MUSCLE ENERGY METABOLISM

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Summary

Muscle is tissue that has the ability to contract. There are three major types of muscle: skeletal, cardiac, and smooth. In all three types of muscle cells, most of the energy produced is used for the demands of muscle contraction, which is achieved by actin molecules sliding on myosin filaments. In addition, energy is used for pumping Ca^{2+} from the sarcoplasma to the sarcoplasmic reticulum after the muscle contraction is over. Pumping sodium and potassium ions through the muscle membrane to maintain ionic gradients also requires energy.

The energy-rich phosphate compound adenosine triphosphate (ATP) is the main fuel in muscle. Muscle ATP supplies, however, can endure only for 1 to 2 seconds. Creatine phosphate (CP), which also contains a high-energy phosphate bond, is a quick energy source for ATP regeneration. CP stores are also limited and capable of providing energy for muscle contractions of only 5 to 8 seconds. The main sources of energy for the muscle are glucose and fatty acids, the consumption of which depends on the load and fitness of the subject as well as on the availability of oxygen. ATP production from cytosolic glycolysis, mitochondrial beta-fatty acid oxidation, and the citric acid cycle, is tightly regulated and responds quickly to muscle demands for more ATP. When energy

demands exceed the capacity of skeletal muscle to provide ATP through the citric acid cycle under oxidative conditions, glycolysis is stimulated and lactic acid is produced, yielding ATP anaerobically—without the use of oxygen.

The cardiac muscle shows great flexibility in its choices of energy substrates and rather minimal dependency on glucose metabolism. Smooth muscle works most efficiently, and needs much less ATP for its activity than do cardiac and skeletal muscles.

1. Introduction and General Considerations

Muscle is body tissue that is characterized by its ability to contract, usually in response to a stimulus from the nervous system. Of three major kinds of muscle, skeletal and cardiac muscles are high consumers of energy. The heart is a muscular pump that circulates the blood through the circulatory system. Despite the small amount of it compared with other muscle types, cardiac muscle has a remarkable share of blood supply with a vivid energy metabolism.

Smooth muscle is mostly found in the respiratory, urinary, and gastrointestinal tract, the reproductive system, and blood vessels. Many vital functions are controlled via the contraction and tonus of smooth muscle in these tissues and organs, such as maintaining blood flow and blood pressure, directing the air stream in the respiratory tract, and propagating contents in the gut and urinary tract. Smooth muscle uses relatively little energy despite the heavy workload it has. The mass of the locomotor system with its skeletal muscle is about two-thirds of the total body mass. At rest its share of cardiac output is one-sixth of the total, and equal to that of the brain. At maximal activation in aerobic work the oxygen consumption of muscle dominates, and its blood circulation corresponds to four-fifths of the cardiac output.

Skeletal muscle is unique in energy metabolism. In addition to its aerobic capacity, it is adapted for short-term anaerobic activity, allowing for both extended lower intensity endurance physical activity and short-term high-energy output. The dynamic range for the change in rate of ATP utilization is large, in excess of a hundredfold for skeletal muscle. Changes in ATP utilization require compensatory adjustments of circulatory, cardiac, and respiratory functions. In humans at rest, skeletal muscle receives about 5 ml of blood per 100 g of tissue. During heavy exercise the share of cardiac output of the muscle tissue can increase in trained subjects to up to four-fifths of the total cardiac output or even more (Figure 1). The extraction of oxygen also increases, as evidenced by the increasing arterio-venous difference from 25% at rest to 80% or even more in maximal exercise. Thus the oxygen consumption in exercising human muscle can increase about a hundredfold, in fact quite a modest increase in comparison with some animals, in which the increase can be a thousandfold.

Muscle metabolism can be understood from a set of basic statements about the biochemical energy balance:

- Chemical energy is stored in muscle cells as ATP and creatine phosphate, which are biochemical capacitors;
- ATP provides the energy for all forms of muscle work;

- ATPases, the enzymes that break down ATP and release the energy for muscle work and metabolism, are the demand side of the balance and define energetic states; and
- This demand is supplied mainly by continuous aerobic metabolism.

