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Amino acid metabolism and regulatory effects in aging

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Abstract

Purpose of review—To examine recent discoveries related to the amino acid metabolism and regulatory effects in aging, focusing on the development and treatment of age-related muscle loss (sarcopenia).

Recent findings—While basal amino acid metabolism may be unaffected by age, elderly subjects appear to have a decreased ability to respond to anabolic stimuli such as insulin and, to a lesser extent, amino acids. Specifically, compared to young subjects, the stimulation of muscle protein synthesis is attenuated in elderly subjects following the administration of mixed meals due to insulin resistance. In addition, the anabolic effect of amino acids appears blunted at low doses. Recent studies, however, have highlighted that these age-related alterations in amino acid metabolism may be overcome by provision of excess leucine, changes in the daily protein intake pattern or exercise, which improve activation of translation initiation and muscle protein synthesis.

Summary—Muscle loss with aging is associated with significant changes in amino acid metabolism, which can be acutely reversed using nutritional manipulations and exercise. Long-term, large clinical trials are, however, needed to determine the clinical significance of these findings in the elderly population, and to establish if nutritional and exercise interventions can help prevent and treat sarcopenia.

Keywords

aging; amino acid; leucine; metabolism; muscle protein; sarcopenia

Introduction

The main amino acid reservoir in the body is skeletal muscle, which contains 50−75% of all proteins in the human body [1,2]. In addition to its role in movement and posture, regulation of metabolism, and storage of energy and nitrogen, skeletal muscle becomes a vital supplier of amino acids to be used as a fuel by the brain and immune system, and as a substrate for wound healing during malnutrition, starvation, injury and disease [3]. The maintenance of body protein mass is critical not only to remain physically independent, but also for survival. The loss of approximately 30% of the body proteins results in impaired respiration and circulation due to muscle weakness, reduced immune function due to lack of nutrients, and inadequate barrier effect of the epithelia, which eventually will result in death [2].

Senescence in humans is characterized by an involuntary loss of muscle mass and function, termed sarcopenia. This degenerative loss of skeletal muscle occurs at a rate of 3−8% per decade after the age of 30 and accelerates with advancing age [4,5]. Sarcopenia is associated with decreased metabolic rate [6], decreased strength [7,8], increased risk of falls and

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fractures [9], increased morbidity [7,10], and loss of independence [7]. When defining sarcopenia as appendicular skeletal muscle mass/height^2 less than 2 standard deviations below the mean for young, healthy reference populations, a quarter to a half of men and women aged 65 and older are likely sarcopenic [8,11]. Given our rapidly aging population, research designed to better understand the development, progression and treatment of sarcopenia is of substantial importance.

The mechanisms underlying the development of sarcopenia are not completely understood and likely numerous, but significant progress has been made over the past few years to identify some of the major contributors to the development of this condition. Here, we will review recent studies related to the regulatory effects and the role of amino acid metabolism in the development and treatment of age-related muscle loss. Following a logical progression of the discoveries in this area, we will begin with a discussion of amino acid and protein metabolism in the basal, postabsorptive state. Subsequently, we will outline the effects of nutrients and, in particular, amino acid on muscle metabolism with aging.

Basal amino acid and protein metabolism in aging

Although the mechanisms leading to sarcopenia are likely numerous, a disproportionate rate of muscle protein breakdown compared to muscle protein synthesis clearly plays a role. Such an imbalance between breakdown and synthesis is smaller in size than that observed in wasting conditions, such as infections or traumatic injuries; however, when protracted over time it can lead to gradual and significant loss of muscle. Since muscle protein degradation has been consistently reported to remain essentially unchanged with advancing age [12-16], there has been an emphasis on studies examining the influence of age on muscle protein synthesis in the basal (postabsorptive) and fed (post-prandial) state. While some researchers have reported a decrease in basal muscle protein synthesis rate with age [17,18], others [14,19] could not confirm those findings in older individuals exhibiting a reduction in muscle mass. The reasons for these discrepancies are still unclear, but it is likely that differences in the health, nutritional status and physical activity level of the different older cohorts enrolled in the various studies [14,19] may have played a significant role. Furthermore, because in the studies reporting a reduced muscle protein synthesis with aging muscle protein breakdown had only been indirectly estimated using whole-body approaches, it is not possible to establish if the subjects were truly experiencing a reduction in net muscle protein balance with aging (i.e. net muscle loss). For example, if a slower muscle protein synthesis was accompanied by a concomitant decrease in breakdown (i.e. decreased turnover) the protein net balance would not change and muscle would not be lost. If there is no age-related difference in basal protein net balance, then it may be inferred that the events contributing to the development of sarcopenia are active outside of the postabsorptive period.

