Protein

Proteins are polymers of amino acids linked via α-peptide bonds. They can be represented as primary, secondary, tertiary, and even quaternary structures, but from a nutritional viewpoint only the primary (amino acid) sequence is of interest. Similarly, although there are many compounds in the body that can be chemically defined as amino acids, we are only concerned with the 20 canonical amino acids encoded in DNA, plus 5 others—ornithine, citrulline, γ-aminobutyrate, β-alanine, and taurine—that play quantitatively important roles in the body. We consume proteins, which are digested in the gastrointestinal tract, absorbed as small peptides (di- and tripeptides) and free amino acids, and then used for the resynthesis of proteins in our cells. Additionally, some amino acids are also used for the synthesis of specific (nonprotein) products, such as nitric oxide, polyamines, creatine, glutathione, nucleotides, glucosamine, hormones, neurotransmitters, and other factors. Again, such functions are not quantitatively important for most amino acids, and the bulk of amino acid metabolism is directly related to protein turnover (synthesis and degradation). For an individual in nitrogen balance, an amount of protein equal to that of the daily protein (nitrogen) intake is degraded each day with the nitrogen being excreted as urea and ammonia (with limited amounts of creatinine and uric acid). The carbon skeletons of the amino acids degraded to urea and ammonia are recovered through gluconeogenesis or ketone synthesis, or oxidized to carbon dioxide.

Of the 20 amino acids present in proteins, 9 are considered nutritionally indispensable (essential) in adult humans because the body is not able to synthesize their carbon skeletons. These 9 amino acids are leucine, valine, isoleucine, histidine, lysine, methionine, threonine, tryptophan, and phenylalanine. In addition, 2 others are made from their indispensable precursors: cysteine from methionine, and tyrosine from phenylalanine. Although arginine is needed in neonates, it appears that adults, with the possible exceptions of pregnancy in females and spermatogenesis in males, can synthesize sufficient arginine to maintain a nitrogen balance. The others, glutamate, glutamine, aspartate, asparagine, serine, glycine, proline, and alanine, can all be synthesized from glucose and a suitable nitrogen source. Under some conditions, glutamine, glutamate, glycine, proline, and arginine may be considered as conditionally indispensable, meaning that the body is not capable of synthesizing them in sufficient quantities for a specific physiologic or pathologic condition (1). Thus, any discussion of dietary protein must consider not only quantity but also quality (ratio of indispensable amino acids).

Deficiencies

Frank deficiencies of dietary protein are usually classified into marasmus, a general wasting due to a deficiency of both protein and energy, and kwashiorkor, characterized by a distinctive edema and a deficiency of both protein quantity and quality. Less severe deficiencies, due to low intake or an imbalance in indispensable amino acid intake, may result in reduced growth in children or a loss of lean body mass in adults. This may then lead to increased susceptibility to disease and subsequent problems.

Dietary Recommendations

The current DRI for adults is 0.8 g protein $\cdot$ kg body weight^{-1} $\cdot$ d^{-1} with an extra 10 or 15 g recommended for pregnant and lactating women, respectively (1). Requirements are also higher for growing children and in some pathologic states. The average intake is ~64 and 104 g for adult women and men, respectively, or ~15% of calories in the United States. Protein deficiency is relatively rare in young adults who consume regular diets in developed countries. Studies have, however, indicated that in the United States $\leq$50% of home-bound elderly subjects may not have adequate intake of $\geq$1 indispensable amino acid (2).

Food Sources and Protein Quality

The protein content of foods varies considerably, but in general animal sources tend to be superior in both protein quantity and quality when compared with plant foodstuffs. Meat, eggs, and milk are all considered excellent sources of high-quality protein and egg protein is often taken as the ideal (complete) protein with which the indispensable amino acid profile of other foodstuffs is compared. Some plant-based foods, most notably legumes such as beans, peas, and lentils, do contain considerable amounts of proteins. Comparatively few plant-based foods, however, provide sufficient amounts of all the indispensable amino acids or glycine. Most legumes tend to be deficient in methionine, and although potatoes contain relatively large amounts of protein, the indispensable amino acid ratios are poor. Other plant foodstuffs tend to contain low amounts of protein with varying limitations in their quality. Cereals, for example, tend to be low in lysine and tryptophan content, although they do contain sufficient methionine. Thus, the combination of different plant-based foods in dishes such as rice and beans, or peanut butter and bread, results in a complementary effect that raises the protein quality when compared with either of these food types consumed alone. Therefore, it is possible for adults to obtain adequate amounts of high-quality protein from a vegetarian or vegan diet. It should be noted,

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however, that taurine may be required for neonates, and that taurine is only present in animal-based foodstuffs.

