Thyroid, Obesity and Thyromimetic Compounds

PRAGATI KAPOOR*, PANKAJ KUMAR†, AK KAPOOR‡

ABSTRACT

Obesity is one of the most important health risks of our times especially owing to modern lifestyle. An association between hypothyroidism and weight gain is well-documented and that thyroid hormones (THs) play a key role in regulating energy homeostasis. An inverse relationship between obesity and energy expenditure (EE) is also well-known. An increase in EE has long been considered for treating obesity. Hence, increasing EE with thyromimetic drugs constitutes an important line of management of obesity. Moreover, TH receptor activation has beneficial effects including lowering of low-density lipoprotein cholesterol and a reduction in whole body adiposity and weight. Selective thyromimetic compounds, though not clinically approved as yet, may be a big leap forward in this direction, because of a close association between THs and EE. The review encompasses the influence of TH in obesity, body mass index, dyslipidemia and thermogenesis. Besides, therapeutic potential of thyromimetic compounds in the treatment of obesity and dyslipidemia as well as their harmful effects have been outlined.

Keywords: Obesity, thyroid hormones, thyromimetic compounds

Obesity is defined as an excessive accumulation of body fat. Recent years have visualized an unprecedented increase in the prevalence of obesity world over, especially in industrialized nations.[1] The enhanced prevalence is basically due to dietary changes associated with modern lifestyles. Obesity is one of the most important health risks of our time[2] because of its association with an increased risk of diabetes, dyslipidemia, kidney disease, cardiovascular disease, all-cause mortality and cancer.[3] Obesity, especially central obesity is linked to many endocrine abnormalities[4] including thyroid dysfunction.[5] Thyroid hormones (THs) are the prime regulators of metabolism and play a pivotal role in regulating energy homeostasis[6] and a definite relationship exists between TH and obesity.[5] Moreover, tri-iodothyronine (T3) regulates energy metabolism and thermogenesis, and plays a critical role in glucose and lipid metabolism, food intake and oxidation of fatty acids.[5] Further, an association between TH and energy expenditure (EE) as well as an inverse relationship between obesity and EE are well-known. Thus, by increasing EE, obesity can be controlled.

Hypothyroidism represented by a higher prevalence of overt and subclinical hypothyroidism (~20%) in morbid obese subjects,[7] is generally associated with increased weight, decreased thermogenesis and metabolic rate. Studies support the clinical evidence that mild thyroid dysfunction is linked to significant changes in body weight and likely represents a risk factor for overweight and obesity.[2] Moreover, subclinical and overt hypothyroidism correlated with higher body mass index (BMI) and higher prevalence of obesity in both smokers and nonsmokers.[8] Conversely, thyroid hyper function leads to weight loss, which could be reversed by proper treatment.[9] This partially justifies involvement of thyroid in obesity. Hence, the role of thyromimetic drugs have been explored because of the influence of TH in obesity and that these agents may provide an opportunity for the treatment of obesity or for weight loss.

THYROID FUNCTION AND RELATIONSHIP BETWEEN TSH AND BODY WEIGHT IN EUTHYROID INDIVIDUALS

Thyroid function is primarily determined by serum thyrotropin (TSH) concentration despite wide fluctuations in TSH levels among healthy individuals,

*Assistant Professor
Dept. of Cardiothoracic Surgery
Nizam Institute of Medical Sciences, Hyderabad, Telangana
†Assistant Professor
‡Professor
Dept. of Pharmacology
Rohilkhand Medical College and Hospital, Bareilly, Uttar Pradesh
Address for correspondence
Dr AK Kapoor
Professor
Dept. of Pharmacology
Rohilkhand Medical College and Hospital, Bareilly - 243 006, Uttar Pradesh
E-mail: drakkapoor@rediffmail.com

although variability exists regarding definition of normal thyroid function.[10,11] Factors like ethnicity, age, sex, health status and probably, BMI may influence TSH normal range.[12] First, the methods for measurement of TSH are highly different in terms of specificity, sensitivity, accuracy and confounding influences such as heterophilic antibodies, second, reference populations used as the basis for a normal range are highly different in terms of e.g., iodine intake, age, gender and presence of thyroid autoantibodies, and should not be confused with cut-off limits.[13] Overt hypothyroidism is diagnosed when serum concentration of TSH is at or above 10 mU/liter with a low serum thyroxine (T4) level, while patients with TSH levels between 4 and 10 mU/liter, and serum T3 and T4 within the normal population-based reference range are defined as having mild (or subclinical) hypothyroidism. However, a consensus on the exact limits for cut-off between normal and subclinical hypothyroid individuals is not around an immediate corner.[10] Interestingly, thyroid dysfunction is more common in older persons. A low metabolic rate, which is associated with high TSH level, denotes longevity. Thus, mild hypothyroidism may be harmless or perhaps beneficial for elderly individuals.

