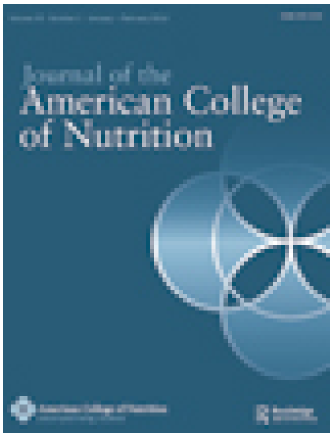

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The Role of Milk- and Soy-Based Protein in Support of Muscle Protein Synthesis and Muscle Protein Accretion in Young and Elderly Persons

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Review

The Role of Milk- and Soy-Based Protein in Support of Muscle Protein Synthesis and Muscle Protein Accretion in Young and Elderly Persons

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Key words: whey, casein, hypertrophy, anabolism, skeletal muscle

The balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB) is dependent on protein consumption and the accompanying hyperaminoacidemia, which stimulates a marked rise in MPS and mild suppression of MPB. In the fasting state, however, MPS declines sharply and MPB is increased slightly. Ultimately, the balance between MPS and MPB determines the net rate of muscle growth. Accretion of new muscle mass beyond that of normal growth can occur following periods of intense resistance exercise. Such muscle accretion is an often sought-after goal of athletes. There needs to be, however, an increased appreciation of the role that preservation of muscle can play in offsetting morbidities associated with the sarcopenia of aging, such as type 2 diabetes and declines in metabolic rate that can lead to fat mass accumulation followed by the onset or progression of obesity. Emerging evidence shows that consumption of different types of proteins can have different stimulatory effects on the amplitude and possibly duration that MPS is elevated after feeding; this may be particularly significant after resistance exercise. This effect may be due to differences in the fundamental amino acid composition of the protein (i.e., its amino acid score) and its rate of digestion. Milk proteins, specifically casein and whey, are the highest quality proteins and are quite different in terms of their rates of digestion and absorption. New data suggest that whey protein is better able to support MPS than is soy protein, a finding that may explain the greater ability of whey protein to support greater net muscle mass gains with resistance exercise. This review focuses on evidence showing the differences in responses of MPS, and ultimately muscle protein accretion, to consumption of milk- and soy-based supplemental protein sources in humans.

Key teaching points:

- The normal feeding-induced response to the intake of protein is an elevation of muscle protein synthesis (MPS) and a minor suppression of muscle protein breakdown (MPB) resulting in a positive net protein balance (i.e., MPS $>$ MPB).
- Consumption of complete proteins after high-intensity resistance exercise enhances the response of MPS such that net muscle protein balance is greater than with feeding alone; eventually, the chronic change in muscle net protein balance (i.e., a long-term period of MPS $>$ MPB) results in protein accretion within muscle fibers and eventually fiber/muscle hypertrophy.
- Milk proteins (whey and casein) and soy proteins are nutritionally complete, highly digestible proteins with high amino scores that contain all amino acids in amounts sufficient to support maintenance of all body proteins.
- Whey, casein, and soy ingestion all result in hyperaminoacidemia that can stimulate MPS and ultimately, if consumed in close temporal proximity (before or after) resistance exercise, muscle protein accretion, leading to enhanced hypertrophy.
- Evidence indicates that whey proteins result in greater muscle hypertrophy than soy proteins do and that mixed milk and whey proteins are more effective than simply energy in promoting hypertrophy. The underlying basis for this finding is, at present, unclear but may be due partly to differences in amino acid composition in combination with a partitioning of amino acids toward peripheral (i.e., muscle) versus splanchnic tissues due to differences in rate of digestion.

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INTRODUCTION

The goal of this review is to examine the acute and chronic responses to nutritional provision of supplemental milk- and soy-based protein sources within the context of resistance training, designed specifically to increase muscle protein synthesis (MPS) and muscle mass. Part of the rationale for selecting milk- and soy-based proteins is that much of the data in this area have come from studies in which these proteins were used [1–9]. We freely acknowledge, however, that other high-quality protein sources can stimulate MPS [10], maintain muscle mass [11–13], and underpin muscle protein accretion [14,15]; however, as a focus of this review, we will primarily examine milk- and soy-based proteins because they are often-used supplemental protein sources. Examination of both young and elderly persons is made with the rationale that maximal gains in muscle mass, and potentially strength, in young persons in response to nutrition and resistance training represents a reasonable strategy to mimic in healthy older persons to offset the deleterious consequences of sarcopenia. While much of our knowledge on these topics comes from studies of younger persons, it is still worth recognizing that even older persons in their 10th decade can gain muscle mass with appropriately formulated resistance exercise programs [16,17] and nutritional support [17,18]. Thus, we stress that despite declines in muscle mass with aging, even senescent muscle can respond to resistance exercise and nutrition, likely in a manner much closer to, rather than different from, younger muscle.