Nutrient intake on amino acid metabolism in aging

The most important anabolic stimulus for muscle proteins is nutrient intake because it allows for replacement of the essential amino acids (EAAs) lost through oxidation. There is clear evidence that increased amino acid or protein availability can enhance muscle protein synthesis and anabolism in young and older subjects [19-21,22•]. It has, however, been suggested that the recommended dietary allowance for protein (0.8 g/kg/day) may not be sufficient for older adults to maintain their muscle mass. In fact, some researchers have reported that the elderly should consume up to 1.2 g/kg/day [23]. In partial support of this conjecture, Thalacker-Mercer *et al.* [24•] reported that inadequate protein intake (0.5 g/kg/day) by older adults resulted in a significant downregulation of muscle transcripts associated with synthesis, energy metabolism and proliferation compared to older adults consuming adequate amounts of dietary protein (1.2 g/kg/day). No measures of muscle protein synthesis or balance were, however, available to determine the net effect of these protein intakes on muscle mass.

Despite suggestions that the elderly should consume more protein [23], the use of high-protein diets alone to increase muscle mass and strength in the elderly has been mostly ineffective [25,26]. There are a number of reasons why these nutritional interventions may have failed to produce positive results. First, when subjects are given nutritional supplements, there is evidence to suggest that they naturally compensate by consuming fewer calories as part of their *ad libitum* diet [25,27] and thus negate any anabolic effects associated with protein supplementation. Second, it is also possible that older adults have a diminished ability to respond to the anabolic effects of the supplements analogous to that observed in old animals. The latter hypothesis is corroborated by the finding that ingestion of an amino acid/glucose mixture stimulated muscle protein synthesis in young, but not older adults [13]. These data have since been confirmed by Guillet *et al*. [28] through the use of a hyperinsulemic/euglycemic clamp while intravenously administering amino acids to emulate the postprandial state.

The existence of insulin resistance of muscle protein metabolism with aging, independent of glucose tolerance, has been further demonstrated in older, healthy and nondiabetic subjects [29]. This defect appears associated with the age-related reduction in endothelium-dependent vasodilation [29], and can be reversed by aerobic exercise through improvements in endothelial function and insulin-induced vasodilation, and insulin signaling [30•]. These data suggest that vasodilation and nutrient flow to the muscle are important regulators of the muscle anabolic response during hyperinsulinemia [29] and during feeding [13]. This hypothesis is further supported by recent data obtained in young individuals where various levels of physiological hyperinsulinemia were induced in the absence of amino acid replacement [31]. In this experiment, the muscle protein anabolic response was mainly related to insulin-induced changes in blood flow and amino acid delivery to the muscle, rather than the absolute insulin level. In other words, in order for hyperinsulinemia to stimulate muscle protein anabolism it must increase capillary recruitment and amino acid flow to the muscle. Altogether, the studies described above highlight the importance of an adequate amino acid supply to the muscle tissue in order to initiate and sustain muscle protein anabolism both in young and older persons.

Amino acids and regulation of muscle metabolism in healthy aging

A number of studies have shown that pure amino acids can stimulate muscle protein synthesis and improve net protein balance in older as well as in younger individuals [19,32-35]. Although older persons have an increased splanchnic extraction of orally administered amino acids at first pass (i.e. immediately after absorption) [34,36], this does not appear to influence the systemic amino acid concentration, which normally increases in the elderly as well as in the young, and consequently the muscle anabolic effect of amino acids [34]. EAAs, in particular, are able to stimulate muscle protein synthesis in the elderly, whereas non-EAAs do not appear to provide any additional benefit with regard to muscle protein deposition and anabolism [35]. Among the EAAs, the branched-chain amino acid (BCAA) leucine has been shown to be a key regulator of muscle protein synthesis in both humans and rats [37-39]. Leucine activates translation initiation in the skeletal muscle cells by increasing the phosphorylation of several signaling proteins including the mammalian target of rapamycin, 70-kDa ribosomal protein S6 kinase and eukaryotic initiation factor 4E-binding protein-1 [37,38,40,41•].

Although large amounts of EAAs exert similar effects in young and older persons [19,34], age-related differences in the muscle anabolic response to submaximal amino acid doses have been recently uncovered. Katsanos *et al*. [42] reported that older subjects had significantly less muscle protein accretion than younger subjects following the ingestion of a 7-g EAA bolus. In a more recent study, the same authors [43••] found that while both a 26% (1.721 g leucine) and a 41% (2.79 g leucine) leucine EAA bolus increased muscle protein synthesis in young men, only the 41% leucine EAA bolus was effective in elderly men. These data are consistent with Paddon-Jones *et al*. [44••] who reported that the iso-caloric ingestion of EAAs containing 2.79 g leucine increased phenylalanine uptake and muscle protein synthesis to a significantly greater degree in older adults than did ingestion of the same amount of a whole protein supplement, whey protein, containing only 1.75 g leucine. Based on these studies it is possible to speculate that aged muscle may be slightly less sensitive to the anabolic effects of leucine than young muscle, but that this age-related difference could be overcome by increased leucine intake.

