

## The Thermogenic Effect of Thyroid Hormone and Its Clinical Implications

J. Enrique Silva, MD

### Clinical Principles

There is a popular belief, even among physicians, that weight changes are frequent manifestations of thyroid dysfunction.

Thyrotoxicosis is usually associated with weight loss and heat intolerance. Cold intolerance, but not weight gain, is a prominent feature of hypothyroidism.

### Physiologic Principles

Thyroid hormones increase heat production only in homeothermic species.

Thermogenesis is energy dissipation as heat.

The thermogenic effect of thyroid hormones is closely linked to increased appetite and lipogenesis to ensure fuel availability and avoid wasting.

Major thermogenic mechanisms include increased turnover of adenosine triphosphate (ATP) and programmed reduction in the efficiency of ATP synthesis.

Reduced efficiency in ATP synthesis is relatively more important than increased ATP turnover in the transition from hypothyroidism to euthyroidism.

Clinicians are very familiar with cold or heat intolerance in patients with altered thyroid function. While non-specific, these symptoms have some predictive value in the diagnosis of thyroid dysfunction. Involuntary changes in weight are also perceived as indicators of abnormal thyroid function, often prompting laboratory testing of thyroid gland function. Most of the clinical manifestations of thyroid dysfunction in adults are directly or indirectly derived from the stimulating effect of thyroid hormone on thermogenesis and energy turnover. Even so, the relationship between these effects and energy balance and body weight is not simple. This review examines the thermogenic effect of thyroid hormone and how it affects some of the manifestations of hypo- and hyperthyroidism, energy balance, and body weight.

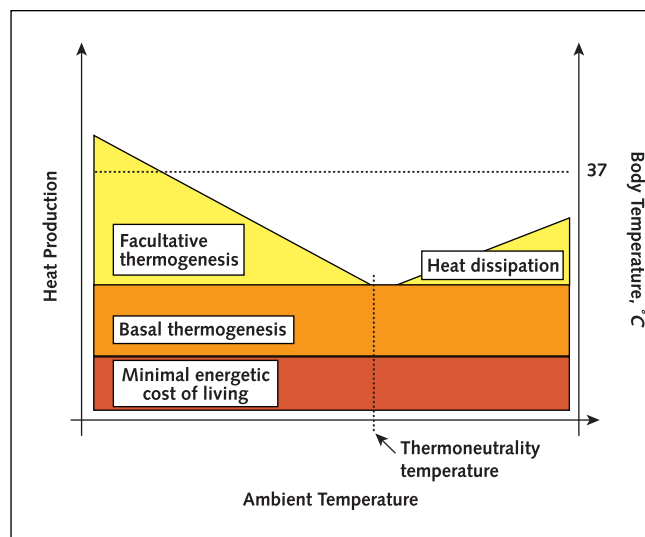
### BASIC DEFINITIONS OF HOMEOTHERMY AND POIKILOOTHERMY

Evolutionary development of homeothermy was an important biological advance because it allowed animal life to expand into environments with temperatures markedly different from those of the body. Tight control of body

temperature homeostasis required the selection of several different mechanisms in the course of evolution that are activated whenever the body's basal heat production is insufficient or excessive. This maintains the core temperature at its setting. Reflecting the fact that the habitat is usually colder than the body, a mainstay of homeothermy is the inherent capacity of homeothermic species to constantly generate more heat than poikilothermic animals.

Heat production, or thermogenesis, is customarily divided into two types: obligatory and facultative. *Obligatory thermogenesis* can be viewed as the constitutive heat production of homeothermic species (Figure 1). Obligatory thermogenesis is well reflected in the so-called basal metabolic rate or the less strict but more practical resting energy expenditure, which are measured under conditions that eliminate the energy cost of physical activity, emotional distress, temperature adaptation, and food processing. Two components can be distinguished in obligatory thermogenesis. As machines involved in energy transformations, and as a result of the fundamental laws of thermodynamics, living organisms generate some heat. This is the heat derived from the *minimal energy cost of living* and is not suf-

**Figure 1. The various forms of thermogenesis in homeothermic species.**



The horizontal line on the right vertical axis indicates that body temperature stays constant, independent of the environment. Thermoneutrality temperature, indicated on the x-axis, is the ambient temperature at which obligatory thermogenesis is sufficient to maintain body temperature without the participation of thermoregulatory mechanisms. In humans, this temperature is approximately 23 °C. See text for details.

sufficient to maintain body temperature in cold environments. Homeothermic species need to produce more heat than poikilotherms, and they do so. When it results from basal metabolic activity, this excess heat is known as *basal thermogenesis*.

As illustrated in **Figure 1**, basal thermogenesis is independent of ambient temperature. Two differences between homeothermic and poikilothermic machines explain basal thermogenesis. First, homeothermic species have a more active metabolism, that is, they sustain a higher number of energy transactions per unit of time (1). Second, a larger fraction of energy involved in these transactions is dissipated as heat, that is, the homeothermic machine has a lower thermodynamic efficiency. For example, for the same amount of mechanical work, the mammalian muscle generates more heat than its reptilian or amphibian counterpart (2).

If obligatory thermogenesis becomes insufficient to maintain body temperature, the body activates heat-conserving mechanisms (cutaneous vasoconstriction, piloerection) and recruits additional thermogenic mechanisms. These latter mechanisms constitute what is called adaptive thermogenesis. Skeletal muscle shivering is the most immediate thermogenic response to a cold environment. If cold is sustained, this form of adaptive thermogenesis is rapidly replaced by so-called nonshivering facultative thermogenesis, or simply facultative thermogenesis.

Facultative thermogenesis is in essence extra heat, produced on demand from the metabolic activity in certain tissues (for example, brown adipose tissue, skeletal muscle).

Facultative thermogenesis of brown adipose tissue is stimulated by the sympathetic nervous system (by mechanisms explained later), which is activated in the hypothalamus in response to signals originating from temperature sensors in the skin. The magnitude of facultative thermogenesis increases steeply as the environment turns colder (**Figure 1**). On the other hand, as ambient temperature becomes warmer, a point is reached at which obligatory thermogenesis is sufficient to maintain body temperature without facultative thermogenesis or ancillary heat-conserving or heat-dissipating mechanisms. This is called *thermoneutrality temperature* (**Figure 1**). It follows from this concept that the lower obligatory thermogenesis is, the higher thermoneutrality temperature will be, while if obligatory thermogenesis is high, colder environments will be needed to activate facultative thermogenesis. Thus, by having higher basal thermogenesis and hence higher obligatory thermogenesis, homeothermic species could stay in environments much colder than the body temperature without needing to activate thermoregulatory mechanisms to maintain their core temperature.

