Role of Exercise and Nutrition in the Prevention of Sarcopenia

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Summary  The age-associated loss of skeletal muscle mass and strength (sarcopenia) has been shown to increase the risk of injury due to falls and incidence of metabolic complications including insulin resistance and diabetes, which subsequently becomes a significant factor to disability among the elderly population. Nutrient intake is the most important anabolic stimulus for skeletal muscle. Specifically, the amino acid leucine and meal-induced insulin both independently stimulate muscle protein synthesis. However, age-specific changes in muscle anabolic responses to leucine become apparent when sub-maximal amounts of amino acids are administered in older subjects. Furthermore, insulin resistance of muscle protein metabolism with aging has been demonstrated in healthy non-diabetic older subjects. Resistance exercise is another anabolic stimulus which increases myofibrillar muscle protein synthesis in both young and older individuals. The increased muscle anabolism is apparent within 2–3 h after a single bout of heavy resistance exercise and remains elevated up to 2 d following the exercise. The mTOR signaling pathway in skeletal muscle is associated with an increased rate of muscle protein synthesis during the early recovery phase following a bout of resistance exercise. Finally, recent evidence on the cumulative effect of resistance exercise in combination with nutritional supplement on muscle protein metabolism will be discussed to propose a possible preventative measure against sarcopenia.

Key Words  muscle protein synthesis, amino acids, exercise, sarcopenia

Sarcopenia is the age-associated loss of skeletal muscle mass and strength that develops slowly over decades and becomes a significant factor for disability among the elderly population. 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 interventions to prevent and/or ameliorate the age-associated changes in muscle protein metabolism in relation to nutrient intake and exercise, which have important implications in the prevention of sarcopenia.

Muscle Anabolic Response to Amino Acids and Protein

Nutrient intake, especially proteins and amino acids, is the most important anabolic stimulus for skeletal muscle. A previous study has indicated that the anabolic action of amino acids on muscle proteins occurs mainly because of essential amino acids (EAA) (1). Among the essential amino acids, branched-chain amino acids (BCAAs) are known to be most involved in the direct stimulation of muscle protein synthesis. 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 (eIF4E-BP1) (2).

Recently, age-specific changes in muscle anabolic response to EAA have been uncovered. One study has demonstrated that older subjects had significantly less muscle protein accretion than younger subjects following the ingestion of a 7 g EAA supplement. 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 (3). Although large amounts of EAA (~15 g) exert similar effects in the elderly and young individuals, these studies indicate that the age-related differences in the muscle anabolic response becomes apparent when sub-maximal amounts of amino acids are administered. Huston et al. (2008) have investigated over 2,000 older subjects, and demonstrated an inverse relationship between loss of muscle mass over a 3-y period and dietary protein intake after adjusting for confounding variables including other dietary intake and physical activities (Fig. 1) (4).

Insulin Resistance of Muscle Protein Synthesis

A mixture of 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. 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. The existence of insulin resistance of muscle protein metabolism with aging, independent of glucose tolerance, has been demonstrated in healthy, non-diabetic elderly subjects. This blunted response of muscle anabolism to insulin is associated with the reduction in endothelium-dependent vasodilation and blood flow (5). 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 (6).

Resistance Exercise and Muscle Protein Metabolism

Resistance exercise is another potent muscle anabolic stimulus. The muscle protein synthesis increases within 2–3 h after a single bout of resistance exercise (7) and remains higher for up to 24 h in trained individuals and up to 48 h in untrained subjects (8).

The upregulation of mRNA translation to protein is an important regulation for the acute increase in exercise-induced muscle protein synthesis (9) (Fig. 2).

The mammalian target of rapamycin complex 1 (mTORC1), consists of mTOR, mLST8, regulatory associated protein of mTOR (Raptor), DEP domain-containing mTOR-interacting protein (DEPTOR) and proline-rich Akt substrate of 40 kDa (PRAS40), which is a key regulator of translation initiation and protein synthesis. Previous studies have demonstrated that resistance exercise activates mTORC1 and muscle protein synthesis (10), while rapamycin, an mTORC1 inhibitor, suppressed muscle protein synthesis and subsequent skeletal muscle hypertrophy in an animal model. Furthermore, a recent human study has shown that the ingestion of rapamycin eliminated the increase in muscle protein synthesis in response to resistance exercise in young males (11). These results indicate that the activation of mTORC1 is a critical regulator for muscle protein synthesis and subsequent skeletal muscle hypertrophy in response to resistance exercise. The activated mTORC1 phosphorylates its downstream signaling protein, p70 ribosomal protein S6 kinase (p70S6K) and eukaryotic initiation factor 4E binding protein 1 (4E-BP1). The phosphorylation of p70S6K, a serine/threonine kinase, contributes to enhance mRNA translation and subsequent muscle protein synthesis. A previous study has shown that the phosphorylation of p70S6K correlated with the increase in muscle mass following 14 wk’ resistance training in human subjects. Furthermore, phosphorylation of 4E-BP1 induces its dissociation from eIF4E, leading to increased mRNA translation initiation. Taken together, resistance exercise activates mTORC1 and its downstream signaling pathway, increasing the muscle protein synthesis. This anabolic response is critical in long-term training-induced skeletal muscle hypertrophy.

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 (12). 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 (13). Furthermore, we have previously 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 with performing resistance exercise in the fasted state (14). In contrast, an enhanced stimulation of muscle protein synthesis was observed when the same EAA + CHO mixture was ingested 1 h after a bout of resistance exercise, indicat-
ing more efficient muscle protein synthesis during the early recovery phase when the supplement was given post-exercise as compared to when administered before exercise (12) (Fig. 3).

**Conclusions**

More evidence is accumulating that support the role of nutritional intake, especially proteins and amino acids, in stimulating muscle protein anabolism regardless of age. 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. Accumulating evidence also indicates 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. Further studies are warranted to clarify the optimal volume and intensity of exercise as well as the amount of amino acids and/or proteins specific to populations with different health, nutrition status, and physical activity levels in order to effectively prevent the progression of sarcopenia.

**REFERENCES**


