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Journal of Endocrinology, Diabetes & Obesity

Mini Review

Role of Thyroid Hormone in Adipocyte Physiology and Metabolism

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Abstract

Adipose tissue composed predominantly of adipocytes (differentiated fat cells) serves as a lipid storage and endocrine organ. It plays a major role in lipid metabolism and glucose homeostasis. Thyroid hormones have been known for years to play a significant role in energy expenditure and adaptive thermogenesis via the brown adipose tissue, while its role in white adipose tissue has been less investigated. In this review we will elucidate what is known so far on the role of thyroid hormone in regulating metabolism and energy homeostasis in both white and brown adipocytes.

Special Issue on

Role of Thyroid Hormone in Metabolic Homeostasis

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Submitted: 12 June 2014

Accepted: 17 July 2014

Published: 19 July 2014

ISSN: 2333-6692

Keywords

- Thyroid hormone
- Adipose tissue
- Lipid metabolism
- Energy balance

ABBREVIATIONS

WAT: White Adipose Tissue; BAT: Brown Adipose Tissue; TH: Thyroid Hormone; TR: Thyroid Hormone Receptor; T_3: Triiodothyroxine; T4: levothyroxine; TRH: Thyrotropin-Releasing Hormone; TSH: Thyroid Stimulating Hormone; D1: Type 1 Deiodinase; D2: Type 2 Deiodinase; D3: Type 3 Deiodinase; DIO2: Gene Encoding Type 2 Deiodinase; NCoR1: Nuclear Receptor Corepressor; SMRT: Silencing Mediator Of Retinoid and Thyroid Hormone Receptor; TRE: Thyroid Hormone Response Element; UCP1: Uncoupling Protein 1; C/EBPα: CCAAT/ Enhancer Binding Protein Alpha; PPARγ: Peroxisome Proliferator Activated Receptor; GAPDH: Gamma Glyceraldehyde-3-Phosphate Dehydrogenase; ME: Malic Enzyme; ACC: Acetyl Coa Carboxylase; FAS: Fatty Acid Synthase; PGC1: PPARγ Coactivator; HDAC: Histone Deacetylasecorepressor; SRC1: Steroid Hormone Receptor 1; LPL: Lipoprotein Lipase; TG: Triglycerides; FFA: Free Fatty Acids; HSL: Hormone-Sensitive Lipase; FA: Fatty Acid; S14: Spot 14; TSHR: TSH Receptor; VAMP2: Vesicle-Associated Membrane Protein 2; GLUT4: Glucose Transporter 4; IRS-1: Insulin Receptor Substrate 1; PI3- Kinase:Phosphoinositide3 Kinase; SAT: Subcutaneous Adipose Tissue; VAT: Visceral Adipose Tissue; SNS: Sympathetic Nervous System; AMPK: AMP-Activated Protein Kinase

INTRODUCTION

Metabolic regulation is vital in maintaining cellular and organismal homeostasis and health. When environmental changes within an organism are detected, metabolic pathways are controlled at different levels to restore stable conditions. For example, as blood glucose levels peak after a meal, the insulin hormone is secreted into the blood stream to bind to insulin receptors on muscle and fat cells which signal translocation of glucose transporters to the plasma membrane to increase glucose uptake. Glucose is subsequently stored as glycogen or fatty acid for later use, and when blood glucose levels plummet, glucagon acts in the opposite manner to signal the release of glucose, and raise blood sugar [1]. Obesity, or excess body fat, increases the likelihood of acquiring type 2 diabetes and other metabolic imbalances, such as high blood pressure, high cholesterol, and high triglycerides [2-4].

Adipocytes, fat cells, are traditionally known for storing and releasing triglycerides in response to energy imbalances, but have more recently been recognized to play a key role in metabolic regulation [5]. Adipocytes produce and secrete several proteins called adipokines with endocrine, autocrine, and paracrine function that regulate physiological processes [6]. Leptin is an adipokine produced in proportion to body fat that signals satiety by binding to receptors in the hypothalamus of the brain [7,8]. Adipocytes are divided into two categories: white adipocytes that store fat, and brown adipocytes that burn fat. White Adipose Tissue (WAT) consists of white adipocytes which store triglycerides in large lipid droplets and have very few mitochondria; Brown Adipose Tissue (BAT) consisting of brown fat cells have several small lipid droplets, and many mitochondria that are rich in Uncoupling Protein 1 (UCP1). UCP1 allows the brown adipocytes to uncouple cellular respiration to release energy as heat and regulate body temperature [9]. Unlike white fat, brown fat found predominantly in human newborns and small mammals may be protective against obesity, although it is not very abundant in adult humans [10]. Adipocytes express receptors for hormones that regulate adipocyte action, such as insulin, glucagon, growth hormone, thyroid-stimulating hormone as well as thyroid hormone, leptin, and more [6].

