10 The Thyroid Hormone Axis: Its Roles in Body Weight Regulation, Obesity, and Weight Loss

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10.1 Introduction: The Hypothalamic-Pituitary-Thyroid Axis

The hypothalamus-pituitary-thyroid (HPT) axis is the central mechanism by which the body maintains thyroid hormone homeostasis (Costa-e-Sousa and Hollenberg 2012). Thyrotropin-releasing hormone (TRH) is released from neurons in the paraventricular nucleus (PVN) of the hypothalamus (Fig. 10.1) (Chiamolera and Wondisford 2009). TRH binds to the TRH receptor at the levels of the pituitary to stimulate the secretion of thyroid-stimulating hormone (TSH) (Bowers et al. 1965; Geras and Gershengorn 1982; Greer 1951; Guillemin et al. 1965, 1963; Schally et al. 1969; Shupnik et al. 1996; Yamada et al. 1995). TSH triggers the release of thyroid hormone, both the predominant prohormone thyroxine (T4) and the active form triiodothyronine (T3), from the thyroid gland into the bloodstream. The HPT axis operates in a negative feedback loop as T3 suppresses TRH and TSH at several levels including gene transcription and prohormone processing (Lechan and Hollenberg 2003; Lechan et al. 1986; Vella and Hollenberg 2009).

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10.1.1 The Regulation of Thyroid Hormone Levels

As discussed in previous chapters, TRH neurons in the PVN of the hypothalamus (PVN) are believed to represent the regulatory core of the HPT axis. Early evidence suggested impairment of TRH neurons severely affects the regulation of TSH secretion (Martin et al. 1970). Additionally, TRH is key to determining TSH bioactivity (Beck-Peccoz et al. 1985; Menezes-Ferreira et al. 1986; Nikrodhanond et al. 2006; Taylor et al. 1986). However, research has demonstrated that the pituitary can increase TSH synthesis during severe hypothyroidism, even in the absence of TRH (Nikrodhanond et al. 2006; Schaner et al. 1997; Yamada et al. 1997). Mature TRH is a tripeptide that is derived from pro-TRH by the action of prohormone convertases (Perello and Nillni 2007; Schaner et al. 1997). Remarkably, both transcription of TRH and its posttranslational processing are suppressed by T3 (Perello et al. 2006; Segerson et al. 1987; Sugrue et al. 2010).

Circulating TSH is a universally accepted biomarker of thyroid hormone action in humans. Given the tight negative regulation of TSH by thyroid hormone, a high TSH level is indicative of low T4 and T3 levels and hypothyroidism. Conversely, a low TSH measurement signals high T4 and T3 levels and hyperthyroidism. Clinicians measure TSH levels in their patients to assess their thyroid hormone status.

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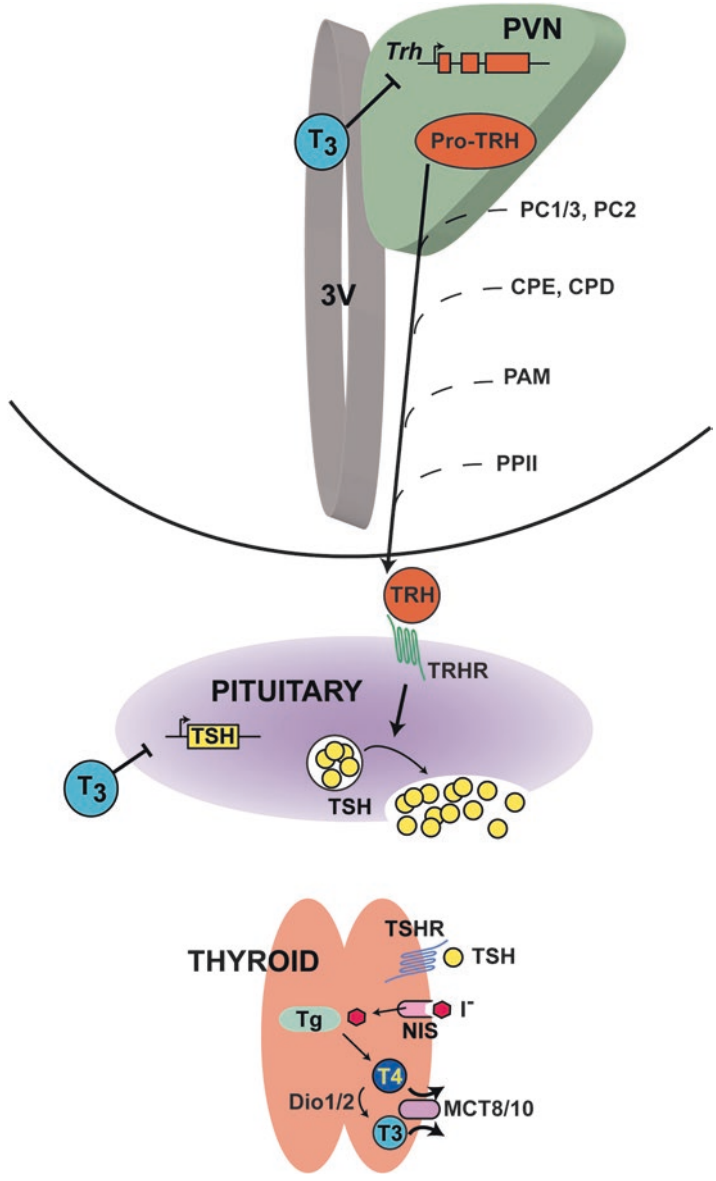