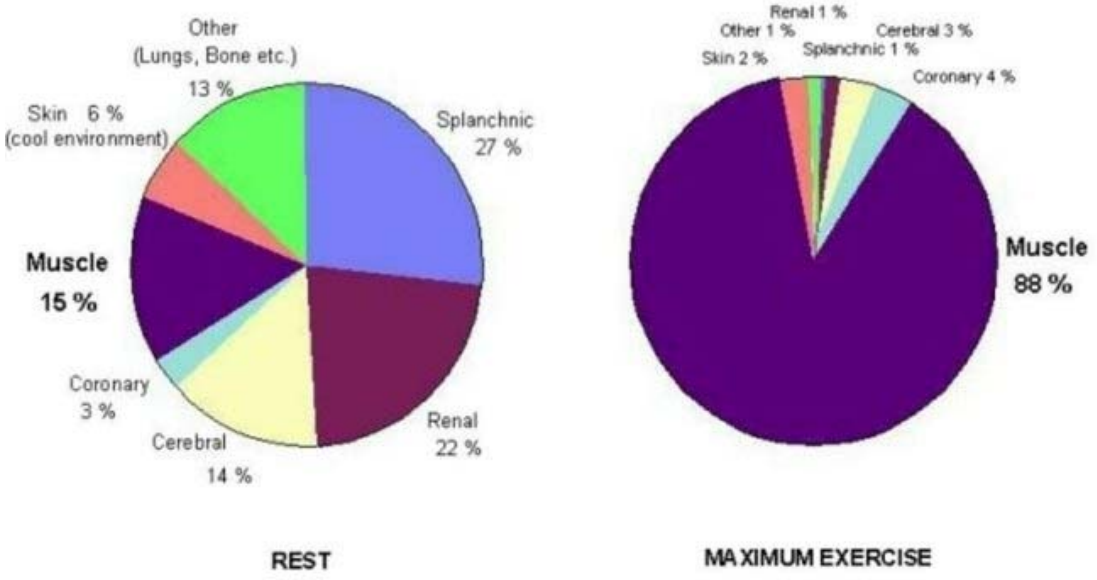

Figure 1. Distribution of cardiac output expressed as blood flow to various tissues at rest and during maximum exercise Source: modified from Hänninen and Atalay (1998), p. 29.

The basic unit of all muscle is the myofibril, a minute, threadlike structure composed of complex proteins. Each muscle cell, or fiber, contains several myofibrils, which are composed of regularly arranged thin and thick myofilaments.

In skeletal muscle, contractions are normally associated with depolarization of the plasma membrane, which initiates the release of calcium ions from intracellular stores within the sarcoplasmic reticulum. Calcium ions bind to troponin C, a regulatory protein associated with the thin filaments, producing a change in protein conformation. This change of shape is transmitted to the other thin filament components (troponin T, troponin I, tropomyosin, and actin) with the result that the actin subunits of the thin filaments are permitted to interact with the neighboring myosin molecules, which consist of thick filaments. The contraction ceases when calcium ions are taken up by the sarcoplasmic reticulum through the operation of an ATP-driven pump, commonly known as Ca^{2+} ATPase.

2. Phosphate Bond Energy

Energy in skeletal muscle is derived mostly from glucose and fatty acids. It is also stored in significant amounts as glycogen and triglycerides, respectively, in the muscle fibers. The chemical energy trapped within the bonds of the carbohydrate, lipid, and protein molecules is extracted as adenosine triphosphate (ATP), an immediate source of energy. Adenosine phosphates have energy receiver and donor cycles: ATP stores are replenished during the oxidation of energy sources and used during skeletal muscle

work. ATP consists of an adenosine molecule linked to three phosphates. The bonds that link the molecule to the outermost phosphates are called high-energy phosphate bonds, since their hydrolysis (when ATP joins with water) releases 7.3 kcal of energy. This reaction is catalyzed by an enzyme called adenosine triphosphatase (ATPase), and the end product is an adenosine molecule containing two phosphate groups called adenosine diphosphate (ADP). Additional energy is produced when the second phosphate bond is hydrolyzed and a single phosphate containing adenosine monophosphate (AMP) is the end product.

