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Review Article

Muscle Protein Metabolism in Critically Illness

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ABSTRACT

Most patients experience a considerable amount of muscle wasting during critical care. A decrease in muscle mass causes weakness which inevitably leads to delayed recovery. Since muscle also plays an important role in protein metabolism, metabolic instability increases as muscle mass decreases. Accordingly, various treatments have been attempted to maintain muscle mass and function in critically ill patients; however, it is still difficult to prevent muscle loss. It is known that muscle wasting in critical illness is primarily due to increased muscle protein breakdown rather than a decrease in muscle protein synthesis. Nutritional therapy and rehabilitation are fundamentally important, but additional anabolic agents may be needed to overcome anabolic resistance. In this review, we will learn about muscle protein metabolism in critically ill patients and how various treatments affect muscle protein metabolism.

Keywords: Critical illness, Metabolism, Muscle proteins, Amino acids, Rehabilitation

INTRODUCTION

Muscle has an essential metabolic role in addition to its ability to move the body and maintain posture.[1] As a part of the whole-body protein pool, skeletal muscle serves as the main reservoir for amino acids and provides hepatic gluconeogenic precursors.[2,3] Therefore, a decrease in muscle mass not only means an impairment of mechanical muscle function but also a reduction in metabolic reserve in stress conditions, such as trauma, burns, or sepsis. Most patients in intensive care units (ICUs) experience muscle wasting.[4] The rate of muscle wasting has been reported to be 1~6% of total muscle protein per day in previous studies.[4-6] Combined with critical illness neuropathy, muscle wasting contributes to the development of ICU-acquired weakness.[7-9] However, the clinical factors that provoke or alleviate the extent of muscle wasting in the ICU are less well investigated.[10] Muscle protein metabolism in critical illness is one of the most relevant research topics in the critical care and nutrition field.

WHOLE-BODY PROTEIN TURNOVER

For normal adults, the amount of whole-body protein is known to be about approximately 10 kg (Fig. 1). Daily, 3% of whole-body protein is recycled.[11] Muscle protein turnover is lower than that in other organs, but since muscle has the largest mass, it accounts for the main portion (33%) of daily protein turnover. Vital organs, such as the liver and kidneys, show relatively high protein turnover, and the rate of turnover itself could increase in critically ill patients. Organs with high turnover may become vulnerable to a reduction in the availability of amino acids. These findings support recent nutritional guidelines not to reduce protein supply in the acute phases of hepatic and renal failure.[12]

NORMAL MUSCLE PROTEIN BALANCE

Muscle is a dynamic organ, both mechanically and metabolically. Muscle protein undergoes simultaneous synthesis and breakdown, and the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB) determines the net protein balance (NPB).[13] The NPB value can

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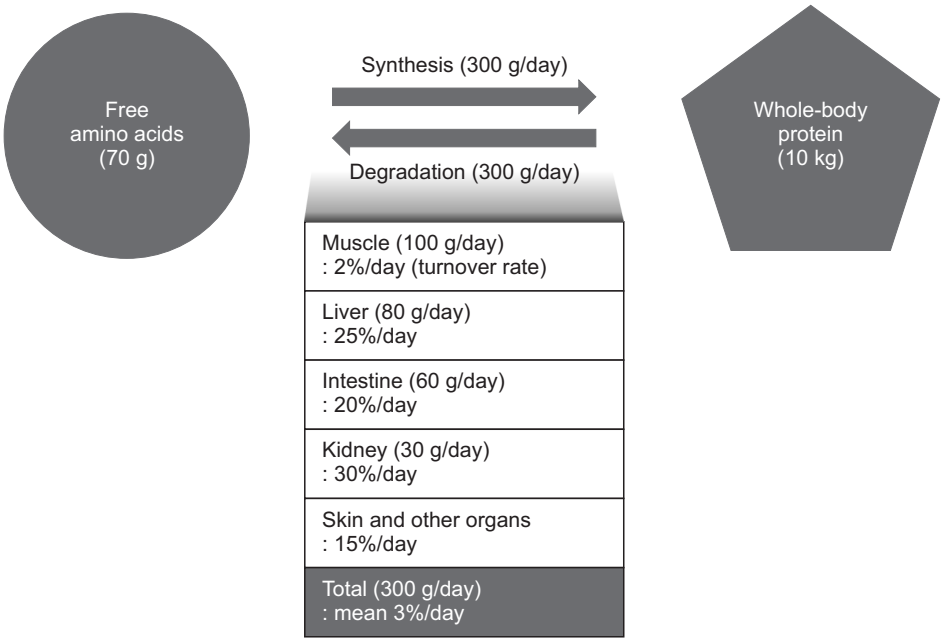