Fig. 10.1 The HPT axis is tightly regulated by a negative feedback system. Thyrotropin-releasing hormone (TRH) is transcribed and processed by several enzymes as it travels down the axon including prohormone convertases 1/3 and 2 (PC1/3 and PC2), carboxypeptidases E and D (CPE and CPD), and peptidyl-amidating monooxygenase (PAM) and pyroglutamyl peptidase II (PPII). TRH is released from the median eminence at the bottom of the hypothalamus where it binds to the TRH receptor (TRHR) and stimulates the release of thyroid-stimulating hormone (TSH). TSH circulates through the blood and binds to the TSH receptor (TSH) to facilitate thyroid hormone release from the thyroid. Iodine (I^-) is taken up by the thyroid through the sodium-iodide symporter (NIS) and pendrin (not shown) transporters. Thyroglobulin (Tg) is processed in the colloid (not shown) and coupled to I^- to create T4 and T3. Then, T4 and T3 are shuttled back into the cell, where T4 can be metabolized to T3 by deiodinases. Finally, T4 and T3 are released into the bloodstream via the monocarboxylate transporters (MCT8 or MCT10). T3 represses the transcriptional and posttranslational processing of TSH in the pituitary and TRH in the PVN of the hypothalamus

However, there are several cases where the levels of TSH in the blood do not accurately interpret T4 and T3 levels (Refetoff et al. 1993).

TSH acts on the thyroid gland to synthesize and secrete thyroid hormone (Fig. 10.1). The thyroid gland produces thyroid hormone through thyroid follicular cells (Kopp 2005). Iodine is essential to thyroid hormone. The follicular cells concentrate iodine within the colloid by using sodium-iodide symporter (NIS) and pendrin transporters. These transporters capture circulating iodine (I^-) and translocate it to the cytoplasm, where I^- is then secreted into the colloid. In the colloid, thyroglobulin incorporates iodine after the iodine is oxidized by peroxide. Iodinated thyroglobulin is then endocytosed back into the cytoplasm of the follicular cell through the actions of TSH on the TSH receptor. In the vesicles containing iodinated thyroglobulin, enzymes cleave T4 off the thyroglobulin.

The discovery of thyroid hormone transporters has challenged the previous theory that T4 and T3 passively cross cell membranes (Friesema et al. 2005). The monocarboxylate transporters 8 and 10 (MCT8 and MCT10) transport T4 and T3 into and out of the cell. MCT8 does have a preference for transporting T3. Additionally, the organic anion transporter (OATP1) and the L-type amino acid transporter (LAT) also transport thyroid hormones across membranes. OATP1 preferentially transports T4 and rT3, whereas LAT transports both T4 and T3 at a lower affinity. Mutations in MCT8 have been found in patients with the Allan-Herndon-Dudley syndrome (AHDS) (Friesema et al. 2010). AHDS is an X-linked disorder. In addition to neurological complications, hypotonia and muscle hypoplasia, patients with AHDS exhibit abnormal thyroid function tests including normal TSH, low free T4, and high levels of circulating T3. The primary structure of MCT8 forms 12 transmembrane subunits that facilitate the bidirectional transport of T3 in favor of its gradient of concentration (Friesema et al. 2010). Interestingly, dimerization of MCT8 also appears to be necessary for its function.

In the bloodstream, T4 and T3 circulate attached to serum proteins including thyroxine-binding globulin (TBG), transthyretin (TTR), thyroglobulin (TBG), and albumin (Benvenga et al. 1994). A small fraction of circulating T_4 is free (FT_4) to be transported into the cytoplasm. Once in the cells of the target tissue, T4 is converted into the bioactive hormone T3 by either the type 1 or type 2 iodothyronine deiodinase (Dio1 or Dio2) (St Germain et al. 2009). Indeed, the deiodinases ultimately regulate intracellular availability of T3. These enzymes are expressed in a tissue-specific pattern where Dio1 is the predominant form in the liver and kidney and Dio2 is expressed in the central nervous system, pituitary, brown adipose tissue, and muscle. Dio1 and Dio2 metabolize T4 to its active form T3 by outer-ring deiodination. T3 binds to thyroid hormone receptors in the nucleus to activate or suppress gene transcription.

