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Dose-Dependent Effects of Protein Ingestion and Resistance Exercise on Muscle Protein Synthesis in Aging Adults: A Literature Review

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Abstract
Introduction: Sarcopenia can lead to physical disability and lower quality of life, but increasing muscle protein synthesis in older adults may reduce its effects. Dose-response curves may be used to determine the optimal protein dose in rested and exercised muscle to elicit maximal muscle protein synthesis.
Methods: A literature review was conducted to explore and summarize the findings on the following topics: the mechanisms of muscle protein synthesis, anabolic resistance, and the dose-responses of muscle protein synthesis to anabolic stimuli in both younger and older individuals.
Results: Reduced phosphorylation in downstream targets of the mammalian target of rapamycin complex 1 pathway is characteristic of muscle protein synthesis in older muscle. Compared to younger muscle, older muscle can elicit a similar maximal muscle protein synthesis response, but is less sensitive to lower doses of protein ingestion. With ingestion of 40g of whey protein, the fractional synthetic rate in older muscle is similar to that of younger muscle with 20g of whey protein ingestion. Marked increases in amino acid oxidation are also observed.
Discussion: Anabolic resistance can be biochemically explained by reduced phosphorylation in the mammalian target of rapamycin complex 1 pathway. Due to this phenomenon, older individuals require greater anabolic stimuli to achieve maximal muscle protein synthesis. However, the most effective protein dose for maximal muscle protein synthesis in older muscle is not well-established.
Conclusion: The muscle protein synthesis dose-response curve for older individuals reveals blunted responses to stimuli due to anabolic resistance. Further research is warranted to determine the optimal protein dose for maximal muscle protein synthesis in older adults.

Keywords: muscle protein synthesis; dose-response; protein ingestion; resistance exercise; anabolic resistance; elderly; mTORC1

Introduction

Sarcopenia, defined as muscle loss with increasing age, has severe implications on frailty and overall mobility [1]. These negative effects can decrease an individual's quality of life and loss of strength could impede everyday functions, such as walking. This gradual phenomenon is accelerated at and past the fifth decade of life [2], and is evident in middle-aged and elderly adults. It is characterized by lower muscle protein synthesis (MPS) than breakdown, which together govern overall skeletal muscle mass. Consequently, maximizing MPS in older individuals is key in reducing sarcopenia [3]. However, induction of maximal MPS requires greater stimuli in older than younger adults [4]. Anabolic resistance is the reduced response of MPS to anabolic stimuli and it is often correlated with sarcopenia [4]. This effect is much more prominent in older populations, blunting the sensitivity to stimulate MPS [5].

Despite the effects of anabolic resistance, there is evidence that older individuals can achieve maximal MPS rates approximately equal to those of younger individuals, given greater anabolic stimulus [6]. Two well-studied, measurable stimuli are protein consumption and exercise volume, namely resistance exercise. These two factors work synergistically to increase MPS by stimulating associated pathways. It is well established that resistance exercise heightens MPS compared to the rested state [7], but the protein dosage sufficient to induce maximal MPS without a severe increase in amino acid (AA) oxidation is more unclear, especially in older adults. Comparing the MPS dose-response to protein ingestion between younger and older individuals may reveal effects of anabolic resistance on MPS and warrant investigation into aging effects on the MPS pathways.

Methods

A literature review was conducted to explore and summarize the findings on the following topics: the mechanisms of MPS, anabolic resistance, and the dose-

responses of MPS to anabolic stimuli in both younger and older individuals. In this review, young or younger individuals are defined as ~ 20 years old and elderly adults are defined as ~70 years old. Articles were found through the following databases: Ovid Medline, Pubmed, and Web of Science. Key search terms used included "muscle protein synthesis", "elderly", "anabolic resistance", "dose-response", "mTORC1", and "whey protein". These terms were combined using the boolean operators "and"/ "or". Studies involving dose-response experiments conducted on animal models or were not pertinent to the research question were excluded. In the end, 10 dose-response studies were included and 59 studies were included in total.

