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Exercise Metabolism: Historical Perspective

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The past 25 years have witnessed major advances in our knowledge of how exercise activates cellular, molecular, and biochemical pathways with regulatory roles in training response adaptation, and how muscle "cross-talk" with other organs is a mechanism by which physical activity exerts its beneficial effects on "whole-body" health. However, during the late 19th and early 20th centuries, scientific debate in the field of exercise metabolism centered on questions related to the sources of energy for muscular activity, diet-exercise manipulations to alter patterns of fuel utilization, as well as the factors limiting physical work capacity. Posing novel scientific questions and utilizing cutting-edge techniques, the contributions made by the great pioneers of the 19th and early 20th centuries laid the foundation on which much of our present knowledge of exercise metabolism is based and paved the way for future discoveries in the field.

Background

The application of molecular techniques to exercise metabolism during the past few decades has provided greater understanding of the multiplicity, complexity, and "cross-talk" between the numerous cellular networks involved in divergent exercise responses. The role of nutrient availability in modifying training adaptation and enhancing exercise capacity has also received much scientific enquiry during this time. However, many of the key contributions that laid the groundwork for the molecular synthesis of the last half-century can be traced back to the outcomes from studies conducted in the late 19th and early 20th centuries. During this time, many investigations employing a variety of exercise and diet manipulations were performed in Universities throughout Europe and North America in an attempt to resolve such questions as "what fuels were utilized by contracting skeletal muscle during exercise" and "what limits exercise capacity?" Many of the "classic" studies undertaken in this period were by pioneers in the field who posed novel scientific questions and developed innovative techniques while working in laboratories that were destined to become "hotbeds" of research into muscle metabolism for future generations. This brief historical synopsis describes how several major discoveries of the past century (and beyond) have impacted on our current knowledge of muscle metabolism during exercise.

The Early Years

Today, it is well accepted that the fuel to support contracting skeletal muscle during continuous exercise of more than a few minutes duration is derived from both intra- and extra-muscular carbohydrate and lipid substrates, with only a minor contribution from amino acids. Furthermore, there is consensus that the primary determinants of the balance of carbohydrate (muscle and liver glycogen and blood glucose from ingested carbohydrate and gluconeogenesis) and lipid (adipose and intramuscular triglycerides as well as blood-borne free fatty acids [FFAs] and triglycerides) fuels for active muscle are the relative exercise intensity (expressed as a percentage of an individual's maximum oxygen uptake [VO_{2max}]) (Romijn et al., 1993; van Loon et al., 2001) and the composition of the diet in the preceding days (Bergström et al., 1967). But this was not always the case! The closing years of the 19th century and the first decades of the 20th were marked by intense debate concerning the relative importance of carbohydrate, fat, and protein as sources of energy for muscular activity. The prevailing view was that carbohydrate was the only fuel that could be used to power muscle contraction and that fat was first transformed into carbohydrate before it could be oxidized as an energy source, with a considerable loss of energy in the process. However, Nathan Zuntz (Zuntz 1896, 1901) and his co-workers (Frentzel and Reach, 1901) were convinced that both fat and carbohydrate could be used as energy sources and showed that manipulation of the proportions of fat and carbohydrate in the diet in the preceding days resulted in corresponding changes in the non-protein respiratory exchange ratio (RER: oxygen uptake [VO_2]/carbon dioxide output [VCO_2]) during subsequent exercise. They also showed a higher oxygen cost of physical activity (~12%) when fat was the principal fuel oxidized.

In the succeeding decades, many others contributed to the debate about the fuel sources for muscular activity, but a resolution was only slowly reached. Part of the uncertainty arose from the limitations of the available methodologies, which did not allow for accurate monitoring of external power output during exercise or of reliable measurement of substrate use. Estimations of fat and carbohydrate oxidation relied entirely on measurement of VO_2 and VCO_2 at the level of the lungs, with methods for the measurement of the composition of expired air being cumbersome and inexact. Urinary nitrogen excretion was used as an index of protein catabolism. August Krogh made several major contributions to the field including the development of a reliable electrically braked cycle ergometer that allowed precise control of power output (Krogh, 1913). He also improved the existing methods for the analysis of oxygen and carbon dioxide, developing a chemical analyzer that permitted determination of the concentrations of these gases in expired air to a precision of

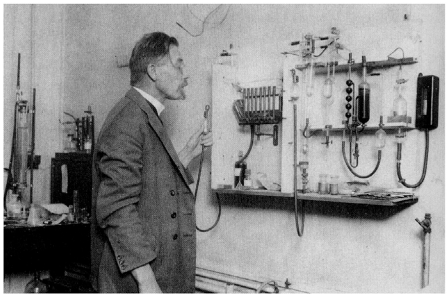

Figure 1. Our Understanding of Exercise Metabolism Was Greatly Advanced by Several Methodological Breakthroughs
August Krogh and the apparatus he developed for the accurate measurement of gas concentrations in expired air.

0.001% (Krogh, 1920). It is worth noting that the accuracy of these methods far exceeds that of the electronic analyzers used in most modern-day exercise physiology laboratories (Figure 1).