Size, which affects the body surface area-to-volume ratio, also helps determine thermoneutrality temperature. Thus, while thermoneutrality temperature is 23 °C in an adult man, it is 28 °C in rats. Likewise, human newborns and infants have higher thermoneutrality temperatures than adults, which explains why brown adipose tissue is so important for temperature homeostasis at this age. Smaller size and immaturity of thermoregulatory mechanisms explain why risk for hypothermia is higher in premature babies than in full-term newborns (3). In addition to being activated by cold, facultative thermogenesis can be activated by food, providing a mechanism to dissipate excess calories. Dumping excess food calories as heat may be a later acquisition in evolution.

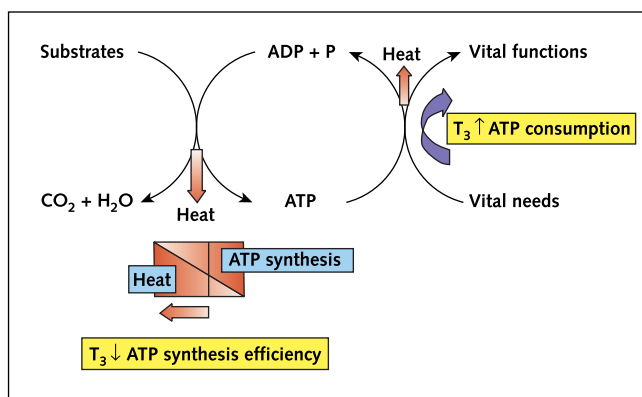
## THYROID HORMONE ACQUIRES A NEW ROLE WITH THE ADVENT OF HOMEOTHERMY

Strong evidence supports an essential role for thyroid hormone in the thermogenesis of warm-blooded species. It has been proposed that the greater thermogenic capacity of the homeothermic biological machine is the result of more active thyroid glands than those in poikilothermic species (4). However, as discussed later, the difference is more qualitative than quantitative (5).

The thyroid gland is present in all vertebrates, and thyroid hormone receptors are found in species as primitive as the sea lamprey (6). Throughout the vertebrate spectrum, thyroid hormone plays an essential role in coordinating development and specific cell functions. However, only in homeothermic species does it acquire a role in metabolic regulation. Only in these species can thyroid hormone increase oxygen consumption and stimulate the activity of certain enzymes involved in metabolic regulation (6).

The effect of thyroid hormone on basal metabolic rate

Figure 2. Energy transformations in biological systems.



The energy released from substrate oxidation is captured in adenosine triphosphate (ATP) and then transferred from this molecule to others to provide energy for the biological processes. A fraction of the energy involved both in the synthesis of ATP and in its utilization is lost as heat. While this fraction is low and constant in ATP utilization, the fraction dissipated as heat in ATP synthesis is higher and apparently subject to regulation. Thyroid hormone increases heat production by increasing ATP utilization and by reducing the thermodynamic efficiency of ATP synthesis. See text for details. ADP = adenosine diphosphate; P = inorganic phosphate;  $\text{T}_3$  = triiodothyronine.

was recognized more than a century ago (7). In the complete absence of thyroid hormone, basal metabolic rate or resting energy expenditure could be reduced by 30% or more, a change associated with markedly reduced cold tolerance. This indicates that as much as 30% of obligatory thermogenesis depends on thyroid hormone and that this fraction of obligatory thermogenesis is essential for temperature homeostasis. In addition, thyroid hormone is important for facultative thermogenesis; in the absence of this hormone, the thermogenic response of brown adipose tissue, the major site of facultative thermogenesis in mammals, is substantially reduced (8, 9). The reduced obligatory thermogenesis in hypothyroidism is partially compensated by cutaneous vasoconstriction (10, 11), which is perceived as cold and causes increased sympathetic stimulation of brown adipose tissue. Yet, despite showing signs of increased sympathetic stimulation in chronically hypothyroid rats (12), brown adipose tissue fails to produce sufficient heat to maintain body temperature, so that hypothyroid animals rapidly develop hypothermia in cold environments (9).

Another evidence of the importance of thyroid hormone for thermogenic function of brown adipose tissue is the abundant presence of type II 5' iodothyronine deiodinase (D2). This enzyme is stimulated by the sympathetic nervous system when brown adipose tissue thermogenesis is needed, increasing the intracellular concentration of triiodothyronine ( $\text{T}_3$ ) to receptor-saturating levels. These high levels of  $\text{T}_3$  are needed to realize the thermogenic potential of brown adipose tissue (9, 13). In addition, D2 activity is increased in hypothyroxinemia. This, along with the increased sympathetic stimulation of brown adipose

tissue in hypothyroidism, protect the brown adipose tissue  $\text{T}_3$  content in hypothyroidism, which must be severe to deplete brown adipose tissue of  $\text{T}_3$  (14).

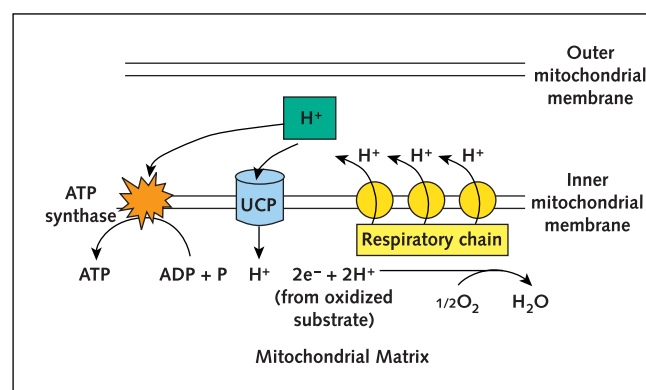
Together, this clinical and experimental evidence supports an essential role for thyroid hormone in both obligatory thermogenesis and facultative thermogenesis. However, two major questions remain unanswered: 1) How did thyroid hormone acquire this thermogenic role during evolution? 2) What biochemical and molecular mechanisms are activated by thyroid hormone to produce heat?

## THERMOGENIC MECHANISMS

Nature has resorted to two mechanisms to augment heat production in homeothermic species, namely increasing energy transactions and lowering thermodynamic efficiency (Figure 2). The energy contained in food is captured largely in the form of adenosine triphosphate (ATP), which is then used to sustain virtually all vital processes and can be considered the “energy currency” of the body. Both in the synthesis of ATP and in its utilization, a fraction of the energy going into these transformations is lost as heat. Therefore, all else being equal, more ATP use will result in more heat production (15). In addition, growing evidence supports the concept that the fraction of energy dissipated as heat in energy transactions can be regulated to respond to temperature or energy homeostasis needs (16).

Of the two arms, ATP synthesis and ATP utilization, the transfer of energy from ATP to sustain vital functions (that is, ATP utilization) seems to be quite efficient, and

Figure 3. Mechanism of action of uncoupling proteins (UCPs) and uncouplers in general.



