Amino Acids Metabolism

Dietary proteins are first broken down to individual amino acids by various enzymes and hydrochloric acid present in the gastro-intestinal tract. Twenty amino acids present in proteins that twelve nonessential amino acids and (eight essential amino acids) must be supplied in the diet since they cannot be synthesized in the body. The remainder is nonessential amino acids that are supplied in the diet but can be formed from metabolic intermediates by transamination, using the amino nitrogen from other amino acids. Several amino acids are also the precursors of other compounds, eg, purines, pyrimidines, hormones such as epinephrine and thyroxin, and neurotransmitters. The liver synthesizes the major proteins (eg, albumin) and also synthesizes muscle from amino acids that Muscle accounts for approximately 50% of body mass and consequently represents a considerable store of protein that can be drawn upon to supply amino acids for gluconeogenesis in starvation.

Digestion in Mouth

There is no digestion of protein in mouth. It starts in stomach.

Digestion in Stomach

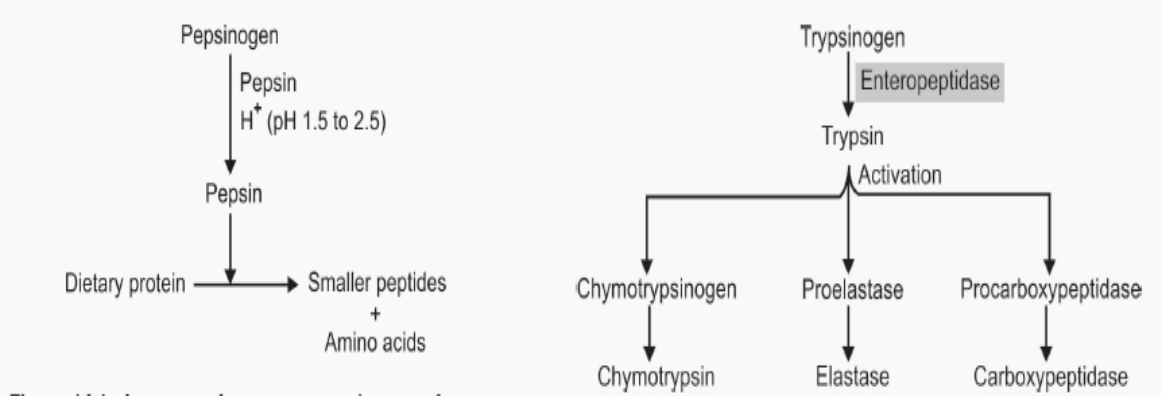
When protein enters the stomach, it stimulates the secretion of the hormone gastrin, from gastric mucosal cells, which in turn, stimulates the release of gastric juice containing hydrochloric acid, proenzyme (zymogen) pepsinogen and rennin in infants.

• **Hydrochloric acid:** Denatures proteins making their internal peptide bonds more accessible to subsequent hydrolysis by proteoses and provides an acid environment for the action of pepsin.

• **Pepsin:** It is secreted as the proenzyme pepsinogen, an inactive form. It is converted into active pepsin in the gastric juice by the enzymatic action of pepsin itself or by high hydrogen ion concentration. Pepsin cleaves those peptide bonds of protein involving the:

1. **Aromatic amino acids** (phenylalanine, tyrosine and tryptophan)
2. **Acidic amino acids** (aspartic acid and glutamic acid).Thus, pepsin cleaves long polypeptide chains into mixture of smaller peptides and some free amino acids.

• **Rennin** is important in the digestive processes of infants. It is absent in adults. Rennin is also called chymosin or rennet. Renin is secreted by kidney and is involved in regulation of water and electrolyte balance and blood pressure. Action of rennin is to clot milk. This is accomplished by the slight hydrolysis of the casein of milk to produce paracasein, which coagulates in the presence of calcium ions, resulting in an insoluble calcium-paracaseinate curd. Calcium paracaseinate is then acted on by pepsin. The purpose of this reaction is to convert milk into a more solid form to prevent the rapid passage of milk from the stomach of infants.



Digestion in Intestine by Pancreatic Enzymes

There are two types of peptidase enzymes secreted by pancreas:

1. Endopeptidase
2. Exopeptidase

Dietary amino acids are hydrolyzed through the concerted actions of gastric and pancreatic peptidases.

