The curious case of anabolic resistance: old wives’ tales or new fables?

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The progressive loss of muscle mass, commonly termed sarcopenia, accompanies the process of healthy aging (27). The underlying basis of this condition, in a very simplistic view, would be at a more advanced age skeletal muscle proteins are being lost because of an imbalance between muscle protein synthesis and degradation rates. It is generally believed that basal muscle protein synthesis rates do not differ between healthy young and older individuals (5, 34). By using an arteriovenous dilution tracer approach there appears to be no measurable age-related impairments in basal muscle protein breakdown either (35). In support, the degree of muscle loss with aging has been estimated to be ~1–2% per year in men and women aged 65 yr and over (9). Such a gradual decline in muscle mass would likely be too small to detect using contemporary stable isotope methodology as it would equate to only minor differences in basal muscle protein turnover rates, expressed as percent per hour, between young and senescent muscle.

In general, it is accepted that the primary modulators of muscle protein turnover, regardless of age, are muscle contraction (3) and essential amino acids (32). Certainly, some insulin is required within a very narrow physiological range, at least in younger muscle, to optimally stimulate muscle protein synthesis rates (12). The insulin paradigm, however, appears to shift to a higher insulin concentration to manifest a significant effect on human muscle protein turnover in older subjects (11, 25, 30, 35). There are several reports suggesting a blunted postprandial anabolic response following amino acid administration (5, 13, 14) and muscle contraction (8, 10, 19) in older subjects. The reduced capacity of the elderly to stimulate a robust increase in muscle protein synthesis rates to nutrition or physical activity has been coined anabolic resistance (24, 26). The term in itself can be puzzling as, more often than not, it must be inferred that anabolic resistance with aging is in reference to muscle protein turnover or intramuscular anabolic signaling phosphorylation and not, for example, lipid or glycogen synthesis. Furthermore, the mechanism(s) underpinning this proposed resistance to anabolic stimuli are likely multifaceted and are far less easy to pin down. Further confusion arises from the fact that some workers have failed to detect differences in muscle protein metabolism between the young and old following intravenous infusion of mixed amino acids (4, 6, 31), ingestion of crystalline amino acids (21, 33), or intact protein in the presence (17, 23, 29) or absence (16, 28) of physical activity. Therefore, attempting to identify the mechanisms of anabolic resistance, and thus the etiology of sarcopenia, prior to the determination of the actual existence of this phenomenon in a group of older subjects will only lead to a situation of a dog chasing its own tail. Given the reported discrepancies in the literature it is clear that anabolic resistance in aging muscle is, in fact, a “curious case” and it is important that this idea is discussed.

So what could explain the reported discrepancies in the literature with regard to the presence, or absence, of this concept commonly referred to as anabolic resistance of aging muscle? It may be argued that the timing of the muscle biopsies is a primary culprit, and examining temporal responses of muscle protein synthesis rates may provide greater mechanistic insight, or simply a better chance to detect differences in peak postprandial muscle protein synthesis rates between the young and old (7, 19). For example, Drummond and colleagues (7) reported a delayed stimulation of muscle protein synthesis rates after resistance exercise and ingestion of 20 g of crystalline essential amino acids in older compared with young subjects. However, differences in the postprandial muscle protein synthesis rates between the young and old were no longer evident when an aggregate muscle protein synthetic response was calculated over a 5-h period (7). Are potential differences in postprandial (peak) muscle protein synthesis rates between young and older subjects detected at 1–2 h after food ingestion more (or less) relevant than responses determined over an aggregated time interval (i.e., 0–6 h)? Clearly, more research is warranted to understand the predictive power of acute postprandial mus-

![Fig. 1. Postprandial mixed muscle protein synthetic responses (FSR) in young (age, 22 ± 1 yr; n = 22) and older (age, 70 ± 1 yr; n = 22) men after ingesting 20–35 g dairy protein (16, 23). Intravenous infusion of [3H]phenylalanine using the plasma free (plasma D5 IV) or muscle free (IC D5 IV) pool to calculate FSR. Ingestion of intrinsically [1-13C]phenylalanine-labeled protein using the plasma free pool to calculate FSR (plasma 13C oral). There were no differences in postprandial muscle protein synthesis rates between young and old (P < 0.05).](http://www.jappl.org)
cle protein responses for determining longer-term outcomes and, as such, clinical relevance.

