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Review

Mechanisms of action of thyroid hormones in the skeleton ☆

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ABSTRACT

Background: Thyroid hormones regulate skeletal development, acquisition of peak bone mass and adult bone maintenance. Abnormal thyroid status during childhood disrupts bone maturation and linear growth, while in adulthood it results in altered bone remodeling and an increased risk of fracture
Scope of Review: This review considers the cellular effects and molecular mechanisms of thyroid hormone action in the skeleton. Human clinical and population data are discussed in relation to the skeletal phenotypes of a series of genetically modified mouse models of disrupted thyroid hormone signaling.
Major Conclusions: Euthyroid status is essential for normal bone development and maintenance. Major thyroid hormone actions in skeletal cells are mediated by thyroid hormone receptor α (TRα) and result in anabolic responses during growth and development but catabolic effects in adulthood. These homeostatic responses to thyroid hormone are locally regulated in individual skeletal cell types by the relative activities of the type 2 and 3 iodothyronine deiodinases, which control the supply of the active thyroid hormone 3,5,3'-L-triiodothyronine (T3) to its receptor.
General Significance: Population studies indicate that both thyroid hormone deficiency and excess are associated with an increased risk of fracture. Understanding the cellular and molecular basis of T3 action in skeletal cells will lead to the identification of new targets to regulate bone turnover and mineralization in the prevention and treatment of osteoporosis. This article is part of a Special Issue entitled Thyroid hormone signaling.

1. Thyroid hormone action

The synthesis and release of the pro-hormone 3,5,3′,5′-L-tetraiodothyronine (thyroxine, T4) and the biologically active thyroid hormone 3,5,3′-L-triiodothyronine (T3) are regulated by a classical negative feedback loop involving the paraventricular nucleus of the hypothalamus and the anterior pituitary thyrotropes.

The hypothalamus secretes TRH (thyrotropin-releasing hormone) into the portal circulation to stimulate production and secretion of TSH (thyrotropin, thyroid-stimulating hormone) by the pituitary. TSH subsequently acts via the TSH receptor (TSHR) on thyroid follicular cells to stimulate synthesis and release of T4 and T3. The circulating thyroid hormones are predominantly bound to carrier proteins including thyroxine binding globulin, transthyretin (previously known as thyroxine binding pre-albumin) and albumin, with only approximately 0.2% of the total T3 and 0.02% of total T4 available as free unbound hormones (fT3, fT4) in plasma. Circulating fT3 and fT4 ultimately act in the hypothalamus and anterior pituitary to inhibit synthesis and secretion of TRH and TSH. Thus, systemic thyroid status is maintained within a normal reference range by the hypothalamic-pituitary-thyroid (HPT) axis negative feedback loop (Fig. 1A). This negative feedback loop maintains a physiological inverse relationship between TSH and circulating T3 and T4 levels that defines the HPT axis set-point [1,2]. Systemic fT4, fT3 and TSH concentrations vary significantly among individuals, indicating each person has a unique HPT axis set point [3]. Twin studies suggest the HPT axis set point is predominantly genetically determined with heritability for fT3, fT4 and TSH of 65% [4]. Consistent with this, genome wide association studies (GWAS) have identified quantitative trait loci for fT4 (14q13 and 18q21), fT3 (7q36, 8q22 and 18q21) and TSH (2q36, 4q32) [5].

Circulating T4 is derived from thyroid gland secretion, whereas the majority of the pool of systemic T3 is generated by deiodination of T4 in peripheral tissues. Thyroid hormone metabolism is mediated by three iodothyronine deiodinases. The type 1 and type 2 enzymes (D1 and D2) catalyze deiodination of the pro-hormone T4 to the active hormone T3 by removal of an iodine atom from the outer ring of T4. Conversely, the type 3 enzyme (D3) irreversibly inactivates both T4 and T3 by removal of an inner ring iodine atom [6]. Circulating thyroid hormones are bound to carrier proteins including thyroxine-binding globulin (TBG), transthyretin and albumin. Uptake into peripheral tissues is mediated by several specific membrane transporter proteins including the monocarboxylate transporters 8 and 10 (MCT8 and MCT10) and the organic anion transporter protein 1c1 (OATP1C1).

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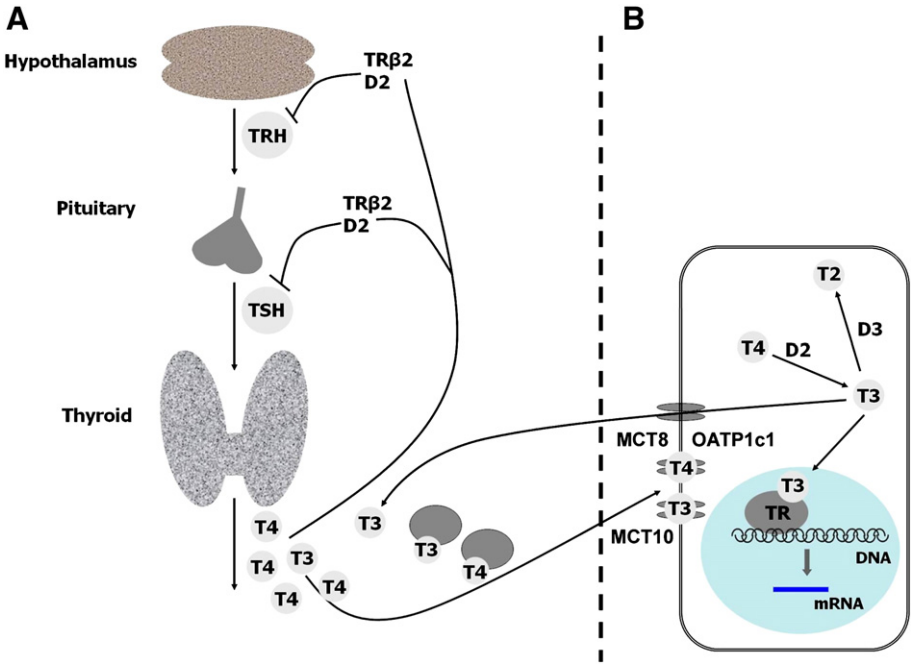

