The Hormonal Control of Myosin Isoform Expression in Skeletal Muscle of Mammals: a Review

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Abstract

After a rapid review of the different myosin isoforms present in skeletal muscles of mammals, a bibliographic survey of their regulation by hormones is made. Of the circulating hormones, it is the thyroid hormones which have been the most extensively studied. From all of the results which have been obtained so far, one can conclude that in striated muscles their role is to activate the expression of myosin isoforms with highest ATPase activity. Other hormones, such as the sexual hormones, are more muscle-specific and further work is needed before we can begin to understand their mechanism of action.

Key words: myosin isoforms, thyroid hormones, hormones

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Commitment, differentiation, and diversification of skeletal muscle fibers

Skeletal muscle fibers are formed by the fusion of mononuclear myoblasts into multinuclear myotubes. With the exception of β-enolase [66], carbonic anhydrase [74], H36 integrin and desmin [65], which are expressed by myoblasts, all other characteristic muscle specific genes are only expressed once cells have entered differentiation. Although myoblasts do not express a full complement of contractile proteins, in particular myosin, these cells are nevertheless committed to differentiate and form muscle fibers. The most likely candidates for this process of commitment to the myogenic lineage are the helix-loop-helix family of muscle regulatory factors (myoD/myf 3, myogenin/myf 4, myf5 and myf-6/MRF4/ herculin). Their mode of action has been described previously [117, 103, 41] and is beyond the scope of this review.

It is now known that distinct types of myoblasts, which have been termed somitic, embryonic, fetal, and satellite cells, appear sequentially during development [120, 23, 84, 110, 87, 108]. This results in the formation of successive generations of muscle fibers, each generation being the product of the different populations of myoblasts. During the subsequent development and maturation of the skeletal muscle a distinct fiber type pattern evolves [92]. The maintenance and modulation of this muscle fiber phenotype is the result of the interaction of factors intrinsic to the myoblast lineage and of extrinsic factors, such as thyroid hormone status, innervation, contractile activity, growth factors and extracellular matrix [52, 58].

The influence of innervation and contractile activity on muscle phenotype has been the object of several reviews in recent years [64, 4, 93, 3, 94]. The role of hormones has also been reviewed [4, 111, 116], but the results concerned mainly the regulation of myosin isoform expression in cardiac muscle [72]. Other authors have dealt with the hormonal control of muscle growth [48, 49]. The object of this review is to present the recent results on the effects of hormones on the expression of myosin isoforms in skeletal muscle fibers.

Types of myosin isoforms present in skeletal muscles

The identification of the different myosin isoforms present in skeletal muscles is one of the criteria, which has been extensively used to distinguish the different types of muscle fibers.

Myosin is a large molecule made up of two heavy chains (Mw about 200 000 D) and of two pairs of light chains (Mw about 20 000 D).

In mammals, 10 distinct myosin heavy chains have been described :

- One slow-twitch heavy chain (I) is present in the histochemically-defined type I fibers of adult mammals; these fibers are slow-contracting, have a low ATPase activity at alkaline pH, and oxidative properties. Myosin heavy chain I is encoded by the same gene as the β myosin heavy chain found in cardiac muscle [77].
- Three fast-twitch heavy chains (IIA, IID/IIX, and IIB). The IIA heavy chain is found in the histochemically-defined type IIA fibers of adult mammals. These fibers are fast-contracting, have a high ATPase activity at alkaline pH, and oxidative properties. The IIB heavy chain is found in the fast contracting histochemically-defined type IIB fibers, which have a high ATPase activity at alkaline pH, and glycolytic properties [see 92 for references]. The IID/IIX heavy chain has been described only recently in rat, mouse, and rabbit [5, 107, 88, 69, 1]; it is found in fibers, with an intermediate oxidative capacity [107, 70, 39].
- One embryonic E and one perinatal P heavy chains have also been identified. They are found in developing and regenerating muscle fibers, and occasionally in some of the head muscles of adult mammals, such as the masseter muscle of rat, mouse, and man [29, 16, 109], the bovine and pig tensor tympani muscle [105] or the rat extraocular musculature [121].
- Two "superfast" heavy chains have also been described, one in the superfast-contracting fibers of cat and dog jaw-closing muscles, myosin IIM [97, 78], and the other in the superfast-contracting fibers of the extraocular muscles, myosin EOM [121, 102], respectively.
- One slow-tonic heavy chain is found in the slow-tonic fibers of rat extraocular and jaw-closing muscles [78, 79]; these fibers are rare in mammals and are mainly observed in the polyinnervated muscle fibers of birds and amphibians.
- One "cardiac-type" heavy chain, the α cardiac, has been identified in masticatory muscles of rabbit and man [12, 31, 89, 24] and in muscle spindle fibres [90].

