REVIEW

Role of thyroid hormone in skeletal muscle physiology

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Abstract

Thyroid hormones (TH) are crucial for development, growth, differentiation, metabolism and thermogenesis. Skeletal muscle (SM) contractile function, myogenesis and bioenergetic metabolism are influenced by TH. These effects depend on the presence of the TH transporters MCT8 and MCT10 in the plasma membrane, the expression of TH receptors (THRA or THRB) and hormone availability, which is determined either by the activation of thyroxine (T_4) into triiodothyronine (T_3) by type 2 iodothyronine deiodinases (D2) or by the inactivation of T_4 into reverse T_3 by deiodinases type 3 (D3). SM relaxation and contraction rates depend on T_3 regulation of myosin expression and energy supplied by substrate oxidation in the mitochondria. The balance between D2 and D3 expression determines TH intracellular levels and thus influences the proliferation and differentiation of satellite cells, indicating an important role of TH in muscle repair and myogenesis. During critical illness, changes in TH levels and in THR and deiodinase expression negatively affect SM function and repair. This review will discuss the influence of TH action on SM contraction, bioenergetics metabolism, myogenesis and repair in health and illness conditions.

Key Words

- ▶ thyroid hormone
- ▶ triiodothyronine
- ▶ skeletal muscle
- ▶ myogenesis
- ▶ illness
- ▶ contraction
- ▶ nonthyroidal illness syndrome

Journal of Endocrinology
(2018) **236**, R57–R68

Introduction

Skeletal muscle (SM) is widely distributed and represents approximately 40% of human body mass (Kim *et al.* 2016); therefore, any change in the energetic profile of SM has important effects on systemic physiology. Indeed, SM is one of the most important tissues involved in energy expenditure and glucose and lipid homeostasis (Salvatore *et al.* 2014, Lombardi *et al.* 2015). In SM, thyroid hormones (TH – thyroxine or T_4 and triiodothyronine or T_3) participate in contractile function, metabolism, myogenesis and regeneration (Simonides & van Hardeveld 2008, Dentice *et al.* 2010, Salvatore *et al.* 2014). Serum TH levels depend on the hypothalamus–pituitary–thyroid (HPT) axis, which, in turn, responds to several changes in homeostasis (Ortiga-Carvalho *et al.* 2016). In addition to serum levels, specific tissue concentrations of TH in SM

depend on local levels of TH transporters, TH receptors and deiodinase activity (Boelen *et al.* 2017). Therefore, in this review, we aim to discuss the main effects of TH in muscular physiological processes.

Skeletal muscle physiology

SM fibres are classified according to twitch speed and primary ATP production pathway. Figure 1 depicts the main characteristics of fibre types, namely, I, IIa, IIx and IIb. SM presents pure or hybrid fibres composed of combinations of these fibre types that are recruited for different performances according to their individual features. In general, sustained contraction is mediated

Figure 1

Characteristics of the different fibre types of muscle and TH regulation. (A) SM presents hybrid fibre types I, IIa, IIx and IIb, which have particular characteristics. Slow fibre type I presents MYH7, while the rapid fibre type IIa has MYH2, fibre type IIx has MYH1 and fibre type IIb has MYH4. Phosphocreatine content is greater in glycolytic IIa and IIb fibres, whereas type II and IIa fibres are more oxidative and have higher mitochondria content. The presence of myoglobin in the cytoplasm gives the reddish colouration, which is expressive in type I fibres and decreases gradually through IIa and IIx fibres and is absent in IIb fibres. Slow fibres present poorly developed SR in contrast to a well-developed SR in fast fibres. Type I fibres express SERCA2a, and type IIa, IIx and IIb fibres present SERCA1a/b. Slow and fast oxidative muscle fibres present higher expression of GLUT4, and at rest, fast fibres accumulate more glycogen than slow fibres. (B) TH induces the fibre type switch to a faster profile of the contraction–relaxation cycle. THs repress slow type I fibre MYH7 expression and stimulate the rapid type II fibres' MYH-2, -1, and -4 expression. TH-induced expression of SERCA 1a and 2a increases relaxation. Local conversion of T_4 to T_3 , via D2, promotes increased stability of *Slc2a4* (GLUT4) mRNA through polyadenylation, which increases the stability and translocation to the sarcolemma. TH increases oxidative capacity due to an increase in mitochondrial content and its protein activity. These regulations occur by nuclear and mitochondrial genome pathways, mediated by THR and p43, respectively, and also by increased *Pgc1a* expression. TH stimulates UCP3 expression that uncouples ATP synthesis. Overall, TH increases oxygen consumption and the resting metabolic rate.

