

# Effect of thyroid hormone on gene expression

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## Purpose of review

Thyroid hormones are key regulators of development and metabolism that modulate transcription via nuclear receptors. Although the molecular actions of thyroid hormones have been thoroughly studied, their pleiotropic effects are mediated by complex changes in expression of numerous, but still largely unknown, target genes. This review summarizes the recent advances in the characterization of target genes in different organs.

## Recent findings

New patterns of gene expression regulation have been described in tissues with known physiological actions of thyroid hormone, that is brain, liver, skeletal and cardiac muscles, and brown and white adipose tissues. The studies have benefited from the numerous transgenic models with altered thyroid hormone receptor expression and the application of DNA microarray technology to mouse and human tissues.

## Summary

Data on thyroid hormone-mediated control of gene expression and on the roles of the different thyroid hormone receptor isoforms bring new clues to our understanding of the molecular mechanisms of thyroid hormone action in physiological situations and, most importantly, in diseases associated with alterations of the thyroid status.

## Keywords

thyroid hormone, nuclear receptors, microarray, gene expression profiling

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## Abbreviations

|              |  |
|--------------|--|
| <b>CPT-I</b> | carnitine palmitoyltransferase I       |
| <b>SERCA</b> | sarcoplasmic Ca <sup>2+</sup> -ATPases |
| <b>T3</b>    | triiodothyronine                       |
| <b>T4</b>    | thyroxine                              |
| <b>TR</b>    | thyroid hormone receptor               |
| <b>TRE</b>   | thyroid hormone response element       |

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## Introduction

Thyroid hormones control essential functions in growth, differentiation and metabolism [1•]. The hormones are required for the normal function of nearly all tissues. Malfunctions of the thyroid gland are very common endocrine disorders. In the nineteenth century, hyperthyroidism was found to be associated with heart dysfunction, exophthalmos and increased metabolic rate and a link was made between hypothyroidism and cretinism. The isolation of thyroxine (T4) in 1914, and later of triiodothyronine (T3), a much more active molecule, paved the way for their therapeutic use and for studies of the molecular basis of thyroid hormone action. The major effects of thyroid hormones are mediated by modulation of gene transcription [2,3]. Some direct effects of T3 on mitochondrial gene transcription have been described [4]. Most gene regulations, however, are explained by the interaction of thyroid hormone receptors (TRs) with thyroid hormone response elements (TREs) within nuclear genes. TRs are nuclear receptors encoded by two genes, TR $\alpha$  and TR $\beta$ . The TR $\alpha$  gene generates several proteins. Only TR $\alpha$ 1 is authentic; the other forms may act as inhibitors. Through alternative promoter use, the TR $\beta$  gene yields TR $\beta$ 1 and TR $\beta$ 2 and other forms, the physiological importance of which is less known. TR $\alpha$ 1 and TR $\beta$ 1 are ubiquitously expressed. The level of expression of TR $\alpha$ 1 is the highest in skeletal muscle and brown adipose tissue, while TR $\beta$ 1 is preferentially expressed in brain, kidney and liver. TR $\beta$ 2 is found in the pituitary gland and in discrete areas of the hypothalamus. TRs are capable of binding to TREs as monomers or homodimers. TRs bind to many TREs, however, as heterodimers with the retinoid X receptor. Most TREs are positive *cis*-acting elements at which gene transcription is repressed by unliganded TRs and activated by T3-occupied TRs. In the presence of ligand, the TR undergoes a conformational change, which results in the replacement of a corepressor complex by a coactivator complex. The coactivator complex histone acetyltransferase activity leads to an open transcriptionally active chromatin state. The recruitment of the TR-associated protein complex may constitute a subsequent step in transcriptional activation by T3. In the absence of ligand, the heterodimer interacts with a corepressor complex with histone deacetylase activity. Histone deacetylation and DNA methylation both lead to transcriptional repression.