These last four heavy chains are quantitatively much less important than the first five heavy chains. However, more variants of heavy chains have been recently described, such as slow-type myosins in jaw muscles of the cat [55] and in fetal rat [38] and fast type myosins in the Syrian hamster [80] and in the rat [104].

The difference between the amino acid sequences of these heavy chains does not exceed 30%, and may be less than 2% [83].

Each heavy chain (HC) is associated with two light chains (LC), of two types, the so-called "essential" and "regulatory" light chains [see 111 and 92 for references]. There are five major essential light chain isoforms and two regulatory light chain isoforms; variants of these light chains have however been described in specific cases [97]. The way they are associated with the heavy chains results in the formation of the various myosin isoforms, which are indicated in Table 1.

All these myosin isoforms display different ATPase activities and are thus responsible, at least in part, for the different contractile speeds of the skeletal muscle fibers, as first proposed by Barany [6]. As stated above, their expression in muscles is under the control of both genetic and epigenetic factors and the contraction velocity of muscles may be modulated to meet the various physiological or pathological requirements imposed on the muscle. Modifications in the concentration of circulating hormones is one of the chief factors which may modify the expression of the myosin isoforms and thus induce changes in the muscle properties.

Effect of thyroid hormones

It is well known that striated muscles are privileged targets for thyroid hormones, which act by repressing or activating the genes coding for the different myosin isoforms [62].

In mammals, perinatal development is associated with a change in the plasmatic concentration of the thyroid hormones T3 and T4. The active hormone is the 3,5,3'triiodo-L-thyronine, T3, which will be considered here. Its concentration, which is barely detectable in embryonic and newborn rats, increases a few days after birth, reaches a peak at about 2 weeks, then slightly decreases to reach a plateau in the adult rat [40]. A similar but more precocious variation is observed for the rabbit [37].

Coincident with this increase in T3, embryonic and perinatal myosin isoforms are progressively repressed and adult fast myosin isoforms are accumulated [4 for review]. This scheme is rather general since it has been observed in the limb muscles of all the mammals which have been investigated: man, sheep, cat, rabbit, rat, mouse, guinea-pig, and hamster [56, 118, 75, 47, 32, 54, 28, 68, 10, 15, 30, 45].

A correlation between the increase in T3 concentration and the activation of the expression of the adult fast myosin isoforms has been proposed and confirmed by hyperthyroidism and hypothyroidism experiments. Rats made hyperthyroid during development display an earlier switch from the embryonic and perinatal isoforms to adult-type fast isoforms, while the contrary holds true for rats made hypothyroid [50, 17, 62, 98, 32, 34, 25]. The hypothyroid *dwarf* mouse mutant, originally described in 1927 by Snell, provided an excellent model system in which one could investigate the direct influence of thyroid hormone on the isoform transitions in the absence of a possible secondary effect due to a stimulation of growth hormone production. In this mutant the developmental isoform transitions are substantially delayed in the skeletal muscle and completely blocked in the heart. A normal adult myosin phenotype can be restored by multiple injections of thyroxine [119, 18, 96].