by type I fibres, which are slow-twitch fibres, whereas type II fibres perform short burst activities and are called fast-twitch fibres (Schiaffino & Reggiani 2011). The SM metabolisms of slow- and fast-twitch fibres are also different. As shown in Fig. 1A, the slow fibres are oxidative and have more mitochondria and myoglobin, whereas fast fibres are more glycolytic and exhibit more glycogen and phosphocreatine. Muscle measurements in the steady state or during developed tension revealed that ATPase activity was higher in fast type IIb fibres than that in IIa and IIx fibres, which all have higher activity than slow type I fibres (Stienen *et al.* 1996). During muscle contraction, the ATP hydrolysis rate increases in all fibre types proportionally to the ATP production speed of each fibre type, which is higher in fast fibres than in the slow ones. Furthermore, the contraction–relaxation rate depends on the regulation of Ca^{2+} uptake and release from the sarcoplasmic reticulum. As shown in Fig. 1A, the type I fibres present poorly developed sarcoplasmic reticulum in contrast to the well-developed sarcoplasmic reticulum in type II fibres independently of their mitochondrial content (Schiaffino *et al.* 1970). Additionally, the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA) type 1 (SERCA1) is associated with faster Ca^{2+} storage compared to type 2a (SERCA2a), which are expressed in type II and I fibres, respectively (Fig. 1A) (Schiaffino & Reggiani 2011). Besides SERCA expression, myosin heavy chain (MYH), the most abundant motor protein in human and rodent SM, is an important intrinsic factor determinant of muscle twitch (Baldwin & Haddad 2001). Type I fibres express myosin heavy chain 7 (MYH7), type IIa fibres present myosin heavy chain 2 (MYH2), type IIx fibres express myosin heavy chain 1 (MYH1) and type IIb fibres present myosin heavy chain 4 (MYH4) (Schiaffino & Reggiani 2011). It is important to note that during SM development, ageing, exercise training and soluble factor stimulus, such as TH, the fibre type profile can be changed; thus, muscle propriety can be changed as well (Simonides & van Hardeveld 2008, Schiaffino & Reggiani 2011, Salvatore *et al.* 2014).

Thyroid hormone action pathway in skeletal muscle

T_3 acts in the SM by its classic pathway based on gene expression regulation through T_3 interaction with nuclear TH receptors α and β (THRA and THRB), which interact with TH response elements (TREs) in specific promoter regions (Ortiga-Carvalho *et al.* 2016). THRs also act as transcription factors independent of the ligand

(Ortiga-Carvalho *et al.* 2015). THRA is the main isoform present in SM (Miyabara *et al.* 2005, Amorim *et al.* 2009, Dentice *et al.* 2010, Milanese *et al.* 2016).

TH also triggers short-term effects in SM, such as regulation of the activity of membrane transporters (Cordeiro *et al.* 2013). T_4 rapidly stimulates the activity of the Na,K-ATPase in skeletal myotubes, resulting in an increase in the transmembrane resting potential and the frequency of spontaneously occurring action potentials (Bannett *et al.* 1984). T_3 increases the pH in L6 myoblasts from rat SM culture via phospholipase C and intracellular calcium mobilization (Incerpi *et al.* 1999, D'Arezzo *et al.* 2004). T_3 modifies the kinase activity of p38 and AMPK, which are important in mitochondrial biogenesis in SM fibres (Irrcher *et al.* 2008).