T3 and T4 can be inactivated and metabolized by several mechanisms locally in the cell including inner ring deiodination by the type 3 deiodinase (Dio3), glucuronidation, and sulfation. In adults, Dio3 is expressed at low levels in all tissues that rely on thyroid hormone, but Dio3 is particularly active during fetal development (Gereben et al. 2015). It degrades T4 into reverse T3 (rT3) and T3 to 3,3′-T2. Dio3 plays a role in the developing cochlea by preventing the premature response to thyroid hormone (Ng et al. 2004, 2009). Silencing D3 in zebrafish during development results in delayed hatching, significantly smaller size, and decreased inflation of the swim bladder (Heijlen et al. 2014).

Sulfation and glucuronidation are phase II detoxification reactions, which increase the water solubility of thyroid hormone to facilitate its clearance through the urine or bile, respectively. Sulfotransferases tag T4 and T3 with a sulfate (T4S and T3S) (Visser 1996). These conjugates are rapidly degraded by Dio1 and then excreted through the urine (Mol and Visser 1985). UDP-glucuronosyltransferases transfer the glucuronic acid component of uridine diphosphate glucuronic acid to T3 and T4 such that thyroid hormone can be excreted through the bile and then

feces (Vansell and Klaassen 2001, 2002). Sulfatransferases and glucuronidases are regulated by several factors including thyroid hormone, fasting, and xenobiotics (Maglich et al. 2004; Qatanani et al. 2005; Visser 1996).

10.1.2 The Role of Thyroid Hormone in Gene Regulation

At the level of transcription, rodents and humans possess two different thyroid hormone receptor-encoding genes termed THRA and THRB. The THRA locus is located on human chromosome 17 and expresses two major isoforms, TRα1 and TRα2. These two isoforms differ at their C-terminal region due to the presence of an alternative exon and only TRα1 binds T3 (Lazar 1993). The THRB locus on chromosome 3 also leads to the expression of two major isoforms TRβ1 and TRβ2 who differ at their amino-termini based upon alternative exon use. Both of the TRβ isoforms bind T_3.

TRα1 and TRβ differ in their tissue expression, but they are homologous in function and their molecular structure is conserved in across species (Brent 2012). All thyroid hormone-binding TR isoforms contain three domains that include highly conserved DNA and ligand-binding domains. The most diverse region of the TR isoforms is the amino-terminal or A/B domains, whose functions have not been well clarified. The thyroid hormone receptors are ligand-activated transcription factor that exist in the nucleus in the presence and absence of thyroid hormone.

To study the functions of the different TR isoforms, researchers have relied on studying knockout mouse models and resistance to thyroid hormone syndrome (RTH) in humans. Mouse knockout studies have demonstrated a unique role for the TRβ isoforms in the regulation of TSH production by the pituitary (Abel et al. 2001; Forrest et al. 1996; Forrest and Vennstrom 2000; Ng et al. 2015). Additionally, the TRβ2 isoform plays a specialized role in the retina allowing for the expression of the opsin photopigments in the retina of mice and thus allowing color vision development (Ng et al. 2001). Interestingly, both TRβ isoforms are important in cochlear development and accordingly hearing development, while TRβ1 is required for adult hearing (Forrest et al. 1996; Ng et al. 2015). In the liver, the TRβ1 isoform is the principal mediator of thyroid hormone action, particularly in mediating cholesterol metabolism (Gullberg et al. 2000, 2002). Similarly, both isoforms target thyroid hormone action in the brain, but TRα1 has clear actions in hypothalamic neurons that regulate sympathetic function (Mittag et al. 2013). TRα1 has the majority of actions in the skeleton, heart, and intestine, but TRβ1 may play a role in certain cell types in these tissues. Taken together, mouse genetic studies have well outlined the actions of the TR isoforms. However, studies using global knockouts of the TR isoforms have their limitations and conditional alleles will allow for the tissue and cell-specific functions of the TR isoforms.

In humans, there are two distinct RTH syndromes due to mutations in the respective TR isoforms. RTHβ was first described in the late 1960s and identified as being secondary to mutations in the TRβ isoforms in the 1980s. Patients with RTHβ present with inappropriately high TSH secretion in the face of elevated thyroid hormone levels proving that this isoform regulates the hypothalamic-pituitary-thyroid (HPT) axis (Refetoff et al. 1993). The clinical signs and symptoms of the disorder align with the TR isoform tissue distribution including goiter. Although TRβ-expressing tissues such as the liver and pituitary are resistant to thyroid hormone, TRα-expressing tissues such as the heart and skeleton sense elevated circulating thyroid hormone levels and are hyperthyroid. As such, RTHβ patients have tachycardia and short stature. Some of the clinical findings in RTHβ may be the result of a combination of effects of resistant TRβ signaling and activated TRα signaling such as attention deficit hyperactivity syndrome (Refetoff et al. 1993).

With the help of mice expressing TRα mutations to model RTHα, TRα isoform mutations and RTHα were not identified in humans until 2012 (Bochukova et al. 2012; Kaneshige et al. 2001).