Fig. 1. Whole-body protein turnover.

be obtained by subtracting the MPB from the MPS value. In healthy adults, the turnover rate of muscle protein is reported to be 1~2% per day.[14] There are alternating periods of positive and negative net protein balance throughout the day.[15] Protein breakdown exceeds synthesis in the fasting state, even in healthy adults.[3] Obligatory oxidation of essential amino acids released into the intracellular space during the fasting period contributes to the negative balance. The amino acids supplied through the following meals replete the loss during the fasting period. As this cycle repeats, the total net protein balance approaches zero and the muscle mass remains constant.

STABLE ISOTOPE TRACER METHOD

In vivo protein turnover in humans can be measured using the stable isotope tracer method.[13] One or more tracers (e.g., stable isotope-labeled amino acids) are infused intravenously, and the plasma levels of tracers are measured repeatedly to calculate the turnover rate of the tracee (e.g., amino acids of interest). In the steady state, after the continuous infusion of a stable isotope tracer at a constant rate, the blood concentration of the tracer and tracee reaches a certain plateau level. The ratio of tracer to tracee (i.e., isotope enrichment) in the steady state is inversely correlated with the rate of appearance of the tracee in plasma. If the rate of appearance of essential amino acids in the fasting state is determined, we can calculate the rate of degradation of whole-body proteins. Isotope enrichment was determined using gas chromatography and mass spectrometry. Kim et al.[13] reviewed the method of metabolic research with stable isotopes in their article.

CRITICAL ILLNESS

Catabolism dominates metabolism in critically ill patients. Increased MPB, rather than decreased synthesis, leads to muscle wasting. Essential amino acids derived from muscle breakdown are utilized to meet the increased demands for acute-phase protein synthesis, immune function, and wound healing. For example, more than 3 g/kg/day of protein, four times the normal daily intake, is required for wound healing of burns affecting 50% of the body surface area.[16] Contrary to common expectations, MPS is also increased in critical illness. Accelerated MPB provides excess intracellular free amino acids and, in turn, these free amino acids serve as substrates and facilitate MPS.[3] However, even with aggressive nutritional therapy, accelerated MPB is difficult to offset by protein synthesis due to anabolic resistance.[17] The change in each component of muscle protein metabolism in various clinical conditions is summarized in Table 1.

1. Anabolic resistance

The mechanisms of anabolic resistance have not been fully investigated, but two possible mechanisms have been suggested. First, the inward transport of essential amino acids into muscle cells is impaired in a critically ill state. Due to this impairment, the supplied amino acids may not exert a sufficient anabolic effect on muscle. Diffusion through the interstitial fluid is the rate-limiting stage for the inward transport of essential amino acids to the muscle cell.[18] The presence of tissue edema, frequently present in critically ill patients, could impede amino acid uptake by muscle cells.[19]

Second, the rates of amino acid efflux from the intracellular space to the plasma and obligatory oxidation of essential

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Table 1. Muscle protein metabolism in various clinical conditions

	MPS	MPB	NPB
Normal (post-prandial)	++	+	+
Normal (fasting)	+	++	-
Catabolic state (fasting)	+++	++++++	---
Catabolic state (protein supply)	++++	++++++	--
Catabolic state (rehabilitation)	?	?	-

The number of (+) or (–) signs indicates the relative rate of synthesis or breakdown of muscle protein, respectively. MPS = muscle protein synthesis; MPB = muscle protein breakdown; NPB = net protein balance.

