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Review

Amino Acid Sensing in Skeletal Muscle

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Aging impairs skeletal muscle protein synthesis, leading to muscle weakness and atrophy. However, the underlying molecular mechanisms remain poorly understood. Here, we review evidence that mammalian/mechanistic target of rapamycin complex 1 (mTORC1)-mediated and activating transcription factor 4 (ATF4)-mediated amino acid (AA) sensing pathways, triggered by impaired AA delivery to aged skeletal muscle, may play important roles in skeletal muscle aging. Interventions that alleviate age-related impairments in muscle protein synthesis, strength, and/or muscle mass appear to do so by reversing age-related changes in skeletal muscle AA delivery, mTORC1 activity, and/or ATF4 activity. An improved understanding of the mechanisms and roles of AA sensing pathways in skeletal muscle may lead to evidence-based strategies to attenuate sarcopenia.

Trends

Aging impairs endothelial cell function in skeletal muscle, thereby reducing delivery of dietary amino acids to skeletal muscle fibers.

Aging promotes anabolic resistance by impairing the ability of amino acids, insulin, or muscle contraction to increase protein synthesis in skeletal muscle.

Anabolic resistance may originate with endothelial dysfunction and impaired amino acid delivery to skeletal muscle fibers, thereby generating two distinct amino acid starvation responses [decreased mammalian/mechanistic target of rapamycin complex 1 (mTORC1) activity and increased activating transcription factor 4 (ATF4) activity], which reduce muscle protein synthesis, leading to muscle weakness and atrophy.

Potential therapeutic strategies include restoration of amino acid delivery to aged skeletal muscle via increased physical activity, dietary protein, pharmacologic vasodilators, and/or small molecules that stimulate mTORC1 and/or inhibit ATF4 in aged skeletal muscle fibers.

Introduction

Aging reduces skeletal muscle strength and muscle quality (i.e., strength per unit muscle mass) and ultimately causes age-related skeletal muscle atrophy, also known as sarcopenia. The early stages of skeletal muscle aging are primarily marked by reduced strength, which becomes apparent around the age of 40, and can progressively impair normal activities and quality of life. The late stage of skeletal muscle aging, sarcopenia, has serious health consequences, including falls, immobility, loss of independent living, and increased mortality [1]. The cellular and molecular mechanisms of skeletal muscle aging are complex, just beginning to be revealed, and still poorly understood. Here, we review current evidence linking skeletal muscle aging to amino acid (AA) sensing mechanisms within skeletal muscle fibers.

Aging Impairs Delivery of Dietary AAs to Skeletal Muscle

Muscle mass is ultimately controlled by the cellular processes of protein synthesis and breakdown (i.e., protein turnover). During conditions of muscle growth or hypertrophy, the rate of protein synthesis exceeds the rate of protein breakdown (i.e., muscle protein anabolism). However, muscle catabolism occurs when the rate of protein breakdown exceeds the rate of protein synthesis. In all types of skeletal muscle atrophy, including sarcopenia, the normal balance between protein synthesis and protein breakdown is disrupted, leading to a net loss of protein and muscle fiber size [2–4]. Although some early studies reported a basal (i.e., following an overnight fast) mismatch between muscle protein synthesis and breakdown in elderly humans (e.g., lower rates of synthesis and/or higher rates of breakdown), most studies have found that the rates of muscle protein turnover are not abnormal in elderly individuals under basal conditions [5–10]. These findings indicated that other factors that influence muscle protein turnover may be responsible for muscle atrophy during aging. Feeding and physical activity are two key factors that control daily muscle protein turnover. In young adults, feeding increases blood AA and insulin concentrations, which stimulates muscle protein anabolism by increasing the rate of protein synthesis and slightly reducing the rate of protein breakdown. By contrast,

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muscle contraction from exercise or physical activity stimulates muscle protein anabolism independent of changes in circulating AAs or insulin. Although aged skeletal muscle exhibits normal protein metabolism under basal conditions, it does not respond appropriately to low, physiologic doses of anabolic stimuli, such as insulin, exercise, or nutrient intake. This phenomenon has been termed 'anabolic resistance' [11].

The etiology of anabolic resistance is complex and multifactorial. One aspect involves a diminished response to protein or AA ingestion. For example, ingestion of an AA and carbohydrate mixture significantly increases muscle protein synthesis in young adults; however, it has no effect on muscle protein synthesis in older adults [12]. Removing carbohydrates and nonessential AAs from the mixture has no effect on the ability of essential AAs to stimulate muscle protein synthesis in young and older adults [13,14], indicating that the essential AAs are solely responsible for the nutrient-induced muscle protein anabolic response. However, anabolic resistance is still detected in aging muscle when essential AAs alone are administered [15,16], and larger doses are required to stimulate muscle protein synthesis than those needed in younger individuals [8,17]. The ability of larger doses of essential AAs to overcome anabolic resistance appears to be due to the content of leucine in the nutrient mixture. For example, a small dose of essential AAs (7 g) is capable of stimulating muscle protein synthesis in young adults but not in older adults [16]. However, if the content of leucine is increased, then a dose of 7 g of essential AAs can stimulate muscle protein synthesis in older adults [18]. This finding has led to the notion of a 'leucine threshold' that must be met in order for AAs to maximize the rate of muscle protein synthesis. In young adults, this threshold appears to be approximately 2 g of leucine, whereas with aging the threshold is approximately 3 g of leucine that must be ingested to adequately stimulate muscle protein synthesis [8,18,19].

Another aspect of anabolic resistance involves an impaired muscle protein anabolic response to insulin or muscle contraction. Infusion of insulin to increase blood insulin to postprandial levels in glucose-tolerant older adults does not stimulate muscle protein synthesis as it does in younger adults [20]. Hyperinsulinemia, above postprandial levels, is required to stimulate muscle protein synthesis in older adults, indicating a true resistance of muscle protein anabolism to insulin [21]. In addition, a bout of resistance exercise significantly increases muscle protein synthesis for up to 48 h following exercise in young adults [22], whereas muscle protein synthesis is not increased in older adults postexercise [23,24]. Therefore, three common stimuli (protein intake, insulin, and physical activity) become less effective at enhancing muscle protein anabolism with advancing age.

Since anabolic resistance can be overcome by increasing the amount of protein ingested or increasing the infusion rate of insulin, the delivery of AAs to muscle tissue might be a rate-limiting factor in stimulating muscle protein synthesis in older adults. This hypothesis was tested via a pharmacological approach to block or induce vasodilation during exposure to AAs or insulin in humans. When insulin was directly infused into the leg of young adults with or without the nitric oxide synthase (NOS) inhibitor N^G-monomethyl-L-arginine (L-NMMA), the normal increase in blood flow, AA delivery, and muscle protein synthesis were blocked when vasodilation was blocked with the NOS inhibitor [25]. In older adults, during an insulin infusion with or without a vasodilator (sodium nitroprusside), enhancing vasodilation during insulin infusion restored blood flow, AA delivery, and muscle protein synthesis [26]. A similar experiment used sodium nitroprusside during AA ingestion and found that vasodilation during hyperaminoacidemia in older adults was capable of increasing blood flow, AA delivery, and muscle protein synthesis to levels similar to that of their young counterparts [27]. These studies indicated that vasodilation of blood vessels in muscle is necessary for increasing AA delivery to muscle in order to increase muscle protein synthesis, and that impairments in AA delivery to muscle may be an underlying cause of anabolic resistance in aging.