TH intracellular availability is a result of TH transport across the plasma membrane and the local activation or inactivation of T_4 and T_3 . TH crosses the plasma membrane by facilitated diffusion, which is mediated by TH transporters. In SM, the primary transporters are the monocarboxylate transporters MCT10 and MCT8, which are found both in humans and rodents (Mebis *et al.* 2009, Di Cosmo *et al.* 2013). Di Cosmo and coworkers observed that MCT8KO mice presented the same motor activity as WT mice (Di Cosmo *et al.* 2013). However, MCT8KO mice had signals of increased TH action, including a decrease in the negatively regulated gene *Myh7* and an increase in the positively regulated *Mhy1* in the slow-twitch SM soleus (Di Cosmo *et al.* 2013). Indeed, the SM of MCT8KO mice presented 30% more T_3 than that of WT mice. Although, in the MCT8D1KO mouse (*Dio1* deleted in the MCT8KO mice), the T_3 intracellular concentration dropped, but it did not reach WT levels, suggesting that the systemic iodothyronine deiodinase type 1 (D1) was associated with an increase in intramuscular T_3 in MCT8KO mice (Di Cosmo *et al.* 2013). A mutation in SLC16A2 (MCT8) in humans causes Allan–Herndon–Dudley syndrome (AHDS) (Brockmann *et al.* 2005), which is characterized by congenital hypotonia that progresses to spasticity, hypoplasia and generalized muscle weakness (Schwartz & Stevenson 2007).

Furthermore, the activity of iodothyronine deiodinases type 2 (D2) and 3 (D3) contributes to the control of intracellular TH levels. D2 converts T_4 to T_3 , which increases T_3 availability and likely its effects as well (Bianco *et al.* 2002). Nonetheless, D3 converts T_4 to reverse T_3 (rT_3) and T_3 to diiodothyronine (T_2), decreasing the classical T_3 nuclear effects (Bianco *et al.* 2002). The balance between SM D2 and D3 activity changes intra-muscle T_3 levels, thus affecting THR occupancy even

if the serum TH levels are unchanged (Ambrosio *et al.* 2017, Boelen *et al.* 2017).

D2 is constitutively expressed in rodent and human SM and its activity is higher in slow-twitch muscle than in fast-twitch muscle (Visser *et al.* 2009, Marsili *et al.* 2010, Ramadan *et al.* 2011). Hypothyroidism and cold exposure increase muscle D2 activity in rodents (Marsili *et al.* 2010, Louzada *et al.* 2014). In humans, D2 modulation by alterations in circulatory levels of TH is controversial. Analysis of D2 and D3 expression in muscle biopsies of thyroidectomized patients before and after T₄ therapy did not show differences in *DIO2* activity and *DIO3* mRNA expression (Heemstra *et al.* 2009, Visser *et al.* 2009). However, short-term fasting decreased circulating T₃ and increased SM D2 activity in euthyroid patients (Visser *et al.* 2009).

Thyroid hormone and skeletal muscle physiology

In the initial stages of postnatal development, different stimuli induce SM maturation, the muscle cell loses polyneuronal innervations, mechanical load to specific muscles increases and TH levels raise simultaneously (Slater 1982, Gambke *et al.* 1983, Cormery *et al.* 2005). Both neuronal innervation and increased serum TH trigger the transformation of the muscle fibre profile, such as the loss of embryonic and neonatal myosin and an increase in adult fast or slow myosin genes in specific muscles (Schiaffino *et al.* 1988, 2015). Hypothyroid rats present a delay in the switch to adult myosin in fast muscle, but not in slow muscle (Gambke *et al.* 1983, Butler-Browne *et al.* 1984, di Maso *et al.* 2000). The postnatal development of slow fibres depends on weight-bearing activity and electrical stimulation, whereas in fast fibres, T₃ signalling is crucial, especially for the transition of neonatal fibre to fibre IIb (Gambke *et al.* 1983, Adams *et al.* 2000, di Maso *et al.* 2000, Baldwin & Haddad 2001). Additionally, the denervation of neonatal fast muscle does not impair the switch of neonatal to adult myosin (Gambke *et al.* 1983). Therefore, physiological levels of TH contribute to the determination of the normal pattern of fibre distributions in each muscle (Mahdavi *et al.* 1987, Baldwin & Haddad 2001). T₃ represses *Myh7* expression, myosin from fibre type I, and stimulates *Myh2*, 1 and 4 expression, myosin from fibres IIa, IIx and IIb, respectively, inducing faster muscle contraction in rats (Fig. 1B) (Larsson *et al.* 1994). Moreover, T₃ stimulates slow-to-fast muscle fibre type conversion by inducing the transition of MYH7 to MYH2,

MYH2 to MYH1 and MYH1 to MYH4 (Simonides & van Hardeveld 2008).