The first TRα patient had features consistent with relative hypothyroidism in TRα-expressing tissues including a skeletal phenotype, short stature, constipation, bradycardia, and neurodevelopmental issues. All of the TRα mutations found to date impair T3 binding and lead to the recruitment of a repressive complex that cannot be released. Certain features like macrocephaly and constipation tend to be uniform across all TRα mutations. Strikingly, mutations in regions of TRα that are common to both the TRα1 and TRα2 isoforms have not revealed any unique biochemical or syndrome-specific features, which suggests that TRα2 may not play an important role in thyroid hormone action.

The TR transcriptional complex recruits coregulatory factors including the corepressors nuclear receptor corepressor 1 (NCoR1) and silencing mediator for retinoid or thyroid hormone receptors (SMRT, also known as NCoR2) and the coactivators SRC-1, SRC-2, and SRC-3 (Alland et al. 1997; Halachmi et al. 1994; Heinzel et al. 1997; Lonard and O'Malley B 2007; Nagy et al. 1997; Onate et al. 1995). Both NCoR1 and SMRT interact with the TR isoforms via C-terminal domains, the nuclear receptor interacting domains (RIDs) (Hu and Lazar 1999; Nagy et al. 1999; Perissi et al. 1999). However, NCoR1 prefers to interact with the TR via its more N-terminal RIDs. The steroid receptor coactivators 1, 2, and 3 (SRC-1, SRC-2, and SRC-3) share structural homology but appear to have a variety of different functions (Lonard and O'Malley B 2007). The SRCs interact with liganded nuclear receptors including the TR isoforms via a central interacting domain that contains a number of LxxLL motifs. A previous study demonstrated that the SRC isoforms can interact with the TRβ2 amino-terminus and that this interaction could be important in thyroid hormone action (Yang and Privalsky 2001). Like the corepressors, members of the SRC family can be differentially expressed in a variety of cell types. Additionally, they play nonredundant roles in physiology with SRC-1 having the most significant role in thyroid hormone action (Vella et al. 2014; Weiss et al. 1999, 2002). Numerous other proteins with coactivator-like activity have been identified and can interact with the TR isoforms, but their roles in thyroid hormone action remain to be determined.

The roles of co-regulators in thyroid hormone action first came to light in the SRC-1 KO mice. Among other steroid receptor signaling deficits, SRC-1 KO mice have RTH elevated TSH levels in the presence of elevated circulating thyroid hormone levels (Weiss et al. 1999, 2002). Until conditional alleles were generated, the roles of NCoR1 and SMRT in vivo were impossible to determine because deleting either paralog led to embryonic lethality (Jepsen et al. 2000, 2008). To address the role of NCoR1 in thyroid hormone action, Astapova et al. developed a mouse model that expressed a Cre-driven hypomorphic NCoR1 allele (NCoRΔID), which lacked the two principal RIDs that interacted with the TR (Astapova et al. 2008). These liver-specific L-NCoRΔID mice had a number of derepressed hepatic TRβ1 targets in the hypothyroid setting consistent with the classic role predicted for NCoR1. A global NCoRΔID mouse had low levels of circulating T4 and T3 with normal TSH levels and normal levels of TRH mRNA in the hypothalamus (Astapova et al. 2011). NCoRΔID mice were not small and had evidence of increased energy expenditure. Furthermore, T3 targets in the liver had normal expression. Thus, global removal of a functional NCoR1 molecule in vivo appears to increase sensitivity to thyroid hormone at the level of the HPT axis and the liver.

Combining the contrasting roles of SRC-1 and NCoR in managing thyroid hormone levels, Vella et al. developed a mouse model that combined both of these genetic alterations (Vella et al. 2014). As expected, deletion of SRC-1 led to RTH at the level of the HPT axis. When NCoRΔID was introduced on this background, normal thyroid hormone sensitivity was reestablished. In the liver, positively regulated T3 target genes in SRC-1 KO/NCoRΔID mice had normal sensitivity and response to T3.

While the in vivo models have clarified the role of co-regulators in thyroid hormone action, many questions remain. Key insight into co-regulator function has only been established in the HPT axis and in the liver. The role of co-regulators in other thyroid hormone-responsive tissues remains unknown.

10.2 Thyroid Hormone's Role in Body Weight Regulation

The interplay between thyroid disease, body weight, and metabolism has been studied for a long time in both humans and other vertebrates (Barker 1951; Du Bois 1936). Indeed, the first studies linking thyroid hormone and energy expenditure were conducted over 100 years ago by Magnus-Levy starting in 1895 (Mangus-Levy 1895). Metabolism or energy expenditure (EE) can be defined by the amount of oxygen used by the body over a specific amount of time. Resting energy expenditure (REE) is the energy required to maintain basic cell and organ function while the body is at rest. Prior to thyroid function tests (measurement of T4, T3, and TSH), REE was one of the earliest indications to test a patient's thyroid status. Poor thyroid gland function was associated with low REE, whereas overactive thyroid gland function was associated with high REE (Fig. 10.2). Upon further study when thyroid hormone measurements were available, it was found that low thyroid hormone levels are linked to low REE and conversely high thyroid hormones linked to high REE. Due to the complexity of the test and the number of factors that can affect REE, testing REE to determine thyroid function is no longer a favorable test.