Endopeptidase

Endopeptidases cleave internal peptide bonds. This results into formation of smaller peptides from large polypeptides. Endopeptidases secreted by pancreas, are trypsin, chymotrypsin and elastase. These are secreted in proenzyme (inactive) forms, trypsinogen, chymotrypsinogen and proelastase

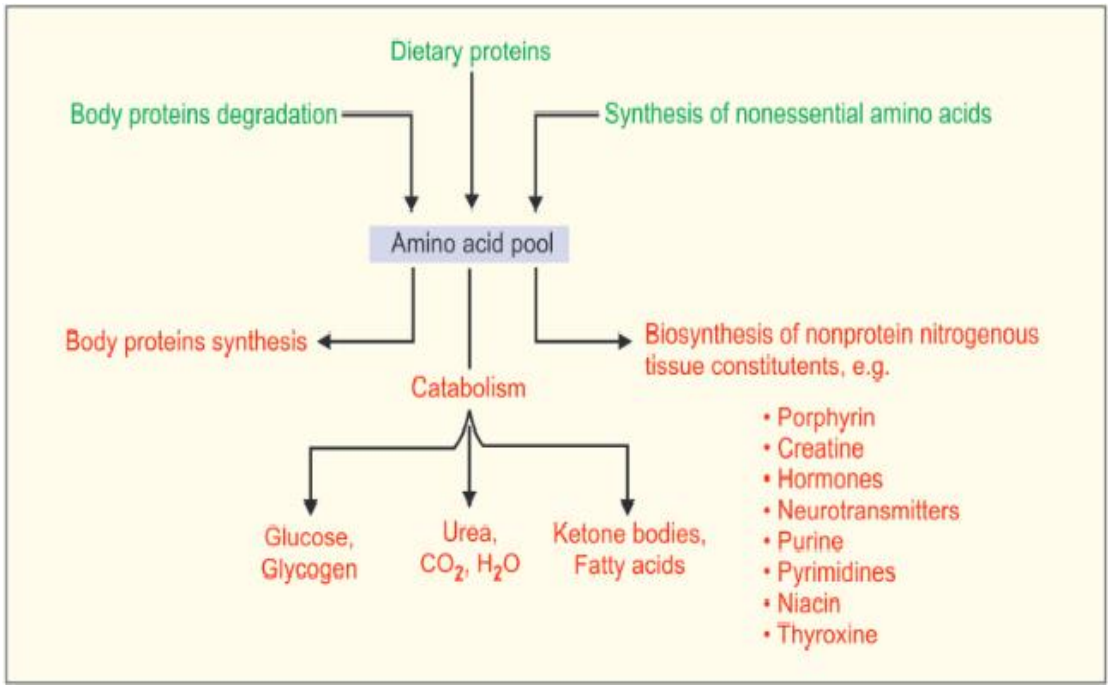
Exopeptidase

Exopeptidase which hydrolyze the peptide bonds of terminal amino acids. Exopeptidase are of two types:

–Carboxypeptidase secreted by pancreas act on C-terminal amino acid.

–Aminopeptidases secreted by mucosal cell act on N-terminal amino acid

The acidic pH optimum for the action of pepsins and trypsin are inhibited when the gastric juice passes from the stomach and is mixed with alkaline pancreatic juice in the duodenum. The remainder of protein digestion occurs within small intestine. Digestion here is primarily the result of the actions of trypsin and chymotrypsin and to a lesser extent by Endopeptidase and Exopeptidase which are secreted by the pancreas. Peptides (2–6 amino acids in length) are absorbed by enterocytes of the proximal jejunum. Some absorption also occurs in the duodenum and a minor amount in the ileum. The free amino acids are then transported across the apical membranes of enterocytes and enter the portal circulation. The protein metabolism are shown in the figure:



