

Protein Digestion and Absorption

NASPGHAN Physiology series

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Proteins are sequences of amino acids (AA) linked by peptide bonds. There are twenty amino acids of which nine are essential and eleven are non-essential. Essential amino acids include phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine, lysine, and histidine. These AA are essential because the body can't synthesize them. They must be present in the diet or they will be deficient. Four amino acids are considered conditionally essential including arginine, tyrosine, glutamine, and cysteine. Serine, glycine and proline are sometimes considered conditionally essential. Conditionally essential AA are typically present, but in certain conditions may be deficient. An example is found in the disease phenylketonuria (PKU). Individuals living with PKU must keep their intake of phenylalanine extremely low to prevent mental retardation and other metabolic complications. However, they cannot synthesize tyrosine from phenylalanine, so tyrosine becomes essential in the diet of PKU patients.

Adults require 0.75g/kg body weight of protein daily. The requirements are increased in infants and ill individuals.

Clinical correlation - Essential AA are found in animal sources, but vegetable sources have limited AA. Vegans must mix their nutrition sources to meet essential AA needs.

The AA structure consist of a central carbon atom bonded to: a hydrogen, a carboxylic acid, an amino group, and an additional side group that is unique to each amino acid. The side group creates unique characteristics for each amino acid so they differ in shape, size, composition, electrical charge, and pH. (See slide 5) Individual AAs are then joined by peptide bonds in specific sequences to form proteins. Most proteins in the body and diet are long polypeptides (100s of AA).

Because whole proteins are not absorbed they must be digested into AAs or di- and tri-peptides prior to absorption. It is important to note that some additional digestion occurs in the cytosol. Digestion begins in the stomach and is accomplished due to both gastric and pancreatic proteases, with the vast majority accomplished by pancreatic proteases (70%). It is important to remember the structures of proteins are more diverse than carbohydrates and thus require a broader spectrum of peptidases and transporters than carbohydrates.

The gastric phase of digestion begins with the secretion of pepsinogen from chief cells and HCl from parietal cells. HCl works to denature proteins and more importantly converts inactive pepsinogen to active pepsin. Pepsin cleaves proteins at large aliphatic or aromatic side groups and completes ~ 10-20% of protein digestion. As the chyme enters the intestines, pepsin is inactivated (at pH >4.5). This protects the intestines from auto-digestion.

Clinical Correlation- The requirement for acidic pH to activate pepsinogen has implications for using proton pump inhibitors which maintains the pH of stomach above 4.5. There are no studies to suggest this affects nutrition or results in deficiencies. Similarly, there is limited effect from gastric bypass.

The intestinal phase is responsible for the bulk of proteolysis and is mainly due to the actions of the pancreatic proteases. 70% of proteins are converted to oligopeptides in the intestines. There are two main forms of pancreatic enzymes: endopeptidase – cleave internal bonds and ectopeptidase – cleave AA at C-terminus. Endopeptidase include trypsin, chymotrypsin and elastase. Ectopeptidase include carboxypeptidase A and carboxypeptidase B. Carboxypeptidase A acts on neutral AA and carboxypeptidase B acts on basic AA.

Pancreatic enzymes are stored in acinar cells as pro-enzymes (zymogens) and are activated by trypsin, which itself is self-activated. Trypsin is also converted from its proenzyme by enterokinase and by itself. (See slide 14-16)

Trypsinogen → Trypsin
Chymotrypsinogen → Chymotrypsin
Procarboxypeptidase A and B → Carboxypeptidase A and B
Proelastase → Elastase

Trypsin inhibitors are small proteins or peptides that are present in plants (Soybeans, peas, beans, wheat), organs (pancreas), and fluids (colostrum). They decrease the activity of trypsin and therefore all proteases. The trypsin inhibitors are inactivated by heat.

Additional protein digestion occurs at the brush border, increasing the amount of protein suited for intracellular transport. Brush border peptidases are integral membrane proteins that produce single amino acids and smaller peptides (di and tri-peptides) from tetrapeptides and larger peptides. The brush border peptidases are membrane bound to the villi tips and are not present in the crypts. Intracellular cytoplasmic peptidases also break down dipeptides and tripeptides into single amino acids. Greater than 99% of protein enters the bloodstream as single amino acids, but some remain in the enterocytes and are used to support the cell.

Most protein absorption takes place in the duodenum and jejunum where oligopeptides (3 to 4 AA and shorter) and AA transported. Oligopeptides have more rapid absorption than free amino acids. There are several different transporters that work by different mechanisms. One active transporter is PEPT1 which is coupled to sodium-hydrogen exchanger (NHE3). PEPT1 transporter accommodates proteins of various sizes and charges. Free AA are transported out of the lumen by several different

mechanisms to include; facilitated diffusion, Na⁺-independent carriers, Na⁺-dependent carriers and proton co-transport.(see Slide 26) Some amino acids share the same transport system, so if a large amount of one particular amino acid is consumed, the absorption of others may be inhibited.

The basolateral membrane of the enterocyte contains additional transporters which export amino acids from the cell into the blood by both diffusion and by both Na⁺ dependent and independent carriers.

Clinical Correlations

Hartnup Disease is due to abnormal transport of neutral AA (i.e. – tryptophan) caused by a mutation in SLC6A19 transporter. There is significant clinical variability in the presentation from no symptoms to rash or neurologic symptoms (developmental delays). Symptoms are due to lack of nicotinamide which is a tryptophan metabolite. Diagnosis is made by high levels of neutral AA in the urine. Treatment involves supplementation with nicotinamide.

Cystinuria is due to decreased intestinal absorption of dibasic AAs (lysine, arginine, cystine) due to a defect in SLC3A1 transporter. Patients present with kidney stones. Cystinuria accounts for 10% of kidney stones. Diagnosis is made by elevated urine cysteine. Treatment includes hydration and dietary limitation of sodium and methionine.

Further Reading:

1. Hannelore Daniel. Molecular and Integrative Physiology of Intestinal Peptide Transport. Annual Review of Physiology. 2004. 66: 361-384
2. R Montgomery and R Grand. Development of the gastrointestinal tract. In:Wylie and Hyams, ed. Pediatric Gastrointestinal and Liver Disease. Philadelphia, PA. Elsevier Press; 2006:14-16.

Review Questions:

1. There are 9 essential amino acids. Please list them –

Answer: phenylalanine, valine, threonine, tryptophan, isoleucine, methionine, leucine, lysine, and histidine

2. The intestinal phase is responsible for the bulk of protein digestion. What enzymes are active in the intestines?
 - a. HCL and Pepsinogen
 - b. Endopeptidase and Ectopeptidase
 - c. Pepsin and Trypsin
 - d. Trypsin, Chymotrypsin and Proelastase

Answer:

B are the pro-enzymes

D are the active enzymes