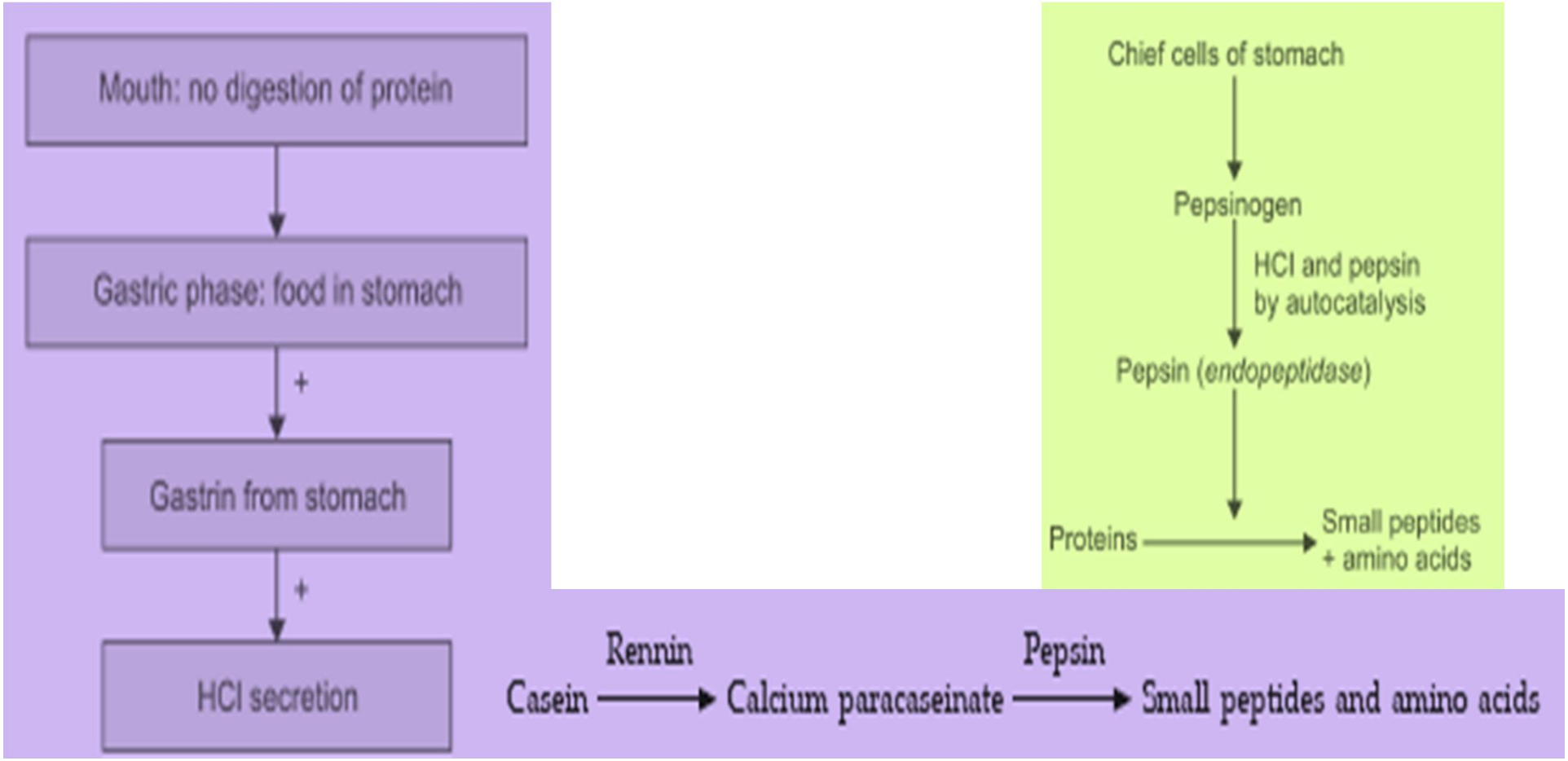
digestion and absorption of proteins

Protein digestion can be divided into gastric, pancreatic and intestinal phases.

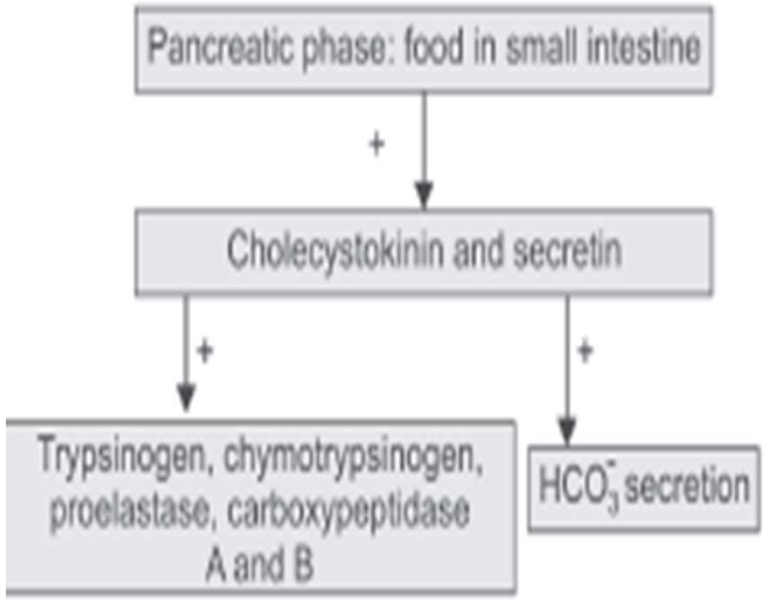
Gastric phase: Food in stomach → (+) gastrin → (+) hydrochloric acid (HCl) secretion