In slow- and fast-twitch muscle, the deletion of *Thra* increased MYH7, while *Thrb* deletion only had an impact on *Myh7* expression in fast-twitch SM (Yu *et al.* 2000). Additionally, T₃ can alter twitch profiles by modulating miRNA expression. miR-133a is induced by T₃ and highly expressed in fast-twitch muscle (Zhang *et al.* 2014). The slow-to-fast transition induced by T₃ is impaired by miR-133a repression (Zhang *et al.* 2014). Additionally, miR-133a-knockout mice have a fast-to-slow SM transition (Liu *et al.* 2011). Thus, target miRNAs could be an indirect mechanism of T₃ action on SM plasticity.

Postnatal sarcoplasmic reticulum development is also dependent on T₃, especially the expression of SERCA1 in fast-twitch muscle (Simonides & van Hardeveld 1989, van der Linden *et al.* 1992). The fast fibre SERCA1 is associated with increased Ca²⁺ storage, which partly explains the increased speed of the contraction–relaxation cycle. Since this process requires elevated energy, it is not sustained for long periods (Schiaffino & Reggiani 2011). As shown in Fig. 1B, TH accelerates relaxation by T₃ direct stimulation of *ATP2A1* (SERCA1A) and *ATP2A2* (SERCA2A) expression (Hartong *et al.* 1994, Muller *et al.* 1994, Simonides *et al.* 1996).

In 2005, it was postulated that SM could participate in the regulation of serum T₃ levels since SM is widely distributed and has a large mass (Maia *et al.* 2005). However, global D2KO mice have normal levels of T₃ and increased levels of T₄ and TSH (Schneider *et al.* 2001). Moreover, knockdown of muscular D2 by approximately 40–50% during muscle development or after muscle fibre differentiation does not significantly change TH serum levels (Werneck-de-Castro *et al.* 2015, Ignacio *et al.* 2017). Although it is important to note that despite normal TH serum levels, D2KO mice present a reduction in SM T₃ levels and a hypothyroid muscle phenotype (Schneider *et al.* 2001, Báñez-López *et al.* 2014).

Thyroid hormone affects skeletal muscle metabolism

T₃ treatment increases maximal oxygen consumption, which is more than two times bigger in the soleus than in the plantaris, which are slow-twitch oxidative fibres and fast-twitch mixed SM, respectively (Bahi *et al.* 2005). The stimulus for switching from a glycolytic fibre to an oxidative one increases not only mitochondrial content but also mitochondrial fusion, forming

elongated mitochondria. As represented in Fig. 1, slow-twitch SM presents more mitochondria than fast-twitch ones (Mishra *et al.* 2015).

T₃ levels promote appropriate muscle responsiveness to insulin, and this effect depends on the conversion of T₄ to T₃ by local D2 as shown in D2-deficient myotube cultures, which present blunted insulin signalling (Grozovsky *et al.* 2009). This effect is partly associated with the increase in glucose uptake by TH upregulation of *Slc2a4* (GLUT4) in basal and insulin-induced conditions (Weinstein *et al.* 1994). THR forms a complex with myogenic differentiation 1 (MYOD1) and myocyte enhancer factor 2 (MEF2) on the TRE of the *Slc2a4* gene promoter in L6E9 muscle cells and rat SM *in vivo*, contributing to transcriptional regulation (Fig. 1B) (Torrance *et al.* 1997, Santalucía *et al.* 2001). Furthermore, TH promotes rapid post-transcriptional effects on *Slc2a4* mRNA polyadenylation, which increases transcript stability and GLUT4 availability and translocation to the sarcolemma in mice (Fig. 1B) (Brunetto *et al.* 2012). Slow and fast oxidative muscle fibres present a higher expression of GLUT4 and a greater glucose uptake capacity than fast glycolytic fibres (Fig. 1A) (Goodyear *et al.* 1991, Kong *et al.* 1994). Thus, hypothyroid mice present decreased glucose uptake induced by insulin. Nonetheless, elevated T₃ levels apparently do not further increase glucose uptake capacity, as thyrotoxicosis models present increased gluconeogenesis and reduced insulin action (Schiaffino & Reggiani 2011).