It appears therefore that the T3 thyroid hormone represses the expression of embryonic and perinatal myosin

Table 1. Myosin types in skeletal muscles.

myosin isoform	heavy chain HC	"essential" LC	regulatory" LC
slow SM1	slow I (or β)	LC 1S	LC 2S
slow SM2	slow I (or β)	LC 1S and LC1'S	LC 2S
slow SM3	slow I (or β)	LC1'S	LC2S
fast AM1	fast IIA	LC 3F	LC 2F
fast AM2	fast IIA	LC 1F and LC 3F	LC 2F
fast AM3	fast IIA	LC 1F	LC 2F
fast BM1	fast IIB	LC 3F	LC 2F
fast BM2	fast IIB	LC1F and LC 3F	LC 2F
fast BM3	fast IIB	LC 1F	LC 2F
fast DM1/ XM1	fast IID/IIX	LC 3F	LC 2F
fast DM2/XM2	fast IID/IIX	LC1F and LC 3F	LC 2F
fast DM3/XM3	fast IID/IIX	LC 1F	LC 2F
embryonic EM	embryonic E	LC 1emb	LC 2F
perinatal PM1	perinatal P	LC 3F	LC 2F
perinatal PM2	perinatal P	LC1F and LC 3F	LC 2F
perinatal PM3	perinatal P	LC 1F	LC 2F
superfast M	superfast IIM	LC 1 variant	LC2variant
superfast EOM1	superfast EOM	LC 1F	LC 2F
superfast EOM2	superfast EOM	LC1F and LC 3F	LC 2F
superfast EOM3	superfast EOM	LC 3F	LC 2F
slow-tonic	slow-tonic	nd	nd
cardiac V1	α	LC 1S	LC 2S

isoforms, while it activates that of adult fast isoforms. Brozanski et al [14] have shown that the disappearance of perinatal myosin isoforms during postnatal development is delayed in the diaphragm of undernourished rat pups compared to controls; this undernutrition is also accompanied by a decrease in the serum T3 levels, which led the authors to suggest that the alterations in myosin isoform transitions are induced by the hypothyroidism which is associated with the undernutrition. In man, excessive levels of thyroid hormone during fetal development has also been shown to produce a precocious accumulation of the adult myosins as well as a precocious maturation of the muscle [15].

All the muscles of the same animal respond to an endogenous increase in thyroid hormone concentration or to its experimental change, but their response has been shown to vary depending on the muscle [28, 25, 91]. In the rat, the diaphragm displays the most precocious switch to adult fast myosin isoforms, while the masseter displays the latest one; in the rabbit, it is the tongue musculature, which displays the most precocious switch [30]. From these results, it appears that different skeletal muscles do not contain the same number of thyroid hormone receptors, which would result in their different sensitivities to the hormone.

This is also suggested by the effect of experimental hyperthyroidism induced in developing rats and by the comparison of the myosin switches in eight muscles of the treated-rats with that in euthyroid rats. Hyperthyroidism barely modifies the myosin switch in the diaphragm, which indicates that the endogenous thyroid hormone concentration is almost optimal for inducing the myosin switch in this muscle. On the contrary, hyperthyroidism accelerates the switch in the other muscles investigated, which become similar to the diaphragm; this result is indicative of a different sensitivity of the individual skeletal muscles to thyroid hormone [25]. In the rat masseter, where there is a persistence of the perinatal myosin isoforms in the young adults, the hyperthyroid treatment induces their total disappearance, whereas hypothyroidism induces their reappearance [77].

The myosin switch from the embryonic and perinatal myosin isoforms to the adult fast myosin isoforms occurs with the same chronology in both male and female rats. In two muscles, differences are however observed. In the masseter of the female and the male rat the half-transition time is 21 and 22 days, respectively, and the perinatal

isoforms are observed to persist longer in the male than in the female [29]. A more striking difference is observed in the case of the levator ani of the rat, where the half-transition time is 20 days for the male and 32 days for the female [26]. This large difference may be attributed, mainly, to a difference in sensitivity of the male and female muscle to thyroid hormone, since it is almost abolished by a hyperthyroid treatment [33]; to our knowledge, there are no other muscles which display different responses to thyroid hormone in the male and female.