## Brain

Thyroid hormones play an essential role in the development of brain. Hypothyroidism during the neonatal

period can cause mental retardation and neurological defects. For the understanding of thyroid hormone action on central nervous system development, identification of regulated genes is important. Hypothyroidism is difficult to induce as the brain is able to convert T4 into T3. To circumvent this problem, microarray analysis was performed on whole brain from Pax8<sup>-/-</sup> mice [5]. The Pax8 gene knockout results in the absence of thyroid follicle and therefore provides a model of congenital hypothyroidism. On the 4000 genes analyzed, only 14 transcripts showed regulation. However, the analysis identified cyclin D2 as a novel thyroid hormone target gene in the cerebellum. Activation of the cyclin D2 gene was dependent both on TR $\alpha$  and TR $\beta$  as revealed by studies on TR $\alpha$  and TR $\beta$  transgenic mice. As cyclin D2 is a key regulator of apoptosis and proliferation in external granular layer cells, its regulation by T3 may be important in the postnatal development of the cerebellum. The identification of a limited number of target genes on whole brain preparation is probably related to time-dependent and brain area-specific regulation. The effect of thyroid hormones on target genes has been studied on primary neuronal cell cultures [6]. Oligonucleotide microarray representing 8000 genes was used to study the early effect of T3. Four genes were found to be regulated. Downregulation of the neuronal apoptosis-inducing gene may be linked to its upregulation in the hypothyroid state, which could participate in granule cell apoptosis. Upregulated genes include the nuclear pore glycoprotein P62, the bone morphogenetic protein 4 that controls neuroblast mitosis and the basic transcription element-binding protein. Regulation of the transcription factor level by T3 participates in the control of the degree of neurite branching, an essential aspect of brain development [7]. Regulation of neuronal proliferation and differentiation by T3 may involve the proto-oncogene c-myc. T3 blocks proliferation and induces differentiation of the neuroblastoma N2a- $\beta$  cells that express the TR $\beta$ 1 isoform. The very rapid repression of c-myc expression in these cells may contribute to cell cycle arrest and elicit differentiation. A negative T3 responsive element has been identified within the first exon of the c-myc gene [8]. In combination with CCCTC binding factor, a zinc finger nuclear factor which binds to an adjacent site, TRs form a repressor complex. Mice with a mutant TR $\beta$ 1 allele that does not bind T3 revealed the importance of the formation of corepressor complex by unliganded TRs in the pathogenesis of the syndrome of resistance to thyroid hormone [9••]. The mice show abnormalities in cerebellar development and function with a decrease in mRNA levels for Pcp2, a Purkinje cell-specific gene. The learning defect, which is also reminiscent of the human pathology, is similar to the deficiency observed in mice with disruption of the brain-derived neurotrophic factor. Indeed, a decrease in brain-derived neurotrophic

