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Muscle Adaptation: Molecular and Cellular Basis of Muscle Adaptation to Training for Athletic Performance

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Abbreviations used:
hc gene, heavy chain gene; IGF-I, insulin-like growth factor-I; MGF, mechano growth factor.

There is a great need to understand how skeletal muscle grows and is maintained so that we can define the activity and nutritional intake required to ensure optimal muscle development in children. In the West there is much concern about the increasing number of "couch potatoes" particularly young people who spend many hours playing computer games or watching television. In the middle aged and elderly it is a matter of maintaining muscle function as long as possible (19). This also applies to the myocardium as this is a muscle which also needs exercise. Here I will restrict my remarks to skeletal muscle and review what we know about how this muscle grows at the cellular level and gene expression is influenced by physical activity. This knowledge will begin to affect the way we prescribe exercise to ensure correct muscle development during post-natal growth and its maintenance in the elderly. It will also help establish the training regimes during rehabilitation following injury or disease and athletic programs where maximal performance is sought.

As an athlete, man is a generalist and the various events of the Olympic games test quite diverse aspects of his ability to perform physical tasks which depend on different physiological systems including the musculoskeletal, the cardiovascular, the respiratory and the central nervous systems. One of the unresolved issues is to what extent athletes "are born and not made". Clearly, exercise training does improve performance but usually the individuals who specialize in a certain type of event have the right genetic predisposition to excel in this activity even before they embark on serious training. Innate ability as opposed to training effects, are difficult to quantify in man because several physiological systems are involved and there is some genetic variation between individuals. Also invasive sampling methods except for taking blood samples are not usually permitted on man for obvious ethical reasons. In exercise training studies with laboratory animals one is never quite sure if the species adapt in the same way of humans but the problem of genetic variation is minimized and this is the only way at present that one can really examine the tissue changes. However, in predicting innate ability in humans, some non-invasive testing is very useful, for example, it can be predicted that young girls of about 12 years of age cannot become world class swimmers unless they have a certain minimum lung volume With the emergence of powerful imaging techniques such as Magnetic Resonance Scanning, the evaluation of athletic potential, as well as the assessment of training effects, is likely to improve very substantially. The other area of study that is likely to have a major impact on athletic performance in the years to come is molecular biology. All humans possess more or less the same genes but it is differential expression of these genes which determines body type and whether an individual's

muscles will be composed primarily of slow fatigue-resistant fibers that are needed for marathon running or the fast contracting fibers that are needed for the 100 meters sprint. Gene probes that will permit the measurements of levels of expression of specific genes during exercise training are now becoming available. Quite frightening, however are the prospects that once we understand more about how subsets of genes are regulated, this may encourage yet more chemical manipulation of tissues. Eventually this might be extended to transferring the gene itself into say muscle cells using techniques of gene transfer that are being actively researched as gene therapy methods e.g., for curing muscular dystrophy etc. Because these genes or their protein (peptide) products are human in origin, it will be extremely difficult, if not impossible, to distinguish these from the endogenous genes or gene products. Recombinant DNA technology will be a boom to mankind but when so much national pride is involved and in the case of certain professional sports, so much money is involved, enhancing athletic performance is one of the areas where gene transfer is likely to be abused.

Means By Which Muscles Produce Force And Movement.

Let us quickly review the structure of skeletal muscle to understand how force is developed and what determines the power output of the muscles. This is a brief overview as more detailed accounts can be found in cell biology and physiology textbooks.

Muscle is made up of cellular units called muscle fibers, which are 20-100μm in diameter. The muscle fibers contain rod-like contractile structures, myofibrils, which are about 1μm in diameter. These are made up of protein filaments arranged in units called sarcomeres. Each sarcomere consists of one set of thick (myosin) filaments and two sets of thin (actin) filaments, and during the contraction of muscle the thin filaments are pulled in over the thick filaments so that each sarcomere shortens. The means by which the filaments slide over each other has not been completely elucidated. However, it is known that there are projections from the thick (myosin) filaments called myosin cross-bridges. Each cross-bridge is an independent force generator, which interacts with a thin filament and pulls it towards the center of the sarcomere. The cross-bridge then detaches from the thin filament and has to be reprimed by adenosine triphosphate (ATP) before it can go through another cycle of force generation. The three dimensional structure of the myosin crossbridge head (S1) has now been determined for a chicken myosin heavy chain (17) and this should lead to an understanding of how this part of the myosin molecule generates force at given rate. Some of our work has shown that the rate at which cross-bridge work and consume energy in the form of ATP varies considerably depending on the type of muscle fiber and the kind of activity for which it is adapted (2). As discussed below, different types of muscle fibers e.g. slow postural muscles have different myosin cross-bridges than the fast phasic muscle fibers which are coded for by separate myosin heavy chain (hc) genes (16).

