecular basis for these changes is largely unclear, although the role of ODC appears to be limited, since its activity is reduced during starvation (D’Agostino et al. 1987). It has been postulated that the increased TA$_3$ levels are responsible for the suppression of TSH observed under these conditions despite low serum TH levels. In addition, TA$_3$ potently suppresses TSH secretion by rat brown and white adipocytes, and since leptin stimulates TSH secretion this may induce a further decline in TSH levels (Medina-Gomez et al. 2004).

**Effects of TA$_3$ on the hypothalamus-pituitary-thyroid (HPT) axis**

The first recognized effect of TA$_3$ was the reduction of goiter in hypothyroid rats (Pitt-Rivers 1953). In line, TA$_3$ effectively restores most clinical and biochemical abnormalities in myxedematous patients (Pitt-Rivers 1955, 1956, Trotter 1955, 1956). Later studies showed that TA$_3$ potently reduces TSH secretion and TRH-receptor expression in mouse thyrotropic pituitary tumor cells (Gershengorn et al. 1979) and TRH-induced TSH release from rat pituitary fragments or cells (Szabolcs et al. 1991, Everts et al. 1994).

In euthyroid and hypothyroid rats, a dose-dependent reduction of serum TSH levels is observed within 6h after TA$_3$ administration, beginning at a dose as low as 10µg/kg (Table 2). From these and other studies it was estimated that 62µg (100nmol)/kg/day TA3 has an equal TSH-suppressive effect as 16µg (20nmol)/kg/day LT$_4$. Interestingly, Mirell and coworkers (Mirell et al. 1989) found that TSH mRNA expression levels are unchanged 6h after TA$_3$ administration, suggesting that the initial decline in serum TSH is not caused by alterations at transcriptional level, but rather points to direct inhibition of TSH secretion by TA$_3$. In contrast, prolonged (>12 days) TA$_3$ administration to rats persistently suppressed pituitary TSH mRNA levels (Juge-Aubry et al. 1995, Liang et al. 1997), resulting in a dose-dependent decrease in serum T$_3$ and T$_4$ levels (Medina-Gomez et al. 2008). Similar effects on TSH levels were found in mice treated with TA$_3$, whereas no effects were observed on hypothalamic TRH mRNA expression (Horn et al. 2013).

A dose-dependent reduction of TSH levels was observed within 6–9h after oral administration of TA$_3$ to euthyroid human subjects, with a lowest dose of 350µg (~5µg/kg) (Burger et al. 1979, Medeiros-Neto et al. 1980, Menegay et al. 1989). Similar effects were observed in hypothyroid subjects and subjects with apparent TH insensitivity (Beck-Peccoz et al. 1983, Salemla et al. 1988, and Table 3). Consequently, serum T$_3$, T$_4$ and T$_3$ levels decrease (Burger et al. 1979, Medeiros-Neto et al. 1980, Beck-Peccoz et al. 1983, 1988, Bracco et al. 1993). Sustained TSH suppression was best achieved upon division of the daily TA$_3$ dose compared with a single morning administration, although both regimes resulted in a similar reduction of serum T$_4$ levels (Medeiros-Neto et al. 1980, Bracco et al. 1993).

Taken together, TA$_3$ inhibits TSH production and secretion by acting at the level of the pituitary, thereby regulating thyroid activity.