$ATP + H_2O \rightarrow ATPase \rightarrow ADP + P + 7.3 \text{ kcal. mol}^{-1}$

The stores of ATP itself are sufficient to provide energy for a few seconds. The total ATP store in human skeletal muscle is approximately 80 g. However, in top-class endurance athletes daily ATP consumption can be up to 75–80% of their body mass, via the continuous restoration of muscle ATP content. ATP is resynthesized at the rate of its consumption, through three main mechanisms: short-term high-energy phosphates (creatine phosphate), medium-term supply (via anaerobic glycolysis), and long-term supply (via the oxidative phosphorylation of glucose and fatty acids to water and CO_2). Major sources of ATP resynthesis are the oxidation of lipids and carbohydrates, which are slow and constant processes. A rapid turnover of ATP is maintained without the use of oxygen through CP, a high-energy phosphate compound. Energy is released with the breakdown of CP, for the immediate synthesis of ATP. ATP and CP together (called a phosphagen system) are a critically important source of muscle contraction, especially in athletic activities that need high power for a short period of time, such as the quick starts of sprinters and high jumpers. A stationary equilibrium between the production and breakdown of ATP must be reached for sustained aerobic metabolism. ATP and CP concentrations are therefore fairly constant (approximately 5 mmol L^{-1} and 30 mmol L^{-1}, respectively). In the recovery phase after muscle contractions, CP is resynthesized from its breakdown products creatine and inorganic phosphate at the cost of ATP. The energy required for the phosphagen replenishment comes from the aerobic metabolism.

3. Anaerobic Energy Metabolism

Glycolysis is the pathway for the catabolism of glucose, occurring in the cytosol. Glycolysis is unique in that it can use oxygen if available (pyruvate → acetyl-CoA), or function without oxygen (pyruvate → lactate). The relative role of glycolysis as a source of energy varies between tissues (for example, slight in the heart, and major in the brain and red cells). In skeletal muscle, glycolysis permits high performance, when aerobic metabolism alone is not sufficient. In skeletal muscle at rest, glycolysis provides nearly half of the acetyl-CoA used in the citric acid cycle. In the process, 6 carbon glucose is catabolized to 3 carbon pyruvate and then to acetyl-CoA, resulting in a net production of 2 NADH and 2 ATP. NADH formed through glycolysis is transported via the malate shuttle into the mitochondria and oxidized in the respiratory chain, with a net yield of 2 ATP per NADH. Thus, in the complete oxidation of 1 mole of glucose under aerobic conditions, glycolysis yields 8 ATP and the citric acid cycle 30 ATP.

Skeletal muscle is also readily subjected to anaerobiosis. This property allows for short-term performance far exceeding the levels that can be handled aerobically. Two of the

three mechanisms of ATP resynthesis are through anaerobic metabolism, which means without the use of oxygen. Anaerobic energy metabolism, also called anaerobic glycolysis, involves the incomplete breakdown of carbohydrates to lactic acid via anaerobic metabolic pathways. Anaerobic glycolysis is involved in muscular activities that last for as short a period as a few minutes, with high energy demand where aerobic metabolism is not adequate for the energy requirements. This process takes place in the cytoplasm, and despite the rapid ATP synthesis anaerobic glycolysis is less efficient than aerobic glycolysis. The lactic acid end-product of anaerobic energy metabolism is associated closely with the performance and duration of exercise. An accumulation of lactic acid decreases intracellular pH, which inhibits the activity of phosphofructokinase, and rate-limiting enzyme of glycolysis. Furthermore muscle NADH decreases during low-intensity exercise, but it increases above resting values during high-intensity exercise. The increase in muscle NADH can result from limited availability of O_2 in the contracting muscle. During intense exercise, the increase in cytosolic NADH inhibits pyruvate dehydrogenase, resulting in increased reduction of pyruvate into lactate through a hydrogen atom extraction from the NADH. Oxidized NAD can act as a hydrogen acceptor, allowing glycolysis to proceed and provide delivery of energy for the reconstitution of the energy-rich phosphates. The formation of ATP anaerobically is, however, at a high cost. Oxidation of 1 mole of glucose results in a net yield of only 2 moles of ATP.