(***Rennin:*** Secreted from stomach of infant; helps in conversion of casein into calcium paracaseinate, which can be acted upon further by pepsin.

Pepsin: The chief cells of stomach secrete inactive pepsinogen, which is activated by HCl.



Pancreatic phase



Trypsinogen —Enterokinase→ Trypsin ⟶ Cleaves peptides at carboxyl group of lysine and arginine (basic amino acids)

Chymotrypsinogen —Trypsin→ Chymotrypsin ⟶ Cleaves at carboxyl group of aromatic amino acids

Proelastase —Trypsin→ Elastase ⟶ Cleaves the carboxyl group of Glycine, Arginine and Serine [MN: GAS]

Procarboxypeptidase A and B —Trypsin→ Carboxypeptidase A and B ⟶ Cleave one amino acid at a time from carboxyl end of peptides

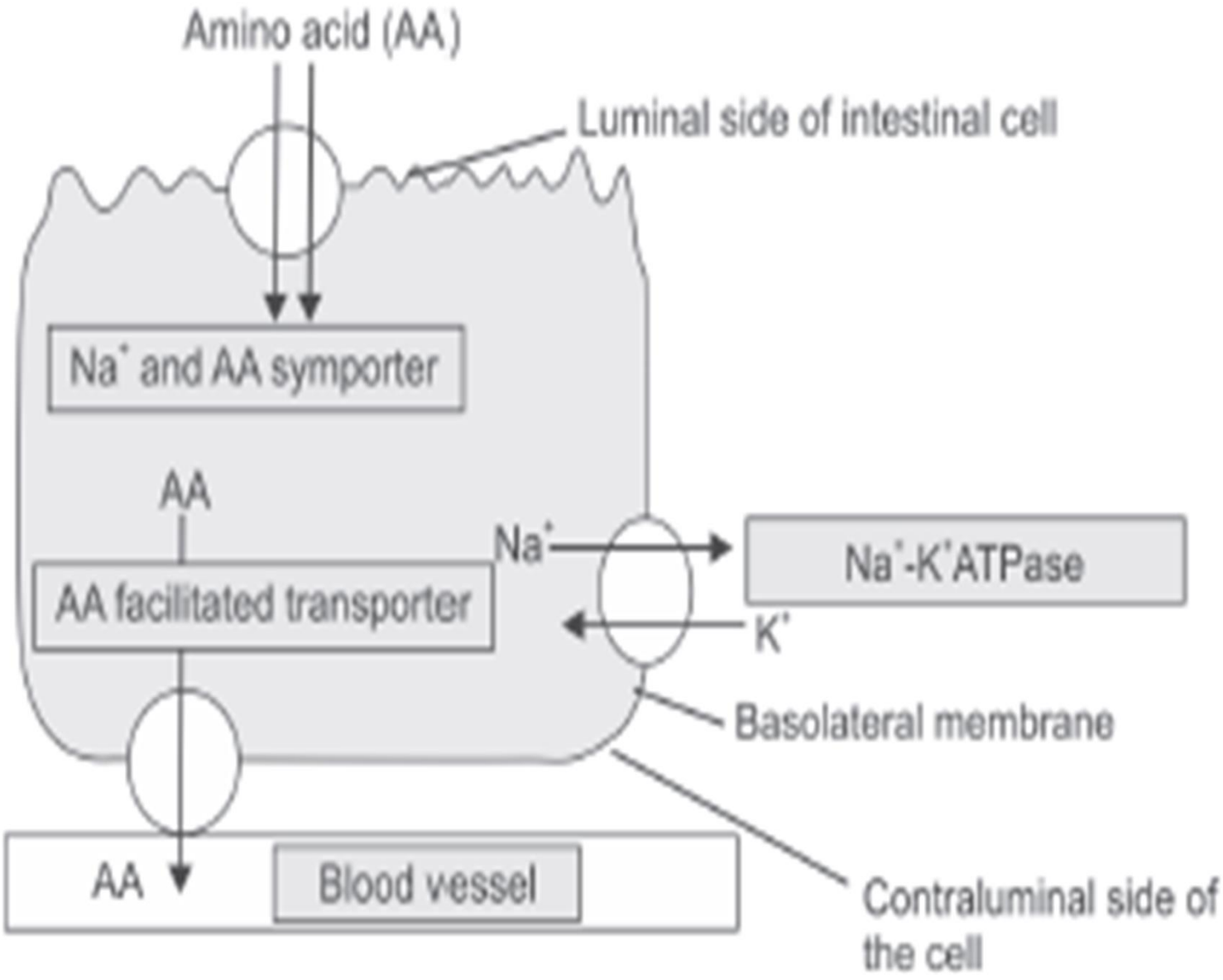
Intestinal phase: Digested products of gastric and pancreatic phase (oligopeptides, tripeptides and dipeptides) enter into intestinal phase of digestion. Aminopeptidase is an exopeptidase that cleaves one amino acid at a time from amino terminals of peptides. Dipeptidases and tripeptidases are endopeptidases. These enzymes convert peptides to amino acids.

