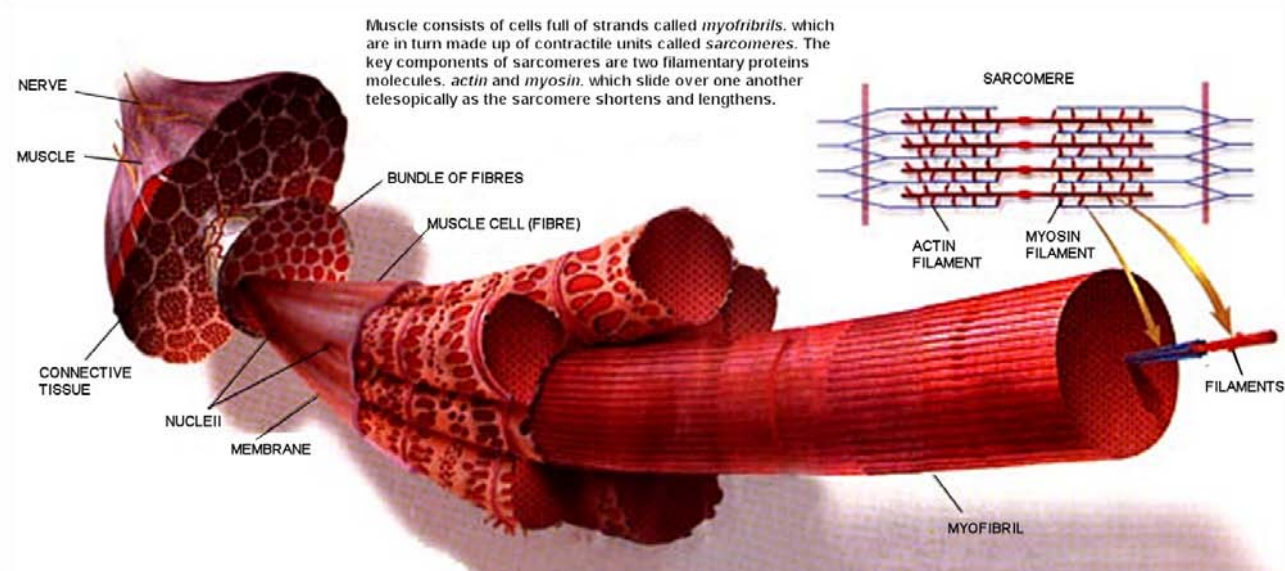


Research on Training of Skeletal Muscles

Skeletal muscle is the most abundant tissue in the human body and also one of the most adaptable. Vigorous training with weights can double or triple a muscle's size, whereas disuse, as in space travel, can shrink it by 20 percent in two weeks. The many biomechanical and biochemical phenomena behind these adaptations are enormously complex, but decades of research have built up a reasonably complete picture of how muscles respond to athletic training.



What most people think of, as a muscle is actually a bundle of cells, also known as fibers, kept together by collagen tissue. A single fiber of skeletal muscle consists of a membrane, many scattered nuclei that contain the genes and lie just under the membrane along the length of the fiber, and thousands of inner strands called myofibrils that constitute the cytoplasm of the cell. The largest and longest human muscle fibers are up to 30 centimeters long and 0.05 to 0.15 millimeter wide and contain several thousand nuclei.

Filling the inside of a muscle fiber, the myofibrils are the same length as the fiber and are the part that causes the cell to contract forcefully in response to nerve impulses. Motor nerve cells, or neurons, extend from the spinal cord to a group of fibers, making up a motor unit. In leg muscles, a motor neuron controls, or innervates, several hundred to 1,000 or more muscle fibers. Where extreme precision is needed, for example, to control a finger, an eyeball or the larynx, one motor neuron controls only one or at most a few muscle fibers.

The actual contraction of a myofibril is accomplished by its tiny component units, which are called sarcomeres and are linked end to end to make up a myofibril. Within each sarcomere are two filamentary proteins, known as myosin and actin, whose interaction causes the contraction. Basically, during contraction a sarcomere shortens like a collapsing telescope, as the actin filaments at each end of a central myosin filament slide toward the myosin's center.

One component of the myosin molecule, the so-called heavy chain, determines the functional characteristics of the muscle fiber. In an adult, this heavy chain exists in three different varieties, known as isoforms. These isoforms are designated I, 2a and 2x, as are the fibers that contain them. Type I fibers are also known as slow fibers; type 2a and 2x

are referred to as fast fibers. The fibers are called slow and fast for good reason: the maximum contraction velocity of a single type I fiber is approximately one tenth that of a type 2x fiber. The velocity of type 2a fibers is somewhere between those of type I and type 2x. The differing contraction speeds of the fibers is a result of differences in the way the fibers break down a molecule called adenosine triphosphate (ATP) in the myosin heavy chain region to derive the energy needed for contraction. Slow fibers rely more on relatively efficient aerobic metabolism, whereas the fast fibers depend more on anaerobic metabolism. Thus, slow fibers are important for endurance activities and sports such as long-distance running, cycling and swimming, whereas fast fibers are key to power pursuits such as weight lifting and sprinting.

