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Skeletal muscle protein balance and metabolism in the elderly

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Abstract

The loss of lean muscle mass occurring with advancing age is termed sarcopenia. This condition often leads to a concomitant loss of strength, increased frailty and risk of falls and an overall loss of functional independence in the elderly. Muscle protein metabolism is a dynamic process characterized by the balance between the synthesis and breakdown of muscle proteins. A disturbance of this equilibrium can lead to the loss of muscle mass, and a perturbation of muscle protein turnover with aging has been proposed to play a role in the development of sarcopenia. However, basal muscle protein synthesis and breakdown rates do not differ between young and old adults, which has led to the hypothesis that older adults are resistant to anabolic stimuli. In support of this hypothesis, older adults have either no response or a blunted response to nutrients, insulin and resistance exercise, and this anabolic resistance is likely a key factor in the loss of skeletal muscle mass with aging. Recent studies have investigated potential interventions to overcome this anabolic resistance. In particular, combining resistance exercise with essential amino acid supplementation restores the muscle protein anabolic response in older men. The novel rehabilitation technique of performing light resistance exercise during blood flow restriction was also successful in overcoming the anabolic resistance to exercise. Future research is needed to determine whether these novel interventions will be successful in preventing sarcopenia and improving muscle strength and function in older adults.

Keywords

aging; FSR; mTOR; exercise; nutrition; sarcopenia

INTRODUCTION

With the worldwide population of individuals over 60 years of age expected to triple in the next fifty years, a greater emphasis has been placed on research concerning the aging process and the many physiological changes that occur with advancing age. The rising age of our global population will have a significant impact on health care systems and maintaining good health during aging is necessary not only to prevent many chronic diseases

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but also to remain independent. A pivotal factor in the ability to remain healthy and functionally independent is the capacity to preserve skeletal muscle mass and strength. A progressive loss of muscle mass often observed with aging is termed sarcopenia [1–4]. This loss of lean mass is accompanied by a concomitant loss of muscular strength [5] which can lead to a greater chance of disability and a loss of functionality in older individuals [6–12]. A recent study by Ruiz et al. demonstrated that all cause, as well as cancer based, mortality was lowest for men in the highest tertile of strength [13]. On a muscle-specific level, sarcopenia is characterized by muscle fiber necrosis, grouping of fiber types, atrophy of type II muscle fibers and a loss of satellite cell content in type II fibers [14–21]. Another consequence of aging on skeletal muscle is reduced muscle specific and whole body oxidative capacity [4,22]. These changes place older individuals at a greater risk of developing chronic diseases such as insulin resistance, hyperlipidemia and hypertension.

The physiological changes that occur with aging are fairly well characterized, yet a basic understanding of the underlying mechanisms driving these changes is still elusive. Greater knowledge of the mechanisms leading to sarcopenia is required to better establish interventions to prevent the onset of symptoms associated with sarcopenia and promote the independent living of older persons. This review examines changes that occur in the regulation of muscle protein metabolism with aging, including information on resistance exercise and nutritional countermeasures that may help attenuate sarcopenia.

AGING AND MUSCLE PROTEIN METABOLISM

The balance between muscle protein synthesis and breakdown is responsible for the quality and maintenance of lean mass. A disturbance of this relationship has been proposed to facilitate the loss of lean muscle mass observed with aging. Early research focused on assessing fasted rates of muscle protein synthesis and breakdown, looking for potential age-related differences [23–29], and several of these studies reported lower rates of muscle protein synthesis in the elderly [24–26,28,29]. Lower rates of muscle protein synthesis have been observed in other chronic wasting conditions, such as renal failure [30], chronic obstructive pulmonary disease [31,32], cancer cachexia [33–35], cirrhosis [36] and thyroid disease [37]. These disease states are often characterized by moderate to severe muscle atrophy, whereas sarcopenia is a much more gradual loss of lean mass, often occurring over several decades. The large discrepancy (~25%) observed in the fasted rates of muscle protein synthesis between young and old [24–26,28,29] would lead to severe muscle wasting in older subjects without an accompanying decrease in the rate of muscle protein breakdown. However, more recent studies have observed little to no difference in the fasting rates of muscle protein synthesis between the young and elderly [23,27,38–41]. It is generally accepted that the difference in fasted rates of muscle protein synthesis or breakdown are not altered in healthy older adults and this has led to the hypothesis that other factors that affect muscle protein turnover (e.g., feeding, insulin, physical activity) may be important in the etiology of sarcopenia.