Studies suggest that even slight variations in thyroid function, lead to the development of regional obesity and tendency to gain weight.[14,15] Besides, BMI has been negatively associated with serum free T4 (FT4), and fat accumulation has been associated with lower FT4,[14,16] and higher TSH levels among slightly overweight euthyroid individuals, thereby resulting in a positive correlation between TSH and the progressive increase in weight with time.[5,14-16]

The correlation between TSH and BMI could be mediated by leptin produced by adipose tissue.[17,18] TSH stimulates leptin secretion by human adipose tissue. Leptin physiologically regulates energy homeostasis and also affects thyroid deiodinase activities with activation of T4 to T3 conversion.[5,19] These observations support the concept of an inverse relationship between TH and leptin. There are still surprising gaps and uncertainties regarding cardiac morbidity and mortality, since evidences are based on surrogate markers such as adverse lipid profile, endothelial dysfunction, increased arterial stiffness and cardiac performance.[20]

THYROID FUNCTION IN OBESE INDIVIDUALS

Workers in the field have observed that in euthyroid obese individuals, the baseline serum TSH levels are generally in the upper limit (or slightly over it) of the normal range.[7,21,22] Further, increased TSH levels are positively correlated with elevated waist circumference and BMI and related to the degree of obesity.[15,21] Further, a positive correlation has also been observed between serum leptin and serum TSH levels in obese individuals,[21] which could reflect the positive association between TSH and BMI.[14-16] Moreover, a moderate increase in total T3 or FT3 levels has been observed in obese individuals.[23,24] Progressive fat accumulations have been associated with a parallel increase in TSH and FT3 levels irrespective of insulin sensitivity and metabolic parameters.[23] A positive association has been reported between FT3 and FT4 ratio and both waist circumference and BMI in obese patients.[23] This suggests a high conversion of T4 to T3 in patients with central fat obesity due to increased deiodinase activity.[23] Interestingly, inspite of high plasma TSH levels, TSH receptors are less expressed on adipocytes of obese versus lean individuals, thus further elevating plasma TSH and FT3 levels.[24] This sequence of events would be reversed by weight loss, which restores the size and function of mature adipocytes.[24] Weight loss leads to significant decrease in both TSH and FT3,[23-25] thereby increasing reverse T3 (rT3) due to reduced 5′-deiodination. The observations that increased TSH, FT3 and leptin levels in obese patients are decreased with weight loss supports the hypothesis that the alteration in thyroid function observed in obese subjects may be reversed by losing weight.[26]

It may be emphasized that evaluation of thyroid structure by ultrasound does not help to diagnose hypothyroidism in obese patients. It may be noted that hypothyroidism should be suspected in obese individuals with slightly increased TSH levels only after measuring plasma levels of THs and thyroid autoantibodies. A link between obesity and risk of autoimmune thyroid dysfunction (AITD); which is the main cause of hypothyroidism in adults, and TSH increase, leptin increase and thyroid morphology alteration have been noted as high levels of leptin increases susceptibility to AITD by regulating immune process, which in turn may facilitate development of subclinical or overt hypothyroidism.[27] Though some authors have found that autoimmunity is not a major cause sustaining the high rate of subclinical hypothyroidism in morbid obese subjects. Morbid obese subjects with higher TSH concentrations have shown regularly higher levels of T3 and in some studies a high T4 levels as well.[25] Further, an Italian study has reported that an increase in FT3 and TSH levels were also associated with BMI, waist circumference and fat accumulation.[23]

One of the major functions of T3 is to control thermogenesis. T3 raises basal metabolic rate and promotes thermogenesis by inducing an increase in the mitochondrial respiratory chain activity.[22] Conditions associated with a lack of physical activity exhibit an increase in serum rT3 levels that denotes an elevated thyroxine 3,5-deiodinase enzyme (D3) activity, which converts T3 to the inactive metabolite rT3.[28] Resting EE (REE) depends on obligatory and adaptive thermogenesis. THs are important for adaptative thermogenesis characterized by an uncoupling of oxidative phosphorylation in cold exposed brown adipose tissue.[29] Around 30% of obligatory thermogenesis depends on TH and this fraction is essential for temperature homeostasis.[22]

PATHOPHYSIOLOGY

The possible mechanism that can unfurl the relation between obesity and thyroid gland activity are being actively explored, since there are conflictive data in the literature regarding relationship between obesity and TH. The positive association between TSH and BMI may be due to changes in TH activity or due to alterations in the regulation of hypothalamic-pituitary thyroid (HPT) axis.[22] A direct effect of TSH may be responsible as TSH receptor is expressed in adipose tissue. Besides, there are a number of factors that contribute to FT3 levels in obese subjects. Moreover, a number of authors reported a direct relationship between FT3 and BMI.[22]

TSH seems to be positively related to degree of obesity.[21] Further, a raised TSH levels in obese individuals may be the result of neuroendocrine dysfunction leading to an abnormal secretion rate of TSH. D2 is the main pituitary deiodinase isoenzyme and its activity is a prime factor to release TSH under T3 control, but it does not work properly or is damaged in obese subjects. Some investigators have suggested that there may be certain TH resistance, as well as decreased T3 receptors in obese individuals. Whereas, other authors have suggested presence of partially bioinactive TSH in obese subjects. Additionally, direct and indirect effects of decreased serum leptin contribute to a decreased activity of thyroid-releasing hormone (TRH) neurons in paraventricular nucleus.[22]

SALIENT FEATURES RELATED TO THYROID HORMONE AND OBESITY

Insulin Resistance

The link between thyroid disease and glucose metabolism is well-documented. Insulin sensitivity can be affected by thyroid function. Insulin resistance with hyperinsulinemia are main features of metabolic syndrome and usually accompany obesity.[30] Insulin resistance noted in hypothyroidism is due to decreased tissue sensitivity to insulin, hence reduced glucose disposal. Though, insulin resistance in hypothyroidism is counterbalanced by a reduction in gluconeogenesis.

