Hyperplasia in Exercise-Induced Muscle Growth?

Carlo Reggiani and Truus te Kronnie

Department of Anatomy and Physiology, University of Padova, Italy and Experimental Zoology Group, Wageningen Institute of Animal Sciences (WIAS), University of Wageningen, The Netherlands

Abstract

Compensatory growth in response to exercise is an important adaptation mechanism of skeletal muscles, as they become in this way able to move heavier mechanical loads. The increase of muscle mass is primarily the result of the increase of muscle fibre size (fibre hypertrophy). Whether increase of fibre number (hyperplasia) also contributes to compensatory growth is still matter of debate. This short review aims to analyse some data in favour or against this possibility.

Key words: exercise, growth, hyperplasia, muscle.

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Compensatory growth in response to exercise is an important adaptation mechanism of skeletal muscles, as they become in this way able to move heavier mechanical loads. The increase of muscle mass is primarily the result of the increase of muscle fibre size (fibre hypertrophy). Whether increase of fibre number (hyperplasia) also contributes to compensatory growth is still matter of debate. This short review aims to analyse some data in favour or against this possibility.

Early work [23, 28] led to the hypothesis that from a fixed number of muscle fibres at birth, postnatal variation in muscle mass was only due to increase or decrease of individual fibre volume. Proliferation processes in muscle would be therefore restricted to early development and to regeneration.

Muscle development is characterized by asynchronous differentiation of two, or possibly three in humans [8], muscle fibre population (for a comprehensive review [18]). Primary myoblasts undergo repeated cycles of duplication and then leave the proliferative cycle and begin to fuse into myotubes which after innervation differentiate to first generation muscle fibres. Remaining myoblasts continue proliferative activity and later undergo fusion to myotubes from which secondary muscle fibres derive. After the second fusion wave a final group of myoblast remains. These latter cells can remain silent for a long time at their location under the basal membrane of adult muscle fibres. These silent myoblasts are generally referred to as satellite cells [26]. They represent the myogenic proliferative potential of muscle tissue. When activated by suitable stimuli they can resume proliferation, generate new myotubes and fuse with pre-existing fibres or produce new muscle fibres. Recent studies [9] have, moreover, provided evidence that satellite cell are not the sole source of myogenic proliferative potential, other cells as for example of bone marrow can be recruited for muscle repair in the case of injury.

In the carp which like other fishes increases its body size all life long myoblasts-satellite cells contribute to adult muscle growth. The increase of fibre thickness alone can not account for the increase of total muscle mass. Moreover a decrease occurs in the proportion of nuclei belonging to the satellite cells over the total number of nuclei of the muscle tissue, suggesting a generation of new fibres using the pre-existing satellite cells [21]. Analysis of the distribution of fibre thickness shows that a population of thin fibres remains even at late stage of growth, confirming that the process of formation of new fibre does not stop [21].

In mammals and in humans satellite cells remain mitotically quiescent until the muscle is damaged or, possibly, until hypertrophying stimuli are applied. A complete regeneration of muscle mechanically or chemically injured or even minced, can occur starting from the pool of satellite cells [3, 4, 33]. Activation occurs within several hours after the injury as demonstrated by the expression of MyoD and myogenin in these cells [17]. The activation appears to be mediated by growth factors which might be released by the injured fibre or might get in contact with the satellite cell following the lesion of the basal membrane [2, 7]. FGF m RNA is detected in activated but not in quiescent satellite cells, as is IGF

mRNA. This also suggests that growth factors might play a regulatory role during satellite cell replication, possibly through an autocrine mechanism (see for a review [35]).

Activation of satellite cells during hypertrophic muscle growth might explain why DNA content of muscle, and not only protein content, increases. Upon activation satellite cells proliferate and either fuse with pre-existing muscle fibres, thus increasing the myonuclei number without changing the fibre number or fuse together producing new fibres. In this latter case the total number of fibre should increase and the increase should be detectable by fibre counting.