**Effects of TA$_3$ on other tissues**

In addition to its potent effect on the HPT axis, TA$_3$ also exerts thyromimetic effects on peripheral tissues (Tables 2 and 3). In evaluating these effects, it should be taken into account that TA$_3$ reduces endogenous TH production when administrated to euthyroid subjects, which also contributes to the changes in tissue TH status. Therefore, the direct effects of TA$_3$ can best be studied in athyroid subjects. An overview of clinical studies with TA$_3$ in humans is provided in Table 4. Table 5 provides an overview of the thyromimetic potency of TA$_3$ in different tissues relative to T$_4$. TA$_3$ and LT$_4$ dose are expressed in µg/kg (if available) or else as total daily dose. Bone formation markers include alkaline phosphatase and osteocalcin (in case of discrepant responses of these parameters within the same study, the response of osteocalcin prevails since this is a more specific marker for bone formation). Bone resorption markers include hydroxyproline or d-pyridinoline (in case of discrepant responses the parameter with the strongest response prevails). In case TA$_3$ and LT$_4$ monotherapy are compared, tissue sensitivity is expressed as TA$_3$ dose/LT$_4$ dose ratio required to obtain a similar effect size on the given parameters. In case of comparison between LT$_4$+TA$_3$ vs LT$_4$ mono-therapy, tissue sensitivity is expressed relative to the TA$_3$ dose/Δ LT$_4$ dose ratio (e.g. <(ratio) means a stronger response of the parameter to low dose LT$_4$+TA$_3$ compared to the high dose LT$_4$ mono-therapy at an equal TSH-suppressive dose). Only studies in which details of >2 organ systems have been provided are included in Table 5.
Table 2  Tissue effects of TA₃ determined in animal studies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect/outcome</th>
<th>Species, thyroid state</th>
<th>Dose; duration; mode of administration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPT-axis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (serum) basal or stim.</td>
<td>↓</td>
<td>Rat, eu/hypo</td>
<td>10 µg/kg/day; 12 day; i.v.</td>
<td>Mirell et al. (1989), Juge-Aubry et al. (1995), Liang et al. (1997), Alvarez et al. (2004), Medina-Gomez et al. (2008)</td>
</tr>
<tr>
<td>T₄ (serum)</td>
<td>↓</td>
<td>Rat, eu</td>
<td>8 µg/kg/day; 12 day; i.v.</td>
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<td>Thyroid weight</td>
<td>↓</td>
<td>Rats, hypo</td>
<td>~5 µg/kg/day; 9 day; s.c.</td>
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<tr>
<td>Heart</td>
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<td></td>
</tr>
<tr>
<td>Heart weight/body weight</td>
<td>↑</td>
<td>Rat (adult), hypo</td>
<td>300 µg/kg/day; 15 day</td>
<td>Olsen et al. (1977), Liang et al. (1997)</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>Rat (newborn)</td>
<td>300 µg/kg/day; 1 year</td>
<td>Symons et al. (1975)</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>Rat (in utero)</td>
<td>300 µg/kg/day; 15 day to pregnant dams</td>
<td>Olsen et al. (1977), Hawkey et al. (1981)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>+</td>
<td>Rat (in utero)</td>
<td>&gt;300 µg/kg/day; 15 day to pregnant dams</td>
<td>Olsen et al. (1977), Symons et al. (1975)</td>
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<td>Cardiac size</td>
<td>↑</td>
<td>Rat (adults)</td>
<td>180 µg/kg/day; 1 year</td>
<td>Symons et al. (1975), Olsen et al. (1977)</td>
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<tr>
<td>Bone</td>
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<td>Bone formation markers (serum)</td>
<td>=</td>
<td>Rat, eu/hypo</td>
<td>250 µg/kg/day; 40 day; i.p.</td>
<td>Alvarez et al. (2004)</td>
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<td>Bone resorption markers (serum)</td>
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<td>250 µg/kg/day; 40 day; i.p.</td>
<td>Alvarez et al. (2004)</td>
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<td>BMD</td>
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<td>Rat, eu/hypo</td>
<td>250 µg/kg/day; 40 day; i.p.</td>
<td>Alvarez et al. (2004)</td>
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<td>Brain</td>
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<tr>
<td>Myelination</td>
<td>↑</td>
<td>Mice, hypo</td>
<td>200 µg/kg/day; 12 day; oral</td>
<td>Kersseboom et al. (2014), Zada et al. (2016)</td>
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<td>Purkinje cell development</td>
<td>↑</td>
<td>Zebrafish, hypo</td>
<td>200 µg/kg/day; 12 day; oral</td>
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<td>Liver</td>
<td></td>
<td>Chicken, hypo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>=</td>
<td>Rats, eu</td>
<td>200 µg/kg/day; 4 week; oral</td>
<td>Autissier et al. (1980)</td>
</tr>
<tr>
<td>Biliary cholesterol</td>
<td>=</td>
<td>Rat, eu</td>
<td>1000 µg/kg/day; 9 day; i.v.</td>
<td>Van Zyl (1957)</td>
</tr>
<tr>
<td>Biliary cholic acid</td>
<td>↓</td>
<td>Rat, eu</td>
<td>1000 µg/kg/day; 9 day; i.v.</td>
<td>Van Zyl (1957)</td>
</tr>
<tr>
<td>Metabolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>Acute ↑</td>
<td>Rats, hypo</td>
<td>1000 µg/kg; single; s.c.</td>
<td>Pitt-Rivers (1953), Wilkinson (1959)</td>
</tr>
<tr>
<td></td>
<td>Gradual ↑</td>
<td>Rats, hypo</td>
<td>600 µg/kg; 4 day; s.c.</td>
<td>Hill et al. (1960)</td>
</tr>
<tr>
<td>Body weight</td>
<td>↓</td>
<td>Rats, hypo</td>
<td>60 µg/kg/day; 9 day; s.c.</td>
<td>Pitt-Rivers (1953)</td>
</tr>
</tbody>
</table>

Explanation of symbols: =, no effect; ↑, stimulatory effect; ↓, inhibitory effect; +, present. In case of =, the highest dose reported to have no effects is listed in the 4th column. In case of ↑ or ↓ the lowest dose at which the effect has been reported is listed in the 4th column.

*Only the studies that corrected for cross-reactivity of TA₃ in the T₃ assay are listed.
i.p., intraperitoneal; i.v., intravenous; s.c., subcutaneous; stim., TRH-stimulated.

**Basal metabolic rate**

Pioneering studies demonstrated that TA₃ rapidly increased oxygen consumption in rat kidney slices (Thibault & Pitt-Rivers 1955) and myeloid leukemic leucocytes (Alexander & Bisset 1958) and stimulates aerobic glycolysis in primary tumour cell cultures more potently than T₃, T₄ or TA₃ (Heimberg et al. 1955).

