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Review Article

Skeletal Muscle Regulates Metabolism via Interorgan Crosstalk: Roles in Health and Disease

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A B S T R A C T

Skeletal muscle is recognized as vital to physical movement, posture, and breathing. In a less known but critically important role, muscle influences energy and protein metabolism throughout the body. Muscle is a primary site for glucose uptake and storage, and it is also a reservoir of amino acids stored as protein. Amino acids are released when supplies are needed elsewhere in the body. These conditions occur with acute and chronic diseases, which decrease dietary intake while increasing metabolic needs. Such metabolic shifts lead to the muscle loss associated with sarcopenia and cachexia, resulting in a variety of adverse health and economic consequences. With loss of skeletal muscle, protein and energy availability is lowered throughout the body. Muscle loss is associated with delayed recovery from illness, slowed wound healing, reduced resting metabolic rate, physical disability, poorer quality of life, and higher health care costs. These adverse effects can be combatted with exercise and nutrition. Studies suggest dietary protein and leucine or its metabolite β-hydroxy β-methylbutyrate (HMB) can improve muscle function, in turn improving functional performance. Considerable evidence shows that use of high-protein oral nutritional supplements (ONS) can help maintain and rebuild muscle mass and strength. We review muscle structure, function, and role in energy and protein balance. We discuss how disease- and age-related malnutrition hamper muscle accretion, ultimately causing whole-body deterioration. Finally, we describe how specialized nutrition and exercise can restore muscle mass, strength, and function, and ultimately reverse the negative health and economic outcomes associated with muscle loss.

Skeletal muscle is integral to physical movement, posture, and vital actions, such as chewing, swallowing, and breathing.[1,2] Skeletal muscle also serves as a regulator of interorgan crosstalk for energy and protein metabolism throughout the body, a less recognized but critically important role. As such, skeletal muscle is a key site for glucose uptake and storage.[3] Skeletal muscle is likewise a reservoir of amino acids that can support protein synthesis or energy production elsewhere in the body when other sources are depleted.[4]

This review of muscle metabolism describes how amino acids stored as protein in muscle can be broken down through proteolysis for ultimate use in energy production. Such breakdown occurs when energy demands are high (as with stress-induced hypermetabolism), or when supplies are low (as in severe starvation or longer-term protein energy malnutrition). Both of these states can be hallmarks of many diseases, either directly as a result of disease-related dysregulation of metabolism (such as in the extreme case of cancer-cachexia) or, more subtly, as a result of the general illness-associated loss of appetite. Muscle is therefore crucially important during illness, both for its role in balancing the metabolic needs of other organs and for its reserves of protein for use in energy production. Yet, during illness, the maintenance of muscle mass through exercise and nutrition are often overlooked or difficult to address, and muscle atrophy develops. Even more subtle is aging-related muscle loss, which can dramatically increase morbidity and mortality of otherwise survivable illnesses in the aged. This review also illustrates the consequences of muscle atrophy in aging and illness and proposes steps to combat these challenges.

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Muscle Basics

Muscle Structure and Classification

Skeletal muscle comprises the fibrillar proteins myosin (a thick filament) and actin (a thin filament) that interact to cause muscle contraction, a process requiring energy in the form of adenosine triphosphate (ATP). Different muscle types have been classified according to histochemical features, structural protein composition, and major metabolic properties.[5,6] Most commonly, skeletal muscles are referred to as either "slow" or "fast" to reflect speeds of contraction, or the shortening of myosin heavy chain (MHC) protein.[6] The velocity of this shortening is dependent on the MHC isoform present; "fast" fiber isoforms MHCIIa and IIb demonstrate a higher shortening velocity than their "slow" fiber MHCI counterparts.[6,7] Classic histochemical staining methods also classify muscle as type I (slow) and type II (fast) based on the myosin ATPase enzyme forms revealed. Recently, these types have been further distinguished based on histology (types I, IC, IIC, IIAC, IIA, IIAB, and IIB).[6]

Muscle Metabolism and Interorgan Crosstalk

Glucose regulation is central to energy balance both within muscle fibers and throughout the body. In the cytoplasm of most cells, glucose undergoes glycolysis to produce the substrate for ATP generation. Muscle fibers are also characterized on the basis of the speed and manner in which they metabolize glucose. The terms "fast" and "slow" can indicate the type of glucose metabolism occurring within the fiber. Slow muscles, which use aerobic metabolism, contain a high density of capillaries and oxidative enzymes that allow a greater resistance to fatigue.[7] Fast muscles, which depend on anaerobic metabolism, or glycolysis, can quickly generate ATP and therefore contract more readily. Fast muscles also fatigue sooner than slow fibers, as the conversion of glucose to pyruvate generates less ATP than can be generated by using the rest of central metabolism, ultimately generating CO_2.