In general, humans entering the fifth decade of life begin to experience declines in overall muscle mass, albeit at a slow rate (for review, see [19,20]). This so-called sarcopenia of aging is associated with increased risk for falls [21], an associated morbidity due to hip fractures and complications arising from this, and reduced mobility [21,22]. Wolfe [23] has also pointed to a far less appreciated aspect of skeletal muscle and its decline with aging, which is the role that skeletal muscle can have on morbidities such as cardiovascular disease, diabetes, and obesity. These morbidities are related to the ability of skeletal muscle to oxidize and store blood glucose, which is diminished if muscle mass is not maintained and is of a low ‘‘metabolic’’ quality (i.e., deconditioned). Skeletal muscle is the largest single site for blood glucose disposal and lipid oxidation in the post-prandial state [24] and is, aside from the liver, the most important tissue contributing to thermogenesis [25]. Thus, preservation of skeletal muscle mass is important not only for strength but also for metabolic health, both of which are outcomes of relevance to the aged.

The underlying cause of sarcopenia is unclear and the process is undoubtedly multifactorial. Other than nutrition and physical activity, other contributors to sarcopenia, including hormonal status (for review, see [26,27]) and oxidative stress [28], have been highlighted. Germane to the focus of the current review, however, is that sarcopenia has been said to be caused by a lower basal fasted rate of MPS [29–32] and/or an increased rate of muscle protein breakdown (MPB) [33]. Others have reported that fasted protein synthesis or turnover do not appear to be different between the young and old [34–36]. In addition, other studies suggest that a lower sensitivity to the insulin-induced stimulation of protein synthesis [35] and a reduced sensitivity to amino acid feeding [36,37] could contribute to the age-induced loss of skeletal muscle. Regardless of the mechanism, what is known is that aged muscle responds similarly to acute exercise and feeding in a qualitative, if not quantitative, fashion as young muscle [29,38–42].

Numerous studies have shown that elderly subjects retain the capacity to increase their muscle mass in response to resistance exercise (for reviews, see [19,43]). Thus, as a target of intervention in elderly persons, resistance exercise to increase muscle mass and strength has been widely studied [16,17,19,44,45]. Of relevance to this review, it appears that protein requirements for elderly persons may be elevated [46,47]; as such, many recent studies have focused on which proteins or amino acid mixtures might be able to support an enhanced rate of MPS, which, in our opinion, is the main variable affecting muscle protein balance in healthy elderly persons free of chronic disease [35,48–51]. While low-intensity activities of daily living, such as walking, improve MPS and insulin-sensitivity in the elderly [52] and, as such, would likely benefit from adequate post-activity protein ingestion to stimulate MPS [53–55], higher-intensity load-bearing exercise, such as resistance training, is required to maintain muscle mass with age [56]. The importance of protein ingestion has been highlighted for elderly persons in the promotion of hypertrophy stimulated by resistance exercise [18]. In fact, we propose that in aged individuals in whom an anabolic resistance to amino acids and/or insulin may be present [35,36], factors such as protein source, timing of ingestion (relative to exercise), and quantity of protein to ingest may be of greater importance for maintaining (i.e., offsetting a sarcopenia decline in muscle mass) and even accruing muscle mass than it is in younger persons.

NUTRITIONAL INFLUENCES ON MUSCLE PROTEIN TURNOVER

A number of recent reviews exist on the topic of nutrition and its effect on muscle protein turnover [57–60], so the present overview is brief. If the balance of MPS and MPB is considered on a daily basis, the switch from fed to post-prandial to fasted states results in changes in protein synthesis that are 10- to 20-fold greater than any measured change in protein breakdown [48,60–63]. Thus, changes in MPS are paramount in determining changes in net muscle protein balance. In fact, in a young, healthy adult, muscle protein balance over 24 hours is driven by changes in MPS and is relatively unaffected by changes in MPB [64]. Protein synthesis is highly influenced by the provision of essential amino acids (EAA, particularly leucine) and carbohydrate (via insulin) [48,63,65–70]. While there may be changes in skeletal muscle gene expression that come under nutritional/contractile/hormonal influence [71–73], these changes cannot ultimately influence the muscle phenotype without a concurrent change in MPS.