The energy released in the oxidation of substrates in the mitochondria is transiently accumulated in the form of a proton ( $\text{H}^+$ ) gradient created as the electrons from the oxidized substrate are transferred downstream along the respiratory chain. The energy accumulated in this gradient is used by the adenosine triphosphate (ATP) synthase to produce ATP from adenosine diphosphate (ADP), which is an endothermic reaction. Uncouplers reduce this gradient, bypassing the ATP synthase. The movement of protons down the gradient is an exothermic process. Uncoupling proteins, the best known and best characterized of which is the brown adipose tissue UCP (now called UCP1), allow the protons to reenter the mitochondria in a regulated manner. P = inorganic phosphate.

there is no evidence that the comparatively low amount of heat generated in this type of process is under-regulation for the sake of temperature homeostasis. On the other hand, the thermodynamic efficiency of ATP synthesis is not as high as that of ATP utilization, and the heat released here may contribute largely to basal thermogenesis. Regulated reduction in the efficiency of ATP synthesis has long been known to occur in brown adipose tissue. As mentioned earlier, this is a thermogenic tissue that is probably the most important site of facultative thermogenesis in small mammals, including the human newborn and infant (17).

Brown adipose tissue contains in its abundant mitochondria a unique protein called thermogenin, or uncoupling protein (UCP), that mediates a homeostatically controlled reduction of the coupling of ATP synthesis to oxidations in this tissue (18). During mitochondrial respiration, protons are extruded from the matrix into the intermembrane space by the respiratory chain enzymes (Figure 3). This creates a gradient between intermembrane space and the mitochondrial matrix. Such proton gradient or proton motive force provides the energy for ATP synthesis from adenosine diphosphate and inorganic phosphate, catalyzed by ATP synthase. Uncoupling protein acts as a regulated proton port, allowing return of protons from the intermembrane space back into the mitochondrial matrix. When open, this proton port decreases the proton motive force, reducing the energy available for ATP synthesis (Figure 3). The return of protons to the matrix following the electrochemical gradient is an exothermic process. On the other hand, the rate of oxidations in the mitochondria varies inversely with the magnitude of the electrochemical gradient, so that mitochondrial respiration rate will increase as the gradient is reduced and decrease as the gradient builds up. Therefore, the activation of UCP will accelerate respiration; a higher proportion of the energy released during the process is now dissipated as heat, and a smaller proportion per atom of oxygen consumed is used for ATP synthesis. The activation or opening of UCP to protons is accomplished by fatty acids liberated as a result of the sympathetic stimulation of hormone-sensitive lipase in brown adipose tissue (18).

Brown adipose tissue is a relatively recent acquisition in evolution, present only in mammals. Since brown adipose tissue was the only tissue in which uncoupling of phosphorylation could be readily demonstrated, the presence of a regulated proton leak in non-brown adipose tissue mitochondria has been only recently considered (19). Now that UCP analogues have been cloned from other tissues, it has become apparent that uncoupling of ATP phosphorylation is indeed an ancient thermogenic mechanism to the extent that UCP analogues have also been found in plants (20) and in birds, homeothermic species that do not have brown adipose tissue (21); however, the role of UCP analogues in plants has yet to be defined.

## THERMOGENIC MECHANISMS USED BY THYROID HORMONE

Hyperthyroidism is evidently associated with an increase in metabolic rate and an acceleration of practically all the metabolic pathways, with a consequent increase in ATP turnover and heat production. For all three macronutrients, namely proteins, carbohydrates, and lipids, both synthetic and catabolic pathways are accelerated. The contribution of this accelerated metabolic cycling, however, accounts for a small percentage of the thermogenic effect of thyroid hormone, altogether probably not more than 15% (22). However, thyroid hormone also increases ATP consumption by other mechanisms. The maintenance of the Na/K gradient across the cell membrane and Ca<sup>2+</sup> between the sarcoplasmic reticulum and cytosol is essential to cell health and accounts for substantial energy use. Thyroid hormone stimulates these processes in various ways. It tends to reduce these gradients as a consequence of the accelerated metabolism, hence increasing the demands for ATP to maintain them. For example, since the Na gradient across the cell membrane is used to transport nutrients inside the cell and thyroid hormone increases such exchange, more ATP is needed to maintain the gradient in hyperthyroidism. Likewise, by causing tachycardia, thyroid hormone forces the myocardial sarcoplasmic reticulum Ca<sup>2+</sup> pump to work more, that is, to use more ATP to restore resting cytosolic Ca<sup>2+</sup> per unit of time. Thyroid hormone also stimulates the expression of corresponding ionic pump genes, the Na/K ATPases and sarcoplasmic Ca ATPases. Finally, it is possible that thyroid hormone creates or favors “leaks” across the plasma and endoplasmic reticulum membranes, which would accomplish the biological purpose of increasing ATP utilization in a futile manner to generate heat.

The increased energy spent in the maintenance of these gradients has received considerable attention as a thermogenic mechanism (23), but the estimates of the contribution of these mechanisms to overall energy expenditure vary widely (15). A careful study in isolated rat hepatocytes showed that oxygen consumption is reduced to a greater extent than ATP turnover in the hypothyroid state, whereas hyperthyroid hepatocytes showed a similar increase in both ATP turnover and oxygen consumption (24). These findings were interpreted as an indication that an important fraction of the thermogenic effect of thyroid hormone was caused by reducing the thermodynamic efficiency of ATP synthesis, that is, controlled uncoupling of ATP phosphorylation, particularly in the transition from hypothyroidism to euthyroidism (24). These authors provided evidence that thyroid hormone increased a proton leak in a regulated manner across the inner mitochondrial membrane (25). Such observations further support the idea that thyroid hormone could decrease the thermodynamic efficiency of the biological homeothermic machine for the sake of increasing thermogenesis. Previous independent



observations are consistent with this concept. It has been shown, for example, that for any amount of mechanical work, a euthyroid rat muscle generates more heat than its hypothyroid counterpart (26); likewise, the energy cost of producing glycogen from lactate is higher in euthyroid than in hypothyroid hepatocytes (4).

