Adaptations of Skeletal Muscle Mitochondria to Endurance Exercise: A Personal Perspective

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Because of my interest in the potential role of exercise in the prevention of coronary heart disease and other diseases, I was recruited by the Heart Disease Control Program of the United States Public Health Service to obtain information about the effects of exercise on cardiac function and coronary heart disease risk factors. On completion of my training in 1961, the United States Public Health Service stationed me at Tom Cureton’s, Ph.D., Physical Fitness Research Laboratory at the University of Illinois. Dr. Tom Cureton was one of the early proponents of endurance exercise training, and he and his students conducted a lunch-hour fitness program for middle-aged faculty members and businessmen. With the help of Jim Skinner, who was a graduate student of Dr. Cureton, and other members of his laboratory, I was able to conduct studies in which we showed that exercise lowers serum triglycerides and improves cardiac contractile function. This was my first experience with endurance exercise, and I was amazed by the large and rapid improvements in endurance that occurred in these sedentary individuals. As a result, I became interested in the effect of training on physical performance and resolved to determine the cellular adaptations in skeletal muscle responsible for the increase in endurance. I developed the hypothesis that endurance exercise induces an increase in muscle mitochondria that plays a major role in the increase in endurance. After leaving the United States Public Health Service and completing a 2-yr postdoctoral fellowship in biochemistry, I obtained a faculty position at Washington University, St. Louis.

I spent my first year learning how to train sedentary rats to become marathon runners and setting up assay procedures for measuring muscle oxidative capacity and mitochondrial enzyme activities. It quickly became evident during my first training study that the exercise program had induced a major adaptive response, with approximately twofold increases in mitochondrial enzymes and in the capacity of skeletal muscle to oxidize pyruvate. My first paper describing some of these findings aroused considerable interest. At that time, the 1960s, most of the research in exercise physiology dealt with VO₂ max, that is, its determinants and its role in performance, and on blood lactate and its role in fatigue. However, a few far-sighted exercise physiologists realized that if the field were to progress it would be necessary to go beyond VO₂ max and lactate, and to study the effects of exercise at a more basic, cellular level. These investigators, such as Charles Tipton and Phil Gollnick, were training a new generation of exercise physiologists who have gone on to reshape the field of exercise research and to add a new, basic research dimension to the American College of Sports Medicine (ACSM).

The interest generated by my first paper on mitochondrial biogenesis attracted a number of the new breed of exercise researchers to my laboratory as postdoctoral fellows. Up to that point, I had been working alone, and the energy, insights, and technical skills of these young researchers greatly amplified the scope and productivity of my research program. My early postdocs included Larry Oscai, who showed that endurance training increases the capacity of muscle to generate ATP via oxidative phosphorylation; Paul Molé, who demonstrated that endurance exercise training increases the capacity of muscle to oxidize fatty acids; Ron Terjung, who showed that exhausting exercise does not disrupt mitochondria; Ken Baldwin, who found that all three muscle fiber types undergo the adaptive increase in mitochondria; Will Winder, who showed that endurance exercise induces an...
increase in the capacity of muscle to oxidize ketones and that thyrotoxicosis also induces an increase in muscle mitochondria; Frank Booth, who found that the exercise-induced increase in mitochondria is mediated by increased synthesis of mitochondrial proteins, with no change in the rates of degradation; Bob Fitts, who showed that running endurance varies with muscle mitochondrial content; and Mitsuru Higuichi, who found that an increase in mitochondrial superoxide dismutase is a component of the adaptive response of muscle mitochondria to exercise. All of these individuals went on to become leaders in the new era of basic research in exercise science. They have played major roles in the development and expansion of the role of basic research in the activities and scientific meetings of the ACSM.

Subsequent studies by Constable, Favier, McLane, and Fell in my laboratory and by Dudley, Tullson, and Terjung showed that the beneficial effects of the exercise-induced increase in muscle mitochondria on substrate metabolism and endurance are mediated by a smaller decrease in high energy phosphates (\(\sim P\)) during contractile activity. As a consequence of smaller decreases in ATP and creatine phosphate, and smaller increases in Pi, ADP, and AMP, at a given submaximal work rate, the rates of glycogen depletion and lactate formation are reduced, and reliance on fat oxidation is increased in the trained state.

Studies by Winder on the effects of thyrotoxicosis and of severe iron deficiency by Louis-Jacques Carriere and Yoshi Ohira suggested that some component of the decrease in \(\sim P\) may provide the signal that leads to increased mitochondrial biogenesis. This possibility was confirmed by the pioneering research of Will Winder showing that activation of AMP kinase induces an increase in muscle mitochondria. This finding was confirmed by studies on skeletal muscle and myotubes in vitro by Edward Ojuka, Dong-Ho Han, Terry Jones, and May Chen in my laboratory. We also found that increases in cytosolic Ca\(^{2+}\) serve as a second signal leading to increased mitochondrial biogenesis. Keith Baar, Edward Ojuka, Terry Jones, and May Chen, working in my laboratory, and by Shin Terada and Isumi Tabata, working elsewhere, provided evidence that these signals lead to increases in mitochondria by inducing the transcriptional coactivator peroxisome proliferator-activated receptor \(\gamma\) coactivator 1.

