Understanding Dietary Protein and Protein Quality

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Many oral nutritional supplements tend to include high levels of protein, in some cases at the expense of other macronutrients, but why? Protein is a key nutrient for the growth and maintenance of skeletal muscle, which is the largest organ in the body and is responsible for locomotion and metabolic homeostasis.[1] It thus follows that skeletal muscle wasting, which is a prominent feature of most communicable and non-communicable diseases including ageing, cancer and diabetes, is associated with poor health outcomes, such as an increased risk of frailty, morbidity and mortality.[2-7] Thus, high protein nutritional supplements can play a crucial role in preventing or minimising muscle wasting, and the ensuing poor health outcomes observed in many pathological scenarios. Dietary protein also has many other pertinent roles that are not just isolated to skeletal muscle. For example, dietary protein stimulates neurotransmitter synthesis in the brain, supplies amino acids which act as precursor molecules to synthesise other amino acids and acts as a primary carbon source for hepatic gluconeogenesis.[8-10]

How does the body process dietary protein foodstuff into amino acids?

The first step involved in the processing of dietary protein is the act of chewing, breaking down large pieces of food into smaller pieces to be swallowed (unless provided in liquid form). Saliva, courtesy of the salivary glands, aids swallowing and the travel of the foodstuff through the oesophagus and into the stomach. Here, gastric juices containing the enzyme pepsin and hydrochloric acid begin breaking down the protein. Proteins still in their three-dimensional structure begin to unfold due to the acidity of the stomach, and pepsin digests the peptide bonds between amino acids, creating smaller peptide chains. Thereafter, stomach contractions blend the partially digested protein into a 'chyme' mixture, which is emptied into the small intestine. Once in the small intestine, digestive enzymes provided by the pancreas and the cells that line the small intestine further break down the remaining smaller protein fragments into tripeptides, dipeptides and individual amino acids, ready for absorption. Amino acids then cross the cells lining the small intestine, known as enterocytes, and enter the blood stream where they are transported to the liver. The liver withholds the amino acids it requires, before allowing the remaining amino acids to enter the systemic circulation, a process known as first pass splanchnic extraction. Amino acids travel through the blood stream and feed into limbs/organs - like skeletal muscle. It is important to note that not all amino acids enter the cell the same way, there are different transport mechanisms depending on the amino acid(s). The amino acids are then present in the cell as a bulk of free amino acids, and these amino acids initiate cellular processes, increasing the rate at which messenger RNA is converted into protein.

Classifying amino acids

There are 20 amino acids required for protein synthesis and these are all 'metabolically essential'. Of these 20 amino acids, 9 must be acquired from dietary sources and are therefore known as 'indispensable' or 'essential' amino acids (**Table 1**). The remaining amino acids do not have to be derived from the diet, provided that there are appropriate and sufficient precursors within the body from which they can be synthesised. These are known as 'dispensable' or 'non-essential' amino acids (**Table 1**). In other situations, such as childhood or certain pathological conditions, a number of amino acids may not be formed in adequate amounts because demand is high, the pathways for their formation are immature, and/or the rate of endogenous formation is inadequate. These are known as 'conditionally essential' amino acids (**Table 1**). For example, glutamine is a fuel source for immune cells, so in situations of heightened inflammation, glutamine is released from muscle cells to feed the immune system, therein indirectly resulting in muscle wasting. In order to compensate for this loss of muscle glutamine, more glutamine may be required from dietary protein.

Table 1: Amino acid classification

Essential amino acids	Conditionally essential amino acids	Non-essential amino acids
Histidine	Arginine	Alanine
Isoleucine	Asparagine	Aspartate
Leucine	Cysteine	Glutamate
Lysine	Glutamine	
Methionine	Glycine	
Phenylalanine	Proline	
Threonine	Serine	
Tryptophan	Tyrosine	
Valine		

How does physical activity and inactivity affect the body's response to dietary protein?

