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Review Article

Thyroid Hormone Signaling in Muscle Development, Repair and Metabolism

Jang-Won Lee[1], Nam-Ho Kim[1] and Anna Milanesi[2]*

[1]Department of Neurosurgery, Cedars-Sinai Medical Center, USA
[2]Department of Medicine, Division of Endocrinology, VA Greater Los Angeles Healthcare System, USA

Special Issue on
Role of Thyroid Hormone in Metabolic Homeostasis

*Corresponding author
Anna Milanesi, Division of Endocrinology, VA Greater Los Angeles Healthcare System andDepartment of Medicine, David Geffen School of Medicine at UCLA 90073, Email: amilanesi@mednet.ucla.edu

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Abstract

Skeletal muscle is a plastic organ made by highly specialize fibers with specific and different structure, function and metabolism. Skeletal muscle fibers can adapt, change, recover/regenerate after injury in response to various stimulators including hormones. Thyroid hormones are important players in the homeostasis of several tissue including skeletal muscle and their genomic action mostly depend on the tissue T3 bioavailability and on the distribution of the thyroid receptor isoforms which act as transcription factors and are modulated by T3. Changing in contractile and metabolic proprieties of the muscle fibers has been described in experimental models of hyper and hypothyroidism. Animal models with disruption of thyroid hormone signaling showed different and specific skeletal muscle phenotypes. By focusing on thyroid hormone signaling in skeletal muscle homeostasis, we review T3 specific action on skeletal muscle development, postnatal growth, function and metabolism.

INTRODUCTION

Thyroid Hormones (THs) act in various tissues during development and post-natal life by modulating genes expression [1-3]. Triiodothyronine (T3) has actions in virtually every tissue, including skeletal muscle [4-7]. Myopathic changes have been found in the majority of the patient with hypothyroidism [8] including muscle weakness and pseudohyperthrophy, myastenic syndrome and rhabdomyolysis. On the other hand different degrees of muscle weakness and atrophy are also well known in hyperthyroid patients [9]. Even the mechanisms are not fully understood, the myopathy secondary to thyroid dysfunctions outlines the importance of THs and their signaling in skeletal muscle phenotypes and functions.

The genomic actions of T3 are mediated by thyroid hormone nuclear receptors (TRs), which act regulating gene transcription [10]. The two TR isoforms, TRα and TRβ, are expressed in specific temporal and spatial patterns during development with relative expression varying in different tissues and cell types [11]. Both TRs are present in the skeletal muscle with predominant expression of TRα [12]. In addition, it has been identified in the mitochondria a 43-KD truncated form of the nuclear receptor TRα1 (p43), important in skeletal muscle development and function, which is stimulated by T3 [13]. Moreover, tissue action of T3 is regulated by deiodinase enzymes that are able to activate T4 to T3 (type 2 deiodinase; DIO2) or inactivate both T4 and T3 (type 3 deiodinase; DIO3) [14]. The presence of DIO2 in skeletal muscle [15] indicates a possible critical role of thyroid hormone signaling in muscle phenotype and homeostasis [16].

Here, we will review the role of THs and their signaling in skeletal muscle development, postnatal growth, function and metabolism.

THYROID HORMONES AND SKELETAL MUSCLE DEVELOPMENT

T3 is considered a regulator of muscle development *in vivo*. During embryonic development muscle progenitor cells are induced to differentiate by signaling from the near tissues such as nothocord, and dorsal and lateral endoderm through activation of myogenic regulatory factors (MRFs). THs stimulate expression of several MRFs, including myogenin and myoblast determination protein 1 (MyoD1) [17,18].

It is well known that T3 stimulates skeletal muscle growth by increasing number and diameter of the muscle fiber [19]. Moreover T3 plays a role in the transition of neonatal to adult myosin isoforms. Immunocytochemical and biochemical studies showed that lack of THs results in a persistent of embryonic myosin in fetal skeletal muscle in rats [20] and excessive THs lead to accumulate myosin heavy chains resulted in precocious muscle maturation [21] of human fetal skeletal muscles (7-40 weeks of gestation). However, the absence of embryonic and fetal MHC isoform in TRs-deficient mice suggests that the transition from neonatal to adult myosin isoforms is not mediated by

only thyroid hormone [22]. In addition, hypothyroidism does not block but delay transitioning from embryonic/fetal to adult myosin [23].

Mice with knockdown of both TR α and β (TRαβ-/-) has significant lower muscle weight at birth resulting from smaller and fewer muscle fibers, indicating a role of TH on skeletal muscle development and possible skeletal muscle wasting [22] (Table 1).