The average healthy adult has roughly equal numbers of slow and fast fibers in, say, the quadriceps muscle in the thigh. But as a species, humans show great variation in this regard; we have encountered people with a slow-fiber percentage as low as 19 percent and as high as 95 percent slow fibers could probably become an accomplished marathoner but would never get anywhere as a sprinter; the opposite would be true of a person with 19 percent slow fibers.

Besides the three distinct fiber types, there are hybrids containing two different myosin isoforms. The hybrid fibers fall in a continuum ranging from those almost totally dominated by, say, the slow isoform to fibers almost totally dominated by a fast one. In either case, as might be expected, the functional characteristics of the fiber are close to those of the dominant fiber type.

Muscle fibers cannot split themselves to form completely new fibers. As people age, they lose muscle fibers, but they never gain new ones. So a muscle can become more massive only when its individual fibers become thicker.

What causes this thickening is the creation of additional myofibrils. The mechanical stresses that exercise exerts on tendons and other structures connected to the muscle trigger signaling proteins that activate genes that cause the muscle fibers to make more contractile proteins. These proteins, chiefly myosin and actin, are needed as the fiber produces great amounts of additional myofibrils.

More nuclei are required to produce and support the making of additional protein and to keep up a certain ratio of cell volume to nuclei. As mentioned, muscle fibers have multiple nuclei, but the nuclei within the muscle fiber cannot divide, so the new nuclei are donated by so-called satellite cells (also known as stem cells). Scattered among the many nuclei on the surface of a skeletal muscle fiber, satellite cells are largely separate from the muscle cell. The satellite cells have only one nucleus apiece and can replicate by dividing. After fusion with the muscle fiber, they serve as a source of new nuclei to supplement the growing fiber.

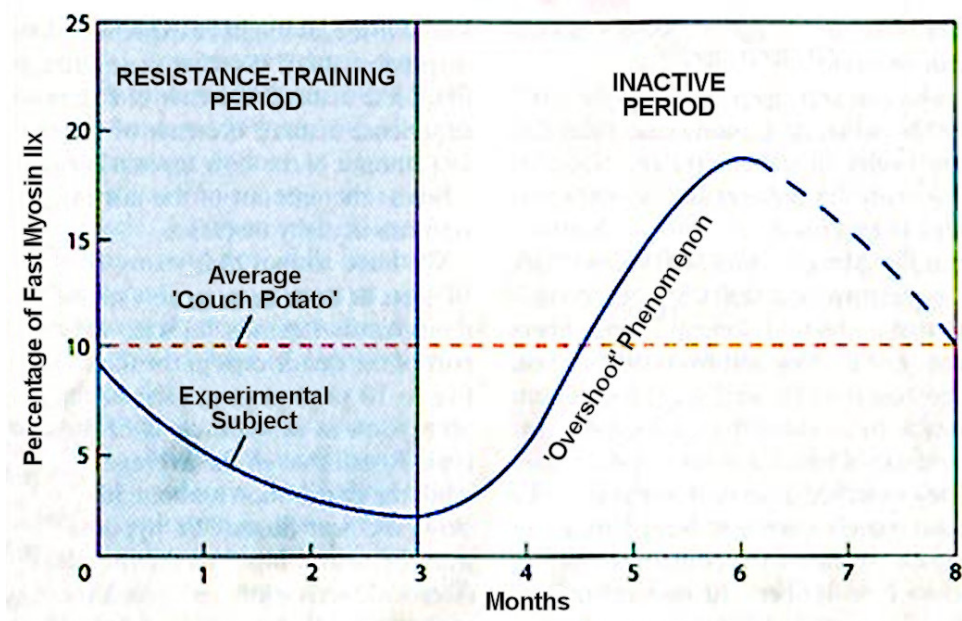
Satellite cells proliferate in response to the wear and tear of exercise. One theory holds that rigorous exercise inflicts tiny microtears in muscle fibers. The damaged area attracts the satellite cells, which incorporate themselves into the muscle tissue and begin producing proteins to fill the gap. As the satellite cells multiply, some remain as satellites on the fiber, but others become incorporated into it. These nuclei become indistinguishable from the muscle cells other nuclei. With these additional nuclei, the fiber is able to churn out more proteins and create more myofibrils.