Besides glucose uptake, TH stimulates oxidative pathways by increasing mitochondrial biogenesis. TH-induced mitochondrial biogenesis occurs through stimulation of the expression of intermediate factors, especially the transcription factor peroxisome proliferator-activated receptor coactivator 1 α (PGC1A), which is a key regulator of mitochondrial biogenesis in SM (Schnyder & Handschin 2015). T₃ positively regulated PGC1A by THR directly on the gene promoter (Fig. 1B) (Wulf *et al.* 2008). Additionally, D2 activity is important to treadmill exercise-induced PGC1A stimulation and its downstream effects on mitochondrial function of the soleus and gastrocnemius muscles (Bocco *et al.* 2016). Recently, Lesmana and coworkers demonstrated that TH-induced mitochondrial biogenesis and activity are dependent on T₃-induced autophagy (Lesmana *et al.* 2016). These TH effects on mitochondria were blocked in L6 myotubes lacking the autophagy-related gene 5 (*Atg5*) by short hairpin RNA (shRNA) lentivirus transformation (Lesmana *et al.* 2016).

Uncouple protein 2 and 3 (UCP2, UCP3) are members of the mitochondrial carrier family and promote

mitochondrial uncoupling in SM, thus dissipating energy in the form of heat and decreasing the energy efficiency of the cell. UCP2 is widely distributed, and UCP3 is primarily expressed in SM (Gong *et al.* 1997, Solmonson & Mills 2016). It was suggested that TH could increase resting metabolic rate (RMR) through modulations in UCP3. The SM mitochondria of UCP3-deficient mice are more coupled and produce more reactive oxygen species (ROS) (Gong *et al.* 2000, Vidal-Puig *et al.* 2000), whereas the opposite effect was observed in mice overexpressing human UCP3 (Clapham *et al.* 2000). T₃ also increases the expression of citrate synthase, which performs the first step of the citric acid cycle (Bahi *et al.* 2005) and stimulates glycerol-3-phosphate dehydrogenase, a key enzyme of intermediary metabolism (Dümmeler *et al.* 1996). Furthermore, TH also stimulates oxidative phosphorylation in male rats due to the increased activity of cytochrome c oxidase 1 and 4 (COX1 and COX4, respectively), the last enzymes in the electron transport chain of mitochondria (Bahi *et al.* 2005). Additionally, healthy young men treated with T₃ for 14 days demonstrated an increase in RMR, UCP3 and UCP2 and a decrease in respiratory quotient, but did not show an increase COX4 or in nuclear respiratory factor 1 (NRF1) mRNA expression (Barbe *et al.* 2001). However, it is unknown whether there is a relationship between the substrate used and the TH levels. Therefore, the mechanism associated with T₃ increased SM mitochondrial activity, and oxygen consumption is related to the stimulation of mitochondrial enzymes and UCP3 (Barbe *et al.* 2001, de Lange *et al.* 2001, Bahi *et al.* 2005).

Analysis of patient samples presenting with the classical form of resistance to TH (RTH-*THRB* mutation) demonstrated an increase in RMR compared to healthy individuals (Mitchell *et al.* 2010). This increased RMR was due to the action of THRA in the muscle, which was responding to the TH excess seen in those patients. When the authors measured muscle substrate oxidation, they found an increased rate (75%) of tricarboxylic acid (TCA) cycle flux and decreased rates of ATP synthase flux, thus decreasing muscle mitochondrial energy uncoupling (ratio of TCA/ATP). Furthermore, the intramyocellular lipid content increased in the soleus muscle of RTH subjects compared to the control (Mitchell *et al.* 2010).

Studying a mouse model of *Thra* deletion, it was observed that these animals preferentially use fat as fuel due to an increase in the expression of lipoprotein lipase in SM, and these mice present an increase in food consumption together with a leaner profile compared to WT mice (Pelletier *et al.* 2008). Moreover, *Thra*-0/0 mice present increased levels of SM D2, which are associated

with an increase in fat oxidation in this tissue (Ramadan *et al.* 2011).

Overall, independent of the metabolized substrate, TH induces increased mitochondrial activity, oxidative phosphorylation and oxygen consumption through the stimulation of mitochondrial enzymes and UCP3 (Fig. 1B) (de Lange *et al.* 2001, Bahi *et al.* 2005).

Thyroid hormone impact on myogenesis

SM function depends on energy turnover, contraction and relaxation rates and on muscle tissue regeneration. SM growth and regeneration are dependent on the proliferation and differentiation of the muscle stem cell population, satellite cells (SC), in a process known as myogenesis. SC niches are located between the muscle fibre sarcolemma and the basal lamina, which are normally close to the endothelial area (Fig. 2) (Christov *et al.* 2007). The muscle stem cell niche location permits SCs to receive extrinsic signals from the bloodstream and intrinsic signals from the muscle fibres. Both stimuli can modulate the proliferation and differentiation of progenitor cells (Beermann *et al.* 1983, Linker *et al.* 2003, Bentzinger *et al.* 2012). The myogenic process is summarized in Fig. 2.