Dipeptidase ⟶ Dipeptides Amino acids

Tripeptidase ⟶ Tripeptides Amino acids

Aminopeptidase ⟶ Oligopeptides Amino acids

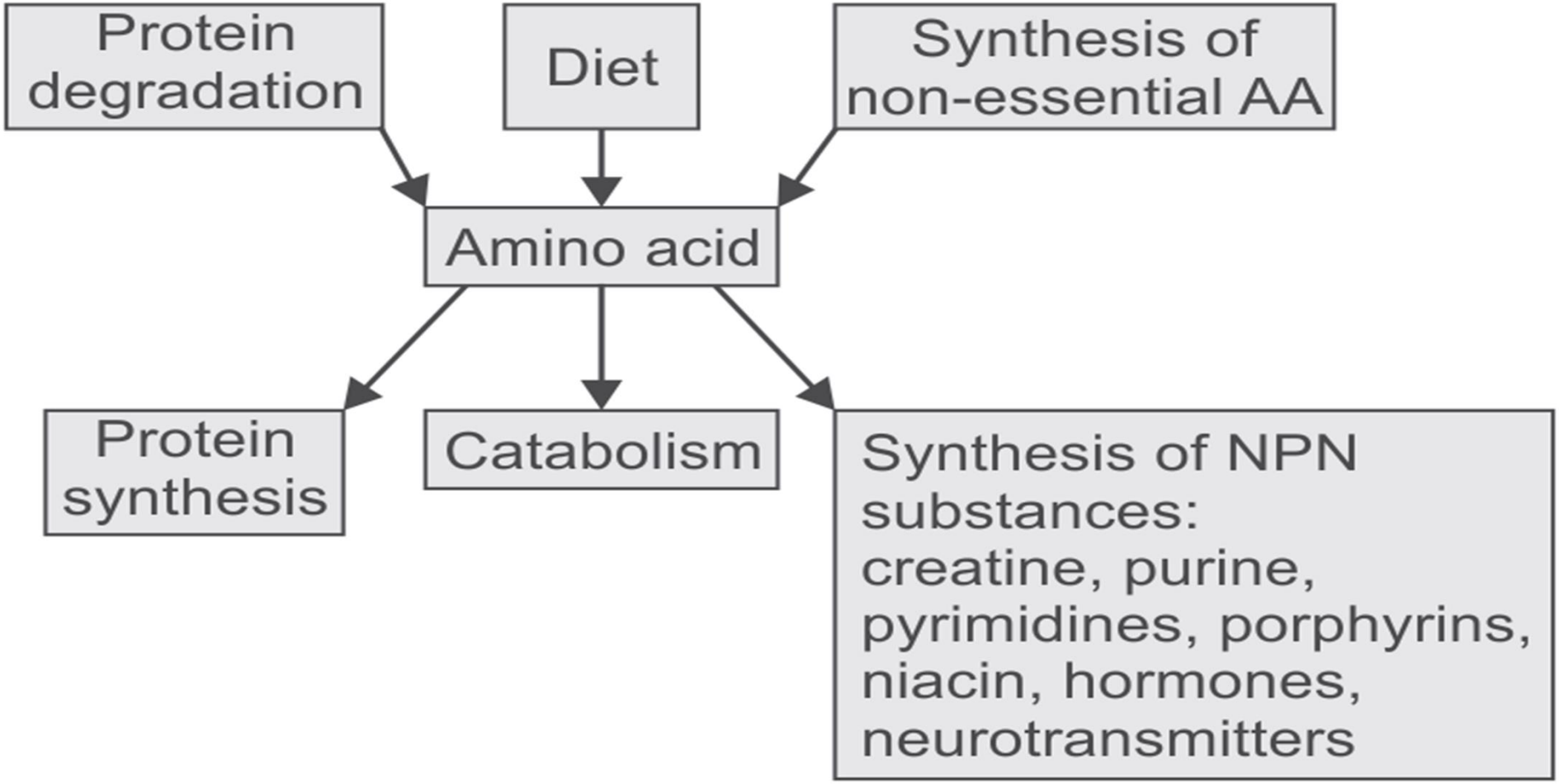
Absorption of amino acids: It occurs from upper small intestine (duodenum and proximal jejunum). Amino acids are absorbed along with sodium (secondary active transport, an energy dependent process (Fig). There are five transport systems for various types of amino acids .Any defect in these transport system can cause disorders.