During contraction the thin filaments slide over the thick filaments, which results in the shortening of each sarcomere and this happens all along the length of the myofibrils, hence the muscle as a whole shortens (11). The biochemistry of muscular contraction is very interesting, and if we look at the proteins that make up the thick and thin filaments we find that not only does the system possess a means of generating force but also a mechanism for "switching on" and "switching off" the contractile apparatus. The thin actin filaments of the sarcomere are rather like a double pearl necklace that is twisted into a spiral or helix. Decorating these thin filaments are regulatory complexes made up of proteins, tropomyosin and troponins I, T and C. When calcium ions bind with the troponin complex this causes a conformational change in the complex, which results in the tropomyosin being pulled to one side. When the tropomyosin position is changed, active sites are exposed that allow the myosin cross-bridges to interact with thin filaments. The cross-bridges go through repeated

cycles of activity until calcium is withdrawn and sequestered by the sarcoplasmic reticulum or until ATP levels are depleted locally. As well as being needed to reprime the myosin crossbridges, energy in the form of ATP is needed to pump the calcium back into the sarcoplasmic reticulum at the end of each contraction cycle.

Different Types Of Muscle Fibers.

Mammalian skeletal muscles consist of populations of different types of muscle fibers. There are three main types of skeletal muscle fibers, some of which are adapted for a high power output over a short period (fast glycolytic type IIb), while others are adapted for a high power output over a longer period of time (fast, oxidative, glycolytic type IIa). Both of these type II fibers possess a type of myosin and other contractile proteins that produce a short cross-bridge cycle time and develop force very rapidly. However, the latter type (IIa) have more mitochondria and a more oxidative metabolism so they are capable of sustaining the high power output over a longer period. The other major type of fiber found in mammalian muscles is the slow oxidative, type I fiber that has a type of myosin and other contractile proteins which result in a slow cross-bridge cycle. This makes these fibers more efficient and more economical for producing slow repetitive movements and sustaining isometric force but not for generating power (3). The type I fiber is particularly numerous in postural muscle such as the soleus, which is a muscle that is activated virtually all the time during standing, walking and running (10). During any activity, except perhaps ballistic movements, the slow fibers are recruited first. When the power or force requirements increase, the fast type II fibers have to be recruited to provide the necessary power output.

The muscle fiber types differ phenotypically in that they express different subsets of myofibrillar isoform genes as well as different types and levels of metabolic enzymes. The inherent ability of skeletal muscle to adapt to mechanical signals is related to its ability to switch on or switch off transcription of different isoform genes and to alter the general levels of expression of different subsets of genes. The fact that there are several myosin heavy chain isoforms means that a muscle fiber can alter its contractile properties by rebuilding its myofibrils using a myosin hc with a slow or fast cross-bridge cycling rate. The intrinsic velocity of contraction (Vmax) of muscle fibers has been related to the specific activity of their myosin ATPase (1,18). The actin attachment site and the ATPase site are located in the S1 region (head of the myosin cross-bridge) of the heavy chains. Associated with the S1 fragment are smaller polypeptides or light chains which are believed to be involved in the transmission of force rather than in the determination of crossbridge cycling rates (15). The different myosin heavy chain isoforms and hence the different kinds of myosin cross-bridges are encoded by separate genes which are members of a multigene family. Muscle genes are known to be influenced by thyroid hormone (12) and physical activity such as stretch and force generation (9).

Adaptation For Increased Muscle Cross-sectional Area And Force Generation.

The number of muscle fibers apparently does not increase during postnatal growth or as a result of exercise training at reasonable intensity levels (4,21). The question is often asked as to whether hyperplasia (increase in cell numbers) occurs as well as hypertrophy (increase in cell size) in response to strenuous exercise training. In general, experiments using normal types of exercise have not shown any change in the total number of fibers. However, partially splitting muscle fibers, not to be confused with splitting myofibrils, can be observed in surgically overloaded muscle. It is therefore possible that muscle fiber splitting may lead to hyperplasia, e.g. under conditions of repeated, incremental exercise. For this to be regarded as an adaptive phenomenon rather than a pathological change, the splitting would have to be complete and resulting fibers innervated. Studies on laboratory animals indicate that the total

number of fibers is indirectly, genetically determined.

