Specific amino acids that regulate muscle mass in health and disease

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Many diseases and conditions such as aging, sepsis and cancer are characterized by a loss of skeletal muscle mass that leads to progressive functional impairment. The loss of muscle significantly impairs quality of life and results in increased morbidity and mortality (Koopman, 2011). Systemic inflammation during ageing and acute illness reduce skeletal muscle protein synthesis and increases protein breakdown by increasing circulating inflammatory cytokines (*e.g.* TNFα and IL-1β) and increasing intracellular [Ca^{2+}] that trigger muscle degradative pathways and impair the normal anabolic response to food intake. Treatments that modulate inflammation and/or the anabolic response to food will have potential to counteract muscle wasting in the elderly and patients.

Protein turnover in skeletal muscle is highly responsive to nutrient intake and changes in hormone levels following a meal. Protein intake in particular strongly stimulates muscle protein anabolism as it provides amino acids, the building blocks needed to synthesise new proteins. Some amino acids have been shown to be more effective in stimulating protein synthesis than others. It has been shown in various cell, animal and human models that the essential amino acids stimulate protein synthesis in a dose-dependent manner, whereas non-essential amino acids do not increase protein synthesis in healthy volunteers. Of the essential amino acids, leucine seems to be the main driver for the post-prandial increase in protein synthesis and has the unique ability to directly increase signalling through mTOR and its downstream targets 4E-binding protein, S6K1 and ribosomal S6 (Koopman, 2011).

Although essential amino acids such as leucine, have purported anabolic properties, many of the non-essential amino acids are considered biologically neutral. However, some non-essential amino acids can modulate protein metabolism during wasting or inflammatory conditions. For example, the non-proteinogenic amino acid citrulline can manipulate skeletal muscle protein metabolism *in vivo* through its conversion to arginine. Additionally, independent of arginine availability, citrulline has protective effects on skeletal muscle cells *in vitro* (Ham, 2013). Glycine, another non-essential amino acid, could be an effective anti-inflammatory agent. Glycine administration can reduce cytokine protein and whole-body inflammation and since inflammation is central to the development of muscle wasting in many conditions, glycine supplementation represents a simple, safe and promising treatment. We have recently shown that glycine protects skeletal muscle from cancer-induced wasting and loss of function, reduces the oxidative and inflammatory burden, and reduces the expression of genes associated with muscle protein breakdown in cancer cachexia (Ham *et al*., 2013).

In summary, amino acids are not just simple building blocks for protein synthesis. The essential amino acids, leucine in particular, have well defined anabolic properties. However, some of the non-essential amino acids such as glycine can effectively modulate protein metabolism during muscle wasting conditions.

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