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Aging and the Control of Amino Acid Metabolism

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Abstract

To investigate the latest developments in amino acid metabolism and their regulatory implications in the context of aging, with a specific focus on addressing and treating age-related muscle loss (Sarcopenia). While the fundamental metabolism of amino acids may remain unaffected by age, older individuals appear to exhibit a diminished capacity to respond to anabolic signals such as insulin and, to a lesser extent, amino acids. Notably, compared to their younger counterparts, aged individuals experience a reduced stimulation of muscle protein synthesis after consuming mixed meals due to insulin resistance. Furthermore, the anabolic effect of amino acids seems to be less pronounced at lower doses. Recent studies, however, suggest that these age-related alterations in amino acid metabolism can be overcome through increased leucine provision, modifications in regular protein intake patterns, or exercise, all of which enhance the activation of translation initiation and muscle protein synthesis. The decline in muscle mass associated with aging is linked to significant changes in amino acid metabolism, and these changes can be acutely reversed through dietary adjustments and physical activity. Nevertheless, extensive clinical trials are needed to determine the clinical significance of these findings in the elderly population and to ascertain whether dietary and exercise interventions can effectively prevent and treat sarcopenia in the long term.

Introduction

Skeletal muscle, comprising 50-75% of all proteins in the human body, serves as the primary reservoir for essential amino acids. Beyond its functions in movement, posture regulation, and energy and nitrogen storage, skeletal muscle plays a crucial role in supplying amino acids for the brain and immune system as fuel, and as a substrate for wound healing during conditions like malnutrition, starvation, injury, and illness. Maintaining body protein mass is essential not only for physical independence but also for survival. A loss of approximately 30% of body proteins leads to impaired respiratory and circulation due to muscle weakness, reduced immune function due to nutrient loss, and compromised epithelial barrier function, ultimately resulting in death [1].

In human senescence, characterized by the involuntary loss of muscle mass and function known as sarcopenia, skeletal muscle degeneration occurs at a rate of 3-8% per decade after the age of 30, accelerating with advancing age. Sarcopenia is associated with lower metabolic rate, diminished energy, increased risk of falls and fractures, prolonged morbidity, and loss of independence. When defined as appendicular skeletal muscles/height^2 less than 2 standard deviations below the mean for young, healthy reference populations, approximately a quarter to half of individuals aged 65 and older may be considered sarcopenia. Given our rapidly aging population, research aimed at better understanding the development, progression, and treatment of sarcopenia is of significant importance [2].

While the mechanisms underlying sarcopenia development are not fully understood and likely multifaceted, recent years have seen substantial progress in identifying key contributors to this condition. In this context, we will review recent studies focusing on the regulatory implications and the role of amino acid metabolism in the development and treatment of age-related muscle loss. Proceeding in a logical sequence of discoveries in this field, we will initiate the discussion with amino acid and protein metabolism in the basal, post-absorptive state, followed by an exploration of the effects of nutrients, particularly amino acids, on muscle metabolism in the context of aging [3].

While the causes of sarcopenia are likely varied, an important factor involves an imbalanced rate of muscle protein breakdown compared to muscle protein synthesis. Although this imbalance is less pronounced than in conditions leading to wasting, such as infections or traumatic injuries, prolonged over time, it can result in gradual and significant muscle loss [4,5]. Muscle protein degradation has been reported to remain relatively unchanged with age, prompting research to focus on the impact of age on muscle protein synthesis in both the basal (post-absorptive) and fed (post-prandial) states. Some studies indicate a reduction in basal muscle protein synthesis with age, while others do not confirm these findings in older individuals with reduced muscle mass. The discrepancies may stem from variations in the health, nutritional status, and physical activity levels of the different older cohorts in various studies. Moreover, because studies reporting reduced muscle protein synthesis in aging indirectly estimated muscle protein breakdown using whole-body approaches, it is challenging to determine if subjects were truly experiencing a decrease in net muscle protein balance with age (i.e., net muscle loss) [6,7]. For instance, if a slower muscle protein synthesis is accompanied by a simultaneous decrease in breakdown, the protein net balance may not change, and muscle may not be lost. If there is no age-related difference in basal protein net balance, it implies that factors contributing to sarcopenia are active outside the post-absorptive period.

Results

The primary anabolic stimulus for muscle proteins is nutrient intake, facilitating the replacement of essential amino acids lost through oxidation. There is clear evidence that increased amino acid or protein availability enhances muscle protein synthesis and anabolism in both younger and older individuals. However, it has been proposed that the recommended dietary allowance for protein (0.8 g/kg/day)

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may be insufficient for older adults to maintain their muscles, with some suggesting an intake of up to 1.2 g/kg/day. Supporting this notion, inadequate protein intake by older adults led to a significant down regulation of muscle transcripts associated with synthesis, energy metabolism, and proliferation compared to those consuming sufficient dietary protein. Yet, measures of muscle protein synthesis or balance were not available to determine the overall impact of these protein intakes on muscles [8].

Discussion

Despite recommendations for increased protein intake in older adults, the use of high-protein diets alone to enhance muscles and strength in the elderly has generally been ineffective. Several reasons may account for the failure of these dietary interventions. Firstly, when subjects receive supplements, there is evidence suggesting that they may compensate by consuming fewer calories as part of their regular diet, thereby negating any anabolic effects associated with protein supplementation. Secondly, it is also possible that older adults have a diminished ability to respond to the anabolic effects of supplements, similar to what is observed in aged animals [9,10]. This hypothesis is supported by findings that the ingestion of an amino acid/glucose combination stimulated muscle protein synthesis in younger but not older adults. These findings have been further confirmed by using a hyperinsulemic/euglycemic clamp while intravenously administering amino acids to mimic the postprandial state.

Conclusion

To sum up, the aging process is linked to a progressive loss of muscle mass, partly attributed to unfavorable changes in protein and amino acid balance. While older adults may still exhibit normal basal muscle protein synthesis, recent evidence suggests a potential age-related decline in the ability of elderly muscles to respond to various anabolic stimuli, including insulin, mixed meals containing amino acids and carbohydrates, and to some extent, amino acids themselves. Therefore, there is a clear need for effective strategies that can maximize muscle protein synthesis and anabolism in the elderly. Based on findings from the latest research, such strategies may involve dietary supplementation with protein or amino acids, particularly leucine, pulse protein feeding, and exercise. It is crucial to note two key factors, however: (i) many studies in the literature have been acute and of small scale, and (ii) elevated physiological levels of amino acids may potentially lead to insulin resistance. Therefore, recommendations regarding specific dietary and/or exercise interventions await large-scale, longitudinal, randomized clinical trials.

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