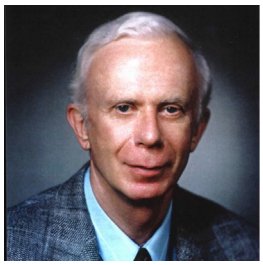
Exercise Metabolism

As a preview of the upcoming Cell Symposium on Exercise Metabolism that *Cell Metabolism* is organizing in Amsterdam July 12–14 (http://www.cell-symposia-exercisemetabolism.com), we asked several of our speakers and other leaders in the field for their short personal viewpoints, "Voices," on the field of exercise biology.

Exercise Biology: Past and Future



John O. Holloszy
Washington University, St. Louis

Early in my career, I became convinced that exercise deficiency is the major cause of the modern epidemics of obesity, type 2 diabetes, and ischemic heart disease. While studying adaptations to endurance exercise in middle-aged men, I was amazed by the large increase in aerobic exercise capacity and decided to elucidate the underlying mechanisms. My discoveries ~50 years ago that endurance exercise training induces increases in muscle mitochondria and that muscle contractions stimulate glucose transport led to a new research field, the Biochemistry and Molecular Biology of Exercise. The discovery of PGC-1α by Spiegelman's group, followed by the discovery that exercise induces an increase in PGC-1α, explained the mechanism underlying the increases in mitochondrial biogenesis and GLUT4 expression. The mechanisms by which exercise induces PGC-1α activation and expression have been elucidated and involve pathways activated by Ca^{2+} and AMP kinase. Studies on lab rodents have shown that life-long exercise increases average longevity, providing evidence for protection against diseases of aging. However, most people do not exercise and cannot be motivated to exercise. So, while further studies of the adaptations to exercise will likely provide interesting biological insights, they will have no effect on public health. I therefore think that major future research emphasis should be on discovering an exercise mimetic.

The Exercise Revolution

David E. James
Sydney University, Australia

Even Hippocrates recognized the health benefits of physical activity 2,500 years ago. Today we have compelling evidence that exercise has greater therapeutic value than most drugs for treating type 2 diabetes and likely many other diseases. I see thousands of people riding furiously past my house on bicycles or pounding the pavement each day, yet metabolic disease continues to escalate. This conundrum gives rise to two key future research topics. First, it is crucial to delineate molecular pathways that get switched on during exercise to transmit long-term benefit. Much excitement has revolved around AMPK, though other kinases are also activated during exercise and have pleiotropic effects on multiple pathways. Defining these pathways and carefully mapping their whole-body physiological benefits is essential to catalyze development of new drugs that may be crucial for those who are unable or unwilling to exercise. Second, investment in preventive strategies to predict individual disease risk and optimal preventive strategies is necessary. This will require appropriate resourcing of long-term clinical research and systems biology. Transmission of such predictors into clinical practice will require changes in clinical medicine and public health combined with cooperation from government. For these and many other reasons, we are sitting at the foothills of the exercise revolution, and the time is ripe to enter this most exciting field.

Resting to Achieve Muscle Power

David Costill
Human Performance Laboratory, Ball State University

Though endurance training increases the metabolic capacity of muscle, it has been repeatedly shown to decrease the explosive power in whole muscles and single fibers. Likewise, reduced (tapering) or no training after exercise training is seen to enhance the speed of contraction and power output of muscle. Though muscle detraining and unloading (bed rest and short-term space flight) decrease muscle size and strength, the maximal contractile velocity of single fibers increases. At the same time, these increased/decreased changes in muscle power with training and unloading have been accompanied by subtle changes in fiber-specific morphology. Though it might be argued that alterations in size and contractile properties of fast-twitch fibers might explain all or part of the muscle's change in explosive power, the underlying cellular mechanisms triggering these functional changes have not been revealed. In simple terms, why do well-trained athletes need periods of reduced training in order to achieve maximal muscular power and speed? Recent work from Trappe and colleagues suggests that the answer might reside in the expression of specific genes, such as fibroblast growth factor-inducible 14, in fast fibers when the metabolic and/or contractile demands on muscle are reduced.