At high doses of 1000–5000 µg/kg/day, TA₃ rapidly raised the oxygen consumption in hypothyroid rats (Pitt-Rivers 1953, Wilkinson 1959), whereas a lower TA₃ dose of 600 µg/kg/day resulted in a more gradual stimulation (Hill et al. 1960) (Table 2). In hypothyroid patients, TA₃ stimulates basal metabolic rate (BMR) only at doses above ~4000 µg/day (50–75 µg/kg/day) (Lerman & Pitt-Rivers 1955, 1956, Trotter 1955, 1956, De Greaff et al. 1957). Trotter (1956) showed that the effects of 4000 µg TA₃/day (50–65 µg/kg/day) on BMR persisted beyond 5 days after treatment cessation. In contrast, administration of 45 µg TA₃/kg/day for up to 3 weeks to euthyroid subjects significantly reduced BMR.
Table 3  Tissue effects of TA₃ determined in humans.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect/outcome</th>
<th>Thyroid state</th>
<th>Dose, duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPT axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (serum), basal or stim.</td>
<td>↓</td>
<td>Eu/hypo/hyper</td>
<td>~5 µg/kg/day; 1 day</td>
<td>Burger et al. (1979), Medeiros-Neto et al. (1980), Menegay et al. (1989), Bracco et al. (1993), Sherman et al. (1997), Brenta et al. (2003)</td>
</tr>
<tr>
<td>T4 (serum)</td>
<td>↓</td>
<td>Eu/hypo/hyper</td>
<td>~20 µg/kg/day; 6 week</td>
<td>Medeiros-Neto et al. (1980), Beck-Peccoz et al. (1988), Lind et al. (1989), Bracco et al. (1993), Brenta et al. (2003)</td>
</tr>
<tr>
<td>T3 (serum)</td>
<td>↓</td>
<td>Eu/hyper</td>
<td>22 µg/kg/day; 3 week</td>
<td>Bracco et al. (1993)</td>
</tr>
<tr>
<td>Goiter volume</td>
<td>↓</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 6–28 week</td>
<td>Burger et al. (1975), Beck-Peccoz et al. (1988)</td>
</tr>
<tr>
<td>Heart (Basal or sleeping)</td>
<td>=</td>
<td>Eu/hypo</td>
<td>50–75 µg/kg/day; 6–28 week</td>
<td>Trotter (1956), Burger et al. (1979), Medeiros-Neto et al. (1980), Beck-Peccoz et al. (1988), Lind et al. (1989), Bracco et al. (1993), Sherman et al. (1997), Pujol et al. (1998), Brenta et al. (2003)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>=</td>
<td>Eu/hypo</td>
<td>50–75 µg/kg/day; 6–28 week</td>
<td>Rall et al. (1956), Trotter (1956), Sherman et al. (1997), Brenta et al. (2003)</td>
</tr>
<tr>
<td>Episodes of angina</td>
<td>↑</td>
<td>Eu (with CHD)</td>
<td>7.5–75 µg/kg/day; 3–10 month</td>
<td>Oliver &amp; Boyd (1957), Ibbertson et al. (1959), Boyd &amp; Oliver (1960)</td>
</tr>
<tr>
<td>Cardiac function</td>
<td>=</td>
<td>Eu/hypo</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997), Pujol et al. (2000)</td>
</tr>
<tr>
<td>Bone formation markers (serum)</td>
<td>↑</td>
<td>Hypo</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>Bone resorption markers (serum)</td>
<td>↑</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>BMD lumbal</td>
<td>=</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>BMD Femoral</td>
<td>↓</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHBG</td>
<td>↑</td>
<td>Eu</td>
<td>20 µg/kg/day; 11 month</td>
<td>Beck-Peccoz et al. (1988), Lind et al. (1989), Bracco et al. (1993), Brenta et al. (2003)</td>
</tr>
<tr>
<td>Ferritine</td>
<td>↑</td>
<td>Hypo</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>Cholesterol (total, LDL)</td>
<td>↓</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>=</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>Apoprotein A1</td>
<td>=</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td>Apoprotein B</td>
<td>↓</td>
<td>Eu</td>
<td>50–75 µg/kg/day; 85–100 day</td>
<td>Sherman et al. (1997)</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>= (↑)</td>
<td>Eu</td>
<td>20 µg/kg/day; 11 months</td>
<td>Trojanowski et al. (2000), Trotter (1956), Medeiros-Neto et al. (1980), Beck-Peccoz et al. (1988), Lind et al. (1989), Bracco et al. (1993), Sherman et al. (1997), Pujol et al. (1998), Brenta et al. (2003)</td>
</tr>
<tr>
<td>Protein oxidation</td>
<td>=</td>
<td>Eu</td>
<td>25–75 µg/kg/day; 12–14 weeks</td>
<td>Trotter (1956), Oliver &amp; Boyd (1957), Bracco et al. (1993)</td>
</tr>
<tr>
<td></td>
<td>↑</td>
<td>Hypo</td>
<td>50–75 µg/kg/day; 6–28 weeks</td>
<td>Sherman et al. (1997), Pujol et al. (1998), Brenta et al. (2003)</td>
</tr>
</tbody>
</table>

(Continued)
and sleeping energy expenditure, presumably due to a reduction of endogenous TH production, whereas protein oxidation was unaffected (Bracco et al. 1993). These parameters significantly increased in subjects treated with 2.4-4.8µgLT₄/kg/day (Bracco et al. 1993). In general, TA₃ exerts similar effects on BMR at 4- to 30-fold lower doses of LT₄ and 15- to 100-fold lower doses of LT₃ (Table 5). Importantly, the TA₃ dose required to increase BMR greatly exceeds that required for adequate TSH suppression.

Liver

Intrahepatic TA₃ levels increase upon TA₃ infusion in rats, which is in line with the important role of the liver in TA₃ clearance (Medina-Gomez et al. 2008). TA₃ also effectively induces the expression of T₃-responsive genes in the liver, including Dio1, to a similar extent as T₃ (Juge-Aubry et al. 1995, Liang et al. 1997, Alvarez et al. 2004, Medina-Gomez et al. 2008). No changes in serum cholesterol and lipid levels or biliary excretion were observed after treatment of euthyroid rats for 4 weeks with 200µgTA₃/kg/day (Van Zyl 1957, Auttissier et al. 1980).

When given at equivalent TSH-suppressive doses to euthyroid or hypothyroid patients, TA₃ induced similar increases in serum sex hormone binding globulin (SHBG) and ferritin levels as LT₄ (Bracco et al. 1993, Sherman et al. 1997). In contrast, Beck-Peccoz and coworkers (Beck-Peccoz et al. 1988) and Lind and coworkers (Lind et al. 1989) did not observe any changes in serum SHBG levels upon TA₃ administration in a similar dose to mildly obese euthyroid subjects on caloric restriction. In hypothyroid subjects, TA₃ also reduced serum total and LDL cholesterol as well as apoprotein B levels, generally within 2 weeks (Table 3). The effect of TA₃ on HDL levels was usually less pronounced. These effects of TA₃ were generally less pronounced in euthyroid subjects as the effects of TA₃ in peripheral tissues were counter-balanced by the reduction in serum T₃ induced by TA₃, although findings vary depending on the precise TA₃ regimen used (Oliver & Boyd 1957, Boyd & Oliver 1960, Medeiros-Neto et al. 1980, Bracco et al. 1993, Brenta et al. 2003). Other liver parameters such as ALAT, ASAT and bilirubin were typically not affected by TA₃ (Burger et al. 1979). Taken together, TA₃ has potent thyromimetic effects in the liver.