Although there is some doubt as to whether there is an increase in fiber number, muscle overload during weight training certainly does result in an increase in fiber cross-sectional area. The increase in fiber cross-sectional area is associated with a large increase in the myofibrillar content of the fibers. This involves a process by which a myofibril undergoes longitudinal splitting into two or more daughter myofibrils (4). In this way the myofibrillar mass becomes subdivided as it increases in volume and this allows the sarcoplasmic reticulum and transverse tubular systems to invade the mass and to come into close juxtaposition with the actin and myosin filaments. The longitudinal splitting of existing myofibrils apparently occurs because there is a built-in mismatch between the actin and myosin lattice so that the actin filaments are slightly displaced as they run from the Z-disc (square lattice) to the A-band (hexagonal lattice). This displacement or oblique pull of the actin filaments causes a mechanical stress to occur in the center of each Z-disc that results in splitting of the myofibril (4). Splitting tends to be more complete in fast contracting fibers and therefore the myofibrils in these fibers are small and punctate. The maximum force production of a muscle is related to the myofibril cross-sectional area so that the physiological significance of this type of adaptation is apparent. However, we still need to ask what biochemical changes are occurring in an overloaded muscle that causes it to respond by producing more myofibrillar proteins.

All types of muscle fibers are capable of undergoing hypertrophy but they do not usually undergo hypertrophy to the same extent. Slow fibers may also increase in size as a response to frequent recruitment, but to a lesser extent than the fast fibers. In repetitive low-intensity exercise and postural activity, the fast fibers may hardly ever be recruited. Under these conditions they may atrophy at the same time as the slow fibers are undergoing some hypertrophy, for example during long distance running or cycling. Thus, there is a selective response depending on the type of training. The other way muscle fibers respond to repetitive type training is to produce more mitochondria and oxidative enzymes. Accompanying this there is also an increase in the number of capillaries per fiber. Thus selective hypertrophy of one fiber type as opposed to another is a means of providing a greater number of fast or slow myosin crossbridges and also a way of altering the mitochondrial density and vascularity of the muscle (7).

Molecular Regulation Of Muscle Mass And Muscle Fiber Type.

Muscle is a tissue which increases in muscle mass at a remarkable rate just after birth. In the male mouse the muscle mass increases by 25% per day (8) and similar rates occur in humans if one adjusts for the different physiological time scale. Muscle is also a tissue in which gene expression is regulated to a large extent by mechanical signals (9). As mentioned, mammalian muscles consist of populations of slow contracting, oxidative, fibers that are adapted for slow repetitive movements and semi-isometric postural activity. They also possess populations of fast contracting fibers that are required for rapid powerful movements. As well as having a higher mitochondrial content than the fast fibers, the slow fibers have different contractile protein isoforms. Using electrical stimulation to control force generation and limb immobilization to alter the degree of stretch, the author's laboratory has studied the role of physical activity in determining fast and slow muscle fiber phenotype. Changes in gene expression were detected by analyzing RNA in hybridization studies employing cDNA probes specific for fast and slow myosin heavy chain genes. The skeletal myosin heavy chain genes belong to a family of genes that are arranged in tandem on chromosome 17 in man. The cardiac muscle myosin genes, for which there are two isoforms a and ß, are on chromosome 14 in man. There are at least five isoform genes for the skeletal myosin heavy chains and these are expressed in the sequence: embryonic, neonatal, adult

fast, adult fast oxidative, and adult slow (20).

As a result of overload in the stretched position, the fast contracting tibialis anterior muscle in an adult rabbit is induced to synthesize a lot of protein and to grow by as much as 35% within a period as short as 4 days. This very rapid hypertrophy was found to be associated with a 250% increase in the RNA content of the muscle and a change in the species of mRNA produced. Both stretch alone and electrical stimulation alone caused some activation of the slow type and repression of the fast-type genes. However, a more complete switch in myosin heavy chain gene expression was achieved when these mechanical stimuli were combined and when higher frequencies of stimulations were used. This leads to the conclusion that muscle fiber adult phenotype is determined by stretch and force generation (passive plus active tension) and that this is controlled at the level of gene transcription. The regulation of growth, however, is probably limited by the rate of translation of the message into protein. In this context it is interesting to note that the ribosomal density is increased very significantly during hypertrophy. It also decreases significantly during postnatal growth in line with the slowing of muscle development. It therefore appears that the translational process, which is known to be much slower than the transcriptional process, is the rate-determining step in hypertrophy. Certainly, the 250% increase in ribosomal RNA during the rapid hypertrophy of an adult muscle means that extra ribosomes are available to translate the message, whatever it may be. Therefore, the rapid synthesis of more ribosomes seems to be the first step in producing muscle fiber hypertrophy.