The role of insulin in the stimulation of protein synthesis is complex. In humans, at low physiologic concentrations, insulin is supportive and mildly stimulatory for protein synthesis [74,75]; however, this stimulation requires the availability of amino acids [61,74,75]. When insulin is elevated to very high-end normal, there is no further stimulation of MPS, indicating that a ceiling exists [75]. While insulin may play a permissive rather than stimulatory role compared to amino acids in stimulating protein synthesis, it has been documented to be a strong suppressor of MPB [75–77] and, in this way, may help to support an anabolic environment in adults.

THE INFLUENCE OF RESISTANCE EXERCISE ON MUSCLE PROTEIN TURNOVER

For a more detailed discussion of this topic, the reader is referred to a series of reviews on the topic of regulation of MPS with exercise [57–59,78,79]. The main point to be made in the context of this discussion is that the primary variable affected by exercise (as in the case of amino acid supplementation) is MPS, which is stimulated 40–100% over and above resting levels with exercise [29,80–83]. While MPB also rises to a small degree (10–25%) with resistance exercise in the fasted state [80,82,83], this rise is completely suppressed with the provision of amino acids [62] or carbohydrates [76]. The synergy between feeding and resistance exercise is not fully understood but is likely rooted in the activation of signaling pathways that switch on MPS and/or inhibit MPB. Recent studies have reported that resistance exercise stimulates the same set of signaling proteins (protein kinase b/akt, mTOR, $p70^{S6k}$, and rpS6; see Fig. 2) that are activated with feeding to initiate protein synthesis [84–86]. Clearly, we know that for resistance exercise to result in a positive net balance, feeding needs to occur sometime in close temporal proximity to the exercise (see discussion below).

INTERACTION OF NUTRITION AND RESISTANCE EXERCISE: ACUTE STUDIES

Fig. 1 shows a schematic diagram of how muscle protein accretion and loss occur in response to normal feeding and with the addition of resistance exercise. In the fasted state, we are in a negative protein balance such that we are losing protein mass. Feeding results in a stimulation of MPS that offsets our fasted state losses. When we consider the effect of resistance exercise, the result is essentially a greater stimulation of MPS in the fed state and a potential attenuation of skeletal muscle loss in the fasted state. Assuming that the acute response results in longer-term responses, studies of acute differences in protein accretion should predict what happens in the long-term with chronic resistance training and different nutritional interventions. In support of the proposed model (Fig. 1), we have recently found that acute changes in muscle protein balance following ingestion of milk or equivalent soy protein [87] qualitatively predicted long-term muscle mass gains in young, male, novice weight-lifters [7]. Thus, acute studies of protein turnover appear to predict, at least in young males, what would happen in the longer-term. Studies in women and older subjects are needed to extend our model to these populations.

Acute studies have manipulated variables such as amino acid composition [69,88], carbohydrate content [66–68,76], training status [83,89], timing of delivery [68,70,90], dose of amino acids [66,67,69], and more recently, the type of protein consumed [87,90–92]. Many of these studies [48,63,65–70] have exploited the experimental flexibility of ingestion of crystalline amino acids in various doses, with and without carbohydrates. The understanding of how protein synthesis kinetics are affected by exercise, amino acids, and carbohydrate has been advanced substantially as a result of these studies [48,63,65–70]. A valid question, however, is how the results of studies in which amino acids have been manipulated compare to what happens with whole intact proteins. For example, studies examining pre- versus postexercise ingestion of crystalline amino acids as compared to whey protein ingestion do not agree with respect to the protein accretion taking place after resistance exercise [70,90]. An important difference between crystalline amino acids and intact proteins exists in the rate of digestion. For instance, a series of studies [50,93–95] show that the digestion rate of proteins is an independent variable influencing protein kinetics and the partitioning of amino acids between splanchnic and peripheral (i.e., non-splanchnic) tissues [96–102]. Since most meals are based on the ingestion of whole proteins and not crystalline amino acids, results have shown that different proteins have unique impacts on protein kinetics of different tissues such as liver and muscle. In particular, these studies [96–102] may have relevant implications for athletes who report consuming a number of protein sources, some supplemental, that are mostly milk-protein based (i.e., whey and/or casein isolates/concentrates) [103–105]. In addition, the response of aged subjects to consumption of different sources of protein differs somewhat from that of young subjects, as whey protein appears to be