Recent studies have examined the influence of leucine supplementation as part of a meal on protein synthesis in older muscle, and confirmed that supplementation with leucine dramatically improves postprandial muscle protein synthesis in both old rats [45,46,47•] and humans [48••]. Data from Koopman *et al*. [49••] further highlight that coingestion of protein and leucine along with carbohydrate increased the muscle protein synthesis rate in young and old men to a similar degree. Rieu *et al*. [47•] also examined the influence of meals supplemented with various milk proteins, containing varying amounts of leucine, on postprandial muscle protein synthesis in old rats. They found that protein supplements with the highest leucine content (e.g. β-lactoglobulin, 14.5% leucine) elicited a significantly greater postprandial response of muscle protein synthesis than protein supplements with lower leucine proportion (e.g. casein, 10% leucine). Thus, strategies capable of significantly increasing plasma levels of leucine appear capable of restoring the stimulatory effects of a meal in aging. This phenomenon may partly explain reports [23,50•,51] that older adults require a higher protein intake or a protein ‘pulse feeding’ pattern, i.e. daily protein intake concentrated on one of the daily meals [52,53], to improve their nitrogen and amino acid balance.

Amino acids and muscle metabolism in chronic disease

The ability of amino acid ingestion to stimulate muscle protein synthesis has also recently been demonstrated in clinical populations [54••,55•]. Killewich *et al*. [55•] measured muscle protein synthesis in the calf muscles of older patients with peripheral arterial disease and sex-matched controls before and after the ingestion of 15 g EAAs. Despite the fact that the peripheral arterial disease patients had reduced leg blood flow and, thus, presumably decreased delivery of EAAs, they experienced a significant increase in muscle protein synthesis comparable to healthy controls. This led the authors to speculate that the decreased muscle perfusion in these patients was not sufficient to influence delivery of EAAs to muscle or to attenuate their anabolic effects. In elderly subjects with chronic obstructive pulmonary disease, Engelen *et al*. [54••] reported that soy protein added with BCAAs stimulated whole-body protein synthesis to a greater degree than did soy protein alone. These data are consistent with previous reports that EAAs, particularly BCAAs, are predominantly responsible for the anabolic effects of amino acid ingestion. Together, these data imply that both healthy and diseased elderly may benefit from amino acid supplementation, and that composition, timing and dosage of the supplement should be carefully considered.

Caution is, however, warranted given reports that high physiologic levels of amino acids can induce insulin resistance in humans [56,57]. Specifically, Tremblay *et al*. [57] have reported that increased availability of amino acids impairs the ability of insulin to attenuate glucose production and the ability of muscle to dispose of excess glucose. Their data suggest that the mechanisms underlying amino acid-induced insulin resistance include overactivation of mammalian target of rapamycin and 70-kDa ribosomal protein S6 kinase, along with the inhibition of insulin receptor substrate-1 via serine phosphorylation. Other than the obvious complications that arise from increased insulin resistance (e.g. metabolic syndrome and type 2 diabetes), a recent study [58] suggests that insulin resistance may accelerate muscle protein degradation. Thus, studies are necessary to determine not only the minimum amount of amino acid and protein intake necessary to maintain an adequate muscle mass in aging, but also the upper limit beyond which side effects could occur.

Conclusion

In summary, aging is associated with a progressive loss of muscle mass, which is at least in part due to negative changes in protein and amino acid homeostasis. While older adults may still exhibit normal basal muscle protein synthesis, recent data imply that there may be an age-related decrease in the ability of aged muscle to respond to various anabolic stimuli, including insulin, mixed meals containing amino acids and carbohydrate, and, to some extent, amino acids themselves. Consequently, there is a clear need for strategies that are effective at maximizing muscle protein synthesis and anabolism in the elderly. Based on results from the most recent studies, such strategies may include nutritional supplementation with protein or amino acids, particularly leucine, pulse protein feeding and exercise. Two important points must be noted, however: (i) many of the studies published in the literature have been acute in nature and small in size, and (ii) high physiologic levels of amino acids may potentially induce insulin resistance. As such, recommendations regarding specific dietary and/or exercise interventions await large longitudinal, randomized clinical trials.

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