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Review

# Thyroid hormones and mitochondria: With a brief look at derivatives and analogues

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ABSTRACT

Thyroid hormones (TH) have a multiplicity of effects. Early in life, they mainly affect development and differentiation, while later on they have particularly important influences over metabolic processes in almost all tissues. It is now quite widely accepted that thyroid hormones have two types of effects on mitochondria. The first is a rapid stimulation of respiration, which is evident within minutes/hours after hormone treatment, and it is probable that extranuclear/non-genomic mechanisms underlie this effect. The second response occurs one to several days after hormone treatment, and leads to mitochondrial biogenesis and to a change in mitochondrial mass. The hormone signal for the second response involves both T3-responsive nuclear genes and a direct action of T3 at mitochondrial binding sites. T3, by binding to a specific mitochondrial receptor and affecting the transcription apparatus, may thus act in a coordinated manner with the T3 nuclear pathway to regulate mitochondrial biogenesis and turnover. Transcription factors, coactivators, corepressors, signaling pathways and, perhaps, all play roles in these mechanisms. This review article focuses chiefly on TH, but also looks briefly at some analogues and derivatives (on which the data is still somewhat patchy). We summarize data obtained recently and in the past to try to obtain an updated picture of the current research position concerning the metabolic effects of TH, with particular emphasis on those exerted via mitochondria.



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## 1. Thyroid hormones and iodothyronines: the general picture

The thyroid gland produces two main iodothyronines: 3,5,3′,5′-tetraiodothyronine (thyroxine or T4) and 3,5,3′-triiodo-L-thyronine (T3). TH release from the thyroid occurs as part of a feedback mechanism involving the pituitary–hypothalamic axis. At any given time, most T4 and T3 in the body is bound to transport proteins, with only a small, "unbound" or "free", fraction being biologically active. The functions of these proteins most probably include: (a) ensuring a constant supply of TH to the cells and tissues by preventing urinary loss, (b) protecting the organism against abrupt changes in thyroid-hormone production and/or degradation, and (c) ultimately protecting against iodine deficiency.

All the circulating T4 is secreted by the thyroid gland, whereas most (about 80%) of the systemic T3 is generated by deiodination of T4 within peripheral tissues. T3 is further deiodinated to yield 3,3′-T2 and also, perhaps, 3,5-T2.

Thyroid-hormone deiodination is mediated by three iodothyronine deiodinases: type I deiodinase (D1), preferentially expressed in the liver but also present in kidney, thyroid, and pituitary; type II deiodinase (D2), present in the central nervous system, anterior pituitary, brown adipose tissue, and placenta; type III deiodinase (D3), present in the central nervous system, placenta, skin, and fetal tissue. For further details on deiodinases, the reader is referred to Orozco et al., 2012; Dentice and Salvatore, 2011; Bianco, 2011.

As mentioned above, T4 is synthesized entirely within the thyroid, while approximately 80% of T3 is formed by peripheral conversion of T4. Uptake of TH into peripheral tissues is mediated by specific membrane transporter proteins. Several transporter families have been identified, among which the monocarboxylate transporter (MCT) family deserves special attention. Fourteen members of this family have been recognized so far, but in only 6 of them has a ligand-binding site been identified. MCT8 and MCT10 have been identified as specific TH transporters. However, while MCT8 is currently known to be highly specific only for TH (Friesema et al., 2003), MCT10 also has the ability to carry different types of amino acid [e.g., the carrier polypeptide of various organic anion transporters (OATP1C1, OATP1A2, OPTP1A4)]. Among the OATPs, OATP1C1 is the most interesting for the present purposes because it displays high specificity and affinity for certain iodothyronines (especially for T4 and rT3, although not for T3). Moreover, its preferential localization within the endothelium of brain capillaries suggests that OATP1C1 is important for the transport of TH across the blood–brain barrier (Mayerl et al., 2012). The physiological roles performed by the TH transporters have been discussed in recent reviews (Kinne et al., 2011; Visser et al., 2011) and so will not be described here any further.

## 2. Actions of thyroid hormones

TH act via two distinct pathways: (1) nuclear pathways and (2) non-nuclear pathways.

