Triiodothyroacetic acid in health and disease

Stefan Groeneweg, Robin P Peeters, Theo J Visser and W Edward Visser

Department of Internal Medicine and Academic Center for Thyroid Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands

Correspondence should be addressed to W E Visser
Email
w.e.visser@erasmusmc.nl

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.

Key Words

- thyroid hormone
- resistance to thyroid hormone (RTH)
- thyroid hormone analog
- thyroacetic acid derivatives
- Triac
- TA_3

Journal of Endocrinology (2017) **234**, R99–R121

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 pro-hormone 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 TRα1, TRβ1 and TRβ2 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_1AM) and thyronamine (T_0AM) (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

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

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 TA_3 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 TA_3.

Kinetic properties of TA_3 in humans

TA_3 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 TA_3 levels below the assay detection limit of ~4 ng/dL (64 pmol/L) (Menegay *et al.* 1989). The free fraction of TA_3 in plasma is relatively low compared to T_3, due its high affinity for plasma binding proteins, exceeding that of T_3 by 16-fold in rats (Ingbar 1960, Gosling *et al.* 1976). In humans, TA_3 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 TA_3 considerably exceeds the clearance rate of T_3 in humans (compiled data shown in Table 1). The clearance rate of TA_3 in rats is more similar to that of T_3 (Table 1; Gosling *et al.* 1976, Liang *et al.* 1997). In humans, the estimated plasma half-life of TA_3 is ~6 h and, thus, is markedly shorter than the half-life of T_3 (~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 TA_3 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 LT_3 substitution (10.1 ± 0.4 µg/day). A caveat in assessing circulating TA_3 concentrations is the interference of T_3 in the TA_3 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 T_3 levels exceed those of TA_3 by about 50-fold, this leads to considerable overestimation of endogenous TA_3 levels.

Together, TA_3 is a naturally occurring TH metabolite, present in humans at ~50-fold lower concentrations than T_3 and is rapidly cleared from the circulation despite its high affinity for plasma binding proteins.

Biosynthesis of TA_3

The first evidence for *in vivo* TA_3 formation was provided by studies in thyroidectomized rats demonstrating the presence of ^{131}I-TA_3 in kidney homogenates after injection of ^{131}I-T3 (Jouan *et al.* 1956). These findings were confirmed by incubation of rat kidney mitochondrial

Table 1 Kinetic properties of T_3 and TA_3 in humans and rats.

Species/ substrate	Serum level (pmol/L)	Peak levels (min)	$t_{1/2}$ (h)	MCR (L/day)	Major binding protein	PR (µg/day)	References
Human							
T_3	1736 ± 168	120–180	23	22.4–36.5	TBG	40.6 ± 2.1	Robbins & Rall (1955), Christensen (1960), Green & Ingbar (1961), Oppenheimer (1974), Burger & Vallotton (1975), Chopra (1976), Gavin et al. (1977, 1980), Nakamura et al. (1978), Burger et al. (1979), Pittman et al. (1980), Engler et al. (1984), Menegay et al. (1989), Lopresti & Dlott (1992)
TA_3	42–244	40	6.5 ± 0.5	222–298	TTR	5.2 ± 1.5	
Rat							
T_3	768	–	~2	4.2–7.3		2.3–2.5	Wilkinson *et al.* (1959), Gosling *et al.* (1976), Cavalieri *et al.* (1984), Nguyen *et al.* (1993), Liang *et al.* (1997)
TA_3	402	–	~1	3.5–9.4			

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; $t_{1/2}$, plasma half life time; TBG, thyroxine binding globulin, TTR, transthyretin.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

extracts (Albright *et al.* 1956), and rat kidney (Tomita *et al.* 1957) or brain (Tata *et al.* 1957) homogenates with ^{131}I-T_4 and ^{131}I-T_3. More recent studies confirmed the *in vivo* formation of TA3 upon T3 injection in rats (Medina-Gomez *et al.* 2008). *In vivo* formation of TA_3 and TA_4 was demonstrated in humans after administration of ^{125}I-LT_4 (Braverman *et al.* 1970), whereas others detected TA_3 after the administration of ^{125}I-TA_4 (Burger *et al.* 1979, Burger 1986) Based on these findings it was assumed that T_3 and/or TA_4 are intermediates in the conversion of T_4 to TA_3.

The mechanism by which iodothyronines are converted to iodothyroacetic acid metabolites has not been fully elucidated. A common hypothesis involves the decarboxylation and successive 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-T_2 to 3,5-diiodothyronamine (T_2AM) and T_4 to 3,3′,5,5′-tetraiodothyronamine (T_4AM) (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-T_1AM and T_0AM *in vivo* (Scanlan *et al.* 2004), other iodothyronamines have not been detected in human serum thus far.

The oxidative deamination of T_1AM and T_3AM 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 (Wood *et al.* 2009). It was suggested that at least one of these enzymes converts 3-T_1AM and T_3AM 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_1) and TA_3, respectively (Wood *et al.* 2009). Of interest, TA_3 modulates the activity of ALDH (McCarthy *et al.* 1968, Mårdh *et al.* 1987, Zhou & Weiner 1997). Conversion of T_4AM to TA_4 has not been demonstrated thus far. Although iodothyronamines are efficiently deiodinated, neither D1 nor D2 catalyzes the conversion of T_4AM to T_3AM (Piehl *et al.* 2008). This indicates that conversion of T_4AM to T_3AM is not an intermediate step in the conversion of T_4 to TA_3 (Fig. 1). Together, these studies support the hypothesis that at least some iodothyronines can be converted to their acetic acid metabolites via a thyronamine 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.

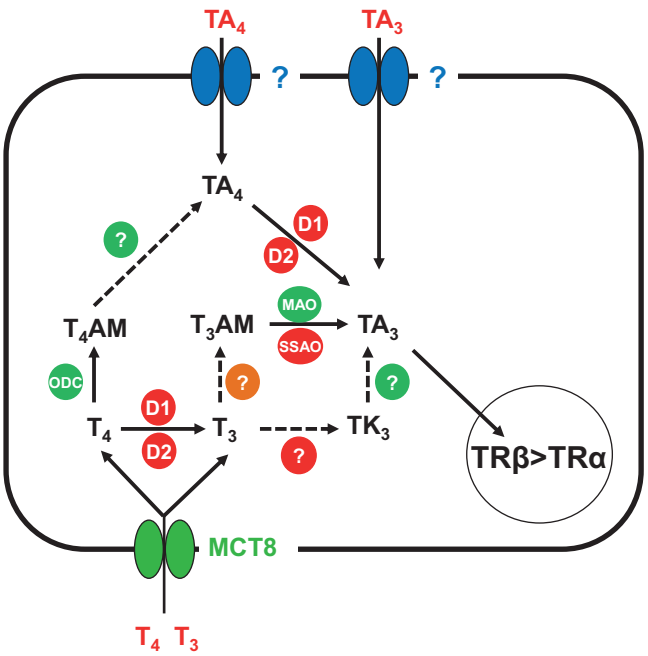

Figure 1
Schematic overview of cellular formation, metabolism and action of TA_3. Dashed lines represent processes for which the involved enzymes/transporters have not been identified but their existence may be assumed based on theoretical grounds or experimental data. D, deiodinase; MAO, monamine oxidase; SSAO, semicarbazide-sensitive amine oxidase; ODC, ornithine decarboxylase; TK_3, 3,3′,5-triiodothyropyruvic acid.

Metabolism of TA_3

TA_3 has been shown to be metabolized via similar pathways as T_3, i.e. stepwise deiodination, and conjugation with glucuronic acid and sulfate.

Deiodination

Early studies found that TA_3 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 TA_3 is efficiently deiodinated to 3,3′-diiodothyroacetic acid (3,3′-TA_2) by D1 and D3 (Rutgers *et al.* 1989*a*,

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Horn *et al.* 2013). TA_3 is even a better substrate for D1 than T_3, illustrated by a 16-fold higher Vmax/Km ratio (Rutgers *et al.* 1989*a*). Similar to T_3, TA_3 induced the expression and activity of D1 in rat liver and kidney (Medina-Gomez *et al.* 2008). Moreover, outer ring deiodination by Dio1 and Dio2 mediates the conversion of TA_4 to TA_3 (Burger *et al.* 1975, Köhrle *et al.* 1986, Horn *et al.* 2013).

In humans, up to 60% of the administrated ^{131}I-TA_3 dose appears in urine as inorganic ^{131}I within 24 h (Green & Ingbar 1961), suggesting that deiodination of (conjugated) TA_3 comprises an important metabolic pathway *in vivo*. In contrast, Flock and coworkers (Flock *et al.* 1962) found that only 20% of ^{131}I-TA_3 administered to dogs appeared as inorganic ^{131}I in urine within 24 h, while 3,3′-TA_2 sulfate was also detected in serum. A similar fraction of ^{131}I-TA_3 was excreted in urine as inorganic ^{131}I in rats (Wilkinson *et al.* 1959, Juge-Aubry *et al.* 1995).

Deiodination of TA_3 ultimately results in the formation of thyroacetic acid (TA_0), which is excreted in urine in humans (Chopra *et al.* 1988). Given that the estimated PRs of TA_4 and TA_3 together amount to ~10 µg/day (Pittman *et al.* 1980, Siegrist-Kaiser & Burger 1994), the urinary TA_0 levels (up to ~15 µg/L) cannot be derived from deiodination of endogenous TA_4 and TA_3 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-T_2, 3-T_1 and T_0 via thyronamine intermediates to their thyroacetic acid derivatives also contributes to urinary TA_0 excretion.

Conjugation

In addition to deiodination, conjugation of TA_3 to its glucuronide (TA_3G) and sulfate (TA_3S) constitutes an important part of TA_3 metabolism. Incubation of rat hepatocytes with ^{131}I-TA_3 results in almost complete metabolism of TA_3 within 3 h, mainly to TA_3G (50%), ^{131}I$^-$ (40%) and TA_3S (<10%) (Rutgers *et al.* 1989*b*). The formation of TA_3G and TA_3S increases to 60% and 16%, respectively, by blocking Dio1 with propylthiouracil (PTU), and TA_3G levels even further increase to 80% by simultaneous inhibition of sulfation, without affecting total TA_3 metabolism (Rutgers *et al.* 1989*b*).

Similar to sulfated iodothyronines, TA_3S is rapidly degraded through IRD (Rutgers *et al.* 1989*a*). The aryl sulfotransferase Sult1a1 (or phenol sulfotransferase 1 (PST1)) mediates the sulfation of TA_3 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 TA_3, whereas mainly labile ester glucuronides at the carboxyl group are formed in humans (Burger 1986, Moreno *et al.* 1994).

Although deiodination of TA_3S appears to be the principal metabolic route of TA_3 in humans, TA_3G is the major TA_3 metabolite excreted in bile (Roche *et al.* 1956, Green & Ingbar 1961). Up to 50% of ^{131}I-TA_3 administered to rats is excreted within 4 h as TA_3G in bile (Rutgers *et al.* 1989*b*), suggesting that glucuronidation is also the main route of TA_3 metabolism in rats. Interestingly, serum TA_3S and biliary TA_3G and TA_3S excretion are increased by blocking deiodination with PTU, without affecting the TA_3 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 TA_3G, accompanied by a compensatory increase of non-specified metabolites in urine (Flock *et al.* 1965). Moreover, newborn sheep reveal a rapid decrease of TA_3S 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 TA_3G formation and a concomitant increase in sulfate conjugates in plasma and urine, most predominantly 3′-TA_1S and 3,3′-TA_2S (Flock *et al.* 1962).

Together, these studies suggest that deiodination and conjugation are responsible for a stable TA_3 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 TA_3

As for TH, the cellular entry of TA_3 is supposed to be transporter-mediated. Studies using rat anterior pituitary cells and cardiomyocytes have shown a similar time course of ^{125}I-TA_3 and ^{125}I-T_3 uptake (Everts *et al.* 1994, Verhoeven *et al.* 2002). Based on free hormone levels, the transport rate of TA_3 even exceeds that of T_3 (Everts *et al.* 1994, Verhoeven *et al.* 2002). Moreover, TA_3 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

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

of TA_3, some of which may work in an ATP and sodium independent manner (Everts *et al.* 1994).

TA_3 transporters have not been identified yet. MCT8, MCT10 and Organic Anion Transporting Polypeptide (OATP)1C1 do not appear relevant for transport of TA_3 (Horn *et al.* 2013, Groeneweg *et al.* 2014, Kersseboom *et al.* 2014). Studies in rodents suggest that the TA_3 transporter(s) are widely expressed, given the increase in TA_3 levels in many tissues after injection of TA_3 (Medina-Gomez *et al.* 2008, Kersseboom *et al.* 2014). However, the transporter(s) involved remain to be identified.

Molecular basis of TA_3 action

TA_3 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 T_3 to TRα1 and a 3- to 6-fold higher affinity than T_3 to TRβ1 and TRβ2 (Schueler *et al.* 1990, Takeda *et al.* 1995, Messier & Langlois 2000, Martínez *et al.* 2009), which may indicate relative TRβ-selective binding and action of TA_3. This is supported by a 2- to 3-fold lower EC_{50} value for TRβ1 compared to TRα1 mediated transcriptional activation by TA_3 (Martínez *et al.* 2009). The preferential binding of TA_3 to TRβ is supported by X-ray crystallography (Martínez *et al.* 2009). Although TA_3 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, Martínez *et al.* 2009). Of clinical importance is the relatively high affinity of TA_3 for several TRβ mutants identified in patients with RTH-β which display reduced T_3 binding (Takeda *et al.* 1995, Messier *et al.* 2001).