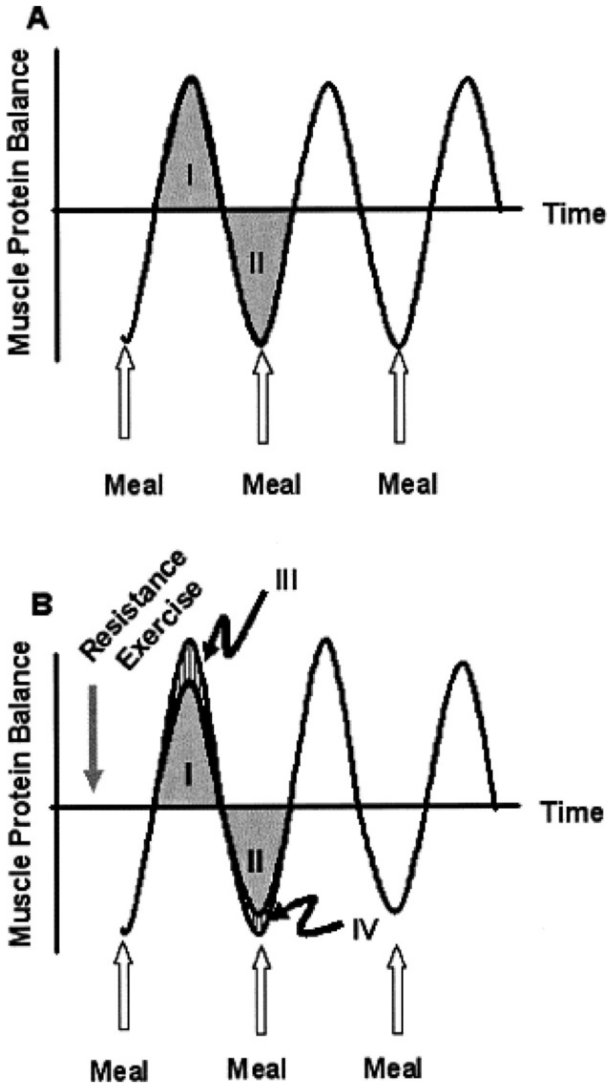

Fig. 1. (A) Normal fed-state gains and fasted-state losses in skeletal muscle protein balance (synthesis minus breakdown). The area under the curve in the fed state (I) would be equivalent to the fasted loss area under the curve (II); hence, skeletal muscle mass is maintained by feeding. (B) Fed-state gains and fasted-state losses in skeletal muscle protein balance with performance of resistance exercise. In this scenario, fasted-state gains are enhanced by an amount equivalent to the stimulation of protein synthesis brought about by exercise (III). In addition, fasted-state losses appear to be less (IV) due to persistent stimulation of protein synthesis in the fasted state. Taken from [57], with permission.

more effective in acutely stimulating protein synthesis in older subjects as compared to casein [95]; clearly, these data may have implications for gains in muscle mass due to exercise to offset sarcopenia.

The impact of protein digestibility on determining the extent of muscle anabolism after exercise can be observed by the work of Elliot and colleagues [91], who examined the ability of fat-free fluid milk (237 ml, 377 kJ, 8.8 g protein), whole milk (237 ml, 627 kJ, 8.0 g protein), and an isoenergetic amount (to the whole milk) of fat-free milk (393 ml, 626 kJ, 14.5 g protein) to support postexercise muscle anabolism. It was found that whole milk resulted in greater threonine and a trend for greater phenylalanine net uptake across an exercised leg, suggesting that whole milk enhances the ability to build muscle after exercise to a greater degree than fat-free fluid milk. These results are likely not due to the fat content of the milk as an energy source since fatty acids do not influence protein turnover [106]. More likely is the fact that the additional fat in milk means a different matrix affecting digestive rates, which may influence protein retention [97,100,102]. Thus, the long-term consequences of consuming isonitrogenous quantities of fat-free versus whole milk would suggest that whole milk may result in greater protein accretion with training in the young.

Acute studies in which subjects have consumed whole milk proteins (as fluid milk or as whey and casein) and soy protein [87,91], both in isolation or in liquid supplements [89,90,92], have all shown that these proteins are able to support muscle protein accretion following resistance exercise. However, there are data to suggest that not all proteins are created equal in their ability to support muscle protein accretion after resistance exercise [87]. When comparing consumption of fat-free fluid milk (500 ml, 745 kJ, 18.2 g protein) with an isonitrogenous, isoenergetic, and macronutrient composition-matched amount of a soy protein beverage, Wilkinson et al. [87] recently found a greater net muscle protein balance and fractional synthetic rate after exercise with milk ingestion in young, healthy men. It was hypothesized that these findings [87] resulted from differences in protein digestion rate that affected the aminoacidemia and subsequently impacted muscle protein anabolism. This is supported by data from studies documenting differences in how milk and soy proteins are partitioned for use between splanchnic and peripheral (i.e., muscle) tissues [97,100]; specifically, soy proteins support greater splanchnic protein synthesis and are converted to urea to a greater extent than are milk proteins. Why exactly aminoacidemia after milk protein ingestion would be directed toward the periphery (making these amino acids more available for MPS) is not yet known. However, studies to date suggest that it is the digestion rate of the proteins that modulates the amino acid rate of appearance, which is an independent modulator of the metabolic fate of ingested amino acids [97,100].