In an attempt to understand whether training can result in satellite cell activation the total number of muscle fibre in human muscle post mortem have been counted. This investigation has shown a pronounced interindividual variability but no significant differences between trained and untrained individuals [22, 27, 30, 36].

Several experimental studies on animals point to the contribution of hyperplasia in muscle growth. Three main protocols have been used to induce muscle hypertrophy: exercise-induced hypertrophy, stretch-induced hypertrophy and compensatory hypertrophy (following tenotomy of agonist muscles). A number of studies have described an increase of muscle fibres in these models of muscle hypertrophy [14, 15, 16, 31]. The validity of fibre counting has been questioned by other studies where fibre counting at one muscle cross section was replaced by total fibre counting of a muscle. Counting of virtually all fibres in the muscles in experiments of unilateral load application in rats [13] and in chicken [12] brought evidence in favour to the conclusion that there was no difference between hypertrophic trained and untrained control muscles. The conflicting results can be explained not only in relation to the methodology employed in fibre counting but also in relation to experimental protocol utilized to stimulate muscle growth. It seems, therefore, difficult to come to a final conclusion about the contribution of hyperplasia to increase of fibre mass from experiments based on hypertrophy induction and fibre counting in animals.

More direct evidence in favour of the involvement of satellite cell activation in muscle mass growth has come from the work by Parry and coworkers [29], who showed that muscle irradiation which destroys the satellite cell population, reduces dramatically the ability of muscles to respond to hypertrophying stimuli like exercise or tenotomy.

Further evidence in favour of the responsiveness of satellite cells to mechanical load on muscle has been provided by radio-labelled thymidine or BrdU incorporation experiments. After a single bout of prolonged downhill treadmill running the number of satellite cells that entered the S phase was far greater than required to repair a small number of damaged necrotic fibres [6]. In young developing rats hindlimb unloading causes in 3-5 days a virtually complete inhibition of satellite cell proliferative activity [34].

Activation of satellite cells in humans has been observed after 6 week of endurance training [1]. One could expect, however, that the contribution of satellite cells to muscle growth would be more important in resistance training where muscle mass growth is greater. No data seems available on this.

These studies prompt to investigate the factors which can regulate satellite cell activation, to ascertain whether only muscle damage or also muscle overload can represent a trigger for satellite cells. As mentioned above [35] local release of FGF and IGF-1 has been demonstrated during regeneration. There are indications that the same growth factors are released also in relation to an increase of mechanical load on muscle [11].

A recent important contribution to the understanding of the mechanism which regulate the number of muscle fibres has been given by the identification of myostatin also called GDF8. Myostatin is a member of transforming growth factor TGF superfamily and is expressed specifically in skeletal muscle fibres [19, 24]. Mutations in the bovine myostatin genes produce a phenotype called “double muscled” because of the increase of muscle size [20, 25]. Knock out of the myostatin gene in the mouse produce a dramatic increase of muscle mass due for a large part to the increase of fibre number accompanied by modest changes in fibre thickness [24]. Myostatin seems to act as a negative regulator of muscle mass growth. Its action is mostly restricted to the period of muscle development : myostatin expression transiently increases during atrophy due to muscle unloading in adult mice, but no close relation between atrophy degree and myostatin expression has been found [5]. Interestingly a correlation is present between myostatin and myosin heavy chain 2B expression [5]: expression of 2B myosin heavy chain isoform increases when mechanical activity is reduced [32]. In a recent study [10] single nucleotide polymorphisms have been reported in the highly conserved exon 2 of the human myostatin gene. Attempts to find correlations with muscle mass in the carriers of these polymorphisms have failed. Further work is necessary to fully understand whether myostatin can act as a regulator of muscle mass and specifically of muscle fibre number in adult muscle. The action of myostatin on satellite cells should be an important target of future work.

Address correspondence to:

Prof. Carlo Reggiani, Dept. Anatomy and Physiology, University of Padova, 35131 Padova, phone +39 049 8275 313, fax +39 049 8275 301, Email reggiani@unipv.it.

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