Mechanism of absorption of amino acids (Na^+, sodium ion; AA, amino acid; K^+, potassium ion; ATPase, adenosine triphosphatase).

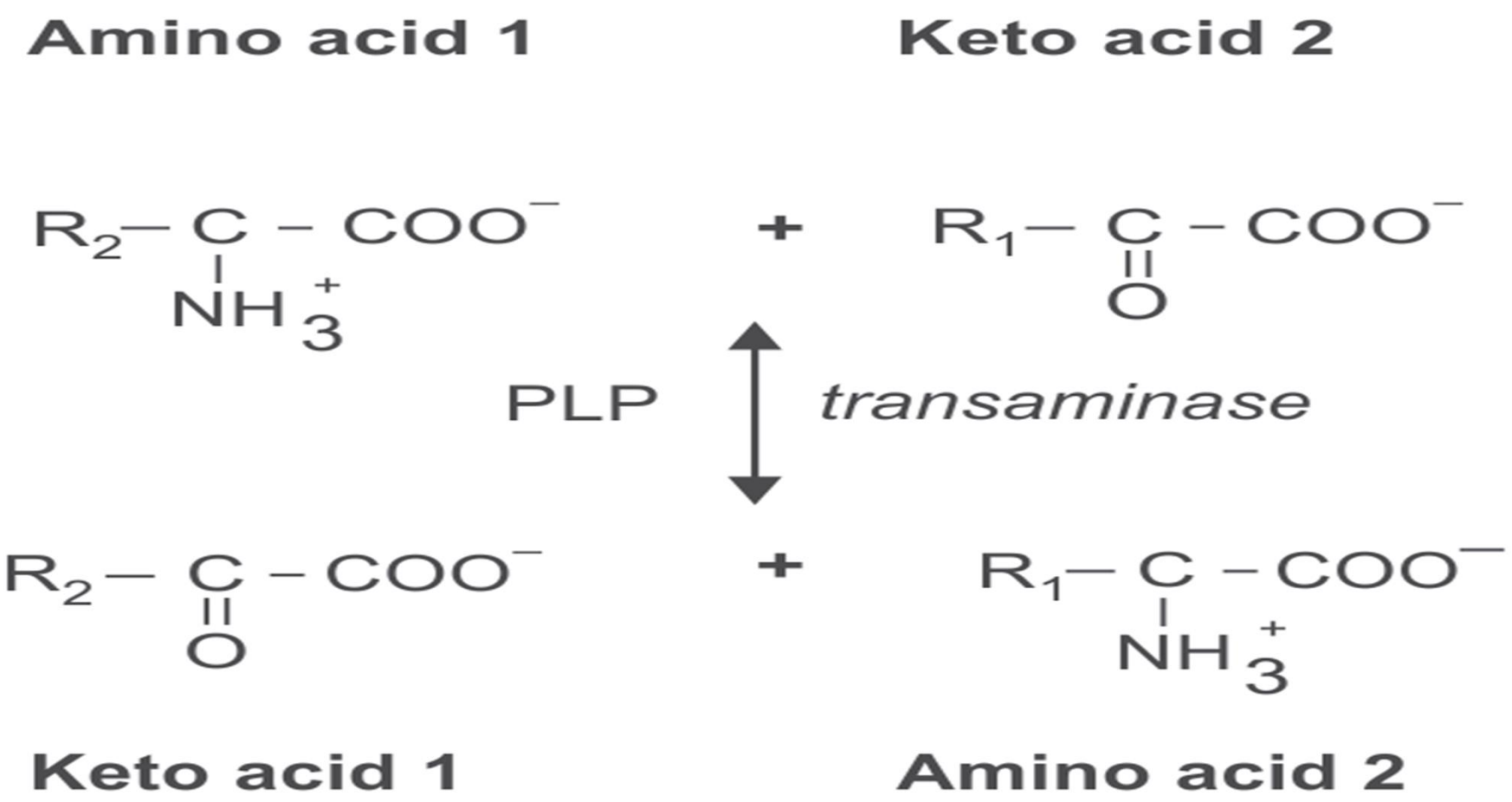
amino acid pool

Amino acid pool is the total pool of amino acids available in blood at any given time for various anabolic and catabolic activities. It is influenced by the type of diet, nutritional status, metabolism, health condition, age, etc. (Fig.).