INTERACTION OF NUTRITION AND RESISTANCE EXERCISE: CHRONIC STUDIES

The resistance exercise–induced stimulation of MPS is at least 48 hours in duration [82]. Hence, resistance exercise and

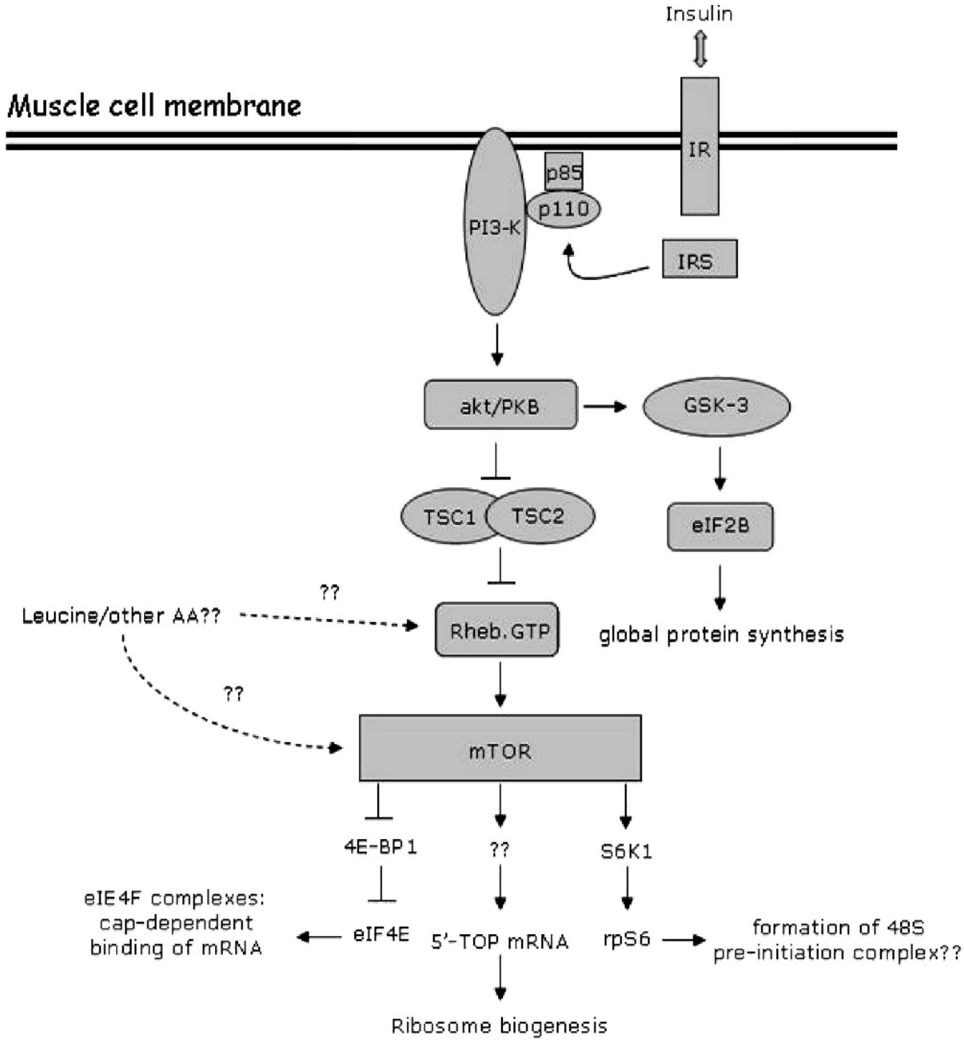

Fig. 2. Schematic representation of signal pathways for activation of mTOR, leading to ribosomal assembly, biogenesis, and global protein synthesis by both amino acids (leucine) and insulin. Adapted from [127].