The physical activity level of the participants may also represent another key factor contributing to the discrepancy regarding the proposed differences in postprandial muscle protein synthesis rates between the young and old. Feeding and exercise are synergistic to the subsequent stimulation of muscle protein synthesis rates. A higher level of physical activity makes the muscle more sensitive to a dietary stimulus that is relatively long lasting (1, 2, 20). In fact, some of the age-related discrepancies in the existence, or nonexistence, of blunted muscle protein synthetic responses to nutritional stimuli may relate to the composition of the habitual diet or levels of physical activity in the adult population studied that are dependent on geographical and cultural trends.

Our research group recently demonstrated that exercise performed prior to the consumption of a 20-g bolus dose of intrinsically labeled micellar casein results in muscle protein synthesis rates that do not differ between young and older participants (23). Given that postprandial aminoacidemia is an important variable to optimally stimulate muscle protein synthesis rates (16, 22), we assessed digestion/absorption kinetics of the ingested protein and observed no impairments in protein digestion and/or amino acid absorption in the old (23). The use of intrinsically labeled protein allows us to assess postprandial muscle protein accretion by measuring the amount of labeled amino acids from the ingested protein that were released into the circulation and subsequently built into de novo muscle protein. Although not unexpected, we found that a greater proportion of the dietary protein derived amino acids were used to synthesize muscle protein when physical activity was performed prior to food intake in both the young and older subjects (23). These data highlight that physical activity, irrespective of age, represents an important factor modulating the muscle protein synthetic response to food ingestion. Thus the proposed age-related impairments in muscle protein synthesis after a contraction stimulus can be overcome by ingesting a greater amount of high-quality protein (23) and/or free essential amino acids (7).

Interestingly, collapsing data from a couple of studies from our lab over the last few years (16, 23) reveals no differences in postprandial muscle protein synthetic responses to protein ingestion between healthy young and older subjects (Fig. 1). This effect is observed irrespective of whether mixed muscle protein fractional synthetic rate is calculated using muscle enrichments obtained after an intravenous infusion of [2H5]phenylalanine or orally ingested [1-13C]phenylalanine-labeled dairy protein. In addition, the choice of precursor pool (plasma free or muscle intracellular free) also does not influence these findings. In all cases, an ample amount of protein was consumed (20–35 g) and the postprandial period was assessed over as long as 6 h. Indeed, some evidence suggests that elderly show a blunted muscle protein synthetic response following ingestion of smaller protein doses (i.e., 7 g essential amino acids, equivalent to ~16–17 g high-quality protein) (14). This attenuated response seems to be overcome when increasing the relative amount of leucine in such a mixture (15). Given all this, it seems that muscle protein synthesis rates do not differ between the young and old provided sufficient amounts of protein are consumed. Certainly, it should not be ignored that a blunted muscle protein synthetic response in the elderly may be prevalent after ingestion of dietary proteins with lower leucine content and/or simply ingestion of lower amounts of protein.

In the end, the progressive loss of skeletal muscle mass that occurs with advancing age is undeniable (9, 18). It is evident that the world’s population aged 60 yr and over is rapidly increasing and this will place considerable strain on our health care system. We are not suggesting that anabolic resistance is an “old story” passed on through the generations, or a newly confabulated event, without any solid scientific support (26). However, there is a lack of general consensus amongst laboratories as to the presence of anabolic resistance in elderly individuals that is hardly discussed. These differences may perhaps arise due to methodological differences, such as the timing of muscle biopsies, muscle protein pool studied (mixed muscle protein vs. myofibrillar protein synthesis), the precursor pool used to determine muscle protein synthesis, or indirect measurements (AV-balance) as opposed to direct precursor-product methods to determine muscle protein synthetic responses. In addition, the characteristics of the subjects (e.g., training status, habitual activity level, insulin-resistance, body composition, or age of the elderly participants and control groups) used in the study protocols may also contribute to the discrepancies. Therefore, first acknowledging and subsequently attempting to understand why these discrepancies exist are vital steps to elucidate the contribution that “anabolic resistance” contributes to the loss of muscle mass with aging. Of course, one solution would be to become more in tune with the physical activity level of the study participants (e.g., accelerometer or self-reported activity level questionnaires would provide some insight). Also, clearly addressing whether there are age-related impairments to stimulate muscle protein synthesis rates after ingestion of suboptimal amounts of dietary protein (10–15 g) and/or different protein sources may be good starting points.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


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