Importantly, despite its higher affinity for TRβ than T_3, 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 T_3 and TA_3 in case of the direct repeat (DR4), the most prevalent TRE configuration in humans (Yen 2001), whereas TA_3 was 1.5- to 2-fold more potent than T_3 in case of palindrome and inverted palindrome TREs. In contrast, Martínez and coworkers (Martínez *et al.* 2009) found that TA_3 was also 6-fold more potent than T_3 in activating TRβ-mediated transcription in case of DR4.

Although not studied in detail, differences in the potency of TA_3 and T_3 to dissociate or recruit co-factors may exist. It was found that TA_3 has a lower efficacy than T_3 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 TA_3 have been scarcely studied (Lin *et al.* 1998, D'Arezzo *et al.* 2004). TA_3 was found to exert a stimulatory effect on the plasma membrane integrin αvβ3 receptor, although less potently compared to T_3 (D'Arezzo *et al.* 2004). Taken together, TA_3 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 TA_3 levels are governed by tissue-specific transporters, deiodinases and conjugating enzymes which also impact the tissue-specific biological actions of TA_3.

Regulation and role of TA_3

TA_3 is an important bioactive hormone in marine invertebrates. Interestingly, the TR of *Branchiostoma floridae* (amphioxus) is selectively activated by TA_3 and not by T_3 (Paris *et al.* 2008, Wang *et al.* 2009). Nevertheless, administration of T_3 to the developing amphioxus stimulates its metamorphosis (Paris *et al.* 2010), suggesting that T_3 is a precursor of the bioactive hormone TA_3. Indeed, TA_3 is present in amphioxus and its administration promotes metamorphosis to a similar extent as administration of T_3 (Paris *et al.* 2008, 2010). In addition, the non-selenodeiodinase bfDy from *B. floridae* specifically catalyzes the IRD of TA_4 and TA_3 but not of T_4 and T_3 (Klootwijk *et al.* 2011). Also in other species, TR activation by TA_3 may differ from the human situation (Oka *et al.* 2013).

Although TA_3 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 TA_4 and TA_3 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 T_3 states', favor the formation of rT_3 and other TH metabolites such as

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

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 leptin 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 6 h after TA_3 administration, beginning at a dose as low as 10 µg/kg (Table 2). From these and other studies it was estimated that 62 µg (100 nmol)/kg/day TA3 has an equal TSH-suppressive effect as 16 µg (20 nmol)/kg/day LT_4. Interestingly, Mirell and coworkers (Mirell *et al.* 1989) found that TSH mRNA expression levels are unchanged 6 h 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_4, whereas no effects were observed on hypothalamic TRH mRNA expression (Horn *et al.* 2013).

A dose-dependent reduction of TSH levels was observed within 6–9 h after oral administration of TA_3 to euthyroid human subjects, with a lowest dose of 350 µg (~5 µg/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_4, rT_3 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.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Table 2 Tissue effects of TA_3 determined in animal studies.

Parameter	Effect/outcome	Species, thyroid state	Dose; duration; mode of administration	References
HPT-axis*				
TSH (serum) basal or stim.	↓	Rat, eu/hypo	10 µg/kg/day; 12 day; i.v.	Mirell *et al.* (1989), Juge-Aubry *et al.* (1995), Liang *et al.* (1997), Alvarez *et al.* (2004), Medina-Gomez *et al.* (2008)
T_4 (serum)	↓	Rat, eu	8 µg/kg/day; 12 day; i.v.	Medina-Gomez *et al.* (2008)
T_3 (serum)	↓	Rat, eu	40 µg/kg/day; 12 day; i.v.	Medina-Gomez *et al.* (2008)
Thyroid weight	↓	Rats, hypo	~5 µg/kg/day; 9 day; s.c.	Pitt-Rivers (1953)
Heart				
Heart weight/body weight	↑	Rat (adult), hypo	300 µg/kg/day; 15 day	Olsen *et al.* (1977), Liang *et al.* (1997)
	↑	Rat (newborn)	300 µg/kg/day; 1 year	Symons *et al.* (1975)
	↑	Rat (in utero)	300 µg/kg/day; 15 day to pregnant dams	Olsen *et al.* (1977), Hawkey *et al.* (1981)
Cardiomyopathy	+	Rat (in utero)	>300 µg/kg/day; 15 day to pregnant dams	Olsen *et al.* (1977), Hawkey *et al.* (1981)
		Rat (newborn)	300 µg/kg/day; 1 year	Symons *et al.* (1975)
Cardiac size	↑	Rat (adults)	180 µg/kg/day; 1 year	Symons *et al.* (1975), Olsen *et al.* (1977)
Bone				
Bone formation markers (serum)	=	Rat, eu/hypo	250 µg/kg/day; 40 day; i.p.	Alvarez *et al.* (2004)
Bone resorption markers (serum)	=	Rat, eu	250 µg/kg/day; 40 day; i.p.	Alvarez *et al.* (2004)
	↑	Rat, hypo	250 µg/kg/day; 40 day; i.p.	Alvarez *et al.* (2004)
BMD	=	Rat, eu/hypo	250 µg/kg/day; 40 day; i.p.	Alvarez *et al.* (2004)
Brain				
Myelination	↑	Mice, hypo	200 µg/kg/day; 12 day; oral	Kersseboom *et al.* (2014), Zada *et al.* (2016)
		Zebrafish, hypo		
Purkinje cell development	↑	Mice, hypo	200 µg/kg/day; 12 day; oral	Kersseboom *et al.* (2014), Delbaere *et al.* (2017)
		Chicken, hypo		
Liver				
Cholesterol	=	Rats, eu	200 µg/kg/day; 4 week; oral	Autissier *et al.* (1980)
Biliary cholesterol	=	Rat, eu	1000 µg/kg/day; 9 day; i.v.	Van Zyl (1957)
Biliary cholic acid	↓	Rat, eu	1000 µg/kg/day; 9 day; i.v.	Van Zyl (1957)
Metabolism				
Oxygen consumption	Acute ↑	Rats, hypo	1000 µg/kg; single; s.c.	Pitt-Rivers (1953), Wilkinson (1959)
	Gradual ↑		600 µg/kg; 4 day; s.c.	Hill *et al.* (1960)
Body weight	↓	Rats, hypo	60 µg/kg/day; 9 day; s.c.	Pitt-Rivers (1953)

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 TA_3 in the T_3 assay are listed.
i.p., intraperitoneal; i.v., intravenous; s.c., subcutaneous; stim., TRH-stimulated.

Basal metabolic rate

Pioneering studies demonstrated that TA_3 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 tumor cell cultures more potently than T_3, T_4 or TA_4 (Heimberg *et al.* 1955).

At high doses of 1000–5000 µg/kg/day, TA_3 rapidly raised the oxygen consumption in hypothyroid rats (Pitt-Rivers 1953, Wilkinson 1959), whereas a lower TA_3 dose of 600 µg/kg/day resulted in a more gradual stimulation (Hill *et al.* 1960) (Table 2). In hypothyroid patients, TA_3 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 TA_3/day (50–65 µg/kg/day) on BMR persisted beyond 5 days after treatment cessation. In contrast, administration of 45 µg TA_3/kg/day for up to 3 weeks to euthyroid subjects significantly reduced BMR

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Table 3 Tissue effects of TA_3 determined in humans.

Parameter	Effect/ outcome	Thyroid state	Dose, duration	References
HPT axis				
TSH (serum), basal or stim.	↓	Eu/hypo/ hyper	~5 µg/kg/day; 1 day	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)
T4 (serum)	↓	Eu/hypo/ hyper	~20 µg/kg/day; 6 week	Medeiros-Neto *et al*. (1980), Beck-Peccoz *et al*. (1988), Lind *et al*. (1989), Bracco *et al*. (1993), Brenta *et al*. (2003)
rT3 (serum)	↓	Eu/hypo	22 µg/kg/day; 3 week	Bracco *et al*. (1993)
T3 (serum)	↓	Eu/hyper	35–40 µg/kg/day; 1 day	Burger *et al*. (1979), Beck-Peccoz *et al*. (1988)
Goiter volume	↓	Eu	20 µg/kg/day; 11 months	Pujol *et al*. (1998), Brenta *et al*. (2003)
Heart				
(Basal or sleeping) heart rate	=	Eu/hypo	50–75 µg/kg/day; 6–28 week	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*. (2000), Brenta *et al*. (2003)
Blood pressure	=	Eu/hypo	50–75 µg/kg/day; 6–28 week	Rall *et al*. (1956), Trotter (1956), Sherman *et al*. (1997), Brenta *et al*. (2003)
Episodes of angina	↑	Eu (with CHD)	7.5–75 µg/kg/day; 3–10 month	Oliver & Boyd (1957), Ibbertson *et al*. (1959), Boyd & Oliver (1960)
Cardiac function	=	Eu/hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997), Pujol *et al*. (2000)
Bone				
Bone formation markers (serum)	=	Eu	45 µg/kg/day; 3 week	Bracco *et al*. (1993), Brenta *et al*. (2003)
	↑	Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
Bone resorption markers (serum)	↑	Eu	20 µg/kg/day; 11 month	Brenta *et al*. (2003)
		Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
BMD *lumbar*	=	Eu	~50 µg/kg/day; 85–100 day	Brenta *et al*. (2003)
BMD *Femoral*	↓			
Liver				
SHBG	↑	Eu	20 µg/kg/day; 11 month	Beck-Peccoz *et al*. (1988), Lind *et al*. (1989), Bracco *et al*. (1993), Brenta *et al*. (2003)
	↑	Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
Ferritine	↑	Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
Cholesterol (total, LDL)	↓	Eu	20 µg/kg/day; 11 month	Trotter (1956), Oliver & Boyd (1957), Boyd & Oliver (1960), Medeiros-Neto *et al*. (1980), Beck-Peccoz *et al*. (1988), Lind *et al*. (1989), Bracco *et al*. (1993), Brenta *et al*. (2003)
	↓	Hypo	~10 µg/kg/day; 2–3 month	Lerman & Pitt-Rivers (1955, 1956), Trotter (1955, 1956), Rall *et al*. (1956), Zondek *et al*. (1956), De Graeff *et al*. (1957), Ibbertson *et al*. (1959), Boyd & Oliver (1960), Hill *et al*. (1960), Lerman (1961), Medeiros-Neto *et al*. (1980), Sherman *et al*. (1997)
Triglycerides	=	Eu	45 µg/kg/day; 3 week	Medeiros-Neto *et al*. (1980), Beck-Peccoz *et al*. (1988), Bracco *et al*. (1993)
	↓	Hypo	~20 µg/kg/day; 6 week	Medeiros-Neto *et al*. (1980), Sherman *et al*. (1997)
Apoprotein A1	=	Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
	=	Eu	45 µg/kg/day; 3 week	Bracco *et al*. (1993), Brenta *et al*. (2003)
Apoprotein B	↓	Hypo	~50 µg/kg/day; 85–100 day	Sherman *et al*. (1997)
	↓	Eu	20 µg/kg/day; 11 m	Bracco *et al*. (1993), Brenta *et al*. (2003)
Metabolism				
BMR, RMR, SEE	= (↓)	Eu	75 µg/kg/day; 12–14 week	Trotter (1956), Oliver & Boyd (1957), Bracco *et al*. (1993)
	↑	Hypo	~50–75 µg/kg/day; 6–28 week	Trotter (1955, 1956), Lerman & Pitt-Rivers (1956), Rall *et al*. (1956), Zondek *et al*. (1956), De Graeff *et al*. (1957), Ibbertson *et al*. (1959), Hill *et al*. (1960), Boyd & Oliver (1960), Lerman (1961), Sherman *et al*. (1997)
Protein oxidation	=	Eu	45 µg/kg/day; 3 week	Bracco *et al*. (1993)

(Continued)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Table 3 Continued.

Parameter	Effect/ outcome	Thyroid state	Dose, duration	References
Body weight	=	Eu	75 µg/kg/day; 12–14 week	Oliver & Boyd (1957), Medeiros-Neto *et al.* (1980), Beck-Peccoz *et al.* (1988)[§], Lind *et al.* (1989), Bracco *et al.* (1993), Brenta *et al.* (2003)
	↓	Hypo	7 µg/kg/day; >12 week	Trotter (1955, 1956), Ibbertson *et al.* (1959), Boyd & Oliver (1960), Sherman *et al.* (1997)
			~20 µg/kg/day; 15 day (i.v.)	Lerman & Pitt-Rivers (1955, 1956), De Graeff *et al.* (1957)
Kidney				
Urinary creatinine excretion	↑	Hypo	140–260 µg/kg/day; 1 day	Rall *et al.* (1956), Ibbertson *et al.* (1959)
			~6.5 µg/kg/day; 15 day (i.v.)	Lerman & Pitt-Rivers (1956), De Graeff *et al.* (1957)

Overview of the effects of TA_3 in humans. Details on the dosing, follow-up time and group size of these individual studies can be found in Table 4.
Explanation of symbols: =, no effect; ↑, stimulatory effect of TA_3; ↓, inhibitory effect of TA_3. 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 TA_3 in the T_3 assay are listed.
BMR, basal metabolic rate; CHD, coronary heart disease; i.v., intravenous; RMR, resting metabolic rate; SEE, sleeping energy expenditure.