Results

mTORC1 pathway

MPS is activated and regulated through the mammalian target of rapamycin complex 1 (mTORC1), a complex commonly associated with tissue growth and MPS [8-12]. mTORC1 acts as a control center receiving inputs from anabolic stimulants, and upon phosphorylation by mTORC1 kinase, leads to a pathway of downstream targets that upregulate translation of mRNA into protein [9, 12]. The phosphorylation of mTORC1 triggers the phosphorylation of two key sets of substrates, eukaryotic initiation factor 4E binding proteins 1 and 2 (4E-BP1/2) and ribosomal S6 kinases 1 and 2 (S6K1/2) [8-13]. The 4E-BPs inhibit formation of the eukaryotic initiation factor 4E (eIF4E) complex, which promotes the smaller 40S subunit to the 5' end of mRNA [12]. Thus, phosphorylation of 4E-BPs permits the formation of eIF4E and the translation initiation complex [8,9,12]. Phosphorylation of S6K1 results in further phosphorylation of ribosomal protein S6 and eukaryotic elongation factor 2 kinase [9]. These proteins enhance translation initiation and elongation [9, 14], and it has been proposed that they play a role in ribosome biogenesis, thereby increasing overall translational capacity in the cell [12].

There are a number of anabolic stimulants that activate MPS, including protein/AA ingestion and muscle contraction. MPS responses are correlated to plasma concentrations of AAs, in particular essential amino acids (EAAs), which are present in many supplemental proteins [13]. Contrastingly, non-essential AAs do not elicit a significant MPS response [15]. Although intramuscular AA concentration is commonly measured in MPS studies, there is no relationship between intramuscular AA concentration and MPS, but there is a single curvilinear relationship between the latter and plasma AA concentration [16]. Leucine, an EAA abundant in whey protein, is an important anabolic AA stimulus that has been associated with phosphorylation of p70S6K1 in the mTORC1 pathway [10]. Intramuscular leucine sensors have also been discovered to activate this pathway, suggesting leucine as a primary AA trigger of MPS [9]. Leucine is also one of three branched-chain AAs, the others being valine and isoleucine,

that are essential for muscle synthesis [17]. These AAs, when ingested together, enhance the activity of kinases and translation initiation factors beyond the abilities of leucine independently [17].

There is an upper limit to the MPS response elicited due solely to AA availability in young men, known as the muscle full effect [13]. Beyond this limit, available AAs no longer act as substrates for MPS and are directed to oxidation, with MPS rates falling to postabsorptive rates, despite sustained increased plasma AA concentration and intramuscular signaling [13, 18]. Resistance exercise sensitizes skeletal muscle to the provision of AAs, which potentiates MPS in response to hyperaminoacidemia [18,19].

Muscle contraction from physical activity, especially resistance exercise, is a well-established MPS stimulus [7, 20]. Resistance exercise performed in the fasted state can result in increased mTORC1 activation and subsequently MPS during the first hour of exercise [14, 21], and can remain increased for up to 48 hours [14, 22], although exactly how muscle contraction results in mTORC1 activation is still unknown [23]. Muscle protein breakdown is also elevated in this state [23], thereby supporting the notion that resistance training combined with protein intake enhances MPS beyond the effect of either stimulus by itself. Numerous studies have demonstrated that resistance exercise before protein ingestion increases the anabolic response, but this potentiation is not observed in rested individuals [24-26].

Anabolic resistance

In experiments investigating the differences between basal MPS between young and elderly individuals, no differences were found [27,28]. However, increases to MPS in response to anabolic stimuli is blunted with aging, a concept known as age-induced anabolic resistance [2, 4, 5, 14, 27, 29-31]. This leads to a downward and rightward shift of the dose-response curve between MPS and available plasma AA concentrations [31]. However, it appears that maximal MPS responses are similar, given adequate anabolic stimuli [5, 20, 32].

The cause of age-related anabolic resistance is currently unknown but there are two major proposed factors: the gradual increase in inactivity and the age-related increase in inflammatory cytokines [33], such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [34]. For the latter, one study using mouse models found that TNF-α was a key determinant in muscle atrophy during sepsis [35]. In humans, TNF-α and IL-6 were found to be markers of anabolic resistance and sarcopenia [36]. Furthermore, TNF-α was also found to interfere with downstream signaling molecules in the mTORC1 pathway to induce decreased MPS [37]. This is in agreement with previous studies that have found that anabolic resistance is correlated with reduced S6K1 and 4E-BP phosphorylation [14, 28, 30, 38].

Diet-related obesity and lipid accumulation are also proposed to be correlated with anabolic resistance [39]. Older, inactive, and obese individuals were once categorized as the most at-risk demographic for age-related anabolic resistance [40, 41]. While the reasons for these correlations are still unknown, it is hypothesized that insulin resistance may be the common factor [39]. Diet-related obesity is often connected to insulin resistance, and downstream effectors in the mTORC pathway have also been identified as contributors to insulin resistance [39].