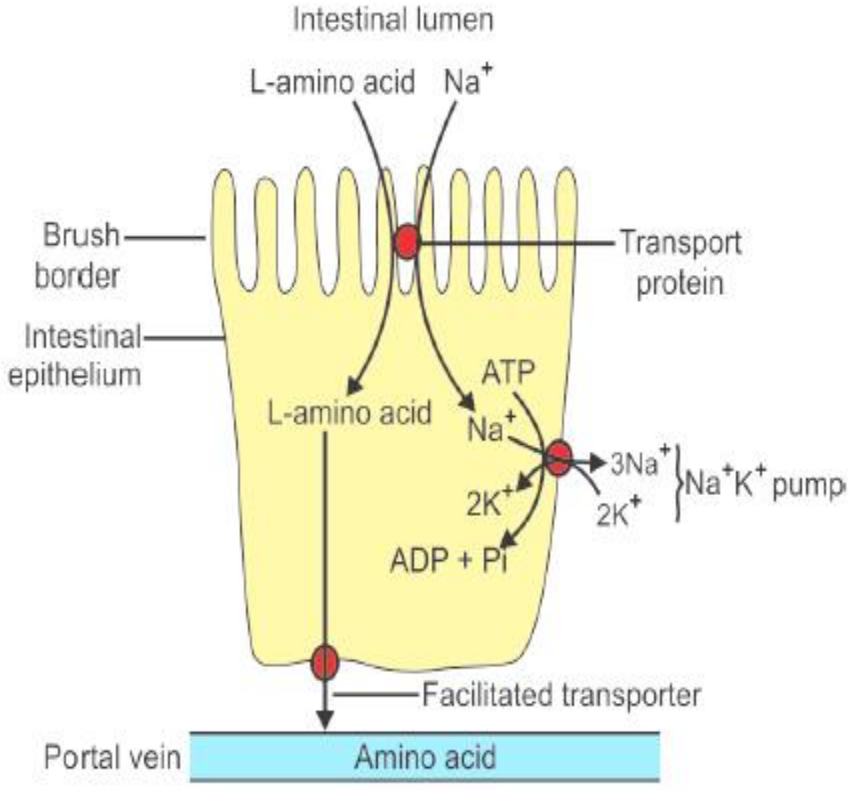
Enzyme	*Peptide bond specificity*
Pepsin	Aromatic amino acids (tyrosine, phenylalanine, tryptophan) Acidic amino acids (glutamic acid and aspartic acid)
Trypsin	It's carboxyl groups are contributed by lysine and arginine
Chymotrypsin	Aromatic amino acids (phenylalanine, tyrosine and tryptophan), leucine, methionine, aspargine, histidine
Elastase	Small nonpolar amino acids alanine, serine and glycine
Carboxypeptidase	Successive C-terminal amino acids
Aminopeptidase	Successive N-terminal amino acids

Digestion in Intestine by Intestinal Proteoses

The digestion products of hydrolysis by pepsin, trypsin, elastase, chymotrypsin and carboxypeptidase is completed by enzymes, secreted by the mucosa of the small intestine such as aminopeptidases and dipeptidases. Aminopeptidase is an exopeptidase; hydrolyze peptide bonds next to N-terminal amino acids of the short peptides. The dipeptidases complete digestion of dipeptides to free amino acids. These dipeptidases can then finally convert all ingested protein into free amino acids. Dipeptidases require cobalt or manganese ions for their activity. The hydrolysis of most proteins is thus completed to their constituent amino acids which are then ready for absorption into the blood.