Heart

TA₃ is efficiently taken up by rat cardiomyocytes (Medina-Gomez et al. 2008), but is a less potent regulator of TH target genes in the heart than T₃ (Liang et al. 1997). Nevertheless, high doses of TA₃ induce cardiac hypertrophy in rats, although less potently than T₃ (Lameloise et al. 2001). At least part of these effects is likely mediated through TA₃. Several rat studies have shown that high doses of TA₃ (300µg/kg/day) administered to pregnant dams induce cardiac hypertrophy and myofibril disorganization in the offspring (Olsen et al. 1977, Hawkey et al. 1981). These abnormalities are less pronounced using a lower TA₃ dose (Olsen et al. 1977), or when TA₃ is administered to the newborns (Symons et al. 1975), and they are prevented by different β-adrenergic blocking agents with membrane stabilizing properties (Hawkey et al. 1981, Pearce et al. 1983, 1985, 1988). Of note, treatment for 13–19 days with TSH-suppressive doses of TA₃ (15–50µg/kg/day) had no effect on the heart to BW ratio or myocardial structure in adult rats (Olsen et al. 1977, Liang et al. 1997).
### Table 4  Overview of clinical studies in humans.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Thyroid state</th>
<th>Daily dose of TA$_3$ (µg/day)</th>
<th>Duration</th>
<th>Effects of TA$_3$</th>
<th>Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myxedema or hypothyroidism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lerman &amp; Pitt-Rivers (1955)</td>
<td>Hypo</td>
<td>1000–4000, i.v.</td>
<td>16–17 day</td>
<td>↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Lerman &amp; Pitt-Rivers (1956)</td>
<td>Hypo</td>
<td>100–4000, i.v.</td>
<td>12–16 day</td>
<td>↓, ↓</td>
<td>Normalization of myxedematous features; higher doses were required to restore BMR</td>
</tr>
<tr>
<td>Trotter (1955)</td>
<td>Hypo</td>
<td>2000–6000, oral</td>
<td>10 day</td>
<td>↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Trotter (1956)</td>
<td>Hypo, eu</td>
<td>1000–6000, oral</td>
<td>2–8 week</td>
<td>↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Rall (1956)</td>
<td>Hypo</td>
<td>5000–15,000, single dose i.v.</td>
<td>36 day follow-up</td>
<td>↓, ↑</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>De Graeff et al. (1957)</td>
<td>Hypo</td>
<td>1000, i.v.</td>
<td>12 day</td>
<td>↓, ↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Ibbertson et al. (1959)</td>
<td>Hypo</td>
<td>10,000–18,000, single dose</td>
<td>3–10 months</td>
<td>↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Lerman (1961)</td>
<td>Hypo</td>
<td>500–6000, oral</td>
<td>2–3 months</td>
<td>↓, ↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Hill et al. (1960)</td>
<td>Hypo</td>
<td>1000–6000, oral</td>
<td>14–52 day</td>
<td>↓</td>
<td>Normalization of myxedematous features</td>
</tr>
<tr>
<td>Zondek et al. (1956)</td>
<td>Hypo</td>
<td>8000–10,000, 2 day oral</td>
<td>15 day follow-up</td>
<td>(↓)</td>
<td>Temporary normalization of myxedematous features</td>
</tr>
<tr>
<td><strong>Lipid-reduction in coronary heart disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliver &amp; Boyd (1957)</td>
<td>Eu</td>
<td>500–5000, oral</td>
<td>12–14 week</td>
<td>(↓)</td>
<td>Not useful for lipid lowering in patients with pre-existent heart disease</td>
</tr>
<tr>
<td>Boyd &amp; Oliver (1960)</td>
<td>Hypo, eu</td>
<td>500–5000, oral</td>
<td>&gt;12 week</td>
<td>(↓)</td>
<td>Not useful for lipid lowering in patients with pre-existent heart disease</td>
</tr>
<tr>
<td><strong>Treatment of euthyroid goiter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brenta et al. (2003)</td>
<td>Eu</td>
<td>1400, oral</td>
<td>11 months</td>
<td>↓, ↓</td>
<td>Effective reduction of goiter size, with fewer side-effects (e.g. palpitations)</td>
</tr>
<tr>
<td>Pujol et al. (2000)</td>
<td>Eu</td>
<td>1400, oral</td>
<td>12–21 month</td>
<td>=</td>
<td>No thyromimetic (side) effects on the heart in long-term treated patients</td>
</tr>
<tr>
<td><strong>Thyroid carcinoma (substitution after thyroid ablation)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mueller-Gaertner &amp; Schneider (1988)</td>
<td>Hypo</td>
<td>500 (+LT$_4$), oral</td>
<td>3 week</td>
<td>↓</td>
<td>Addition of a low dose TA$_3$ to LT$_4$ monotherapy further reduced basal and stimulated TSH levels</td>
</tr>
<tr>
<td>Sherman &amp; Ladenson (1992)</td>
<td>Hypo</td>
<td>1400 (+LT$_4$), oral</td>
<td>6–8 week</td>
<td>↓, ↓</td>
<td>Compared to LT$_4$ alone, a 40–50% lower LT$_4$ dose was required if combined with TA$_3$ to obtain equivalent or even better TSH suppression, without affecting TH action in peripheral tissues</td>
</tr>
<tr>
<td>Sherman et al. (1997)</td>
<td>Hypo</td>
<td>3500, oral</td>
<td>3 months</td>
<td>↓, ↓</td>
<td>At a dose required for equivalent TSH suppression, TA$_3$ has a stronger thyromimetic effect on liver and bones than LT$_4$</td>
</tr>
</tbody>
</table>

**Effects of TA$_3$**
- TSH: Thyroid stimulating hormone
- Chol: Cholesterol
- TO: Total osteocalcin
- BW: Body weight
- BMR: Basal metabolic rate
- HR: Heart rate
- Myx: Myxedema
- Side effects: Potential complications

**Conclusion(s)**
- Normalization of myxedematous features
- Higher doses were required to restore BMR
- Normalization of myxedematous features
- Temporary normalization of myxedematous features.
Mechelany et al. (1991)  
**Hypo** 8–17 µg/kg/day TA₃  
(=500–1000 µg/day) + 1.8 µg/kg/day LT₄ (oral)  
6 months  ↓ ↓ ↑ = ↑ 

**Reduction of lipid levels and body weight in mild obesity**  
Beck-Peccoz et al. (1988)  
Eu 2800, oral  
>2 months  ↓ 

Lind et al. (1989)*  
Eu 3000, oral  
8 day  ↓ = = = 

**TSH suppressive therapy in addition to anti-thyroid drugs in Graves’ disease**  
Pujol et al. (1998)  
Eu ~1350, oral  
~18 months 

Bracco et al. (1993)  
Eu 1700–3400, oral  
6 week  ↓ ↓ ↑ = = 

Burger et al. (1979)  
Eu 150–2400, oral  
1 day  ↓ 

Menegay et al. (1989)  
Hyper Eu 600, oral  
350–2800, oral,  
1 dose 1 day ↓ /= 

Medeiros-Neto et al. (1980)  
Eu, hypo 1400, oral  
6 week  ↓ ↓ = = = 

**Pregnancy**  
Cortelazzi et al. (1999)  
Eu on PTU 2100–2800, oral  
13 week 

Nicolini et al. (1996)  
Eu on PTU 2100–2800, oral  
10 week 

Asteria et al. (1999)  
RTHβ 2100–3500, oral  
13 week ↑ 

An overview of all studies, of which at least the abstract was available to the authors, in which TA₃ has been applied as a treatment for a variety of clinical conditions. 