In the adult rat, thyroid hormone represses the slow isoform, which is clearly observed in the soleus and diaphragm of the rat [60, 62]. On the other hand, it generally favours the accumulation of the fast isoforms. Hyperthyroidism, induced in rats by injections of T3 every other day for 20 weeks, produces in the soleus a significant decrease in the proportion (93 → 69 %) of slow myosin, and a parallel increase in the amount of fast myosin, presumably the type IIA isoform [19]. This myosin transformation in the soleus is accompanied by an increase in the contractile velocity of the muscle, which is in good agreement with the concept that the rate of cross-bridge cycling is directly linked to the type of myosin isoform present in the muscle fiber. In contrast, no significant change, either in the myosin isoform content, or in the contraction velocity, is observed in the plantaris, which contains almost only type II myosin isoforms. Experimental hypothyroidism on the contrary has an overall slowing effect on the muscle, which is correlated with an increase in the amount of slow myosin in fast-twitch muscles [71, 20].

Similar results were obtained by Fitzsimons et al [46] when studying the effect of hyperthyroidism on the red and white regions of the rat medial gastrocnemius. The red region showed an increase in the fast isoform and a corresponding decrease in the slow isoform, whereas there were no changes in the white region of the muscle. However, differences may be observed depending on the muscle [53, 62]. For example, expression of the IIA heavy chain is activated by thyroid hormone in the soleus, but repressed in the masseter; in that case, it is the IIB heavy chain, which is activated [62].

Thus it seems that thyroid hormone acts to induce the expression of a myosin isoform of higher ATPase activity. In the case of the soleus, where the predominant isoform is the slow isoform, the expression of IIA myosin will increase together with the contraction velocity of the muscle; in the case of the masseter, which contains IIA and IIB myosins, the IIB myosin, which has a higher ATPase activity, is favoured. The effect of thyroid hormone on the expression of the IID/IIX isoform has not yet been studied. However, if one believes that there is a preferential sequence for the transformation of myosin isoforms: I ↔ IIA ↔ IID/IIX ↔ IIB [106, 112, 81], then one can guess that muscles containing mainly type I and IIA isoforms will express the IID/IIX isoform in hyperthyroid rats, whereas muscles containing predominantly the IID/IIX isoform will express the IIB isoform in hyperthyroid rats (Table 2).

Table 2. Scheme of the shift in myosin heavy chains produced by hyperthyroidism (+T3) and by hypothyroidism (-T3).

myosin heavy chain	+ T3	- T3
slow I	IIA	I
fast IIA	IID/IIX, IIB	I
fast IID/IIX	IIB	IIA
fast IIB	IIB	IID/IIX

The cardiac V1 isoform, when present in the masticatory muscles of the rabbit, is not sensitive to thyroid hormone [27], whereas it is well known that it is activated by thyroid hormone in the cardiac ventricle of mammals [73].

The mechanism of action of thyroid hormones has been the subject of many studies. Abundant evidence now indicates that the responses of the muscle to thyroid hormone are mediated by cellular receptors localized in the cell nucleus [86, 101, 13 for reviews]. A debate has risen on the question as to whether the hormone acts directly, or by the intermediary of the nerve. This question has not yet been resolved, since contradictory results were obtained after denervation of the muscle [63, 122, 85, 98]. It is however clear that thyroid hormone binds to specific nuclear protein receptors [86, 43, 101, 13 for reviews], which in turn either activate or repress the different myosin genes. The results obtained in the cardiac ventricle suggest that modulation in the expression of the α and β myosin heavy chain genes by thyroid hormones is regulated at the transcriptional level [73, 22].

The recent report that thyroid hormone positively regulates MyoD1 gene transcription also opens a new way to investigate the mechanisms that orchestrate myosin expression [21].

Effect of sexual hormones

Androgens are known to contribute to the difference in size of male and female muscles and androgen-regulated gene expression is currently under investigation [9, 7 for reviews]. The effect of sexual hormones on the expression of myosin isoforms has been less well investigated. In adult mammals, one does not in general observe differences between the myosin content of male and female muscles, which indicates the absence of an effect of the sexual hormones on the expression of the myosin isoforms. Thus androgenic hormone treatment does not alter the myosin expression in female rat soleus and plantaris muscles [113] and its withdrawal does not affect the myosin phenotype of the male rat plantaris muscle [11]. On the other hand, chronic administration of an anabolic steroid hormone, nandrolone phenylpropionate, to female rats for 6 weeks does result in a small increase in the number of type IIA

fibres in the *extensor digitorum longus* [42], whereas a similar hormone, nandrolone decanoate, induces no significant effect in the same muscle of the rabbit [100].

