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REVIEW

Thyroid hormone action in postnatal heart development

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Abstract Thyroid hormone is a critical regulator of cardiac growth and development, both in fetal life and postnatally. Here we review the role of thyroid hormone in postnatal cardiac development, given recent insights into its role in stimulating a burst of cardiomyocyte proliferation in the murine heart in preadolescence; a response required to meet the massive increase in circulatory demand predicated by an almost quadrupling of body weight during a period of about 21 days from birth to adolescence. Importantly, thyroid hormone metabolism is altered by chronic diseases, such as heart failure and ischemic heart disease, as well as in very sick children requiring surgery for congenital heart diseases, which results in low T3 syndrome that impairs cardiovascular function and is associated with a poor prognosis. Therapy with T3 or thyroid hormone analogs has been shown to improve cardiac contractility; however, the mechanism is as yet unknown. Given the postnatal cardiomyocyte mitogenic potential of T3, its ability to enhance cardiac function by promoting cardiomyocyte proliferation warrants further consideration.

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Introduction

Thyroid hormone (TH) is a critical regulator of many physiological and developmental processes, following its activation from the stable prohormone (L-thyroxine, T4) to the short-lived active hormone, triiodothyronine (3,5,3′-triiodo-L-thyronine, T3) (Fig. 1). T3 induces amphibian metamorphosis by stimulating the remodeling of specific tissues and organs (Tata, 1993). In mammals, T3 is essential for development, with congenital hypothyroidism resulting in growth retardation, deafness, impaired neurogenesis, and congenital heart malformations (Legrand, 1986; Olivieri et al., 2002). THs also have important effects on oxygen consumption and metabolism. The actions of THs are mediated by the products of two TH receptor (TR) genes, the nuclear proteins, TRα and TRβ, which show differential patterns of expression in development and in adult tissues (Mai et al., 2004). Stimulation of these receptors results in the direct transcriptional activation of a wide range of genes (genomic effects). More recently, non-genomic effects of TH initiated at the cell surface, in the cytoplasm or in mitochondria have also been identified (Davis and Davis, 2002; Davis et al., 2011). Adding further complexity, TH signaling is highly regulated by the expression of cell and tissue-specific TH transporters that concentrate THs in target cells, by the relative expression and distribution of TR isoforms, by interaction of TRs with corepressors and coactivators, by cross-talk with several other signaling pathways, and by the sequence and location of the TH response element. Furthermore, TH signaling is tightly regulated by the activation and catabolism of THs by three selenoenzyme iodothyronine deiodinases: D1, D2 and D3—considerations that have been comprehensively reviewed elsewhere (Zoeller et al., 2007; Kress et al., 2009; Brent, 2012).

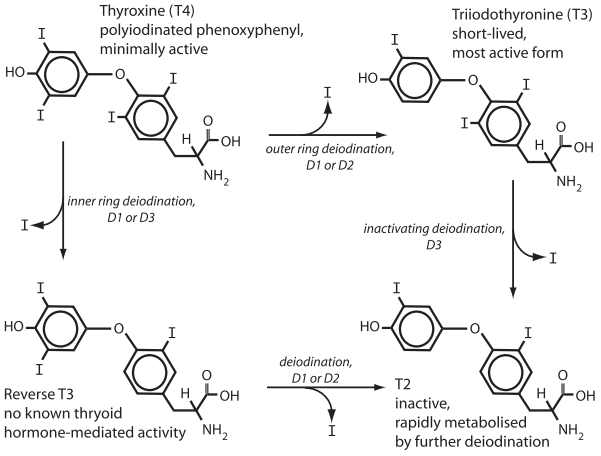

Figure 1 Deiodinase-mediated metabolism of thyroid hormone. Deiodination of the outer, phenolic ring of T4 catalyzed by type 1 or type 2 iodothyronine deiodinases (D1 or D2, respectively) converts T4 to active T3. Both T4 and T3 are inactivated by deiodination of the inner tyrosyl ring by Type 3 iodothyronine deiodinase (D3) to yield reverse T3 or T2, respectively. D1 can also convert T4 to reverse T3, which is further metabolized to T2 by D1 or D2.

T3 has profound effects on the cardiovascular system with chronic hyperthyroidism in adulthood resulting in a physiological-type of cardiac hypertrophy, characterized by a predominant increase in cardiomyocyte (CM) length rather than width, and by enhanced expression of α-MHC, as well as a marked reduction in systemic vascular resistance accompanied by increased cardiac contractility, systolic hypertension, and increased cardiac output. In contrast, prolonged hypothyroidism results in diastolic hypertension, reduced cardiac output and stroke volume, as well as cardiac dilatation and even overt heart failure. The effects of T3 on the heart are due to the transcriptional regulation of a number of contractile and calcium handling genes (Maillet et al., 2013). These effects have been most widely studied with respect to their role in postnatal heart development, and under the premise that CMs exit the cell cycle and become terminally differentiated soon after birth.

Here, after a brief consideration of TH biology, we revisit the role of TH in postnatal heart development, given recent evidence indicating that the proliferative competence of CMs may be retained until well after the neonatal period, allowing murine CMs to undergo a proliferative burst during preadolescence in response to a T3 surge (Naqvi et al., 2014); that T3 can induce DNA synthesis in terminally differentiated adult CMs (Ledda-Columbano et al., 2006), and that remodeling post-myocardial infarction in mice is associated with local hypothyroidism of spared myocardium due to re-expression of D3, a thyroid-inactivating enzyme normally expressed only in the fetus (Janssen et al., 2013).

TH biology

TH production and ontogeny of the hypothalamic–pituitary–thyroid axis

TH is synthesized and secreted by the thyroid gland, a follicular organ that synthesizes TH by iodination of tyrosine residues in the glycoprotein, thyroglobulin. Thyroid stimulating hormone (TSH) secreted by the anterior pituitary in response to thyrotropin releasing hormone (TRH) elaborated by neurons of the hypothalamic paraventricular nucleus activates TSH receptors expressed on the basolateral membrane of thyroid follicular cells. This results in adenylyl cyclase activation and enhanced iodide uptake into the thyroid gland via the sodium/iodide symporter, which in turn is used in the biosynthesis of THs. Both T4 and T3 are synthesized and released from the thyroid gland, are carried in the circulation bound to specific proteins (thyroxine-binding globulin, transthyretin and albumin), and exert a negative feedback on both the release of pituitary TSH as well as on the activity of TRH on hypothalamic neurons.