

historical perspectives

Skeletal muscle adaptation to exercise: a century of progress

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Hamilton, Marc T., and Frank W. Booth. Skeletal muscle adaptation to exercise: a century of progress. *J. Appl. Physiol.* 88: 327–331, 2000.—Skeletal muscle physiology and biochemistry is an established field with Nobel Prize-winning scientists, dating back to the 1920s. Not until the mid to late 1960s did there appear a major focus on physiological and biochemical training adaptations in skeletal muscle. The study of adaptations to exercise training reveals a wide range of integrative approaches, from the systemic to the molecular level. Advances in our understanding of training adaptations have come in waves caused by the introduction of new experimental approaches. Research has revealed that exercise can be effective at preventing and/or treating some of the most common chronic diseases of the latter half of the 20th century. Endurance-trained muscle is more effective at clearing plasma triglyceride, glucose, and free fatty acids. However, at the present time, most of the mechanisms underlying the adaptation of human skeletal muscle to exercise still remain to be discovered. Little is known about the regulatory factors (e.g., *trans*-acting proteins or signaling pathways) directly modulating the expression of exercise-responsive genes. Because so many potential physiological and biochemical signals change during exercise, it will be an important challenge in the next century to move beyond “correlational studies” and to identify responsible mechanisms. Skeletal muscle metabolic adaptations may prove to be a critical component to preventing diseases such as coronary heart disease, type 2 diabetes, and obesity. Therefore, training studies have had an impact on setting the stage for a potential “preventive medicine reformation” in a society needing a return to a naturally active lifestyle of our ancestors.

physical inactivity; history; mechanism; metabolism; review; gene; physiology

HISTORY IS REplete WITH EFFORTS to expand the known limits of human existence. Explorers such as Marco Polo, Christopher Columbus, Sir Edmund Hillary, and Neil Armstrong provide several examples. Similarly, exercise researchers in the past century have been motivated by the desire to understand how the biological limits of the human body can be extended. History shows that much progress in this area has been accomplished through the heroic research efforts of investigators studying the skeletal muscle training adaptations,

such as August Krogh, P. D. Gollnick, J. O. Holloszy, and B. Saltin. At the present time, most of the mechanisms underlying the adaptation of human skeletal muscle to exercise still remain to be discovered.

One purpose of this review is to outline the historical flow of varied research studies attempting to elucidate the mechanisms of skeletal muscle adaptations to exercise.¹ Exercise physiology is one of the oldest biological sciences. The principle that muscle mass

Invited historical perspective on “Molecular and Cellular Basis of Exercise Adaptation.”

¹ With minor exceptions, we decided not to cite a full list of works by author’s names and publications, due to the page limitations given to us for this review. For this we apologize, as we have omitted hundreds of important contributors (over 15,000 papers published since 1966

adapts during progressive strength training had been well established by the time of the Greek and Roman dynasties. In 1628, William Harvey stated, "the more muscular and powerful men are, the firmer the flesh; the stronger, thicker, denser, and more fibrous their hearts, the thicker, closer, and stronger are the auricles and arteries" (9). Therefore, William Harvey was not only a precursor in using the scientific method and a father of physiology (6, 7) but also an exercise physiologist. In 1777, Lavoisier demonstrated that oxygen is taken in by the body and carbon dioxide is given off during respiration (see Ref. 6 for the history of calorimetry). In 1842, it was shown that protein, carbohydrate, and fat were oxidized by the body, but the first definitive association of carbohydrate metabolism with muscle contraction was not made until 1867. The heat values of fat, protein, and carbohydrate were provided in 1884, and calorimetry studies were common by the end of the 19th century. These early studies laid the foundation for many exercise studies between 1970 and 2000, documenting energy expenditure and fuel partitioning during exercise. We now know that one of the hallmarks of endurance training is a shift in substrate utilization from carbohydrate to fat during exercise.