Thyroid and Adipokines

Fat cells produce leptin are thus considered an active endocrine organ.[5] Leptin physiologically regulates energy homeostasis. Relationship and modulatory role of leptin on the pituitary-thyroid axis has been investigated.[22,31] A leptin regulatory effect on TSH secretion and BMI has been visualized though reasons for this relationship are not clear. Hypothyroidism has been associated with serum leptin levels below,[32] above[33] or in the normal[34] range. Authors observed a significant positive correlation between circulating leptin and TSH levels in obese men and women, whereas correlation between leptin and age was negative.[17,22]

Leptin directly stimulates TRH secretion[29] and subsequently TSH and TH. Besides, leptin has been shown to have a direct inhibitory effect on several components involved in TH production from thyrocytes,[31] and, leptin may directly affect the sensitivity of thyrotroph or the thyrocytes. Leptin modulates the neuroendocrine and behavior responses to overfeeding thereby regulating food intake and energy expenditure. Leptin also effects thyroid deiodinase activities with activation of T4 to T3 conversion.[5,19] This supports the concept of an inverse relationship between TH and leptin. Additionally, serum ghrelin levels are reversibly increased by 32% in hypothyroid patients and that a relationship between ghrelin levels and thyroid function exist.[35]

THYROMIMETIC COMPOUNDS AND OBESITY

A reduction in body weight can be achieved by a negative caloric balance though caloric deprivation usually results in reduction of both fat tissue (desirable) and fat-free mass. However, a reduction in fat-free mass is not desirable as loss of fat-free mass due to reduction in muscle tissue is partly responsible for a reduction in resting EE (REE), which contributes to frequent phenomenon of weight regain. Intense caloric deprivation is usually associated with a decrease in plasma leptin, T3 and sometimes T4 concentrations, and a rise in rT3 as an adaptation process to reduce metabolic needs.[36] A number of trials have been carried out to promote weight loss and avoid weight regain with TH supplementation. Selective modulation

of TH actions is an important therapeutic tool for the treatment of obesity and some of its complications. The purpose of thyroid hormone supplementation is to increase fat loss by increasing oxygen consumption and fatty acid oxidation without having either TSH suppression or side effects on muscle, central nervous system (CNS), bone or cardiac function.[22]

Several animal experimental studies as well as recent human clinical trials strongly point out that thyromimetics are an important group of pharmacological agents that can modify serum lipids without affecting heart rate and causing other major adverse events. Attempts have been made for rational drug designing of synthetic structural analogs of TH that may avoid the adverse cardiac effects of TH, while maintaining its calorogenic, thermogenic activity. It is well-known that TH receptor agonist has beneficial effects including lowering of low-density lipoprotein (LDL) cholesterol and a reduction in whole body adiposity and weight for this reason, TH agonists are among the first antiobesity agents. In a nutshell, they will be useful for the treatment of both obesity and hypercholesterolemia.

THYROID HORMONES

Thyroid hormones are the prime hormones for normal development and are major modulator of metabolic efficiency, EE and thermogenesis. Thyroid dysfunction is associated with changes in body weight and composition, body temperature, and total and REE independent of physical activity. Both subclinical and overt hypothyroidism are frequently associated with weight gain, decreased thermogenesis and metabolic rate.[2] However, the mode of action of TH in promoting mitochondrial uncoupling, which reflects to TH-induced calorigenesis and thermogenesis still remained elusive.

Obesity and thyroid dysfunction are quite common yet TH have been inappropriately and frequently used to induce weight loss in obese euthyroid subjects; there is no indication for their administration to control body weight except in obese hypothyroid subjects. In fact, long-term treatment with TH does not significantly improve weight loss in obese subjects without thyroid dysfunction and may cause adverse effects.[37] Moreover, TH have a plethora of physiological effects/targets hence their therapeutic usefulness in dyslipidemia and obesity is fairly limited. Lomenick et al[38] investigated short-term and long-term changes in weight with T4 treatment of hypothyroidism in children. The authors did not support the view that hypothyroidism as a cause of obesity, and observed that one should not expect significant changes in weight following treatment in most children with hypothyroidism.

In a recent review exhibiting results observed in 14 studies with TH treatment (T3 administration) in obese patients submitted to caloric deprivation failed to draw any firm conclusions owing to heterogeneity in the quality and designs of these trials. No studies evaluated body composition vis-a-vis changes in fat tissues or fat-free mass components. Besides, only a few studies measure REE, nitrogen balance, protein breakdown and 3-methylhistidine urinary excretion, with no consistent results. No clear variations in heart rate were seen. Moreover, these studies did not demonstrate any sustained benefit on weight loss despite T3-induced subclinical hyperthyroidism.[37]

Thyroid extract were quite popular for treating obesity throughout the 20th century but were later abandoned due to severe side effects consisting of cardiac dysrhythmias, osteoporosis, electrolyte and loss of lean body mass.