The mechanism of the increased proton leak stimulated by thyroid hormone remains unexplained. It was thought that the cloning of brown adipose tissue UCP homologues in other tissues, the most important being UCP2 and UCP3, would explain this part of the thermogenic effect of thyroid hormone. These newly cloned UCPs are 58% homologous to brown adipose tissue UCP (which has been dubbed UCP1 since the cloning of new UCPs). Uncoupling protein 2 and UCP3, like UCP1, are found in the inner mitochondrial membrane and can reduce the proton gradient but, in contrast with UCP1, have a more ubiquitous distribution. However, studies in mice lacking the *ucp2* or *ucp3* gene do not support the concept that these two proteins mediate the thyroid hormone–dependent mitochondrial proton leak. Such experimental models do not show gross energy balance or thermoregulatory problems and seem to increase metabolic rate normally in response to thyroid hormone (27, 28). On the other hand, these negative results should not be readily accepted as definitive. Experiments in transgenic animals with gene knockouts have shown that nature is rich in backup mechanisms, and a compensated thermogenic defect in mice lacking the *ucp2* or *ucp3* gene has not been excluded.

Thyroid hormone could also decrease the efficiency of ATP synthesis through the glycerol 3-phosphate (G3P) shuttle. Oxidations occurring in the cytoplasm ultimately reduce nicotinamide–adenine dinucleotide (NAD) to NADH, which does not enter the mitochondria and has thus to be oxidized back to NAD through the so-called NADH shuttles. There are two of these, namely the malate–aspartate and G3P shuttles, which regenerate NAD by transferring the reducing equivalents,  $H^+$  and  $e^-$ , into the mitochondria, the former at the NADH dehydrogenase level, the latter one step below, at the flavin–adenine dinucleotide (FAD) level of the respiratory chain (29). Thus, for each pair of electrons (or atom of oxygen reduced to  $H_2O$ ), the use of the malate–aspartate shuttle results in the generation of three ATP molecules, whereas the use of the G3P shuttle generates only two. The rate-limiting enzyme in the G3P shuttle is the mitochondrial G3P dehydrogenase (mGPD), which is in the inner mitochondrial membrane and uses FAD as a coenzyme. It has long been known that this enzyme is stimulated by thyroid hormone, but only in the tissues and species in which thyroid hormone increases oxygen consumption. Furthermore, there is a good correlation between the level of stimulation of oxygen consumption and that of mGPD when thyroid hormone is given to hypothyroid rats (30, 31). In theory, the preferential use of this shuttle will result in less ATP produced per atom of oxygen, but the overall impact will

depend on the extent to which NADH and G3P are generated in the cytoplasm. The possibility that mGPD plays a role in thyroid hormone thermogenesis is currently being investigated in our laboratory, in mice with deletion of the *mGPD* gene. Of course, it is possible that *mGPD* is important for adjusting the cells to accommodate other demands imposed by the actions of thyroid hormone but is not essential to the hormone's thermogenic effect.

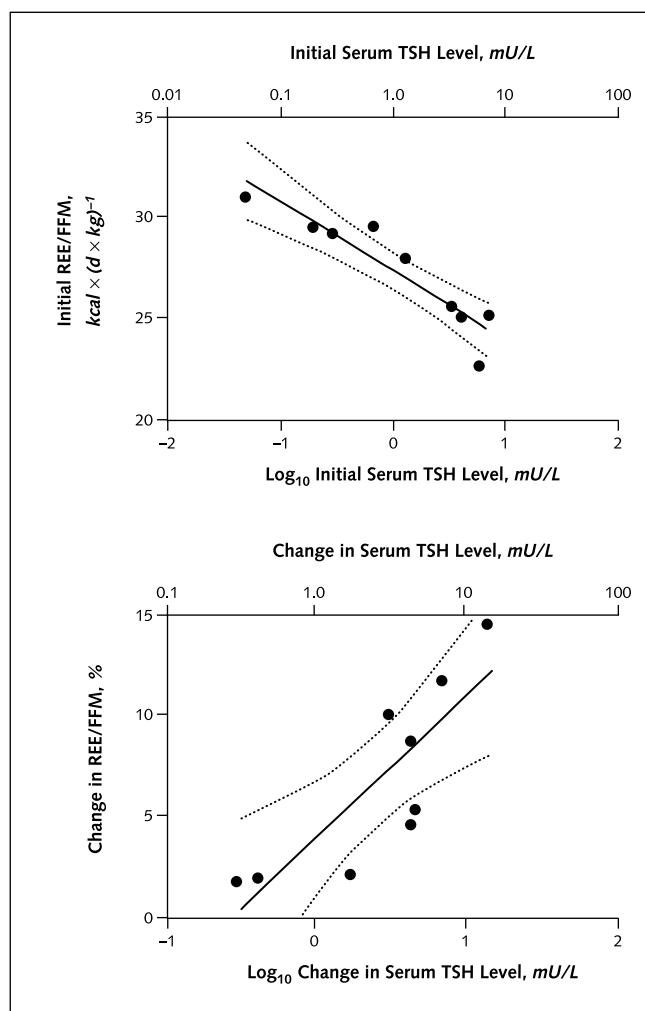
In summary, thyroid hormone increases basal thermogenesis, and therefore obligatory thermogenesis, by accelerating ATP turnover and reducing the efficiency of ATP synthesis. Reduced efficiency of ATP synthesis seems to account for most of the effect in the transition from hypothyroidism to euthyroidism; however, in the transition from the euthyroid to the thyrotoxic state, increased ATP use becomes relatively more important. Although the molecular mechanisms remain to be identified, increasing evidence favors the idea that thyroid hormone uses not one but several means to accomplish its thermogenic role.

For many years, it was assumed that thyroid hormone stimulated only obligatory thermogenesis, a concept that has been challenged only recently. When the essential role of brown adipose tissue in facultative thermogenesis became evident, the effect of thyroid hormone on the function of this tissue was promptly investigated. Thyroid hormone was indeed proved necessary for an efficient response of brown adipose tissue to cold, but further analysis showed that brown adipose tissue of hypothyroid rats appeared to be under increased sympathetic stimulation (12). The induction of thyrotoxicosis did not further enhance UCP activation but reduced its activity (32). Such observations gave rise to the concept that thyroid hormone plays a permissive role in brown adipose tissue thermogenesis. The subsequent discovery of D2 in brown adipose tissue and its activation by the sympathetic nervous system and inhibition by hyperthyroxinemia (33) provided an explanation for those findings. Moreover, it was precisely the experimental manipulation of D2 that allowed researchers to show the importance of locally generated  $T_3$  in brown adipose tissue for the UCP response to adrenergic stimulation, and thus for cold adaptation (13). It was later found that  $T_3$  directly stimulated the rat *ucp* gene, acting on a discrete, separate sequence from which it interacted synergistically with cyclic adenosine monophosphate–dependent signals to cause maximal stimulation of the gene (34).