Transaminases

Definition: These are enzymes that catalyze the reversible transfer of an amino group between one 'α' amino acid and an 'α' keto acid (Fig.).



Features of transaminases

• Catalyze reversible reaction
• Require pyridoxal phosphate (PLP) as coenzyme
• Except lysine, threonine, proline and hydroxyproline, all amino acids undergo this reaction
• Transaminase levels will be increased in hepatitis, myocardial infarction, etc.—useful in diagnosis
• Transaminases funnel amino groups from excess dietary amino acids to those amino acids (e.g. glutamate) that can be deaminated.

Functions of transamination

• Degradation of surplus amino acids
• Synthesis of essential amino acids
• Gluconeogenesis.

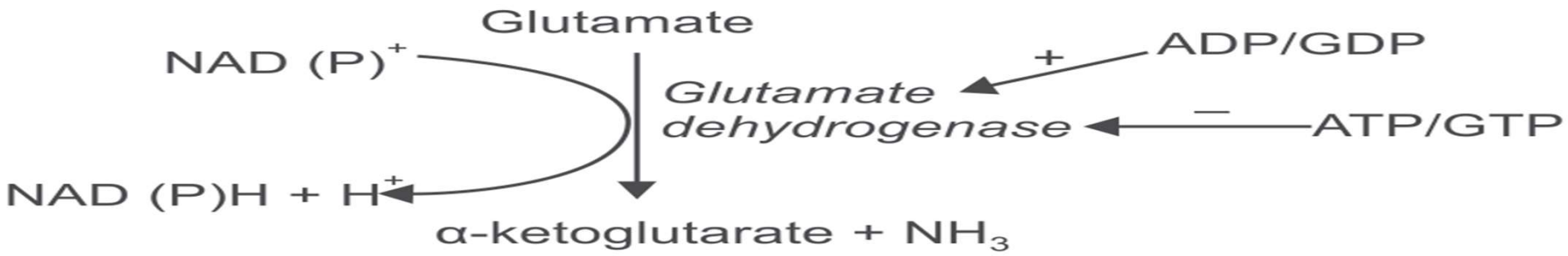
What are deamination reactions? What is its significance?

Definition: These reactions cause removal of amino group from an amino acid.

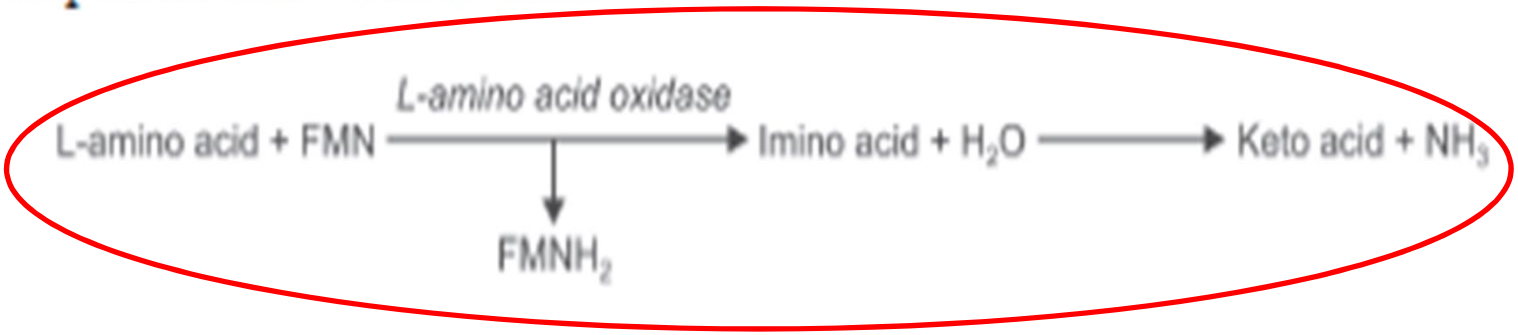
Classification

a. *Oxidative deamination*

• Glutamate dehydrogenase (major pathway of oxidative deamination): Catalyzes removal of nitrogen group from amino acid pool (Fig.).

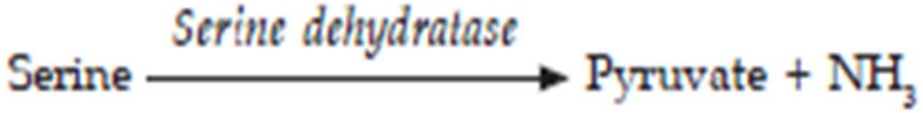


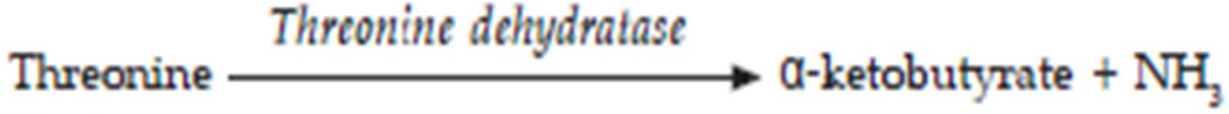
- L and D-amino acid oxidase (minor pathway): Catalyzes removal of nitrogen from amino acids in peroxisomes of liver cells.



b. *Non-oxidative deamination*: Following are the examples for non-oxidative deamination.

