Exercise, nutrition, and aging in the regulation of muscle protein synthesis

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Abstract Sarcopenia is the age-associated loss of skeletal muscle mass and strength that develops slowly over decades and becomes a significant factor to disability among the elderly population. Recent studies have indicated that blunted anabolic response to nutritional stimuli significantly contributes to the development of sarcopenia. In the present article, we will review recent findings on the role of nutritional intake on muscle protein metabolism in the elderly. This review will particularly focus on acute anabolic responses to amino acids and protein intake, age-associated changes in the response of muscle protein to meal intake, and the role of insulin resistance in muscle protein metabolism. The relationship between age-associated decline of sex steroid hormones and muscle anabolism will also be discussed in addition to the benefits of resistance exercise in muscle protein anabolism. Additionally, recent evidence on the time-course of anabolic response, molecular regulation of muscle protein synthesis, and long-term training effects will be discussed. Finally, recent evidence on the cumulative effect of resistance exercise in combination with nutritional supplementation on muscle protein metabolism will be discussed to propose possible preventative measures against sarcopenia.

Keywords: muscle protein synthesis, amino acids, exercise, sarcopenia

Introduction

Aging is associated with a progressive reduction in skeletal muscle mass and concomitant reduction in strength. This aging-associated loss of muscle mass is called sarcopenia. After 30 years of age, approximately 3 - 5% of muscle mass is lost per decade, and this reduction is further accelerated after 60 years. Sarcopenia increases the risk of injury due to falls that may impair an individual’s physical independence, and may lead to disability. Loss of skeletal muscle also reduces physical activity levels, leading to metabolic complications such as osteoporosis, obesity, and glucose intolerance. Skeletal muscle is also an important source of amino acids that provide substrates for wound healing during malnutrition, starvation, injury, and diseases. The mechanisms that trigger sarcopenia have not been clarified yet, but they are likely to be multifactorial; and they all appear to affect the balance between muscle protein synthesis and breakdown rate, which subsequently results in the loss of muscle mass.

This review will be focused on age-associated changes in muscle protein metabolism in relation to nutrient intake and exercise, which have important implications in the prevention of sarcopenia.

Protein requirement for the elderly population

The Institute of Medicine has reported that the daily protein requirement for older adults is estimated to be similar to that of adults of 55 years and younger (0.8 g kg\(^{-1}\) day\(^{-1}\)). However, information regarding the dietary protein requirement of an older population is still limited. Although several studies support this 0.8 g kg\(^{-1}\) day\(^{-1}\) recommendation, other studies have suggested that the moderately higher protein intake of 1.0 - 1.3 g kg\(^{-1}\) day\(^{-1}\) is required to maintain a nitrogen balance and muscle mass in elderly individuals. In support of this hypothesis, Campbell et al. reported that protein intake of 0.8 g kg\(^{-1}\) day\(^{-1}\) for a 14-week period in a metabolic ward resulted in a significant reduction of muscle cross-sectional area of the thighs in elderly subjects, even while consuming a weight maintenance diet. A recent cohort study, which investigated over 2000 older subjects, demonstrated an inverse relationship between loss of muscle mass over a 3-year period and dietary protein intake. The same authors also showed that most of those who have retained muscle mass were those who consumed the highest amount of dietary proteins, whereas the most muscle loss was seen among those with the least amount of dietary protein intake (Fig. 1). Further studies are warranted to clarify the optimal amount of dietary protein intake needed for the older population to prevent muscle mass loss with aging.

Muscle anabolic response to amino acids and protein

Nutrient intake, especially proteins and amino acids, is the most important anabolic stimuli for skeletal muscle. Amino acid ingestion and the subsequent rise of their
blood concentration rapidly increases the inward transport of amino acids into muscle cells and, subsequently, increases muscle protein synthesis in a dose-dependent manner\(^{11,12}\).

In order for orally ingested amino acids to reach the systemic target tissue, they first need to pass through splanchnic tissue (e.g., gut and liver). Although amino acid extraction, by passing through splanchnic tissue, is higher in older subjects than in young people\(^{13}\), this does not appear to influence the systemic amino acid concentration\(^{14}\). Consequently, oral amino acid intake increases amino acid delivery to the leg and muscle protein synthesis, to the same extent in the elderly and young subjects.

In contrast to fast absorbing amino acids, the speed of digestion for intact proteins and amino acid absorption from the gut has a major effect on whole-body protein anabolism. In young subjects, proteins that are digested slowly (e.g., casein) appear to induce an overall better anabolic response at the whole-body level as compared to proteins that are digested more rapidly (e.g., whey protein)\(^{15}\). In elderly individuals, however, it appears that proteins that are rapidly digested and absorbed induce a better anabolic response than those digested slowly\(^{16}\).