Hypothyroidism is a disease marked by low T4 and T3 and higher TSH. There are several diseases that can lead to hypothyroidism including an autoimmune disease such as Hashimoto's thyroiditis, where the immune system attacks the thyroid gland. Other causes of hypothyroidism include too little or too much iodine in the diet, illness, medicines, congenital hypothyroidism, and treatments for thyroid disease and thyroid cancer where the thyroid is surgically removed or treated with radioactive iodine (I-131). Hypothyroidism has long been associated with a small weight gain, usually about 5–10 pounds. This is due to the lower REE in patients with hypothyroidism. In cases of severe hypothyroidism, the weight gain is often greater. The cause of the weight gain in hypothyroid individuals is also complex and can be attributed to several factors including excess fat accumulation or excess accumulation of salt and water. Interestingly, thyroid hormone levels have no root cause in the

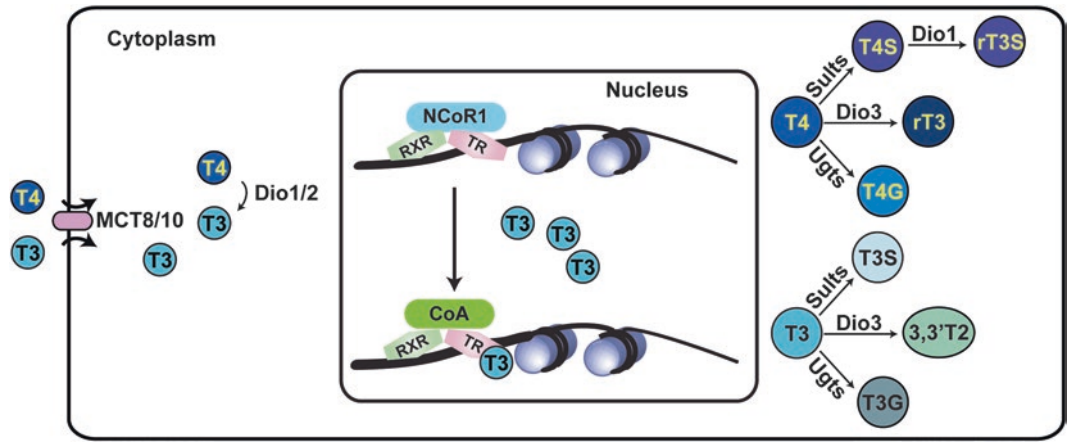

Fig. 10.2 At the cellular level, T4 and T3 enter through thyroid hormone transporters such as the monocarboxylate transporters (MCT8, MCT10). T4 is converted in the bioactive thyroid hormone, T3. Once in the nucleus, T3 binds to the thyroid hormone receptor to recruit transcriptional machinery on positive T3 target genes including coactivators like SRC-1. In the absence of T3, transcriptional repression machinery is recruited as TR binds NCoR1 or other corepressors. The TR forms dimers, sometimes with RXR. T4 and T3 are metabolized by several factors including the type 3 deiodinase (Dio3). Dio3 converts T4 into reverse T3 (rT3) and T3 into 3,3'T2. Sulfotransferases tag T4 and T3 with sulfates. T4S is converted to rT3S by Dio1. Sulfation of thyroid hormone increases its solubility and excretion via urine (T4S, rT3S, and T3S). UDP-glucuronosyltransferases (Ugts) increase thyroid hormone solubility and excretion through the bile and feces (T4G and T3G)

obesity and weight gain seen in modern times. However, a study comparing treatment of hypothyroid patients with T3 demonstrated significant weight loss and reduction in total cholesterol without adverse cardiovascular outcomes (Celi et al. 2011).

In hyperthyroidism, T4 and T3 are elevated thus elevating REE. Weight loss can be a symptom as patients can experience elevated body temperature and increased REE despite increased food intake in some cases. Severe cases of hyperthyroidism can cause extreme weight loss. Graves' disease is a cause of hyperthyroidism, where the immune system causes overstimulation and growth of the thyroid. Other possibilities include goiter and a temporary condition called thyroiditis, which is normally linked to a viral infection.

Given the small influence of thyroid disease on body weight, the focus of this next chapter will be on the effects of thyroid hormone on whole body metabolism, how it influences EE, and how researchers hope to harness its effects as a treatment for obesity.

10.2.1 Thyroid Hormone Has Direct and Indirect Effects on Metabolism

At the cellular level, thyroid hormone has effects on several processes including glycolysis and glucogenesis, fatty acid oxidation and lipogenesis, and protein turnover (Mullur et al. 2014; Vaitkus et al. 2015). With a small effect on EE, thyroid hormone has been shown to reduce reactive oxygen species while increasing energy expenditure (Grant 2007). Additionally, thyroid hormone has been shown in increase ion leakage over the cellular membrane through the Na+/K+ ATPase ion leak and the sarco/endoplasmic reticulum Ca^{2+} ATPase (Haber et al. 1988; Silva 2006).

