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PERSPECTIVES

Leucine: a nutrient 'trigger' for muscle anabolism, but what more?

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The loss of skeletal muscle mass with advancing age (termed sarcopaenia), impairs physical function, thereby reducing independent living in older adults and causing growing concern to the public healthcare sector. The precise mechanisms underpinning sarcopaenia are not fully elucidated, but almost certainly involve alterations in muscle protein metabolism culminating in protein loss (i.e. when the rate of muscle protein breakdown chronically exceeds synthesis). There is likely to be some programme in sarcopaenia that is truly a consequence of ageing *per se*, but it is undoubtedly exacerbated through periods of muscle unloading and disuse. Periods of disuse, for example during hospitalization (i.e. leg casting or bed rest), can reduce postabsorptive and, more dramatically, postprandial rates of muscle protein synthesis, outcomes even healthy young muscles cannot escape when inactive (Glover *et al.* 2008)! Blunting of the normally robust muscle protein synthetic response to amino acids with disuse/inactivity has been termed 'anabolic resistance'. It is intuitive to expect that as we age the times spent physically inactive due to illness will become more frequent. During such times, dramatic loss of muscle mass and impairments in the ability of older muscles to recover anabolic sensitivity upon resuming normal activities of daily living are thought to be the underlying basis for sarcopaenia (Breen & Phillips, 2011).

As an example of how frequent periods of physical inactivity may induce anabolic resistance in older muscles, we recently showed that healthy older adults require a greater dose of protein to acutely increase muscle protein synthesis above fasting rates compared with the young (Yang *et al.* 2012). With this in mind, dietary strategies to assist in muscle maintenance and hypertrophy during ill health and subsequent recovery are critical for older adults. In this issue of *The Journal of Physiology*, Magne *et al.* (2012) elegantly examine the effectiveness of different dietary protein interventions for assisting in the recovery of muscle mass in old rodents following dramatic disuse-induced atrophy. Specifically, rats were fed a standard casein or casein plus free leucine diet over 40 days of recovery from a period of hindlimb immobilization. The branched chain amino acid leucine occupies a position of prominence in that it alone can act as a stimulatory signal for muscle protein synthesis (Atherton *et al.* 2010). Furthermore, peak leucinaemia appears, at least in part, to dictate the amplitude of the muscle anabolic response to protein ingestion (Norton *et al.* 2009; Breen & Phillips, 2011). It has been demonstrated that long-term free leucine supplementation does not promote muscle hypertrophy in healthy older adults (Verhoeven *et al.* 2009). However, little is known of how leucine supplementation during and after immobilization might affect muscle mass.

Magne *et al.* (2012) demonstrate that immobilization atrophied the gastrocnemius by ∼20%. In addition, isotopic tracer techniques allowed the authors to show that the atrophied muscles were no longer able to mount a 'normal' muscle protein synthetic or intramuscular signalling response to food intake, congruent with disuse-induced anabolic resistance observed in humans (Glover *et al.* 2008). What was most intriguing was the finding that consumption of additional free leucine on top of a normal casein diet during recovery did not promote any gains in muscle mass, despite the fact that the anabolic sensitivity of muscles returned to pre-immobilization levels. In explanation of this paradoxical finding, the authors hypothesized that leucine merely acts as a 'trigger' for muscle protein synthetic machinery, and that despite transiently elevating rates of synthesis the response was not sustained long enough to result in net protein accretion and hypertrophy. It is known that free leucine is rapidly digested and, thus, the lag between the anabolic actions of leucine and the availability of other amino acid substrates required to prolong the muscle protein synthetic response (Norton *et al.* 2009) may explain the absence of any hypertrophic response.

To verify the importance of synchronization between the leucine 'signal' and amino acid availability, the authors conducted a pilot experiment in which they provided two additional groups of rodents with (i) a whey protein diet or (ii) a whey plus casein protein diet (high protein) during recovery from immobilization. Whey protein has been well defined as a rapidly digested, leucine rich intact protein source providing all other essential amino acids, whereas casein is slowly digested resulting in prolonged aminoacidaemia compared with whey (Boirie *et al.* 1997). As hypothesized, the authors were able to show that consumption of whey protein during recovery, alone or in addition to a normal casein diet, induced a gain of ∼60% of the muscle lost. Mechanistically, the benefits of whey and whey plus casein protein diets on the recovery of muscle mass may be explained by the sustained aminoacidaemia that was observed, which may have prolonged the muscle protein synthetic response.

In conclusion, Magne *et al.* (2012) have affirmed that impairments in the recovery of muscle mass following disuse are due to a blunted response to normally robust anabolic stimuli (i.e. amino acids). Furthermore, they have presented us with intriguing evidence that despite the potent anabolic properties of leucine supplementation, a full complement of essential amino acids, in a rapidly digestible form of whey, is required to facilitate the anabolic actions of leucine leading to muscle protein accretion and hypertrophy. Finally, as human physiologists, we acknowledge it is difficult to draw parallels between rodents and humans due to complex differences in the biology of wasting between species. From a nutritional standpoint, however, the work of Magne *et al.* (2012) allows us to gain valuable insight into the efficacy of amino acid and protein supplementation for muscle remodelling following disuse. Hopefully, we might be able to apply this knowledge to older humans in the very near future.

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