Using these new methods, Krogh and Lindhard (1920) performed an extensive series of studies (albeit on a small number of experimental subjects) on the effects of diet composition on muscle substrate use. They essentially confirmed the results of Zuntz and co-workers (Frentzel and Reach, 1901; Zuntz 1896, 1901) showing that the proportions of fat and carbohydrate oxidized during steady-state exercise varied with the composition of the preceding diet and that the oxygen cost of exercise was about 11% lower when using carbohydrate rather than fat. These workers believed that the contribution of protein to oxidative metabolism was small, but on the basis of an increased urinary excretion of nitrogen, Cathcart (1925) proposed that the contribution of protein to overall metabolism increased during ‘‘very prolonged’’ or intense exercise. Even as late as 1924, A.V. Hill was of the opinion that conversion of fat to carbohydrate before oxidation might still be necessary and cited the higher oxygen cost of fat-based fuels as support for this argument (Hill, 1924). These findings continued to be disputed, with Reynolds et al. (1927) reporting no difference in mechanical efficiency during exercise after different diets were fed to subjects. During his illustrious career, Krogh made several trips abroad and established links with, among others, the Harvard Fatigue Laboratory in Boston. The first and only scientific director of the Harvard Fatigue laboratory was Dr. David Bruce Dill, who was an influential driving force behind the laboratory's numerous scientific accomplishments. Dill's group undertook studies of their own on exercise metabolism and the limits to work capacity (Dill et al., 1932), while also fostering lasting collaborations with many scientists throughout the world.

In 1922, Hill received the Nobel Prize for Physiology or Medicine for his work on heat production in contracting muscle and was anxious to reconcile the physical processes occurring during muscle contraction with the prevailing metabolic activity. The English school of biochemists, led by Fletcher and Hopkins, had already established the importance of the formation of lactic acid during contraction of amphibian muscles under anaerobic conditions and the concomitant suppression of lactate formation in the presence of oxygen (Fletcher, 1907). Subsequently, muscle glycogen was confirmed as the source of the lactate. Otto Meyerhof shared the 1922 Nobel Prize with Hill for his discovery that the lactate produced during intense exercise can be reconverted to glycogen or further metabolized to CO_2 and H_2O during recovery after exercise. Hill also articulated the debate, which continues to this day, as to whether maximal exercise is limited by oxygen delivery to the working muscles or by metabolic events occurring within the muscle. In 1923, Hill and Meyerhof proposed that energy needs of contracting muscle could be met by anaerobic or aerobic metabolic pathways (Hill and Meyerhof, 1923). Embden and others later filled in the missing pieces of the metabolic pathways involved in carbohydrate metabolism, but much of this work was disrupted and delayed by the tensions in Europe at this time.

In the late 1920s a high-energy phosphate compound (‘‘phosphagen’’) was also found in muscle and was identified as creatine phosphate (Eggleton and Eggleton 1927; Fiske and Subbarow 1927). Creatine phosphate was proposed to be the immediate energy source for active muscle but later studies showed that phosphagen was not a single entity. Indeed, it was not until 1962 that Cain and Davies (1962) finally proved the immediate energy source to be adenosine triphosphate (ATP).

Back in Copenhagen, Erik Hohwü Christensen completed his doctoral studies with Krogh and Lindhard on the physiological responses to heavy exercise. Together with Erling Asmussen and Marius Nielsen, Christensen contributed to an intensely productive period of research into muscle metabolism. With Ole Hansen, he undertook a series of studies demonstrating the importance of carbohydrate availability for exercise performance and the influence of the prevailing exercise intensity and duration on muscle metabolism. As is the case today, some early investigators were interested in exercise performance while others viewed exercise merely as another tool that could be used to study physiology and metabolism. The work of Christensen and Hansen (1939a, 1939b) showing that manipulation of the carbohydrate content of the preceding diet resulted in changes in the time for which work at a fixed power output could be sustained was highly predictable from the earlier work of Krogh and Lindhard (1920) who had reported that subjects perceived a fixed, submaximal exercise task to be easier after several days consuming a high carbohydrate diet than when the preceding diet was low in carbohydrate and high in fat. Nevertheless, the studies of Christensen and Hansen (1939a, 1939b) are now widely recognized as landmark discoveries, perhaps because of their practical implications. In the early 1940s, Christensen moved to Stockholm and was a mentor to Drs. Per-Olof Åstrand and Bengt Saltin, who themselves became pioneers in the fields of exercise and muscle physiology.

The ‘‘Classic’’ Period of Exercise Biochemistry: 1960–1985

The 25 years that began in the 1960s and progressed through the mid-1980s have been called the ‘‘classic period’’ of exercise biochemistry (Brooks and Mercier 1994) and included major advances in our understanding of how exercise promotes the biosynthesis of mitochondrial proteins in skeletal muscle, the impact of exercise training and diet manipulations on muscle substrate stores and endurance capacity, the fate of lactate during exercise and recovery, and the regulation of muscle protein