Triiodothyroxine (T3), is the active form of Thyroid Hormone (TH), and is important in metabolic regulation of all major organs. TH regulates cellular gene expression, tissue differentiation, development, and metabolism, by binding to its nuclear receptor, Thyroid Hormone Receptor (TR) [11]. In fat, T3 is involved in regulating adipogenesis, lipogenesis, lipolysis, adipokine secretion, and UCP-1 expression, among other processes [12]. The hypothalamic/pituitary/thyroid axis is responsible for TH signaling and homeostasis, and consists of the hypothalamus, pituitary and thyroid glands [12]. The hypothalamus produces Thyrotropin-Releasing Hormone (TRH) which travels from the hypothalamus to the anterior pituitary of the pituitary gland, where thyrotroph cells are stimulated to produce and release Thyroid Stimulating Hormone (TSH). TSH reaches the thyroid gland, and binds to thyroid follicular cells that signal for the production and release of thyroid hormone. However, greater quantities of the inactive form of thyroid hormone, levothyroxine (T4), than the active T3 are released. Deiodinase enzymes activate the thyroid hormone by catalyzing the removal of the additional iodine from T4 to generate T3 in target tissues.

There are three deiodinase isoforms, Type 1 (D1), Type 2 (D2), and Type 3 (D3), whose tissue specific expression regulates TR availability locally. DI catalyzes the removal of iodine from T4 to form the active T3, or the inactive, reverse T3, (rT3), and from T3 to form 3, 3'-diiodo-L-thyronine (T2). DI is found mainly in the liver, kidney, thyroid and pituitary, and is important in maintaining circulating T3 levels [13]. D2 displaces iodine from T4 to form T3, and is the major deiodinase regulating local T3 availability in target tissues such as the thyroid, central nervous system, pituitary, brown and white adipose tissue, and skeletal muscle [13-16]. D3 deactivates TH by converting T4 to rT3, or T3 to T2, and is expressed in tissues that may be harmed by excess T3 like fetal tissues, or adult placenta, brain, and skin [17].

TR is a nuclear receptor transcription factor that activates expression of specific target genes by binding the ligand T3. In the absence of T3, TR is bound to corepressors, nuclear receptor corepressor (NCoR1) and silencing mediator of retinoid and thyroid hormone receptor (SMRT), and a repression complex (including histone deacetylase activity) to inactivate transcription of genes by binding to DNA sequences containing Thyroid Hormone Response Elements (TREs) [18]. The corepressors and repression complex are released from TR when the receptor undergoes a conformational change due to T3 binding to its ligand-binding domain. The release of corepressors allows for the recruitment of coactivators that increase gene transcription of the specific target genes. Two genes, TRα and TRβ, code for the different TR iso forms, TRα1, TRα2, TRβ1, and TRβ2. TR isoforms are distributed to different tissues, and differentially regulate target genes and adipocyte metabolism [19-22].

Thyroid dysfunction can disrupt metabolic activities of all tissues. Hypothyroidism or insufficient TH can lead to weight gain, cold intolerance, and tiredness, while hyperthyroidism causes weight loss due to increased metabolic activity. This review will focus specifically on the effects of thyroid hormone on adipocyte physiology and metabolism in WAT and BAT.

MOLECULAR BASIS OF THYROID HORMONE REGULATION OF ADIPOGENESIS AND LIPID METABOLISM IN ADIPOSE TISSUES (FIGURE 1)