Thyroid Hormone Receptors and Molecular Basis of Thyroid Hormone Action

TH genomic action is mediated by binding of the hormone to nuclear TH receptors (THRs). Binding affinity is higher for T3 hormone than its T4 precursor. THRs are members of the family of nuclear receptors that regulate the expression of genes. THRs are encoded by the α and β C-erbA genes located on chromosomes 17 and 3, respectively, and are expressed as several spliced isoforms. The C-erbA α gene encodes the TH-binding receptor THR α_1 and two spliced variants that do not bind hormone (THR α_2 and THR α_3), whereas the C-erbA β gene encodes the THRβ_1, THRβ_2 and THRβ_3 isoforms. The three β isoforms differ in their aminoterminal domains. Both THRα_1 and THRβ_1 are expressed ubiquitously. However, THRα_1 has its highest expression in skeletal muscles and cardiac muscle, bone and brown fat, whereas THRβ_1 is highly expressed in liver, brain and kidney.[39] Additionally, TH genomic action may be complemented by TH nongenomic action which require high dose.

Dextrothyroxine and TRIAC

Thyroid hormone analogs have been used in past for reduction of fat mass or control of hyperlipidemia and weight loss while avoiding side effects on bone, brain and heart. A large number of TH analogs were synthesized and tested on experimental animal models for their lipid-lowering activity. Dextrothyroxine was

the first such compound. Analogs may cause weight loss by increasing EE as well as improving lipid profiles in obese patients with low T3 during continued caloric deprivation, though use of dextrothyroxine for hyperlipidemia therapy has been unsuccessful.[40] Tri-iodothyroacetic acid, a natural TH metabolite has shown thermogenic capacity in brown adipocytes in culture,[41] yet no clinical studies demonstrated its efficacy in obesity treatment. The pace of development of thyroid analogs was slowed down firstly, because of associated mortality with use of analogs, and secondly, because of introduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, usually referred to as 'statins' into clinical practice to lower plasma cholesterol.

Selective Thyroid Hormone Receptor Activation

Presence of selectivity has led to the resurgence of this novel class of drugs. The existence of distinct isoforms of THRs and the knowledge of their tissue distribution, regulation and crystal structure has given impetus for the development of selective thyromimetics. More recently agents with specific liver selectivity (affinity to THRβ isoforms) have been developed based on the so called HepDirect liver targeting approach. Thus, selective THRβ analogs have been designed to target liver by adding substituents that promote hepatic first-pass, rather than systemic distribution.

Selective modulation of TH actions represents a promising therapeutic tool for the treatment of obesity and some of its complications. Mechanisms of TH action at the cellular level have shown that selective applications of different THR forms are responsible for tissue-specific responses to TH.

There are two THR isoforms (α and β) that are encoded by two genes. Thus, THRα mostly present in brain and heart regulates cardiac function; while THRβ present in liver controls effects of TH on lipid metabolism.[42] Further, THRβ_1 is the systemic form, while THRβ_2 is the pituitary form which controls TSH secretion.

Investigators have opined that selective THR activation may be beneficial for therapeutic application in some diseases namely dyslipidemia and obesity. Thus, selective thyroid receptor activation for obesity treatment may bring about a rise in REE, a reduction in fat mass, an improvement in insulin sensitivity and lipid profile though, TH overexposure may cause adverse events such as muscle wasting, bone loss, nervousness, hypertension and cardiac dysfunction (arrhythmias, heart failure).[22] Hence, development of THRβ-selective modulators which preferentially have an effect on liver metabolism will be a step in the right direction.

Thus, selective compounds are synthetic structural analogs of TH having tissue-specific TH actions i.e., they bring about lowering of LDL cholesterol and fat loss by an effect on THRβ_1 isoforms in the liver. They do not alter the heart rate mediated through THRα_1 isoforms in the heart.[43] Presently liver selective, cardiac-sparing TH analogs (THRβ-selective compounds) as lipid modifying agents have been developed and have been tested on different animals. A few such compounds are in various phases of human clinical trials.

THRβ Agonists

The first liver-selective, cardiac-sparing thyromimetics were produced by substitution of iodine moieties by arylmethyl groups at the 3' position. Other structural TH analogs such as 3,5-diiodothyropropionic acid (DITPA) followed soon thereafter.

Sobetirome

A selective thyromimetic compound, GC-1 (3,5-dimethyl-4-(4-hydroxy-3-isopropylbenzyl) phenoxy acetic acid - sobetirome) has 10 times more selective action on THRβ_1 than over THRα_1. Since, affinity of GC-1 for THRα_1 is 10 times lower than T3 hence less stimulation of heart rate in relation to increase in energy expenditure. The compound caused an increase in EE of 5-10% and mild tachycardia in mice.[44] In a phase 1 clinical trial on 24 patients over 2 weeks. LDL cholesterol was reduced up to 41% at 100 μg/day.[45] Further GC-1 administration to primates causes increase in oxygen consumption and reduction of body weight and minimal effect on skeletal muscle mass.[46] Animal studies have shown that GC-1 may have a promising role as an antiobesity agent, since it reduces fat mass without increasing food intake and controls dyslipidemia, without causing a deleterious effects on heart or bone mass.[45] It increases fatty acid oxidation, decreases inflammatory markers and reduction of liver steatosis and reduction in TSH. Sobetirome is generally well-tolerated and exhibits a promising role as an antiobesity agent. It causes no changes in heart mass, and skeletal mass is minimally affected and induces 20% reduction in fat mass without increasing food intake.

KB-141

KB-141 is another THRβ agonist, is 10 times more selective for stimulating metabolic rate and 30 times more selective for cholesterol-lowering than for increase

in heart rate. Besides, KB-141 has been shown to cause weight reduction as well as reduction of cholesterol and lipoprotein(a).[22] Increase in EE, reduction of fat mass, increase LDL receptor expression has been observed.