**Role of essential amino acids**

A previous study has indicated that the anabolic action of amino acids on muscle proteins is mainly because of essential amino acids (EAA)\(^{17}\). This has been confirmed in older subjects by administering nutritional supplements containing only essential amino acids, or a balanced essential and nonessential amino acid mixture containing the same amount of essential amino acids but double the amount of amino acids and amino-nitrogen. Under these conditions, muscle protein synthesis was stimulated to the same extent by either supplement in the elderly subjects\(^{17}\).

Among the essential amino acids, branched-chain amino acids (BCAAs) are known to be most involved in the direct stimulation of muscle protein synthesis. More specifically, leucine is the most potent of the BCAAs. Intake of leucine alone can activate several intracellular signaling proteins involved in the initiation of mRNA translation, including the mammalian target of rapamycin (mTOR), 70-kDa ribosomal protein S6 kinase (S6K1), and eukaryotic initiation factor 4E binding protein-1 (4E-BP1)\(^{18}\).

Recently, age-specific changes in muscle anabolic response to EAA have been revealed. Katsanos et al. demonstrated that older subjects have significantly less muscle protein accretion than younger subjects following the ingestion of a 7 g EAA supplement\(^{19}\). The same authors also reported that while both 26% (1.7 g leucine in 7 g EAA) and 41% (2.8 g leucine in 7 g EAA) leucine EAA ingestion increased muscle protein synthesis in young men, only the 41% leucine EAA bolus was effective in stimulating muscle protein synthesis in elderly men\(^{20}\).

Although large amounts of EAA (~15 g) exert similar effects in the elderly and young individuals\(^{14,21}\), these studies indicate that age-related differences in the muscle anabolic response become apparent when sub-maximal amounts of amino acids are administered.

**Insulin resistance of muscle protein synthesis**

Mixing amino acids with other nutrients, specifically carbohydrates, has a profound impact on endogenous hormone response and muscle metabolism. When carbohydrates are added to the amino acid mixture, muscle protein synthesis almost doubles in young subjects, while the addition of carbohydrate does not induce any additional anabolic response in older subjects\(^{22}\). In fact, in a previous study, the addition of carbohydrates interfered with muscle protein breakdown as well as muscle protein anabolism by amino acids, leading to decreased muscle protein turnover\(^{22}\).

Insulin is a potent muscle anabolic agent. However, insulin resistance of muscle protein metabolism with aging appears to be responsible for the blunted response to mixed supplements. Recent data, using various levels of physiological hyperinsulinemia, demonstrated that vasodilation and a subsequent increase in nutrient flow to the muscle are important regulators of muscle anabolic response during hyperinsulinemia\(^{23}\). The existence of insulin resistance of muscle protein metabolism with aging, independent of glucose tolerance, has been demonstrated in healthy, non-diabetic elderly subjects\(^{24}\). This blunted response of muscle anabolism to insulin is associated with a reduction in endothelium-dependent vasodilation and blood flow\(^{24}\). Interestingly, this insulin resistance of
muscle protein metabolism in the elderly can be reversed by aerobic exercise through improved endothelial function, insulin-induced vasodilation, and intracellular insulin signaling\(^{25}\).

**Exercise-induced muscle protein synthesis**

Another important contributor to sarcopenia is inactivity. Although it is difficult to causally determine the relative importance of a sedentary lifestyle in the development of sarcopenia, it is very well known that short-term muscle inactivity severely reduces muscle mass and strength even in young individuals. Typical examples are bed rest and weightlessness\(^{26-27}\). It is also recognized that these muscle changes can be counteracted by exercise, typically resistance exercise\(^{28}\). Several researchers have found that acute resistance exercise increases myofibrillar muscle protein synthesis both in young and older adults\(^{20,21}\). The increased muscle protein synthesis is apparent within 2 - 3 h after a single bout of heavy resistance exercise\(^{29-31}\) and remains elevated for up to 24 h in trained individuals\(^ {32}\) and up to 48 - 72 h in untrained subjects\(^ {32,33}\). The acute increase in muscle protein synthesis appears to be mediated by changes in mRNA translation rather than changes in transcription. In particular, the mTOR signaling pathway in human skeletal muscle is associated with an increased rate of muscle protein synthesis during the early recovery phase following a single bout of resistance exercise\(^ {30}\). Consequently, progressive resistance exercise training has also been shown to induce muscle hypertrophy, and increase strength in the elderly, and even among physically frail adults\(^ {34,36}\).