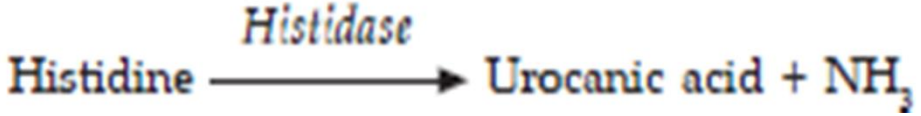
- Dehydration





- Desulfhydration

- Straight deaminations



Explain the formation and metabolism of ammonia. Add a note on regulation of urea cycle.
Reactions, which generate ammonia in the body:

Transamination: Glutamate $\longrightarrow$ α-ketoglutarate + NH_3

Deamination (oxidative): Glutamate $\longrightarrow$ α-ketoglutarate + NH_3

Dehydration: Serine $\longrightarrow$ Pyruvate + NH_3

Desulfhydration: Cysteine $\longrightarrow$ Pyruvate + NH_3

Direct deamination: Histidine $\longrightarrow$ Urocanic acid + NH_3

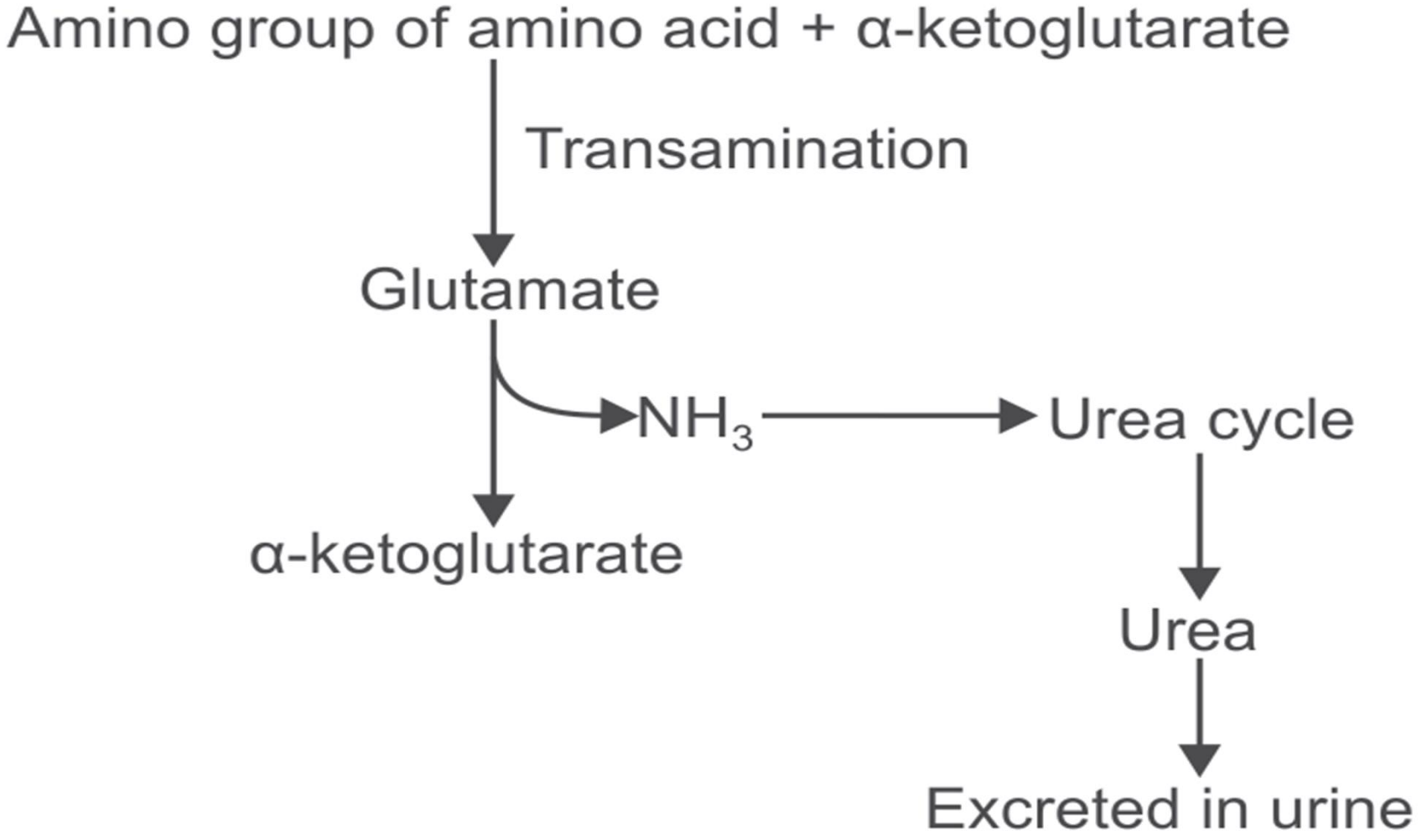
Intestinal putrefaction: Urea $\longrightarrow$ NH_3 (bacterial urease enzyme)

Purine and pyrimidine catabolism $\longrightarrow$ NH_3

Transport: Ammonia is very toxic, so it is transported in blood as glutamate (by transamination of amino acids), glutamine (from brain to liver) and alanine (from muscle).