GC-24

GC-24 again a THRβ agonist having 40-100 times preference for THRβ over THRα.[47] It also reduces body fat accumulation and increases EE.[48] These effects are noted without any change in food intake or a significant effect on myocardium. Besides, this compound reduces glucose response to glucose load, improves insulin sensitivity and normalizes the previous hypertriglyceridemia. Total cholesterol is marginally affected and there is no effect on free fatty acids or interleukin (IL-6) levels. Additionally, the compound has significant thermogenic effects as well as effects on EE.[22] It prevents increase in fat mass, there reduction in cholesterol and triglycerides, reduction in TSH, T3 and T4 and it has no effect on heart.

Eprotirome

Chemically eprotirome (KB-2115) is 3-((3,5-dibromo-4-(4-hydroxy-3-(1-methylethyl)-phenoxy) phenyl)amino)-3-oxopropanoic acid. It is also THRβ selective compound that has been administered to human beings. It has seven times greater affinity for the β isoforms of TH receptor than does T3.[49] The tissue uptake of eprotirome is highly liver selective; uptake in nonhepatic tissues is minimal.[50] KB2115 compound leads to 40% reduction in total and LDL cholesterol after 14 days treatment probably owing to an increase in bile acid synthesis. Also, there is a dose-dependent reduction in total and FT4 levels without any affect on TSH concentrations.[51]

In human data from a clinical trial of 98 hyperlipidemic patients, eprotirome caused 25% reduction in LDL apolipoprotein B, along with 37% decrease in lipoprotein A at 100 μg/day after 16 weeks. There was 40% decline in hyperlipidemia. No cardiac, bone or muscle effects were observed, though mild transient elevation in liver enzymes was noted.[50] In phase II trial, eprotirome in combination with atorvastatin or simvastatin caused additional lipid reduction. However, phase III trials to evaluate eprotirome safety and efficacy profile was terminated because of cartilage damage.[49] No changes in metabolic rate, body weight, EE or heart have been observed.

3,5-Diiodothyropropionic Acid

DITPA chemically is 3,5-diiodothyropropionic acid. It is an early but less selective thyromimetic agent. The compound has low THR selectivity. In animal experimentations, DITPA did increase the cardiac output by reducing the end-diastolic pressure but was without any positive chronotropic effects on the heart.[49] A pilot study on DITPA in 19 patients led to increased cardiac index and decreased vascular resistance index.[49] After 24 weeks, it reduced serum LDL cholesterol by 30% and increased cardiac index by 18%, but there was no evidence of symptomatic benefit in congestive heart failure (CHF).[52] DITPA was poorly tolerated in a phase II clinical trial of 86 patients with CHF. DITPA was also associated with a significant reduction in body weight of 5.7 kg and an increased bone turn over.[53] The compound caused suppression of the hypothalamic pituitary thyroid axis and increased bone turnover. Cardiac symptoms are unaffected.[53,54] Reduction in TSH, T3 and T4 and increase in heart rate have been observed.

MB07811

This prodrug undergoes first pass hepatic extraction and cleavage of prodrug generates the negatively charged active THR agonist (3,5-dimethyl-4-(4′hydroxy-3-isopropyl benzyl) phenoxy) methylphosphonic acid (MB07344) in liver microsomes, which gets poorly distributed in most tissues and is rapidly eliminated into the bile.[55] This is essential in limiting the extra hepatic side effects associated with this class of agents. In rats and mice, MB07811 reduces not only cholesterol and triglycerides levels but also hepatic steatosis. Further, in combination with atorvastatin it has additive effects on LDL cholesterol-lowering in animal models. The human phase 1b clinical trial also noted a reduction in LDL cholesterol and triglyceride levels. The main mechanism underlying MB07811 effects seems to be an increased metabolic rate in liver and specifically an increased rate of mitochondrial β-oxidation. Further, in therapeutic doses it is devoid of measurable extra hepatic effects.

Bile Acids

Administration of bile acids can modulate EE as well as TH activation via changes in D2 expression, an enzyme involved in BAT thermogenic pathways that regulate EE.[56,57] Kaempferol may increase skeletal myocyte oxygen consumption by increasing cAMP generation and inducing protein kinase A activation. Besides, the agent may influence expression of genes involved in thermogenesis, such as UCP-3, and to upregulate D2 gene expression; prolonging its half-life.[58] These pathways may be targeted for the treatment of obesity and other metabolic disorders.

USE OF THYROMIMETICS IN DYSLIPIDEMIA

THRβ-selective thyromimetics serve as an important pharmacological tool to modify serum lipids and to treat dyslipidemia. The mechanism of lowering of LDL cholesterol by thyromimetics is different from that of statins, which are first-line drugs for the treatment of hypercholesterolemia. Interestingly, thyromimetics have synergistic action when combined with statins.[53] Following are several mechanisms through which thyromimetics act in dyslipidemia.[49]