Effects Of Stretch On Muscle

Stretch has been shown to be a very powerful stimulant of muscle growth and muscle protein synthesis. During post-natal growth, skeletal muscles fibers elongate by adding new sarcomeres (6,22) serially to the ends of existing myofibrils (4). Even mature muscles have been shown to be capable of adapting to a new functional length by adding or removing sarcomeres in series (22). In this way sarcomere length is adjusted back to the optimum for force generation, velocity and hence power output. The stretch effect and the adaptation to an increased functional length is known to be associated with increased protein synthesis (5,13). More recently we have studied the way gene expression in muscle is influenced by stretch which was achieved by casting the limb with the muscle either in the shortened or lengthened position (14). Several interesting findings emerged from this study including the fact that a slow soleus muscle which does not normally express fast type IIb myosin hc genes, begins to transcribe the fast myosin hc gene after only a day if its muscle fibers are not stretched passively or are not producing force. As mentioned stretch combined with electrical stimulation was also found to induce very rapid hypertrophy of the tibialis anterior in the adult animal. Both force generation and stretch are major factors in activating protein synthesis and the combination of these stimuli apparently has a pronounced additive effect. Associated with this very significant increase in muscle size there was a marked increase (up to 250%) in RNA content of the muscles which was found to peak after 2 days of the commencement of stretch. This rapid increase in total RNA, which is presumably mainly ribosomal RNA indicates that muscle fiber hypertrophy may be controlled mainly at the level of translation and that the rapid increase in the number of ribosomes means that more message can be translated into protein. There are situations when abundant message is present but the fibers are still undergoing atrophy e.g. lack of stretch (with and without stimulation). This again indicates that muscle size unlike muscle phenotype may be regulated mainly at the level of translation. When both stretch and electrical stimulation are combined, the fast tibialis anterior of the rabbit apparently becomes completely reprogrammed for the transcription of slow myosin hc and to repress the expression of the fast myosin hc gene within only 4 days (9).

There are two ways in which the contractile properties and hence the energy efficiency of

a muscle can be altered during training. These include the interconversion of fibers, for example fast into slow, and the selective hypertrophy of a given fiber type (4). Basically, these may represent the same mechanism, as fibers do not exist as discrete types but as a continuum. Indeed, all fibers have a mixture of the different contractile protein isoforms, but in fast fibers there is a predominance of the fast myosin heavy chain and other fast contractile protein isoforms. This resolves down to which isoform genes are induced and which are repressed. So far our studies have indicated that the fast adult genes are the default genes. However, when the muscle is subjected to stretch or to repeated stimulation it will express the slow adult genes. There may be a window of a certain time period needed for switching on the slow genes so that they are only switched on by long bursts of activity. The cellular signals for the muscle gene switching are not understood, but these may include changed metabolite or calcium levels.

Requirements For Different Types Of Athletic Activity.

It is fairly obvious, even at a superficial level that weight lifters require different types of muscles to sprinters or long distance runners. To excel at weightlifting the individual needs large muscles and the exercising training for weightlifting is associated with extensive muscle hypertrophy. At the level of a single muscle, strength can be defined as the maximum force that it can develop during a single contraction. This is related to the number of myosin cross-bridges in parallel that can interact with the actin filaments and generate force. For most practical purposes it is convenient to relate the maximum force developed to the muscle fiber cross-sectional area. Providing the myofibrillar content of the fibers does not differ markedly, this is a reasonably accurate way of predicting the force that a muscle can develop. It is often more convenient to relate strength to muscle cross-sectional area. However, it must be realized that this is more imprecise because the percentage of extracellular space and the arrangement of muscle fibers varies from muscle to muscle. With regard to the former, it seems that one of the earliest responses to strength training is for a consolidation of the tissue as the muscle fibers increase in girth at the expense of extracellular spaces. That is to say, the initial response is for the muscle fiber cross-sectional area to increase without a commensurate increase in muscle cross-sectional area taking place. This is another reason why there is initially an increase in strength without an obvious increase in muscle bulk.