Thyroid hormone has a large effect on stimulating mitochondrial biogenesis through several mechanisms including effects on mitochondrial genes like cytochrome c, promoting mitochondria gene transcription through p43, p28, and a truncated TRα1 and establishing a positive feedback loop in which thyroid hormone increases nuclear expression of intermediate factors that in turn increase mitochondrial transcription such as PGC-1α (Psarra et al. 2006; Rodgers et al. 2008; Thijssen-Timmer et al. 2006; Wrutniak et al. 1995; Wulf et al. 2008). Thyroid hormone can also work within the mitochondria in processes like non-shivering thermogenesis. Here chemical energy is converted directly into heat. Thyroid hormone plays an important role in the regulation of uncoupling protein 1 (UCP1), which renders the inner membrane of the mitochondria permeable to electrons and allows for the generation of heat. UCP1 is expressed primarily in brown adipose tissue (BAT). Until recently, human BAT was thought to only exist in infants and not significant in adults. Recent PET and CT imaging studies have shown a significant amount of BAT exists in adults, especially in the subscapular and chest region (Cypess et al. 2009; van Marken Lichtenbelt et al. 2009).

Fatty acid oxidation, the catabolic breakdown of fatty acids in the cell, is regulated in part by thyroid hormone. In the heart, thyroid hormone has been shown to affect carnitine/acylcarnitine transporter (CACT), the mitochondrial carrier protein involved in fatty acid metabolism (Paradies et al. 1996). In hyperthyroid rats, researchers found an increased rate of palmitoylcarnitine/carnitine exchange and increased fatty acid oxidation in heart mitochondria. In hypothyroid rats, fatty acid oxidation is reduced in rat heart mitochondria due to a decreased CACT activity. Hypothyroid rats supplemented with T3 restored normal CACT activity (Paradies et al. 1997). In the liver, T3 stimulates several genes involved with fatty acid oxidation including in the transcription of carnitine palmitoyltransferase 1 (CPT1) gene (Flores-Morales et al. 2002; Jackson-Hayes et al. 2003; Santillo et al. 2013). CPT1 transforms fatty acids to carnitine esters when it is localized to the outer mitochondrial membrane. Also in the liver, thyroid hormone stimulates the citrate carrier (CiC) gene expression and activity, another inner mitochondrial

membrane carrier protein (Giudetti et al. 2006; Paradies and Ruggiero 1990). More work has to be done to determine how T3 influences the fatty acid oxidation process, especially in terms of carrier gene expression and activity.

Thyroid hormone has been shown to stimulate gluconeogenesis, the metabolic process that generates glucose from substrates such as lactate, glycerol, and glucogenic amino acids. Thyroid hormone treatment increases genes involved in gluconeogenesis including phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting step in gluconeogenesis (Park et al. 1999). In the liver, PEPCK mRNA was stimulated 3.5-fold in hyperthyroid rats (Klieverik et al. 2008). The affect of thyroid hormone on liver gluconeogenesis might have a central component as administration of T3 to the PVN of the hypothalamus in rats increased glucose production (Klieverik et al. 2009).

Cholesterol synthesis can be regulated by thyroid hormone through multiple mechanisms. Thyroid hormone stimulates the low-density lipoprotein receptor (LDLR) gene, which increases uptake of cholesterol and enhanced cholesterol synthesis (Lopez et al. 2007). Patients with hypothyroidism experience mild to severe hypercholesterolemia (Klein and Danzi 2007; Thompson et al. 1981). Thyroid hormone replacement reverses the increased serum levels of cholesterol (Klein and Danzi 2007). Thyroid hormone also regulates cholesterol through the sterol response element-binding protein (SREBP)-2, which regulates LDLR (Goldstein et al. 2006). SREBP-2 is a member of the transcription factor family that regulates glucose metabolism, fatty acid synthesis, and cholesterol metabolism. In hypothyroid rats, SREBP-2 mRNA is suppressed, but this is reversed when T3 levels are restored (Shin and Osborne 2003).

The physiological benefit of thyroid hormone is multicellular and across most tissues. Indeed, hypothyroidism is linked to poor gluconeogenesis, fatty acid oxidation, and cholesterol synthesis. Treatment with thyroid hormone reverses these conditions. As obesity and metabolic syndrome have similar deficits as above, there is great potential in thyroid hormone or thyroid hormone analogs as therapeutics.

