Protein Digestion and Absorption

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Learning Objectives

- Describe protein digestion in the organs of the digestive tract.
- Understand the roles of enzymes and compounds in the stomach and small intestine.
- Explain how amino acids and peptides cross the apical membrane of the enterocyte.
- Understand that free amino acids cross the basolateral membrane.
- Explain why not all amino acids are absorbed into the bloodstream.

Digestion

Stomach

Enzymatic digestion of protein begins in the stomach. Hydrochloric acid (HCl), secreted by parietal cells, initiates protein denaturation by lowering the pH. This unfolds the quaternary, tertiary, and secondary structures, disrupting hydrogen and electrostatic bonds but leaving peptide bonds intact.

HCl also activates pepsinogen (from chief cells) into pepsin, which functions as an endopeptidase—hydrolyzing interior peptide bonds, particularly adjacent to hydrophobic or aromatic amino acids.

The result: linear polypeptide chains and oligopeptides.

Small Intestine

As chyme enters the small intestine, hormones secretin and CCK slow gastric digestion and stimulate pancreatic juice release. This juice contains bicarbonate and zymogens including:

- **Trypsinogen** ($\rightarrow$ trypsin)
- **Chymotrypsinogen** ($\rightarrow$ chymotrypsin)
- **Procarboxypeptidase** ($\rightarrow$ carboxypeptidase)

Enteropeptidase activates trypsinogen to trypsin, which then activates the other zymogens.

Chymotrypsin targets peptide bonds next to tyrosine, phenylalanine, or tryptophan (large neutral amino acids).

Reflection: What are the end products of chymotrypsinogen?

Carboxypeptidase is an exopeptidase that cleaves from the C-terminal, producing free amino acids and shorter peptides.

Brush border enzymes include:

- **Aminopeptidases**: N-terminal cleavage
- **Tripeptidases**: act on tripeptides
- **Dipeptidylaminopeptidases**: act on dipeptides

Absorption

Small Intestine

Digestion products—free amino acids, dipeptides, and tripeptides—must cross:

- Apical membrane (facing lumen)
- Through enterocyte
- Basolateral membrane (facing bloodstream)

Most absorption happens in the lower duodenum and upper jejunum. About 70% of apical absorption occurs as di/tripeptides via the PEPT1 transporter, co-transporting with H^+ ions.

To maintain gradients:

- H^+ exchanged for Na^+
- Na^+ pumped out by Na/K ATPase

Free amino acids use carrier-mediated systems. Their transport is influenced by:

- Side chain structure
- Electrical charge

System	Target Amino Acids
L System	Branched-chain and aromatic AAs
X^- System	Acidic AAs
$B^{0,+}$ System	Neutral and basic AAs
ASC System	Small neutral AAs

Table 1: Selected Free Amino Acid Transport Systems (Apical Membrane)

Inside the enterocyte, peptides are hydrolyzed to amino acids. These are then transported across the basolateral membrane into capillaries, ultimately reaching the liver via the portal vein.

Reflection: How does amino acid competition affect absorption?

Not all amino acids enter circulation—some are retained for:

System	Notes
LAT1	Large neutral AAs
y^+LAT1	Basic AAs
TAT1	Aromatic AAs
SNAT	Sodium-dependent neutral AAs

Table 2: Basolateral Membrane Transport Systems

- Protein synthesis
- Nitrogen-containing compounds
- Oxidation for energy

Large Intestine

About 10–20 g of amino acids escape absorption daily. Gut bacteria use these for growth, and the rest are excreted in feces.

Reflection Questions

1. A patient on long-term proton pump inhibitor (PPI) therapy has virtually no gastric acid secretion. Trace the downstream consequences for protein digestion, starting from the failure to activate pepsinogen and explaining how this affects the subsequent cascade of zymogen activation in the small intestine. Predict which protein structures would be most resistant to incomplete digestion under these conditions.
2. Two athletes consume identical amounts of protein: one as a rapidly digested whey shake (yielding mainly di- and tripeptides), the other as whole egg whites (requiring complete digestion to free amino acids before absorption). Using your knowledge of PEPT1 transport vs. free amino acid carrier systems, predict which source would result in faster peak absorption and why — and explain whether speed of absorption has practical significance for muscle protein synthesis.
3. Large neutral amino acids — including BCAAs, phenylalanine, and tryptophan — compete for the L-system transporter at the apical membrane. A PKU patient on a low-phenylalanine diet begins taking high-dose BCAA supplements. Evaluate how excess BCAAs in the intestinal lumen could affect absorption of other large neutral amino acids sharing the same transporter, and predict any potential downstream consequences.

References