protein ingestion should interact to synergistically stimulate protein synthesis at any time within 48 hours following exercise cessation and ultimately lead to protein accretion. However, evidence exists to support the contention that consumption of protein (or amino acids), and not simply energy as carbohydrate, in close temporal proximity, both before and/or after, resistance exercise is important to support greater hypertrophy [7,18,107–109]. These chronic training studies suggest that the ''window'' during which consumption of protein or amino acids should be consumed is likely 30–45 minutes before and/or <2 hours after exercise in order to support greater increases in lean body mass and muscle hypertrophy in younger individuals. With respect to the elderly, it is possible that the ''window'' for nutrition may even be as little as 1 hour after exercise [18]. It is notable that one acute study has shown that a full anabolic response in young individuals can be mounted by skeletal muscle at both 1 hour and 3 hours postexercise with crystalline amino acid consumption [68]; however, it has not been investigated whether this feeding pattern would translate into similar increases in muscle hypertrophy with training. Therefore, in order to support greater hypertrophy with resistance training at any age it would be beneficial to consume a source of protein within 1 hour after exercise cessation.

PROTEIN-DIGESTIBILITY CORRECTED AMINO ACID SCORES (PDCAAS): POTENTIAL FLAWS

Recent evidence suggests that even within what are considered to be nutritionally adequate and complete proteins (Table 1), the matched or equivalent consumption of these proteins can have differential impacts on muscle hypertrophy.

Table 1. The Amino Acid Composition (mg Amino Acids/g Protein), Calculated PDCAAS Score, and NPU for Milk-Based and Soy Protein

Amino Acid Content (mg/g)	Milk Solids (nonfat)[a]	Casein[b]	Whey[c]	Soy[d]	Body Protein[e]
Histidine	20	27	20	28	27
Isoleucine	63	54	76	44	35
Leucine	77	82	108	62	75
Lysine	54	73	101	62	73
Methionine (+ Cys)	33	28	48	20	35
Phenylalanine (+ Tyr)	48	100	67	88	73
Threonine	37	54	44	32	42
Tryptophan	15	12	26	10	12
Valine	55	64	72	54	49
PDCAAS	121[f]	123[g]	115[g]	104[h]	
NPU	86[g]	78[g]	92[g]	72[i]	

All values are in mg amino acids/g protein. NPU = net protein utilization (proportion of protein intake that is retained), PDCAAS = protein digestibility corrected amino acid score. The indispensable amino acid pattern used in the PDCAAS scores was taken from the Dietary References Intakes for protein with protein digestibilities of 95 for milk proteins, 99 for whey and casein, and 97 for soy [122]. Data from acid hydrolysis carried out as described in Wilkinson et al. [87] of commercially available:
[a] Skim milk powder.
[b] Micellar casein.
[c] Isolated whey proteins.
[d] Isolated soy protein.
[e] From reference [123].
[f] From reference [111].
[g] From reference [124].
[h] Calculated according to reference [125].
[i] Estimated based on net postprandial protein utilization and reported nutritional values of NPU for soy protein from references [97,126].

These findings are nonintuitive since these proteins, according to PDCAAS, would be considered as complete high-quality proteins able to fully support a maximal protein synthetic response. The concept of the PDCAAS score and its ''artificial'' truncation at 100 for all proteins has been challenged, however, and it may be that under certain circumstances proteins that are by arbitrary standards ''equivalent'' are, in fact, not [110–112]. For example, in aged humans it has been shown that the response of protein synthesis is impaired in response to feeding [94,95]; this anabolic ''resistance'' to amino acids is somewhat akin to insulin resistance in that for any given dose of amino acids, aged skeletal muscle does not accrue the same amount of muscle protein. More importantly, however, is the idea that higher-quality, so-called ''fast'' proteins (whey) appear to be more beneficial in stimulating protein synthesis than ''slow'' proteins (casein) in the elderly, despite almost-equivalent PDCAAS [94,95]. These findings [94,95] demonstrate that factors other than the PDCAAS play a role in making whey protein more anabolic in the elderly than casein protein. Such factors include, but are not limited to, higher leucine content (Table 1) and/or the ability of other whey-derived peptide components to stimulate protein synthesis in aged muscle.

Highlighting another shortcoming of the truncated PDCAAS, a recent paper showed that soy protein was required to be supplemented with exogenous branched-chain amino acids to result in altered inter-organ amino acid flux that favored muscle protein anabolism in aged and diseased patient populations [113]. Moreover, the findings of Engelen et al. [113] beg the question of whether or not truncating the PDCAAS at 100, which can lead to small, likely sub-clinical but potentially physiologically relevant ''deficiencies'' in amino acids, could in turn alter muscle protein accretion in populations such as the elderly and those with chronic disease. In fact, our working hypothesis is that if any tissue is going to pay the ''price'' for consumption of predominantly lower-quality proteins, it is skeletal muscle, the body's largest reservoir of amino acids.