Increased lactic acid production can hamper the function of neuromuscular junctions, muscle fibers themselves, cells of the connective tissue, and also vessels, but it is also a stimulus for adaptive changes in metabolism, which are an important element in training, for example for sports.

The intensive use of oxygen also results in the profound generation of different forms of oxygen, including reactive oxygen species (ROS) (Figure 2).

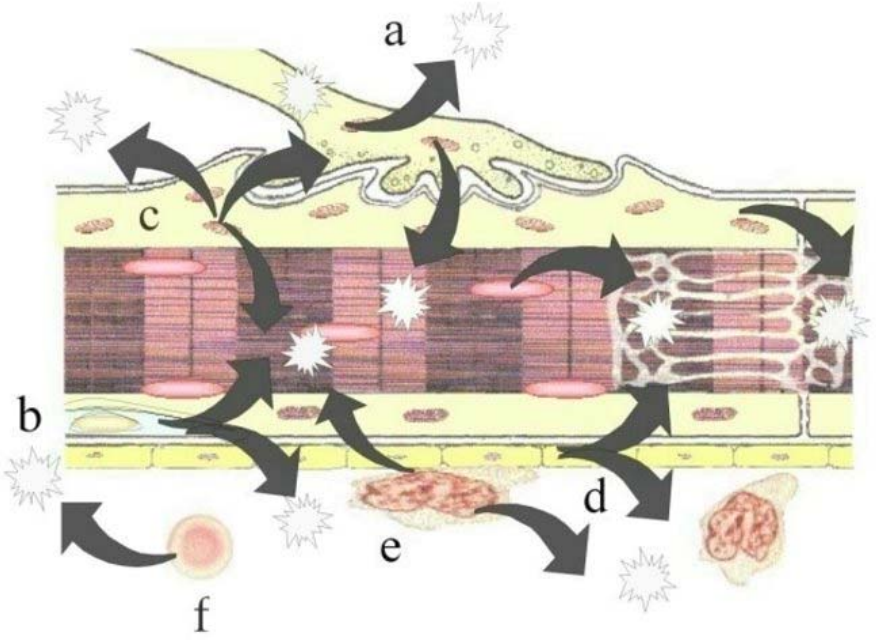

Figure 2. Free radical production in mitochondria of (A) neuromuscular junction, (B)

fibroblast and (C) skeletal muscle fiber as well as in (D) endothelium, (E) neutrophils and (F) erythrocytes. Source: modified from Hänninen and Atalay (1998), p. 30.

ROS promote muscle fatigue and tissue damage. Muscle tissue has a number of antioxidant defense systems of aqueous and lipid phase, which protect the tissue from the deleterious effect of ROS produced in excess. Skeletal muscle is capable of synthesizing glutathione (GSH), which has a central role in the maintenance of the antioxidant defense. It is an oxidizable substrate itself and helps to maintain the vitamins C (in the soluble phase) and E (in the lipid phase) in their reduced forms. Enzymes of the glutathione system like glutathione peroxidase and glutathione-S-transferases complement catalase in peroxide metabolism.

4. Mitochondria and Aerobic Metabolism

Oxygen is transported by the respiratory cascade to the site of oxidation in active tissues. During intensive exercise, active skeletal muscle cells finally determine the aerobic demand, as over 90% of energy is spent in muscle cells. Oxygen is transported in the circulation bound to hemoglobin of erythrocytes, while substrates are transported in the plasma. The supply of oxygen must be continuous, because there are only minimal oxygen stores in the body of most mammalian species, while substrates are stored in significant quantities both within muscle cells and in tissue substrate stores.

4.1. Mitochondrial Oxidative Phosphorylation

Aerobic energy metabolism takes place in the mitochondria, and it results in the greatest release of energy. As the name implies, though, it requires oxygen. Aerobic glycolysis is the most efficient method of energy production. Anaerobically only 2 moles of ATP are synthesized from 1 mole of glycogen, whereas a total of 38 moles of ATP could be synthesized from the same amount of glycogen in the presence of oxygen (Figure 3).