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 2.4–4.8 µg LT_4/kg/day (Bracco *et al.* 1993). In general, TA_3 exerts similar effects on BMR at 4- to 30-fold lower doses of LT_4 and 15- to 100-fold lower doses of LT_3 (Table 5). Importantly, the TA_3 dose required to increase BMR greatly exceeds that required for adequate TSH suppression.

Liver

Intrahepatic TA_3 levels increase upon TA_3 infusion in rats, which is in line with the important role of the liver in TA_3 clearance (Medina-Gomez *et al.* 2008). TA_3 also effectively induces the expression of T_3-responsive genes in the liver, including Dio1, to a similar extent as T_3 (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 200 µg TA_3/kg/day (Van Zyl 1957, Autissier *et al.* 1980).

When given at equivalent TSH-suppressive doses to euthyroid or hypothyroid patients, TA_3 induced similar increases in serum sex hormone binding globulin (SHBG) and ferritin levels as LT_4 (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 TA_3 administration in a similar dose to mildly obese euthyroid subjects on caloric restriction. In hypothyroid subjects, TA_3 also reduced serum total and LDL cholesterol as well as apoprotein B levels, generally within 2 weeks (Table 3). The effect of TA_3 on HDL levels was usually less pronounced. These effects of TA_3 were generally less pronounced in euthyroid subjects as the effects of TA_3 in peripheral tissues were counter-balanced by the reduction in serum T_3 induced by TA_3, although findings vary depending on the precise TA_3 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 TA_3 (Burger *et al.* 1979). Taken together, TA_3 has potent thyromimetic effects in the liver.

Heart

TA_3 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 T_3 (Liang *et al.* 1997). Nevertheless, high doses of TA_4 induce cardiac hypertrophy in rats, although less potently than T_4 (Lameloise *et al.* 2001). At least part of these effects is likely mediated through TA_3. Several rat studies have shown that high doses of TA_3 (300 µg/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 TA_3 dose (Olsen *et al.* 1977), or when TA_3 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 TA_3 (15–50 µg/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).

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Table 4 Overview of clinical studies in humans.

Reference	Thyroid state	Daily dose of TA_3 (µg/day)	Duration	Effects of TA3								Conclusion(s)
				TSH	Chol	Bone TO	BW	BMR	HR	Myx	Side effects	
Myxedema or hypothyroidism												
Lerman & Pitt-Rivers (1955)	Hypo	1000–4000, i.v.	16–17 day		↓		↓	=		↓		Normalization of myxedematous features
Lerman & Pitt-Rivers (1956)	Hypo	100–4000, i.v.	12–16 day		↓		↓	↑		↓		Normalization of myxedematous features; higher doses were required to restore BMR
Trotter (1955)	Hypo	2000–6000, oral	10 day		↓		↓	↓		↓		Normalization of myxedematous features
Trotter (1956)	Hypo, eu	1000–6000, oral	2–28 week		↓			↓				Normalization of myxedematous features
Rall (1956)	Hypo	5000–15,000, single dose i.v.	36 day follow-up		↓			↑				Normalization of myxedematous features
De Graeff *et al.* (1957)	Hypo	1000, i.v.	12 day		↓		↓	=		↓		Normalization of myxedematous features
Ibbertson *et al.* (1959)	Hypo	10,000–18,000, single dose oral 500–6000, oral	3–10 months		↓		↓	↑		↓	[a]	Normalization of myxedematous features; higher doses were required to restore BMR
Lerman (1961)	Hypo	500–4000, i.v.	2–3 months		↓			=				Normalization of myxedematous features; higher doses were required to restore BMR
Hill *et al.* (1960)	Hypo	1000–6000, oral	14–52 day		↓			↑				Normalization of myxedematous features at >4000µg/day
Zondek *et al.* (1956)	Hypo	8000–10,000, 2 day oral	15 day follow-up		(↓)			↑		↓		Temporary normalization of myxedematous features
Lipid-reduction in coronary heart disease												
Oliver & Boyd (1957)	Eu	500–5000, oral	12–14 week		(↓)		=	=			[b]	Not useful for lipid lowering in patients with pre-existent heart disease
Boyd & Oliver (1960)	Hypo, eu	500–5000, oral	>12 week		(↓)						[c]	Not useful for lipid lowering in patients with pre-existent heart disease
Treatment of euthyroid goiter												
Brenta *et al.* (2003)	Eu	1400, oral	11 months	↓	↓	↑			=			Effective reduction of goiter size, with fewer side-effects (e.g. palpitations)
Pujol *et al.* (2000)	Eu	1400, oral	12–21 month						=		[d]	No thyromimetic (side) effects on the heart in long-term treated patients
Thyroid carcinoma (substitution after thyroid ablation)												
Mueller-Gaertner & Schneider (1988)	Hypo	500 (+LT_4), oral	3 week	↓							[e]	Addition of a low dose TA_3 to LT_4 mono-therapy further reduced basal and stimulated TSH levels
Sherman & Ladenson (1992)	Hypo	1400 (+LT_4), oral	6–8 week	↓	↓	↑	=	=	=			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
Sherman *et al.* (1997)	Hypo	3500, oral	3 months	↓	↓	↑						At a dose required for equivalent TSH suppression, TA_3 has a stronger thyromimetic effect on liver and bones than LT_4

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Mechelany *et al.* (1991)	Hypo	8–17 µg/kg/day TA_3 (=500–1000 µg/day) + 1.8 µg/kg/day LT_4 (oral)	6 months	↓	↓	↑	=	↑		Compared to LT_4 mono-therapy, a 40–50% lower LT_4 dose was required once combined with TA_3 to obtain equivalent or even better TSH suppression, without affecting TH action in peripheral tissues
Reduction of lipid levels and body weight in mild obesity										
Beck-Peccoz *et al.* (1988)	Eu	2800, oral	>2 months	↓						No additional effect on body weight and serum cholesterol levels over dietary restrictions alone
Lind *et al.* (1989)*	Eu	3000, oral	8 day	↓	=		=		=	No additional effect on body weight and serum cholesterol levels over dietary restrictions alone
TSH suppressive therapy in addition to anti-thyroid drugs in Graves' disease										
Pujol *et al.* (1998)	Eu	~1350, oral	~18 months							Effective reduction of goiter size
TA_3 kinetics and general effects										
Bracco *et al.* (1993)	Eu	1700–3400, oral	6 week	↓	↓	↑		=	=	Reduction of serum TSH levels with dose-dependent effects on liver and bone, but not BMR
	Eu	4 dd 350, oral	3 week	↓						More sustained TSH suppression by dividing daily dose
Burger *et al.* (1979)	Eu	150–2400, oral	1 day	↓						Reduction of serum (TRH stimulated) TSH and T_3, but not T_4 levels, persisting until 5 days after administration
	Hyper	600, oral	1 day	↓/=						Reduction of serum T_3 levels in 2/7 subjects
Menegay *et al.* (1989)	Eu	350–2800, oral, 1 dose	1 day	↓						Reduction of serum TSH levels after a single dose ≥350 µg
Medeiros-Neto *et al.* (1980)	Eu, hypo	1400, oral	6 week	↓	↓		=	=	=	Reduction of serum TSH levels, without affecting markers of tissue TH status except cholesterol
Pregnancy										
Cortelazzi *et al.* (1999)	Eu on PTU	2100–2800, oral	13 week							Effective reduction of fetal goiter size, normal neurodevelopment of neonate at 20 months
Nicolini *et al.* (1996)	Eu on PTU	2100–2800, oral	10 week							Effective reduction of fetal goiter size, normal neurodevelopment the neonate at 20 months
Asteria *et al.* (1999)	RTHβ	2100–3500, oral	13 week						[f]	Effective reduction of fetal goiter size. Normal neurodevelopment of neonate (with RTHβ) at 24 months

An overview of all studies, of which at least the abstract was available to the authors, in which TA_3 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.

Table 5 An overview of the thyromimetic potency of TA_3 in different tissues relative to LT_4.

		Dose regime			HPT
Reference	**Thyroid state**	TA_3 dose	A. LT_4 Dose B. Δdose LT_4	A. Ratio TA_3/LT_4 dose or B. $TA_3/\Delta LT_4$ ratio	TSH ↓
A. Comparison to LT_4					
Sherman *et al.* (1997)	hypo	48 µg/kg/day	2.2 µg/kg/day	17	17
Bracco *et al.* (1993)	eu	23–46 µg/kg/day	2.4–4.8 µg/kg/day	9–19	9
Brenta *et al.* (2003)	eu	19.6 µg/kg/day	1.7 µg/kg/day	12	12
Ibbertson *et al.* (1959)	hypo	5–60 µg/kg/day	1–3 µg/kg/d	1.5–20	
B. LT_4+TA_3 vs LT_4 mono-therapy					
Mechelany *et al.* (1991)	hypo	8.5–17 µg/kg/day	0.7 µg/kg/day	13–25	13–25
Sherman & Ladenson (1992)	hypo	1500 µg	87 µg	17	17

In adult human subjects, no detrimental effects of TA_3 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 T_3 (Koury *et al.* 2009) or its lack of non-genomic effects on Na^+ flux and Ca^{2+}-ATPase activity in cardiomyocytes as observed with T_3 (Rudinger *et al.* 1984, Huang *et al.* 1999). The effects of TA_3 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, TA_3 appeared more potent in upregulating *Ucp1* and *Dio2* expression than T_3 (Medina-Gomez *et al.* 2003). Also *in vivo*, low doses of TA_3 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, TA_3 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 TA_3 on bone resorption exceed those on bone formation in fetal rat long bones, whereas the overall effects of TA_3 on fetal mouse calvarial bones were less pronounced (Kawaguchi *et al.* 1994*a*,*b*).

However, daily injection of 250 µg/kg TA_3 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 TA_3-treated and control animals (Alvarez *et al.* 2004). In hypothyroid animals on the same TA_3 dose, an increase in β-CTX serum levels was observed without concomitant increase in serum bALP. However, BMD did not differ significantly between TA_3-treated and control animals (Alvarez *et al.* 2004).

In athyroid human subjects, Sherman and coworkers (Sherman *et al.* 1997) showed that TA_3 stimulated bone turnover more potently than LT_4, 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 TA_3 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, TA_3 stimulates bone resorption and bone formation, although the currently available data are inconclusive regarding the balance between both processes.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Liver						Heart	Muscle	Bone			General	
TC ↓	LDL ↓	HDL ↓	TG ↓	SHBG ↑	Ferritin ↓	HR ↑	CK ↓	Formation ↑	Resorption ↑	BMD ↓	BW ↓	BMR ↑
<17	<17	17	17	<17	<17	17		<17			<17	
9	9	9	>19	10		19		9				>19
12	12	–	12	–		–		–	<12	12		
6–10						20					15	>15
				13–25		13–25	13–25	<13			>25	
<17	17	17	<17	<17	<17	(+)		<17	17		17	17

–, 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.

Brain and neurogenesis

TA_3 regulates the expression of well-known TH target genes, including *Dio2* and *Dio3*, in SH-SY5Y 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).

TA_3 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 µg TA_3/kg/day from postnatal day 1 (Kersseboom *et al.* 2014). The stimulatory effects on myelination are in line with previous studies (Van Wynsberghe *et al.* 1978). Similar effects have been found with TA_4 (Horn *et al.* 2013). In addition, the administration of low TA_3 doses (30 µg TA_3/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 TA_3 may have an antidepressive effect mediated through its β-adrenergic stimulatory effects (Massol *et al.* 1987, 1988*a*,*b*).

Effects of TA_3 and TA_4 on the developing human brain are largely unknown. However, several cases have been reported where TA_3 has been administered to a pregnant woman for the treatment of fetal hypothyroidism. Cortelazzi and coworkers (Cortelazzi *et al.* 1999) showed that TA_3 administration (2100–2800 µg/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 TA_3 in the treatment of a pregnant woman with RTHβ because of suspected hypothyroidism in the fetus carrying the same heterozygous mutation in TRβ. 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 TA_3 administration during pregnancy should be carefully weighted. Nevertheless, these studies suggest that TA_3 has T_3-like effects on the developing human brain.

Skin

Topical application of TA_3 increases dermal thickness and prevents glucocorticoid-induced skin atrophy in mice and humans (Faergemann *et al.* 2002, Yazdanparast *et al.* 2006*a*,*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 TA_3 in muscle and kidney. In hypothyroid rats, TA_3 is efficiently taken up in striatal muscle and kidney, where the latter is also an important site for TA_3 metabolism (Medina-Gomez *et al.* 2008). Mechelany and coworkers (Mechelany *et al.* 1991) have shown that TA_3 reduced serum creatine kinase levels. TA_3 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).

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Therapeutic applications of TA_3 in humans

Because of its thyromimetic properties, the use of TA_3 in the treatment of different thyroid diseases has been explored, which is summarized in Table 4.

Myxedema

The therapeutic application of TA_3 was first studied in cases of severe hypothyroidism (myxedema). In general, TA_3 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 1955, 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 TA_3 occur more rapidly compared to T_3 (Zondek *et al.* 1956, Ibbertson *et al.* 1959).

Thus, TA_3 effectively restores euthyroidism in hypothyroid patients, but is less potent than LT_4 and LT_3. Taken together, an obvious benefit for the use of TA_3 over LT_4 in the treatment of myxedematous patients is lacking.