AGING AND NUTRIENT INGESTION

Essential amino acids, leucine in particular, are potent stimulators of skeletal muscle with the rise in intracellular amino acid concentrations driving the increase in muscle protein synthesis following meal ingestion [42,43]. The ingestion or infusion of large quantities of amino acids/protein yield similar increases in muscle protein synthesis in both young and older individuals [40,43–48]. Each of these studies provided a large bolus of protein or amino acids, typically 30–40g, which was effective in stimulating muscle protein synthesis in adults regardless of age [40,43–48]. This would indicate that if sufficient amino acids or protein is ingested in the elderly, the ability of amino acids to stimulate muscle protein synthesis would not be compromised. However, it is well known that older adults often do not eat a sufficient amount of protein and a few recent studies have shown that older subjects are resistant to the ingestion of smaller amounts of essential amino acids (6–15g) [38,39]. This effect appears to be due to nutrient signaling deficits in the mammalian target of rapamycin (mTOR) signaling pathway [27,49]. It is the essential amino acids (EAA), leucine in particular, that are responsible for the post-prandial increase in muscle protein synthesis [48,50–53]. EAA, leucine in particular, can activate mTOR signaling through various associative proteins, allowing mTOR to directly stimulate protein synthesis through improved translation initiation and elongation [51,54–56]. Leucine's ability to stimulate muscle protein synthesis has been demonstrated in recent studies where its addition to an EAA bolus or a balanced meal led to a greater stimulation of muscle protein synthesis than either intervention alone [39,57]. These studies provide some evidence that the addition of excess leucine to meals may be able to overcome the anabolic resistance to feeding with aging, which could have important clinical implications in the design of nutritional interventions. One countermeasure for this nutritional anabolic resistance that we have recently proposed is that older adults should ingest a sufficient amount of protein (25–30 grams) at each meal in order to generate a significant muscle protein anabolic response to feeding [58]. However, long-term clinical trials are required to determine whether this nutritional approach would be able to prevent sarcopenia.

The role of insulin in regulating muscle protein synthesis is less well understood. Insulin is thought to have a relatively permissive and/or smaller effect on the stimulation of muscle protein synthesis [41,59–64] than amino acids and protein. However, recent studies show a blunted anabolic response to insulin with aging [41,59], perhaps partly due to insulin's inability to stimulate vasodilation, and therefore increase amino acid delivery and overall nutritive flow to skeletal muscle in older adults. In a study by Fujita et al., the anabolic effect of insulin on muscle protein synthesis was rescued in older subjects with a 45 minute bout of aerobic exercise the day prior [65]. This would suggest that physical activity is capable of improving insulin sensitivity for muscle protein metabolism, and perhaps that a reduction in physical activity in older adults contributes to the anabolic resistance of feeding [27,49].

As mentioned above, the less than optimal diet chosen by many older individuals may also contribute to the loss of lean muscle mass observed with aging [66–68]. Specifically, inadequate protein intake can facilitate the loss of muscle and strength through insufficient stimulation of muscle protein synthesis [66–68] and the digestion and absorption of amino acids and protein is impaired in older individuals [40,69,70]. The appearance of amino acids

in the circulatory system is also affected by absorption of nutrients in the small intestine, and older individuals have been shown to have a greater splanchnic uptake of amino acids than young controls, which would imply fewer amino acids available for uptake by skeletal muscle to be used for protein synthesis [40,69,70]. The digestion rates of different proteins can also affect net protein retention following ingestion of a meal. In young subjects, the ingestion of a slowly-digested protein (casein) yields greater protein retention than the ingestion of a quickly-digested (whey) protein [69,71–73]. However, the opposite is true in older subjects, with the ingestion of a quickly-digested protein leading to greater retention of protein [72,73]. This may be attributed to a smaller rise in intracellular amino acids with a slowly-digested protein, whereas a quickly-digested protein can cause a much more rapid and larger rise in the intracellular concentration of amino acids, thereby overcoming the anabolic resistance to nutrients [39]. Similarly, the act of protein pulse feeding, giving up to 80% of the daily requirement of protein in one meal, yielded greater protein retention in older women compared to equal protein intake distributed over four meals [74,75]. There is some debate as to the timing and amount of protein intake throughout the day, especially in an older population [58,76], but it is apparent that ingestion of a sufficient amount of protein and/or increasing physical activity in older adults is capable of restoring the muscle protein anabolic response to amino acids and insulin.

