Maximizing muscle protein anabolism: the role of protein quality

Jason E. Tang and Stuart M. Phillips

Exercise Metabolism Research Group, Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada

Correspondence to Stuart M. Phillips, PhD, Exercise Metabolism Research Group, Department of Kinesiology, McMaster University, Hamilton, ON, Canada L8S 4K1
Tel: +1 905 525 9140; fax: +1 905 523 4025; e-mail: phillis@mcmaster.ca, http://www.mcmaster.ca/kinesiology/

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Purpose of review

Muscle protein synthesis (MPS) and muscle protein breakdown are simultaneous ongoing processes. Here, we examine evidence for how protein quality can affect exercise-induced muscle protein anabolism or protein balance (MPS minus muscle protein breakdown). Evidence is highlighted showing differences in the responses of MPS, and muscle protein accretion, with ingestion of milk-based and soy-based proteins in young and elderly persons.

Recent findings

Protein consumption, and the accompanying hyperaminoacidemia, stimulates an increase in MPS and a small suppression of muscle protein breakdown. Beyond the feeding-induced rise in MPS, small incremental addition of new muscle protein mass occurs following intense resistance exercise which over time (i.e. resistance training) leads to muscle hypertrophy. Athletes make use of the paradigm of resistance training and eating to maximize the gains in their skeletal muscle mass. Importantly, however, metabolically active skeletal muscle can offset the morbidities associated with the sarcopenia of aging such as type II diabetes, decline in aerobic fitness and the reduction in metabolic rate that can lead to fat mass accumulation.

Summary

Recent evidence suggests that consumption of different proteins can affect the amplitude and possibly duration of MPS increases after feeding and this effect interacts and is possibly accentuated with resistance exercise.

Keywords

casein, hypertrophy, muscle mass, soy, whey

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Introduction

In adult humans, small increases in skeletal muscle mass (i.e. hypertrophy) can arise when resistance exercise is combined with positive energy balance and sufficient dietary protein intake [1–3]. To achieve hypertrophy requires acute periods of imbalance between muscle protein synthesis (MPS) (stimulated by resistance exercise and feeding) and muscle protein breakdown (MPB), which result in a positive net protein balance (i.e. MPS > MPB). Over time, the summation of these acute periods of positive protein balance yields a net gain in muscle fiber protein content and consequently cross-sectional area.

If the balance of MPS and MPB is considered on an hour-to-hour basis, the switch from a fed to postprandial to fasted states results in changes in protein synthesis that are 10–20-fold greater than any measured change in protein breakdown [4–9]. Hence, the regulation, at least in healthy noncatabolic (i.e. nondiseased) persons, of muscle mass is via protein synthesis, which will be the likely site of metabolic control for any feeding-induced change in muscle protein mass. Thus, it is likely that alterations in MPS are the primary determinants in the acute nutrient-induced changes in protein turnover.

Similar to feeding, the primary variable affected by resistance exercise is MPS, which is stimulated 40–100% over and above resting levels with exercise [6,10–13]. Although MPB also rises with resistance exercise in the fasted state [10,11], the provision of amino acids [7] or carbohydrate [14–16] completely inhibits this response. We know that for resistance exercise to result in a positive net balance, feeding needs to occur sometime within the few hours following exercise [9,17]. In fact, several studies suggest that provision of protein within the acute period following exercise may be quite important for hypertrophy [18–20]. Recent evidence suggests that the type (i.e. source) of protein consumed may affect the anabolic response to resistance exercise [21–24]. The purpose of this review, therefore, is to examine our current understanding of the role of protein quality in maximizing muscle anabolism.

The importance of protein in supporting postexercise anabolism

Resistance exercise performed in the absence of an increase in amino acid availability improves net muscle protein balance, but there remains a net loss of muscle protein [10]. However, when resistance exercise is accompanied by an increased availability of amino acids, the result is a synergistic stimulation of protein synthesis, greater than that achieved by either stimulus alone [7]. Moreover, this increase in protein synthesis occurs concomitantly without increases in protein breakdown, which is the usual response to resistance exercise when fasted, thus resulting in a net positive protein balance, which over time will lead to muscle mass accretion [7,25]. Such an effect has been demonstrated both with the consumption of crystalline amino acids [7,25,26] as well as whole proteins [19,27–29,30••].