Exercise Studies Have Been Performed by Nobel Prize Winners

Between the years 1910 and 1920 in Denmark, August Krogh developed instruments such as the "tilting spirometer," the electromagnetic bicycle ergometer, and an apparatus for gas analysis (18). This was a forerunner of a historical trend for utilizing technological advancements to fuel discoveries in exercise physiology. These instruments allowed Krogh to demonstrate the relative value of carbohydrate and fat as sources of energy for muscular contraction. Moreover, he showed that an oxygen deficiency developed at the beginning of work was not replaced until the conclusion of work, and he also emphasized the importance of venous blood return to the heart (7, 18). Krogh went on to win the Nobel Prize in Medicine and Physiology in 1920 for his "discovery of the regulation of the motor mechanism of capillaries" (13). His studies of capillaries were extended to exercise when he found that the average diameter of open microvessels was wider in working than in resting muscles (7, 18). Shortly thereafter, in 1922, A. V. Hill of England won the Nobel Prize in Medicine and Physiology for his discovery relating to the production of heat in muscles. He was also associated with seven papers published in 1923–1924 that focused on the oxygen utilization, fuel selection, and lactic acid production in exercising humans. Hill introduced the concept that the circulatory and respiratory systems imposed limitations in maximal oxygen uptake during exercise in humans (10). Additional contribu-

tions of Nobel Prize winners, O. Meyerhoff of Germany and J. C. Eccles of Australia, will be discussed later. Muscle physiology/biochemistry during exercise is a fascinating science that has driven some of the greatest scientific minds.

1960s: Advent of the Explosion of Research Into Skeletal Muscle Adaptations

Interestingly, the number of both animal and human training studies increased dramatically at about the same time. Before the late 1960s, studies of the biochemical and physiological adaptations in exercise-trained skeletal muscle were few and far between. For example, between 1927 and 1947, work from the Harvard Fatigue Laboratory, led by D. B. Dill and others, produced many insightful studies on physiological changes in humans responding to exercise and various stressful stimuli, but this work did not include skeletal muscle adaptations (12). Until the 1960s, physiological research in exercise had focused on the responses and adaptations of the cardiovascular system and oxygen delivery to muscle. Although it was very well recognized that skeletal muscle is hypertrophied with high-resistance weight training (19) and that cardiac volume is enlarged after endurance training in humans and animals (19), it was not generally thought that skeletal muscle adapts metabolically to aerobic exercise training. This is documented most interestingly by contrasting the very few citations about skeletal muscle training adaptation in the early edition of the classic exercise textbook (1). Very few studies had even attempted to study skeletal muscle metabolic adaptations. An interesting exception was the finding that daily electrical stimulation of rabbit muscle delayed rigor mortis, associated with slower appearance of inorganic phosphate and ammonia in the "dying" trained muscle (see Ref. 19). Therefore, 100 years from now, scientists will probably describe the research amassed in the past 30 years as the foundational years for understanding biochemical adaptations in muscle.

In the case of human research, the reintroduction of the muscle needle biopsy for exercise research by Bergström and Hultman (2) illustrates how a relatively simple technological advancement can have major impact on years of future research. Prior to 1966, the metabolic response of human skeletal muscle to exercise was largely inferred from chemical measurements made in blood and expired air (17). Initially, biopsies of exercised human skeletal muscle were often used for measurements of glycogen and muscle fiber type. Approximately 1,300 listed Medline publications since 1966 had these four words "biopsy," "muscle," "human," and "exercise" in their abstracts. However, this number most likely underestimates the use of the muscle biopsy technique, since abstracts may not always include methodology terms such as "biopsy" (the words "muscle," "human," and "exercise" were contained in 11,667 abstracts). The simple advancement of the needle biopsy allowed direct measurements of muscle chemistry.

How have exercise-training studies in skeletal muscle progressed historically? The answer to this question

list the words "exercise" and "muscle" in their abstracts). With our limited space, we decided that it was more important to present perspectives on concepts and ideas rather than an extensive bibliography. Nevertheless, we are sad to have omitted so much.

can be described by using three examples: skeletal muscle microcirculation, fiber type, and fuel selection.

Microcirculation. The history of microcirculatory research during exercise may be one of the richest to date in exercise physiology, having been boosted by a Nobel Prize in 1920 awarded to Krogh. The influence of exercise on muscle blood flow exemplifies an area that has consistently produced surges of answers following application of new experimental approaches to exercise research. Catheterization of arteries and veins in exercising humans, determination of human limb blood flow, and the development of one-limb human exercise machines in the 1960s and 1970s permitted the development of many currently acknowledged concepts. Findings such as the fact that the capacity for maximal blood flow is greater than the maximal cardiac output and that blood flow is redistributed to working muscles during exercise are no longer in question. Even by 1934 it had been reported that treadmill training increased vascularization of guinea pig leg muscles, but not in the nonrecruited masseter muscle of the jaw (1). Led by M. H. Laughlin and R. A. Armstrong in the 1980s, extensive use of microsphere techniques enabled much of our present understanding about how blood flow is redistributed to match energy demands. For example, muscle blood flow in exercising animals is not evenly distributed and varies among fiber types, ranging from 60 to 400 ml/min in white and red fiber types, respectively. The ability to isolate and study microvessels from skeletal muscles has led to a surge of productivity in the 1990s regarding the regulatory mechanisms for blood flow. Additionally, using molecular biology techniques, we are currently on the leading edge of a new wave of research into the growth factors and signaling pathways responsible for the angiogenesis induced by endurance training. Recombinant DNA technology is presently providing a tool for exercise researchers to overexpress growth factors and induce capillary growth in skeletal muscle. An example of the use of such technology would be a reexamination of what we truly know about the functional benefits of increased capillary density to exercise performance in skeletal muscle.