Lipid reduction in coronary heart disease and obesity

The observed dissociated effect of low doses TA_3 on serum cholesterol levels and BMR prompted several small studies to the lipid lowering effect of TA_3 in euthyroid subjects with coronary heart disease. However, relatively high TA_3 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 TA_3 dose, which subsided after TA_3 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 TA_3/kg/day in healthy subjects.

TA_3 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, T_4 and T_3 levels, no significant changes were found in serum cholesterol and triglyceride levels in the TA_3 treated group compared with females on caloric restriction alone.

There is no evidence that TA_3 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 TA_3 on the HPT axis, several studies evaluated TA_3 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 LT_4 monotherapy (2.6 ± 0.7 µg/kg/day) upon addition of 500 µg TA_3 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 LT_4 monotherapy alone or in combination with TA_3. The TA_3 dose was adjusted to achieve TSH levels <0.1 U/L, as during LT_4 monotherapy. Sherman and Ladenson (1992) performed similar studies, but adjusted the LT_4 dose in order to achieve a similar degree of TSH suppression. In both studies, patients required 40–50% less LT_4 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 TA_3 vs LT_4 monotherapy. Following a baseline period (phase I) on a TSH-suppressive dose LT_4 (2.7 µg/kg/day), patients received starting doses of 24 µg TA_3/kg twice daily or 1.9 µg LT_4/kg/day, which were then titrated until TSH levels were below 0.1 U/L (phase II). Subjects receiving TA_3 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

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

to the LT_4 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 LT_4 treated group received a 10–20% lower final LT_4 dose in phase II than during phase I of the study. Moreover, it appears that it was not required to further escalate the TA_3 starting dose of 24 µg TA_3/kg twice daily in order to obtain TSH suppression <0.1 U/L.

In conclusion, TA_3 monotherapy is an adequate TSH-suppressive therapy, while at the same time providing sufficient thyromimetic effects in the peripheral tissues. TA_3 may especially have augmented thyromimetic effects on the pituitary, liver and bone. Based on the available studies, there is no obvious benefit of using TA_3, alone or in combination with LT_4, as TSH-suppression therapy, unless LT_4 is not tolerated.

Goiter

Brenta and coworkers (Brenta *et al.* 2003) showed that TA_3 (19.6 µg/kg/day) and LT_4 (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 TA_3 (42%) vs LT_4 (17%) treated group (although not statistically significant), while less side effects were reported. TSH levels were adequately reduced in both groups and FT_4 levels decreased in the TA_3 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 TA_3 treated patients, which suggest an increase in bone resorption.

Pujol and coworkers (Pujol *et al.* 1998) studied the effect of TA_3 and T_3 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, TA_3 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 LT_4 nor TA_3 is advised for goiter reduction.

TA_3 abuse in dietary supplements

Multiple cases have been reported over the last decades on the abuse of dietary supplements, metabolic enhancers and mesotherapies containing TA_3. 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 TA_3.

Application of TA_3 in RTH syndromes

RTH syndromes results from alteration of local TH signaling due to defective cellular entry, intracellular metabolism or receptor function. The finding that TA_3 clearly exerts thyromimetic effects but differs from T_3 in its cellular transport mechanism and affinity for mutant TRβ variants, prompted studies to explore the application of TA_3 (and TA_4) 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 TA_3 is able to bind and activate a subset of these mutant receptors (Takeda *et al.* 1995). The effects of TA_3 treatment in RTHβ patients have been described on a case-by-case basis and are currently the most wide-spread off-label application of TA_3. In a subgroup of RTHβ patients, TA_3 is able to decrease TSH and consequently the high serum T_4 and T_3 levels. Since the thyromimetic effects of TA_3 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,

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Crino *et al.* 1992, Dulgeroff *et al.* 1992, Ueda *et al.* 1996, Darendeliler & Basx 1997, Radetti *et al.* 1997, Clifton-Bligh *et al.* 1998, Persani *et al.* 1998, Asteria *et al.* 1999, Kong *et al.* 2005, Torre *et al.* 2005, Wu *et al.* 2006, Gurgel *et al.* 2008, Santos *et al.* 2008, Guran *et al.* 2009, Anzai *et al.* 2012, Ferrara *et al.* 2012, Ramos-Prol *et al.* 2013, Stagi *et al.* 2014, Chatzitomaris *et al.* 2015, Xue *et al.* 2015). However, some patients do not respond to TA_3 treatment, which is assumed to depend on the type or location of the mutation (Hamon *et al.* 1988, Persani *et al.* 1998). These reports have been reviewed in more detail in Groeneweg and coworkers (Groeneweg *et al.* 2017). In order to prevent overtreatment, pre-clinical analysis of the impact of mutations on T_3 and TA_3 binding and transactivation potency may predict which patients benefit from TA_3 treatment.

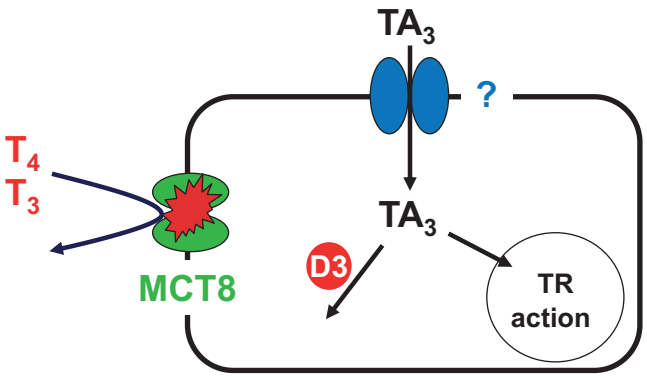

Figure 2
Schematic representation of a T_3 target cell that relies on MCT8 for its TH uptake. The proposed working mechanism of TA_3 (and other TH analogues) in case of defective MCT8 entails cellular uptake in an MCT8-independent way, binding to the TRs and preferably degradation through similar pathways as TH, which are all fulfilled by TA_3 as outlined in this review.

MCT8 deficiency

Mutations in MCT8 result in the AHDS, which is characterized by severe intellectual and motor disability and increased serum T_3 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 T_3 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 LT_4 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, TA_3 fulfills these criteria (illustrated in Fig. 2). Indeed, several pre-clinical studies have supported the therapeutic potency of TA_3 and its less rapidly metabolized precursor TA_4 in AHDS.

Mct8 KO mice show the characteristic serum TFT pattern of AHDS (Trajkovic *et al.* 2007, Trajkovic-Arsic *et al.* 2010), which is effectively normalized by TA_4 treatment (Horn *et al.* 2013). However, *Mct8* KO mice lack a neurological phenotype, since *Oatp1c1* is likely to function as an alternative TH transporter at the BBB in mice. Indeed, in *Mct8/Oatp1c1* 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 T_3, TA_3 (200–400 µg/kg/day) or TA_4 (400 µg/kg/day) from postnatal day 1 (Horn *et al.* 2013, Kersseboom *et al.* 2014), suggesting that TA_3 and TA_4 can replace T_3 and T_4 during brain development in mice. Such effects of TA_4 were also observed in *Pax-8/Mct8* DKO mice, confirming that its transport across the BBB is MCT8-independent. Most importantly, TA_3 administration (400 µg/kg/day) from postnatal day 1–12 rescued several markers of disrupted brain development in *Mct8/Oatp1c1* DKO mice, including the abnormal cerebellar Purkinje cell development and myelination (Kersseboom *et al.* 2014). In addition, TA_3 and TA_4 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 TA_3 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 TA_3 as a therapy for human AHDS patients is currently under investigation in a prospective interventional cohort study, the Triac Trial (NTC02060474), primarily assessing its potency to restore the peripheral thyrotoxicosis. If TA_3 would be an effective therapy, it can be anticipated that early intervention may have effects on the neurocognitive phenotype. Although TA_3 readily crosses the placenta (Asteria *et al.* 1999, Cortelazzi *et al.* 1999), there are many medical

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

and ethical considerations before justifying prenatal administration of TA_3 to mothers who are pregnant of an AHDS child.

Concluding remarks

TA_3 is a bioactive TH metabolite that has tissue-specific thyromimetic activities (Table 5). Although TA_3 clearly has a potent TSH-suppressive effect, its metabolic effects on liver and bone are at least as potent. In general, higher doses of TA_3 are required to achieve equal thyromimetic effects as LT_4 (and LT_3), mainly due to its rapid clearance. Based on the available studies, the therapeutic benefits of TA_3 over LT_4 treatment is generally limited to primary thyroid diseases. However, TA_3 holds potential in the treatment of subsets of RTHβ 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).

References

Aguilar Diosdado M, Escobar-Jimenez L, Fernandez Soto ML, Garcia Curiel A & Escobar-Jimenez F 1991 Hyperthyroidism due to familial pituitary resistance to thyroid hormone: successful control with 3,5,3′ triiodothyroacetic associated to propranolol. *Journal of Endocrinological Investigation* **14** 663–668. (doi:10.1007/BF03347890)

Albright EC, Larson FC, Tomita K & Lardy HA 1956 Enzymatic conversion of thyroxine and triiodothyronine to the corresponding acetic acid analogues. *Endocrinology* **59** 252. (doi:10.1210/endo-59-2-252)

Alexander WD & Bisset SK 1958 Immediate effect of triiodothyroacetic acid on oxygen consumption of myeloid leukæmic leucocytes in vitro. *Lancet* **7059** 1265. (doi:10.1016/S0140-6736(58)91393-X)

Alvarez L, Burgueño A, Zeni S, Randi AS, Hernández S, Hockl P, Pisarev MA & Kleiman de Pisarev DL 2004 Comparison of the effects of 3,5,3′-triiodothyroacetic acid and triiodothyronine on goiter prevention and involution and on hepatic and skeletal parameters in rats. *Hormone and Metabolic Research* **36** 291–297. (doi:10.1055/s-2004-814485)

Anzai R, Adachi M, Sho N, Muroya K, Asakura Y & Onigata K 2012 Long-term 3,5,3′-triiodothyroacetic acid therapy in a child with hyperthyroidism caused by thyroid hormone resistance: pharmacological study and therapeutic recommendations. *Thyroid* **22** 1069–1075. (doi:10.1089/thy.2011.0450)

Asteria C, Rajanayagam O, Collingwood TN, Persani L, Romoli R, Mannavola D, Zamperini P, Buzi F, Ciralli F, Chatterjee VK, et al. 1999 Prenatal diagnosis of thyroid hormone resistance. *Journal of Clinical Endocrinology and Metabolism* **84** 405–410. (doi:10.1210/jcem.84.2.5479)

Autissier N, Dumas P, Loireau A & Michel R 1980 Thyroid status and effects of 3,5,3′ triiodothyroacetic acid and fenproporex in genetically lean and obese female rats. *Biochemical Pharmacology* **29** 1612–1615. (doi:10.1016/0006-2952(80)90621-8)

Bárez-López S, Obregon MJ, Martínez-de-Mena R, Bernal J, Guadaño-Ferraz A & Morte B 2016 Effect of triiodothyroacetic acid treatment in Mct8 deficiency: a word of caution. *Thyroid* **26** 618–626. (doi:10.1089/thy.2015.0388)

Bauer BA, Elkin PL, Erickson D, Klee GG & Brennan MD 2002 Symptomatic hyperthyroidism in a patient taking the dietary supplement tiratricol. *Mayo Clinic Proceedings* **77** 587–590. (doi:10.4065/77.6.587)

Beck-Peccoz P, Piscitelli G, Cattaneo MG & Faglia G 1983 Successful treatment of hyperthyroidism due to nonneoplastic pituitary TSH hypersecretion with 3,5,3′-triiodothyroacetic acid (TRIAC). *Journal of Endocrinological Investigation* **6** 217–223. (doi:10.1007/BF03350611)

Beck-Peccoz P, Sartorio A, De Medici C, Grugni G, Morabito F & Faglia G 1988 Dissociated thyromimetic effects of 3,5,3′-triiodothyroacetic acid (TRIAC) at the pituitary and peripheral tissue levels. *Journal of Endocrinological Investigation* **11** 113–118. (doi:10.1007/BF03350116)

Beck-Peccoz P, Roncoroni R, Mariotti S, Medri G, Marcocci C, Brabant G, Forloni F, Pinchera A & Faglia G 1990 Sex hormone-binding globulin measurement in patients with inappropriate secretion of thyrotropin (IST): evidence against selective pituitary thyroid hormone resistance in nonneoplastic IST. *Journal of Clinical Endocrinology and Metabolism* **71** 19–25. (doi:10.1210/jcem-71-1-19)

Bernal J, Guadaño-Ferraz A & Morte B 2015 Thyroid hormone transporters – functions and clinical implications. *Nature Reviews Endocrinology* **11** 406–417. (doi:10.1038/nrendo.2015.66)

Blondeau JP, Osty J & Francon J 1988 Characterization of the thyroid hormone transport system of isolated hepatocytes. *Journal of Biological Chemistry* **263** 2685–2692.