- The anti-atherogenic effects of selective thyromimetic is primarily due to upregulation of the LDL receptor in the liver, which leads to a strong reduction in plasma LDL particles, associated with a significant reduction in plasma total cholesterol and triglycerides.
- Inhibition of hepatic transcription factor, sterol regulatory element-binding protein 1 (SREBP-1), leading to reduced very LDL assembly.
- Facilitation of the reverse cholesterol transport, which describes the transport of cholesterol from extra hepatic tissues, for example plaque macrophages, back to liver for fecal excretion.
- Increase hepatic expression of the HDL receptor, scavenger receptor B-1 (SRBI), which increases the clearance of HDL cholesterol without affecting the HDL particle number, thus promoting the delivery of HDL cholesterol derived from atherosclerotic macrophages.
- In human beings, HDL cholesterol can be transferred to LDL particles through the cholesterylester transfer protein (CETP) and then cleared through hepatic LDL receptor. Hepatic cholesterol is than excreted into bile either directly by the transporters ABCG5 and ABCG8 or gets converted into bile acids by cholesterol 7 α-hydroxylase (CYP7A1). Both these mechanisms are facilitated by selective thyromimetics.
- Thyromimetics probably reduce intestinal absorption of dietary sterols due to competition with sterols of biliary origin.

Moreover, selective thyromimetics may have additive LDL cholesterol-lowering when used in combination with statins in animal models.[59]

USE IN OBESITY AND HEPATIC STEATOSIS

THs reduce body fat by increasing basal metabolic rate without muscle wasting and effect on heart rate.[45,60] Loss of weight was observed in the phase II clinical trial with DITPA.[53]

Sobetirome reduces body fat in animal studies by increasing fatty acid β-oxidation and increasing oxygen consumption and body temperature. Besides, development and progression of hepatic steatosis is prevented owing to increased mitochondrial and peroxisomal fatty acid β-oxidation and reduced levels of inflammatory marker.[54,61] Sobetirome is also less effective than THs in promoting weight loss.[49]

Similarly, MB07811 reduced hepatic steatosis through increased fatty acid oxidation in animal models. A reduction of hepatic and body fat may be beneficial for glucose homeostasis and type 2 diabetes.[62] It may be emphasized, that long-term human clinical trials are required to prove whether thyromimetics will be of use in the treatment of obesity and hepatic steatosis.

Potential Harmful Effects

Since, the selectivity of thyromimetics for THRβ and/or the liver is not absolute, but a relative one, hence high doses still activate THRα resulting in adverse events related to positive chronotropic and inotropic cardiac effects as well as enhance bone resorption and muscle catabolism.[63] However, muscle and bone catabolism are fairly less common in therapeutic dose.[49,50]

Less selective DITPA has shown increased bone turnover in human trials.[53] Landenson et al,[53] in phase II study with DITPA, also noted poor tolerability profile in patients with pre-existing CHF. Development of positive chronotropic effect is deleterious in cases of CHF.

Selective THRβ agents may influence regulation of HPT axis as this receptor is also expressed in the pituitary gland and regulates the feedback loop over TSH.[49] In human being, eprotirome reduced serum T4, although TSH and serum T3 levels are not significantly affected.[50,53] Besides, patients receiving eprotirome may also be watched for mild reversible increases in the levels of serum alanine aminotransferase and potential hepatic toxicity.[53]

Potential Limitations

THRβ-selective thyromimetics may result in novel nongenomic effects, hence the safety of THRβ-selective thyromimetic have to be screened particularly in subjects suffering from CHF or coronary heart disease (CHD).[52]

Some potential limitations of a liver-specific antisteatotic agent such as MB07811 are, firstly burning hepatic fat may not be sufficient for patients with nonalcoholic steatohepatitis (NASH) (those who really need

therapy) because the metabolic imbalance, in particular peripheral insulin resistance, will continue and the beneficial effect of thyromimetics could be counteracted by increased lipogenesis in the liver or lipolysis in adipocytes, secondly burning hepatic fat may not be appropriate in a liver, which already has some degree of damage, thirdly systemic fibrogenic stimuli, such as hyperinsulinemia pathways may remain unaffected by thyromimetic agents.

CONCLUSION

TH-induced calorigenesis and thermogenesis have been shown to reflect uncoupling of mitochondrial oxidative phosphorylation though the mechanism remained elusive. Future therapy of obesity, fatty liver, type 2 diabetes, dyslipidemia, etc. needs designing of new compounds, which selectively modify different metabolic pathways. Till date, therapeutic usefulness of selective thyromimetics in the treatment of dyslipidemia, obesity and atherosclerosis is still hanging in balance at least till the final outcome of long-term phase III clinical trials.