amino acids within the intracellular space increase in the catabolic state.[3] As a result, the concentration of essential amino acids required for the re-synthesis of muscle protein is reduced. Regardless of metabolic status, sarcopenia in the elderly is known to be associated with evolving anabolic resistance with aging.[20]

2. Protein supplement

In healthy adults, increasing protein supplementation causes a net gain in body protein. Kim et al. [21] proved that when the same amount of calories but different amounts of protein (30 g vs. 70 g) are provided, the net protein balance increases proportionally to the amount of protein supplied. Furthermore, essential amino acids are the vital components in stimulating MPS. Volpi et al. [22] showed that if essential amino acid content was equal, the protein synthesis rate was identical, regardless of the non-essential amino acids content. Katsanos et al. [23] showed that there is no increase in protein synthesis when only non-essential amino acids are supplied. Although anabolic resistance exists, the intracellular concentration of amino acids has a linear correlation with protein synthesis, so maintaining a sufficient protein supply in critically ill patients is crucial to improving the net protein balance.[24] Liebau et al. [25] reported that supplying an additional 1 g/kg of amino acids to critically ill patients increases MPS but does not affect MPB. In both healthy and critically ill states, the supply of proteins increases protein synthesis but has little effect on protien breakdown.

3. Rehabilitation

Due to sedation, bed rest, or weakness most critically ill patients move less, which exacerbates muscle wasting.[26] It is well known that the rate of MPS decreases during immobilization.[27] Although there is not yet definitive evidence, MPB appears to temporarily increase at the beginning of immobilization and then returns to the normal rate as inactivity continues.[28]

There is a growing body of evidence that rehabilitation in critically ill patients is associated with an improvement in clinical outcomes, such as physical function, ventilator-free days, and length of ICU or hospital stay.[29,30] However, few studies have shown that rehabilitation leads to physical improvements in the muscles themselves, such as increasing muscle mass.[10,31] In healthy adults, resistance exercises increase MPS by synergizing with the supply of amino acids.[15] In addition, aerobic exercise enhances the muscle protein anabolic response after nutrient intake in the elderly.[32] Further research is needed to determine whether the benefits of exercise in healthy adults will be equally observed in critical patients. The NEXIS (Nutrition and Exercise in Critical Illness) trial, which will simultaneously evaluate the effects of amino acid supply and rehabilitation in critically ill patients, is in progress.[33] Myostatin, a member of the transforming growth factor-β family known to inhibit muscle differentiation and growth, appears to be suppressed and maintained at a low level throughout rehabilitation.[28] MPB may increase with rehabilitation, especially in the early stages, which is known to be related to skeletal muscle remodeling.[34]

4. Anabolic agent

Elevated levels of stress hormones, such as catecholamine, cortisol, and glucagon, induce hypermetabolic and catabolic states in critical illness. In this situation, the use of anabolic or anti-catabolic agents, in addition to appropriate nutritional therapy, is theoretically promising. Several potential agents have been studied, including insulin, IGF1/IGFBP-3, propranolol, and androgens (testosterone and oxandrolone).[35-38] Interestingly, the metabolic effects of agents often differ from those in normal healthy adults. For example, propranolol, which has no anabolic effect under normal conditions, causes a strong anabolic effect in fed burn patients.[39] Insulin and testosterone exert anabolic effects by inhibiting MPB under normal circumstances, but by increasing MPS in burn patients.[40] Each agent should be used in consideration of their inherent pharmacologic effects and possible adverse reactions.

CONCLUSION

Muscle is an organ that plays an important role in metabolism and movement. Thus, a decrease in muscle mass causes metabolic instability, as well as weakness, both of which adversely affect clinical outcomes in critically ill patients. Increased muscle protein degradation rather than decreased

muscle protein synthesis leads to muscle wasting in critical illness, but direct treatment targeting protein breakdown has not been well established. In addition to sustained efforts to increase the supply of protein and provide high-quality rehabilitation, research on clinical factors and treatments to maintain muscle mass in critically ill patients is needed.

CONFLICTS OF INTEREST

The author of this manuscript has no conflicts of interest to disclose.

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