10.2.2 Thyroid Hormone as a Treatment for Obesity

Due to thyroid hormone's effects on metabolism, researchers asked if it would be a potential therapeutic for obesity and dyslipidemia. While T3 has many beneficial effects, supraphysiologic thyroid hormone levels induce tachycardia, bone loss, muscle wasting, and neuropsychiatric disturbances (Burch and Wartofsky 1993). Several have pursued thyroid hormone derivatives that are tissue or TR isoform specific with hopes that this would affect metabolism and have no response in the heart and bone. The synthetic thyroid hormone analog GC-1 (sobetirome) has been shown to prevent or reduce hepatosteatosis and reduce serum triglyceride levels and cholesterol levels without significant side effects on heart rate (Perra et al. 2008; Trost et al. 2000). In a separate study, GC-1 has been shown to increase EE and prevent fat accumulation in female rats (Villicev et al. 2007). Another thyroid hormone analog MB07811 exhibits increased TR activation in the liver and reduces hepatic triglyceride levels and increases hepatic fatty acid oxidation in both chow-fed and high-fat diet rodent models (Cable et al. 2009; Erion et al. 2007). In human clinical trials, MB07811 reduced LDL cholesterol and triglyceride levels without severe adverse effects (Baxter and Webb 2009).

Thyroid hormone derivatives including 3,3′,5-triiodothyronine (rT3), thyronamines (TAMs), and 3,5-diiodothyronine (T2) have been found to have some effects on body weight in rodents. The effects of TAMs, primarily 3-iodothyronamine (3-T1 AM) and thyronamine (T0 AM), have been studied in rodent and include hypothermia, reduction in energy expenditure, hyperglycemia, and reduction of fat mass (Piehl et al. 2011). Studies using rT3 in rodents have found that it can enhance actin cytoskeleton repair in neurons and astrocytes in the hypothalamus following a hypothyroid-induced decline (Farwell et al. 1990; Siegrist-Kaiser et al. 1990). Also, studies in chickens revealed that rT3 inhibits the surge in free fatty acids seen after treatment with dexamethasone or adrenaline (Bobek et al. 2002). A larger number of studies have been

done using T2. T2 will stimulate mitochondrial activity and elevate resting EE in rats (Lombardi et al. 1998; Moreno et al. 1997). In high-fat diet rat models, T2 administration prevented hepatosteatosis, insulin resistance, and obesity while stimulating mitochondrial uncoupling (Grasselli et al. 2008; Lanni et al. 2005; Mollica et al. 2009; Moreno et al. 2011). When T2 was administered in human studies, euthyroid subjects had a significant elevation in REE, reduced body weight, and normal thyroid and cardiac function (Antonelli et al. 2011).

Thyroid hormone analogs and alternatives show some promise as obesity therapeutics. GC-1 and T2 both challenge EE and have beneficial effects in the liver. However, more studies must be done to determine efficacy and safety of TAMs, rT3, and MB07811.

10.3 The Effects of Weight Loss on Thyroid Hormone

As global obesity rates rise, understanding the complex neurocircuitry regulating energy expenditure is increasingly pivotal to finding preventative measures and therapies. Thyroid hormone levels affect the molecular mechanisms governing basal metabolic rate, energy expenditure, and temperature regulation. Individuals trying to lose weight experience a decrease in thyroid hormone, both the prohormone, thyroxine (T4), and the bioactive form, triiodothyronine (T3) (Katzeff et al. 1990). This is accompanied by decreases in leptin levels, energy expenditure, and sympathetic nervous system tone (Rosenbaum et al. 2002, 2005). These effects are counterproductive to weight loss maintenance. Thyroid hormone replacement alleviates these effects but has ramifications including muscle wasting, atrial fibrillation, and osteoporosis. Understanding the molecular mechanisms that regulate thyroid hormone will uncover therapeutic targets that alleviate metabolic disorders and assist in weight loss maintenance.

In rodents, a similar physiology exists where T4 and T3 are suppressed following 24–48 h of fasting along with reduced energy expenditure (Ahima et al. 1996; Connors et al. 1985; Legradi et al. 1997). Indeed, the entire hypothalamic-pituitary-thyroid axis is suppressed in fasted rodents including thyrotropin-releasing hormone (Trh) mRNA in the paraventricular nucleus of the hypothalamus and thyroid-stimulating hormone (TSH) in the pituitary (Blake et al. 1991, 1992; Spencer et al. 1983). In previous studies, melanocortin and neuropeptide Y (NPY) signals are important for communicating fasting signals to the hypothalamic-pituitary-thyroid (HPT) axis (Bjorbaek and Hollenberg 2002; Fekete et al. 2000, 2001, 2002; Legradi and Lechan 1998). Using NPY/melanocortin 4 receptor ($Npy^{-/-}Mc4r^{-/-}$) whole-body double-knockout mice, NPY was found necessary to suppress the hypothalamic-pituitary-thyroid (HPT) axis during fasting (Vella et al. 2011).

In an association study between TSH and cardiometabolic risk factors in $n = 1167$ euthyroid adolescents, TSH was found to strongly correlate with BMI, systolic blood pressure, total cholesterol, high fasting glucose, and insulin resistance (Le et al. 2016). Additionally, the free T3 to free T4 ratio was found to correlate with BMI, systolic blood pressure, triglycerides, fasting glucose, and insulin resistance suggesting that this ratio could be a useful marker of higher cardiometabolic risk. This study highlights again that although T4 and T3 are not altered with obesity in adults and adolescents, other factors that are regulated by T4 and T3 are altered including TSH. This suggests that while homeostatic T4 and T3 are normal, their physiological functions may be impaired in obesity (Fig. 10.3).