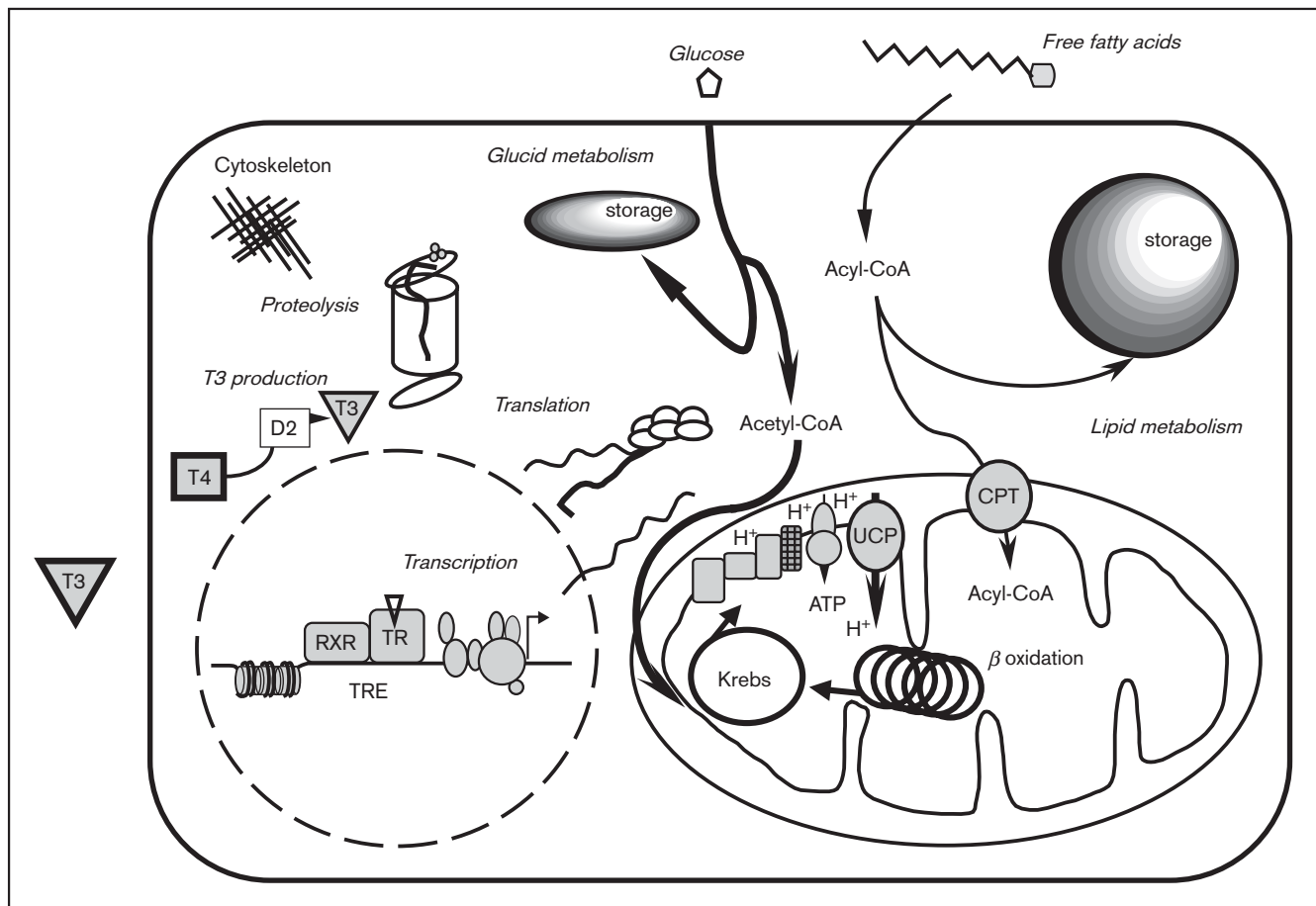
factor expression was observed in the hippocampus of the mutant TR $\beta$ 1 mice. In another mutant TR $\beta$ 1 knock-in model, alteration of gene expression was observed in the pituitary with a marked upregulation of the  $\alpha$ -glycoprotein subunit of thyroid-stimulating hormone and, to a lesser extent, an increase in the thyroid-stimulating hormone-specific  $\beta$  subunit [10]. Growth hormone mRNA levels were decreased. Therefore, despite an increase in thyroid hormone levels, the response of T3 target genes was attenuated in the pituitary of mutant mice. Hormone-mediated repression and activation was largely suppressed. *In vivo*, thyroid hormone concentrations are controlled by a feedback inhibition of thyroid-stimulating hormone synthesis by pituitary thyrotrophs. However, thyroid-stimulating hormone synthesis is also regulated by thyrotropin-releasing hormone, originating from hypothalamic paraventricular neurons. Recent work on transgenic animals showed that T3-induced regulation of thyrotropin-releasing hormone expression in the hypothalamic paraventricular nucleus is mediated by TR $\beta$ 2 [11•]. This is in contrast with the thyrotrophs where both TR $\alpha$  and TR $\beta$  isoforms mediate negative regulation.

### Liver

Hyperthyroid patients have elevated metabolic rate, and lipid and glucid turnover [12]. Thyroid hormones have profound effects on fatty acid oxidation (Fig. 1). This process takes place in mitochondria and involves key rate-controlling enzymes such as carnitine palmitoyl-transferase I (CPT-I), located in the outer mitochondrial membrane. In hyperthyroid rats, the induction of CPT-I $\alpha$  mRNA is higher in the liver than in other tissues. Studies on transgenic mice showed that the first intron of the CPT-I $\alpha$  mRNA is required for T3 induction and hepatic expression [13]. Furthermore, in hyperthyroid rats, carnitine bioavailability is increased through an upregulation of the mRNA encoding  $\gamma$ -butyrobetaine hydroxylase that catalyzes the last reaction of carnitine synthesis [14]. Complementary to acyl coenzyme A transport from the cytosol to the mitochondrial matrix, the mitochondrial malate/aspartate and  $\alpha$ -glycerophosphate shuttles provide reduced nicotinamide adenine dinucleotide for adequate electron transport respiratory chain activity. It was reported in rat liver that T3 increases mRNA levels for  $\alpha$ -glycerophosphate shuttle but not for the malate/aspartate shuttle [15]. Thyroid hormones also stimulate lipogenesis. Pax8<sup>-/-</sup> mice show an accumulation of triglyceride in the liver and a decrease in apolipoprotein B RNA editing without change in apolipoprotein B mRNA level. The effect on apolipoprotein B RNA editing is due to a downregulation of apobec-1 complementation factor mRNA level [16••].