Fate of ammonia (Fig.)

Fig. Metabolism of amino group



Urea cycle: Converts the toxic ammonia into less toxic and more soluble urea, which is excreted in the urine (Fig.).

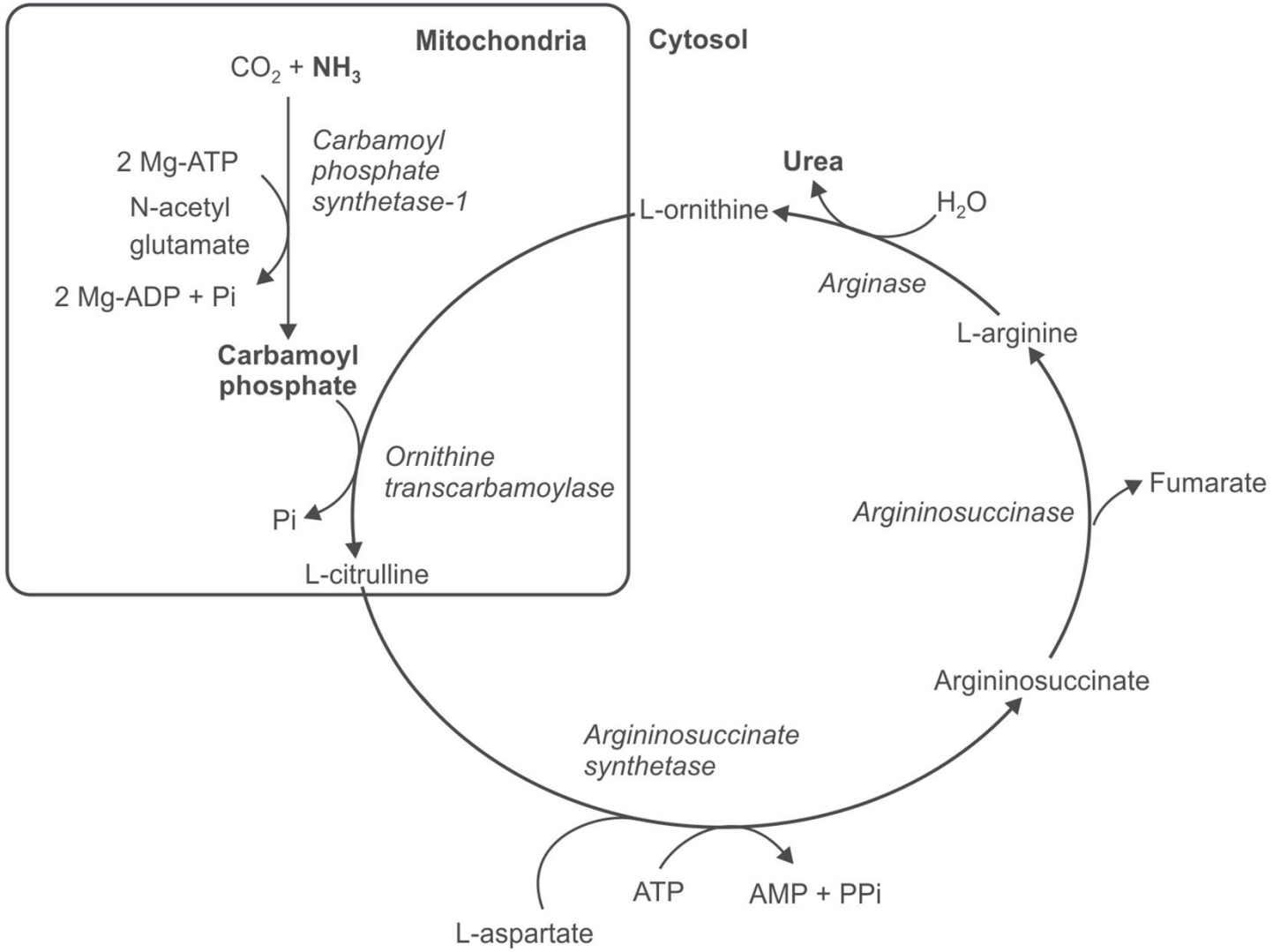
Requirements

- *Starting material:* CO_2 and NH_3
- *Site:* Liver
- *Subcellular site:* Partly mitochondrial and partly cytosolic
- *Nitrogen atom donors in cycle:* Ammonia and aspartate (amino group)
- *Energy (ATP):* Three ATPs are used.