The protein quantity in a food is usually reported as the total nitrogen content multiplied by 6.25. This is justified since most amino acids contain 16% nitrogen, but it should be recognized that foods may contain additional, nonprotein, nitrogenous compounds, and thus for some foodstuffs the reported protein content may be an under- or overrepresentation. A more accurate indication of both protein quantity and quality of a food can be determined from the analysis of its constituent amino acids (the chemical score). From the chemical score, it is possible to list those indispensable amino acids that are limiting, but ideally this should be complemented with a biologically based test to assess the availability of those amino acids.

In the United States, if the suppliers of a food are claiming it to be a significant source of protein, or if the food is designed to be fed to children <4 y of age, further analyses taking into account amino acid availability are required. For many years, this was based on the Protein Efficiency Ratio (determined in growing rats), as it still is in Canada, but since the early 1990s the Protein Digestibility Corrected Amino Acid Score (PDCAAS) has been employed (3, 4). The PDCAAS is determined from the chemical score for the limiting amino acid in the food, times the "fecal true digestibility" (in rats). Under this system, no protein has a score >100 (adequate in the limiting amino acid) which does not take into account an excess of ≥1 amino acid that could enhance or reduce the value of the protein. Furthermore, the PDCAAS may overvalue a protein if some of that protein is fermented in the colon by the microbiota and where the amino acids released would not be available to the body. This means that "fecal true digestibility" does not represent the true digestibility of dietary protein. Thus, a new standard, the Digestible Indispensable Amino Acid Score (DIAAS), has been recommended to overcome some limitations of the PDCAAS (3–5). The DIAAS method attempts to measure digestibility at the end of the small intestine (ileum). This can be done in humans, pigs, rats, or even an artificial gut system. The DIAAS, therefore, attempts to take into account antinutrient-type problems, where the protein is not digested in the small intestine, and the values are not limited to 100, meaning that any excess of an indispensable amino acid may be considered in the protein quality. The recommendation to use the DIAAS has not yet been widely used, in part due to technical problems and a paucity of standard values on true ileal digestibility of dietary proteins in humans, and therefore the PDCAAS and the Protein Efficiency Ratio remain in widespread use.

Clinical Uses

The use of supplemental amino acids or a general increase in total protein intake may be appropriate in a disease-specific circumstances. Conversely, in some conditions, such as renal failure or inborn errors of the urea cycle, a low-protein diet may be prescribed, but this does not mean that protein requirements have decreased; indeed, they may have increased. Similarly, various inborn errors of amino acid metabolism may result in restriction of certain amino acids and possibly increased requirements for others. For example, dietary phenylalanine should be restricted in patients with phenylketonuria but, due to a lack of tyrosine synthesis in such patients, tyrosine now becomes essential. Similarly, patients with inborn errors of the urea cycle (with the exception of a deficiency of arginase) require a source of arginine in the diet. It is therefore important to provide specific amino acids as appropriate for these and other inborn errors of amino acid metabolism.

Toxicity

There is little information regarding the toxicity of either protein or individual amino acids in healthy humans. Protein consumption as high as 35% of energy appears to be well tolerated, but there is insufficient data to establish a tolerable upper level, although there may be some conditions where protein restriction is recommended. Healthy 1- to 3-y-old children can tolerate dietary intake of 5 g protein · kg body weight^{-1} · d^{-1}, and healthy adults can tolerate long-term consumption of 2 g dietary protein · kg body weight^{-1} · d^{-1} or even a higher amount (6). Some amino acids may be toxic, as is seen in various genetic metabolic disorders, but detailed toxicity data are rare. Other amino acids, e.g., glutamine, seem to be readily tolerated at doses ≤40–50 g/d with no adverse effects (7). According to the DRI for protein and amino acids, "caution should be exercised with regard to using any single amino acid at levels significantly higher than those found in normal food" (1).

Recent Research

Extensive research is currently being undertaken to definitively determine the dietary recommendations for each indispensable amino acid across the life span, such as the needs of the elderly, and in response to other changes in physiologic and pathologic status (5). Much of such work involves the use of stable isotopes and methodologies such as the indicator amino acid oxidation method. Similarly, there is continuing research into both the benefits of "nutritionally dispensable amino acids," and the value of supplemental amino acids, together with fuller attempts to determine their toxicity. Results from such studies should provide much more accurate recommendations for dietary protein and amino acid intake over the next few years.

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