Muscle has the ability to store glucose in the form of glycogen, which facilitates the rapid initiation of energy production for contraction even when glucose is not readily available from the diet. This unique capacity, shared also by the liver and kidneys, makes skeletal muscle an important metabolic organ that helps all organs have access to essential energy substrates during fasting. Furthermore, the amino acids stored in muscle as protein can be broken down as a last resort during times of starvation or extreme energy shortfalls.[4] Patterns of glucose utilization throughout the body as a whole reflect feeding status (Figure 1; Table 1). Based on a classic study of the fed state (measurement within 3 hours of eating), researchers estimated that 25% to 35% of an ingested carbohydrate load was quickly extracted from circulation and stored by the liver.[3] Of the remaining glucose, approximately 40% was disposed in the muscle and 10% in the kidney.[3] The brain used 15% to 20% of post-meal glucose.[3]

In the fasted state (after 14 to 16 h without eating), the liver provides approximately 80% of glucose that is released into circulation. About half of this glucose comes from the breakdown of stored glycogen, and the rest from the metabolism of sources other than carbohydrate or glycogen, including certain amino acids, through a process known as gluconeogenesis.[8] Interactions between muscle and liver are largely responsible for regulating carbohydrate metabolism and for achieving energy balance in normal fed and fasted states; the kidneys play a role similar to that of the liver, but to a lesser extent.[3,8] In addition, muscle tissue stores amino acids as protein, and adipose tissue serves as a depot of glycerol and fatty acids. As needed, amino acids and fatty acids can be metabolized to form acetyl coenzyme A for the tricarboxylic acid (TCA) cycle.

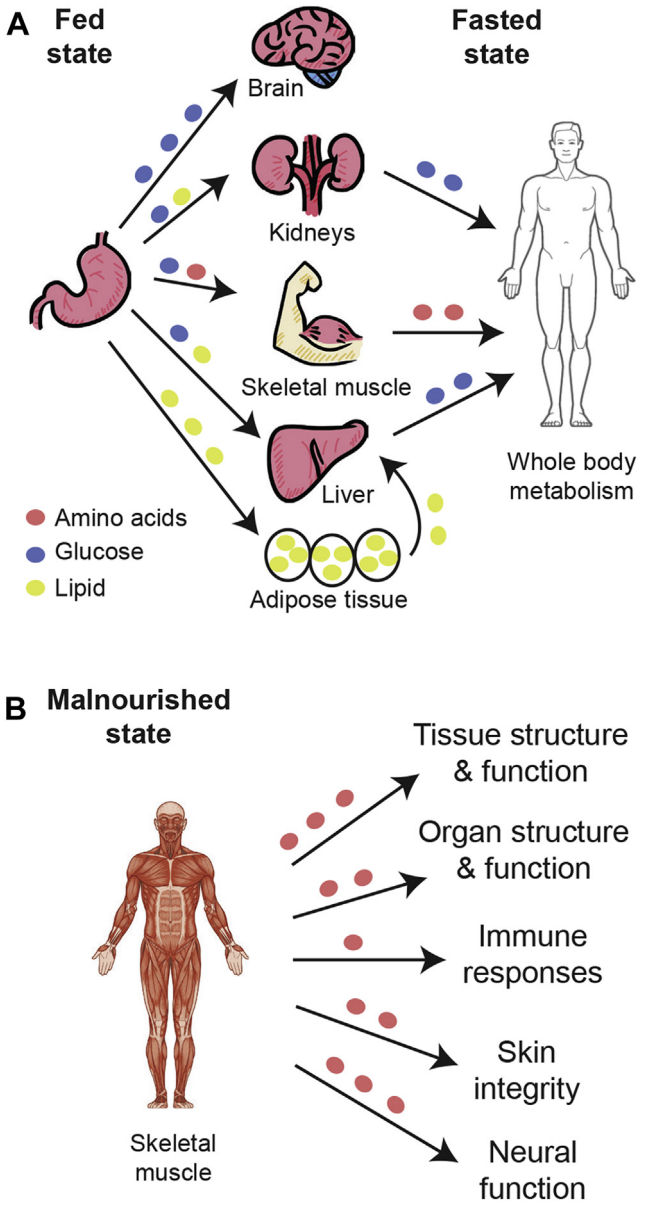

Fig. 1. Glucose metabolism in fed, fasted and malnourished states. A, Glucose, lipids, and amino acids from the diet circulate during the fed state for use or storage in body organs. In the fasted state, glucose is released from the muscles, kidneys, and liver for whole-body metabolism, along with lipids from adipose tissue and amino acids from the muscle. B, When glucose stores have been depleted, amino acids are provided by the muscles to support crucial bodily functions.

As glycogen stores become depleted, increasingly more glucose is produced by gluconeogenesis. Gluconeogenesis provides 70% of glucose released into the body 24 hours after eating, and 90% by 48 hours.[8] As fasting is prolonged, the kidneys contribute increasingly higher amounts of glucose from gluconeogenesis.

Ultimately, amino acids stored in skeletal muscle are metabolized when the need for gluconeogenesis substrate is greatest. Skeletal muscle houses nearly 75% of all protein in the body and constitutes an important contributor to gluconeogenesis in states of drastic depletion. Maintenance of muscle protein content depends on the balance between protein synthesis and degradation.[5] Under normal conditions, muscle protein mass gains during the fed state balance losses during the fasted state.[4] However, under severe metabolic stress generated by serious illness or injury, muscle protein can become