Under conditions of increased ''anabolic drive,'' such as after the performance of resistance exercise, it may be that subtle differences in protein digestion rates, differences in branched-chain amino acid content, alone or in combination with differences in PDCAAS, can impact the ability of the protein to support a full (amplitude and duration) synthetic response, particularly in skeletal muscle. We have recently compared the impact of soy and milk ingestion on postexercise MPS [87]. Our findings showed that ingestion of fluid skim milk induced a greater net amino acid uptake and protein synthesis in exercised muscle than did isolated soy protein [87]. These acute differences have recently been shown to be maintained in a longer-term (12-week) training study [7]. Importantly, however, the greater training-induced increases in lean muscle seen in the milk-supplemented group did not translate into significantly greater strength increases [7]. This may be due to a lack of statistical power in combination with the high variability of determining strength using voluntary single repetition maximum. Clearly, there is room for more work to be done in establishing how acute studies are predictive of long-term gains in lean mass and muscle strength.

Other studies have also shown different gains in lean mass with different, although apparently complete and high quality, protein sources such as whey and soy [1–9,114,115]. In an effort to determine the efficacy of milk-based as well as soy-based protein and carbohydrate (i.e., energy) in promoting lean mass gains, we reviewed a number of studies that had as their goal the promotion of hypertrophy through protein supplementation in combination with resistance exercise [1–9,114,115]. When the lean mass gains of these studies are compiled, including muscle mass gains in both men and women (albeit fewer women), the overall gain in lean mass with ~11 weeks of resistance training is 1.9 ± 0.6 kg. Gains in lean mass induced by supplements containing milk proteins, whey, soy, or carbohydrate (i.e., placebo) were then averaged and compared to each other as well as the overall mean gain in lean mass. Taken together, the summarized results (Fig. 3) suggest that whey protein is more effective than soy and simply energy (as carbohydrate) in supporting muscle mass accretion with resistance training and that milk proteins (including whey) are better than carbohydrate alone. The data from these studies are generated primarily from younger men and so the concepts may not be directly transferable to the aged population. However, insofar as stimulation of MPS is concerned, it would appear that protein sources higher in leucine and having a full complement would be of greater benefit [38,39,94].

LEUCINE AS A REGULATOR OF MPS

Of the proteins studied and/or compared directly, whey is highest in the branched-chain amino acids, in particular, leucine. As shown in Table 1, the leucine content of milk proteins is higher than that of soy. This difference in leucine content may have an important mediating influence in maintaining and possibly increasing muscle mass with age since leucine, in and of itself, is able to stimulate the activation of proteins that regulate MPS (reviewed in [116]). In fact, Rieu et al. [117] showed that leucine-supplemented meals (0.4 g protein/kg/5 h plus 0.052 g leucine/kg/5 h) supported a greater rate of MPS in the elderly at rest than nonsupplemented meals. With respect to resistance exercise, acute studies in humans have shown that leucine co-ingestion with carbohydrate and protein stimulated a similar rise in postexercise MPS between young and elderly men [39]. However, when comparing within the elderly, it was demonstrated that addition of leucine to a protein-carbohydrate drink had no additional benefit on postexercise anabolism [118]. We speculate that this result [118] was due to the fact that the amount of protein consumed during the protocol (almost 1 g/kg/6 h) was more than sufficient to provide the amount of EAA, and likely leucine, to maximally stimulate protein synthesis in the elderly. Comparing the results of the 2 studies [117,118], it may be that the divergent ability of leucine to augment protein synthesis is due to the protein dose ingested such that with higher protein doses, leucine intake is already sufficient to maximally activate the regulatory proteins for MPS.