In the case of the guinea-pig temporalis, which belongs to a small group of sexually dimorphic muscles, Lyons et al. [76] have shown that the male muscle contains IIA myosin isoforms, whereas the female muscle contains IIB myosin isoforms; moreover, a treatment of females by testosterone induces the synthesis of the IIA isoforms, whereas castration of the males induces the synthesis of the IIB isoforms. The levator ani of the rat is another sexually dimorphic muscle, which grows normally in the male, but remains atrophied in the female; in this muscle, no difference is observed between the myosin isoform content of the male and female muscles [26]. Whereas as reported above the chronological difference between the myosin transitions in the male (t1/2 = 20 days) and in the female (t1/2 = 32 days) is abolished in hyperthyroid rats, testosterone-treated females display the same myosin transition as the control females [33] and castrated males display the same myosin transition as the control males [26].

In the rabbit masseter, the developmental expression of the cardiac V1 isoform is the same in males and females until 2 months; from 2 months onwards, the curves start to diverge, at the time corresponding to the onset of spermatogenesis [8]; the inhibiting effect of androgenic hormones on the expression of V1 is further demonstrated by the effect of male castration [27].

Parallel mechanisms are currently invoked for the actions of both steroid and thyroid hormone receptors, *i.e.* that these receptor proteins, upon association with the specific hormones, undergo a transformation to a state where they are able to interact with chromatin and regulate the transcription of specific genes [43, 113, 115]. However recent studies have suggested that certain members of the steroid hormone receptor superfamily can be activated in a hormone-independent manner, which provides new insights into the activation of the steroid hormone receptors [94].

Effect of other hormones

Other hormones, such as somatomedines, insulin, glucocorticoids and cathecolamines, have been shown to have an effect on myogenesis [116, 49 for reviews]. However, the effect of these hormones on the myosin isoform expression has been the subject of only a few studies. Insulin has been shown to influence myosin isoform expression in fast-twitch muscle, since experimental diabetes induces a decrease in fast and an increase in slow isoforms, whereas no effect is observed in slow-twitch muscle [99]. On the other hand glucocorticoid treatment has been shown to induce a fiber shift, corresponding to a slight modification in the proportions of type IIA and IIB fibers [44].

Combined effects

In a few cases, the resulting effect of two factors on myosin expression have been studied. Administration of testosterone to female rats dramatically increases insulin resistance and induces changes in slow muscle morphology, with an increase in the number of type II fibers [57]. On the other hand, steroid treatment of suspended rats does not modify the myosin isoform pattern induced by mechanical unloading [114], while hypothyroidism predominates over mechanical unloading in the regulation of myosin isoforms in slow muscle [38]. Finally, the treatment of hypophysectomized rats by human growth hormone increases the proportion of slow-type myosin, in skeletal muscle [2].

The antagonistic effects of chronic low frequency stimulation and thyroid hormone on myosin expression have been observed in rat fast-twitch muscles [67] and a dominant effect of hyperthyroidism over hypertrophy has been observed in all rat muscles [59]. The means by which thyroid hormone predominates over other potential influences on myosin expression is unknown at the present time and does not allow one to discrimination between common or separate signal pathways.

Concluding remarks

Skeletal muscles are known to be privileged targets for hormones, which induce changes in their weight, metabolism, and fiber type profile. In this review, we have concentrated on describing the action of hormones on the myosin phenotype of skeletal muscles. Whereas much work has been carried out on the action of thyroid hormone, which allows one to conclude that thyroid hormone activates the genes coding for the myosins of highest ATPase activities, the precise action of other hormones remains to be defined. The cloning of various hormone receptors [61, 35, 82, 51] should allow one to obtain a greater understanding of the mechanism of action of these hormones.

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