Anabolic Resistance of Muscle Protein Synthesis with Aging

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Articles

Abstract In Brief Author Information Article Outline

Aging has been associated with a reduced muscle protein synthetic response to protein intake, termed “anabolic resistance.” Physical activity performed before protein intake increases the use of protein-derived amino acids for postprandial muscle protein accretion in senescent muscle. Thus, the level of habitual physical activity may be fundamental to maintain the anabolic responsiveness to protein intake with aging.

We provide evidence to suggest that maintenance of physical activity can reduce the anabolic resistance of muscle protein synthesis to protein intake with aging.

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INTRODUCTION

In healthy young individuals not involved in any progressive exercise training regimen, skeletal muscle mass remains virtually unchanged provided that adequate calories are consumed. Muscle mass maintenance is achieved through sinusoidal fluctuations in muscle protein synthesis and breakdown rates that are eventually counterbalanced such that net muscle protein balance remains zero by the end of each day. However, with aging, a progressive decline in skeletal muscle mass becomes apparent ([12]). This age-related loss of muscle protein must be attributed to an imbalance between muscle protein synthesis and breakdown rates, resulting in a negative muscle protein balance and, over time, a decline in skeletal muscle mass (Fig. 1). The accurate measurement of muscle protein breakdown

rates *in vivo* in humans is challenging. As discussed by Rennie *et al.* ([28]), however, the available data in humans imply that normal "healthy aging" is not accompanied by accelerated muscle protein breakdown rates or associated with an increased expression of single-point measurements of molecular readouts associated with muscle proteolysis.

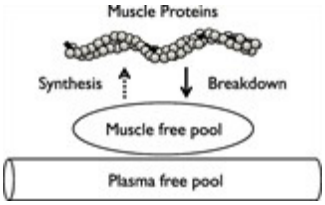

Figure 1

A few authors have suggested that a gradual decline in post–absorptive muscle protein synthesis may underpin the age-related loss of muscle mass ([29]), but not all researchers agree that (detectable) derangements in basal muscle protein synthesis rates occur with healthy aging ([5,34]). As a consequence, the research focus has been redirected to the search for impairments in the muscle protein synthetic responses to the main anabolic stimuli, food intake or physical activity, in the older populations. Recent work seems to suggest that the elderly show a blunted muscle protein synthetic response to amino acid administration ([5,15,16,32]) and physical activity ([8,21]) when compared with that in the young. It is speculated that impairments in protein digestion and amino acid absorption ([1]), insulin-mediated muscle tissue perfusion ([27]), amino acid uptake in muscle ([6]), or a reduced amount or activation status of key signaling proteins ([5,8,21]) may contribute to this proposed anabolic resistance of muscle protein synthesis with aging (Fig. 2). Our laboratory recently has demonstrated recently that physical activity performed before protein intake allows for greater use of dietary protein–derived amino acids for *de novo* muscle protein accretion in senescent muscle ([26]). In fact, the physical activity–mediated stimulation of postprandial muscle protein synthesis seems to persist for several days ([3]). This review will highlight the hypothesis that lack of sufficient habitual physical activity is the key factor responsible for the proposed anabolic resistance of muscle protein synthesis with aging.

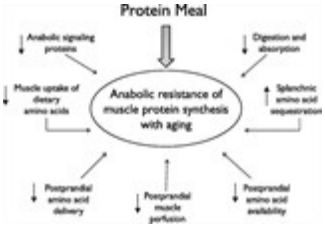

Figure 2

POSTPRANDIAL MUSCLE PROTEIN SYNTHESIS

Cuthbertson *et al.* ([5]) applied euglycemic insulin clamps to isolate the dose-response effects of amino acid ingestion from the associated hormonal response on the subsequent stimulation of muscle protein synthesis rates in the young and old. It was demonstrated that ingestion of 40 g essential amino acids (equivalent to ~100 g high-quality protein) lacked the capacity to stimulate muscle protein synthesis rates in the elderly, as opposed to the young ([5]). Interestingly, stimulation of muscle protein synthesis rate was maximal after ingesting 10 g of essential amino acids in the young subjects ([5]). These data suggested that the ability to stimulate muscle protein synthesis following amino acid feeding is severely impaired in the elderly (a reduced sensitivity to a given protein load as compared with that in the young).