Adipogenesis (adipocyte differentiation) consists of an initial proliferative phase of preadipocytes (mesenchymal stem cell origin), followed by differentiation into lipid filled adipocytes. Thyroid hormone plays an important role in the adipogenesis of both white and brown adipocytes, where in general TH activity is inhibited during the proliferative phase, and increased during the differentiation phase [23]. The differentiation program progresses by sequential and coordinated gene expression. It is initiated by two master adipogenic transcription factors CCAAT/enhancer binding protein alpha (C/EBPα) and peroxisome proliferator activated receptor gamma (PPARγ) which transcribe specific lipogenic genes such as Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH), Malic Enzyme (ME), Acetyl Coa Carboxylase (ACC), Fatty Acid Synthase (FAS) [24]. TR isoforms are tissue specific and have specific roles in mediating thyroid hormone actions in adipogenesis. Mice expressing mutated TRα1 have decreased WAT [25]. TRα1 is thought to be predominantly involved in adipogenesis in both WAT and BAT [12,23]. In 3T3-L1 cell lines expressing mutated TRα1, C/EBPα and PPARγ gene expression and adipogenesis are more severely reduced than in mutated TRβ1 expressing cells [26]. Conversely in another study [27] PPARγ and C/EBPα gene expression were not affected by T_3 in 3T3-L1 cells, although T3 has been shown to regulate C/EBPα in brown adipocytes [28]. In BAT, the PPARγcoactivator (PGC1), D2 and UCP1 are induced to complete adipogenesis [12,23]. TRβ isoform is thought to play an important role in this induction.

Thyroid Hormone Receptor (TR) transcription of genes is regulated by corepressors such as NcoR1, SMRT, Histone Deacetylasecorepressor (HDAC) and coactivators such as steroid hormone receptor 1 (SRC1), and histone acetyltransferase complex [18,29,30]. TRα1 mutants aberrantly bind tightly to NcoR1, and are not able to bind the ligand T_3 to activate transcription of target genes. NcoR1 readily recruits mutated TRα1 isoform than TRβ isoform, to bind to C/EBPα promoter, to inhibit gene expression and consequently, adipogenesis [31,32]. Heterozygous mutated TRα1/+ mice display decreased WAT mass, decreased C/EBPα and PPARγ gene expression, as well as decreased adipogenesis of 3T3-L1 cells [25,26]. A genetic polymorphism in TRα is associated with development of obesity with high saturated fat diets in humans [33].

Lipid metabolism in adipocytes is dynamic due to the constant uptake and release of substrates and highly integrated with systemic energy balance. Adipocytes acquire substrates from circulating lipoproteins through the actions of Lipoprotein Lipase (LPL). LPL hydrolyzes Triglycerides (TG) into Free Fatty Acids (FFA) and glycerol to allow uptake into the fat cell. Once inside, the FFA and glycerol are esterified to form TG for storage [24]. Adipocytes can also synthesize fatty acids from acetyl-CoA to form TG through the process of lipogenesis. Lipogenesis is sensitive to nutritional changes, and responds to inhibiting hormones, like leptin, and stimulatory hormones, such as insulin [34]. Thyroid hormone regulates lipogenic enzymes, and lipogenesis, differentially in WAT, BAT, liver, and other tissues [12,35,36]. LPL-mediated lipogenesis is dependent on insulin