MPS dose-response in young individuals

The literature surrounding acute MPS in response to graded protein intakes and resistance exercise is sparse, with almost all studies focused on young (~20 years old) or elderly (~70 years old) men. The results of studies regarding the dose-response of MPS in young adults are presented here [42-44]. Two studies used traditional dose-response methods, involving multiple graded doses to a maximum of 40g of bolus protein, following a bout of resistance-based leg exercises [43-44]. Although the protein used in the studies were different, egg protein [40] versus whey protein [43], both concluded that 20g of the respective proteins was sufficient in eliciting a maximal MPS response. 40g of protein failed to produce a significantly increased fractional synthetic rate (FSR), the fraction of the protein pool synthesized per unit time [45], but there was a marked increase in AA oxidation [43, 44], in agreement with the muscle full effect. Studies also compared graded dose-responses between rested and non-rested muscles. With increasing doses of whey protein, MPS was greater in all exercised muscles compared to the non-exercised muscles [43, 46], and incorporation of AAs into protein was consistently higher for exercised muscles [5]. This increase in postprandial MPS in response to exercise was persistent after 24 hours after exercise [47]. Another study [42] investigated MPS in response to whole-body resistance exercise and only included methods using 20g and 40g of whey protein. In contrast to studies that measured MPS in a single muscle, 40g of bolus whey protein induced a 20% higher FSR than the 20g dose, however the total muscle involved in the exercise likely influenced the dose-response of MPS [42].

MPS dose-response in elderly individuals

Comparing the MPS responses in young versus elderly individuals may provide insight on the effects of aging on maximal MPS responses and anabolic resistance. Several studies have investigated the MPS response to protein ingestion at rest and after resistance exercise in elderly. Dose-response studies have confirmed that older adults can reach an approximately equal maximal MPS as younger adults, however they need to consume more protein in order to stimulate this maximal response [48, 49].

The optimal dose needed to elicit maximal MPS in rested, elderly muscle is not well established [4]. One study by Yang et al. reported no significant difference in FSR between ingestion of 20g and 40g of whey protein, but there was a significant increase in consuming 20g or 40g compared to 0g [48]. In a subsequent experiment using soy protein instead of whey protein, the authors found that at rest neither 20g or 40g elicited a significant difference in FSR from basal values like the whey protein had [49]. Moreover, the study using whey protein was included in a retrospective analysis investigating the relative (to body weight) protein required to stimulate maximal MPS at rest, and found that older men require 0.4g/kg/meal [6]. Applying this figure to the average weight of the participants included in the whey protein study would imply that ~30g of whey protein elicits maximal MPS, not 20g.

In exercised muscle, resistance training potentiates the MPS response to whey protein. Yang et al. found that FSR was greater in the exercised muscle compared to the non-exercised muscle for all whey doses [48]. Unlike the results from rested state, there was a significant increase in FSR (32%) following 40g of whey protein ingestion compared to 20g for the exercised muscle [48]. The requirement of a substantially greater protein dose to stimulate maximal MPS in exercised elderly muscle is generally agreed upon across different types of protein. In the study conducted by the same authors using soy protein, 40g was also found to stimulate significantly increased MPS [49]. 36g of beef protein elicited the greatest MPS compared to lower doses, however, there was also a marked increase in AA oxidation [50]. The participants of this study were middle-aged adults (~60 years old), and there was little difference between the MPS dose-response of these individuals versus elderly adults [50].

Low doses of whey, soy, and beef protein (0-10g) elicited blunted MPS responses in both rested and exercised older muscles [6, 41, 48-50]. This form of anabolic resistance has been shown to be correlated with reduced p70S6K1 phosphorylation in the mTORC1pathway [30]. 40g of whey protein was found to induce the greatest and most sustained increase in p70S6K1 phosphorylation when compared to other doses [51].

Discussion

In efforts to reduce sarcopenia, increasing MPS in older adults has been extensively studied. Dose-response curves provide insight on the optimal bolus protein dose to elicit a maximal MPS response. In addition, comparing MPS markers between younger and older individuals may reveal effects of aging on relevant pathways, such as mTORC1.