To produce a protein, a muscle cell-like any cell in the body-must have a blueprint to specify the order in which amino acids should be put together to make the protein-in other words, to indicate which protein will be created. This blueprint is a gene in the cells nucleus, and the process by which the information gets out of the nucleus into the cytoplasm, where the protein will be made, starts with transcription. It occurs in the nucleus when a genes information (encoded in DNA) is copied into a molecule called

messenger RNA. The mRNA then carries this information outside the nucleus to the ribosome, which assemble amino acids into the proteins-actin or one of the myosin isoforms, for example-as specified by the mRNA. This last process is called translation. Biologists refer to the entire process of producing a protein from a gene as expression of that gene.

Two of the most fundamental areas of study in skeletal muscle research—ones that bear directly on athletic performance—revolve around the way in which exercise and other stimuli cause muscles to become enlarged (a process called hypertrophy) and how such activity can convert muscle fibers from one type to another. Others and we have pursued these subjects intensively in recent years and have made some significant observations.

The research goes back to the early 1960s, when A.J. Buller and John Carew Eccles of the Australian National University in Canberra and later Michael Barany and his CO-workers at the Institute for Muscle Disease in New York City performed a series of animal studies that converted skeletal muscle fibers from fast to slow and from slow to fast. The researchers used several different means to convert the fibers, the most common of which was cross-innervation. They switched a nerve that controlled a slow muscle with one linked to a fast muscle, so that each controlled the opposite type of fiber. The researchers also electrically stimulated muscles for prolonged periods or, to get the opposite effect, cut the nerve leading to the muscle.



Images:
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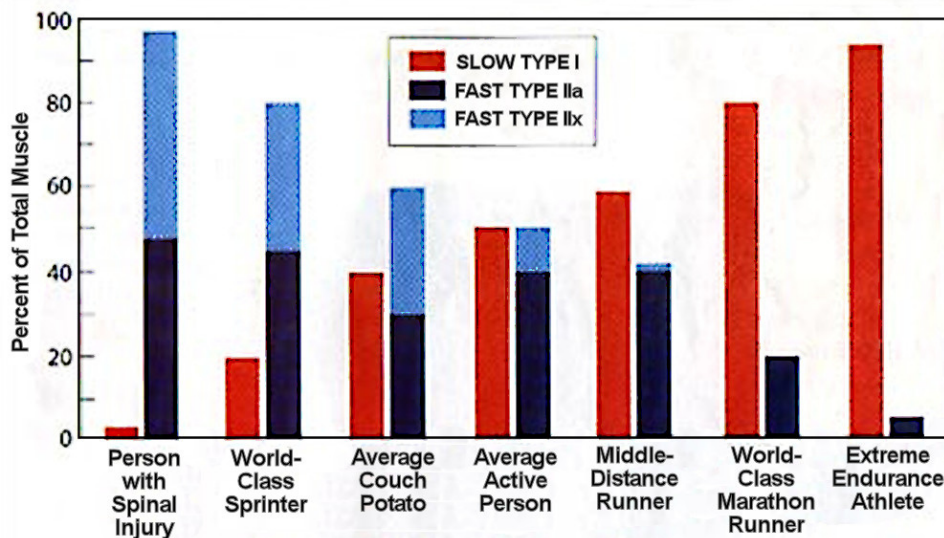
In the 1970s and 1980s muscle specialists focused on demonstrating that the ability of a muscle fiber to change size and type, a feature generally referred to as muscle plasticity, also applied to humans. An extreme example of this effect occurs in people who have suffered a spinal cord injury serious enough to paralyze their lower body. The lack of nerve impulses and general disuse of the muscle cause a tremendous loss of tissue, as might be expected. More surprisingly, the type of muscle changes dramatically. These paralyzed subjects experience a sharp decrease of the relative amount of the slow myosin isoform, whereas the amount of the fast myosin isoforms actually increases.

We have shown that many of these subjects have almost no slow myosin in their vastus lateralis muscle, which is part of the quadriceps in the thigh, after five to 10 years of paralysis; essentially all myosin in this muscle is of the fast type. Recall that in the average healthy adult the distribution is about 50-50 for slow and fast fibers. We hypothesized that the neural input to the muscle, by electrical activation, is necessary for

maintaining the expression of the slow myosin isoform. Thus, electrical stimulation or electrically induced exercise of these subjects muscles can, to some extent, reintroduce the slow myosin in the paralyzed muscles.

Conversion of muscle fibers is not limited to the extreme case of the reconditioning of paralyzed muscle. In fact, when healthy muscles are loaded heavily and repeatedly, as in a weight-training program, the number of fast 2x fibers declines as they convert to fast 2a fibers. In those fibers the nuclei stop expressing the 2x gene and begin expressing the 2a. If the vigorous exercise continues for about a month or more, the 2x muscle fibers will completely transform to 2a fibers. At the same time, the fibers increase their production of proteins, becoming thicker.