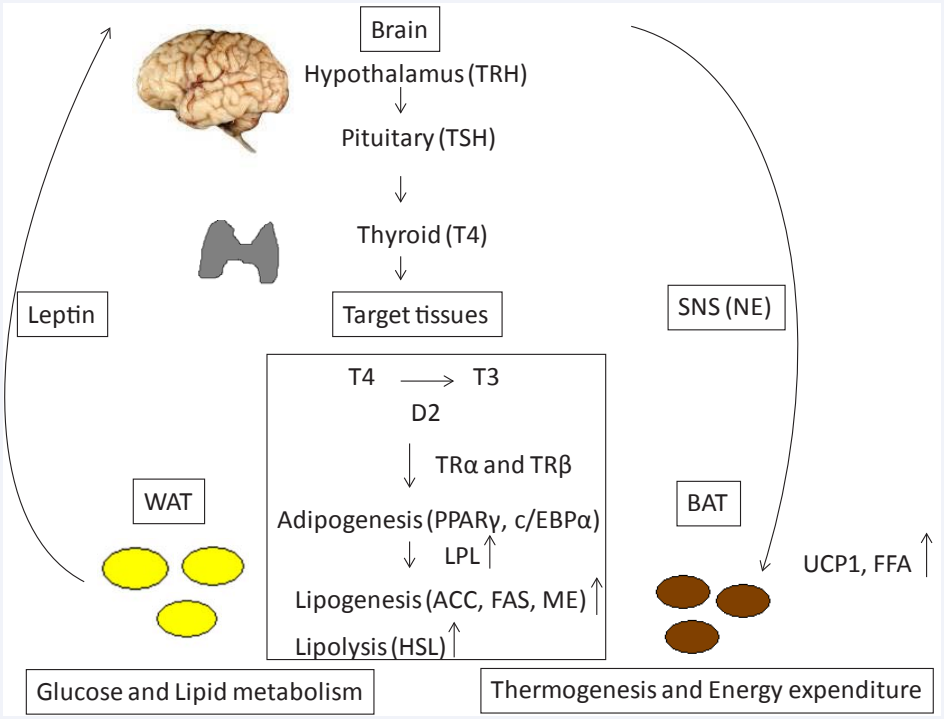

Figure 1 Thyroid hormone regulation of adipocyte function.

The hypothalamic-pituitary-thyroid axis is responsible for generating circulating levels of thyroid hormone. However deiodinases such as D2 (Type 2 deiodinase) convert the inactive thyroid hormone T_4 secreted from thyroid gland to triiodothyroxine (T_3), the active form in target tissues. T_3 binds to thyroid hormone receptor (TR α and β) in adipocytes, and regulates adipogenesis, lipogenesis, lipolysis, adipokine secretion, and energy expenditure, among other processes. Thyroid hormone receptors alpha (TRα1) mediate adipogenesis in white and brown adipocytes by increasing expression of CCAAT/enhancer binding protein alpha (C/EBPα) and peroxisome proliferator activated receptor gamma (PPARγ), master adipogenic transcription factors. c/EBPα and PPARγ, in turn, transcribe acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and malic enzyme (ME), enzymes that promote lipogenesis. Leptin is generated in proportion to WAT, and targets receptors in the hypothalamus to increase TRH gene expression, decrease appetite and increase energy expenditure. T3-bound TRβ1 and SNS act synergistically toup-regulate Free Fatty Acids (FFAs) anduncoupling protein 1 (UCP1) gene expression in Brown Adipose Tissue (BAT), increasing thermogenesis and energy expenditure. Lipid metabolism in adipocytes is dynamically balanced between lipogenesis (uptake of fatty acids from circulating lipoproteins regulated by lipoprotein lipase LPL and storage as triglycerides), lipolysis (regulated byhormone sensitive lipase, HSL which breaks down triglycerides), fatty acid oxidation and eneargy expenditure depending on systemic and local thyroid hormone milieu and whole body energy balance. Other key terms in figure: TRH-thyrotropin-releasing hormone; TSH- thyroid stimulating hormone; SNS-sympathetic nervous system; NE-norepinephrine.

levels; elevated postprandial insulin concentrations promote FFA uptake and storage of TG by adipocytes [24]. Lipolysis is the process of hydrolyzing TG into FFA and glycerol. Lipolysis of TG in adipocytes is controlled by hormone-sensitive lipase (HSL), and is essential to providing energy to other organs by releasing FFA and glycerol into circulation [35]. HSL action, TG breakdown for liberation into circulation as energy for other tissues, is suppressed by high insulin levels [37].

Most of the studies of thyroid hormone effects on lipolysis and lipogenesis have been in BAT. T3 induces early FA (fatty acid) synthesis and lipogenesis in BAT, followed later by fat oxidation and lipolysis in thermogenesis [38]. Fat specific *DIO2* (gene encoding the deiodinase, D2) knockout results in decreased fatty acid oxidation, diet induced weight and fat gain, and increases energy expenditure from carbohydrate oxidation, rather than fat oxidation in BAT [39]. In another study, targeted disruption of *DIO2* resulted in decreased BAT lipogenesis and impaired thermogenesis in cold-exposed mice [40]. This suggests the importance of thyroid hormone action in regulating the balance between lipogenesis and lipolysis in adipose tissues in energy homeostasis.

T_3 exposure increased triglyceride content and mRNA of a lipogenic enzyme GAPDH, in 3T3-L1 mouse adipocytes which express TRα1 predominantly [27]. GAPDH catalyzes the conversion of glyceraldehyde-3-phosphate to 1, 3-bisphosphoglycerate in glycolysis, the pathway that supplies metabolites for lipogenesis. In TRα knockout mice, increased plasma levels of T3 are observed, along with increased LPL and D2 levels in BAT [41]. In brown adipose tissue, mRNA expression of lipogenic enzymes, acetyl-coa carboxylase (ACC), Fatty Acid Synthase (FAS), and S14 (Spot 14) mRNA were up-regulated in hypothyroid subjects. In white adipose, ACC, FAS, and S14 mRNA were increased in hyperthyroid subjects [42-44]. In thyrotoxicosis (excessive thyroid hormone), circulating TG-derived FA uptake was unaffected in WAT and decreased in BAT, although increased in other oxidative tissues. On the other hand in hypothyroidism, TG-derived FA uptake was increased in WAT along with increased LPL activity but unaffected in BAT [45].