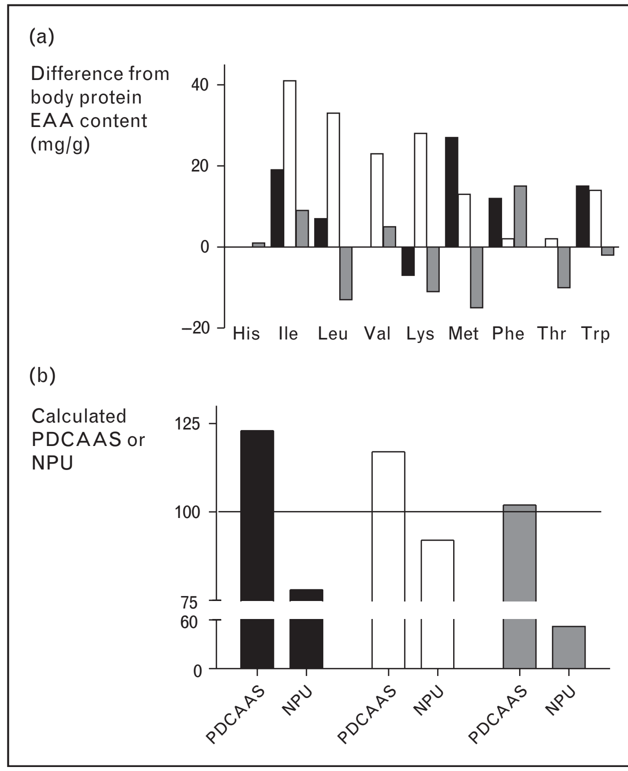
Some evidence indicates that early provision of nutrients (specifically protein) is important [31••,32–34], or perhaps necessary [35,36], for promoting muscle hypertrophy. Most evidence indicates that the period immediately postexercise (or at least within approximately 2–3 h) produces a muscle environment that favors augmented protein synthesis over and above that provided by amino acids/protein alone [37–39]. Chronic studies support this notion showing that individuals receiving protein in the postexercise period gain greater lean mass compared with those receiving nothing or simply energy as carbohydrate [31••,32–36].

Muscle protein synthesis also appears to respond in a dose-dependent manner to essential amino acid consumption [26,40–42]. An excellent study by Cuthbertson *et al.* [43] demonstrated that a dose of essential amino acids of approximately 10 g maximally stimulates rates of both myofibrillar and sarcoplasmic protein synthesis at rest. We have recently found that 20 g of protein (or approximately 8.5 g of essential amino acids) also maximally stimulates myofibrillar protein synthesis after resistance exercise, with minimal increases in amino acid oxidation (M. Sheffield-Moore *et al.*, unpublished observation).

Differences in 'high-quality' proteins and the support of muscle anabolism

Ingestion of milk, whey, casein and soy following resistance exercise has been reported to stimulate MPS when consumed in isolation or in liquid supplements [19,27,29,44]. It appears from a series of studies that not all 'high-quality' proteins are equal in how they are digested and how this variable affects protein retention [21–24]. Instead, despite high protein quality (Fig. 1) [45–50], the digestion rate of proteins (e.g. whey and casein as well as soy protein) influences protein turnover and how amino acids support protein synthesis in central versus peripheral tissues [51–54].

Figure 1 Comparison of the amino acid contents of casein, whey, and soy protein to body protein (a) and comparison of the same proteins by their respective protein digestibility corrected amino acid scores and net protein utilization (b)



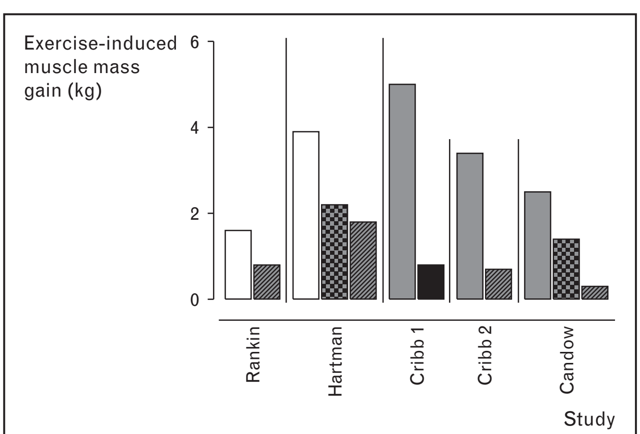
(a) Differences between human body protein essential amino acid content [45] and the essential amino acid (EAA) content and that of whey, casein and soy. Data from acid hydrolysis carried out as described in Wilkinson *et al.* [30••] of commercially available micellar casein, isolated whey proteins, isolated soy protein. All values are in mg amino acids/g protein. (b) Protein digestibility corrected amino acid score (PDCAAS) and net protein utilization (NPU – proportion of protein intake that is retained) for isolated casein, whey, and soy. The EAA pattern used in the PDCAAS (line of truncation shown at 100) scores was taken from the Dietary References Intakes for protein with protein digestibility of 99 for whey and casein and 97 for soy [46]. Whey and casein PDCAAS from reference [47] and soy PDCASS calculated according to reference [48]. NPU for casein and whey from reference [49]. NPU for soy from reference [50]. ■, casein; □, whey; ▩, soy.