Fig. 1. Hypothalamic-pituitary-thyroid axis and thyroid hormone action. (A) The thyroid gland secretes the pro-hormone T4 and a small amount of the active hormone T3. Their circulating concentrations are regulated by a classical negative feedback loop. TRH is synthesized and secreted in the hypothalamus and acts on pituitary thyrotropes to stimulate synthesis and secretion of TSH. TSH acts on thyroid follicular cell to stimulate growth of the gland and thyroid hormone secretion. T4 and T3 subsequently inhibit secretion of TRH and TSH acting via TRβ2 to complete a negative feedback loop. (B) Thyroid hormones enter target cells via specific membrane transporters including MCT8, MCT10 and OATP1C1. The intracellular concentration of T3 is determined by the relative activities of the deiodinases, D2 and D3. T3 enters the nucleus and bind to TRs, which act as hormone inducible transcription factors to regulate expression of T3-target genes.

Thyroid hormone action is mediated primarily via the nuclear thyroid hormone receptors (TRα and TRβ), which act as ligand-inducible transcription factors that mediate diverse cellular responses including proliferation, differentiation and apoptosis. The 3 functional TR proteins, TRα1, TRβ1 and TRβ2 are encoded by *THRA* and *THRB*. TRα1 and TRβ1 are expressed in virtually all tissues, but their abundance and roles differ, depending on the developmental stage of the organism and on the particular tissue type. By contrast, expression of TRβ2 is restricted to the hypothalamus, pituitary and sensory organs where it regulates the HPT axis and timing of the onset of hearing and color vision [7]. TRs bind to specific thyroid hormone response element sequences (TREs) located in promoter regions of T3-target genes and regulate their expression in a ligand-dependent manner (Fig. 1B).

2. Skeletal development

The skeleton forms by two distinct mechanisms, endochondral and intramembranous ossification (Fig. 2). Long bones form via endochondral ossification, during which mesenchymal stem cells differentiate into chondrocytes that proliferate and secrete cartilage matrix to form a scaffold or anlage [8,9] (Fig. 2A). Chondrocytes undergo hypertrophic differentiation commencing at the centre of the anlage and this process is followed by cartilage mineralization, chondrocyte apoptosis and vascular invasion. This calcified cartilage forms a template for bone formation by invading osteoblasts that lay down and mineralize bone matrix (osteoid). Chondrocytes at both ends of the anlage organize to form epiphyseal growth plates and secondary ossification centers. The ordered process of growth plate chondrocyte proliferation, hypertrophic differentiation, apoptosis and subsequent new bone formation mediates linear growth until adulthood [10]. Progression of endochondral ossification and the rate of linear growth are tightly regulated by multiple systemic hormones (including thyroid hormones, growth hormone, insulin-like growth factor 1, glucocorticoids and sex steroids) and various cytokines and growth factors (including parathyroid hormone-related peptide (PTHrP), Indian hedgehog (Ihh), bone morphogenetic proteins, fibroblast growth factors, vascular endothelial growth factors) that act in a paracrine and autocrine manner [11]. By contrast, the skull vault is formed by intramembranous ossification, in which condensations of mesenchyme differentiate into osteoblasts, which secrete and mineralize osteoid to form bone directly without an intermediate cartilage model [12] (Fig. 2B). During these processes of skeletal development and linear growth, bone mass accumulates and mineralization increases until peak bone mass [13] is achieved in early adulthood. Throughout adult life there is a gradual loss of bone mass, which in women is accelerated at the menopause.

3. Adult bone remodeling

Structural integrity and strength of the adult skeleton is maintained by a continual process of regeneration and repair. The bone remodeling cycle has a duration of 150–200 days and is characterized by sequential periods of activation, bone resorption, reversal, bone formation and quiescence (Fig. 3). The cycle is mediated by osteoclasts and osteoblast-derived cells located in basic multicellular units (BMU) [14]. In the adult human skeleton up to 2 million BMUs are active and separated both spatially and temporally, thus demonstrating the importance and scale of continuous bone turnover and renewal. Local activation of bone remodeling is initiated by changes in mechanical load, structural damage or in response to systemic or paracrine factors. Activation of bone lining cells results in the recruitment of osteoclast progenitor cells and their differentiation to multinucleated bone-resorbing osteoclasts. Mature osteoclasts adhere to activated bone surfaces and resorb bone by creating a localized microenvironment into which they secrete acid and proteases resulting in demineralization of bone and degradation of matrix proteins. Subsequently reversal cells, which are alkaline phosphatase-expressing precursor cells of uncertain phenotype probably arising from the osteoblast lineage, engulf and remove demineralized and undigested matrix fragments from the resorbed bone surface [15,16]. The bone