In the early 1990s Geoffrey Goldspink of the Royal Free Hospital in London suggested that the fast 2x gene constitute a kind of default setting. This hypothesis has held up in various studies over the years that have found that sedentary people have higher amounts of myosin 2x in their muscles than do fit active people. Moreover, complementary studies have found a positive correlation between myosin 2a and muscle activity.



What happens when exercise stops? Do the additional 2a fibers then convert back to 2x? The answer is yes, but not in the precise manner that might be expected. To study this issue, we took muscle samples (biopsies) from the vastus lateralis muscle of nine young, sedentary Danish men. We then had the subjects conduct heavy resistance training, aimed mainly at their quadriceps muscle, for three months, ending with another muscle biopsy. Then the subjects abruptly stopped the resistance training and returned to their sedentary lifestyle, before being biopsied for a third and final time after a three-month period of inactivity (corresponding to their behavior prior to entering the training).

As expected, the relative amount of the fast myosin 2x isoform in their vastus lateralis muscle was reduced from an average of 9 percent to about 2 percent in the resistance-training period. We then expected that the relative amount of the 2x isoform would simply return to the pretraining level of 9 percent during the period of inactivity. Much to our surprise, the relative amount of myosin 2x reached an average value of 18 percent three months into the detraining. We did not continue the biopsies after the three-month period, but we strongly suspect that the myosin 2x did eventually return to its initial value of about 9 percent some months later.

We do not yet have a good explanation for the overshoot phenomenon of the expression of the fast myosin 2x isoform. Nevertheless, we can draw some conclusions

that can have useful applications. For instance, if sprinters want to boost the relative amount of the fastest fibers in their muscles, the best strategy would be to start by removing those that they already have and then slow down the training and wait for the fastest fibers to return twofold! Thus, sprinters would be well advised to provide in their schedule for a period of reduced training, or tapering, leading up to a major competition. In fact, many sprinters have settled on such a regimen simply through experience, without understanding the underlying physiology.

Conversion between the two fast fiber types, 2a and 2x, is a natural consequence of training and detraining. But what about conversion between the slow and fast fibers types 1 and 2? Here the results have been somewhat murkier. Many experiments performed over the past couple of decades found no evidence that slow fibers can be converted to fast, and vice versa. But in the early 1990s we did get an indication that a rigorous exercise regimen could convert slow fibers to fast 2a fibers.

Our subjects were very elite sprinters, whom we studied during a three-month period in which they combined heavy resistance training with short-interval running (these are the foundation exercises in a sprinters yearly training cycle). At around the same time, Mona Esbornsson and her CO-workers at the Karolinska Institute in Stockholm reported similar findings in a study involving a dozen subjects who were not elite athletes. These results suggest that a program of vigorous weight training supplemented with other forms of anaerobic exercise converts not only type 2x fibers to 2a but also type 1 fibers to 2a.

If a certain type of exertion can convert some type 1 fibers to 2a, we might naturally wonder if some other kind could convert 2a to 1. It may be possible, but so far no lengthy human training study has unambiguously demonstrated such a shift. True, star endurance athletes such as long-distance runners and swimmers, cyclists and cross-country skiers generally have remarkably high proportions-up to 95 percent, as mentioned earlier-of the slow type 1 fibers in their major muscle groups, such as the legs. Yet at present we do not know whether these athletes were born with such a high percentage of type 1 fibers and gravitated toward sports that take advantage of their unusual inborn trait or whether they very gradually increased the proportion of type 1 fibers in their muscles as they trained over a period of many months or years. WE do know that if fast type 2a fibers can be converted to type 1, the time required for the conversion is quite long in comparison with the time for the shift from 2x to 2a.

It may be that great marathon runners are literally born different from other people. Sprinters, too, might be congenitally unusual: in contrast with long-distance runners, they of course would benefit from a relatively small percentage of type 1 fibers. Still, a would-be sprinter with too many type 1 fibers need not give up. Researchers have found that hypertrophy from resistance training enlarges type 2 fibers twice as much as it does type 1 fibers. Thus, weight training can increase the cross-sectional area of the muscle covered by fast fibers without changing the relative ratio between the number of slow and fast fibers in the muscle. Moreover, it is the relative cross-sectional area of the fast and slow fibers that determines the functional characteristics of the entire muscle. The more area covered by fast fibers, the faster the overall muscle will be.

In a study published in 1988 Michael Sjoström and his CO-workers at the University of Umeå, Sweden, disclosed their finding that the average cross-sectional areas of the three main fiber types were almost identical in the vastus lateralis muscles of a group of marathon runners. In those subjects the cross-sectional area of type 1 fibers averaged 4,800 square microns; type 2a was 4,500; and type 2x was 4,600. For a group of sprinters, on the other hand, the average fiber sizes varied considerably: the type 1 fibers averaged 5,000 square microns; type 2a, 7,300; and type 2x, 5,900. We have results from a group of sprinters that are very similar.