Regulation of muscle protein metabolism by nutrition and exercise

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Abstract Skeletal muscle is an essential tissue that regulates glucose metabolism and locomotive ability. Therefore, gaining skeletal muscle mass is important for maintaining or improving health as well as athletic sport performance. Over the past decade, resistance exercise has been shown to be the most effective method for gaining muscle mass. Acute resistance exercise increases muscle protein anabolism, and repeated training induces protein accumulation and muscle hypertrophy. Similarly, protein anabolism by nutrition intake, particularly protein and amino acid ingestion, is important for regulating skeletal muscle mass. Moreover, recent studies have indicated that a combination of resistance exercise and nutrition intake augments the anabolic effect more than exercise and/or nutrition intake alone. In this review, we discuss the mechanism underlying protein anabolism based on exercise and nutrition intake, as well as recommendations for optimizing protein anabolism by each stimulus based on the latest findings. Finally, recent evidence related to the cumulative effect of resistance exercise in combination with nutritional supplements on muscle protein metabolism is discussed.

Keywords: skeletal muscle, resistance exercise, amino acids

Introduction

Skeletal muscle mass is critical for sports performance, particularly for sports that require high power output to increase performance. With respect to health promotion, maintaining skeletal muscle mass in older populations is critical to prevent not only falls, but also diabetes and cardiovascular diseases. In this review, the molecular mechanisms and anabolic response to nutrition and exercise are discussed, focusing on the effective combination of these two anabolic stimuli based on recent scientific findings.

Anabolic response to protein/amino acid intake

The muscle protein synthesis rate is dramatically increased within 1 h after acute protein and/or amino acid ingestion. Protein is digested and absorbed in the gastrointestinal tract, after which it is transported to the skeletal muscle through circulation. Intramuscular amino acids are stored in a free amino acid pool, and are made available for muscle protein synthesis when appropriate. It was previously reported that essential amino acids are involved in stimulating muscle protein synthesis, whereas non-essential amino acids do not have an anabolic effect. A recent study revealed that leucine, a branched chain amino acid, is not only a structural component of protein, but also an important amino acid involved in appestat, insulin secretion, and muscle protein anabolism. Leucine activates the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway and subsequent protein synthesis via mRNA translation control. How leucine is sensed and mTORC1 is regulated in the skeletal muscle was previously poorly understood. However, a recent study by Wolfson et al. revealed that sestrin2 acts as a leucine sensor. Sestrin2 dissociates from GATOR2 (a complex of GTPase activator) by leucine bound to sestrin2, which functions to increase GATOR2 activity and subsequently induce mTORC1 activation. Intramuscular amino acid concentration is reflected by the circulating concentration. Therefore, augmenting the amino acid concentration in the circulation is essential for stimulating the leucine sensor and muscle protein synthesis.

It was previously reported that the minimum protein intake required to significantly increase the acute muscle protein synthesis rate in young people is 0.26 g/kg. Subjects in this study ingested high-quality protein (whey or egg protein) in a fasted state. Therefore, the protein requirement per body weight may be higher than 0.26 g/kg when typical mixed food with other nutrients (i.e. fat) is ingested. In normal dietary habits, protein intake over three meals each day is higher at dinner and lower at breakfast and lunch. Thus, protein intake at breakfast after the longest fasting (sleeping) should be increased given the importance of protein intake at each meal.

Muscle protein turnover after an acute bout of resistance exercise

Acute resistance exercise induces mTORC1 activation and ribosome biogenesis by mechanical stimuli, complex 1 (mTORC1) signaling pathway and subsequent protein synthesis via mRNA translation control. How leucine is sensed and mTORC1 is regulated in the skeletal muscle was previously poorly understood. However, a recent study by Wolfson et al. revealed that sestrin2 acts as a leucine sensor. Sestrin2 dissociates from GATOR2 (a complex of GTPase activator) by leucine bound to sestrin2, which functions to increase GATOR2 activity and subsequently induce mTORC1 activation. Intramuscular amino acid concentration is reflected by the circulating concentration. Therefore, augmenting the amino acid concentration in the circulation is essential for stimulating the leucine sensor and muscle protein synthesis.

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contraction-induced growth factors\(^{[3,14]}\), and metabolic stress\(^{[15]}\), and subsequently augments muscle protein synthesis by accelerating translation. Acute resistance exercise also increases muscle protein breakdown. In contrast, the net balance of muscle protein turnover becomes positive, as the rate of muscle protein synthesis is higher than that of muscle protein breakdown, after exercise (Fig. 1). Previous studies revealed that the exercise-induced increase in muscle protein synthesis persists until 48 h after exercise\(^{[16]}\). It is thought that chronic training induces constant increases in muscle protein synthesis and leads to skeletal muscle hypertrophy via muscle protein accumulation.

**Factors influencing the anabolic response to resistance exercise**

Previous studies have reported that several factors during exercise, such as exercise volume (force-time integral)\(^{[17,18]}\), exercise time\(^{[19]}\), and contraction mode\(^{[20]}\), affect the post-exercise muscle protein synthesis rate. Many previous studies investigated factors that dominantly affect the muscle protein synthesis rate after exercise.

**Exercise intensity:** Kumar et al. focused on exercise intensity and found that the muscle protein synthesis rate is proportional to exercise intensity from 20% one-repetition maximum (1RM) to 60% 1RM, and levels off at more than 60% 1RM for the same exercise volume\(^{[21]}\). Burd et al. confirmed these results by comparing the muscle protein synthesis rate between volume-matched subjects performing 30% 1RM and 90% 1RM resistance exercise\(^{[18]}\).