## RESTING ENERGY EXPENDITURE IN HUMANS IS HIGHLY SENSITIVE TO THYROID HORMONE

It has recently been reported that resting energy expenditure, a good measure of obligatory thermogenesis, is remarkably responsive to thyroid hormone around the euthyroid state in humans (35). In athyreotic patients who maintained a euthyroid state by taking exogenous thyroxine ( $T_4$ ), minimal changes in daily dose to ensure that serum concentrations of free  $T_4$  moved within the normal

**Figure 4.** Correlation between resting energy expenditure (REE), which largely reflects obligatory thermogenesis, and thyroid-stimulating hormone (TSH) in hypothyroid patients receiving maintenance L-thyroxine replacement therapy.



Resting energy expenditure has been corrected by lean body mass or fat-free mass (FFM). After the initial evaluation, the dose of L-thyroxine was slightly changed to move the TSH level around the normal range. In the top panel,  $r = 0.92$  and  $P < 0.001$ ; in the bottom panel,  $r = 0.82$  and  $P < 0.007$ . See reference 35 and the text for details. Adapted with permission from al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab.* 1997;82(4):1118-25; copyright owner, The Endocrine Society.

range were associated with clearly detectable changes in resting energy expenditure. However, no changes were detected in measures of thyroid hormone action used clinically, such as levels of low-density lipoprotein cholesterol, sex hormone-binding protein, or angiotensin-converting enzyme. Yet thyroid-stimulating hormone, the most sensitive marker of thyroid hormone action, correlated inversely and closely with resting energy expenditure. For a maximal excursion of thyroid-stimulating hormone between 0.05 and 10 mU/L induced by the change in L-thyroxine dose, resting energy expenditure changed by 15% ( $r = 0.82$ ;

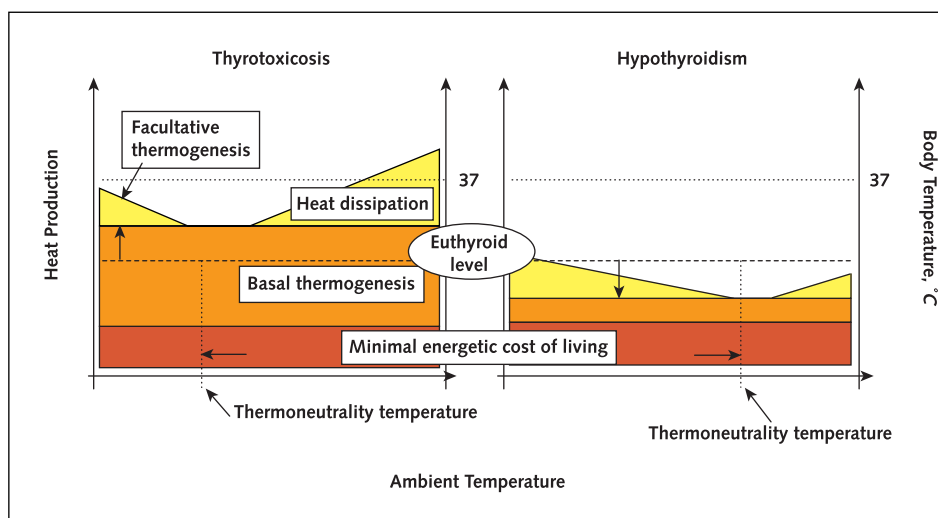
$P < 0.001$ ) (35) (Figure 4). Such levels of thyroid-stimulating hormone are well within those seen in subclinical thyroid dysfunction. Moreover, it has been subsequently reported that spontaneous fluctuations in free  $T_4$  concentration in lean normal men are also associated with significant changes in resting energy expenditure (36).

### THYROID HORMONE THERMOGENESIS IS LINKED TO LIPOGENESIS AND INCREASED FOOD INTAKE

Despite the sensitivity of resting energy expenditure to thyroid hormone stimulation, the transition from hypothyroidism to euthyroidism is not associated with wasting. Patients with mild hyperthyroidism, endogenous or iatrogenic (for example, patients with thyroid cancer treated with a slight excess of thyroid hormone), do not lose weight. This is probably because the thermogenic effect of thyroid hormone is coupled to increased food intake and lipogenesis. It is well known that hyperthyroid patients have increased appetite. In addition, thyrotoxic rats eat more, have increased lipogenesis, and predominantly burn fat (22). Such a relationship is obviously advantageous; without it, the thermogenic effect of thyroid hormone would be wasting and probably would have been eliminated during evolution. The role of increased appetite in maintaining weight in the presence of accelerated metabolism can clearly be seen in the accelerated weight loss that occurs when food intake is limited in hyperthyroidism (37). Increased lipogenesis, on the other hand, secures fuel for heating the body, thus preventing thermogenesis from depleting fat stores and body protein. Like thermogenesis, the lipogenic effect of thyroid hormone is demonstrable only in warm-blooded species. For example, malic enzyme, a key enzyme in the synthesis of fatty acids, is vigorously stimulated by  $T_3$  in the homeothermic rat but not in the poikilothermic trout (6). The coupling between lipogenesis and thermogenesis is also evident in the tissues of a given species, so that thyroid hormone stimulates lipogenesis only in tissues in which it stimulates thermogenesis. For instance, even though thyroid hormone is essential for brain development and function, it stimulates neither oxygen consumption nor lipogenesis in the brain (30, 38, 39).

The rather close relationship of thermogenesis to food intake and lipogenesis suggests that the biological role of thyroid hormone thermogenesis is in temperature homeostasis, not in dumping calories to protect the body from obesity. On the other hand, the depression of thyroid function associated with the so-called euthyroid sick syndrome indicates that thermogenesis is sacrificed when food availability is reduced or when the preservation of body mass is needed in catabolic states. In such conditions, a reduction of leptin (40) and increased cytokines (41) are the signals to reduce, respectively, synthesis of thyroid-releasing hormone and  $T_4$ -to- $T_3$  conversion. Thus, because of the relationship of appetite and lipogenesis to thyroid hormone thermogenesis and the defense of the body fat stores and lean body mass, changes in weight associated

Figure 5. The changes in thermogenesis that occur in thyrotoxicosis and hypothyroidism.



For comparison with the euthyroid state, see Figure 1 (figures are on scale). The heat derived from the minimal energetic cost of living changes little with thyroid status. The most important component of thermogenesis affected by thyroid status is basal thermogenesis. Facultative thermogenesis is reduced in both states but for different reasons. Thermoneutrality temperature is displaced down in thyrotoxicosis and up in hypothyroidism. See text for further details.

with thyroid dysfunction are seen not in mild thyroid dysfunction but only when such homeostatic mechanisms are impaired or overwhelmed by the severity of the dysfunction. Another variable in weight effects of thyroid dysfunction could be diet composition. The stimulation of lipogenesis by thyroid hormone is potentiated by dietary carbohydrates and inhibited by dietary fat (22, 42). Of interest, thyroid hormone produces craving for carbohydrates (43). Total caloric intake and diet composition could therefore explain varying weight loss in patients with thyroid dysfunction.