Myogenesis is controlled by a hierarchical expression of transcription factors that is dependent on

environmental conditions and the differentiation state of the cell (Bentzinger *et al.* 2012, Dumont *et al.* 2015b). Pax7 regulates the expression of the myogenic regulatory factors (MRF), a family of transcription factors that are essential to the progression of myogenesis, such as myogenic factor 5 (MYF5) and MYOD1 (Oustanina *et al.* 2004, Relaix *et al.* 2006, Collins *et al.* 2009, Bentzinger *et al.* 2012, Dumont *et al.* 2015b). They have redundant roles in myogenesis and induce myogenin (MYOG) and MRF4 expression by myoblasts (Dumont *et al.* 2015a). MYOD1 and MYOG are involved in terminal myogenic differentiation and are positively regulated by T_3 (Fig. 2) (Carnac *et al.* 1992, Downes *et al.* 1993). MYOD1 expression after muscle injury is similar between euthyroid and hypothyroid mice; however, the SC from hyperthyroid regenerative sites express more MYOD1 (Anderson *et al.* 1998).

The control of intracellular T_3 levels is fundamental to myogenesis progression (Ambrosio *et al.* 2017). *Dio3* expression is one of the controllers of proliferation and survival signalling in SCs (Dentice *et al.* 2014, Ambrosio *et al.* 2017). D3 is highly expressed in activated and proliferating SCs; however, it is downregulated during the differentiation process (Fig. 2) (Dentice *et al.* 2014). D3 ablation induces committed SC apoptosis, as T_3 activates the FOXO3 and MYOD1 pro-apoptotic axis (Fig. 2) (Dentice *et al.* 2014, Ambrosio *et al.* 2017). *Foxo3* expression is also important

Figure 2

Myogenesis and TH. The SC niches are next to blood vessels, between the basal lamina and the myofiber. Pax7 and Foxo3 are expressed by quiescent SCs, and these factors are involved in cell survival and self-renewal. Under the appropriate stimulus, SCs enter the differentiation pathway and thus turn into committed SCs expressing PAX7 and D3. The low intracellular T_3 favors the survival and cell proliferation. The activated SCs express PAX7 and MYF5 and decrease the expression of D3; thus, intracellular T_3 can increase and induce the expression of FOXO3, which induces the expression of D2 and represses D3. Both T_3 and FOXO3 induce MYOD1 leading to the progression of the differentiation of activated SC into the proliferative myoblast. In these, THRA1 represses MYOD1 and myogenin expression, whereas MYOD1 induces *Thra1* expression. Additionally, FOXO3 induces D2 expression, leading to an increase in intracellular T_3 , which represses AP1 and induces the expression of MYOD1 and myogenin. T_3 , MYF4 and myogenin are involved in the terminal differentiation of myocytes into myotubes/myofibers, and these factors stimulate the expression of MYH and SERCA.

in SC self-renewal, as it is associated with the return of SC quiescence after cell division (Mammucari *et al.* 2007). As indicated in Fig. 2, D3 expression is downregulated during the differentiation process, and D2 is upregulated. These changes in expression lead to alterations in intracellular TH levels, which are required for myogenesis progression, suggesting that intracellular T_3 should be maintained at a low level only in the beginning of the myogenic process (Dentice *et al.* 2010, 2014). This suggestion is reinforced by D2KO myogenesis data; these mice had impaired muscle development after birth and reduced regeneration (Dentice *et al.* 2010). However, downregulation of muscular D2 in adult mice did not impair muscle function or T_3 signalling (Werneck-de-Castro *et al.* 2015). Furthermore, T_3 stimulation of myoblast differentiation involves the inhibition of AP1, an inhibitor of differentiation, via THRA (Fig. 2) (Cassar-Malek *et al.* 1996).

