Peripheral Regulation of Energy Metabolism by Thyroid Hormones

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ABSTRACT

Thyroid hormone is long known as an important regulator of metabolism. It exerts general effects such as increased cycling of metabolites and stimulation of ATP turnover in spite of reduced efficiency of oxidative phosphorylation, but also very specific effects in peripheral tissues. This article reviews the most relevant metabolic effects of thyroid hormone in peripheral tissues, including the specific contributions of the two different thyroid hormone receptor isoforms. Special focus is put on the thermogenic effects of thyroid hormone in muscle and brown adipose tissue as well as the exclusive role of the thyroid hormone receptor β in hepatic cholesterol metabolism.

Keywords: thermogenesis, brown adipose tissue, liver, glucose, metabolism, cholesterol
Introduction

It is known for over 100 years that thyroid hormone (TH) has a major impact on metabolism (1), and the metabolic rate has long been used as an indicator for the thyroid state. The connection between TH and metabolism becomes most evident in patients substituted with thyroxine (T4): after initiation of the treatment increased oxygen consumption is registered after 24 hours, reaching maximal levels after 4 days (2). Moreover, minimal dose changes, which do not move the serum free T4 out of the normal range, are readily detectable as changes in the metabolic rate (3). The higher energy expenditure caused by TH is usually accompanied by increased appetite; if food is restricted, weight loss occurs (4). This has lead to the idea to use TH as diet pill, but the unwanted side effects such as tachycardia, muscle loss and osteoporosis outweigh the beneficial effects.

TH and its receptors

Two forms of TH are secreted from the thyroid gland: the prohormone T4 and the receptor-active form T3. Within the target tissue, T3 levels are fine-tuned by the activation or inactivation through deiodinating enzymes. While it has been assumed for long time that TH enters the cell due to its lipophilic properties, the view has changed with the recent discovery of specific TH transporters such as MCT8 or OATP14 (for review see (5)).

Within the cell, most effects of TH are mediated by nuclear TH receptors (TRs), which are encoded by the two distinct genes TRα and TRβ. It is still a matter of controversy whether the TRα1 and TRβ isoforms can fully compensate for each other; however, the degree of redundancy seems to depend to a large extent on the level of TR isoform coexpression within a given celltype. The expression of TRα1 is high in e.g. brown adipose tissue, skeletal muscle, brain and heart, while TRβ is predominantly expressed in liver and kidney (for review see (6)).

A special feature of TRs is the ability to actively repress or activate target genes as aporeceptors in the absence of the ligand T3. This activity is the reason for the relatively mild phenotype of TR knockout mice (7-9) compared to mutants lacking TH or carrying mutations that impair TH binding to the TRs (10-14). The aporeceptor-function and the widespread partially overlapping expression
of the TRs make the interactions of TH with peripheral metabolism extremely complex including simultaneous actions at many different levels.

**Metabolic Lessons from Animal Models**

In most of the available animal models, targeting of the TR isoforms occurs in all tissues, thus the corresponding phenotypes are difficult to interpret. For instance, mice carrying a mutation in TRβ which abolishes binding of T3, or transgenic mice expressing a mutant human TRβ both exhibit reduced body weight and size, but also high levels of TH due to the impaired negative feedback control of the pituitary (15, 16). Therefore, the metabolic effects are difficult to assign to a specific tissue and can be caused by either the high levels of TH acting on the intact TRα1 or by the mutant TRβ itself.

The situation is likewise complex for TRα1. So far, four different mutations have been introduced into TRα1, and the phenotypes range from metabolically lean (17), dwarfism with impaired adipogenesis (18, 19) or reduced fat content (20), to animals with visceral adiposity and increased fasting glucose and insulin (21, 22). As serum TH levels are surprisingly normal in these animals, the differences seem to be caused by the location of the mutation within the TRα1 itself, which may affect interactions with cofactors or nuclear receptors such as PPARs (21).

However, hypothyroid mice as well as mice lacking all functional TRs show decreased metabolism (23). Furthermore, TRα1/-TRβ/- double mutants do no longer respond metabolically to TH. These observations indicate that the metabolic effects of TH are mediated largely by TRα1 and TRβ (23) and underline the importance of TH for the maintenance of normal metabolism.