Lactate: From Fatigue Agent to Therapeutic

George A. Brooks
University of California, Berkeley

Fifty years ago as an undergraduate, understanding of the biochemistry and physiology was simple. The accumulation of lactate/lactic acid indicated O_2 debt; lactate was a dead-end metabolite, a metabolic waste that caused muscle rigor, fatigue, cramps, and soreness. Certainty abounded because those ideas came from founders of biochemistry and muscle physiology. From a teleological view, those beliefs made no sense to this 20-year-old, and further, the ideas seemed dated and inconsistent with emerging ideas in mitochondrial energetics and muscle contraction. In contrast, in support of Lactate Shuttle Theory, today we know that lactate is continuously produced under fully aerobic conditions and is a major fuel for muscle, heart, and brain, the major gluconeogenic precursor, and a signaling molecule. Given the early history, how paradoxical it is that we and others are evaluating the efficacy of using lactate-containing solutions to provide support in the setting of critical care medicine. Specifically, for treatment of traumatic brain injury, lactate formulations directly support neuronal metabolism when glucose uptake is limited following injury, achieve exquisite glycemic control by supplying the major gluconeogenic precursor for liver and kidneys, and limit cerebral swelling. In the last century, a very insightful man once said: "Gott würfelt nicht!" So it is that lactate production and use is to be viewed as a basic biological response that is accelerated to mitigate metabolic stress.

Selection on Exercise in Rat

Lauren Gerard Koch and Steven L. Britton
University of Michigan

The linkage between low exercise capacity and high morbidity and mortality is statistically strong yet mechanistically unresolved. By connecting clinical observation with a theoretical base, we hypothesized that variation in capacity for energy transfer metabolism is the central mechanistic determinant between disease and health (energy transfer hypothesis). As a predictive test of this hypothesis, we show that two-way selective breeding of rats for low and high intrinsic treadmill running capacity (used as a surrogate for energy transfer) also produces rats that differ for numerous disease risks including the metabolic syndrome, neurodegeneration, cognitive decline, fatty liver disease, susceptibility to cancer, and reduced longevity. The lines are termed Low Capacity Runners (LCR) and High Capacity Runners (HCR) and, after 36 generations of selection, differ by over 8-fold in running capacity. We integrate ideas from Ilya Prigogine, Hans Krebs, and Peter Mitchell to formulate a theoretical explanation for the energy transfer hypothesis: (1) evolution was driven by non-equilibrium thermodynamic energy dissipation mechanisms (order from disorder), and (2) emergence of complexity was coupled to the high energetic nature afforded by oxygen. We look to this scheme to guide new hypotheses and suggest that this principle-based contrasting animal model system may prove useful for understanding complex biology and disease risks at all levels of biologic organization.

Exercise Benefits the Brain

Henriette van Praag
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With the increase in human lifespan, more aging-related cognitive disorders are being diagnosed. In the absence of effective medications, physical activity is a simple, low-cost intervention that may prevent or delay the onset of memory loss. We have accumulated substantial knowledge about the changes exercise evokes in the brain. In rodents, wheel running increases neurogenesis, neurotrophins, neurotransmitters, and angiogenesis in the hippocampus, a brain area important for learning and memory. In humans, hippocampal volume and cerebral blood flow is increased. However, the systemic, metabolic peripheral triggers that elicit these brain processes are virtually unknown. Recent research indicates that young blood-borne systemic factors can counteract the age-related decline of adult neurogenesis and brain function. Upon activation by exercise, skeletal muscle may release factors into the circulation that communicate with the brain, and identification of these candidate metabolites will be important. Moreover, not everyone can exercise due to circumstances, disease, or senescence-related frailty. Muscle-derived factors that mimic the effects of exercise on the brain may be developed as therapeutics to improve cognition. Future research with a more integrative, holistic approach to the effects of exercise on body and mind may allow us to stave off memory loss in the elderly.