*Studies of which only the abstract was available; a Worsening of pre-existent ischemic heart disease (1 case); b Worsening of pre-existent ischemic heart disease (2/12 cases); c Worsening of pre-existent ischemic heart disease (3/18 cases); d No side effects on cardiac structure in adults; e Only minor clinical side effects (4/25 participants); f Severe complications due to cordocentesis BMR, basal metabolic rate; BW, body weight; chol, cholesterol; eu, euthyroid; HR, heart rate; hyper, hyperthyroid; hypo, hypothyroid; myx, myxedema; TO, turn-over. 

Compared to LT₄ mono-therapy, a 40–50% lower LT₄ dose was required once combined with TA₃ to obtain equivalent or even better TSH suppression, without affecting TH action in peripheral tissues. 

No additional effect on body weight and serum cholesterol levels over dietary restrictions alone. 

No additional effect on body weight and serum cholesterol levels over dietary restrictions alone. 

Effective reduction of goiter size. 

Reduction of serum TSH levels with dose-dependent effects on liver and bone, but not BMR. 

More sustained TSH suppression by dividing daily dose. 

Reduction of serum (TRH stimulated) TSH and T₃ but not T₄ levels, persisting until 5 days after administration. 

Reduction of serum T₃ levels in 2/7 subjects. 

Reduction of serum TSH levels after a single dose ≥350 µg. 

Reduction of serum TSH levels, without affecting markers of tissue TH status except cholesterol. 

Effective reduction of fetal goiter size, normal neuromotor development of neonate at 20 months. 

Effective reduction of fetal goiter size, normal neuromotor development the neonate at 20 months. 

Effective reduction of fetal goiter size. Normal neuromotor development of neonate (with RTHβ) at 24 months.
Table 5  An overview of the thyromimetic potency of TA₃ in different tissues relative to LT₄.

<table>
<thead>
<tr>
<th>Dose regime</th>
<th>ΔLT₄ ratio</th>
<th>HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Comparison to LT₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sherman et al. (1997)</td>
<td>hypo</td>
<td>48 µg/kg/day</td>
</tr>
<tr>
<td>Bracco et al. (1993)</td>
<td>eu</td>
<td>23–46 µg/kg/day</td>
</tr>
<tr>
<td>Brenta et al. (2003)</td>
<td>eu</td>
<td>19.6 µg/kg/day</td>
</tr>
<tr>
<td>Ibbertson et al. (1959)</td>
<td>hypo</td>
<td>5–60 µg/kg/day</td>
</tr>
<tr>
<td>B. LT₄+TA₃ vs LT₄ mono-therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechelany et al. (1991)</td>
<td>hypo</td>
<td>8.5–17 µg/kg/day</td>
</tr>
<tr>
<td>Sherman &amp; Ladenson (1992)</td>
<td>hypo</td>
<td>1500 µg</td>
</tr>
</tbody>
</table>

In adult human subjects, no detrimental effects of TA₃ have been observed on cardiac structure or function (Sherman et al. 1997, Pujol et al. 2000). In general, no overt chronotropic effects have been noted (Tables 2 and 3), although incidentally episodes of palpitations and tachycardia have been reported (Trotter 1956). This may be attributed to its lower potency to activate TRα1 compared with T₃ (Koury et al. 2009) or its lack of nongenomic effects on Na⁺ flux and Ca²⁺-ATPase activity in cardiomyocytes as observed with T₃ (Rudinger et al. 1984, Huang et al. 1999). The effects of TA₃ on the heart have not been systematically studied in humans, although several case-reports of children with RTHβ have not reported any cardiac side effects (Anzai et al. 2012).

Adipose tissue

TH importantly regulates basal and facultative thermogenesis, mainly through induction of uncoupling protein Ucp1 in BAT (Nicholis et al. 1986). In rat adipocytes, TA₃ appeared more potent in upregulating Ucp1 and Dio2 expression than T₃ (Medina-Gomez et al. 2003). Also in vivo, low doses of TA₃ resulted in upregulation of Ucp1 in BAT and induced ectopic Ucp1 expression in WAT, without affecting tissue TH levels (Medina-Gomez et al. 2008). In addition, TA₃ inhibited leptin expression and secretion in rat brown and white adipocytes (Medina-Gomez et al. 2004).

Bone

TH stimulates bone turnover, particularly bone resorption. Prolonged hyperthyroidism results in a reduction of bone mass and bone mineral density (BMD). Similarly, in vitro studies suggest that the stimulatory effects of TA₃ on bone resorption exceed those on bone formation in fetal rat long bones, whereas the overall effects of TA₃ on fetal mouse calvarial bones were less pronounced (Kawaguchi et al. 1994a,b).

However, daily injection of 250 µg/kg TA₃ in euthyroid rats for 40 days did not increase serum bone alkaline phosphatase (bALP) or carboxy-terminal telopeptide region of type I collagen (β-CTX), which are markers for bone formation and resorption, respectively (Alvarez et al. 2004). In addition, the BMD of the femur did not differ significantly between TA₃-treated and control animals (Alvarez et al. 2004). In hypothyroid animals on the same TA₃ dose, an increase in β-CTX serum levels was observed without concomitant increase in serum bALP. However, BMD did not differ significantly between TA₃-treated and control animals (Alvarez et al. 2004).