**Overall Effects of TH**

TH generally enhances the turnover of lipids, carbohydrates and proteins, sometimes even simultaneously in reverse metabolic pathways (metabolic cycling). While fatty acids can be used up in this process, no protein is used for calorigenesis and the excretion of nitrogen as well as renal gluconeogenesis remain constant (2). Metabolic cycling, however, accounts for only 15% of
the increase in resting energy expenditure after TH administration (2), indicating that other processes such as ATP wasting and reduced efficiency of oxidative phosphorylation play a more important role in mediating the metabolic effects of the hormone. The main energy waste is achieved by a combined increase of ATP consuming proteins, such as Na\(^+/\)K\(^+\)- or Ca\(^{2+}\)-ATPases, and a stimulation of the ATP synthesizing machinery (3). TH enhances the mitochondrial oxidation capacity by e.g. increasing the amount of the adenine-nucleotide translocase 2 (ANT2), which transports ADP in and ATP out of the mitochondria (24), and the cytochromes c and c1 (25), which are part of the oxidizing machinery. Simultaneously, the efficiency of the ATP synthesis itself is reduced; consequently, more fuel is needed for the same amount of biochemical work. In certain tissues such as the brown fat, this is achieved by a reduction of the coupling efficiency between mitochondrial proton gradient and ATP production through Uncoupling Protein 1 (UCP1). This protein generates artificial leaks in the mitochondrial membrane; however, UCP-independent mechanisms have also been reported (26). Moreover, at the cytosolic level, TH increases the expression of glycerol-3-phosphate dehydrogenase (24), which participates in one of the two shuttle systems that deliver NADH to the mitochondria. This shuttle system, which only yields 2 ATP molecules per NADH, is consequently preferred over the malate-aspartate shuttle, which generates 3 ATP per NADH (3). Thus, the efficiency of ATP production is additionally hampered.

**Effects on the Adipose Tissue**

In adipose tissue, TH stimulates lipolysis and lipogenesis simultaneously, which is in line with the concept of metabolite cycling. Lipolysis is enhanced by TH through a raised activity of hormone-sensitive lipase and an increased sensitivity of the adipose tissue to adrenergic stimulation, leading to higher levels of free-fatty acids in the serum. The expression of lipogenic enzymes such as malic enzyme, spot14 or fatty acid synthetase is also increased already after a few hours; the first de novo synthesis of fatty acids is detected about 10 hours later (2). Interestingly, the TRβ-selective agonist GC1 does not induce fat loss to the same extent as T3, despite a similar increase in oxygen consumption (27). This demonstrates an important role for
TRβ in the initial raise in energy expenditure, which differs from TRα1-dependent adipose tissue activation. Indeed, the activity of the adipose tissue accounts for less than 5% of the increase in oxygen consumption after T3 administration, suggesting that the effects of TH on this tissue are a more long-term metabolic response. This correlates with the fact that the compensating food intake after TH treatment does not occur until 4 days later, most probably as a consequence of the reduced secretion of the satiety hormone leptin from the shrinking adipose tissue.

The effects of TH differ in the two types of adipose tissue. While the white adipose tissue is mainly a fat store and the induction of lipolysis generates fatty acids for the export, the brown adipose tissue (BAT) uses lipolysis, de novo synthesis and import of free fatty acids as fuel to maintain body temperature. TH does not induce thermogenesis by itself, but it is essential for the proper activation of this tissue (26). The activity of the BAT is mainly controlled by sympathetic signaling via the β3-adrenergic receptor and completely dependent on UCP1; in its absence there is almost no sympathetic inducible thermogenesis (28). As there is good evidence that BAT also exists in humans (29), the thermogenic role of TH in mice and men will be elucidated in greater detail.

**Thermogenic Effects of TH**

TH stimulates obligatory thermogenesis (generated by basal metabolism) and is essential for facultative thermogenesis (generated by specialized mechanisms with the purpose to maintain body temperature) (3, 30). The latter is induced, if obligatory thermogenesis is not sufficient to maintain body temperature, and is divided into a fast response by e.g. muscle shivering and a slow but more long-lasting response through the BAT. The BAT response is based on heat production through uncoupling; mice lacking UCP1 loose more than 10°C body temperature when exposed to cold, whereas mice with an ablation of 60-70% of BAT are still cold resistant (31).

Interestingly, TRα1/-/TRβ/-/ double knockout mice and hypothyroid mice such as the hyt/hyt mouse cannot survive cold at all (23, 32). While the BAT response is severely impaired in hypothyroid animals (33), UCP1 is inducible by adrenergic signaling in the TRα1/-/TRβ/-/ double mutants (23). However, this is still not sufficient for survival in the cold; thus, proper TH signaling seems to be more important than BAT functionality alone.
Furthermore, TR aporeceptor activity plays an important role in this process: the T3 induced relief of apo-TR mediated repression seems required for sympathetic stimulation. While the UCP1 induction is restored by T3 and GC1 in hypothyroid mice, the sympathetic response is only rescued with T3. This indicates that TRβ is involved in controlling UCP1 expression, while the adrenergic signaling is modulated mainly by TRα1 signaling (33).

Vice versa, the adrenergic activation enhances TH signaling by inducing the T4 activating enzyme deiodinase type II (D2) (34), which in turn produces enough T3 to saturate all TRs in BAT (35). In the absence of D2, BAT adrenergic response is impaired. Consequently, D2-/- mice develop hypothermia if exposed to cold, but still survive in contrast to hypothyroid animals, as the thermogenesis by shivering is not affected (36).