DOSE-RESPONSE

An important issue that has received less attention is the relationship between dose of ingested protein and the response of MPS. Cuthbertson et al. [36] has published what has to be considered one of the best studies addressing this issue, in which they showed that in younger subjects, 10 g of crystalline EAA resulted in a maximal stimulation of myofibrillar MPS (i.e., more than 5 g and equivalent to 20 g). Maximal stimulation of MPS in older subjects was also achieved at a dose of 10 g of EAA, but the response was much lower than that seen in young persons, indicating an age-related ‘‘resistance’’ to amino acid–mediated stimulation of MPS. The authors [36] reported that this amino acid resistance was due to signaling defects in aged skeletal muscle; namely, a reduced phosphorylation of mammalian target of rapamycin (mTOR) and p70^{S6k}. Assuming that the dose of EAA at which MPS is maximally stimulated can be translated into dietary protein, 10 g of EAA would translate into ~25 g of whey or casein proteins (each ~42–45% by composition EAA [87]). Given the population variance in determining fractional synthetic rate (~15%), it is unlikely that incrementally larger doses of protein above those determined by Cuthbertson et al. [36] to maximally stimulate MPS would be beneficial, especially considering that large doses would also stimulate urea production and irreversible amino acid oxidation [119,120]. With respect to postexercise nutrient ingestion, preliminary data from our dose-response study following resistance exercise indicates that only 20 g of isolated egg protein (~41% by content essential amino acids) maximally stimulates MPS [121]. Hence, to obtain a long-term anabolic benefit, we speculate that single doses of protein need not exceed 20–25 g to maximally stimulate MPS, either at rest or after resistance exercise [36]. At a minimal effective dose, increments in MPS over and above basal or postexercise fasted values can be seen after ingestion of as little as 3–5 g of EAA (equivalent to 8–10 g of whey/casein and 10–12 g of soy) [36,65,67]. However, key long-term studies with differing doses of proteins that monitor meaningful outcomes, such as changes in lean mass, strength, and metabolic indices, would be required to give a definitive answer to the question of a minimally effective dose of protein that would not contribute

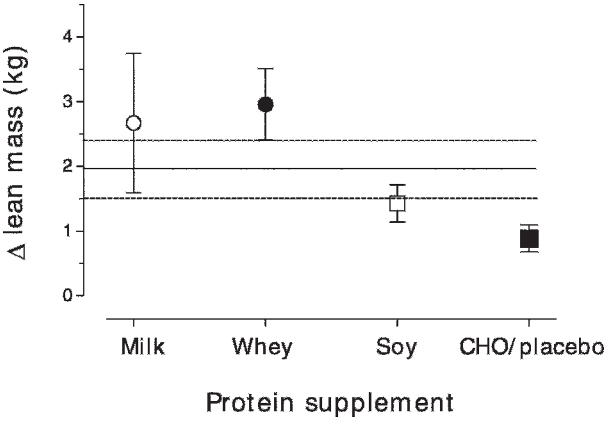

Fig. 3. Resistance training–induced changes in lean mass in studies of subjects receiving supplemental protein sources. A total of 9 studies [1–9] are incorporated (n = 241 subjects for all studies; n = 223 men and 18 women) into the figure with protein supplements of either fluid milk (3 studies; n = 42 total subjects), whey protein (8 studies; n = 91 total subjects), isolated soy protein (3 studies; n = 51 total subjects), or carbohydrate (7 studies; n = 67 total subjects). Studies in which other components were included in the supplement (i.e., creatine or crystalline amino acids) are omitted from this analysis unless these compounds were present in all supplements, in addition to the protein source itself. All studies were at least 8 weeks in duration and up to as long as 16 weeks (mean 11.2 weeks). Mean gains in muscle mass as a result of resistance training and protein supplementation were as follows (means ± SD): milk = 2.7 ± 1.3 kg (range, 1.9–3.9 kg); whey = 2.9 ± 1.6 kg (range, 0.2–5 kg); soy = 1.4 ± 0.6 (range, 1.5–2.0 kg); and carbohydrate (CHO)/placebo = 0.9 ± 0.6 kg (range, 0.3–1.8 kg). The solid line represents the mean change in lean body mass in all of the studies with its accompanying 95% confidence limits (dashed lines).

to excessive oxidation or urea formation (i.e., consuming ''excess'' amino acids).

CONCLUSION

Intact proteins, when ingested, result in systemic hyperaminoacidemia that supports MPS. With the added stimulus of resistance exercise, MPS is stimulated even further than with feeding, which, over time, results in protein accretion and can lead to muscle hypertrophy. There are inherent differences in amino acid composition, beyond those reflected by the PDCAAS, and also in how proteins are digested, that appear to have an impact on post-prandial protein kinetics. The consequences of the differences in protein digestion, possibly with some small but important differences in PDCAAS or amino acid score, appear to influence how muscle protein is accrued with resistance exercise. Thus, while milk and soy proteins appear to be better than energy alone (as carbohydrate) in promoting hypertrophy, the data in total suggest that whey supports muscle hypertrophy most effectively in young adults (Fig. 3). As we have stated, protein ingestion in close temporal proximity to exercise has been shown to be critical in the elderly [18]. The anabolic resistance to amino acids and/or insulin that appears to exist in aged individuals [35,36] likely makes factors such as protein source [94], timing of ingestion (relative to exercise), and quantity of protein to ingest of greater relevance in offsetting sarcopenic declines and gaining muscle mass than in younger persons. Further studies in the elderly are needed to determine whether the responses identified in the young translate to improved maintenance of muscle mass with age.

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