**Exercise volume (force-time integral):** Previous studies reported that exercise volume (i.e. total amount of lifted weight) also affects muscle protein synthesis after exercise. Burd et al. compared muscle protein synthesis between a single set and 3 sets of resistance exercise at 70% 1RM, and they found that the post-exercise muscle protein synthesis rate was higher after 3 sets compared with after a single set at 29 h after exercise\(^{[17]}\). Additionally, Burd et al. compared the muscle protein synthesis rate after resistance exercise until fatigue failure at 30% 1RM and 90% 1RM; interestingly, the muscle protein synthesis rate was higher after 30% 1RM exercise than after 90% 1RM exercise. Simultaneously, a larger exercise volume load was performed by the 30% 1RM subjects than by the 90% 1RM subjects\(^{[18]}\). Therefore, recent studies indicate that high exercise intensity is not required to increase muscle protein synthesis, suggesting that it is more efficient to conduct high-volume exercise than to augment intensity (Fig. 2).

**Physiological adaptation to chronic resistance training**

As described above, previous findings suggest that increased exercise volume and ‘reach to fatigue failure’ rather than augmentation of exercise intensity is important for maximizing muscle protein synthesis after resistance exercise. A study comparing the effects of 10 weeks of resistance training (3-times per week, 3 sets of leg extension until fatigue failure) performed at 30% 1RM and 80% 1RM also supports the results of other studies comparing exercise volume and fatigue\(^{[22]}\). Moreover, muscle hypertrophy was observed in resistance training performed to fatigue failure independently of exercise intensity in well-

![Fig. 1 Muscle protein synthesis rate, breakdown rate and net balance of protein metabolism after acute resistance exercise.](image)

*Significantly different from rest (P < 0.05)
Adapted from Phillips et al. 1997.
trained subjects\textsuperscript{29}. In summary, recent studies indicate that skeletal muscle mass can be increased to the same extent for low-load exercise until fatigue and high-load exercise.

**Anabolic effect of combining resistance exercise and protein intake**

Increased muscle protein synthesis following protein and/or amino acid intake is sustained for only a few hours. In contrast, as described above, an increased muscle protein synthesis rate after resistance exercise continues until approximately 48 h after exercise in young subjects. Previously, many groups reported that protein intake after acute resistance exercise additively augments the muscle protein synthesis rate by more than exercise and/or protein intake alone\textsuperscript{24,25}. The most effective timing of protein intake is immediately after exercise\textsuperscript{26}, as the additive effect decreases over time\textsuperscript{27} (Fig. 3). Although this effect on the muscle protein synthesis rate is highest immediately after exercise, the synergistic effect of muscle protein synthesis by resistance exercise and protein intake is expected to occur until 48 h after exercise. In fact, a study showed that after resistance exercise at different intensity levels, muscle protein synthesis increased more significantly when combined with protein ingestion than that of exercise alone at 24 h after exercise. Interestingly, muscle protein synthesis after protein intake at 24 h after exercise did not differ based on exercise intensity when the exercise was performed until failure, suggesting that the additive effect of exercise and nutrition is sustained the day after exercise regardless of exercise intensity\textsuperscript{28} (Fig. 4). These findings indicate that attention should be given to habitual dietary protein intake as well as protein supplementation immediately following exercise to maximize the effects of exercise and nutrition.

**Effect of different sources of protein**

Several studies reported that resistance exercise and intake of various combinations of protein sources (i.e. milk protein, which contains whey and casein, soy protein, egg white, and beef) augments muscle protein synthesis after exercise more than exercise alone\textsuperscript{29,30}.

However, the source of protein affects muscle protein synthesis after exercise, even when the same amount of protein is consumed. This may be attributed to either a difference in leucine content or the speed and effi-
iciency of digestion and absorption for the same amount of protein. Milk protein contains high levels of leucine compared to soy protein. Therefore, 20 g of milk protein contains higher levels of leucine compared to the same amount of soy protein, and milk protein causes a greater increase in muscle protein synthesis compared to soy protein intake after resistance exercise\(^3\). Accordingly, it is important to consider protein “quality” in order to efficiently augment muscle protein synthesis after exercise. A comparison of whey and casein in milk protein shows that although whey is rapidly absorbed and exported from the gastric environment because of its acidic character, casein intake results in a lower peak blood leucine concentration because it is coagulated and precipitated by gastric acid and more slowly exported from the gastric environment. Previous studies comparing the effect of whey and casein showed that whey intake induced higher muscle protein synthesis compared to casein intake both in a resting state and after an acute bout of resistance exercise\(^3\). Therefore, the influence of digestion and absorption characteristics should be considered when we consume protein as a meal and/or functional food.

Dose of protein after resistance exercise

An increased intramyocellular leucine concentration stimulates muscle protein synthesis in a concentration-dependent manner\(^3\). This increase in muscle protein synthesis after protein ingestion also depends on the amount of protein consumed. A previous study examining the consumption of whey as a protein source showed that muscle protein synthesis is increased commensurate with protein ingestion, reaching a peak at 20-25 g (i.e. leucine 2.5-3.5 g) of protein intake after resistance exercise. In general, 20-25 g whey protein intake is recommended after exercise\(^3\). This value is based on a study involving lower limb exercise in 70-80 kg young male subjects, and thus the value may differ in subjects with different body weights such as a 50-kg long-distance runner and 100-kg bodybuilder.

Conclusion

In sport nutrition research, muscle protein synthesis and breakdown can be directly measured by using amino acid stable isotope tracers, greatly advancing studies of protein metabolism\(^3\). Determining the effect of protein anabolism for exercise and nutrition combinations enables the development of efficient exercise and nutrition programs, as well as methods for augmenting athletic performance or preventing/ameliorating sarcopenia. A combination of resistance exercise and nutrition is essential for efficient muscle hypertrophy. Efficient dietary protein ingestion as well as functional food intake during the training period contributes to maximizing physical adaptation with exercise.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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