**Resistance exercise in combination with nutrient intake**

The provision of essential amino acids, with or without carbohydrates, following resistance exercise, increases the rate of muscle protein synthesis\(^ {30,37,38}\). Recent studies have shown that the ingestion of whole proteins, such as whey or casein, following an acute bout of resistance exercise, augments muscle protein synthesis\(^ {39-41}\). Furthermore, we have recently reported that ingestion of an essential amino acid and carbohydrate (EAA+CHO) mixture, 1 h prior to a bout of resistance exercise, did not further increase muscle protein synthesis during post-exercise recovery, compared to performing resistance exercise in the fasted state\(^ {42}\). In contrast, our recent findings indicated an enhanced stimulation of muscle protein synthesis when the same EAA+CHO mixture was ingested 1 h after a bout of resistance exercise\(^ {43}\), indicating more efficient muscle protein synthesis during the early recovery phase when the supplement was given post-exercise, as compared to when administered before exercise (Fig. 2).

**Age-associated decline in sex steroid hormones and sarcopenia**

Sex steroid hormones, which are secreted mainly by the ovary, testis, and adrenal cortex, regulate diverse physiological processes in target tissues, including reproductive organs, bone, liver, the cardiovascular system, brain, and skeletal muscle\(^ {43}\). As precursors of sex steroid hormones, dehydroepiandrosterone (DHEA) and its sulfate derivative (DHEA-S) play critical physiological roles in maintaining steroidogenesis in peripheral tissues\(^ {43}\).

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**Fig. 2** Effect of timing of amino acid supplementation on muscle protein synthesis when combined with resistance exercise.
Mixed muscle protein synthesis assessed by the stable isotope tracer method at baseline (Baseline), 3 h after a bout of resistance exercise at fasted state (EX), amino acid ingestion 1 h prior to exercise (Pre-EX), and amino acid ingestion 1 h after exercise (Post-EX). Data represent the mean ± SE; * P < 0.05 vs. Baseline, # P < 0.05 vs. other groups. Adapted from Fujita et al., 2009 and Dryer et al., 2008.
DHEA is converted to testosterone by 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD, which is converted to 5α-dihydrotestosterone (DHT) by 5α-reductase. In our previous study, we demonstrated that skeletal muscle could synthesize testosterone, estradiol, and DHT from DHEA locally in cultured skeletal muscle and rat muscle tissue models. In our recent study, chronic DHEA administration in obese rats, with impaired muscle steroidogenesis and reduced muscle sex steroid hormone levels, induced a significant increase in both gastrocnemius and soleus muscles, compared to those with exercise training. Therefore, the attenuation of aging-induced decline in intramuscular steroidogenesis may be crucial in preventing aging-associated complications.

Nutritional supplementation, coupled with exercise, is one of the ways to improve impaired muscle steroidogenesis and increase muscle sex steroid hormone levels. In our recent study, chronic DHEA administration in obese rats, with impaired muscle steroidogenesis and reduced muscle sex steroid hormone levels, induced a significant increase in both gastrocnemius and soleus muscles, compared to those with exercise training (Fig. 3). Therefore, habitual exercise and/or DHEA supplementation may reverse aging-induced impairment of steroidogenesis in skeletal muscle, as well as improve muscle mass and function.

**Conclusions**

Aging is associated with a progressive loss of muscle mass, which is most likely caused by a negative balance between muscle protein synthesis and protein breakdown rate. More evidence is accumulating that supports the role of nutritional intake, especially proteins and amino acids, in stimulating muscle protein anabolism regardless of age. However, insulin resistance specific to muscle protein metabolism is apparent with aging. Aging is also associated with a reduced anabolic response to an amino acid and carbohydrate mixture, as well as amino acids themselves, when administered in a small quantity. Long-term clinical studies with a larger sample size are needed to clarify dietary protein requirements, and to assess the specific amount of daily protein and amino acid supplementation needed for preventing sarcopenia among the elderly population. Accumulating evidence also shows the role of resistance exercise in stimulating muscle protein synthesis and in preventing sarcopenia. Recent evidence supports the cumulative effect of resistance exercise, in combination with amino acids/proteins, to further facilitate muscle hypertrophy. Additional studies are warranted to clarify the optimal volume and/or intensity of exercise, as well as determine the amount of amino acids and/or proteins needed specific to populations with different health, nutritional status, and physical activity levels.

**References**

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