Bogazzi F, Bartalena L, Brogioni S, Burelli A, Grasso L, Dell'Unto E, Manetti L & Martino E 1997 L-thyroxine directly affects expression of thyroid hormone-sensitive genes: regulatory effect of RXRbeta. *Molecular and Cellular Endocrinology* **134** 23–31. (doi:10.1016/S0303-7207(97)00156-1)

Boyd GS & Oliver F 1960 The effect of certain thyroxine analogues on the serum lipids in human subjects. *Journal of Endocrinology* **21** 33–43. (doi:10.1677/joe.0.0210033)

Bracco D, Morin O, Schutz Y, Liang H, Jéquier E & Burger AG 1993 Comparison of the metabolic and endocrine effects of 3,5,3′-triiodothyroacetic acid and thyroxine. *Journal of Clinical Endocrinology and Metabolism* **77** 221–228. (doi:10.1210/jcem.77.1.8325946)

Braverman LE, Ingbar SH & Sterling K 1970 Conversion of thyroxine (T4) to triiodothyronine T3 in athyreotic human subjects. *Journal of Clinical Investigation* **49** 855. (doi:10.1172/JCI106304)

Brenta G, Schnitman M, Fretes O, Facco E, Gurfinkel M, Damilano S, Pacenza N, Blanco A, Gonzalez E & Pisarev MA 2003 Comparative efficacy and side effects of the treatment of euthyroid goiter with levo-thyroxine or triiodothyroacetic acid. *Journal of Clinical Endocrinology and Metabolism* **88** 5287–5292. (doi:10.1210/jc.2003-030095)

Bres O & Eales JG 1986 Thyroid hormone binding to isolated trout (Salmo gairdneri) liver nuclei in vitro: binding affinity, capacity, and chemical specificity. *General and Comparative Endocrinology* **61** 29–39. (doi:10.1016/0016-6480(86)90246-7)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Burger AG 1986 Nondeiodinative pathways of thyroid hormone metabolism. In *Thyroid Hormone and Metabolism*, chap. 8. Ed G Hennemann. New York, NY, USA: Dekker Marcel.

Burger A & Vallotton MB 1975 The metabolism of tetraiodothyroacetic acid and its conversion to triiodothyroacetic acid in man. In *Proceedings of the International Conference of Thyroid Hormone Metabolism*, p 223. Eds WA Harland & JS Orr. London, UK: Academic Press.

Burger A, Suter P, Nicod P, Vallotton MB, Vagenakis A & Bravemran L 1976 Reduced active thyroid hormone levels in acute illness. *Lancet* **1** 653–655. (doi:10.1016/S0140-6736(76)92774-4)

Burger AG, Engler D, Sakoloff C & Staeheli V 1979 The effects of tetraiodothyroacetic and triiodothyroacetic acids on thyroid function in euthyroid and hyperthyroid subjects. *Acta Endocrinologica* **92** 455–467. (doi:10.1530/acta.0.0920455)

Carlin K & Carlin S 1993 Possible etiology for euthyroid sick syndrome. *Medical Hypotheses* **40** 38–43. (doi:10.1016/0306-9877(93)90194-U)

Cavalieri RR, Castle JN & McMahon FA 1984 Effects of dexamethasone on kinetics and distribution of triiodothyronine in the rat. *Endocrinology* **114** 215–221. (doi:10.1210/endo-114-1-215)

Chan WB, Chow CC & Cockram CS 2004 A patient with low free T4 and low thyroid-stimulating hormone without hypopituitarism. *International Journal of Clinical Practice* **58** 983–984. (doi:10.1111/j.1742-1241.2004.00037.x)

Chatzitomaris A, Köditz R, Höppner W, Peters S, Klein HH & Dietrich JW 2015 A novel de novo mutation in the thyroid hormone receptor-beta gene. *Experimental and Clinical Endocrinology and Diabetes* **123** 1–3.

Chopra IJ 1976 An assessment of daily production and significance of thyroidal secretion of 3,3′,5′-triiodothyronine (reverse T3) in man. *Journal of Clinical Investigation* **58** 32–40. (doi:10.1172/JCI108456)

Chopra IJ, Boado RJ, Geffner DL & Solomon DH 1988 radioimmunoassay for measurement of thyronine and its acetic acid analog in urine. *Journal of Clinical Endocrinology and Metabolism* **67** 480–487. (doi:10.1210/jcem-67-3-480)

Chow WS & Lam KS 1998 An overweight woman with galactorrhoea. *Postgraduate Medical Journal* **74** 121–122. (doi:10.1136/pgmj.74.868.121)

Christensen LK 1960 The binding to serum protein of acetic and propionic acid analogues of thyroxine and triiodothyronine. *Endocrinology* **67** 407–412. (doi:10.1210/endo-67-3-407)

Clifton-Bligh RJ, de Zegher F, Wagner RL, Collingwood TN, Francois I, Van Helvoirt M, Fletterick RJ & Chatterjee VK 1998 A novel TR beta mutation (R383H) in resistance to thyroid hormone syndrome predominantly impairs corepressor release and negative transcriptional regulation. *Molecular Endocrinology* **12** 609–621. (doi:10.1210/mend.12.5.0113)

Cohen-Lehman J, Charitou MM & Klein I 2011 Tiratricol-induced periodic paralysis: a review of nutraceuticals affecting thyroid function. *Endocrine Practices* **17** 610–615. (doi:10.4158/EP10137.RA)

Cortelazzi D, Morpurgo PS, Zamperini P, Fisher DA, Beck-Peccoz P & Wu SY 1999 Maternal compound W serial measurements for the management of fetal hypothyroidsm. *European Journal of Endocrinology* **141** 570–578. (doi:10.1530/eje.0.1410570)

Crinò A, Borrelli P, Salvatori R, Cortelazzi D, Roncoroni R & Beck-Peccoz P 1992 Anti-iodothyronine autoantibodies in a girl with hyperthyroidism due to pituitary resistance to thyroid hormones. *Journal of Endocrinological Investigation* **15** 113–120. (doi:10.1007/bf03348675)

Danilovic DL, Bloise W, Knobel M & Marui S 2008 Factitious thyrotoxicosis induced by mesotherapy: a case report. *Thyroid* **18** 655–657. (doi:10.1089/thy.2007.0233)

Darendeliler F & Basx F 1997 Successful therapy with 3,5,3′-triiodothyroacetic acid (TRIAC) in pituitary resistance to thyroid hormone. *Journal of Pediatric Endocrinology and Metabolism* **10** 535–538.

Davis PJ, Davis FB, Mousa SA, Luidens MK & Lin HY 2011 Membrane receptor for thyroid hormone: physiologic and pharmacologic implications. *Annual Review of Pharmacology and Toxicology* **51** 99–115. (doi:10.1146/annurev-pharmtox-010510-100512)

D'Agostino L, Daniele B, Pignata S, Barone MV, D'Argenio G & Mazzacca G 1987 Modifications in ornithine decarboxylase and diamine oxidase in small bowel mucosa of starved and refed rats. *Gut* **28** (Supplement) 135–138. (doi:10.1136/gut.28.suppl.135)

D'Arezzo S, Incerpi S, Davis FB, Acconcia F, Marino M, Farias RN & Davis PJ 2004 Rapid nongenomic effects of 3,5,3′-triiodo-L-thyronine on the intracellular pH of L-6 myoblasts are mediated by intracellular calcium mobilization and kinase pathways. *Endocrinology* **145** 5694–5703. (doi:10.1210/en.2004-0890)

De Graeff J, Wicht CL & Querido A 1957 Metabolic effects of intravenous triiodothyroacetic acid in primary myxedema. *Journal of Clinical Endocrinology and Metabolism* **17** 328. (doi:10.1210/jcem-17-2-328)

Delbaere J, Vancamp P, Van Herck SL, Bourgeois NM, Green MJ, Wingate RJ & Darras VM 2017 MCT8 deficiency in Purkinje cells disrupts embryonic chicken cerebellar development. *Journal of Endocrinology* **232** 259–272. (doi:10.1530/JOE-16-0323)

De Vrieze E, van de Wiel SM, Zethof J, Flik G, Klaren PH & Arjona FJ 2014 Knockdown of monocarboxylate transporter 8 (mct8) disturbs brain development and locomotion in zebrafish. *Endocrinology* **155** 2320–2330. (doi:10.1210/en.2013-1962)

Dlott RS, LoPresti JS & Nicoloff JT 1992 Evidence that triiodothyroacetate (triac) is the autocrine thyroid hormone in man. *Thyroid* **2** (Supplement 1) S-94.

Dulgeroff AJ, Geffner ME, Koyal SN, Wong M & Hershman JM 1992 Bromocriptine and Triac therapy for hyperthyroidism due to pituitary resistance to thyroid hormone. *Journal of Clinical Endocrinology and Metabolism* **75** 1071–1075. (doi:10.1210/jc.75.4.1071)

Dumitrescu AM, Liao XH, Best TB, Brockmann K & Refetoff S 2004 A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *American Journal of Human Genetics* **74** 168–175. (doi:10.1086/380999)

Engler D & Burger AG 1984 The deiodination of the iodothyronines and their derivatives in man. *Endocrine Reviews* **5** 151. (doi:10.1210/edrv-5-2-151)

Engler D, Merkelbach U, Steiger G & Burger AG 1984 The monodeiodination of triiodothyronine and reverse triiodothyronine in man: a quantitative evaluation of the pathway by the use of turnover rate techniques. *Journal of Clinical Endocrinology and Metabolism* **58** 49–61. (doi:10.1210/jcem-58-1-49)

Evans RW, Farwell AP & Braverman LE 1983 Nuclear thyroid hormone receptor in the rat uterus. *Endocrinology* **113** 1459–1463. (doi:10.1210/endo-113-4-1459)

Everts ME, Visser TJ, Moerings EP, Docter R, van Toor H, Tempelaars AM, de Jong M, Krenning EP & Hennemann G 1994 Uptake of triiodothyroacetic acid and its effect on thyrotropin secretion in cultured anterior pituitary cells. *Endocrinology* **135** 2700–2707. (doi:10.1210/endo.135.6.7988460)

Faergemann J, Särnhult T, Hedner E, Carlsson B, Lavin T, Zhao XH & Sun XY 2002 Dose-response effects of tri-iodothyroacetic acid (Triac) and other thyroid hormone analogues on glucocorticoid induced skin atrophy in the haired mouse. *Acta Dermato-Venereologica* **82** 179–183. (doi:10.1080/00015550260132451)

Faglia G, Beck-Peccoz P, Piscitelli G & Medri G 1987 Inappropriate secretion of thyrotropin by the pituitary. *Hormone Research* **26** 79–99. (doi:10.1159/000180687)

Farwell AP 2013 Nonthyroidal illness syndrome. *Current Opinion in Endocrinology, Diabetes and Obesity* **20** 478–484. (doi:10.1097/01.med.0000433069.09294.e8)

Ferner RE, Burnett A & Rawlins MD 1986 Tri-iodothyroacetic acid abuse in a female body builder. *Lancet* **1** 383. (doi:10.1016/S0140-6736(86)92345-7)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Ferrara AM, Onigata K, Ercan O, Woodhead H, Weiss RE & Refetoff S 2012 Homozygous thyroid hormone receptor β-gene mutations in resistance to thyroid hormone: three new cases and review of the literature. *Journal of Clinical Endocrinology and Metabolism* **97** 1328–1336. (doi:10.1210/jc.2011-2642)

Flock EV, Bollman JL & Stobie GH 1962 Metabolic pathways of tetraiodothyroacetic acid, triidothyroacetic acid, tetraiodothyropropionic acid and triiodothyropropionic acid. *Biochemical Pharmacology* **11** 627–637. (doi:10.1016/0006-2952(62)90124-7)

Flock EV, Bollman JL, Owen CA Jr & Zollman PE 1965 Conjugation of thyroid hormones and analogs by the Gunn rat. *Endocrinology* **77** 303–314. (doi:10.1210/endo-77-2-303)

Forrest D, Hanebuth E, Smeyne RJ, Everds N, Stewart CL, Wehner JM & Curran T 1996 Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. *EMBO Journal* **15** 3006–3015.

Friesema EC, Grueters A, Biebermann H, Krude H, von Moers A, Reeser M, Barrett TG, Mancilla EE, Svensson J, Kester MH, *et al*. 2004 Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* **364** 1435–1437. (doi:10.1016/S0140-6736(04)17226-7)

Gavin LA, Livermore BM, Cavalieri RR, Hammond ME & Castle JN 1980 Serum concentration, metabolic clearance, and production rates of 3,5,3′-triiodothyroacetic acid in normal and athyreotic man. *Journal of Clinical Endocrinology and Metabolism* **51** 529–534. (doi:10.1210/jcem-51-3-529)

Gavin L, Castle J, McMahon F, Martin P, Hammond M & Cavalieri RR 1977 Extrathyroidal conversion of thyroxine to 3,3′,5′-triiodothyronine (reverse-T3) and to 3,5,3′-triiodothyronine (T3) in humans. *Journal of Clinical Endocrinology and Metabolism* **44** 733–742. (doi:10.1210/jcem-44-4-733)

Gershengorn M, Geras E, Marcus-Samuels BE & Rebecchi MJ 1979 Receptor affinity and biological potency of thyroid hormones in thyrotropic cells. *American Journal of Physiology: Endocrinology and Metabolism* **237** E142–El46.