During the myoblast proliferative phase, THRA1 represses MYOD1 and MYOG transcriptional activity independently of T_3 presence (Daury *et al.* 2001); however, MYOD1 induces the transcriptional activity of THRA1, inducing a negative feedback loop in MYOD1 activity as demonstrated in Fig. 2 (Busson *et al.* 2006). Recently, Milanesi and coworkers used a genetic approach to show that THRA is essential to the proliferation and differentiation of myoblasts by activating the Wnt/beta-catenin signalling pathway (Milanesi *et al.* 2016). T_3 administration to primary avian myoblast cell culture reduced the proliferation rate and increased the myotube fusion index three days after myogenic differentiation induction (Marchal *et al.* 1993).

An increase in intracellular T_3 levels is important to myocyte terminal differentiation, whereas T_3 positively regulates *Myod1* and *Myog* expression (Fig. 2, myocytes and myotube panel) (Ambrosio *et al.* 2017). Additionally, T_3 , MYOG and MYF4 effects are crucial for the terminal differentiation of myotubes, inducing the expression of MYH and SERCA (Marsili *et al.* 2010, Schiaffino & Reggiani 2011, Ambrosio *et al.* 2017). Thus, as summarized in Fig. 2, low intracellular T_3 levels are important to supporting initial SC proliferation, whereas an increase in intracellular TH responsiveness is associated with SM terminal differentiation.

Influence of illness on skeletal muscle thyroid hormone signalling

Critical illness induces changes in the hypothalamic–anterior–pituitary–peripheral–hormonal axis, including

decreased plasma TH levels with no significant increase in TSH (Van den Berghe 2016). This condition is known as ‘non-thyroid illness syndrome’ (NTIS). Acute and critical illnesses also induce changes in TH metabolism, including alterations in SM responsiveness to TH (Fliers *et al.* 2014). Deiodinase, THR and TH transporter expression are modulated in SM during acute, chronic and systemic inflammation (Boelen *et al.* 2011, Bloise *et al.* 2016, Van den Berghe 2016). These changes affect TH responsiveness and can lead to altered muscle function.

During NTIS, the plasma levels of pro-inflammatory cytokines are increased. These cytokines exert their action via the NF κ B, ERK1/2 and AP1 signal transduction pathways. NF κ B and AP1 response elements have been characterized in the D2 promoter (Gereben & Salvatore 2005, Zeold *et al.* 2006), suggesting that activation of these pathways affects D2 expression. However, the NF κ B pathway does not seem to be involved in the regulation of muscle D2 expression during illness in mice (Kwakkel *et al.* 2009). Not much is known about the mechanism involved in muscle D3 regulation during inflammation. Although D3 can be stimulated via the ERK1/2 and p38 signalling pathways in human non-muscular cells, little is known about these effects in SM (Pallud *et al.* 1999, Wajner *et al.* 2011).

It has been shown that muscle D2 mRNA and activity are increased in patients with prolonged critical illness compared to healthy controls (Mebis *et al.* 2006). Nevertheless, septic patients had decreased SM *DIO2* expression, whereas muscle *DIO3* expression increased (Rodriguez-Perez *et al.* 2008). In this sense, murine severe *Streptococcus pneumoniae* infection decreased limb muscle and diaphragm *Dio2* expression, whereas *Dio3* remained unchanged in limb muscle, but increased in the diaphragm (Kwakkel *et al.* 2009, Bloise *et al.* 2016). Furthermore, acute inflammation induces an increase in *Dio2* and a decrease in *Dio3* expression in hind limb (Kwakkel *et al.* 2009, Boelen *et al.* 2017). Taken together, in sepsis and acute inflammation, there is a decrease in muscle D2; thus, it could lead to a decrease in the local conversion of T_4 to T_3 . Meanwhile, chronic aseptic inflammation induces the expression of D2 and D3 in limb muscle (Kwakkel *et al.* 2009), probably leading to an increase in intracellular T_2 . However, *Dio3* expression decreased and *Dio2* expression did not significantly change in the diaphragm of mice under chronic aseptic inflammation (Bloise *et al.* 2016). Conversely, intramuscular T_4 and T_3 decrease in different NTIS models, lipopolysaccharide (LPS) induction of acute inflammation, chronic aseptic inflammation and bacterial sepsis (Boelen *et al.* 2017). Additionally, SM from acute

inflammation challenged mice decrease expression of the T_3 -positively regulated gene *Myog*; however, in the chronic model, it was observed to increase (Boelen *et al.* 2017). These data suggest that muscle response is dependent on the type of inflammatory stimulus and could be different according to the SM type and/or function.