However, animal studies have shown that they are quite effective as lipid-lowering agents with minimal effects on heart rate and bone catabolism. Further, more knowledge and clinical trials are required to decipher mechanisms of action, safety and tolerability profile of newer agents. Moreover, newer thyromimetic agents should be safe to heart, bone, HPT axis and CNS. At the moment, the major indication of this novel class of drugs seems to be the treatment of dyslipidemia which is a major cardiovascular risk factor, and they have limited prospects in treating human obesity.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA. 2010;303(3):235-41.
2. Biondi B. Thyroid and obesity: an intriguing relationship. J Clin Endocrinol Metab. 2010;95(8):3614-7.
3. Golden SH, Robinson KA, Saldanha I, Anton B, Ladenson PW. Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. J Clin Endocrinol Metab. 2009;94(6):1853-78.
4. Kokkoris P, Pi-Sunyer FX. Obesity and endocrine disease. Endocrinol Metab Clin North Am. 2003;32(4):895-914.
5. Reinehr T. Obesity and thyroid function. Mol Cell Endocrinol. 2010;316(2):165-71.
6. Yen PM. Physiological and molecular basis of thyroid hormone action. Physiol Rev. 2001;81(3):1097-142.
7. Michalaki MA, Vagenakis AG, Leonardou AS, Argentou MN, Habeos IG, Makri MG, et al. Thyroid function in humans with morbid obesity. Thyroid. 2006;16(1):73-8.
8. Asvold BO, Bjøro T, Vatten LJ. Association of serum TSH with high body mass differs between smokers and never-smokers. J Clin Endocrinol Metab. 2009;94(12):5023-7.
9. Silva JE. Fat and energy economy in hypo- and hyperthyroidism are not the mirror image of one another. Endocrinology. 2010;151(1):4-6.
10. Brabant G, Beck-Peccoz P, Jarzab B, Laurberg P, Orgiazzi J, Szabolcs I, et al. Is there a need to redefine the upper normal limit of TSH? Eur J Endocrinol. 2006;154(5):633-7.
11. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab. 2005;90(9):5489-96.
12. Fatourechi V. Upper limit of normal serum thyroid-stimulating hormone: a moving and now an aging target? J Clin Endocrinol Metab. 2007;92(12):4560-2.
13. Waise A, Price HC. The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism. Ann Clin Biochem. 2009;46(Pt 2):93-8.
14. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen L, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab. 2005;90(7):4019-24.
15. Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med. 2008;168(6):587-92.
16. Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C, Stamatelopoulos K. Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. Eur J Endocrinol. 2009;161(3):459-65.
17. Santini F, Galli G, Maffei M, Fierabracci P, Pelosini C, Marsili A, et al. Acute exogenous TSH administration stimulates leptin secretion in vivo. Eur J Endocrinol. 2010;163(1):63-7.
18. Oge A, Bayraktar F, Saygili F, Guney E, Demir S. TSH influences serum leptin levels independent of thyroid hormones in hypothyroid and hyperthyroid patients. Endocr J. 2005;52(2):213-7.
19. Zimmermann-Belsing T, Brabant G, Holst JJ, Feldt-Rasmussen U. Circulating leptin and thyroid dysfunction. Eur J Endocrinol. 2003;149(4):257-71.
20. Fazio S, Palmieri EA, Lombardi G, Biondi B. Effects of thyroid hormone on the cardiovascular system. Recent Prog Horm Res. 2004;59:31-50.
21. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. Clin Endocrinol (Oxf). 2005;62(4):487-91.

22. Galofre JC, Fruhbeck G, Salvador J. Obesity and thyroid function: Pathophysiological and therapeutic implications. Hot Thyroidol. 2010;6:1-22.
23. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf). 2007;67(2):265-9.
24. Nannipieri M, Cecchetti F, Anselmino M, Camastra S, Niccolini P, Lamacchia M, et al. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: effects of weight loss. Int J Obes (Lond). 2009;33(9):1001-6.
25. Kok P, Roelfsema F, Langendonk JG, Frölich M, Burggraaf J, Meinders AE, et al. High circulating thyrotropin levels in obese women are reduced after body weight loss induced by caloric restriction. J Clin Endocrinol Metab. 2005;90(8):4659-63.
26. Bray GA, Fisher DA, Chopra IJ. Relation of thyroid hormones to body-weight. Lancet. 1976;1(7971):1206-8.
27. Marzullo P, Minocci A, Tagliaferri MA, Guzzaloni G, Di Blasio A, De Medici C, et al. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab. 2010;95(8): 3965-72.
28. van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SW. Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. J Clin Endocrinol Metab. 2005;90(12):6403-9.
29. Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. Ann Intern Med. 2003;139(3): 205-13.
30. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. Arch Intern Med. 2000;160(7):898-904.
31. Feldt-Rasmussen U. Thyroid and leptin. Thyroid. 2007;17(5):413-9.
32. Iglesias P, Díez JJ. Influence of thyroid dysfunction on serum concentrations of adipocytokines. Cytokine. 2007;40(2):61-70.
33. Syed MA, Thompson MP, Pachucki J, Burmeister LA. The effect of thyroid hormone on size of fat depots accounts for most of the changes in leptin mRNA and serum levels in the rat. Thyroid. 1999;9(5):503-12.
34. Sesmilo G, Casamitjana R, Halperin I, Gomis R, Vilardell E. Role of thyroid hormones on serum leptin levels. Eur J Endocrinol. 1998;139(4):428-30.
35. Gjedde S, Vestergaard ET, Gormsen LC, Riis AL, Rungby J, Møller N, et al. Serum ghrelin levels are increased in hypothyroid patients and become normalized by L-thyroxine treatment. J Clin Endocrinol Metab. 2008;93(6):2277-80.
36. Adler SM, Wartofsky L. The nonthyroidal illness syndrome. Endocrinol Metab Clin North Am. 2007;36(3):657-72, vi.
37. Kaptein EM, Beale E, Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. J Clin Endocrinol Metab. 2009;94(10):3663-75.
38. Lomenick JP, El-Sayyid M, Smith WJ. Effect of levo-thyroxine treatment on weight and body mass index in children with acquired hypothyroidism. J Pediatr. 2008;152(1):96-100.
39. Pascual A, Aranda A. Thyroid hormone receptors, cell growth and differentiation. Biochim Biophys Acta. 2013;1830(7):3908-16.
40. Denke MA. Diet, lifestyle, and nonstatin trials: review of time to benefit. Am J Cardiol. 2005;96(5A):3F-10F.
41. Moreno M, de Lange P, Lombardi A, Silvestri E, Lanni A, Goglia F. Metabolic effects of thyroid hormone derivatives. Thyroid. 2008;18(2):239-53.
42. Bookout AL, Jeong Y, Downes M, Yu RT, Evans RM, Mangelsdorf DJ. Anatomical profiling of nuclear receptor expression reveals a hierarchical transcriptional network. Cell. 2006;126(4):789-99.
43. Webb P. Thyroid hormone receptor and lipid regulation. Curr Opin Investig Drugs. 2010;11(10):1135-42.
44. Trost SU, Swanson E, Gloss B, Wang-Iverson DB, Zhang H, Volodarsky T, et al. The thyroid hormone receptor-beta-selective agonist GC-1 differentially affects plasma lipids and cardiac activity. Endocrinology. 2000;141(9):3057-64.
45. Villicev CM, Freitas FR, Aoki MS, Taffarel C, Scanlan TS, Moriscot AS, et al. Thyroid hormone receptor beta-specific agonist GC-1 increases energy expenditure and prevents fat-mass accumulation in rats. J Endocrinol. 2007;193(1):21-9.
46. Grover GJ, Egan DM, Sleph PG, Beehler BC, Chiellini G, Nguyen NH, et al. Effects of the thyroid hormone receptor agonist GC-1 on metabolic rate and cholesterol in rats and primates: selective actions relative to 3,5,3′-triiodo-L-thyronine. Endocrinology. 2004;145(4):1656-61.
47. Borngraeber S, Budny MJ, Chiellini G, Cunha-Lima ST, Togashi M, Webb P, et al. Ligand selectivity by seeking hydrophobicity in thyroid hormone receptor. Proc Natl Acad Sci U S A. 2003;100(26):15358-63.
48. Amorim BS, Ueta CB, Freitas BC, Nassif RJ, Gouveia CH, Christoffolete MA, et al. A TRbeta-selective agonist confers resistance to diet-induced obesity. J Endocrinol. 2009;203(2):291-9.
49. Salam RF. Thyroxine mimetics. Egyptian J Int Med. 2013;25:171-6.
50. Koch L. Lipids: Eprotirome shows promise as a novel way to target dyslipidemia. Nat Rev Endocrinol. 2010;6(7):354.
51. Berkenstam A, Kristensen J, Mellström K, Carlsson B, Malm J, Rehnmark S, et al. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. Proc Natl Acad Sci U S A. 2008;105(2):663-7.