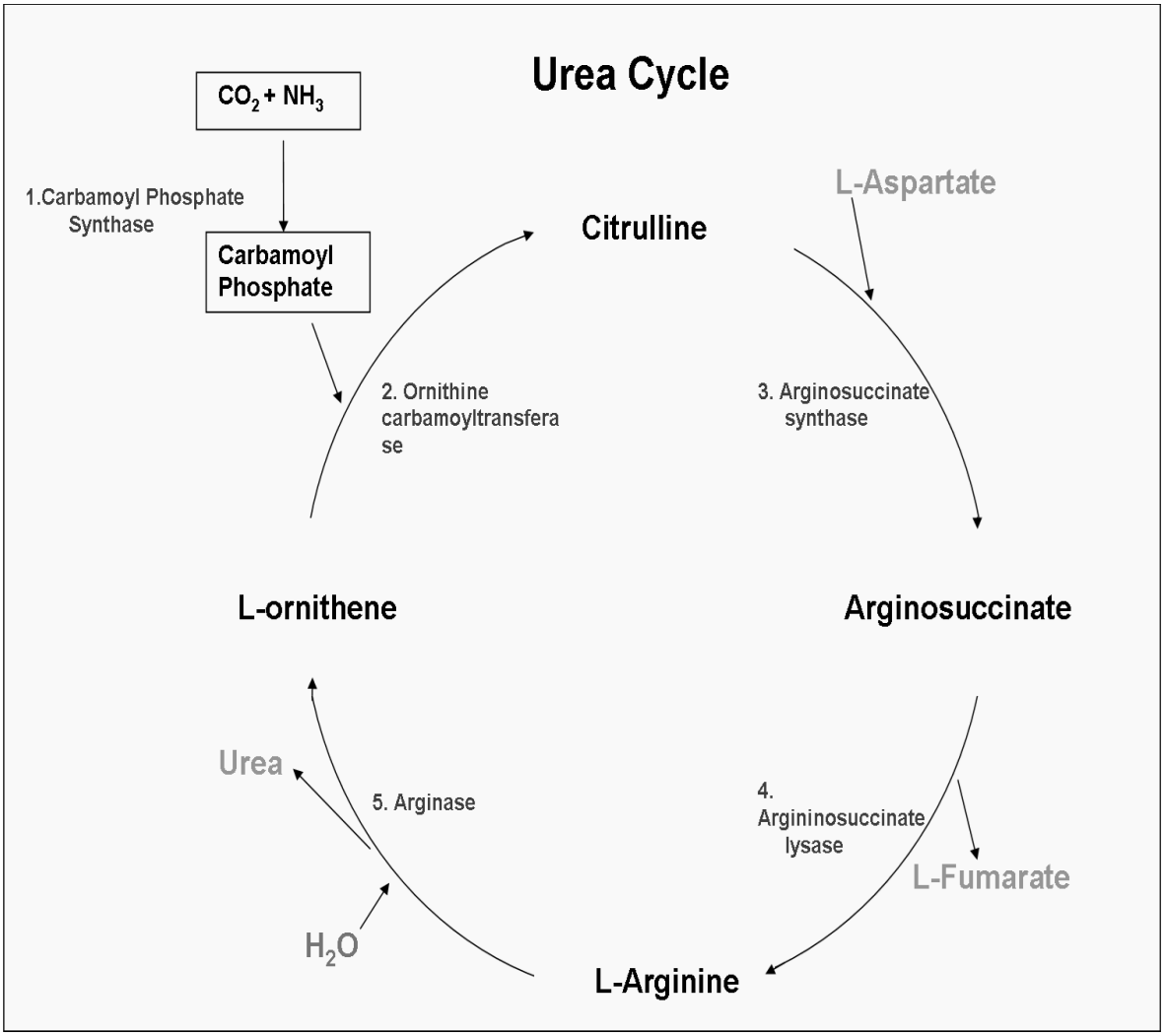
Absorption of Amino Acids

The absorption of most amino acids involves an active transport mechanism, requiring ATP and specific transport proteins in the intestinal mucosal cells. Many transporters have Na+ dependent mechanisms, coupled with Na+ K+ pump, similar to those described for glucose absorption. Several Na+ independent transport proteins are found in the brush-border membrane that are not specific for each amino acid but rather for the groups of structurally similar amino acids.