Goslings B, Schwartz HL, Dillmann W, Surks MI & Oppenheimer JH 1976 Comparison of the metabolism and distribution of I-triiodothyronine and triiodothyroacetic acid in the rat: a possible explanation of differential hormonal potency. *Endocrinology* **98** 666–675. (doi:10.1210/endo-98-3-666)

Green WL & Ingbar SH 1961 The peripheral metabolism of tri- and tetraiodothyroacetic acids in man. *Journal of Clinical Endocrinology and Metabolism* **21** 1548–1565. (doi:10.1210/jcem-21-12-1548)

Groeneweg S, Friesema EC, Kersseboom S, Klootwijk W, Visser WE, Peeters RP & Visser TJ 2014 The role of Arg445 and Asp498 in the human thyroid hormone transporter MCT8. *Endocrinology* **155** 618–626. (doi:10.1210/en.2013-1521)

Groeneweg S, Peeters RP, Visser TJ & Visser WE 2017 Therapeutic applications of thyroid hormone analogues in resistance to thyroid hormone (RTH) syndromes. *Molecular and Cellular Endocrinology* [in press]. (doi:10.1016/j.mce.2017.02.029)

Guran T, Turan S, Bircan R & Bereket A 2009 9 years follow-up of a patient with pituitary form of resistance to thyroid hormones (PRTH): comparison of two treatment periods of D-thyroxine and triiodothyroacetic acid (TRIAC). *Journal of Pediatric Endocrinology and Metabolism* **22** 971–978. (doi:10.1515/JPEM.2009.22.4.363)

Gurgel MH, Montenegro Junior RM, Magalhaes RA, Lima GE, Montenegro RM, Magalhães PK & Maciel LM 2008 E449X mutation in the thyroid hormone receptor beta associated with autoimmune thyroid disease and severe neuropsychomotor involvement. *Arquivos Brasileiros de Endocrinologia e Metabologia* **52** 1205–1210. (doi:10.1590/S0004-27302008000800002)

Hawkey CM, Olsen EG & Symons C 1981 Production of cardiac muscle abnormalities in offspring of rats receiving triiodothyroacetic acid (triac) and the effect of beta adrenergic blockade. *Cardiovascular Research* **15** 196–205. (doi:10.1093/cvr/15.4.196)

Hamon P, Bovier-Lapierre M, Robert M, Peynaud D, Pugeat M & Orgiazzi J 1988 Hyperthyroidism due to selective pituitary resistance to thyroid hormones in a 15-month-old boy:efficacy of D-thyroxine therapy. *Journal of Clinical Endocrinology and Metabolism* **67** 1089–1093. (doi:10.1210/jcem-67-5-1089)

Heimberg M, Harting Park J, Isaacs A & Pitt-Rivers R 1955 The effects of the acetic acid analogs of thyroxine and triiodothyronine on glycolysis in ascites tumor cells *in vitro*. *Endocrinology* **57** 756–758. (doi:10.1210/endo-57-6-756)

Hennemann G, Docter R, Friesema E, De Jong M, Krenning EP & Visser TJ 2001 Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. *Endocrine Reviews* **22** 451–476. (doi:10.1210/edrv.22.4.0435)

Hill SR Jr, Barker SB, McNeil JH, Tingley JO & Hibbett LL 1960 The metabolic effects of the acetic and propionic acid analogues of thyroxine and triiodothyronine. *Journal of Clinical Investigation* **39** 523–533. (doi:10.1172/JCI104066)

Hoefig CS, Renko K, Piehl S, Scanlan TS, Bertoldi M, Opladen T, Hoffmann GF, Klein J, Blankenstein O, Schweizer U, *et al*. 2012 Does the aromatic L-amino acid decarboxylase contribute to thyronamine biosynthesis? *Molecular and Cellular Endocrinology* **349** 195–201. (doi:10.1016/j.mce.2011.10.024)

Hoefig CS, Wuensch T, Rijntjes E, Lehmphul I, Daniel H, Schweizer U, Mittag J & Köhrle J 2015 Biosynthesis of 3-iodothyronamine from T_4 in murine intestinal tissue. *Endocrinology* **156** 4356–4364. (doi:10.1210/en.2014-1499)

Hoefig CS, Zucchi R & Koehrle J 2016 Thyronamines and derivatives: physiological relevance, pharmacological actions and future research directions. *Thyroid* **26** 1656–1673. (doi:10.1089/thy.2016.0178)

Horn S, Kersseboom S, Mayerl S, Müller J, Groba C, Trajkovic-Arsic M, Ackermann T, Visser TJ & Heuer H 2013 Tetrac can replace thyroid hormone during brain development in mouse mutants deficient in the thyroid hormone transporter mct8. *Endocrinology* **154** 968–979. (doi:10.1089/thy.2016.0178)

Huang CJ, Geller HM, Green WL & Craelius W 1999 Acute effects of thyroid hormone analogs on sodium currents in neonatal rat myocytes. *Journal of Molecular and Cellular Cardiology* **31** 881–893. (doi:10.1006/jmcc.1998.0930)

Ibbertson K, Fraser R & Alldis D 1959 Rapidly acting thyroid hormones and their cardiac action. *BMJ* **2** 52. (doi:10.1136/bmj.2.5141.52)

Ingbar SH 1960 The interaction of the thyroid hormones with the proteins of human plasma. *Annals of the New York Academy of Sciences* **86** 440. (doi:10.1111/j.1749-6632.1960.tb42821.x)

Jouan P, Michel R, Roche J & Wolf W 1956 The recovery of 3:5:3′-triiodothyroacetic acid and 3:3′-diiodothyronine from rat kidney after injection of 3:5:3′ triiodothyronine. *Endocrinology* **59** 425–432. (doi:10.1210/endo-59-4-425)

Juge-Aubry CE, Morin O, Pernin AT, Liang H, Philippe J & Burger AG 1995 Long-lasting effects of Triac and thyroxine on the control of thyrotropin and hepatic deiodinase type I. *European Journal of Endocrinology* **132** 751–758. (doi:10.1530/eje.0.1320751)

Kaplan MM, Visser TJ, Yaskoski KA & Leonard JL 1983 Characteristics of iodothyronine tyrosyl ring deiodination by rat cerebral cortical microsomes. *Endocrinology* **112** 35. (doi:10.1210/endo-112-1-35)

Kawaguchi H, Pilbeam CC, Woodiel FN & Raisz LG 1994*a* Comparison of the effects of 3,5,3′-triiodothyroacetic acid and triiodothyronine on bone resorption in cultured fetal rat long bones and neonatal mouse calvariae. *Journal of Bone and Mineral Research* **9** 247–253. (doi:10.1002/jbmr.5650090214)

Kawaguchi H, Pilbeam CC & Raisz LG 1994*b* Anabolic effects of 3,3′,5-triiodothyronine and triiodothyroacetic acid in cultured neonatal mouse parietal bones. *Endocrinology* **135** 971–976. (doi:10.1210/endo.135.3.7520864)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Kersseboom S, Horn S, Visser WE, Chen J, Friesema EC, Vaurs-Barrière C, Peeters RP, Heuer H & Visser TJ 2014 In vitro and mouse studies supporting therapeutic utility of triiodothyroacetic acid in MCT8 deficiency. *Molecular Endocrinology* **28** 1961–1970. (doi:10.1210/me.2014-1135)

Klootwijk W, Friesema EC & Visser TJ 2011 A nonselenoprotein from amphioxus deiodinates triac but not T3: is triac the primordial bioactive thyroid hormone? *Endocrinology* **152** 3259–3267. (doi:10.1210/en.2010-1408)

Köhrle J, Auf'mkolk M, Rokos H, Hesch RD & Cody V 1986 Rat liver iodothyronine monodeiodinase. Evaluation of the iodothyronine ligand-binding site. *Journal of Biological Chemistry* **261** 11613–11622.

Kong AP, Lam CW, Chan AO, Yiu SF & Tiu SC 2005 Resistance to thyroid hormone in a Chinese family with R429Q mutation in the thyroid hormone receptor beta gene. *Hong Kong Medical Journal* **11** 125–129.

Koury EJ, Pawlyk AC, Berrodin TJ, Smolenski CL, Nagpal S & Deecher DC 2009 Characterization of ligands for thyroid receptor subtypes and their interactions with co-regulators. *Steroids* **74** 270–276. (doi:10.1016/j.steroids.2008.11.014)

Kunitake JM, Hartman N, Henson LC, Lieberman J, Williams DE, Wong M & Hershman JM 1989 3,5,3′-triiodothyroacetic acid therapy for thyroid hormone resistance. *Journal of Clinical Endocrinology and Metabolism* **69** 461–466. (doi:10.1210/jcem-69-2-461)

Lameloise N, Siegrist-Kaiser C, O'Connell M & Burger A 2001 Differences between the effects of thyroxine and tetraiodothyroacetic acid on TSH suppression and cardiac hypertrophy. *European Journal of Endocrinology* **144** 145–154. (doi:10.1530/eje.0.1440145)

Lazar MA 1993 Thyroid hormone receptors: multiple forms, multiple possibilities. *Endocrine Reviews* **14** 184–193. (doi:10.1210/edrv-14-2-184)

Lerman J 1961 Dissociation of response to triiodothyroacetic acid in myxedema: comparison with response to thyroid substance. *Journal of Clinical Endocrinology and Metabolism* **21** 1044–1053. (doi:10.1210/jcem-21-9-1044)

Lerman J & Pitt-Rivers R 1955 Physiologic activity of triiodothyroacetic acid. *Journal of Clinical Endocrinology and Metabolism* **15** 653. (doi:10.1210/jcem-15-5-653b)

Lerman J & Pitt-Rivers R 1956 Physiologic activity of triiodo- and tetraiodothyroacetic acid in human myxedema. *Journal of Clinical Endocrinology and Metabolism* **16** 1470–1479. (doi:10.1210/jcem-16-11-1470)

Liang H, Juge-Aubry CE, O'Connell M & Burger AG 1997 Organ-specific effects of 3,5,3′-triiodothyroacetic acid in rats. *European Journal of Endocrinology* **137** 537–544. (doi:10.1530/eje.0.1370537)

Lin HY, Martino LJ, Wilcox BD, Davis FB, Gordinier JK & Davis PJ 1998 Potentiation by thyroid hormone of human IFN-gamma-induced HLA-DR expression. *Journal of Immunology* **161** 843–849.

Lin HY, Tang HY, Davis FB, Mousa SA, Incerpi S, Luidens MK, Meng R & Davis PJ 2012 Nongenomic regulation by thyroid hormone of plasma membrane ion and small molecule pumps. *Discovery Medicine* **14** 199–206.

Lind P & Eber O 1986 Treatment of inappropriate TSH secretion with Triac. *Acta Medica Austriaca* **13** 13–16.

Lind P, Langsteger W, Költringer P & Eber O 1989 3,5,3′-Triiodothyroacetic acid (TRIAC) effects on pituitary thyroid regulation and on peripheral tissue parameters. *Nuklearmedizin* **28** 217–220.

LoPresti JS & Dlott RS 1992 Augmented conversion of T3 to triac (T3AC) is the major regulator of the low T3 state in fasting man. *Thyroid* **2** (Supplement 1) S-39.

LoPresti JS, Dlott RS, Nicoloff RS & Nicoloff JT 1993 'In vivo' induction of Triac (T3AC) formation in fasting man. *Clinical Research* **41** 83A.

Luo M, Faure R & Dussault JH 1986 Ontogenesis of nuclear T3 receptors in primary cultured astrocytes and neurons. *Brain Research* **381** 275–280. (doi:10.1016/0006-8993(86)90077-6)

Ma RC, Chan MH, Poon WT, So WY & Chow CC 2008 Thyroid dysfunction due to over-the-counter usage of tiratricol. *Internal Medicine Journal* **38** 611–612. (doi:10.1111/j.1445-5994.2008.01708.x)

Mårdh G, Auld DS & Vallee BL 1987 Thyroid hormones selectively modulate human alcohol dehydrogenase isozyme catalyzed ethanol oxidation. *Biochemistry* **26** 7585–7588. (doi:10.1021/bi00398a008)

Martínez L, Nascimento AS, Nunes FM, Phillips K, Aparicio R, Dias SM, Figueira AC, Lin JH, Nguyen P, Apriletti JW, *et al*. 2009 Gaining ligand selectivity in thyroid hormone receptors via entropy. *PNAS* **106** 20717–20722. (doi:10.1073/pnas.0911024106)

Massol J, Martin P, Soubrié P & Simon P 1987 Triiodothyroacetic acid-induced reversal of learned helplessness in rats. *European Journal of Pharmacology* **134** 345–348. (doi:10.1016/0014-2999(87)90367-0)

Massol J, Martin P, Brochet D, Puech A & Simon P 1988*a* Antidepressant-like effects of triiodothyroacetic acid in mice. *Psychopharmacology* **94** 97–102. (doi:10.1007/BF00735888)

Massol J, Martin P, Soubrié P & Puech AJ 1988*b* Triiodothyroacetic acid (TRIAC) potentiation of antidepressant-induced reversal of learned helplessness in rats. *European Journal of Pharmacology* **152** 347–351. (doi:10.1016/0014-2999(88)90730-3)

Matheus MG, Lehman RK, Bonilha L & Holden KR 2015 Redefining the pediatric phenotype of X-linked monocarboxylate transporter 8 (MCT8) deficiency: implications for diagnosis and therapies. *Journal of Child Neurology* **30** 1664–1668. (doi:10.1177/0883073815578524)

Mayerl S, Müller J, Bauer R, Richert S, Kassmann CM, Darras VM, Buder K, Boelen A, Visser TJ & Heuer H 2014 Transporters MCT8 and OATP1C1 maintain murine brain thyroid hormone homeostasis. *Journal of Clinical Investigation* **124** 1987–1999. (doi:10.1172/JCI70324)

McCarthy K, Lovenberg W & Sjoerdsms A 1968 The mechanism of inhibition of horse liver alcohol dehydrogenase by thyroxine and related compounds. *Journal of Biological Chemistry* **243** 2754–2760.