MUSCLE PROTEIN METABOLISM AND RESISTANCE EXERCISE

It is well accepted that resistance exercise training over time yields a net accrual of muscle proteins and muscle hypertrophy. The basic principal of resistance exercise is to provide an overload stimulus, or a load heavier than that which the muscle typically contracts against. Numerous studies have shown that older individuals, like their younger counterparts, respond to resistance training with increases in strength and lean muscle mass [77–90] although the response is typically less in the older adults. This is important in an aging population, as muscle strength and power are inversely associated with risk of falls and fractures and overall functional independence [91–98] and reducing the risk or incidence of falls is highly significant, as falling often denotes a loss of independence and a sharp decline in overall quality of life.

Resistance exercise increases muscle strength through hypertrophy of muscle fibers, which is accomplished through the net accrual of myofibrillar proteins. A single bout of resistance exercise has been shown to stimulate muscle protein synthesis in as little as 1–4 hours in young adults [99,100], with protein synthesis remaining elevated for 24–48 hours following exercise [100–102]. The rate of muscle protein breakdown is also stimulated following a bout of resistance exercise [100,103], but to a lesser extent than the rate of synthesis. This yields an improvement in net muscle protein balance (rate of muscle protein synthesis – rate of muscle protein breakdown), but the overall net protein balance remains negative following exercise. It is only when nutrients, namely amino acids or protein, are ingested following resistance exercise that a positive net protein balance occurs [104–109]. It is well established that the ingestion of nutrients following exercise enhances muscle protein synthesis to a greater extent than resistance exercise or nutrients alone. For an in depth review of the effect of nutrient timing in relation to resistance exercise, see Drummond et al. [110].

A few groups have studied the ingestion of proteins/amino acids before or during a bout of resistance exercise to see if the post-exercise rate of protein synthesis is augmented. A study by Beelen et al. looked at protein co-ingestion during a bout of resistance exercise and observed increases in both whole body and mixed muscle protein synthesis during exercise [104]. However, a recent study by our research group provided young subjects with essential amino acids and carbohydrate 1 hour prior to exercise and observed no improvement in muscle protein synthesis following exercise as compared to a fasted exercise group [111]. It remains unclear whether nutrient ingestion prior to or during exercise is beneficial to the anabolic response of resistance exercise whereas nutrient ingestion following exercise clearly has an additive effect. The ingestion of carbohydrates following resistance exercise is known to stimulate the release of insulin, which aids in the reduction of muscle protein breakdown [112–114], but exerts only a modest effect on muscle protein synthesis without a concomitant increase in plasma amino acid availability [27,115–117]. Nutrient ingestion (EAA or EAA+Carbohydrates) following resistance exercise leads to a greater anabolic response through activation of the mTOR signaling pathway and subsequent activation of muscle protein synthesis [118–120].

As with essential amino acids, resistance exercise increases muscle protein synthesis through activation of the mTOR signaling pathway [99,119,121–123]. Recently, Drummond et al. showed the importance of mTOR in the anabolic response to exercise in young men, when the activation of several proteins in the mTOR signaling pathway was attenuated with the administration of rapamycin, an mTOR inhibitor [124]. This also led to a blunting of the post-exercise increase in muscle protein synthesis [124]. However, evidence also indicates that the extracellular-related kinase (ERK) 1/2 signaling pathway contributes to the contractile-induced increase in muscle protein synthesis following resistance exercise [122,125,126] in both an mTOR dependent [127] and independent manner [125,126,128]. The ERK1/2 signaling pathway signals downstream through map kinase-interacting kinase 1 (MNK1), which can activate the translation initiation complex through eukaryotic initiation factor 4E (eIF4E) [125,126,128]. While the phosphorylation status of signaling proteins is often difficult to correlate with changes in protein turnover [129], increases in the phosphorylation of ribosomal p70S6 Kinase 1 (S6K1) is a good marker for muscle hypertrophy following resistance exercise training [130,131].

RESISTANCE EXERCISE AND AGING MUSCLE

Resistance exercise training stimulates muscle hypertrophy and improves muscular strength in older individuals, albeit to a lesser extent than in their younger counterparts [81,82,88,132,133]. This difference may be attributed to a blunted anabolic response to resistance exercise in older adults. A few recent studies have observed a blunted muscle protein synthesis response following an acute bout of resistance exercise in older subjects [134–136]. Kumar et al. observed that signaling to 2 downstream targets of mTOR, eukaryotic initiation factor 4E binding protein 1 (4E-BP1) and S6K1, was depressed in older subjects in addition to the blunted muscle protein synthesis response [135]. The dysregulation of anabolic signaling in response to resistance exercise may be a driving cause of the diminished response to exercise that has been observed recently. This goes in line with the proposed anabolic resistance of aging noted with nutrient ingestion [27,129] and the

response to insulin [65,137]. It has also been observed that the expression of proteolytic genes, such as MuRF1 and Atrogin-1, are upregulated in older muscle compared to younger controls at rest and following resistance exercise [138]. This implies that muscle protein breakdown through the ubiquitin proteasome pathway may be up-regulated in the elderly. Whether they experience an increase in protein breakdown following exercise or just a blunted synthesis response, older individuals clearly have a less robust anabolic response to resistance exercise or training as their younger counterparts.