Thyroid hormone and postnatal muscle growth and repair

Maintenance and repair of skeletal muscles during post-natal life primarily rely on specialized myofiber-associated mononuclear cells called Satellite Cells (SCs). SCs are located in close contact with muscle fibers and beneath the basal lamina [24], and express early myogenic transcription factors, such as paired box protein 7(Pax7). Proliferation and differentiation of SCs are crucial to maintain normal muscle mass during adult life and regenerate new muscle fibers after injury [25]. To be activated SCs require the induction of MyoD and Myf5. Activation of SC consists of both proliferation and differentiation, which is prerequisite to supply new fully differentiated myofibers as well as maintain a pool of SCs with 'Stemness' [26]. Any perturbation in this process will result in the impaired regeneration of skeletal muscles in response to injury and skeletal muscle wasting overtime. Mice carrying mutation of the Pax7 gene are the critical example. Mice with Pax7 deletion can be born alive with normal but smaller skeletal muscles and then they initiate developing severe and lethal muscle wasting [27-29].

T3 has a crucial role in post-natal muscle growth. The level of T3 and the DIO2 activity significantly increase immediately after birth in mice [15], which corresponds to the switch from fetal to adult muscle fiber. Addition of T3 to the myogenic culture medium stimulates myoblast toward terminal differentiation [30] which can be mediated by cell cycle exit of myoblasts [30]. It is well known that myogenin and MyoD are induced by T3 [17,18]. Moreover, in proliferating avian myoblasts TRα transcriptional activity is directly stimulated by MYOD expression, and vice versa TRα represses MyoD activity [31]. Considering that MyoD is an important transcription factor during myoblast proliferation and onset of myoblast differentiation, there should be a feedback mechanism between TRα and MYOD that could potentially play a critical role in regulating myoblast homeostasis. In addition to the inhibition of MyoD, TRα inhibits AP-1 activity [32], which is a strong inhibitor of differentiation. These observations raise the possibility that T3 regulates both myoblast proliferation and differentiation, depending on the stage of proliferation/differentiation processes.

Interestingly, mice with knockout of the predominant enzyme in muscle that activates T4 by converting it to T3, 5'-Deiodinase 2 (DIO2), showed impaired differentiation of muscle derived stem cells to myotubes *in vitro* and defective *in vivo* muscle regeneration after injury [15] (Table 1).

A mouse model with deletion of the mitochondrial T3 receptor p43 developed muscle hypertrophy [33] (Table 1). On the other hand, over expressing p43 [13] leads to muscle wasting with aging [34] (Table 1), suggesting a possible toxic effect of a prolonged stimulation of mitochondrial activity that leads to deficit of new skeletal muscle fiber replacement and differentiation overtime.

Thyroid hormones and skeletal muscle function

Functional muscle alterations are common in both hyper- and hypothyroidism. A number of genes critical for muscle function and metabolism are T3 regulated [35].

In skeletal muscle, myosin is a critical protein necessary for the production of mechanic work and motion. There are 10 Myosin Heavy Chain (MHC) isoforms in the striated muscle of mammals. All members of MHC family respond to T3 [36,37], but the response is muscle and muscle fiber specific [38], ie., even the same myosin can be stimulated or inhibited depending on muscles [38]. The skeletal muscle has 4 major muscle fibers from the slowest contraction speed (type I muscle fiber) to progressively higher speeds (type IIa, IIx, IIb). Increased frequency of Type 2 fibers has been reported in muscle biopsy of patients with hyperthyroidism [39,40]. In hypothyroid mice, it has been described a mild switch from fast to slow fiber and

Table 1: Animal models with altered thyroid hormone signaling.

Study	species	model	Development	Repair/ Maintenance	Function	Metabolism
Pessemesse et al. [33]	Mice	p43 $^{-/-}$	Muscle hypertrophy			↑ glycolytic metabolism
Casas et al. [34,44]	Mice	p43 over expression		Muscle atrophy with aging	Switch to type I MHC	↑ oxidative ↓glycolytic metabolism
Yu [22]	Mice	TRα($^{-/-}$)β($^{-/-}$)	Muscle hypotrophy		Switch to type I MHC	↑ oxidative ↓glycolytic metabolism
Yu [22]	Mice	TRα($^{-/-}$)			Switch to type I MHC	↑ oxidative ↓glycolytic metabolism
Dentice [15]	Mice	DIO2 ($^{-/-}$)		Impaired muscle regeneration		Insulin resistance
Fonseca [63]	Mice	SKM-D2KO				No metabolic phenotype

Abbreviations: MHC: Myosin Heavy Chain; TR: Thyroid Receptor; SKM-D2KO: Skeletal Muscle- Deiodinase 2 Knockout Mice

an increase of hybrid fibers [41]. Muscle with the prevalence of slow fibers has been shown to respond more dramatically to hypothyroidism up to a complete switch from fast to slow fibers [4]. Moreover, T3 directly stimulates the expression of sarcoplasmic reticulum Ca2+-ATPase 1 (SERCA1) that is crucial for the fast skeletal muscle fibers [42], and reduces expression and activity of calcineurin that is involved in the slow muscle fiber phenotype [35].