In the non-exercised state, skeletal muscle is only transiently receptive to the anabolic effects of amino acids. Following protein intake, it takes ~45-90 minutes for digestion, absorption and arrival of the amino acids at the target tissue.[11] These, now intracellular, amino acids activate anabolic signalling pathways, increasing muscle protein synthesis (MPS) by ~two-to-three-fold. MPS peaks at ~1.5-2 hours, afterwards, returning to baseline ~2-3 hours following protein ingestion.[11] Thereafter, MPS is refractory to available essential amino acids and elevated intracellular anabolic signalling, a phenomenon termed 'muscle full', whereby muscle cells sense excess essential amino acids and divert them towards oxidation.[12]

Physical activity prolongs the transient anabolic effects of dietary protein (i.e., physical activity delays the onset of 'muscle full').[9] Specifically, resistance exercise combined with dietary protein intake increases the magnitude and duration of the MPS response, meaning that a greater number of amino acids are taken up into the muscle, supporting muscle growth and remodelling.[13]

Physical inactivity, on the other hand, impairs the ability of getting amino acids into the muscle. For example, in situations of bed rest – due to injury or illness – skeletal muscles still waste despite elevated protein intake.[14] In fact, there is currently limited evidence to support that dietary protein (up to 1.6 g protein/kg/d) can offset muscle wasting during disuse, which may be because of the emerging nature of this area still requiring further investigation (e.g., trialling protein diets >1.6 g protein/kg/d during periods of bed rest).[14]

The mechanisms underpinning enhanced and diminished amino acid use following physical activity and inactivity, respectively, are still not fully known. From a clinical standpoint, devising optimal protein nutrition to minimise negative health effects is critical, but so is getting people physically active – if physically able to – in order to potentiate the anabolic benefits of protein nutrition.

Dietary protein quality

The anabolic response to dietary protein is dependent on multiple factors, such as: the amount of protein given, the digestion and absorption kinetics of the protein source and the amino acid profile of the protein source. Nonetheless, it is generally accepted that dietary proteins containing more essential amino acids are more likely to stimulate a greater MPS response and are therefore typically considered higher quality sources of protein.

Animal-derived protein sources, like those directly originating from animal sources such as meat, fish, poultry, eggs, whey and casein, are regarded as 'complete' proteins, which means they provide adequate amounts of all essential amino acids to meet human requirements.[15] Animal-derived protein (~20-25 g whey) elicits a rapid post-prandial increase in circulating plasma essential amino acids and subsequently a robust increase in MPS.[16] In fact, leucine primarily drives the MPS response to protein feeding, with as little as 3 g essential amino acids containing 40% leucine maximally stimulating MPS.[17]

However, concerns surrounding environmental sustainability mean that there is increasing interest in plant-derived proteins such as wheat or soy, as alternative/adjuvant dietary sources.[15] Generally, plant-derived proteins have a lower leucine content, inferior digestibility (due to the fibre and tannins content) and lack one or more amino acids, particularly lysine and/or methionine, and are thus less anabolic, compared to animal-derived protein sources.[15] Although, there may be exceptions. To give an example, the essential amino acid content of potato-derived protein is comparable to casein or egg protein, and the leucine content is purportedly higher, so in theory, potato-derived protein could prompt similar, or perhaps more robust, MPS responses compared to animal-derived sources.[18] Certain strategies can also be used to overcome the inherently inferior anabolic properties of plant-derived protein. For example, increasing the amount of plant protein consumed thereby matching the leucine content of animal-derived protein can elicit comparable MPS responses. Another potential strategy is to fortify plant-derived protein sources with the amino acids it is deficient in.

Collagen-derived proteins (i.e., proteins derived from gelatin and/or collagen hydrolysates that originate from animal sources such as bone, pigskin, fish skin) are also potential protein sources, although they are not considered 'complete' proteins because they are low in essential amino acids, high in non-essential amino acids (e.g., proline, glycine) and lack tryptophan.[15] Dietary collagen does, however, have superb digestibility and becomes rapidly bioavailable following consumption, and so may have some nutritional value.

To overcome the amino acid inadequacies of some dietary protein sources, specific amino acid sources are added, or different sources of protein can be blended together to produce an anabolic mixture. Most protein blends so far have involved combining animal and plant sources in order to exploit the digestive properties of each protein source with the aim of maximising amino acids availability and potentially enhancing and/or extending the MPS response.[19]

More recently, other potentially viable and anabolic protein sources have been investigated, including the breading of insects, the growing of yeast, micro-algae, fungi and the culture of lab-grown meat. Although investigations into these protein options is still in its infancy, some emerging evidence indicates anabolic promise. As an example, protein derived from the culture of fungus – mycoprotein – contains a similar amino acid composition to dairy protein sources, demonstrates good digestibility, and stimulates MPS similar to that of leucine-matched milk protein.[20]

Dietary protein digestibility scoring methods

Protein quality is based on protein digestibility scoring methods and has traditionally been measured using the Protein Digestibility Corrected Amino Acid Score (PDCAAS). This compares the essential amino acid composition of a protein source to a reference. Using PDCAAS, a protein source providing all essential amino acids, such as whey, achieves the highest score of 1.0, whereas incomplete protein sources, such as nuts, achieve a lower score of ~0.4 (**Table 2**).