However, a few recent studies have been able to rescue the effects of exercise in older subjects with the provision of nutrients in the form of protein/amino acids and carbohydrates following a bout of exercise. Koopman et al. provided older subjects with protein or protein with leucine following 30 minutes of physical activity similar to various activities of daily living [139]. Both groups saw similar increases in muscle protein synthesis following ingestion of nutrients, and the authors concluded that excess leucine did not further stimulate the response to nutrient ingestion following physical activity when ample protein was ingested [139]. Drummond et al. provided young and older subjects with essential amino acids 1 hour after performing a bout of resistance exercise [122]. Subjects were observed for 6 hours following exercise, and both young and old subjects had similar increases in muscle protein synthesis over the 6 hour post-exercise period [122]. Interestingly, younger subjects had a more rapid increase in muscle protein synthesis in the first 3 hours of post-exercise recovery, with older subjects displaying a delayed anabolic response through the first 3 hours of recovery [122]. This result may have been due to greater activation of anabolic signaling proteins, such as ERK 1/2 or its downstream target MNK1, in the younger group [122], and goes in line with other studies showing a blunted anabolic signaling response to resistance exercise in older subjects [135]. While age-related differences in activation of the mTOR and ERK 1/2 pathways following exercise have been noted, the exact mechanisms underlying the diminished response to exercise with aging remain to be elucidated.

We recently published a study of the effect of low-intensity resistance exercise in combination with a reduction in blood flow to the working muscles on muscle protein synthesis in older men [140]. Following a bout of exercise with blood flow restriction, subjects had an increased rate of muscle protein synthesis and a stimulation of both mTOR and ERK1/2 intracellular signaling [140]. This novel exercise method, capable of stimulating both anabolic signaling and muscle protein synthesis in older subjects, could serve as a potential muscle rehabilitation intervention to counteract sarcopenia [140]. We propose that, to achieve a maximal stimulation of muscle protein synthesis following exercise, concurrent activation of both the mTOR and ERK1/2 pathways is needed. In a previous study, younger subjects were able to activate both pathways and saw an increase in the rate of protein synthesis following resistance exercise and EAA ingestion, whereas older subjects only activated the mTOR pathway and saw a delayed increase in the rate of protein synthesis [122]. The delayed response may be due to an inability of older muscle to adequately stimulate both mTOR and ERK signaling pathways following resistance exercise [122], which may explain the blunted anabolic response to exercise observed in older individuals. More research is needed to further investigate blood flow restricted exercise as a novel rehabilitation exercise method in older subjects.

CONCLUSIONS

An associated loss of muscle mass and strength clearly occurs with the aging process. Sarcopenia, the age associated loss of lean muscle mass, is a debilitating process that can lead to an increased risk of falls, fractures and an overall loss of independence. Research has shown minimal differences in basal, fasted rates of muscle protein synthesis which most likely cannot account for the chronic loss of muscle seen with advancing age. On the other hand, anabolic resistance has been observed for three major anabolic stimuli: amino acid intake, insulin and resistance exercise. Fortunately, recently tested interventions can restore the anabolic response to these stimuli. Specifically, the following interventions are likely to counteract sarcopenia: 1) ingestion of a sufficient amount of protein (25–30 grams) at each meal and/or increase of overall physical activity of older adults to restore the anabolic effect of feeding; 2) essential amino acid supplementation following traditional resistance exercise; and 3) blood flow restriction exercise. However, more research (e.g., clinical trials) is needed to determine whether these three interventions will improve muscle strength and function to promote more independence in older adults at risk for sarcopenia.