In summary, TRs exert well-defined tissue- and isoform specific roles in maintaining body temperature (Table 1). However, as mutations in TRα1 also affect the sympathetic output from the brain (17), the central effects of TH on thermogenesis and metabolism might be underestimated to date. In addition, yet unknown TH effects on the vascular system might contribute to explain the reduced body temperature despite increased oxygen consumption in some animal models.

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Body Temperature (relative to controls)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyt/hyt</td>
<td>-2.5°C</td>
<td>severely hypothyroid, cold intolerant</td>
</tr>
<tr>
<td>TRβ-/-</td>
<td>normal</td>
<td>increased TH levels, not cold sensitive</td>
</tr>
<tr>
<td>TRα1-/-</td>
<td>-0.5°C</td>
<td>not cold sensitive</td>
</tr>
<tr>
<td>TRα0/0</td>
<td>-0.4°C</td>
<td>no facultative thermogenesis at room temperature, but higher O2 consumption</td>
</tr>
<tr>
<td>TRα2-/-</td>
<td>+0.4°C</td>
<td>overexpress TRα1</td>
</tr>
<tr>
<td>TRα1R384C</td>
<td>-0.9°C</td>
<td>despite higher O2 consumption</td>
</tr>
<tr>
<td>TRα1P398H</td>
<td>-0.5°C</td>
<td>obese</td>
</tr>
<tr>
<td>TRα1L400R</td>
<td>normal</td>
<td>lean dwarfs</td>
</tr>
<tr>
<td>TRα1-/-TRβ-/-</td>
<td>-0.4°C</td>
<td>increase metabolism and UCP1 upon cold, but still cold intolerant</td>
</tr>
</tbody>
</table>

Table 1: Body temperature of animal models with impairments in TH signaling (9, 17, 20, 22, 23, 32, 37-39)
Effects on the Muscle

The muscle is a versatile tissue regarding its use of metabolites. While the resting muscle consumes fatty acids, the active muscle requires large amounts of glucose. TH mainly affects muscle glucose metabolism; it increases glycolysis and almost doubles the amount of the insulin dependent glucose transporter GLUT4 on the cell surface (40). Consequently, the import, the flux through the Krebs-Cycle, and the oxygen consumption are all elevated; however, as the mitochondrial efficiency is also reduced by TH, the overall ATP production remains almost constant (41). Moreover, TH promotes further waste of energy by increasing the protein Ca\(^{2+}\)-ATPase, which transports Ca\(^{2+}\) from the cytosol into the sarcoplasmic reticulum (SR), and simultaneously raising the levels of the ryanodine receptor, which mediates the Ca\(^{2+}\) release from the SR back into the cytosol (42, 43). This mechanism alone accounts for an almost 2-fold increase in oxygen consumption between a hypo- and a hyperthyroid muscle (43), which raises the question for a physiological function as the muscle is dependent on an efficient ATP supply for proper function. However, as the muscle is also the first line of defence against hypothermia and TH actions in the muscle are absolutely required for survival in the cold, in the eye of TH the muscle is predominantly seen as a thermo- rather than a movement generator.

Effects on the Heart

It is well known that the consequences of thyrotoxicosis on the heart such as tachycardia closely resemble those of catecholamine excess; but surprisingly, catecholamine levels are normal if not lowered in hyperthyroidism. This suggests that TH increases cardiac responsiveness to catecholamines; however, not at the level of the adrenergic receptors (44).

The direct molecular effects of TH include an increase in HCN2 ion channels as well as an elevation of myosin heavy chain and SR-Ca\(^{2+}\)-ATPase 2, thus leading to an enhanced cardiac output and decreased the relaxation time (45). These effects are not observed with the TR\(\beta\) selective compound GC1, underlining that TR\(\alpha1\) of major importance in the heart (27, 46). Correspondingly, mice lacking TR\(\alpha1\) have a decreased heart rate, while those overexpressing
TRα1 exhibit an increased heart rate (9, 39). As for the BAT, any central effects of TH might additionally affect cardiac function e.g. via changes in the autonomic nervous system.

**Effects on the Liver**

As the liver acts at the crossroads of many metabolic pathways – the most important one being glucose homeostasis - it is not surprising that more than 5% of all genes expressed in the liver are regulated by TH (47, 48). These targets mediate general T3-effects such as increased oxygen consumption and ATP turnover (49), but also shift metabolic processes from glycogen synthesis to glycogenolysis and from glycolysis to gluconeogenesis, thus enhancing the endogenous hepatic glucose production (50). Moreover, T3 stimulates enzymes involved in lipogenesis such as malic enzyme, glucose-6-phosphate dehydrogenase and fatty acid synthetase. Although many of these target genes show redundant function for TRα1 and TRβ in the rodent liver (51), some such as spot14 (52) are predominantly regulated by TRβ, the isoform accounting for 80% of hepatic T3 binding capacity (53).