The finding that endurance exercise induces an increase in muscle mitochondria in rats rapidly led to studies of this phenomenon in humans. The first of these, by Morgan, Short, and Cobb in Seattle, was rapidly followed by studies by Bengt Saltin’s group in Stockholm and by Costill et al. at Ball State. Studies by Ed Coyle, assisted by Chip Martin, John Ivy, Jim Hagberg, Mike Joyner, and Sue Bloomfield, determined the time course of the loss of the mitochondrial, cardiovascular, metabolic, and muscle capillary adaptations to prolonged endurance training. The subjects in this study, which was carried out as a collaboration between my laboratory and Ollie Lowry’s laboratory, were all similarly highly trained, but differed widely in their athletic ability, that is, genetic endowment, with VO\(_2\) max values ranging from approximately 50 to 76 mL·kg\(^{-1}\)·min\(^{-1}\).

By comparing these subjects, Ed Coyle was able to show that individuals who train equally hard, in relative terms, have similar adaptive increases in muscle mitochondria. He further showed that the large differences in VO\(_2\) max and performance capacity between competitive endurance athletes and highly trained individuals who are not able to become competitive endurance athletes are the result of differences in stroke volume and maximal cardiac output. Maximal stroke volume and cardiac output seem to be genetically determined and to limit VO\(_2\) max and endurance athletic performance. Subsequently, Bob Spina and Eric Gulve examined the time course of development of the adaptive increase in mitochondria. They showed that, as in rats, the adaptive increase in mitochondria in response to a fixed (i.e., not progressively increased), powerful exercise stimulus occurs rapidly, with an estimated half-time of approximately 7 d.

Andy Coggan further advanced this area of research by studying the adaptive response of muscle mitochondria to exercise in older people. He showed that the capacity of muscle to adapt to endurance exercise with increases in mitochondria and capillaries is retained with advancing age, at least up to the age of 70 yr, the oldest age he studied.

These individuals, as well as many others who studied topics other than the adaptive response of muscle mitochondria, such as glucose tolerance and insulin action, lipid metabolism, cardiovascular function, muscle protein synthesis, and so forth, have bridged the areas of laboratory animal research and research on humans. This group includes a number of individuals who were postdoctoral fellows with me or were closely associated with my research program, including Jim Hagberg, Bob Hickson, Greg Heath, Ben Hurley, Doug Seals, Gail Dalsky, Doug King, Marc Rogers, Ray Bourre, Kevin Yarasheski, John Kirwin, Matt Vukovich, Jeff Zachwieja, Bob Hickner, Susan Racette, and Jeff Greive. Many of these individuals have gone on to distinguished careers of independent research, conducting hypothesis-based, mechanistic research on the effects of exercise in humans. By serving as role models, and by their participation in the educational and scientific programs of the ACSM, these individuals have enhanced the field of exercise science and the ACSM by demonstrating that so-called applied physiology research on humans can be just as “basic” and cutting edge as research on laboratory animals or cells in culture.

With regard to the future, I am certain that within the next 10 yr, the steps leading from increases in cytosolic Ca\(^{2+}\) and activation of AMPK to increased mitochondrial biogenesis will be discovered. Investigators currently in the forefront of this line of research include David Hood, Isumi Tabata, Darryl Neuffer, and other ACSM members. Exercise deficiency is a serious public health problem in the United States. It is largely responsible for development of the abdominal obesity syndrome, muscle insulin resistance, type 2 diabetes, ischemic heart disease, and accelerated decline in skeletal muscle, cardiovascular, and metabolic functional capacities with aging. Although exercise can be used empirically, it seems reasonable that it can be applied more effectively if its method of action is understood. As we increase our basic understanding of the mechanisms, it seems probable that we will be able to mimic the adaptations of skeletal muscle to endurance exercise by pharmacologic or gene therapy interventions, or both. These approaches seem appropriate for people who are unable to exercise because of disease,
old age, or frailty. However, they are a poor substitute for the physical and mental benefits of regular, vigorous exercise for which we have been genetically conditioned throughout evolution. Therefore, I strongly believe that the most important future area of research, that I hope will be championed by the ACSM, is to find practical, effective ways to motivate our current generation of couch potatoes to incorporate regular exercise into their daily lives. Although perhaps less mentally stimulating than hypothesis-driven, mechanistic research, finding ways to motivate people to exercise should prove to be equally satisfying because of the realization that success in this area could have a greater beneficial effect on health and functional capacity of the general public than any other research endeavor.