Thyroid stimulating hormone (TSH) stimulates lipolysis in vitro in adipocytes, through phosphorylation of HSL and perilipin [46]. Expression of TSH receptor (TSHR) in mice lacking functional TSHR, increases HSL dependent lipolysis [47]. In hyperthyroid rat adipocytes, PDE (phosphodiesterase) decreases and lipolysis increases, whereas the opposite is true in hypothyroid animals [48].Thus T_3 action on lipid metabolism (a balance between lipogenesis and lipolysis) is highly tissue specific and dependent on systemic and local hormone status (Table 1).

THYROID HORMONE ROLE IN INSULIN SIGNALING, AND ENERGY HOMEOSTASIS

Thyroid hormone influences insulin signaling, glucose uptake and lipid metabolism, in insulin sensitive tissues including adipose tissue and affects energy balance. T3 promotes glucose uptake in 3T3-L1 adipocytes, by up-regulating insulin mediated Akt phosphorylation, and translocation of vesicle-associated membrane protein 2 (VAMP2) and glucose transporter 4 (GLUT4) to the plasma membrane [49]. In diabetic leptin receptor-deficient (db/db) mice, T3/TRα1 enhanced insulin/ insulin receptor substrate 1 (IRS-1)/ phosphoinositide 3 kinase (PI3- kinase) signaling and insulin sensitivity [50]. Mutations in a corepressor of TR, SMRT, increases lipid accumulation in WAT and BAT, adipocyte hypertrophy in VAT and SAT, and decreases insulin sensitivity in diet induced obesity [51]. SMRT and NCOR, corepressors of TR inhibit adipogenesis and insulin sensitivity [52]. Several studies have demonstrated associations between polymorphisms in *DIO2*, insulin sensitivity and Type 2 diabetes attesting to the role of TH in insulin signaling [53-55]. *DIO2* KO mice are prone to diet induced obesity and glucose intolerance at thermoneutrality [56]. Circulating TSH and T3 levels are up-regulated in obese patients, whereas TSHR and TRα1 levels are down-regulated in Subcutaneous Adipose Tissue

Table 1: Summary of thyroid hormone signaling in adipose tissues.

Tissue	Function	Reference Number
Adipogenesis		
White adipocytes	TH activity is decreased during proliferative phase and increased during differentiation phase	[23]
	Adipogenesis is mediated by TRα1	[12,23]
	Mutant TRα1 decreases WAT	[25]
	Mutant TRα1 decreases adipogenesis, and C/EBPα and PPARλ gene expression	[26,31,32]
	Mutant TRα1 binds to corepressorNCoR1 and cannot bind T3 to begin transcription	
Brown adipocytes		
	Adipogenesis is mediated by TRα1	[12,23]
	TH shown to regulate C/EBPα expression	[28]
Lipogenesis		
White adipocytes		
	Hyperthyroid subjects had higher mRNA levels of lipogenic enzymesACC, FAS etc.	[42-44]
	Hypothyroid subjects had increased FA uptake and LPL activity	[45]
Brown adipocytes	T3 induces early FA synthesis and lipogenesis in BAT	[38]
	DIO2 knockout decreased lipogenesis and thermogenesis	[40]
	Hypothyroid subjects had higher mRNA levels of lipogenic enzymes ACC, FAS etc.	[42,43,44]
	Thyrotoxic subjects had decreased FA uptake	[45]
3T3-L1 cells	T3 increased triglyceride content and lipogenic GAPDH mRNA	[27]
Lipolysis		
White adipocytes	TSH stimulates lipolysis via phosphorylation of HSL and perilipin	[46]
	Hyperthyroid rats have decreased PDE (cAMP degradation), and increased lipolysis while the opposite is true in hypothyroid animals	[48]
Brown adipocytes	T3 increases fat oxidation and lipolysis in thermogenesis	[38]
	DIO2 knockout decreased FA oxidation	[39]
Thermogenesis		
Brown adipocytes	*DIO2* knockout impaired thermogenesis	[40]
	TRβ1 induces PGC1, D2, and UCP1	[12,23]