Fiber type. Skeletal muscle is not homogenous but is composed of different types of muscle fibers, each of which has its own phenotype. A. J. Buller, J. C. Eccles, and R. M. Eccles provided the first important stimulus for studies on exercise-induced changes in muscle fiber type in 1960 when they reported the occurrence of fiber transformations during the cross-innervation of slow muscles by fast nerves and vice versa (4). J. C. Eccles later won the Nobel Prize in 1963 for establishing the relationship between nerve cell inhibition and repolarization of the cell membrane. In the 1970s, muscle biopsies and histochemistry allowed for the discovery that the skeletal muscles of world-class sprinters contain a high percentage of fast-twitch fibers, whereas the skeletal muscles of elite endurance athletes have a high percentage of slow-twitch fibers. In the past two decades, studies have shown that both endurance and strength training can cause fibers to shift away from the fastest (and most fatigable) fiber type to express

slower myosin isoforms exhibiting higher endurance. In contrast, models of physical inactivity cause a shift in the opposite direction. Clues to how exercise induces the conversion between myosin isoforms are now being studied with the use of transgenic mice to determine DNA regulatory elements. The metabolic characteristics of fiber type that influence fatigability and power output may also have significant impact on risk for developing disease. Today, associations between a high percentage of fast fibers and the "metabolic syndrome" (the metabolic clustering of atherosclerosis, type II diabetes mellitus, and hypertension) are being reported. A cause-and-effect relationship between myosin isoforms and health does not likely exist per se; rather, it is the metabolic properties associated with different fiber types that appear to influence predisposition to disease, according to preliminary studies. In the next century, it will be important to continue searching for molecular mechanisms that regulate the differences in metabolic phenotypes among fiber types.

Fuel selection. In the 19th century, the fuel used by skeletal muscle for work was suggested to be protein. However, in 1907, it was observed that there is a rapid accumulation of lactic acid in muscle exercised to fatigue (see Ref. 5). This eventually led to the awarding of the Nobel Prize in 1922 to O. Meyeroff for his discovery of the fixed relationship between oxygen consumption and lactic acid metabolism in muscle. Meyeroff published the concept that lactic acid formation was an indispensable energy source for muscular contraction; however, ATP had yet to be discovered at this time. E. Lundsgaard (14) disproved Meyeroff's hypothesis in 1930 when he reported that monoiodoacetic acid-treated muscles (in which glycolysis is inhibited at 3-phosphoglyceraldehyde dehydrogenase) can work anaerobically without lactic acid formation. Lundsgaard also showed the linear relationship between mechanical work performed under a variety of conditions and the amount of phosphate released from phosphocreatine.

The remainder of the 20th century was devoted largely to understanding the fuel sources supplying ATP for muscle contractions (3, 16). Utilization of biochemistry, histochemistry, metabolic isotopes, and nuclear magnetic resonance imaging, among others, has contributed to great progress in our understanding of how skeletal muscle adapts to training. Molecular biology techniques are just beginning to elucidate the mechanisms regulating expression of critical genes. We now know that there is a great difference in the source of fuel utilized between endurance-trained and untrained muscles during and after exercise. Endurance training increases the capacity for clearance of plasma glucose, free fatty acids, and triglycerides by skeletal muscle. Excessive exposure to these plasma metabolites has a negative influence on the health of a variety of tissues. It is therefore interesting to note that trained skeletal muscle can be considered as a "sink" for metabolites associated with diseases such as diabetes, hypertension, obesity, and coronary heart disease. For example, dating back to J. O. Holloszy's work in the

1960s, it has been established that exercise training reduces plasma triglycerides (since associated largely with enhanced skeletal muscle lipoprotein lipase) (11) and that contraction of skeletal muscle increases the uptake of sugar independent of insulin (since associated largely with contraction-induced recruitment of the GLUT-4 glucose transporter) (8). Thus discoveries of exercise-training effects on skeletal muscle will likely play a large role in the prevention of some of the most common and costly diseases currently plaguing sedentary societies.