Mice lacking of thyroid receptor α (TRα-/-) showed the significantly reduced number of fast type II fibers and relatively increase of slow type I fibers comparing with both normal and TRβ knockout mice (TRβ-/-). Mice lacking of both TRs (TRαβ -/-) showed even more pronounce phenotype than the TRα-/- [22] (Table 1). Skeletal muscles from TRα-/- mice had a 20-60% longer contraction and relaxation time compared with ones from TRβ-/- and wild type animals [43]. This data can be explained by distribution patterns of TRs in tissue types [12] and/or tissue specific effect of TRα and TRβ.

On the other hand, mice over expressing p43, the mitochondrial T3 receptor, showed increased mitochondrial biogenesis and oxidative metabolism in the skeletal muscle, switching from the fast MHC IIα to the slow type I fiber in soleus muscles [44]. All of these data delineate the crucial contribution of thyroid hormones to skeletal muscle plasticity.

Thyroid hormones and metabolism

T3 is a well-known regulator of thermogenesis and lipid metabolism. TRα has been shown to be important for the metabolic phenotype [45-47]. Interestingly, the increased metabolic rate in skeletal muscle has been described in humans with resistance to TRβ, which is characterized by elevated levels of circulating thyroid hormones and unopposed TRα action [48].

THs regulate glycolytic and oxidative pathways in skeletal muscle. T3 induces an overall shift to faster muscle fibers, displaying a reduced mitochondrial density with the predominant glycolytic metabolism. T3-dependent stimulation of SERCA and myosin expression increases energy turnover and generation of heat during activity [35]. At the same time T3 regulates proliferator-activated receptor γ coactivator 1α (PGC-1α) that is crucial for mitochondrial biogenesis through a specific mitochondrial thyroid receptor isoforms (p43) [49,50]. Over expression of p43 *in vivo* increases mitochondrial DNA synthesis, respiration and a switch to slow muscle fibers with reduced glycolytic metabolism and increased oxidative phenotype [44].

Mitochondrial Uncoupling Protein 3 (UCP3) has been suggested to promote energy expenditure in skeletal muscle and is stimulated by thyroid hormone [51]. T3 activates the expression of UCP3 in mice and humans [52]. Administration of thyroid hormone increases UCP3 expression in skeletal muscle and raises the resting metabolic rate in mice [53]. Moreover, T3 directly stimulates the muscle glycerol-3-phosphate dehydrogenase that is highly present in mitochondria of the fast muscle fibers [54] and crucial for T3-mediated stimulation of oxygen consumption.

In addition to metabolic rate and energy expenditure, THs regulate glucose homeostasis. Both hyperthyroidism and hypothyroidism has been linked to insulin resistance [55]. GLUT4 is the major glucose transporter in the skeletal muscle [56] and plays a pivotal role in modulating insulin-stimulated glucose transporter. Interestingly it has been reported that GLUT4 gene contains a thyroid hormone receptor element in its promoter region [57]. Congenital hypothyroidism impairs GLUT4 expression in skeletal muscle [58], which can be reversed by T3 administration resulting in increase of GLUT4 expression and translocation to the plasma membrane in rat skeletal muscle [59]. In addition, T3 induces uptake of fatty acid in skeletal muscle that can be translated to the increased utilization of fatty acid and reduced deposits of tissue triglyceride [60].

On the other hand the role of DIO2 in skeletal muscle metabolism is contradictory. DIO2 (-/-) mice (table 1) has been shown to be insulin resistant [61] and myoblasts with DIO2 deficiency show impaired action of insulin [62]; however a mouse model that lacks of DIO2 only in the skeletal muscle did not show any significant changes of metabolic phenotype compared with wild type animals, indicating that DIO2 in muscle does not have a significant metabolic role [63].

CONCLUSION

Thyroid hormones are important regulators of gene expression and the importance of thyroid hormone signaling in skeletal muscle physiology is well known. Classically, thyroid hormone action in skeletal muscle is mostly recognized for gene regulation and metabolism. With knowledge gained from animal models with altered thyroid hormone signaling, a more complex picture can be merged where thyroid hormones are crucial regulator of skeletal muscle homeostasis from development to post-natal maintenance, regeneration and functions.

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