The requirements for running are somewhat different. In these sort of events muscle power output is all important. Power is work done (force x distance) per unit time, hence, the important parameters are speed of contraction (Vmax) and force production. The higher and the more rapid the force generation, the greater the power output.

The overall velocity of shortening of the muscle is, in part, determined by the number of sarcomeres in series. Animals or individual human beings with long legs would have longer muscles and thus more sarcomeres in series. In this respect one might say that longer limbs are an advantage. However, there is the problem of inertia of a long limb. The velocity of shortening is also determined by the intrinsic velocity (Vmax) of the sarcomeres which in turn is dependent on the predominant type of myosin cross-bridge. Thus sprinters have well developed muscles that are able to contract rapidly but they are not usually very tall.

During sprint running all the fibers will be activated because of the high power output require. The slow fibers, however, will contribute very little as they will not be able to keep up with the rate of contraction and they will be more or less moved passively. In this respect a high proportion of slow fibers in a muscle would be tend to hamper the fast fibers. Therefore one expects individuals who excel at sprinting to have a very high proportion of type II fibers. In training for sprinting it is not advisable to engage in the kind of training used by weightlifters as muscle overload of reasonably long duration results in the muscle expressing slow type genes. Short bursts of very intensive activity such as sprinting itself are the best type of

training as this induces hypertrophy but the duration of the exercise is not long enough to turn on the slow genes.

The important muscle parameter for long distance and indeed intermediate distance running is sustainable power. This has to involve several 'trade offs' as the muscle of the endurance athlete must be fatigue resistant. This means that he or she should not be carrying any extra muscle mass and the total myofibrillar cross-sectional area will be reduced by the additional mitochondria need to supply ATP at the same rate at which it is used. As is seen from sections of muscle taken by needle biopsy from the quadriceps muscle from different types of athlete e.g. a high jumper and a marathon runner, the athlete who excels at the stamina events has a much greater percentage of slow contracting fibers. This makes physiological sense as these are adapted for performing slow movements efficiently and economically (3). In order for muscle fibers to work at maximum efficiency, their intrinsic rate of shortening, has to be matched to the rate to the velocity they are required to shorten. Therefore, the slow fibers with the slow myosin cross-bridges are much more efficient and economical for producing the slow repetitive contractions for say, long distance running. As the slow type myosin crossbridges of the slow fibers use ATP at a slow rate, the mitochondria which are abundant in these fibers are able to supply ATP at the same rate at which it is used. Therefore, these muscles are fatigue resistant and work in a steady state for most of the race except at the end when the athlete puts on a spurt and the muscles become anoxic. In endurance events, where it is important to sustain power output, the training, has to be directed towards increasing the percentage of slow type contractile proteins more mitochondria and improved vascularity. This is best achieved by putting in as many hours on the running track as possible.

The Future

A great deal of scientific effort is now being directed towards sequencing the human genome. Once all the genes have been catalogued, this will inevitably lead to study of the differences between individuals. As performance of any athletic event involves many different parameters involving several body systems, e.g. central nervous system, cardiovascular, muscle, etc., it is unlikely that predictions of performance will be made on this basis, at least for many years to come. However, emerging methods in molecular biology do offer the prospect of optimizing training regimes by assessing alterations in gene expression. By attaching synthetic DNA (oligonucleotides) probes to each end of a specific gene sequence, it is possible to amplify that particular DNA sequence by a million times within a couple of hours using the polymerase chain reaction (PCR). *In situ* hybridization is another method that is sensitive and which has the advantage that the expression of a specific gene can be detected in a given muscle fiber type. This procedure we believe is very suitable for use on muscle biopsy sections, which can also be stained using monoclonal antibodies, etc. In this way athletic and rehabilitation training regimes for power production or for endurance can be optimized. Regrettably the potential of recombinant DNA technology may be abused as this might be extended to transferring the engineered genes into muscle cells using techniques now being developed for gene therapy.

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Geoffrey Goldspink became a professor when still only 32. He was awarded the chair for his contribution to the understanding of how muscle grows and develops. He has held nine professorships, including a visiting professorship at Harvard University.