Table 2: Protein scores for different dietary protein sources using the DIAAS or PDCAAS method[24, 25]

Dietary Protein	DIAAS	PDCAAS
Whey protein isolate	1.09	1.00
Whole milk	1.14	1.00
Egg (hard boiled)	1.13	1.00
Soy protein isolate	0.90	0.98
Almonds	0.40	0.39

As with many scoring methods, PDCAAS does suffer from limitations, such as the fact that it uses faecal protein digestibility, which can provide inaccurate values of true protein digestibility because of substantial bacterial metabolism of amino acids in the colon.[21] Further, PDCAAS values are truncated at 1, implying that amino acids available over those contained in a reference protein provide no additional nutritional benefit, and so proteins of higher quality are not identified.[21]

As a consequence of the limitations associated with PDCAAS, the Food and Agriculture Organisation of the United Nations more recently recommends the use of the Digestible Indispensable Amino Acid Score (DIAAS) scoring method.[22] DIAAS estimates protein digestibility based on true ileal digestibility, which is determined at the end of the small intestine where the amino acids are absorbed.[21] It evaluates protein quality by determining the ratio of digestible amino acid content to the amino acid reference pattern taken from age-specific amino acid requirements.[21] DIAAS is also not without its limitations as it does not account for amino acid absorption kinetics – the rate at which amino acids are being absorbed – it only accounts for overall protein absorbability, the cumulative absorption.

In order to overcome the limitations associated with both DIAAS and PDCAAS, a minimally invasive dual-stable-isotope tracer method has recently been developed, which permits the simultaneous measurement of ileal digestibility of different indispensable amino acids from dietary protein sources.[23]

Dietary protein quality is important in older people

Optimising protein intake in older adults is a key strategy to help offset age-related declines in muscle mass (sarcopenia).[2] The European Society for Clinical Nutrition and Metabolism (ESPEN) working group currently recommends healthy older adults consume 1.0-1.2 g protein/kg/day, which increases to 1.2-1.5 g protein/kg/day for older adults who are malnourished or are at risk of malnutrition because of acute or chronic illness.[26] Older adults have higher protein requirements, compared to their younger counterparts, since they develop a resistance to the anabolic effects of dietary protein – termed 'anabolic resistance' – which may be because of reduced digestive capacity, enhanced splanchnic extraction of amino acids, reduced postprandial amino acid availability, reduced postprandial muscle perfusion, reduced uptake of dietary amino acids into the muscle and/or reduced anabolic signalling for protein synthesis.[11, 26] Older adults also tend to have a reduced appetite and lower set point for satiety, thus requiring protein mixtures that maximise anabolism (i.e., animal sources and/or leucine) with minimal satiety.

Is there an 'ideal' dietary protein intake or amino acid profile?

There is no single ideal protein intake, or amino acid profile, since amino acid requirements will depend on multiple factors such as, but not limited to, age, disease or injury. For example, chronic kidney disease (CKD) patients with end stage renal disease and undergoing dialysis are at a high risk of protein energy wasting, which is the progressive and simultaneous depletion of systemic protein and energy stores.[27] As such, they are recommended to consume ≥1.2 g protein/kg/day, which is nearly double the recommendation of 0.6-0.8 g protein/kg/day for pre-dialysis CKD patients, where lower protein intake is recommended in order to reduce uremia, ultimately slowing CKD progression and the need for dialysis.[28-29] Dialysis patients are also advised to limit/avoid plant-derived protein sources due to the phosphorus and potassium content, instead, favouring animal-derived protein sources which are (typically) characterised by superior bioavailability and greater essential amino acid profiles, although protein sources in this context have been debated recently.[30]

Conclusion

Dietary protein is a fundamental nutrient for the maintenance and growth of skeletal muscle. The anabolic effects of dietary protein are driven mainly by the essential amino acids, particularly leucine, and are transient in nature. This 'muscle full' state cannot be overcome by further feeding but can be delayed by physical activity via increased sensitivity of the muscle to essential amino acids, extending the duration and magnitude of MPS. Physical inactivity, on the other hand, results in a premature onset of muscle full. The anabolic response to dietary protein is dependent on the amount of protein given, the digestion and absorption kinetics of the protein source and the amino acid profile of the protein source, which reflects the overall protein 'quality'. Protein 'quality' can differ between animal-, plant- and collagen-derived protein sources, which must be considered when developing personalised protein strategies for specific populations (e.g., ageing, protein energy wasting).

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