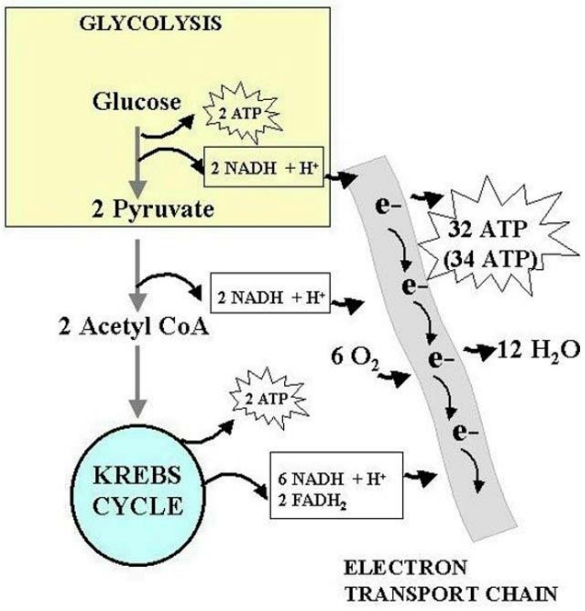

Figure 3. Breakdown of glucose to yield 36–38 moles net of ATP through glycolysis,

the Krebs cycle, and electron transport chain

The net yield is 36 moles of ATP when 2 moles of ATP consumption is subtracted (38 molecules in heart muscle as well as in the liver and kidney). In mitochondria of muscle cells, hydrogen atoms are extracted from the reducing equivalents that are formed during the citric acid cycle, in a process called oxidative phosphorylation. Consequently special electron transport proteins extract electrons from the hydrogen atoms and transfer them finally to molecular oxygen. The energy released during the transfer of electrons to oxygen is conserved as ATP. Electrons flow in the respiratory chain in order of increasing redox potential, from the more electronegative components to the more electropositive oxygen.

In cells at high oxygen pressures, energy demand determines the rate of mitochondrial respiration, but substrate supply determines the cellular energy level at which that rate is attained. The pool of ATP and CP is small compared with the energy required by active muscle cells. As a result of the small size of the high-energy phosphate pool, the rate of ATP utilization can be greater than or less than the rate of ATP synthesis for only very short periods of time. Synthesis of ATP must therefore occur at a rate that, on average, is equal to that at which the cellular processes hydrolyze it. Mitochondrial oxidative phosphorylation is thus tightly coupled to several different metabolic pathways, and it quickly responds to changes in the tissue demands for ATP. The coupling of the respiratory chain is not perfect, however. About 1–3% of oxygen consumed in the respiratory chain at rest has been estimated to escape as superoxide. Such generation of reactive oxygen species may have implications both in the resting state and with exercise.

4.2. Citric Acid Cycle

In skeletal muscle, mitochondria consume most of the oxygen and serve as the primary source of metabolic energy for sustained work. The citric acid cycle (also known as the Krebs or tricarboxylic acid cycle) is a series of reactions in the mitochondria, which bring about the catabolism of acetyl-CoA, liberating hydrogen equivalents that are used in oxidative phosphorylation for the generation of ATP from ADP. The citric acid cycle plays a pivotal role in aerobic metabolism. The citric acid cycle is the common final pathway for glucose (glycolysis), lipid (fatty acid beta-oxidation), and protein catabolism. Both at rest and during exercise, fatty acid beta-oxidation and glycolysis provide over 95% of acetyl-CoA entering the citric acid cycle.

In the citric acid cycle, acetyl-CoA condenses with oxaloacetate to form citrate. In subsequent reactions, oxaloacetate is again formed. In the process, 3 NADH, 1 $FADH_2$, 1 GTP, and 2 CO_2 are produced. The hydrogen equivalents subsequently undergo oxidative phosphorylation. The 3 NADH and 1 $FADH_2$ yield in the process 11 ATP. Thus one turn of the citric acid cycle generates 12 ATP.

5. Metabolism of Glucose and Glycogen in Muscle Fibers

Skeletal muscle derives glucose from glycogenolysis or by transport from the blood. Glucose can be stored as glycogen up to the level of 4–5% of the wet weight of the

muscle tissue. Glycogen is the major supply of glucose during moderate and intensive exercise, and is a limiting factor in endurance events such as the marathon. Glycogen and glucose catabolic rates are best described as exponential functions of exercise intensity, but with a greater gain in slope of the glycogen than glucose response.