Sepsis and chronic inflammation mouse models decrease hind limb muscle *Thra* expression, whereas *Thra* is increased in the diaphragm during chronic inflammation (Kwakkel *et al.* 2009, 2010, Bloise *et al.* 2016, Boelen *et al.* 2017). During acute inflammation, the decrease in muscle expression of *Dio3* is dependent on *Thra*; however, *Dio2* upregulation is not impacted by *Thra* in mouse limb muscle (Kwakkel *et al.* 2009). *SLC16A2* (MCT8) is upregulated in SM biopsies from critically ill patients in the intensive care unit (ICU) compared to acute surgical stressed biopsies (Mebis *et al.* 2009). Furthermore, muscle *SLC16A2* expression was inversely correlated to serum TH concentrations in these patients (Mebis *et al.* 2009). Because the low free T_4 levels are associated with the severity of the disease (Van den Berghe 2016), these data suggest that the sickest patients would have an increase in MCT8 expression in muscle cells. Meanwhile, murine diaphragm *Slc16a2* expression decreases during sepsis; however, chronic inflammation did not change its expression (Bloise *et al.* 2016). In addition, hind limb *Slc16a2* expression did not change during acute or chronic inflammation, although it decreased during bacterial sepsis (Boelen *et al.* 2017). Thus, during critical illness, TH transport increases in association with the severity of the disease in humans and decreases in NTIS mouse models. Taking together, the murine and patient data, MCT8 expression is differently regulated by the type of inflammation, which contributes to changes in TH transport across the plasma membrane.

Critical illnesses frequently lead to diaphragm muscle dysfunction. Thus, these patients need mechanical ventilation and are sent to the ICU. After ICU discharge, patients can present muscle weakness and fatigue even 12 months after recovery from the initial disease (Herridge *et al.* 2003). The loss of muscle strength and increase in fatigue are associated with decreased mitochondrial function in critically ill patients (Fredriksson *et al.* 2005, 2006). Interestingly, septic patients have decreased mitochondrial content in both leg and respiratory muscles; however, this decrease minimally impacts energy production in respiratory muscle (Fredriksson *et al.* 2006, Fredriksson & Rooyackers 2007). Additionally, SM dysfunction is associated with

decreased mitochondrial bioenergetics in septic mice (Zolfaghari *et al.* 2015). LPS administration to C2C12 myotubes was used as an inflammatory infection model to investigate the role of inflammation on muscular mitochondrial function. LPS induces a decrease in muscle mitochondrial function *in vitro*, which is at least partly dependent on the decrease in *Dio2* expression (Bloise *et al.* 2016).

A reduction of serum TH levels during illness is postulated as a physiological adaptation to reduce energy requirements during acute illness (Fliers *et al.* 2015). SM is the primary organ responsible for glucose uptake in response to insulin and in high energy-demanding conditions, such as disease. In these situations, muscular protein catabolism can be stimulated to maintain an energy supply to other organs (Argilés *et al.* 2016). Therefore, reducing the anabolic response mediated by TH in SM could favour energy conservation during illness. Thus, NTIS would be an adaptation to save energy (Van den Berghe 2016). However, during prolonged illness, low levels of TH could be deleterious and may require clinical intervention. The muscle wasting observed in ICU patients could be associated with decreased TH signalling. Taken together, deiodinase, transporters and THR data suggest that the type and duration of an inflammatory response lead to different patterns of SM TH responsiveness. Additionally, SM type is also differently modulated by inflammation.

Conclusions

TH are key regulators of the development, regeneration and metabolism of SM. T_3 stimulates the expression of MYH characteristic of fast-twitch fibres, increases mitochondrial biogenesis and the relaxation–contraction rate. During myogenesis, the intracellular T_3 concentration is precisely regulated by D2 and D3, which is crucial for the progression of muscle progenitor cell differentiation. Additionally, illness influences SM function through the regulation of TH responsiveness in this tissue. Therefore, TH influences diverse aspects of muscle physiology by different mechanisms. Thus, the field still needs further studies to bring new insights on the pathophysiology of SM under TH action.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This work was supported by grants from the Brazilian Endocrine and Metabolism Society – Thyroid department (SBEM), CAPES, CNPq and FAPERJ Foundation (Brazil).

Acknowledgements

The authors would like to thank Thiago Ladeira for designing the figures.

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Received in final form 22 September 2017

Accepted 19 October 2017

Accepted Preprint published online 19 October 2017