In athyroid human subjects, Sherman and coworkers (Sherman et al. 1997) showed that TA₃ stimulated bone turnover more potently than LT₄, at a similar degree of TSH suppression, as is evidenced by higher ALP and osteocalcin levels (bone formation markers) and urinary pyridinoline and deoxypyridinoline excretion (bone resorption markers). Some studies suggested that TA₃ preferentially stimulates bone formation (Mechelany et al. 1991, Sherman & Ladenson 1992), whereas others demonstrate a more selective stimulation of bone resorption and a decrease in BMD of the femoral neck but not of the lumbar spine (Brenta et al. 2003).

Taken together, TA₃ stimulates bone resorption and bone formation, although the currently available data are inconclusive regarding the balance between both processes.
Brain and neurogenesis

$T_A$ regulates the expression of well-known TH target genes, including $Dio2$ and $Dio3$, in SH-SYSY neuroblastoma cells and rat brain homogenates, and stimulates the dendritic arborization of cerebellar Purkinje cells (PCs) as efficiently as $T_3$ (Liang et al. 1997, Horn et al. 2013, Kersseboom et al. 2014).

$T_A$ also exerts $T_3$-like effects on neurogenesis in vivo. Pax-8 KO mice lack endogenous TH production and consequently have a severely impaired brain development illustrated by a strongly reduced myelination and dendritogenesis of PCs. These abnormalities are largely prevented by administration of 200$\mu$g $T_A$/kg/day from postnatal day 1 (Kersseboom et al. 2014). The stimulatory effects on myelination are in line with previous studies (Van Wynsberge et al. 1978). Similar effects have been found with $T_A$ (Horn et al. 2013). In addition, the administration of low $T_A$ doses (30$\mu$g $T_A$/kg/day) to WT mice resulted in a reduction of intracerebral $T_3$ and $T_4$ levels but did not alter the expression levels of some positively regulated TH-dependent genes in the striatum or cerebral cortex (Bárez-López et al. 2016). Several preclinical studies in rodents also indicated that $T_A$ may have an antidepressive effect mediated through its $\beta$-adrenergic stimulatory effects (Massol et al. 1987, 1988a,b).

Effects of $T_A$ and $T_A$ on the developing human brain are largely unknown. However, several cases have been reported where $T_A$ has been administered to a pregnant woman for the treatment of fetal hypothyroidism. Cortelazzi and coworkers (Cortelazzi et al. 1999) showed that $T_A$ administration (2100–2800$\mu$g/day) between 26 and 39 weeks of gestation to a hyperthyroid pregnant woman treated with PTU effectively reduced fetal goiter size within 15 days. A similar case was reported by Nicolini and coworkers (Nicolini et al. 1996). In addition, Asteria and coworkers (Asteria et al. 1999) reported on the use of $T_A$ in the treatment of a pregnant woman with RTH$\beta$ because of suspected hypothyroidism in the fetus carrying the same heterozygous mutation in $T_R\beta$. In all three cases, the infant showed a normal neuro(psycho) logical development at 20–24 months of age. Obviously, the risks and benefits of $T_A$ administration during pregnancy should be carefully weighted. Nevertheless, these studies suggest that $T_A$ has $T_3$-like effects on the developing human brain.

Skin

Topical application of $T_A$ increases dermal thickness and prevents glucocorticoid-induced skin atrophy in mice and humans (Faergemann et al. 2002, Yazdanparast et al. 2006a,b), and stimulates procollagen synthesis and keratinocyte proliferation in human skin (Yazdanparast et al. 2004, Zhang et al. 2012), but has no beneficial effects on plaque psoriasis (Vahlquist et al. 2004).

Muscle and kidney

Little is known about the effects of $T_A$ in muscle and kidney. In hypothyroid rats, $T_A$ is efficiently taken up in striatal muscle and kidney, where the latter is also an important site for $T_A$ metabolism (Medina-Gomez et al. 2008). Mechelany and coworkers (Mechelany et al. 1991) have shown that $T_A$ reduced serum creatine kinase levels. $T_A$ also increased urinary creatine levels in hypothyroid subjects, suggesting an increase in glomerular filtration rate (Lerman & Pitt-Rivers 1956, Rall et al. 1956, De Graeff et al. 1957, Ibbertson et al. 1959).

<table>
<thead>
<tr>
<th>Liver</th>
<th>Heart</th>
<th>Muscle</th>
<th>Bone</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC ↓</td>
<td>LDL ↓</td>
<td>HDL ↓</td>
<td>TG ↓</td>
<td>SHBG ↑</td>
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<td>&lt;17</td>
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<td>6–10</td>
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<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*–, no effect. Only studies in which details of >2 organ systems have been provided are included in this table.*

BW, body weight; HR, heart rate; TC, total cholesterol; TG, thyroglobulin.
Therapeutic applications of TA₃ in humans

Because of its thyromimetic properties, the use of TA₃ in the treatment of different thyroid diseases has been explored, which is summarized in Table 4.

Myxedema

The therapeutic application of TA₃ was first studied in cases of severe hypothyroidism (myxedema). In general, TA₃ doses of 10–30 µg/kg/day improved the myxedematous appearance and restored several parameters that reflect tissue TH status, including plasma cholesterol levels, urinary creatine excretion, electrocardiographic abnormalities and body weight, whereas no effect on BMR was observed (Lerman & Pitt-Rivers 1955, 1956, Trotter 1953, 1956, De Graeff et al. 1957, Ibbertson et al. 1959, Boyd & Oliver 1960). Normalization of BMR is generally observed in a dose range of 50–75 µg/kg/day (Table 4). In general, the effects of TA₃ occur more rapidly compared to T₄ (Zondek et al. 1956, Ibbertson et al. 1959).

Thus, TA₃ effectively restores euthyroidism in hypothyroid patients, but is less potent than LT₄ and LT₃. Taken together, an obvious benefit for the use of TA₃ over LT₄ in the treatment of myxedematous patients is lacking.