What are the potential mechanisms that could explain the reduced sensitivity of senescent muscle to amino acid or dietary protein administration? Impairments in protein digestion and amino acid absorption, which limit the appearance of dietary protein–derived amino acids into the circulation, have been postulated as a mechanism

underpinning a reduced postprandial muscle protein synthetic response to food intake in the elderly ([1]). Moreover, it has been demonstrated that the splanchnic area retains a greater portion of ingested amino acids after intestinal absorption in older compared with young populations ([1,33]). This implies that, in the older population, fewer amino acids may become available for muscle protein synthesis. There also is evidence to suggest that reductions in insulin-mediated capillary recruitment and limitations in postprandial muscle tissue perfusion, ultimately reducing amino acid delivery, may be responsible for anabolic resistance of senescent muscle ([9,27,31]). For example, Timmerman *et al.* ([31]) have demonstrated that pharmaceutical manipulation of vasodilation (via sodium nitroprusside) during insulin infusions improves microvascular perfusion and increases muscle protein synthesis rates in older men.

The differential regulation of amino acid transporters and subsequent uptake of amino acids into muscle between the young and elderly may be another potential site of impairment to food intake ([6]). It is assumed that the activity of certain amino acid transporters serves as the "link" between postprandial amino acid availability and the regulation of the postprandial muscle protein synthesis. So far, the relevance of acute changes in mRNA and protein expression of these transporters on the actual amino acid transport capacity remains to be clearly elucidated in a human model. In fact, it has been demonstrated that changes in mRNA expression of select amino acid transporters are not dependent on circulating leucine concentrations ([4,6]), a variable that seems to be an important modulator of the postprandial muscle protein synthetic response in the elderly ([24,35]). The mammalian target of rapamycin complex 1 (mTORC1) functions as a fundamental site of integration for anabolic signals that stimulate muscle protein synthesis rates in human skeletal muscle. Interestingly, Cuthbertson *et al.* ([5]) have demonstrated that protein concentrations of mTORC1, and its downstream target p70S6K, differ between healthy young and older individuals. Differences in the availability of such key regulatory proteins may contribute to the reduced capacity of the muscle protein synthetic machinery to "sense" a nutrient signal in senescent muscle ([5]). Other authors have reported that skeletal muscle p70S6K phosphorylation is impaired on intravenous insulin and amino acid infusions in older compared with that in young individuals, which may provide a mechanistic basis underlying the proposed anabolic resistance of aging ([15]). Of course, any correlation between single-point measurements of the phosphorylation status of intramuscular anabolic signaling molecules and the dynamic measurement of postprandial muscle protein synthesis rates could simply be a matter of coincidence and should be assessed with extreme caution ([13]). Considering that such age-related impairments in anabolic signaling exist, these observations may represent a mere consequence of the aforementioned issues and simply may be secondary to an attenuated rise in postprandial amino acid availability in senescent muscle. Overall, it is evident that there are various processes at different levels that can contribute to the development of anabolic resistance with aging (Fig. 2).

POSTPRANDIAL AMINOACIDEMIA MODULATES MUSCLE PROTEIN SYNTHESIS RATES

Some data suggest that the dose-response of muscle protein synthesis rates to the ingestion of increasing amounts of protein also may be shifted upward in the elderly. Specifically, greater amounts of dietary protein may be required to maximally stimulate the muscle protein synthetic response in the older population ([17,35]). In fact, by combining the ingestion of intrinsically L-[1-^{13}C]phenylalanine–labeled whey protein with continuous intravenous L-[ring-$^{2}H_5$] phenylalanine infusions, our laboratory recently demonstrated that ingestion of 35 g of whey protein results in more of the amino acids being released into the circulation and subsequently used for *de novo* muscle protein synthesis when compared with the ingestion of smaller amounts of protein in the elderly ([25]). Importantly, our findings also highlighted that the ingestion of 10 g of whey protein still is being used for muscle protein turnover ([1-^{13}C]phenylalanine incorporation in the muscle protein pool) but did not lead to muscle protein synthesis rates that exceeded postabsorptive values in the older population ([25]). Although dose-response data using intrinsically labeled protein are not available in the young, the available evidence suggests that consumption of greater amounts of protein (>20 g) results in the amino acids being lost to oxidation rather than used for *de novo* muscle protein