Skeletal Muscle Communicates With Other Organs

The concept discussed above, whereby muscle metabolism plays a role in the health of nonmuscle tissues, is one example of "integrative biology" (a recently invoked term). Another example is the link between skeletal muscle and cardiovascular variables such as control of heart rate and blood pressure (15). Myoneurography studies have demonstrated that sympathetic tone is diminished after exercise training, which contributes to decreased peripheral vascular resistance and accounts for reduced hypertension in some people. Furthermore, others have suggested that there is less discharge from type III and IV afferent nerves in trained muscle, leading to attenuated autonomic activity of the heart and blood vessels (exercise pressor response). Therefore, exercise studies have revealed that skeletal muscle does much more than produce power output for locomotion. Recent studies have shown that trained skeletal muscle also influences other organs as well as the health of the whole person.

Exercise Research Requires Integrative Approaches

The ability of exercise physiologists to conduct research on different levels of structural organization (from the human body to organs to cells to organelles to molecules) has had an incredibly important impact on advancing knowledge of human adaptation. A. Krogh, A. V. Hill, and O. Meyerhoff appreciated the critical need to understand mechanisms at the "micro" level in the context of physiological systems. Departments of physiology, medicine, and biochemistry rarely hire integrative scientists anymore, and, according to Citation Index, most recent "hot papers" within the general field of medical biology were in fields other than physiology. In contrast, from 1964 to 1970, J. O. Holloszy had 5 of his first 19 peer-reviewed publications listed as Citation Classics (ISI Current Contents). We believe that if exercise researchers are to continue to be valuable scientists in the areas of disease prevention and biological discovery, then the leading programs must also appreciate the need for defining mechanisms in physiological systems. The technological difficulties of performing such experiments in live animals may explain why reductionistic approaches using cell-culture models (e.g., muscle development) progress more rapidly than do mechanistic studies of whole body exercise adaptation. Unfortunately, valid cell-culture systems that model exercising skeletal muscle were not developed in the 20th century.

The Retrograde Strategy

It is generally easier for an explorer to find a way out of a forest after having left a hut than to enter into the forest and try to find a hut when there are many trails to choose. In this analogy, the trails are the biochemical pathways causing an exercise adaptation, and the targeted hut would be the expression of an important gene. Any given exercise training protocol likely involves multiple signals including, but not limited to, paracrine, autocrine, hormonal, and neural factors, fluxes in metabolic intermediates, mechanical forces, and multiple intracellular signaling pathways. Because there may be hundreds of potential incoming signals to skeletal muscle cells during and after an exercise stimulus, exercise physiologists have historically attempted to decipher which signals are responsible for the adaptive change in the expression of specific proteins. Given that some of the exercise signals are probably redundant, some are probably synergistic, and still others appear to be contradictory, it has proven very difficult to identify the mechanisms underlying specific skeletal muscle adaptations that occur with training. Indeed, although some progress is being made, we are hard pressed to list any completely intact signaling pathway that can be conclusively said to cause changes in gene expression during exercise training.

An essential paradigm of molecular biology is that *trans*-acting factors (usually DNA- and RNA-binding proteins) interact with *cis*-acting regulatory elements (short stretches of DNA or RNA nucleotides) to change gene expression. As defined by us, the retrograde strategy follows a signaling pathway upstream from a specific nucleotide-regulatory element on a certain gene/mRNA to the origin of the exercise signal at the tissue level or whole body level. This strategy has provided researchers in other fields with great success in linking changes in gene expression to complex physiological processes involving multiple potential signals. Therefore, it is essential, but difficult, to identify regulatory elements on exercise-responsive genes, to determine how exercise may influence the binding of *trans*-acting factors to these regulatory elements, and, finally, to determine which signaling pathway is involved.

History Predicts the Future

The history of muscle adaptation to training is rich with discoveries by very skilled scientists applying new technologies and approaches. We are thus confident that we will not have to wait until the end of the 21st century before exercise physiologists demonstrate many of the mechanisms related to how exercise improves health and human performance on a molecular/genetic basis.

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