Microarray technology has been used to temporally compare liver gene expression in TR $\beta$ -deficient and

Figure 1. Schematic view of thyroid hormone effect on gene expression in adipose tissues, skeletal muscle and liver



Triiodothyronine (T3) can be converted from thyroxine (T4) within the cell through type 2 5'-deiodinase (D2). The activity is high in brown adipose tissue. T3 modulates gene transcription through activation of thyroid hormone receptors (TRs) that bind thyroid hormone response elements (TREs) as heterodimers with retinoid acid X receptor (RXR). Microarray analysis revealed an effect on both protein translation and proteolysis in skeletal muscle, the net result being protein breakdown. Cytoskeleton proteins were also regulated. In liver, many genes involved in lipid and glucid metabolism were regulated. Genes involved in mitochondrial energy metabolism are affected by thyroid status in all tissues. Not represented here is the regulation of many signal transduction and transcription genes observed in skeletal muscle and liver. CPT, carnitine palmitoyl transferase; UCP, uncoupling protein.

hypo and hyperthyroid wild type mice [17••]. Among 2000 expressed genes, 200 were regulated under T3. As expected, numerous genes involved in lipogenesis, lipid mobilization and  $\beta$  oxidation were upregulated. Genes of mitochondrial oxidative phosphorylation were upregulated. Surprisingly, most of the genes involved in glucid utilization were decreased. Many genes participating in signal transduction were either up or downregulated. Use of TR $\beta$ -deficient mice allowed the identification of T3-regulated genes under the dependence of the TR $\beta$ 1 isoform, which is the main form expressed in the liver. Interestingly, the data reveal that TR $\beta$  is dispensable for about 40% of the genes, suggesting a previously underappreciated role for TR $\alpha$ 1.

The importance of transcriptional coactivator in TR-mediated gene regulation was addressed by the study

of steroid receptor coactivator-1-deficient mice [18•]. The regulation by thyroid hormone of 5'-deiodinase and malic enzyme was not altered. In hypothyroid mice, however, inactivation of the coactivator gene resulted in a lack of induction of Spot14 mRNA. As the level of Spot14 mRNA was increased in hypothyroid knockout mice, steroid receptor coactivator-1 may participate in ligand-dependent suppression of the Spot14 gene. Unliganded TRs interact with corepressors to repress transcription of target genes. Liver-specific overexpression of a dominant negative mutant of the corepressor NcoR leads to a derepression of Spot14, 5'-deiodinase, but not malic enzyme in hypothyroid mice [19•]. The two studies reveal differences between T3-regulated genes, suggesting promoter-dependent assembly of coactivator and corepressor complexes.

### Skeletal muscle and heart

Thyroid deficiency leads to muscular weakness and cardiac deficiency characterized by a global reduction in contractile functions and metabolic alterations, for example, carbohydrate turnover, free fatty acid oxidation and respiratory chain activity. Thyroid hormones control the expression of genes encoding many myosin isoforms, Na<sup>+</sup>/K<sup>+</sup>ATPases and sarcoplasmic Ca<sup>2+</sup>-ATPases (SERCA). Hypothyroidism causes a shift in myosin heavy chain isoform expression from myosin heavy chain IIb to myosin heavy chain IIa. A recent paper reviewed the implication of T3 in the regulation of SERCA 1, the fast-muscle isoform and SERCA 2a, the slow-muscle isoform [20]. Both genes are regulated by T3 in skeletal muscle. Cold exposure which is accompanied by a rise in plasma T3 and an increase in type 2 5'-deiodinase gene expression and activity induces SERCA 1 expression in slow-type fibers. The alteration of cardiac function according to thyroid status has been studied in TR $\alpha$  and TR $\beta$  knockout mice [21]. This investigation showed that myosins, SERCA 2, the K<sup>+</sup> channels KV4.2 and minK, and the nucleotide-gated channels HCN2 and HCN4 mRNAs are regulated through TR $\alpha$ 1, the lack of TR $\alpha$ 1 not being compensated by TR $\beta$ . Moreover, TR $\alpha$ 1 is more abundant than TR $\beta$  in mouse heart. Therefore, the cardiac functions regulated by T3 appear to be predominantly mediated by TR $\alpha$ . Thyroid hormones regulate the ability of tissues to utilize carbohydrates. A study on thyroid hormone regulation of enolase, a glycolytic enzyme, showed opposite regulation during heart and skeletal muscle development [22]. Such differences between glycolytic skeletal muscle and oxidative cardiac muscle underlined the physiological adjustment to energy demand of these two types of muscle.

