Basic metabolism: proteins

Hussam Rostom

Brian Shine

Abstract

Proteins serve a range of physiological functions in health and in disease. Their overall structure is determined predominantly by the sequence of amino acids when they are synthesized, which in turn is a derivative of the sequence of nucleotides in the corresponding segment of DNA. There is a constant turnover of body protein, the rate of which exceeds dietary protein intake and therefore suggests a degree of recycling. Some amino acids that enter the body protein pool can be synthesized ('non-essential' amino acids) while others can only be obtained through dietary means ('essential' amino acids). During critical illness and significant trauma there appears to be dysregulation such that synthesis of some non-essential amino acids is limited, while there is an increase in amino acid oxidation. Modification of dietary intake to address the potential imbalance in illness is probably insufficient in isolation to prevent muscle wasting.

Keywords Amino acids; metabolism; protein; protein breakdown; protein catabolism; protein synthesis; protein turnover

Introduction

Proteins are composed of chains of amino acids linked by peptide bonds, the structure of which is defined at four levels. The primary structure describes the sequence of amino acids; the secondary structure is the arrangement of segments of this sequence into three-dimensional components (α-helices or β-pleated sheets); the tertiary structure is the overall folding of these segments into the proteins; the quaternary structure, applicable only to some proteins, is the interaction of separate protein subunits to form a functional unit.

A wide variety of essential roles are served by proteins—these are summarized in Table 1. Their essential role can be seen in cases where mutations manifest as clinical disease—from a single substitution in sickle cell disease to the expansion of trinucleotide repeats in Huntington's disease, and from the frameshift mutation in cystic fibrosis to the deletion in 22q11.2 deletion syndrome. Proteins play a key role in regulating inflammation and healing during critical illness and trauma, but alterations in protein metabolism in disease states can lead to negative consequences. The shifts in body protein following critical illness, trauma and major surgery may lead to significant muscle wasting, with adverse effect. Understanding the processes that may underlie this may help to provide therapeutic approaches to stop wasting.

Brian Shine *MD FRCPath, Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford, UK. Conflicts of interest: none declared.*

Hussam Rostom *MA BMBCh MRCP, Specialty Registrar in Chemical Pathology & Metabolic Medicine, John Radcliffe Hospital, Oxford, UK. Conflicts of interest: none declared.*

Physiological roles of proteins

Function	Example
Enzymatic	Amylase (carbohydrate digestion)
Receptor	Thyroid stimulating hormone (TSH) receptor
Transport: specific	Glucose transporters
Transport: multiple	Albumin
Structural	Collagen
Immunity	Immunoglobulins, complement
Other	Albumin—buffering, maintaining oncotic pressure

Table 1

Amino acids are the building blocks of proteins and there are 21 different amino acids utilized in protein synthesis. Certain amino acids can be synthesized by the body — these are so-called non-essential amino acids and include alanine, asparagine, aspartic acid and glutamic acid. Others cannot be made by the body and must therefore be obtained through the diet — there are nine such essential amino acids, including leucine, isoleucine and phenylalanine. Conditionally, essential amino acids are those that can be synthesized by the body and are usually non-essential but in times of illness or stress cannot be synthesized in sufficient quantity to meet demand. Examples include cysteine, glutamine, tyrosine, proline and serine. It is worth also noting that following incorporation into proteins, amino acids may be modified further through reactions such as phosphorylation, glycosylation and methylation.

Unlike their counterparts in carbohydrates and fats, amino acids contain nitrogen — this makes measurement of nitrogen content of a material one method of estimating protein content. Similarly, protein breakdown yields nitrogen containing excretion products which can be measured. Therefore nitrogen balance is correlated with protein synthesis and degradation.

Dietary intake, digestion and absorption

Nitrogen equilibrium refers to the situation where protein intake is equal to that lost by the body. It appears that some nitrogen intake is essential — when dietary intake of nitrogen is zero, and energy and all other necessary nutrients are consumed in sufficient quantities, there remains an obligatory nitrogen loss. The demand for protein synthesis must be met by adequate amounts of amino acids of a suitable composition.

Most nitrogen in the diet comes from protein, but can also come from free amino acids, nucleotides and creatine. Digestion of proteins commences in the stomach, where the acidic environment favours denaturation, improving accessibility for proteases. The main proteolytic enzyme in the stomach is pepsin, which is maximally active in the low pH of the stomach. Further breakdown of protein continues in the small intestine through the proteolytic enzymes secreted by the pancreas. The products include smaller chains, oligopeptides and free amino acids. Additional digestion takes place on the brush border of the small intestine epithelium, where N-aminopeptidases remove amino acids from the amino-terminal end. Absorption of amino acids occurs through sodium-dependent amino acid transporters, while peptides no longer than four amino acids are taken up via a

Please cite this article in press as: Rostom H, Shine B, Basic metabolism: proteins, Surgery (2018), https://doi.org/10.1016/j.mpsur.2018.01.009

transporter labelled PepT1. In general, intact proteins are not absorbed, but there are situations where protein absorption does occur—for example, the absorption of intact immunoglobulins in the infant gastrointestinal tract is an important form of immunity in the early part of life.

