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Stretch and force generation induce rapid hypertrophy and myosin isoform gene switching in adult skeletal muscle

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Stretch and force generation induce rapid hypertrophy and myosin isoform gene switching in adult skeletal muscle

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Summary

Using electrical stimulation to control force generation and limb immobilization to alter the degree of stretch, we have studied the role of mechanical activity in inducing hypertrophy and in determining fast and slow muscle fibre phenotype. Changes in gene expression were detected by analysing the RNA in hybridization studies employing cDNA probes specific for fast and slow myosin heavy chains and other genes. As a result of overload in the stretched position, the fast contracting tibialis anterior muscle in an adult rabbit is induced to synthesize much new protein and to grow by as much as 30% within a period as short as 4 days. This very rapid hypertrophy was found to be associated with an increase of up to 250% in the RNA content of the muscles and an abrupt change in the species of RNA produced. Both stretch alone and electrical stimulation alone caused repression of the fast-type genes and activation of the slow-type genes. It appears that the fast-type IIB genes are the default genes, but that the skeletal slow genes are expressed as a response to overload and stretch. These findings have implications as far as athletic training and rehabilitation are concerned.

Introduction

Muscle is a tissue in which gene expression is regulated to a large extent by mechanical signals. Mammalian muscle consists of populations of slow-contracting, oxidative fibres and fast-contracting fibres which are characterized by different protein isoforms. Therefore, post-natal growth and the differentiation into the fast type or the slow type of fibres must presumably involve the regulation of expression of different subsets of genes. Here we have focused on the expression of myosin heavy chain genes and their response to mechanical stimuli.

The intrinsic velocity of contraction (V_{max}) of muscle fibres is related to the specific activity of their myosin ATPase [1]. Myosin is a double molecule that consists of two heavy chains each of about 220 kDa. The actin-attachment site and the ATPase site are located in the S1 region (head of the myosin

Abbreviation used: TA, tibialis anterior.

molecule) of each heavy chain. Associated with the S1 fragment are smaller polypeptides called light chains which are believed to modulate the cross-bridge ATPase activity [2]. Subtypes of fast muscle fibre have been identified histochemically and these may exist because of different combinations of myosin heavy and light chains and different mitochondrial content. Slow fibres differ in several ways from fast fibres in that they have many more mitochondria, different cytoplasmic isoenzymes, as well as different isoforms of myofibrillar proteins. The isoforms of myosin have been shown to be the product of a multigene family and their expression is tightly regulated in a stage-specific and tissue-specific manner [3, 4]. Phenotypic expression of muscle genes is known to be influenced by thyroid hormone [5, 6] and altered patterns of innervation [7]. However, the influence of physical activity at the gene level was unclear. We have, therefore, studied changes in transcriptional levels of the fast and slow myosin heavy chain genes in response to stretch and force generation.

Methods

Stimulation and acute-stretch procedures

Tibialis anterior (TA) muscles in adult Netherland dwarf rabbits were stimulated using Teflon-coated stainless-steel electrode wires implanted into the popliteal fossa [8] under valium/Hypnorm anaesthesia. The electrode wires were externalized at the back of the neck and attached to a miniature stimulation circuit which was held in position by a small saddle fashioned out of an elastic bandage. Several circuit designs were used which generated biphasic pulses at frequencies ranging from 2 Hz continuous to 120 Hz intermittent. A 30 Hz intermittent circuit was designed to give the same number of pulses/min as a 2 Hz continuous, and a 120 Hz and 60 Hz intermittent circuit gave the same number of pulses/min as a 10 Hz continuous circuit. In this way, the hypothesis that it is the number of pulses delivered which determines muscle fibre phenotype could be tested. The pulse length was 0.1 ms and the pulse amplitude was adjustable from 1 to 3 V and each miniature stimulator was fitted with an on/off switch. Muscle

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