Muscle extracts glucose from blood through insulin-dependent mechanisms. Exercise increases skeletal muscle insulin sensitivity. During exercise, muscle also increases glucose uptake through the contraction-induced increase in membrane permeability to glucose as well as through an enhanced metabolic rate.

Other regulatory mechanisms such as increased glycogenolysis or higher resting glycogen concentration have been shown to inhibit glucose uptake. Glucose uptake during exercise may also be decreased by increased concentrations of free fatty acids, although there is controversy about this issue. Muscle glucose transporter levels such as GLUT4, an important limiting factor of glucose utilization, and glycogen synthase activity, increase in response to exercise training. Increased GLUT4 levels may not necessarily mean increased glucose uptake, however. Moreover, genotypic adaptation for aerobic capacity as well as phenotypic adaptations to short- and long-term physical activity are important determinants of the balance of substrate utilization during intensive muscle work.

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Biographical Sketches

Dr. Mustafa Atalay was born in 1963 in Ankara, Turkey, and received his M.D. degree in the University of Ankara School of Medicine in 1986. He specialized in family practice in the State Hospital of Ankara in 1992, and continued his postgraduate studies on exercise physiology and sports medicine in Kuopio, Finland, from the beginning of 1993. In 1995 he received a Master of Public Health degree from the Department of Public Health, University of Kuopio. In 1998 he defended his Ph.D. thesis on "Tissue Antioxidant Responses to Physical Exercise-Induced Oxidative Stress" in the department of Physiology, University of Kuopio, and he received the degree of "Docent of Sports Medicine" from the National Board of High Education of Turkey in 1999. He was selected as a Fellow of the American College of Sports Medicine same year. He completed his postdoctoral fellowship at Ohio State University Medical Center and Laboratory of Molecular Medicine between 2000 and 2001. His research interest is in exercise-induced oxidative stress and antioxidant defenses. Currently he is working in the University of Kuopio, Finland, as a senior lecturer and researcher.

Osmo Otto Päiviö Hänninen, Dr. Med. Sci., Ph.D. Professor of Physiology, Chairman of the Department, University of Kuopio, was born in 1939 in Lahti, Finland. He studied at the University of Helsinki and University of Turku, Finland where he obtained the Master of Sciences (Biochemistry) in 1962, Licentiate of Medicine (M.D.) in 1964, Doctor of Medical Sciences (Dr.Med.Sci.) in 1966 and passed his dissertation in biochemistry for a Ph.D. in 1968. He has also studied genetics. He has been a specialist in sports medicine since 1986. He has served as Research Assistant to Prof. K. Hartiala 1962–1964, Assistant of Physiology 1964–1965, Laborator of Physiology 1966–1967, Docent of Physiology from 1967, and Associate Professor of Biochemistry 1969–1971 in the University of Turku. He was Acting Professor in the Planning Office 1971–1972 and from 1972 he has been Professor of Physiology and Chairman of the Department of Physiology at the University of Kuopio. He was Vice-President (1972–1979) and President (1981–1984) of the University of Kuopio. He served as Visiting Professor of Physiology, Shanghai Medical University, China in 1991–19922 and Sun Yatsen Medical University, Guangzhou, China, in 1998–1999. He became a Foreign Member of the Russian Academy of Natural Sciences in 1994, and was Secretary General, International Council for Laboratory Animal Science, 1988–1995. He was President of Societas Physiologica Finlandiae 1990–1999, has been President of the International Society for Pathophysiology since 1994 and Treasurer of the International Union of Biological Sciences from 1997.

His special interests in research are biotransformation and adaptation to chemical loading, biomonitoring of toxicants, comparative biochemical toxicology; muscle metabolism and function; and ergonomics.

He has written 266 papers for refereed journals, 72 articles published in proceedings , and 55 reviews, as well as 30 books and book chapters. He serves on the editorial board of four international journals and is at present the European Journal Editor of *Pathophysiology*.

Of his postgraduate students (32 in biotransformation, 27 in muscle metabolism and physiology, and 5 others), 12 serve as professors in China, Finland, Greece, Sweden, and the USA.