accretion ([22]), a finding that seems to be different when compared with that of the aged population ([25,35]). Hence, as illustrated in Figure 3, the elderly may have reduced sensitivity of muscle protein synthesis to the ingestion of smaller amounts (<20 g) of dietary protein ([25,35]).

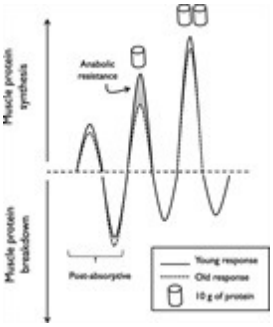

Figure 3

The evidence of anabolic resistance of muscle protein synthesis rates with aging becomes less clear when studied during more physiological conditions, such as the ingestion of a meal-like bolus of dietary protein, as opposed to the setting where amino acid infusions are applied under insulin clamped conditions ([5]). Our laboratory has compared protein digestion and absorption kinetics and the subsequent stimulation of muscle protein synthesis rates after ingesting 20 to 35 g intrinsically L-[1-^{13}C]phenylalanine–labeled casein between healthy young and older males ([20,26]). In these studies, exogenous phenylalanine appearance rates and the total amount of dietary phenylalanine that appeared into the circulation did not differ between healthy young and elderly subjects ([20,26]). Importantly, this work also demonstrated that postprandial muscle protein synthesis rates are not reduced in healthy elderly men when ample amounts of dietary protein are ingested ([20,26]).

Previously, we assessed whether postprandial aminoacidemia could be modulated by ingestion of hydrolyzed, as opposed to intact, casein ([18]). Naturally, casein clots in the stomach and results in a prolonged aminoacidemia after its ingestion. However, hydrolysis of casein will, expectantly, facilitate the digestion and absorption and subsequently increase amino acid availability. We found that ingestion of hydrolyzed casein, as opposed to intact casein, resulted in accelerated digestion and absorption rates, greater plasma amino acid availability, and augmented postprandial muscle protein synthesis rates ([18]). In a separate study, ingestion of whey (which, by nature, is rapidly digested and absorbed) resulted in greater postprandial muscle protein accretion when compared with intact casein or casein hydrolysate ([24]). The greater stimulation of muscle protein synthesis rates after whey ingestion was likely related to its faster digestion and absorption kinetics and higher leucinemia ([24]). Collectively, these data ([18,24]) suggest that peak postprandial aminoacidemia, and leucine in particular, is a fundamental variable modulating the muscle protein synthetic response and may contribute to the discussion why “anabolic resistance” is not a consistent finding ([2]). For example, ingestion of the same absolute amount of protein often results in greater peak postprandial plasma amino acid availability in the elderly when compared with that in the young ([19,20,26]). Such an effect may be related to a reduced whole-body amino acid flux or a smaller distribution volume for some amino acids in the elderly. Regardless, the greater difference in plasma amino acid availability in the elderly after bolus ingestion of the same meal-like amount of protein may compensate for any age-related differences in postprandial muscle protein synthesis rates. In a similar way, postprandial plasma insulin concentrations have been observed to be higher after dietary protein ingestion in the elderly ([26]). Because the skeletal muscle vasodilatory response to insulin may be impaired in the elderly ([9]), the higher insulinemia also may be regarded as another compensatory mechanism for the elderly to maintain more “youthful” postprandial muscle protein synthesis rates after ingestion of meal-like amounts of dietary protein.