Mechelany C, Schlumberger M, Challeton C, Comoy E & Parmentier C 1991 Triac (3,5,3′-triiodothyroacetic acid) has parallel effects at the pituitary and peripheral tissue levels in thyroid cancer patients treated with L-thyroxine. *Clinical Endocrinology* **35** 123–128. (doi:10.1111/j.1365-2265.1991.tb03509.x)

Medeiros-Neto G, Kallas WG, Knobel M, Cavaliere H & Mattar E 1980 Triac (3,5,3′-triiodothyroacetic acid) partially inhibits the thyrotropin response to synthetic thyrotropin-releasing hormone in normal and thyroidectomized hypothyroid patients. *Journal of Clinical Endocrinology and Metabolism* **50** 223–225. (doi:10.1210/jcem-50-2-223)

Medina-Gomez G, Hernandez A, Calvo RM, Martin E & Obregon MJ 2003 Potent thermogenic action of triiodothyroacetic acid in brown adipocytes. *Cellular and Molecular Life Sciences* **60** 1957–1967. (doi:10.1007/s00018-003-3158-9)

Medina-Gomez G, Calvo RM & Obregón MJ 2004 T3 and Triac inhibit leptin secretion and expression in brown and white rat adipocytes. *Biochimica et Biophysica Acta* **1682** 38–47. (doi:10.1016/j.bbalip.2004.01.007)

Medina-Gomez G, Calvo RM & Obregon MJ 2008 Thermogenic effect of triiodothyroacetic acid at low doses in rat adipose tissue without adverse side effects in the thyroid axis. *American Journal of Physiology: Endocrinology and Metabolism* **294** E688–E697. (doi:10.1152/ajpendo.00417.2007)

Menegay C, Juge C & Burger AG 1989 Pharmacokinetics of 3,5,3′-triiodothyroacetic acid and its effects on serum TSH levels. *Acta Endocrinologica* **121** 651–658. (doi:10.1530/acta.0.1210651)

Messier N & Langlois MF 2000 Triac regulation of transcription is T(3) receptor isoform- and response element-specific. *Molecular and Cellular Endocrinology* **165** 57–66. (doi:10.1016/S0303-7207(00)00266-5)

Messier N, Laflamme L, Hamann G & Langlois MF 2001 In vitro effect of Triac on resistance to thyroid hormone receptor mutants: potential basis for therapy. *Molecular and Cellular Endocrinology* **174** 59–69. (doi:10.1016/S0303-7207(00)00446-9)

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Mirell CJ, Yanagisawa M & Hershman JM 1989 Triac reduces serum TSH without decreasing alpha and beta TSH messenger RNAs. *Hormone and Metabolic Research* **21** 123–126. (doi:10.1055/s-2007-1009170)

Moreno M, Kaptein E, Goglia F & Visser TJ 1994 Rapid glucuronidation of tri- and tetraiodothyroacetic acid to ester glucuronides in human liver and to ether glucuronides in rat liver. *Endocrinology* **135** 1004–1009. (doi:10.1210/endo.135.3.8070342)

Mueller-Gaertner HW & Schneider C 1988 3,5,3′-Triiodothyroacetic acid minimizes the pituitary thyrotrophin secretion in patients on levo-thyroxine therapy after ablative therapy for differentiated thyroid carcinoma. *Clinical Endocrinology* **28** 345–351. (doi:10.1111/j.1365-2265.1988.tb03665.x)

Nakamura Y, Chopra IJ & Solomon DH 1978 An assessment of the concentration of acetic acid and propionic acid derivatives of 3,5,3′-triiodothyronine in human serum. *Journal of Clinical Endocrinology and Metabolism* **46** 91–97. (doi:10.1210/jcem-46-1-91)

Neves FA, Cavalieri RR, Simeoni LA, Gardner DG, Baxter JD, Scharschmidt BF, Lomri N & Ribeiro RC 2002 Thyroid hormone export varies among primary cells and appears to differ from hormone uptake. *Endocrinology* **143** 476–483. (doi:10.1210/endo.143.2.8631)

Nguyen TT, DiStefano JJ 3rd, Yamada H & Yen YM 1993 Steady state organ distribution and metabolism of thyroxine and 3,5,3′-triiodothyronine in intestines, liver, kidneys, blood and residual carcass of the rat in vivo. *Endocrinology* **133** 2973–2983. (doi:10.1210/endo.133.6.8243325)

Nicholls D, Cunningham SA & Rial E 1986 The bioenergetic mechanisms of brown adipose tissue mitochondria. In *Brown Adipose Tissue*, pp 52–85. Eds P Trayhurn & DG Nicholls. London, UK: Edward Arnold.

Nicolini U, Venegoni E, Acaia B, Cortelazzi D & Beck-Peccoz P 1996 Prenatal treatment of fetal hypothyroidism: is there more than one option? *Prenatal Diagnosis* **16** 443–448. (doi:10.1002/(SICI)1097-0223(199605)16:5<443::AID-PD892>3.0.CO;2-2)

Oka T, Mitsui-Watanabe N, Tatarazako N, Onishi Y, Katsu Y, Miyagawa S, Ogino Y, Yatsu R, Kohno S, Takase M, *et al*. 2013 Establishment of transactivation assay systems using fish, amphibian, reptilian and human thyroid hormone receptors. *Journal of Applied Toxicology* **33** 991–1000. (doi:10.1002/jat.2825)

Oliver MF & Boyd GS 1957 The influence of triiodothyroacetic acid on the circulating lipids and lipoprotems m euthyroid men with coronary disease. *Lancet* **1** 124. (doi:10.1016/S0140-6736(57)90200-3)

Olsen EG, Symons C & Hawkey C 1977 Effect of triac on the developing heart. *Lancet* **2** 221–223. (doi:10.1016/S0140-6736(77)92836-7)

Oppenheimer JH, Schwartz HL, Dillman W & Surks MI 1973 Effect of thyroid hormone analogues on the displacement of 125I-L-triiodothyronine from hepatic and heart nuclei in vivo: possible relationship to hormonal activity. *Biochemical and Biophysical Research Communications* **55** 544–550. (doi:10.1016/0006-291X(73)91177-7)

Oppenheimer JH, Schwartz HL & Surks MI 1974 Erratum: revised calculations of common parameters iodo-thyronine metabolism and distribution by noncompartmental analysis. *Journal of Clinical Endocrinology and Metabolism* **41** 1172–1173. (doi:10.1210/jcem-41-6-1172)

Ortiga-Carvalho TM, Hashimoto K, Pazos-Moura CC, Geenen D, Cohen R, Lang RM & Wondisford FE 2004 Thyroid hormone resistance in the heart: role of the thyroid hormone receptors beta isoform. *Endocrinology* **145** 1625–1633. (doi:10.1210/en.2003-1031)

Paris M, Escriva H, Schubert M, Brunet F, Brtko J, Ciesielski F, Roecklin D, Vivat-Hannah V, Jamin EL, Cravedi JP, *et al*. 2008 Amphioxus postembryonic development reveals the homology of chordate metamorphosis. *Current Biology* **18** 825–830. (doi:10.1016/j.cub.2008.04.078)

Paris M, Hillenweck A, Bertrand S, Delous G, Escriva H, Zalko D, Cravedi JP & Laudet V 2010 Active metabolism of thyroid hormone during metamorphosis of amphioxus. *Integrative and Comparative Biology* **50** 63–74. (doi:10.1093/icb/icq052)

Pearce PC, Hawkey CM, Symons C & Olsen EG 1983 Effect of triac and beta-adrenergic blocking agents on the myocardium of developing rats. *Cardiovascular Research* **17** 7–14. (doi:10.1093/cvr/17.1.7)

Pearce PC, Hawkey C, Symons C & Olsen EG 1985 Role of calcium in the induction of cardiac hypertrophy and myofibrillar disarray. Experimental studies of a possible cause of hypertrophic cardiomyopathy. *British Heart Journal* **54** 420–427. (doi:10.1136/hrt.54.4.420)

Pearce PC, Hawkey CM, Symons C & Olsen EG 1988 The importance of membrane stabilization in protecting the developing rat myocardium from the actions of triac. *American Journal of Cardiovascular Pathology* **2** 173–179.

Persani L, Borgato S, Romoli R, Asteria C, Pizzocaro A & Beck-Peccoz P 1998 Changes in the degree of sialylation of carbohydrate chains modify the biological properties of circulating thyrotropin isoforms in various physiological and pathological states. *Journal of Clinical Endocrinology and Metabolism* **83** 2486–2492. (doi:10.1210/jcem.83.7.4970)

Piehl S, Heberer T, Balizs G, Scanlan TS, Smits R, Koksch B & Köhrle J 2008 Thyronamines are isozyme-specific substrates of deiodinases. *Endocrinology* **149** 3037–3045. (doi:10.1210/en.2007-1678)

Pitt-Rivers R 1953 Physiological activity of the acetic-acid analogues of some iodinated thyronines. *Lancet* **2** 234–235. (doi:10.1016/S0140-6736(53)90164-0)

Pittman CS, Shimizu T, Burger A & Chambers JB 1980 The nondeiodinative pathways of thyroxine metabolism: 3,5,3′,5-tetraiodothyroacetic acid turnover in normal and fasting human subjects. *Journal of Clinical Endocrinology and Metabolism* **50** 712–716. (doi:10.1210/jcem-50-4-712)

Pujol P, Osman A, Bringer J & Jaffiol C 1997 Prevention of thyroid neoplasm recurrence with Triac and levothyroxine. *Clinical Endocrinology* **46** 121–122. (doi:10.1046/j.1365-2265.1997.d01-1746.x)

Pujol P, Osman A, Grabar S, Daurès JP, Galtier-Dereure F, Boegner C, Baldet L, Raye R, Bringer J & Jaffiol C 1998 TSH suppression combined with carbimazole for Graves' disease: effect on remission and relapse rates. *Clinical Endocrinology* **48** 635–640. (doi:10.1046/j.1365-2265.1998.00466.x)

Pujol P, De Boisvilliers F, Bringer J & Jaffiol C 2000 Effects of thyrotropin suppression with tri-lodothyroacetic acid on radionuclide cardiovascular parameters. *Thyroid* **10** 1017–1018. (doi:10.1089/thy.2000.10.1017)

Radetti G, Persani L, Molinaro G, Mannavola D, Cortelazzi D, Chatterjee VK & Beck-Peccoz P 1997 Clinical and hormonal outcome after two years of triiodothyroacetic acid treatment in a child with thyroid hormone resistance. *Thyroid* **7** 775–778. (doi:10.1089/thy.1997.7.775)

Rall JE, Pearson OH, Lipsett MB & Rawson RW 1956 Metabolic effects in man of the acetic acid analogues of thyroxine and triiodothyronine. *Journal of Clinical Endocrinology and Metabolism* **16** 1299. (doi:10.1210/jcem-16-10-1299)

Ramos-Prol A, Antonia Pérez-Lázaro M, Isabel del Olmo-García M, León-de Zayas B, Moreno-Macián F, Navas-de Solis S & Merino-Torres JF 2013 Differentiated thyroid carcinoma in a girl with resistance to thyroid hormone management with triiodothyroacetic acid. *Journal of Pediatric Endocrinology and Metabolism* **26** 133–136. (doi:10.1515/jpem-2012-0230)

Refetoff S, Weiss RE & Usala SJ 1993 The syndromes of resistance to thyroid hormone. *Endocrine Reviews* **14** 348–399.

Robbins J & Rall JE 1955 Effects of triiodothyronine and other thyroxine analogues on thyroxine-binding in human serum. *Journal of Clinical Investigation* **34** 1331–1336. (doi:10.1172/JCI103180)

Roche J, Michel R, Etling N & Jouan P 1956 Sur le metabolism hepatique de l'acide 3:5:3′-triiodothyroacetique. *Comptes Rendus des Séances de la Société de Biologie* **150** 1320.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Rudinger A, Mylotte KM, Davis PJ, Davis FB & Blas SD 1984 Rabbit myocardial membrane Ca2+-adenosine triphosphatase activity: stimulation in vitro by thyroid hormone. *Archives of Biochemistry and Biophysics* **229** 379–385. (doi:10.1016/0003-9861(84)90165-6)

Rutgers M, Heusdens FA & Visser TJ 1989*a* Metabolism of triiodothyroacetic acid (TA3) in rat liver. I. Deiodination of TA3 and TA3 sulfate by microsomes. *Endocrinology* **125** 424–432. (doi:10.1210/endo-125-1-424)

Rutgers M, Heusdens FA, Bonthuis F & Visser TJ 1989*b* Metabolism of triiodothyroacetic acid (TA3) in rat liver. II. Deiodination and conjugation of TA3 by rat hepatocytes and in rats in vivo. *Endocrinology* **125** 433–443. (doi:10.1210/endo-125-1-433)

Salmela PI, Wide L, Juustila H & Ruokonen A 1988 Effects of thyroid hormones (T4,T3), bromocriptine and Triac on inappropriate TSH hypersecretion. *Clinical Endocrinology* **28** 497–507. (doi:10.1111/j.1365-2265.1988.tb03684.x)

Santos J, Paiva I, Baptista C, Beck-Peccoz P & Carvalheiro M 2008 Resistance to thyroid hormones (RTH): study of a family. *Endocrine Abstracts* **16** P734.