Lipid reduction in coronary heart disease and obesity

The observed dissociated effect of low doses TA₃ on serum cholesterol levels and BMR prompted several small studies to the lipid lowering effect of TA₃ in euthyroid subjects with coronary heart disease. However, relatively high TA₃ doses, up to 5 mg daily (~70 µg/kg/day), were needed to reduce serum cholesterol levels in these studies, with usually only transient effects (Oliver & Boyd 1957, Boyd & Oliver 1960). In non-controlled studies, at doses not affecting BMR, more episodes of transient thoracic pain and increased exercise intolerance have been reported in hypothyroid and euthyroid subjects independent of the TA₃ dose, which subsided after TA₃ withdrawal (Oliver & Boyd 1957, Ibbertson et al. 1959, Boyd & Oliver 1960). In contrast to these early studies, Brenta and coworkers (Brenta et al. 2003) already observed a reduction in cholesterol levels using a dose of 20 µg TA₃/kg/day in healthy subjects.

TA₃ has also been studied as a lipid lowering drug in mildly obese euthyroid females with caloric restriction (Beck-Peccoz et al. 1988). Despite a strong reduction in serum TSH, T₄ and T₃ levels, no significant changes were found in serum cholesterol and triglyceride levels in the TA₃ treated group compared with females on caloric restriction alone.

There is no evidence that TA₃ is suitable for the long-term control of hypercholesterolemia in euthyroid subjects with or without coronary heart disease.

TSH suppression after thyroidectomy in differentiated thyroid carcinoma

TSH-suppression therapy is initiated after total thyroidectomy in patients with differentiated thyroid carcinoma. Driven by the preferential effects of TA₃ on the HPT axis, several studies evaluated TA₃ as a TSH-suppressive therapy in such patients.

Mueller-Gartner and Scheider (1988) observed a reduction in mean basal and TRH-stimulated TSH levels in patients on LT₄ monotherapy (2.6 ± 0.7 µg/kg/day) upon addition of 500 µg TA₃ daily, while only minor side effects were reported in 4 out of 25 patients. However, neither the impact on recurrence and survival rates, nor the effects on the TH state in peripheral organs were evaluated. Pujol and coworkers (Pujol et al. 1997) reported similar findings.

Mechelany and coworkers (Mechelany et al. 1991) compared LT₄ monotherapy alone or in combination with TA₃. The TA₃ dose was adjusted to achieve TSH levels <0.1 U/L as during LT₄ monotherapy. Sherman and Ladenson (1992) performed similar studies, but adjusted the LT₄ dose in order to achieve a similar degree of TSH suppression. In both studies, patients required 40–50% less LT₄ during combination therapy to achieve equivalent or even better TSH suppression. However, markers that reflect tissue TH action showed only minor or no significant differences between both treatment regimes. These findings implicate that the thyromimetic effects of TA₃, at an equal TSH-suppressive dose, are at least as potent as those of LT₄ in most peripheral organs.

Sherman and coworkers (Sherman et al. 1997) compared TA₃ vs LT₄ monotherapy. Following a baseline period (phase I) on a TSH-suppressive dose LT₄ (2.7 µg/kg/day), patients received starting doses of 24 µg TA₃/kg twice daily or 1.9 µg LT₄/kg/day, which were then titrated until TSH levels were below 0.1 U/L (phase II). Subjects receiving TA₃ showed a stronger increase in serum levels of SHBG, ferritin, and bone turnover markers, and a stronger decrease in serum total and LDL cholesterol and apoprotein B over baseline levels after 2 months of treatment at the final dose (48 ± 3 µg/kg/day) compared...
to the LT₄ treated group (final dose: 2.2±0.1 µg/kg/day). No significant differences were observed in cardiac parameters, energy expenditure or body weight between both groups. Remarkably, upon dose-escalation subjects in the LT₄ treated group received a 10–20% lower final LT₄ dose in phase II than during phase I of the study. Moreover, it appears that it was not required to further escalate the TA₃ starting dose of 24 µg TA₃/kg twice daily in order to obtain TSH suppression <0.1 U/L.

In conclusion, TA₃ monotherapy is an adequate TSH-suppressive therapy, while at the same time providing sufficient thyromimetic effects in the peripheral tissues. TA₃ may especially have augmented thyromimetic effects on the pituitary, liver and bone. Based on the available studies, there is no obvious benefit of using TA₃, alone or in combination with LT₄, as TSH-suppression therapy, unless LT₄ is not tolerated.

Goiter

Brenta and coworkers (Brenta et al. 2003) showed that TA₃ (19.6 µg/kg/day) and LT₄ (1.7 µg/kg/day) were equally effective in reducing goiter size in patients with euthyroid goiter, although the proportion of patients in whom goiter size was reduced by more than 50% was higher in the TA₃ (42%) vs LT₄ (17%) treated group (although not statistically significant), while less side effects were reported. TSH levels were adequately reduced in both groups and FT₄ levels decreased in the TA₃ treated group. Most parameters that reflect peripheral TH state, including heart rate, showed insignificant changes in both treatment arms. Nevertheless, a significant decrease in serum total and LDL cholesterol as well as femoral BMD and increased deoxypyridinoline levels were observed in the TA₃ treated patients, which suggest an increase in bone resorption.

Pujol and coworkers (Pujol et al. 1998) studied the effect of TA₃ and T₃ as a TSH-suppressive therapy in addition to the anti-thyroid drug carbimazole in the treatment of Graves’ disease, which both significantly reduced goiter volume, but did not significantly improve remission and relapse rates of Graves’ disease.

Taken together, TA₃ treatment effectively reduces goiter volume in patients with (non-)toxic diffuse and nodular goiter. Since TSH-suppressive therapy is not recommended as useful goiter-reductive treatment, neither LT₄ nor TA₃ is advised for goiter reduction.

TA₃ abuse in dietary supplements

Multiple cases have been reported over the last decades on the abuse of dietary supplements, metabolic enhancers and mesotherapies containing TA₃. Subjects presented with clinical signs of thyrotoxicosis, while TH and TSH levels were found to be suppressed (Ferner et al. 1986, Chow & Lam 1998, Bauer et al. 2002, Scally & Hodge 2003, Chan et al. 2004, Ma et al. 2008, Danilovic et al. 2008, Cohen-Lehman et al. 2011). For this reason, the US Food and Drug Administration has repeatedly issued an official warning against the consumption of dietary supplements or metabolic enhancers containing TA₃.