PHYSICAL ACTIVITY ENHANCES THE ANABOLIC

SENSITIVITY TO FOOD INTAKE

Interesting is the observation that physical activity performed before food intake can improve postprandial muscle protein synthesis rates, irrespective of age ([26]). We have demonstrated that physical activity performed before the ingestion of a single meal-like amount (20 g) of protein results in a greater amount of the dietary-derived amino acids to be used for *de novo* muscle protein accretion ([26]). What is noteworthy is that resistance exercise can enhance the sensitivity of the muscle protein synthetic responses to dietary amino acid provision for days after cessation of an exercise session ([3]). Certainly, the intensity of physical activity required to increase postprandial muscle protein synthesis rates remains to be defined. However, low-intensity treadmill walking seems to abolish the age-related insulin resistance of muscle protein synthesis ([10]). These data are promising because they reveal that the intensity of contraction required to improve skeletal muscle anabolic sensitivity may be relatively low. Thus, a strategy that may offset, at least in part, the age-related loss of muscle mass is to encourage the elderly to maintain, or rather increase, daily habitual physical activity (*e.g.,* mowing the lawn, gardening, grocery shopping, etc.). Importantly, recent work supports the idea that increasing habitual physical activity improves the postprandial muscle protein synthetic response to food intake in the elderly ([30]).

Consistent with this idea that habitual physical activity is important for maintaining a normal postprandial muscle protein synthetic response to food intake (Fig. 4), it has been reported that anabolic resistance also develops in models of inactivity or muscle disuse in young adults. For instance, Glover *et al.* ([11]) have demonstrated that a blunted muscle protein synthetic response to amino acid provision can be induced in young adults by simply unloading the muscle for as little as 10 d. This provides an attractive paradigm to explain the reported anabolic resistance of muscle protein synthesis to amino acids in the elderly ([5]). In fact, some researchers have speculated that short successive periods of muscle disuse, because of sickness or recurrent hospitalization, may be at the root of the age-related loss of muscle mass ([7,23]). Specifically, multiple transient periods of anabolic resistance of postprandial muscle protein synthesis imposed by disuse may lead to muscle protein loss that is never fully regained after returning ambulant.

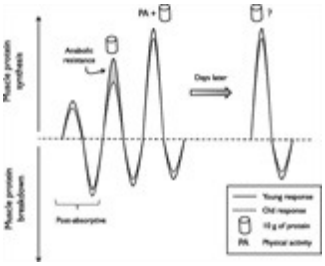

Figure 4

CONCLUSIONS

The current review has highlighted that a multitude of factors may contribute toward the anabolic resistance of muscle protein synthesis to food intake with aging (Fig. 2). However, these factors may impose minimal differences on postprandial muscle protein synthesis rates when comparing healthy young and older individuals after ingesting ample amounts of protein ([20,26]). In addition, we reasoned that a reduced level of habitual physical activity forms the basis for the observed anabolic resistance in the older population. Increasing the physical activity level in the elderly will increase postprandial muscle protein synthesis rates ([26]) and, ultimately, support healthy aging. In addition to this, we have confirmed our hypotheses that the amount ([25]), protein source ([18,24]), and time of day ([14]) that dietary protein is consumed further modulate the amplitude of the stimulation of postprandial muscle protein synthesis rates, thereby improving net muscle protein accretion.

There are research gaps, however, that limit our understanding of the regulation of muscle mass maintenance. It is important to recognize that most postprandial muscle protein synthesis data have been measured after a single isolated protein meal following an overnight fast. Our knowledge is lacking with regard to how the anabolic response is affected by (a) previous meal(s) and if a differential regulation of postprandial muscle protein synthesis occurs when the protein meal is coingested with carbohydrates and lipids. Moreover, regulation of basal post–absorptive muscle protein synthesis likely is linked with the responsiveness of postprandial muscle protein synthesis rates, but the mechanisms underlying such an interaction remains to be elucidated. Habitual physical activity and proper dietary protein intake will prove to be of fundamental importance to maintain post–absorptive muscle protein synthesis rates and ensure a proper postprandial anabolic responsiveness. Consequently, lifestyle interventions that combine an increase in physical activity with established dietary interventions are able to offset the age-related loss of muscle mass and function, which is important for the support of a healthy independent lifestyle.

The authors recognize the work of other scientists that could not be cited because of reference limitations.

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Keywords:
sarcopenia; dietary protein; exercise; amino acids; mTORC1