Several studies have explored the relationship between weight loss and decreased thyroid hormone levels. Indeed, in adults following a 10% body weight loss and reduced leptin levels, thyroid hormone levels, REE, sympathetic and parasympathetic nervous system tone, and TSH are all suppressed 20–30% (Katzeff et al. 1990; Rosenbaum et al. 2002, 2005). This is counterproductive to the maintenance of weight loss. Interestingly, leptin replacement restores sympathetic nervous system

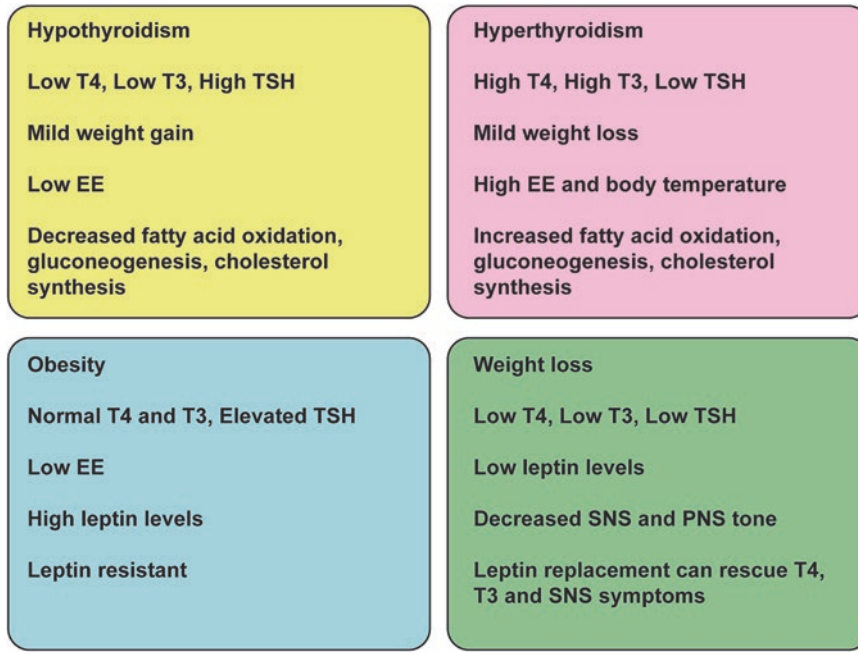

Fig. 10.3 A summary of the differences in thyroid hormone and TSH levels, body weight levels, energy expenditure, leptin levels, and thyroid hormone-responsive cellular functions like fatty acid oxidation, gluconeogenesis, and cholesterol synthesis between hypothyroidism, hyperthyroidism, obesity, and weight loss

tone and T3 and T4 levels, but not parasympathetic nervous system tone or TSH levels to pre-weight loss levels. The incomplete reversal of the weight- reduced phenotype following leptin repletion suggests that there are non-leptin-dependent mechanisms affected by weight loss. Further study is required to understand what causes the decrease in thyroid hormone levels? Is it just centrally? Or are thyroid hormone metabolic mechanisms activated in peripheral tissues? If peripheral mechanisms are activated, are they also responsive to leptin? Furthermore, how does leptin rescues thyroid hormone levels and sympathetic nervous system tone? Is this centrally through the hypothalamus or through some peripheral tissue? Studies have shown that thyroid hormone levels can still be suppressed 2–5 years following weight loss. Is leptin a long-term therapeutic for weight loss? Or will leptin resistance develop? Are there other methods for elevating thyroid hormone after weight loss?

10.4 Conclusions

Research continues to understand the relationships between thyroid hormone, body weight, and energy expenditure. Indeed there is a link between the central axis and whole body weight maintenance. Thyroid hormone has direct and indirect effects on mitochondrial function, gluconeogenesis, and fatty acid oxidation. While T3 is a poor therapeutic due to complications in the heart, muscle, and bone, thyroid hormone analogs and metabolites have promise as treatments in obesity. GC-1 and T2 have been shown to prevent hepatosteatosis and promote weight loss. While there is little evidence to support hypothyroidism as a cause of obesity, thyroid hormone does play a very important role in the maintenance of weight loss and this is directly linked to leptin. Future studies should explore this further as this would help the 75–80% of individuals who regain weight after weight loss.

Review Questions

1. Describe the mechanisms by which HPT axis is a negative feedback loop. Are there conditions when this negative feedback is disrupted (i.e., low thyroid hormone levels, low TRH and TSH)?
2. Are hypothyroidism and hyperthyroid strongly associated with large changes in body weight?
3. Thyroid hormone has diverse effects in many tissues in the body. Describe how the thyroid hormone works in the mitochondria and how this affects energy expenditure.
4. Weight loss in humans results in decreases in thyroid hormone levels among others. Is there a rodent model in which this can be studied?
5. What are the detrimental effects of supplementing with T3? What are the beneficial effects?

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