52. Ladenson PW, Kristensen JD, Ridgway EC, Olsson AG, Carlsson B, Klein I, et al. Use of the thyroid hormone analogue eprotirome in statin-treated dyslipidemia. N Engl J Med. 2010;362(10):906-16.
53. Ladenson PW, McCarren M, Morkin E, Edson RG, Shih MC, Warren SR, et al. Effects of the thyromimetic agent diiodothyropropionic acid on body weight, body mass index, and serum lipoproteins: a pilot prospective, randomized, controlled study. J Clin Endocrinol Metab. 2010;95(3):1349-54
54. Goldman S, McCarren M, Morkin E, Ladenson PW, Edson R, Warren S, et al. DITPA (3,5-Diiodothyropropionic acid), a thyroid hormone analog to treat heart failure: phase II trial veterans affairs cooperative study. Circulation. 2009;119(24):3093-100.
55. Erion MD, Cable EE, Ito BR, Jiang H, Fujitaki JM, Finn PD, et al. Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. Proc Natl Acad Sci U S A. 2007;104(39):15490-5.
56. Watanabe M, Houten SM, Mataki C, Christoffolete MA, Kim BW, Sato H, et al. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. Nature. 2006;439(7075):484-9.
57. de Jesus LA, Carvalho SD, Ribeiro MO, Schneider M, Kim SW, Harney JW, et al. The type 2 iodothyronine deiodinase is essential for adaptive thermogenesis in brown adipose tissue. J Clin Invest. 2001;108(9):1379-85.
58. da-Silva WS, Harney JW, Kim BW, Li J, Bianco SD, Crescenzi A, et al. The small polyphenolic molecule kaempferol increases cellular energy expenditure and thyroid hormone activation. Diabetes. 2007;56(3):767-76.
59. Tancevski I, Wehinger A, Demetz E, Hoefer J, Eller P, Huber E, et al. The thyromimetic T-0681 protects from atherosclerosis. J Lipid Res. 2009;50(5):938-44.
60. Cable EE, Finn PD, Stebbins JW, Hou J, Ito BR, van Poelje PD, et al. Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. Hepatology. 2009;49(2):407-17.
61. Perra A, Simbula G, Simbula M, Pibiri M, Kowalik MA, Sulas P, et al. Thyroid hormone (T3) and TRbeta agonist GC-1 inhibit/reverse nonalcoholic fatty liver in rats. FASEB J. 2008;22(8):2981-9.
62. Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nat Rev Drug Discov. 2009;8(4):308-20.
63. Yehuda-Shnaidman E, Kalderon B, Bar-Tana J. Thyroid hormone, thyromimetics, and metabolic efficiency. Endocr Rev. 2014;35(1):35-58.

■■■■