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LIST OF ABBREVIATIONS

EAA	Essential Amino Acids
mTOR	Mammalian Target of Rapamycin
ERK1/2	Extracellular Related Kinase 1/2
MNK1	Map Kinase-Interacting Kinase 1
eIF4E	Eukaryotic Initiation Factor 4E
4E-BP1	Eukaryotic Initiation Factor 4E Binding Protein 1
S6K1	Ribosomal Protein S6 Kinase 1
MuRF1	Muscle RING Factor 1

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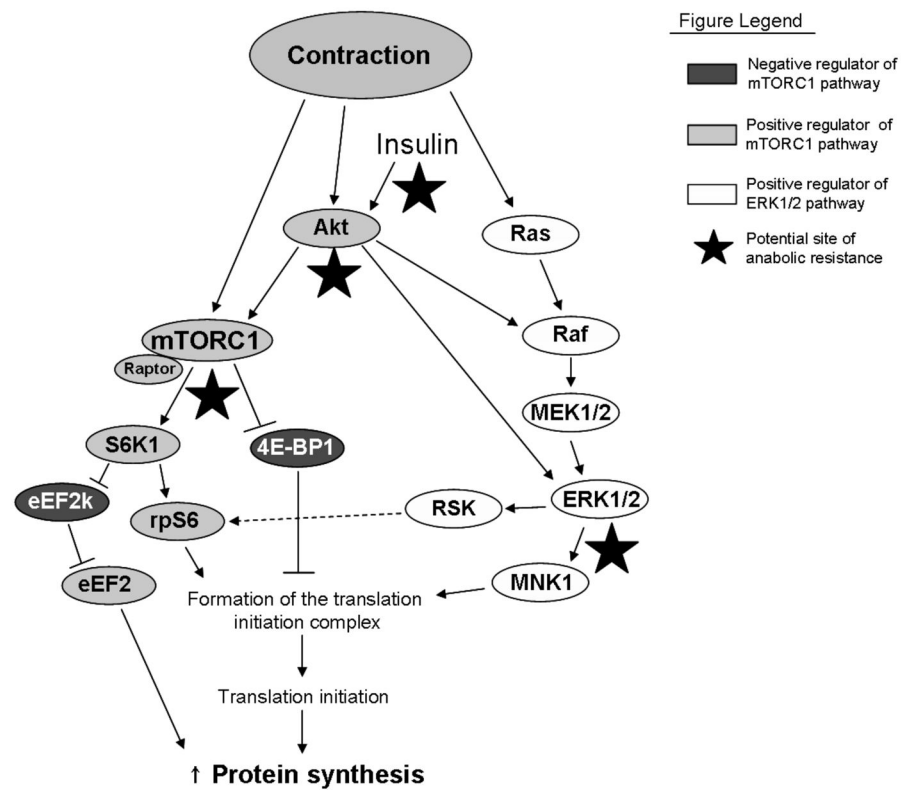


Figure 1.

A simplified diagram of mTORC1 and ERK1/2 signaling following muscle contraction. We hypothesize that dual activation of both pathways is required to maximally stimulate muscle protein synthesis following a bout of resistance exercise. The mTORC1 pathway is indicated in green and red and the ERK1/2 pathway is indicated in blue. Akt, protein kinase B; mTORC1, mammalian target of rapamycin complex 1; Raptor, regulatory associated protein of mTOR; S6K1, p70 ribosomal S6 kinase 1; rpS6, ribosomal protein S6; eEF2K, eukaryotic elongation factor 2 kinase; eEF2, eukaryotic elongation factor 2; 4E-BP1, eukaryotic initiation factor 4E binding protein 1; MEK1/2, mitogen activated protein kinase kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2; MNK1, map kinase-interacting kinase 1; RSK, p90 ribosomal protein S6 kinase.

Table 1

Age-associated differences in measures of muscle protein turnover.

Parameter	Response of older subjects compared to young
<i>Basal Protein Turnover</i>	
Resting rate of MPS	↔
Resting rate of MPB	↔
<i>Anabolic Resistance</i>	
MPS response to insulin	↓
MPS response to small dose of AA/protein	↓
MPS response to mixed meal	↓
MPS response to RE	↓
mTOR signaling response to nutrition	↓
mTOR signaling response to RE	↓
ERK1/2 signaling response to RE	↓
Digestion/absorption of AA/protein	↓
<i>Interventions that Overcome Anabolic Resistance</i>	
MPS response to large dose of AA/protein	↔
MPS response to BFR exercise	↔
MPS response to RE and AA/protein	↔

MPS - muscle protein synthesis; MPB - muscle protein breakdown; AA - amino acids; RE - resistance exercise; mTOR - mammalian target of rapamycin; ERK1/2 - extracellular- related kinase 1/2; BFR - Blood Flow Restriction