### 2.1. Overview of nuclear pathways

At the beginning of the 1960s, Tata and coworkers were the first to show that administration of TH to hypothyroid rats induced an increase in their basal metabolic rate, while the simultaneous injection of an inhibitor of transcription (such as actinomycin-D) inhibited this effect (Tata, 1963). These data implicated the nucleus as the locus for the above action. In other experiments, using isolated nuclei, they showed that T3 stimulated DNA-dependent RNA-polymerase activity. Later, Samuels et al. and Oppenheimer et al. identified high-affinity nuclear binding sites for TH, suggesting that thyroid hormone nuclear receptors (TR) mediated the effects of T3 (Tata et al., 1962; Tata et al., 1963; Samuels et al., 1974; Oppenheimer et al., 1974; Bassett et al., 2003). In the ensuing years, efforts were made to purify the receptors, but the results did not allow detailed investigation of their molecular properties until the simultaneous cloning of the receptors by Sap et al. (1986) and Weinberger et al. (1986). In mammals, two genes, TRalpha and TRbeta, encode several thyroid-receptor isoforms (TRalpha1, the two splicing variants TRalpha2 and TRalpha3; TRbeta1, TRbeta2, and TRbeta3, respectively). All TRbeta isoforms retain T3-binding activity, whereas only TRalpha1 of the TRalpha isoforms possesses binding activity. The existence of various isoforms of TRs raises the question as to whether they have distinct or redundant roles. Their tissue-dependent expressions and developmentally regulated differential expression suggest that they mediate specific isoform-dependent actions. In view of their substantial amino-acid homology with respect to steroid hormone receptors, all TR isoforms are considered to be members of the large superfamily of nuclear receptors that also includes the receptors for retinoic acid, vitamin D and peroxisomal proliferator activators. These receptors contain multiple functional domains that include, in particular, a DNA-binding domain (DBD) and a carboxyl-terminal ligand-binding domain (LBD). The DBD domain contains about 70 amino acids forming two "zinc fingers". This region is highly conserved and interacts with the specific DNA segments known as "thyroid-hormone response-elements" (TREs). T3 receptors are transcription factors: they modulate transcription mainly by binding TREs. In the absence of T3, the TR has an intrinsic transcriptional repressor function. In most cases, the TRs act as heterodimers with a 9-cis retinoic acid receptor (RXR), but there are also multiple TR complexes that bind to TREs (Farach-Carson and Davis, 2003). In addition to RXR, many other molecules are directly or indirectly functionally associated with TRs (vitamin D3, peroxisome proliferator-activated receptor (PPAR), corepressors, coactivators, etc.). The transcriptional activity of TRs is regulated at multiple levels: by T3 itself; by the type of TRE located on the promoters of T3 target genes; by the developmental- and tissue-dependent expressions of TR isoforms; and by a host of nuclear coregulatory factors (coactivators and corepressors) with T3-dependent activity. Deeper consideration of these mechanisms can be found in some recent reviews (Oetting and Yen, 2007; Yen et al., 2006; Cheng et al., 2010; Flamant and Gauthier, 2012; Tata, 2012).

### 2.2. Overview of non-nuclear pathways

A number of effects mediated by iodothyronines have been described for which a binding to TRs can be excluded, and it is currently assumed that these effects involve extranuclear binding sites in several compartments of the cell (including the plasma membrane, the cytoskeleton, the cytoplasm, and mitochondria: for review, see Cheng et al., 2010). Unlike the nuclear effects, the extranuclear ones: (i) are independent of thyroid hormone nuclear receptors; (ii) may occur within a short time (seconds to minutes); and (iii) may be mediated by signal-transducing pathways such as cAMP and protein kinases (Bassett et al., 2003; Farach-Carson and Davis, 2003; Saelim et al., 2004; Axelband et al., 2011). Some studies have demonstrated that plasma membrane-initiated actions begin at a binding site on integrin αVβ3, a heterodimer protein that interacts both with extracellular matrix proteins and thyroid hormones (Bergh et al., 2005; Cody et al., 2007). Other molecules – such as stilbene, resveratrol (Lin et al., 2007, 2008), and dihydrotestosterone (Lin et al., 2009a) – also bind to this integrin (Davis et al., 2009). Lin et al. (2009b) demonstrated that the hormone-binding domain comprises two binding sites. One site is solely for the binding of T3 and activates the phosphatidylinositol 3-kinase (PI3K) pathway, leading to cytoplasm-to-nucleus shuttling

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