While thyroid hormone seems to increase lipogenesis by stimulating lipogenic enzyme genes (22), the mechanisms by which it stimulates food intake remain undefined. Thyroid hormone does not seem to have major effects on leptin levels, except indirectly by affecting body fat content (44). Neuropeptides at the hypothalamic level, particularly neuropeptide Y, play an important role in controlling appetite and food intake (45), yet no consistent effect of thyroid hormone on neuropeptides has been found (46). It is more likely (47) that thyroid hormone acts by modifying the level of monoamines (serotonin, dopamine) in the hypothalamus and possibly the signals emanating from the gastrointestinal tract, which could explain the short satiety observed in hyperthyroid patients (43, 47–49). Nonetheless, this area remains largely unexplored.

Thyroid hormone action is initiated by interaction with receptors that belong to the superfamily of nuclear receptors. These are ligand-activated transcription factors that interact with discrete sequences of the regulated genes and then influence transcription rates as a function of the amount of ligand bound (50). Thyroid hormone receptors ( $T_3R$ s) are encoded by two separate genes, the proto-onco-

genes *c-erbA- $\alpha$*  and *c-erbA- $\beta$*  ( $\alpha T_3R$  and  $\beta T_3R$  genes), which generate three major forms of the receptors (called isoforms) resulting from alternate splicing:  $\alpha_1 T_3R$ , from the  $\alpha T_3R$  gene, and  $\beta_1 T_3R$  and  $\beta_2 T_3R$ , from the  $\beta T_3R$  gene. Thyroid hormone receptors are expressed in almost all tissues, but the relative proportion of the isoforms varies and is affected in utero by developmental stage and later by age (51, 52). The affinity of the  $T_3R$  isoforms for  $T_3$  is similar, and it was accepted until recently that the three major forms of  $T_3R$  were functionally interchangeable. Emerging information from mice with deletion of either gene shows that, while many effects of thyroid hormone could be mediated by  $\alpha T_3R$  or  $\beta T_3R$ , some may be mediated more effectively by one isoform over the other, and some may even strictly require either  $\alpha T_3R$  or  $\beta T_3R$  (53). For instance,  $\beta_2 T_3R$  is important for the feedback of thyroid hormone at hypothalamic and pituitary levels, growth, and development of the cochlea, while  $\beta_1 T_3R$  is important for cholesterol metabolism and lipogenesis and  $\alpha_1 T_3R$  is important for the effect of thyroid hormone on the heart and for maintaining body temperature (54–57). Mice with deletion of  $\alpha T_3R$ , but not  $\beta T_3R$ , have body temperatures 0.5 °C to 1 °C lower than normal mice. A recent study showed that although the administration of a selective  $\beta T_3R$  ligand, GC1, could not correct the thermogenic defect of hypothyroid mice, this thyroid hormone analogue vigorously stimulated malic enzyme (58).

These are very important observations that could provide insight into evolutionary aspects of thyroid hormone thermogenesis as well as the possibility of dissociating the thermogenic effects from lipogenesis. Thyroid hormone is probably the most powerful physiologic stimulator of obligatory thermogenesis, yet this effect is linked to lipo-

genesis and stimulation of food intake. The design of analogues with T<sub>3</sub>R isoform selectivity may allow independent manipulation of these effects for therapeutic purposes.

## THERMOGENESIS IN THYROTOXICOSIS AND HYPOTHYROIDISM

Figure 5 provides an integrated view of the components of thermogenesis in thyroid dysfunction. Lower obligatory thermogenesis necessitates increased facultative thermogenesis to maintain body temperature, and vice versa. Thyroid hormone is necessary for both forms of thermogenesis and has the potential to stimulate both. In hyperthyroidism, the two effects would be additive, creating the risk for hyperthermia. Even so, hyperthermia is rarely a manifestation of hyperthyroidism, in the so-called thyroid storm or thyrotoxic storm. As mentioned earlier, there is evidence in rodents that hyperthyroidism is associated with reduced brown adipose tissue facultative thermogenesis (32, 59). Hyperthyroidism decreases sympathetic stimulation of tissues, probably acting at a central level (60), and T<sub>4</sub> directly inhibits D2 (61). Thyroid hormone also rapidly reduces the expression of β<sub>3</sub>-adrenergic receptors in brown adipose tissue (62). These changes may explain the reduced UCP activation and synthesis responses to cold in thyrotoxic rats (59). The hyperthermia of thyroid storm might result from the failure of these or similar mechanisms that prevent activation of facultative thermogenesis in human hyperthyroidism. Type II 5' iodothyronine deiodinase is present in human muscle (63), and thermogenesis in humans may depend on T<sub>3</sub> locally generated by this enzyme (35). The inhibition of D2, suppression of the sympathetic activity, or both could be impaired in the thyrotoxic storm. This view is consistent with clinical features of the thyrotoxic storm, such as its proximity to stressful situations and its alleviation by sympathetic blockade.

In hypothyroidism, obligatory thermogenesis is reduced and the body increases stimulation of brown adipose tissue (64). Although this tissue shows signs of adrenergic stimulation, such as hyperplasia and increased protein content (12), the lack of T<sub>3</sub> in brown adipose tissue drastically limits its thermogenic response to sympathetic stimulation (13). The reduced obligatory thermogenesis is compensated by heat-saving mechanisms and shivering, which are effective only in a narrow range of temperature. In the absence of effective facultative thermogenesis, if ambient temperature decreases further or if the compensations are reduced (for example, by central nervous system depression due to alcohol or barbiturates, sympathetic blockade, or muscle relaxation), hypothermia supervenes.

From Jewish General Hospital, Montreal, Quebec, Canada.

**Grant Support:** By grants from the Medical Research Council of Canada (MT-11550, MT-15101) and Canadian Institutes of Health Research (MOP-44071).

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** J. Enrique Silva, MD, Division of Endocrinology, Jewish General Hospital, Room E-104, 3755 Chemin de la Côte-Ste-Catherine, Montreal, Quebec H3T 1E2, Canada; e-mail, enrique.silva@staff.mcgill.ca.