Scally MC & Hodge A 2003 A report of hypothyroidism induced by an over-the-counter fat loss supplement (Tiratricol). *International Journal of Sport Nutrition and Exercise Metabolism* **13** 112–116. (doi:10.1123/ijsnem.13.1.112)

Scanlan TS, Suchland KL, Hart ME, Chiellini G, Huang Y, Kruzich PJ, Frascarelli S, Crossley DA, Bunzow JR, Ronca-Testoni S, *et al*. 2004 3-Iodothyronamine is an endogenous and rapid-acting derivative of thyroid hormone. *Nature Medicine* **10** 638–642. (doi:10.1038/nm1051)

Schueler PA, Schwartz HL, Strait KA, Mariash CN & Oppenheimer JH 1990 Binding T3 and its analogs to the in vitro translational products of c-erb A protooncogenes: differences in the affinity of the α- and β-forms for the acetic acid analog and failure of the human testis and kidney-2 products to bind T3. *Molecular Endocrinology* **4** 227–234. (doi:10.1210/mend-4-2-227)

Sekura RD, Sato K, Cahnmann HJ, Robbins J & Jakoby WB 1981 Sulfate transfer to thyroid hormones and their analogs by hepatic aryl sulfotransferases. *Endocrinology* **108** 454. (doi:10.1210/endo-108-2-454)

Sherman SI & Ladenson PW 1992 Organ-specific effects of tiratricol: a thyroid hormone analog with hepatic, not pituitary, superagonist effects. *Journal of Clinical Endocrinology and Metabolism* **75** 901–905. (doi:10.1210/jcem.75.3.1517383)

Sherman SI, Ringel MD, Smith MJ, Kopelen HA, Zoghbi WA & Ladenson PW 1997 Augmented hepatic and skeletal thyromimetic effects of tiratricol in comparison with levothyroxine. *Journal of Clinical Endocrinology and Metabolism* **82** 2153–2158. (doi:10.1210/jcem.82.7.4054)

Siegrist-Kaiser C & Burger AG 1994 Modification of the side chain of thyroid hormones. In *Thyroid Hormone Metabolism*, pp 17–198. Eds SY Wu & TJ Visser. Boca Raton, FL, USA: CRC Press, Inc.

Smallridge RC, Parker RA, Wiggs EA, Rajagopal KR & Fein HG 1989 Thyroid hormone resistance in a large kindred: physiologic, biochemical, pharmacologic, and neuropsychologic studies. *American Journal of Medicine* **86** 289–296. (doi:10.1016/0002-9343(89)90298-2)

Smith HC, Robinson SE & Eastman CJ 1980 Binding of endogenous iodothyronines to isolated liver cell nuclei. *Endocrinology* **106** 1133–1136. (doi:10.1210/endo-106-4-1133)

Sorimachi K & Yasumura Y 1981 High affinity of triiodothyronine (T3) for nonphenolic ring deiodinase and high affinity of tetraiodothyroacetic acid (TETRAC) for phenolic ring deiodinase in cultured monkey hepatocarcinoma cells and in rat liver homogenates. *Endocrinologia Japonica* **28** 775. (doi:10.1507/endocrj1954.28.775)

Stagi S, Manoni C, Cirello V, Covelli D, Giglio S, Chiarelli F, Seminara S & de Martino M 2014 Diabetes mellitus in a girl with thyroid hormone resistance syndrome: a little recognized interaction between the two diseases. *Hormones* **13** 561–567.

Symons C, Olsen SC & Hawkey CM 1975 The production of cardiac hypertrophy by triiodothyroacetic acid. *Journal of Endocrinology* **65** 341–346. (doi:10.1677/joe.0.0650341)

Szabolcs I, Schultheiss H, Astier H & Horster FA 1991 Effects of triiodothyronine, triiodothyroacetic acid, iopanoic acid and iodide on the thyrotropin-releasing hormone-induced thyrotropin release from superfused rat pituitary fragments. *Acta Endocrinologica* **125** 427–434 (abstract). (doi:10.1530/acta.0.1250427)

Takeda T, Suzuki S, Liu RT & DeGroot LJ 1995 Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. *Journal of Clinical Endocrinology and Metabolism* **80** 2033–2040. (doi:10.1210/jcem.80.7.7608251)

Tata JR, Rail JE & Rawson RW 1957 Metabolism of L-thyroxine and L-3:5:3′-triiodothyronine by brain tissue preparations. *Endocrinology* **60** 83. (doi:10.1210/endo-60-1-83)

Thibault O & Pitt-Rivers R 1955 Immediate effects of thyroxine analogues on biological oxidations in vitro. *Lancet* **265** 285–286. (doi:10.1016/S0140-6736(55)90111-2)

Tomita K, Lardy HL, Larson FC & Albright EC 1957 Enzymatic conversion of thyroxine to tetraiodothyroacetic acid and triiodothyronine to triiodothyroacetic acid. *Journal of Biological Chemistry* **224** 387–397.

Torre P, Bertoli M, Di Giovanni S, Scommegna S, Conte C, Novelli G & Cianfarani S 2005 Endocrine and neuropsychological assessment in a child with a novel mutation of thyroid hormone receptor: response to 12-month triiodothyroacetic acid (TRIAC) therapy. *Journal of Endocrinological Investigation* **28** 657–662. (doi:10.1007/BF03347267)

Trajkovic M, Visser TJ, Mittag J, Horn S, Lukas J, Darras VM, Raivich G, Bauer K & Heuer H 2007 Abnormal thyroid hormone metabolism in mice lacking the monocarboxylate transporter 8. *Journal of Clinical Investigation* **117** 627–635. (doi:10.1172/JCI28253)

Trajkovic-Arsic M, Müller J, Darras VM, Groba C, Lee S, Weih D, Bauer K, Visser TJ & Heuer H 2010 Impact of monocarboxylate transporter-8 deficiency on the hypothalamus-pituitary-thyroid axis in mice. *Endocrinology* **151** 5053–5062. (doi:10.1210/en.2010-0593)

Trotter WR 1955 Effect of triiodothyroacetic acid in a case of myxedema. *Lancet* **2** 374. (doi:10.1016/S0140-6736(55)92356-4)

Trotter WR 1956 Effect of triiodothyroacetic acid on blood-cholesterol levels. *Lancet* **2** 885. (doi:10.1016/S0140-6736(56)91347-2)

Ueda S, Takamatsu J, Fukata S, Tanaka K, Shimizu N, Sakata S, Yamaji T, Kuma K & Ohsawa N 1996 Differences in response of thyrotropin to 3,5,3′-triiodothyronine and 3,5,3′-triiodothyroacetic acid in patients with resistance to thyroid hormone. *Thyroid* **6** 563–570. (doi:10.1089/thy.1996.6.563)

Vahlquist A, Törmä H & Carlsson B 2004 Inefficacy of topical thyroid hormone analogue TriAc in plaque psoriasis: results of a double-blind placebo-controlled trial. *British Journal of Dermatology* **151** 489–491. (doi:10.1111/j.1365-2133.2004.06037.x)

Van Wynsberghe DM, Bhatia S & Klitgaard HM 1978 Effects of thyroxine and triiodothyroacetic acid on cerebral myelin lipids. *Life Sciences* **22** 15–18. (doi:10.1016/0024-3205(78)90405-8)

Van Zyl A 1957 Note on the effects of thyroidectomy and thyroid hormone administration on the concentration of bile cholesterol and cholic acid. *Journal of Endocrinology* **16** 213–216. (doi:10.1677/joe.0.0160213)

Verhoeven FA, Van der Putten HH, Hennemann G, Lamers JM, Visser TJ & Everts ME 2002 Uptake of triiodothyronine and triiodothyroacetic acid in neonatal rat cardiomyocytes: effects of metabolites and analogs. *Journal of Endocrinology* **173** 247–255. (doi:10.1677/joe.0.1730247)

Visser TJ 1994 Sulfation and glucuronidation pathways of thyroid hormone metabolism. In *Thyroid Hormone Metabolism: Molecular Biology and Alternate Pathways*, pp 85–117. Eds SY Wu & TJ Visser. Ann Arbor, MI, USA: CRC Press.

Visser TJ 1996 Pathways of thyroid hormone metabolism. *Acta Medica Austriaca* **23** 10–16.

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.

Visser TJ 2007 Thyroid hormone transporters. *Hormone Research* **68** (Supplement 5) 28–30. (doi:10.1159/000110469)

Visser WE, Vrijmoeth P, Visser FE, Arts WF, van Toor H & Visser TJ 2013 Identification, functional analysis, prevalence and treatment of monocarboxylate transporter 8 (MCT8) mutations in a cohort of adult patients with mental retardation. *Clinical Endocrinology* **78** 310–315. (doi:10.1111/cen.12023)

Wagner RL, Huber BR, Shiau AK, Kelly A, Cunha Lima ST, Scanlan TS, Apriletti JW, Baxter JD, West BL & Fletterick RJ 2001 Hormone selectivity in thyroid hormone receptors. *Molecular Endocrinology* **15** 398–410. (doi:10.1210/mend.15.3.0608)

Wang LH, Zakim D, Rudolph AM & Benet LZ 1986 Developmental alterations in hepatic UDP-glucuronosyltransferase. A comparison of the kinetic properties of enzymes from adult sheep and fetal lambs. *Biochemical Pharmacology* **35** 3065–3070. (doi:10.1016/0006-2952(86)90387-4)

Wang S, Zhang S, Zhao B & Lun L 2009 Up-regulation of C/EBP by thyroid hormones: a case demonstrating the vertebrate-like thyroid hormone signaling pathway in amphioxus. *Molecular and Cellular Endocrinology* **10** 57–63. (doi:10.1016/j.mce.2009.08.024)

Wilkinson JH 1957 Recent work on thyroid hormones. *Postgraduate Medical Journal* **33** 333–337. (doi:10.1136/pgmj.33.381.333)

Wilkinson JH 1959 The biological action of substances related to thyroxine. 11 Acetic acid analogues of thyroxine and tri-iodothyronine. *Biochemical Journal* **73** 334. (doi:10.1042/bj0730334)

Wood WJ, Geraci T, Nilsen A, DeBarber AE & Scanlan TS 2009 Iodothyronamines are oxidatively deaminated to iodothyroacetic acids in vivo. *Chembiochem* **10** 361–365. (doi:10.1002/cbic.200800607)

Wu SY, Cohen RN, Simsek E, Senses DA, Yar NE, Grasberger H, Noel J, Refetoff S & Weiss RE 2006 A novel thyroid hormone receptor-beta mutation that fails to bind nuclear receptor corepressor in a patient as an apparent cause of severe, predominantly pituitary resistance to thyroid hormone. *Journal of Clinical Endocrinology and Metabolism* **91** 1887–1895. (doi:10.1210/jc.2005-2428)

Wu SY, Polk DH, Huang WS, Ho E, Kattan JM & Fisher DA 2008 3′-Monoiodothyronine sulfate and Triac sulfate are thyroid hormone metabolites in developing sheep. *Pediatric Research* **63** 149–153. (doi:10.1203/PDR.0b013e31815f6551)

Xue J, Jia X, Li J, Gao R, Zhang F & Yang A 2015 Description of the thyroid hormone resistance syndrome illustrated by such a case, which had two different carcinomas and was mistreated with iodine-131. *Hellenic Journal of Nuclear Medicine* **18** 247–251.

Yazdanparast P, Carlsson B, Oikarinen A, Risteli J & Faergemann J 2004 A thyroid hormone analogue, triiodothyroacetic acid, corrects corticosteroid-downregulated collagen synthesis. *Thyroid* **14** 345–353. (doi:10.1089/105072504774193168)

Yazdanparast P, Carlsson B, Sun XY, Zhao XH, Hedner T & Faergemann J 2006*a* Action of topical thyroid hormone analogues analogues on glucocorticoid-induced skin atrophy in mice. *Thyroid* **16** 273–280. (doi:10.1089/thy.2006.16.273)

Yazdanparast P, Carlsson B, Oikarinen A, Risteli J, Lavin T & Faergemann J 2006*b* Action of topical thyroid hormone analogue, triiodothyroacetic acid in reversing glucocorticoid-induced skin atrophy in humans. *Thyroid* **16** 1157–1162. (doi:10.1089/thy.2006.16.1157)

Yen PM 2001 Physiological and molecular basis of thyroid hormone action. *Physiological Reviews* **81** 1097–1142.

Zada D, Tovin A, Lerer-Goldshtein T & Appelbaum L 2016 Pharmacological and BBB-targeted genetic therapies for thyroid hormone-dependent hypomyelination. *Disease Models and Mechanisms* **9** 1339–1348. (doi:10.1242/dmm.027227)

Zhang B, Zhang A, Zhou X, Webb P, He W & Xia X 2012 Thyroid hormone analogue stimulates keratinocyte proliferation but inhibits cell differentiation in epidermis. *International Journal of Immunopathology and Pharmacology* **25** 859–869. (doi:10.1177/039463201202500404)

Zhou J & Weiner H 1997 Binding of thyroxine analogs to human liver aldehyde dehydrogenases. *European Journal of Biochemistry* **245** 123–128. (doi:10.1111/j.1432-1033.1997.00123.x)

Zondek H, Leszynsky HE & Zondek GW 1956 Triiodothyroacetic acid in hypothyroidism. *Lancet* **2** 255–256. (doi:10.1016/S0140-6736(56)90946-1)

Received in final form 26 May 2017
Accepted 30 May 2017
Accepted Preprint published online 1 June 2017

http://joe.endocrinology-journals.org
DOI: 10.1530/JOE-17-0113

Published by Bioscientifica Ltd.