One pathway exclusively regulated by TRβ is cholesterol metabolism. Again, TH affects both ends: it induces the rate-limiting enzyme HMG-CoA reductase, thus stimulating de novo cholesterol synthesis, but also increases the expression of the LDL-receptor and CYP7A, the rate-limiting enzyme in bile-acid synthesis from cholesterol (54, 55). Together, this leads to a better clearance of serum LDL-cholesterol and an increased cholesterol breakdown. Consequently, hypothyroidism is associated with hypercholesterolemia in men and mice due to a reduced clearance of serum LDL-cholesterol and a reduced bile-acid production by CYP7A (56). The TRβ dependency of this process can be used to ameliorate this condition by the administration of the TRβ selective compound GC1, which reduces serum cholesterol by 25% and leads to an increased faecal excretion of bile-acids (46, 57). Moreover, it reverses fatty livers and reduces the hepatic triglyceride content, indicating an important exclusive role of TRβ also in fatty acid metabolism (58). Surprisingly, GC1 was found to be even more efficient than T3 in this context (46), which suggests opposite roles of TRα1 and TRβ in hepatic lipid metabolism. A similar reverse
The effect of the TRs was observed in the regulation of PEPCK, the rate-limiting enzyme in gluconeogenesis (Vujovic, Vennström & Mittag, unpublished observations). These unique isoform-specific effects might be partially caused by the zonated hepatic expression of the TRs: TRβ is limited to areas around the central vein, while TRα1 is more widespread and the only periportal TR isoform (59-61). As a consequence, the isoforms cannot compensate for each other and might interact with different cellular cofactors in the different hepatic zones.

Despite the many well investigated direct effects of TH on hepatic gene expression, it should be kept in mind that TH also affects several hepatic metabolic pathways in an indirect manner, e.g. via the autonomic nervous system (62) or by enhancing the effects of other hormones such as insulin, glucagons or glucocorticoids (25).

**Concluding Remarks**

Besides the overall and long-known effects such as increase metabolic cycling and ATP turnover, many specific effects of TH in peripheral metabolism were identified over the last years, using e.g. novel TRβ selective compounds and animal models with defective TH signaling (see Table 2).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>TR isoform</th>
<th>T3 Effect</th>
</tr>
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<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>1. metabolite cycling ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. ATP use and production ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. efficiency of ATP production ↓</td>
</tr>
<tr>
<td>White Fat</td>
<td>TRα1+TRβ</td>
<td>lipolysis, lipogenesis, export of FFA ↑</td>
</tr>
<tr>
<td>Brown Fat</td>
<td>TRα1</td>
<td>adrenergic responsiveness, heat ↑</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>TRα1&gt;&gt;TRβ</td>
<td>Ca²⁺ cycling, glucose &amp; ATP use ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>oxygen consumption, heat ↑</td>
</tr>
<tr>
<td>Heart</td>
<td>TRα1&gt;&gt;TRβ</td>
<td>tachycardia, cardiac output ↑</td>
</tr>
<tr>
<td>Liver</td>
<td>TRβ (80%)</td>
<td>lipogenesis (malic enzyme, spot14, FAS) ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gluconeogenesis (PEPCK) ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glycogenolysis ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glycolysis (pyruvate kinase) ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glycogensynthesis ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cholesterol ↓</td>
</tr>
<tr>
<td>Other</td>
<td>TRα1</td>
<td>gluconeogenesis ↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>required for proper development and function of the autonomic nervous system</td>
</tr>
<tr>
<td></td>
<td>TRα1, TRβ</td>
<td>effects of glucocorticoids, insulin, glucagons, catecholamines ↑</td>
</tr>
</tbody>
</table>

Table 2: Role of TH and TRs in different tissues; ¹perivenously ²periportally; FAS = fatty acid synthetase; FFA = free fatty acids; PEPCK = phosphoenol pyruvate carboxykinase
This identification of TR isoform specific functions opened the possibility to target defined metabolic pathways. The TRβ selective compounds KB2115 and GC1, for instance, were shown to be very efficient in reducing serum cholesterol in different animal models without the characteristic cardiac effects of T3 (63, 64). Unfortunately, the Holy Grail, a TH based diet pill, is still not achieved, as weight loss is usually accompanied by a compensatory increased food intake and weight regain on drug withdrawal. However, recent discoveries of novel TH dependent pathways, such as the actions of bile acids on TH-dependent activation of the BAT (65) or the hypothermic effects of the TH-derivate 3-iodothyronamine (66), impressively demonstrate the outstanding role of TH in the regulation of metabolism and reminds us, in spite of the many novel metabolic regulators, not to forget the “old” players.

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