## References

- Else PL, Hulbert AJ. Comparison of the "mammal machine" and the "reptile machine": energy production. *Am J Physiol.* 1981;240:R3-9. [PMID: 6257122]
- Wolledge RC. Energy transformations in living muscle. In: Wieser W, Gnaiger E, eds. *Energy Transformations in Cells and Organisms.* New York: Georg Thieme Verlag; 1989:36-45.
- Dollberg S, Demarini S, Donovan EF, Hoath SB. Maturation of thermal capabilities in preterm infants. *Am J Perinatol.* 2000;17:47-51. [PMID: 10928604]
- Berry MN, Gregory RB, Grivell AR, Henly DC, Phillips JW, Wallace PG, et al. The thermodynamic regulation of cellular metabolism and heat production. In: Wieser W, Gnaiger E, eds. *Energy Transformations in Cells and Organisms.* New York: Georg Thieme Verlag; 1989:18-27.
- Hulbert AJ, Else PL. Comparison of the "mammal machine" and the "reptile machine": energy use and thyroid activity. *Am J Physiol.* 1981;241:R350-6. [PMID: 7304780]
- Weirich RT, Schwartz HL, Oppenheimer JH. An analysis of the interrelationship of nuclear and plasma triiodothyronine in the sea lamprey, lake trout, and rat: evolutionary considerations. *Endocrinology.* 1987;120:664-77. [PMID: 3803297]
- Magnus-Levy A. Ueber den respiratorischen Gaswechsel unter Einfluss der Thyroidea sowie unter verschiedenen pathologischen Zuständen. *Berlin Klin Wochschr.* 1895;32:650-2.
- Seydoux J, Giacobino JP, Girardier L. Impaired metabolic response to nerve stimulation in brown adipose tissue of hypothyroid rats. *Mol Cell Endocrinol.* 1982;25:213-26. [PMID: 6276252]
- Bianco AC, Silva JE. Intracellular conversion of thyroxine to triiodothyronine is required for the optimal thermogenic function of brown adipose tissue. *J Clin Invest.* 1987;79:295-300. [PMID: 3793928]
- Weiss M, Milman B, Rosen B, Zimlichman R. Quantitation of thyroid hormone effect on skin perfusion by laser Doppler flowmetry. *J Clin Endocrinol Metab.* 1993;76:680-2. [PMID: 8445026]
- Vagn Nielsen H, Hasselstrom K, Feldt-Rasmussen U, Mehlsen J, Siersbaek-Nielsen K, Friis T, et al. Increased sympathetic tone in forearm subcutaneous tissue in primary hypothyroidism. *Clin Physiol.* 1987;7:297-302. [PMID: 3621867]
- Mory G, Ricquier D, Pesquies P, Hemon P. Effects of hypothyroidism on the brown adipose tissue of adult rats: comparison with the effects of adaptation to cold. *J Endocrinol.* 1981;91:515-24. [PMID: 7328374]
- Bianco AC, Silva JE. Optimal response of key enzymes and uncoupling protein to cold in BAT depends on local T<sub>3</sub> generation. *Am J Physiol.* 1987;253:E255-63. [PMID: 3631256]
- Carvalho SD, Kimura ET, Bianco AC, Silva JE. Central role of brown adipose tissue thyroxine 5'-deiodinase on thyroid hormone-dependent thermogenic response to cold. *Endocrinology.* 1991;128:2149-59. [PMID: 2004619]
- Silva JE. Thyroid hormone control of thermogenesis and energy balance. *Thyroid.* 1995;5:481-92. [PMID: 8808101]
- Rolfe DF, Brown GC. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol Rev.* 1997;77:731-58. [PMID: 9234964]
- Nicholls DG, Locke RM. Thermogenic mechanisms in brown fat. *Physiol Rev.* 1984;64:1-64. [PMID: 6320232]
- Cannon B, Nedergaard J. The biochemistry of an inefficient tissue: brown adipose tissue. *Essays Biochem.* 1985;20:110-64. [PMID: 3928372]
- Brand MD. Regulation analysis of energy metabolism. *J Exp Biol.* 1997;200(Pt 2):193-202. [PMID: 9050227]
- Laloi M, Klein M, Riesmeier JW, Muller-Rober B, Fleury C, Bouillaud F, et al. A plant cold-induced uncoupling protein [Letter]. *Nature.* 1997;389:135-6.



[PMID: 9296489]