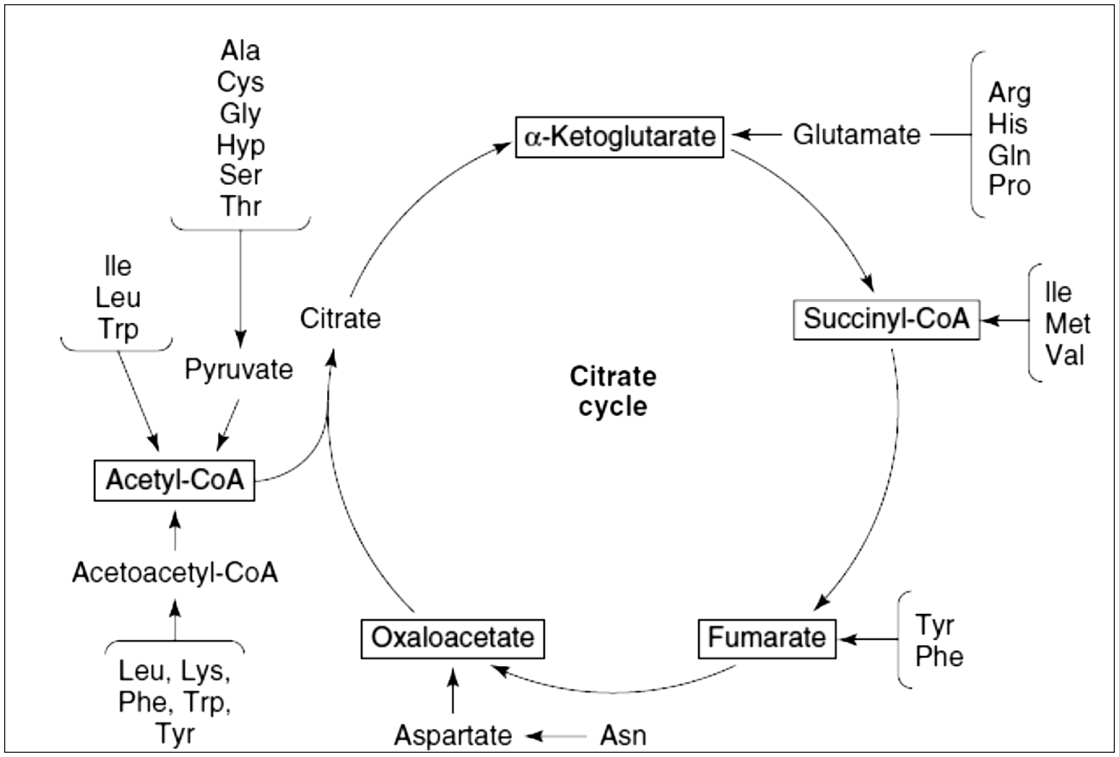
Biosynthesis of urea

The urea cycle is a cycle of biochemical reactions occurring in many animals that produces urea $(NH_2)_2CO$ from ammonia (NH_3). Organisms that cannot easily and quickly remove ammonia usually have to convert it to some other substance like urea which are much less toxic. Insufficiency of the urea cycle occurs in some genetic disorders and liver failure. The result of liver failure is accumulation of nitrogenous waste, mainly ammonia, which leads to hepatic encephalopathy, urea cycle as shown in figure:



Transamination typically initiates amino acid catabolism

Removal of amino nitrogen by transamination is the first catabolic reaction of amino acids except in the case of proline, hydroxyproline, threonine, and lysine. The residual hydrocarbon skeleton is then degraded to amphibolic intermediates as shown in the Figure:



Krebs cycle intermediates formed from the carbon skeletons of amino acids.

Heme & Porphyrins & Bile Pigments

These topics are closely related together, because heme is synthesized from porphyrins and iron, and the products of degradation of heme are the bile. In the Table there are examples of some important human and animal hemoproteins:

Examples of some important human and animal hemoproteins.

Protein	Function
Hemoglobin	Transport of oxygen in blood
Myoglobin	Storage of oxygen in muscle
Cytochrome *c*	Involvement in electron transport chain
Cytochrome P450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrrolase	Oxidation of trypotophan

[1]The functions of the above proteins are described in various chapters of this text.

Whereas the various porphyrins are all colored. In the study of porphyrins or porphyrin derivatives, the characteristic absorption spectrum that each exhibits in both the visible and the ultraviolet regions of the spectrum is of great value. An interesting application of the photodynamic properties of porphyrins is their possible use in the treatment of certain types of cancer, a procedure called cancer phototherapy. Tumors often take up more porphyrins than do normal tissues.

Bilirubin

Bilirubin results from the breakdown of hemoglobin in the RBCs and is a byproduct of hemolysis (RBC destruction). Bilirubin removed from body by the liver. Bilirubin is soluble in water, but its solubility in plasma is increased by noncovalent binding to albumin. A number of compounds such as antibiotics and other drugs compete with bilirubin for the high-affinity binding site on albumin. In the liver, the bilirubin is removed from albumin and convert unconjugated bilirubin to conjugated bilirubin by adding glucuronic acid molecules to it. which is readily excreted in the

bile, As the conjugated bilirubin reaches the terminal ileum and the large intestine, the glucuronides are removed by specific bacterial and converted to urobilinogens. In the terminal ileum and large intestine, a small fraction of the urobilinogens is reabsorbed and reexcreted through the liver to constitute the enterohepatic urobilinogen cycle and the other urobilinogen excreted in the urine. Normally, most of the colorless urobilinogens formed in the colon by the fecal flora are oxidized there to urobilins (colored compounds) and are excreted in the feces.

In Clinical Implications of Bilirubin:

1-Total Bilirubin elevations accompanied by jaundice may be due to hepatic, obstructive, or hemolytic causes:

a. Hepatocellular jaundice results from injury or disease in the liver and can be caused by the following conditions: Viral hepatitis, Cirrhosis

b. Obstructive jaundice is usually the result of obstruction of the common bile or hepatic ducts due to stones or neoplasms. The obstruction produces high conjugated Bilirubin levels due to bile regurgitation.

c. Hemolytic jaundice is due to overproduction of bilirubin resulting from hemolytic processes that produce high levels of unconjugated bilirubin. Hemolytic jaundice can be found in the following conditions: After blood transfusions, especially those involving many units, anemia
Transfusion reactions (ABO or Rh incompatibility)

2. Elevated indirect (unconjugated) bilirubin levels occur in the following conditions:

a. hematoma

b. Trauma

3. Elevated direct (conjugated) bilirubin levels occur in the following conditions:

a. Cancer of the head of the pancreas

c. Dubin-Johnson syndrome**:** This benign autosomal recessive disorder consists of conjugated hyperbilirubinemia in childhood or during adult life. In all these situations, bilirubin accumulates in the blood, and when it reaches a certain concentration (approximately 2–2.5 mg/dL), it diffuses into the tissues, which then become yellow. That condition is called jaundice. In clinical studies of jaundice, measurement of bilirubin in the serum is of great value.