For example, ingestion of full fat whole milk (3.5% milk fat) postexercise resulted in greater amino acid net uptake across an exercised leg, suggesting whole milk is superior to fat-free fluid milk in its ability to build muscle after exercise [27]. Such an effect could be because of the difference in energy content or to how whole milk might be digested differently as versus fat-free milk. When comparing consumption of fat-free fluid milk matched with a soy protein beverage, we observed a greater nitrogen balance and muscle protein synthetic response following weightlifting [30••]. We hypothesized that these findings [30••] resulted because of minor differences in amino acid composition and possibly protein digestion rate. Data showing how milk and soy proteins are partitioned for use between splanchnic and peripheral (i.e. muscle) tissues [53,54] have shown that soy proteins are preferentially directed toward splanchnic protein synthesis and are converted to urea to a greater extent than milk proteins.

Resistance exercise results in a greater stimulation of MPS, in particular myofibrillar protein synthesis, in the fed state and attenuates skeletal muscle losses in the fasted state [55]. Thus, the short-term acute response should predict, for a large part, responses in the long-term with chronic resistance training and nutritional interventions [55]. Indeed, acute changes in muscle protein balance following ingestion of milk or equivalent soy protein [30••] qualitatively predicted long-term muscle mass gains [31••]. It is worth noting that the persons' diets were controlled only for 2 h prior to and following the resistance exercise bout, which appears to be an important time in which to obtain some protein to take advantage of the exercise-induced 'turning on' of the protein synthetic machinery [37,38,56,57].

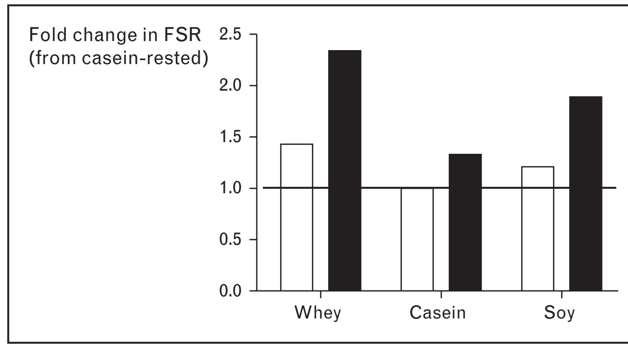
Differences in lean mass gains with resistance training have also been observed when comparing other apparently complete and high-quality protein sources such as whey and soy [58]. When we examine the findings of these studies collectively, the results appear to indicate that milk proteins are superior to soy in supporting muscle mass accretion with resistance training and that both are superior to carbohydrate (i.e. energy) alone

Figure 2 Resistance training-induced changes in lean mass in studies of patients receiving supplemental protein sources – soy, whey, or casein or an energy-matched carbohydrate drink



Values are presented as the absolute exercise-induced mean gain (±SD) in lean mass. The studies included are those of Rankin *et al.* [59], Hartman *et al.* [31••], Cribb *et al.* [60,61], Candow *et al.* [58]. □, milk; ■, whey; ■, casein; ▩, soy; ▨, CHO.

Figure 3 Mixed muscle protein fractional synthetic rate following whey, casein, or soy consumption at rest and after resistance exercise



Data are shown as fold changes from the lowest value (casein-rest) obtained (J.E. Tang *et al.*, unpublished observation). □, rest; ■, exercise.