At rest, the most effective protein dose for older individuals is inconclusive. Two studies conducted by Yang et al. using whey and soy protein found that 20g of whey protein was sufficient to elicit maximal MPS at rest in elderly individuals, but ingestion of neither 20g nor 40g of soy protein stimulated a significant increase in MPS

[48, 49]. These differing results may in part be due to the faster digestion and absorption kinetics of whey protein [52]. However, the results from the whey protein study conducted by Yang et al. [48] are at odds with the retrospective analysis by Moore et al. [6], which suggests a 30g dose of whey protein required to stimulate maximal MPS in the participants in Yang et al.'s study. It is important to note only 2 out of the 6 papers included in the analysis included elderly individuals as participants in experiments, one of these papers being the whey protein study by Yang et al. [6]. The other paper did not measure acute MPS nor did it include a dose-response in the study design [53]. Therefore, no definitive optimal dose to stimulate maximal MPS at rest has been reported.

More studies have conducted MPS dose-response curves in resistance-exercised muscle. Numerous studies have reported that ~35-40g of protein (whey, soy, and beef) elicits MPS responses similar to those of young individuals [48-50, 54]. Moreover, there is a significant increase in AA oxidation at this protein dose, suggesting that even greater doses may result in inefficient consumption of protein [50]. With this said, these recent dose-responses lack a plateau that is characteristic of the muscle full effect seen in younger adults, and the effects of doses greater than 40g of protein on exercised muscle have not been thoroughly explored [4].

The studies included in this review use different types of protein, including whey, soy, and beef. However, the type of protein influences rates of postprandial MPS [52]. Whey protein contains high leucine content, which has been identified as one of the main nutritional signals to stimulate MPS through the mTORC1 pathway [52]. Furthermore, it is a fast-digestible protein, and may increase acute MPS more potently than other proteins [52]. Compared to soy protein, whey produces a significantly increased FSR following resistance exercise, but there is only a slight, non-significant increase in the rested state [55]. Contrastingly, beef is a slow-digestible protein, producing sustained increases in plasma AA concentrations over hours, compared to the peak in plasma AA concentration at 30 minutes following consumption by whey protein [56]. The rate of digestion affects the effect of the protein on acute MPS.

In addition to the various types of proteins studied, there has also been interest in investigating the effects of supplemental leucine on MPS. As aforementioned, leucine is regarded as a trigger of MPS, and studies involving both young and elderly participants have concluded that leucine supplementation can significantly increase MPS independent of other AAs [57, 58]. In young, exercised males, a low protein dosage supplemented with a high leucine dosage elicited the same FSR rates as a high dose of protein [58]. For elderly individuals, leucine supplementation has been proposed as a method to slow the effects of sarcopenia [59].

The most agreed upon results include that older individuals exhibit anabolic resistance to protein ingestion, and this has been proven through reduced phosphorylation of downstream targets in the mTORC1 pathway [30]. Additionally, greater protein doses are required for older individuals to elicit a maximal MPS response comparable to their younger counterparts [6]. These conclusions are broad and further research must be conducted to come to a consensus on the optimal dosage required for maximal MPS in older individuals. Additionally, only one study has conducted a dose-response with middle aged (~60 years old) adults, and no differences in MPS dose-response between middle-aged and elderly individuals [50]. Further research to include a more diverse age range is required to better understand this across the lifespan.

Conclusions

Overall, this review summarized the findings in published MPS dose-response experiments following protein ingestion in rested and exercised muscle. Comparing MPS responses between younger and older individuals, older muscle is resistant to anabolic stimuli, requiring greater protein doses to achieve maximal MPS in the exercised state. Approximately 35-40g of whey protein is required to stimulate elderly MPS rates similar to those of maximal young MPS rates in exercised muscle. Further research must be conducted to clearly establish the dose-response in rested muscle, but a practical consumption dosage between 20-30g of whey protein per meal or sitting is likely sufficient to stimulate maximal MPS. Confirming the MPS dose-response in older individuals will inform future recommendations on protein ingestion to minimize the effects of sarcopenia.

List of Abbreviations Used

MPS: muscle protein synthesis
FSR: fractional synthetic rate
AA: amino acid
mTORC1: mammalian target of rapamycin complex 1
4E-BP1/2: eukaryotic initiation factor 4E binding proteins 1 and 2
S6K1/2: ribosomal S6 kinases 1 and 2
eIF4E: eukaryotic initiation factor 4E
EAA: essential amino acid
TNF-α: tumor necrosis factor alpha
IL-6: interleukin 6

Conflicts of Interest

The author declares that she has no conflict of interests.

Ethics Approval and/or Participant Consent

This literature review did not require ethics approval and/or participant consent.

Authors' Contributions

CQ: contributed to the conception of study, conducted literature review, analysed and interpreted data, drafted the manuscript, and gave final approval of the version to be published.

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