WAT: White Adipose Tissue; BAT: Brown Adipose Tissue; TH: Thyroid Hormone; TR: Thyroid Hormone Receptor; T_3: Triiodothyroxine; TSH Thyroid Stimulating Hormone; DIO2: Gene Encoding Type 2 Deiodinase; D2: Type 2 deiodinase; PGC1: PPARγcoactivator; NCoR1: Nuclear Receptor Corepressor; UCP1: Uncoupling Protein 1; C/EBPα: CCAAT/ Enhancer Binding Protein Alpha; PPARγ: Peroxisome Proliferator Activated Receptor; ACC: Acetyl coA Carboxylase; FAS: Fatty Acid Synthase; LPL: Lipoprotein Lipase; HSL: Hormone-Sensitive Lipase; FA: Fatty Acid ; PDE: Phosphodiesterase

(SAT) and Visceral Adipose Tissue (VAT) regardless of glucose tolerance status. These conditions are reversed with weight loss suggesting a role for obesity- related adipose tissue thyroid hormone resistance [57].

BAT modulates energy expenditure through oxidation of fatty acids and thermogenesis. In BAT, FFAs generated through SNS signaling and other intracellular mechanisms are utilized as fuel by mitochondria via β oxidation of fatty acids [35]. UCP1, the mitochondrial inner membrane protein is the key molecule that uncouples oxidative phosphorylation from respiration generating heat. TRβ is the TR isoform that binds T_3 in BAT and synergizes Sympathetic Nervous System (SNS) stimulation, increasing mitochondrial biogenesis and up-regulating UCP1 gene expression and β-oxidation of fatty acids in thermogenesis [58-60]. D2 plays a vital role in up-regulating UCP1 also. Adrenergic stimulation by the SNS (binding of norepinephrine to β3 adrenergic receptors) of brown adipocytes, in addition to stimulating cAMP, Protein Kinase A (PKA), HSL and FFA synthesis, also activates *DIO2* gene expression. Tissue specific *DIO2* knockout mice displayed reduced lipogenesis and thermogenesis [40]. BAT specific *DIO2* knockout demonstrated that T3 generation in BAT is important in directly regulating fatty acid oxidation, and energy homeostasis [39]. Thyroid hormone regulation of β-oxidation of fatty acids has also been shown in cell cultures [36].

Central control of energy homeostasis by thyroid hormones is recently being investigated [22,35,61]. This has elucidated the role of thyroid hormones in central regulation of BAT thermogenesis, energy expenditure, food intake and metabolism [22,35,39]. AMP-Activated Protein Kinase (AMPK) is the master fuel sensor and regulator in energy homeostasis, by integrating central and peripheral signals. AMPK activation promotes fatty acid oxidation while turning off fatty acid synthesis and lipogenesis. T_3 mediated inhibition of AMPK activity in the brain has been shown to increase hypothalamic lipogenesis in key areas, resulting in activation of SNS mediated BAT thermogenesis, hypophagia and weight loss [61,62]. Mutated TRα1 (with low affinity for $T_{3)}$ expression in the hypothalamus also causes activation of thermogenesis in BAT [35].

There have been conflicting reports of associations between abnormal levels of adipokines that cause insulin resistance, dyslipidemia and atherosclerosis, and hypo- or hyperthyroidism [12,63-65]. T_3 reduces serum levels of inflammatory adipokines such as leptin in obese rats [66]. The adipokine, leptin stimulates Thyrotropin-Releasing Hormone (TRH) gene expression in the hypothalamus and influences levels of thyroid hormone, thus regulating energy metabolism and body weight [7].

SUMMARY

Thyroid hormone signaling in energy metabolism is highly complex and tissue specific, depending on specific deiodinases and receptor isoforms, resulting in tissue specific function. Thyroid hormones (systemic and local) influence adipocyte differentiation, lipogenesis and lipolysis in both WAT and BAT, although BAT is predominantly involved in energy expenditure. Whole body energy homeostasis is maintained by the integration of thyroid hormone signaling in CNS and peripheral tissues including WAT and BAT.

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Cite this article

Nair S, Martinez C (2014) Role of Thyroid Hormone in Adipocyte Physiology and Metabolism. J Endocrinol Diabetes Obes 2(3): 1049.