Application of TA₃ in RTH syndromes

RTH syndromes result from alteration of local TH signaling due to defective cellular entry, intracellular metabolism or receptor function. The finding that TA₃ clearly exerts thyromimetic effects but differs from T₃ in its cellular transport mechanism and affinity for mutant TRβ variants, prompted studies to explore the application of TA₃ (and TA₃) in RTHβ and MCT8 deficiency.

RTHβ

RTHβ is caused by mutations in TRβ and biochemically characterized by elevated serum TH levels in the context of non-suppressed TSH levels. RTHβ results in decreased T3 action in tissues that express TRβ, whereas tissues that predominantly express TRα, such as the heart and brain, are relatively thyrotoxic in response to the high serum TH levels (Refetoff et al. 1993, Forrest et al. 1996). In vitro studies have shown that TA₃ is able to bind and activate a subset of these mutant receptors (Takeda et al. 1995). The effects of TA₃ treatment in RTHβ patients have been described on a case-by-case basis and are currently the most wide-spread off-label application of TA₃. In a subgroup of RTHβ patients, TA₃ is able to decrease TSH and consequently the high serum T₃ and T₄ levels. Since the thyromimetic effects of TA₃ itself do not fully compensate the reduction in endogenous TH levels, it alleviates the thyrotoxic symptoms including tachycardia, goiter, excessive sweating and behavioral problems (Beck-Peccoz et al. 1983, Lind & Eber 1986, Faglia et al. 1987, Salmela et al. 1988, Kunitake et al. 1989, Smallridge et al. 1989, Beck-Peccoz et al. 1990, Aguilar Diosdado et al. 1991, Cohen-Lehman et al. 2011).

MCT8 deficiency

Mutations in MCT8 result in the AHDS, which is characterized by severe intellectual and motor disability and increased serum T₃ levels (Dumitrescu et al. 2004, Friesema et al. 2004). Transport of TH across the BBB and into neuronal cells largely depends on MCT8. Hence mutations in MCT8 result in a hypothyroid state in the brain, compromising brain development (Matheus et al. 2015). In contrast, tissues that rely on other transporters are exposed to the high serum T₃ levels resulting in thyrotoxic tissues. Putative therapies should aim to restore TH signaling in the brain and at the same time alleviate the thyrotoxic state in the peripheral tissues. Although combination therapy of LT₄ and PTU alleviates the peripheral thyrotoxicosis, this approach does not restore TH signaling in the brain (Visser et al. 2013). The ideal therapy comprises a TH analog that enters the cell independently from MCT8, but exerts similar effects as TH. As outlined in this review, TA₃ fulfills these criteria (illustrated in Fig. 2). Indeed, several pre-clinical studies have supported the therapeutic potency of TA₃ and its less rapidly metabolized precursor TA₄ in AHDS.

Mct8 KO mice show the characteristic serum TFT pattern of AHDS (Trjakovic et al. 2007, Trjakovic-Arsic et al. 2010), which is effectively normalized by TA₄ treatment (Horn et al. 2013). However, Mct8 KO mice lack a neurological phenotype, since Outp1c1 is likely to function as an alternative TH transporter at the BBB in mice. Indeed, in Mct8/Outp1c1 double KO (DKO) mouse brain development is severely disturbed and closely resembles the abnormalities observed in Pax-8 KO mice (Mayerl et al. 2014). The abnormal brain morphology in Pax-8 KO mice is largely prevented by administration of T₄, TA₃ (200–400 µg/kg/day) or TA₄ (400 µg/kg/day) from postnatal day 1 (Horn et al. 2013, Kersseboom et al. 2014), suggesting that TA₃ and TA₄ can replace T₄ and T₃ during brain development in mice. Such effects of TA₃ were also observed in Pax-8/Mct8 DKO mice, confirming that its transport across the BBB is MCT8-independent. Most importantly, TA₃ administration (400 µg/kg/day) from postnatal day 1–12 rescued several markers of disrupted brain development in Mct8/Outp1c1 DKO mice, including the abnormal cerebellar Purkinje cell development and myelination (Kersseboom et al. 2014). In addition, TA₃ and TA₄ ameliorate the neurodevelopmental abnormalities in zebrafish models for MCT8-deficiency (De Vrieze et al. 2014, Zada et al. 2016) and improve cerebellar Purkinje cell development in Mct8 deficient chicken (Delbaere et al. 2017). So far, it has not been studied in these animal models to what extent TA₃ still has positive effects on brain development once treatment is initiated at a later developmental stage. This is particularly important to predict its therapeutic potency in human AHDS patients, when initiated at a relatively advanced age.

The putative role of TA₃ as a therapy for human AHDS patients is currently under investigation in a prospective interventional cohort study, the Triac Trial (NCT02060474), primarily assessing its potency to restore the peripheral thyrotoxicosis. If TA₃ would be an effective therapy, it can be anticipated that early intervention may have effects on the neurocognitive phenotype. Although TA₃ readily crosses the placenta (Asteria et al. 1999, Cortelazzi et al. 1999), there are many medical...
and ethical considerations before justifying prenatal administration of TA₃ to mothers who are pregnant of an AHDS child.

**Concluding remarks**

TA₃ is a bioactive TH metabolite that has tissue-specific thyromimetic activities (Table 5). Although TA₃ clearly has a potent TSH-suppressive effect, its metabolic effects on liver and bone are at least as potent. In general, higher doses of TA₃ are required to achieve equal thyromimetic effects as LT₄ (and LT₃), mainly due to its rapid clearance. Based on the available studies, the therapeutic benefits of TA₃ over LT₄ treatment is generally limited to primary thyroid diseases. However, TA₃ holds potential in the treatment of subsets of RTH patients and possibly in AHDS. Clinical studies are needed to assess if and how this ‘old’ molecule can have full therapeutic potential in specific RTH syndromes.

**Declaration of interest**

W E V is the principal investigator of the Triac Trial in MCT8 patients (NTC02060474).

**Funding**

This work was supported by a grant from the Netherlands Organisation for Health Research and Development (project number 113303005, 2014) (to W E V) and from the Sherman Foundation (to W E V, 2016).

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Received in final form 26 May 2017

Accepted 30 May 2017

Accepted Preprint published online 1 June 2017