21. Vianna CR, Hagen T, Zhang CY, Bachman E, Boss O, Gereben B, et al. Cloning and functional characterization of an uncoupling protein homolog in hummingbirds. *Physiol Genomics*. 2001;5:137-45. [PMID: 11285367]
22. Oppenheimer JH, Schwartz HL, Lane JT, Thompson MP. Functional relationship of thyroid hormone-induced lipogenesis, lipolysis, and thermogenesis in the rat. *J Clin Invest*. 1991;87:125-32. [PMID: 1985090]
23. Clausen T, Van Hardeveld C, Everts ME. Significance of cation transport in control of energy metabolism and thermogenesis. *Physiol Rev*. 1991;71:733-74. [PMID: 2057526]
24. Harper ME, Brand MD. The quantitative contributions of mitochondrial proton leak and ATP turnover reactions to the changed respiration rates of hepatocytes from rats of different thyroid status. *J Biol Chem*. 1993;268:14850-60. [PMID: 8392060]
25. Harper ME, Ballantyne JS, Leach M, Brand MD. Effects of thyroid hormones on oxidative phosphorylation. *Biochem Soc Trans*. 1993;21(Pt 3):785-92. [PMID: 8224511]
26. Leijendekker WJ, van Hardeveld C, Elzinga G. Heat production during contraction in skeletal muscle of hypothyroid mice. *Am J Physiol*. 1987;253:E214-20. [PMID: 3618771]
27. Gong DW, Monemdjou S, Gavrilova O, Leon LR, Marcus-Samuels B, Chou CJ, et al. Lack of obesity and normal response to fasting and thyroid hormone in mice lacking uncoupling protein-3. *J Biol Chem*. 2000;275:16251-7. [PMID: 10748195]
28. Arsenijevic D, Onuma H, Pecqueur C, Raimbault S, Manning BS, Miroux B, et al. Disruption of the uncoupling protein-2 gene in mice reveals a role in immunity and reactive oxygen species production. *Nat Genet*. 2000;26:435-9. [PMID: 11101840]
29. Lehninger AL, Nelson DL, Cox MM. *Principles of Biochemistry*. 2nd ed. New York: Worth; 1993.
30. Barker SB, Klitgaard HM. Metabolism of tissues excised from thyroxine-injected rats. *J Physiol (Lond)*. 1952;170:81-6.
31. Lee YP, Lardy HA. Influence of thyroid hormones on l- $\alpha$ -glycerophosphate dehydrogenases and other dehydrogenases in various organs of the rat. *J Biol Chem*. 1965;240:1427-36.
32. Triandafillou J, Gwilliam C, Himms-Hagen J. Role of thyroid hormone in cold-induced changes in rat brown adipose tissue mitochondria. *Can J Biochem*. 1982;60:530-7. [PMID: 7104831]
33. Silva JE, Larsen PR. Interrelationships among thyroxine, growth hormone, and the sympathetic nervous system in the regulation of 5'-iodothyronine deiodinase in rat brown adipose tissue. *J Clin Invest*. 1986;77:1214-23. [PMID: 3958187]
34. Silva JE, Rabelo R. Regulation of the uncoupling protein gene expression. *Eur J Endocrinol*. 1997;136:251-64. [PMID: 9100546]
35. al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *J Clin Endocrinol Metab*. 1997;82:1118-25. [PMID: 9100583]
36. Boivin M, Camirand A, Carli F, Hoffer LJ, Silva JE. Uncoupling protein-2 and -3 messenger ribonucleic acids in adipose tissue and skeletal muscle of healthy males: variability, factors affecting expression, and relation to measures of metabolic rate. *J Clin Endocrinol Metab*. 2000;85:1975-83. [PMID: 10843184]
37. Mooradian AD. Age-related differences in body weight loss in response to altered thyroidal status. *Exp Gerontol*. 1990;25:29-35. [PMID: 2318280]
38. Sood A, Schwartz HL, Oppenheimer JH. Tissue-specific regulation of malic enzyme by thyroid hormone in the neonatal rat. *Biochem Biophys Res Commun*. 1996;222:287-91. [PMID: 8670197]
39. Blennemann B, Leahy P, Kim TS, Freake HC. Tissue-specific regulation of lipogenic mRNAs by thyroid hormone. *Mol Cell Endocrinol*. 1995;110:1-8. [PMID: 7672439]
40. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, et al. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996;382:250-2. [PMID: 8717038]
41. Bartalena L, Bogazzi F, Brogioni S, Grasso L, Martino E. Role of cytokines in the pathogenesis of the euthyroid sick syndrome. *Eur J Endocrinol*. 1998;138:603-14. [PMID: 9678522]
42. Clarke SD, Hembree J. Inhibition of triiodothyronine's induction of rat liver lipogenic enzymes by dietary fat. *J Nutr*. 1990;120:625-30. [PMID: 2352037]
43. Pijl H, de Meijer PH, Langius J, Coenegracht CI, van den Berk AH, Chandie Shaw PK, et al. Food choice in hyperthyroidism: potential influence of the autonomic nervous system and brain serotonin precursor availability. *J Clin Endocrinol Metab*. 2001;86:5848-53. [PMID: 11739450]
44. 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;9:503-12. [PMID: 10365683]
45. Wilding JP. Neuropeptides and appetite control. *Diabet Med*. 2002;19:619-27. [PMID: 12147141]
46. Lopez M, Seoane L, Senaris RM, Dieguez C. Prepro-orexin mRNA levels in the rat hypothalamus, and orexin receptors mRNA levels in the rat hypothalamus and adrenal gland are not influenced by the thyroid status. *Neurosci Lett*. 2001;300:171-5. [PMID: 11226638]
47. Calza L, Forrest D, Vennstrom B, Hokfelt T. Expression of peptides and other neurochemical markers in hypothalamus and olfactory bulb of mice devoid of all known thyroid hormone receptors. *Neuroscience*. 2000;101:1001-12. [PMID: 11113349]
48. Read NW. Role of gastrointestinal factors in hunger and satiety in man. *Proc Nutr Soc*. 1992;51:7-11. [PMID: 1508932]
49. Meguid MM, Fetisov SO, Varma M, Sato T, Zhang L, Laviano A, et al. Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition*. 2000;16:843-57. [PMID: 11054589]
50. Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev*. 2001;81:1097-142. [PMID: 11427693]
51. Hodin RA, Lazar MA, Chin WW. Differential and tissue-specific regulation of the multiple rat c-erbA messenger RNA species by thyroid hormone. *J Clin Invest*. 1990;85:101-5. [PMID: 2153150]
52. Freake HC, Santos A, Goldberg Y, Ghysdael J, Oppenheimer JH. Differences in antibody recognition of the triiodothyronine nuclear receptor and c-erbA products. *Mol Endocrinol*. 1988;2:986-91. [PMID: 2903441]
53. Forrest D, Vennstrom B. Functions of thyroid hormone receptors in mice. *Thyroid*. 2000;10:41-52. [PMID: 10691312]
54. Gloss B, Trost S, Bluhm W, Swanson E, Clark R, Winkfein R, et al. Cardiac ion channel expression and contractile function in mice with deletion of thyroid hormone receptor alpha or beta. *Endocrinology*. 2001;142:544-50. [PMID: 11159823]
55. Johansson C, Gothe S, Forrest D, Vennstrom B, Thoren P. Cardiovascular phenotype and temperature control in mice lacking thyroid hormone receptor-beta or both alpha1 and beta. *Am J Physiol*. 1999;276:H2006-12. [PMID: 10362681]
56. Weiss RE, Murata Y, Cua K, Hayashi Y, Seo H, Refetoff S. Thyroid hormone action on liver, heart, and energy expenditure in thyroid hormone receptor beta-deficient mice. *Endocrinology*. 1998;139:4945-52. [PMID: 9832432]
57. Wikstrom L, Johansson C, Salto C, Barlow C, Campos Barros A, Baas F, et al. Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. *EMBO J*. 1998;17:455-61. [PMID: 9430637]
58. Ribeiro MO, Carvalho SD, Schultz JJ, Chiellini G, Scanlan TS, Bianco AC, et al. Thyroid hormone—sympathetic interaction and adaptive thermogenesis are thyroid hormone receptor isoform—specific. *J Clin Invest*. 2001;108:97-105. [PMID: 11435461]
59. Sundin U. GDP binding to rat brown fat mitochondria: effects of thyroxine at different ambient temperatures. *Am J Physiol*. 1981;241:C134-9. [PMID: 7282915]
60. Silva JE. Catecholamines and the sympathoadrenal system in thyrotoxicosis. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2000:642-51.
61. Silva JE, Larsen PR. Hormonal regulation of iodothyronine 5'-deiodinase in rat brown adipose tissue. *Am J Physiol*. 1986;251:E639-43. [PMID: 3538896]
62. Rubio A, Raasmaja A, Silva JE. Thyroid hormone and norepinephrine signaling in brown adipose tissue. II: Differential effects of thyroid hormone on beta 3-adrenergic receptors in brown and white adipose tissue. *Endocrinology*. 1995;136:3277-84. [PMID: 7628361]
63. Larsen PR. Mammalian type 2 deiodinase sequences: finally, the end of the beginning [Editorial]. *J Clin Invest*. 1996;98:242-3. [PMID: 8755629]
64. Silva JE. Catecholamines and the sympathoadrenal system in hypothyroidism. In: Braverman LE, Utiger RD, eds. *Werner and Ingbar's The Thyroid*. 8th ed. Baltimore: Lippincott Williams & Wilkins; 2000:820-3.