Gastrointestinal dysfunction is common following major trauma or surgery, particularly where the abdomen is implicated, as well as in the critically ill patient.[1] Dysmotility is often seen in such contexts, and may be related to intestinal manipulation, metabolic changes, medications, other physiological changes, or a combination of these. There may also be changes independent of gut transit, including changes in the barrier function of the small intestine. Through cytokines, vascular changes, alterations of mucosal secretions and intestinal flora, there seems to be changes to absorption within the small intestine. Such changes may result in impaired ability to absorb protein and non-protein nutrients in enteral feed.

Essential and non-essential amino acids

Certain amino acids cannot be synthesized by humans, and are only obtained from the diet. These 'essential' amino acids are produced only in microorganisms and plants, with their biosynthetic pathways lost early in animal evolution. They are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. If intake of an essential amino acid falls below the requirement of an individual, protein synthesis will be impaired, even in the presence of adequate total nitrogen intake.

A group of amino acids, namely arginine, cysteine, glycine, glutamine, proline and tyrosine, can be considered 'conditionally essential'. They can be synthesized in the human body, but the rate of this synthesis is limited — in times of illness or stress, the body's demand for them may exceed the ability to produce them.

'Non-essential' amino acids can be synthesized in the body at sufficient levels to meet body demand. These include alanine, asparagine, aspartate, glutamate and serine. They are formed by transamination of their α-keto acid carbon skeletons using the α-amino nitrogen of another amino acid, most often glutamate. Therefore a supply of α-amino nitrogen is essential for production of these amino acids. When considering nutrition, it is important to consider the balance of amino acids obtained through the diet in addition to the total intake.

Fate of free amino acids

Absorbed amino acids are used for protein synthesis, oxidation to urea, or conversion to other compounds. An overview of amino acid metabolic pathways can be seen in Figure 1.

Formation of proteins

The fate of most circulating amino acids is incorporation into protein. The adult human body synthesizes approximately 300–400g of protein per day — four times the average dietary protein intake — while maintaining an approximately neutral protein balance. It appears, therefore, that protein breakdown makes up the deficit and there is a constant turnover of body protein. During periods when muscle mass is increasing, such as during growth phases, synthesis exceeds breakdown.

Protein recycling persists in the absence of protein intake, suggesting that it is obligatory. In this setting, there is continued conversion of amino acids to other compounds and oxidation to urea. Therefore in the absence of dietary protein, there will be net loss of body protein as breakdown will exceed synthesis. It follows that there must be a minimum intake of protein in order to maintain body protein mass. Conversely, it seems that amino acids stimulate cellular protein synthesis, and thus their provision may have effects other than simply limiting protein breakdown.[2]

Oxidation of amino acids and conversion to other compounds

Individual proteins have substantially differing lifetimes, ranging from minutes to weeks (or longer). Nutritional and hormonal factors also influence the rate of protein degradation in each cell. Proteins can be degraded through lysosomal degradation, through ubiquitination or through the proteasome.

Free amino acids generated through the breakdown of cellular protein, as well as those obtained through dietary means, may undergo further degradation intracellularly. This involves a step in which the α-amino group is removed and the often converted to ammonia, which is subsequently incorporated into urea for excretion. The carbon skeleton of the amino acid can be broken down into other compounds. The catabolism of amino acids is outlined in Figure 2.

The urea cycle takes place in the liver through means of urea cycle enzymes. This cycle consumes two molecules of ammonia and one molecule of carbon dioxide to produce urea, with a view to disposing of potentially toxic ammonia. The importance of this collection of processes can be seen in patients with urea cycle disorders, such as ornithine transcarbamylase deficiency, where individuals are at risk of ammonia accumulation. Urea is less toxic and requires less water for excretion. The majority of urea generated by the liver is excreted by the kidneys into the urine. However, the quantity of urea produced by the liver exceeds that which is found in urine — the remainder appears to be converted by colonic bacteria to ammonia, which may be important in de novo protein synthesis in the body, particularly in times of starvation. It appears that at least 80% of urea is excreted in the urine, approximately 10% in the faeces, and the remainder via other smaller scale losses including sweat.

Amino acids are broken down to compounds that can be further metabolized to carbon dioxide and water or used in gluconeogenesis. Approximately 10–15% of energy utilized comes from the oxidative breakdown of amino acids. Some amino acids convert to the glucose precursors pyruvate, α-ketoglutarate, fumarate, oxaloacetate or succinyl-CoA — these are called glucogenic amino acids. Ketogenic amino acids, on the other hand, are broken down to acetoacetate or acetyl-CoA. Some amino acids can produce both carbohydrate and ketone body precursors.

A minority of the total free amino acid pool is used for other purposes within the body. They serve important roles as precursors of nucleotides, nucleotide co-enzymes, neurotransmitters, hormones and haem. For example, decarboxylation of the relevant precursor amino acid is involved in the production of adrenaline, noradrenaline, dopamine, serotonin, histamine and γ-aminobutyric acid (GABA), all of which provide key physiological functions. Glycine is required for the production of porphobilinogen, which in turn is a precursor for the synthesis of haem. Amino acids may also have regulatory roles themselves,

Please cite this article in press as: Rostom H, Shine B, Basic metabolism: proteins, Surgery (2018), https://doi.org/10.1016/j.mpsur.2018.01.009