(Fig. 2) [59–61]. Resistance exercise also appears to augment the effect of whey protein in supporting lean mass gains when compared to either casein or milk. We have recently collected acute data using a unilateral model in which the response of MPS was examined both at rest and following resistance exercise after ingestion of whey hydrolysate, soy isolate and micellar casein (J.E. Tang *et al.*, unpublished observation). Figure 3 shows the responses of MPS as a percentage of the lowest response we observed, which was the response of MPS at rest following ingestion of casein. Our data suggest that the more rapid appearance of amino acids in the circulation following whey protein ingestion, which may normally be oxidized or deaminated before being directed toward urea synthesis, are instead taken up and used effectively by muscle tissues for protein synthesis when combined with the anabolic stimulus of resistance exercise. A critical factor in turning on the protein synthetic machinery when a rapid feeding-induced rise in amino acids occurs is likely to be the appearance of leucine, which might serve to explain our results of a greater rise in MPS both at rest and following resistance exercise. This model would suggest that the protein synthetic machinery is not turned on until a critical leucine or leucine trigger point concentration is reached.

Protein feeding and muscle anabolism with aging

By the age of 40, almost all humans show some decline in total muscle mass, albeit at a slow rate (for reviews see [62–64]). Termed sarcopenia of aging, this involuntary loss of muscle mass results in reductions in muscle strength and power that are associated with reduced mobility [65,66] as well as an increased risk for falls [66] and associated morbidity. There is an increasing realization, however, that preservation of skeletal muscle mass has consequences that extend beyond preservation of ambulation. Skeletal muscle is the largest single site for blood glucose disposal and lipid oxidation in the postprandial state [67] and is, aside from the liver, the most important metabolic tissue contributing to thermogenesis [68]. As a result, a reduction in metabolically active skeletal muscle mass (i.e. high oxidative potential and capacity for carbohydrate and fat storage) can lead to an increased risk for cardiovascular disease, diabetes and obesity [69–71]. Thus, its preservation with aging should be a goal of primary importance.

The underlying cause of aging-induced sarcopenia is unclear; some have attributed it to a lower basal rate of protein synthesis [12,72,73] or increased rate of protein breakdown [74], whereas others have reported no difference in the rates of synthesis and breakdown between the young and old [75,76], but a diminished ability to use ingested amino acids for protein synthesis [43,77]. Why sarcopenia occurs may be less important, however, than the knowledge that elderly persons retain the capacity to increase their muscle mass in response to resistance exercise (for reviews see [78–80]). This finding suggests that one can rescue the sarcopenic phenotype with the use of appropriate exercise and feeding strategies.

Several studies have identified a so-called anabolic resistance of older muscle to amino acids [23,24,81]. When sufficient amino acids, or possibly sufficient leucine, are provided, other investigations, however, have noted no difference between young and old [81–83]. Thus, it appears that elderly muscle can increase MPS in response to feeding, so long as adequate amino acids are available. If a threshold of leucine is the 'trigger' for protein synthesis in muscle, this may explain the observations of Dangin *et al.* [24]. These researchers showed that the paradigm of how 'fast' and 'slow' proteins affect protein anabolism, however, differs in the elderly whereby whey proteins appear to be more effective in stimulating whole-body protein synthesis as opposed to casein [24]. In addition to digestion rate, the mechanism by which whey more effectively promotes protein gain than casein in the elderly may also be related to the slightly higher leucine content of whey (Fig. 1) [84,85], especially if the 'leucine trigger' has a higher set-point for older individuals. We also speculate that the ability of whey-derived peptide components to stimulate protein synthesis by suppressing inflammation [86,87] or possibly activation of satellite cells in aged muscle [88,89] may also be important.

Conclusion

Feeding and resistance exercise independently stimulate MPS. Ingesting protein after resistance exercise, however, is crucial to maximizing postexercise anabolism. Several studies have indicated that high-quality proteins such as milk, whey, casein and soy can support MPS. Differences in the rate of digestion of these proteins can modulate the MPS response both after an acute bout of resistance exercise and following long-term training. Such differences may be related to the macronutrient content and matrix of the protein (i.e. fat-free versus whole milk) or inherent properties of the protein itself (e.g. whey versus casein) that affect postprandial protein kinetics. An important component in determining the response of MPS may well be the leucine content of the protein, particularly for the elderly. When seeking to maximize protein, it appears milk proteins and their isolated forms, whey and casein, offer an anabolic advantage over soy proteins in promoting muscle hypertrophy (Fig. 2).

References and recommended reading

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- •• of outstanding interest

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