A pangenomic analysis has been performed in skeletal muscle from healthy humans with T3 treatment for 2 weeks [23••]. Interestingly, most of the target genes were upregulated under T3. They represented a wide range of cellular functions including transcriptional control, mRNA maturation, protein turnover, signal transduction, cellular trafficking and energy metabolism. Among the genes involved in energy metabolism, the mRNA level for uncoupling protein 3, a mitochondrial inner membrane carrier, was increased, as earlier shown by quantitative reverse transcriptase polymerase chain reaction [24]. T3 also induced the expression of adenine nucleotide translocator-1 as observed in heart [25]. The profound effect of thyroid hormone on mitochondria was further illustrated by the regulation of several components of the respiratory chain and enzymes of the citric acid cycle. Among the protein metabolism genes, there was an upregulation of many components of the ubiquitin-proteasome pathway, providing a clear molecular signature of the well known proteolytic impact of thyroid hormones.

### Adipose tissues

Thyroid status influences both brown and white adipose tissue development and metabolism. Effects include modulation of fatty acid synthesis via regulation of expression of lipogenic enzymes, modulation of other hormone sensitivity and increase in oxygen consumption. Hyperthyroidism enhances various responses to catecholamines. Thyroid hormones and catecholamines are known to be necessary for the expression of the uncoupling protein 1 which is responsible for the thermogenic role of brown adipose tissue [26]. Thyroid hormone contributes to brown adipose tissue thermogenesis by stimulating the expression of elements of the norepinephrine signaling pathway and by direct induction of the uncoupling protein 1 gene. Activation of catecholamine signaling is mediated by the TR $\alpha$ 1 isoform while TR $\beta$  is sufficient to stimulate uncoupling protein 1 gene expression [27•]. The contribution of brown adipose tissue to T3 production by local deiodination of T4 through type 2 5'-deiodinase activation has been widely documented. The effect of hyperthyroidism on the enzyme is mainly exerted through adrenergic stimuli. It has recently been shown that, in primary cultures of rat brown adipocytes, T3 by itself also increases type 2 5'-deiodinase mRNA levels [28]. The mRNA for the ubiquitously expressed uncoupling protein 2 is upregulated in human white adipose tissue from hyperthyroid patients [29] and in T3-treated isolated adipocytes [30]. Concerning the lipolytic pathway, thyroid hormones are well known to modify the response to catecholamines and insulin. In-vitro treatment of human adipose tissue explants with T3 revealed that thyroid hormones directly regulate the expression of genes controlling intracellular cAMP level and thereby contribute to the enhanced ability of catecholamines to induce lipolysis [30]. Furthermore, 1200 cDNA macroarray experiments showed that the expression of genes encoding proteins involved in signal transduction, lipid metabolism, apoptosis and inflammatory response were modified by thyroid hormones. Among the genes involved in lipid metabolism, the transcription factor SREBP 1c was downregulated by T3 in mature adipocytes. SREBP 1c is a member of the basic helix-loop-helix family of transcription factors which stimulates adipogenesis, enhances the expression of genes involved in lipogenesis and is upregulated during adipocyte differentiation.

### Conclusion

Recent gene expression studies revealed previously unknown patterns of regulation controlled by T3, providing new insights into the action of thyroid hormones (Fig. 1). Thyroid hormones exert cellular effects that are common to many cell types, for example, on mitochondrial energy metabolism. To date, the few comprehensive analyses based on microarray data show

limited T3-regulated gene overlap between tissues. Future microarray analyses with full coverage of the human and mouse genomes and *ad hoc* statistical analysis will undoubtedly reveal the common and the tissue-specific regulated pathways. To progress in the understanding of T3 action *in vivo*, numerous transgenic models have been generated. Use of the transgenic models with modified expression of TRs [31•] and gene expression profiling techniques will provide information on the roles of each receptor isoforms, including naturally occurring mutations. Data in humans remain scarce. Transcriptome analysis on adipose tissue and possibly on skeletal muscle of patients with thyroid diseases would contribute to unravel the pathological consequences of the perturbances of thyroid status on peripheral tissues.

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