Regulation of urea cycle: At the level of key enzyme carbamoyl phosphate synthetase-1 (CPS-1).

***Short-term regulation*:** N-acetyl glutamate is positive allosteric effector of CPS-1.

***Long-term regulation*:** By induction of enzymes of urea cycle at the gene level.


Mitochondria
Cytosol
CO_2 + NH_3
2 Mg-ATP
N-acetyl glutamate
2 Mg-ADP + Pi
Carbamoyl phosphate synthetase-1
Carbamoyl phosphate
Ornithine transcarbamoylase
Pi
L-citrulline
Argininosuccinate synthetase
ATP
AMP + PPi
L-aspartate
Argininosuccinate
Argininosuccinase
Fumarate
L-arginine
Arginase
Urea
H_2O
L-ornithine

General clinical features: Ammonia intoxication causes vomiting, mental retardation, convulsions, slurring of speech and blurring of vision.

Mechanism for toxicity

↑ NH_3 → ↑conversion of α-ketoglutarate to glutamate/glutamine → ↓ activity of Krebs cycle and decreased ATP formation

↑ Glutamate → ↑ γ-aminobutyric acid (GABA) = an inhibitory neurotransmitter in brain

↑ Glutamine → ↑ osmotic effect → cerebral edema

Biochemical picture in urea cycle defects: ↑ glutamine, citrulline or arginine (blood and urine); ↑ ammonia, ↓ urea in blood and respiratory alkalosis.

Treatment of urea cycle defects

Hemodialysis: Removes ammonia from blood.

Low-protein diet: For less ammonia formation.

Arginine supplementation (in certain defects of urea cycle): Activates N-acetylglutamate synthase and gives ornithine, which is required for first reaction of urea cycle.

Citrulline supplementation (in certain defects of urea cycle): Helps to generate ornithine (as mentioned in above sentence).

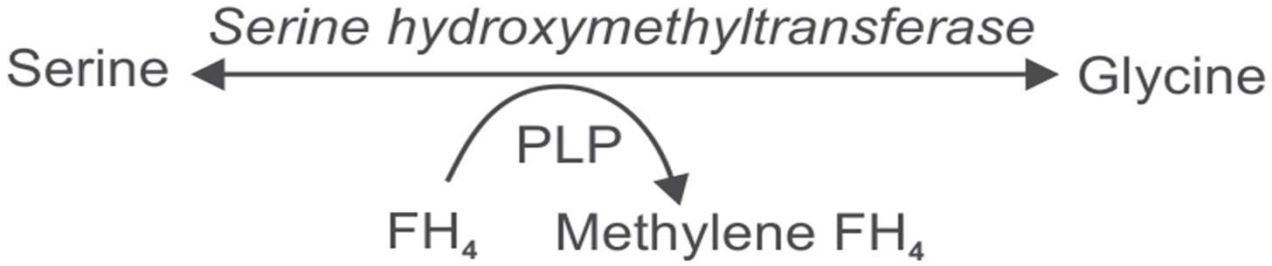
Sodium benzoate and sodium phenylbutyrate: Covalently bind glycine (forming hippurate) and glutamine (forming phenylacetylglutamine) respectively, which are excreted.

glycine metabolism (anabolism + catabolism).

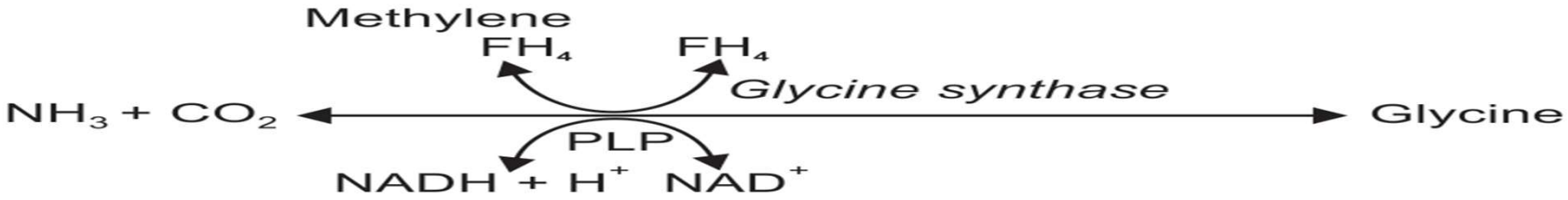
Glycine is the simplest aliphatic amino acid without asymmetric carbon atom and nutritionally non-essential.

Glycine biosynthesis: Glycine can be synthesized from serine, threonine, ammonia, glyoxylate **[MN: STAG]** and choline.

a. *Serine*



b. *Glycine synthase:* substrates—CO2 and NH3



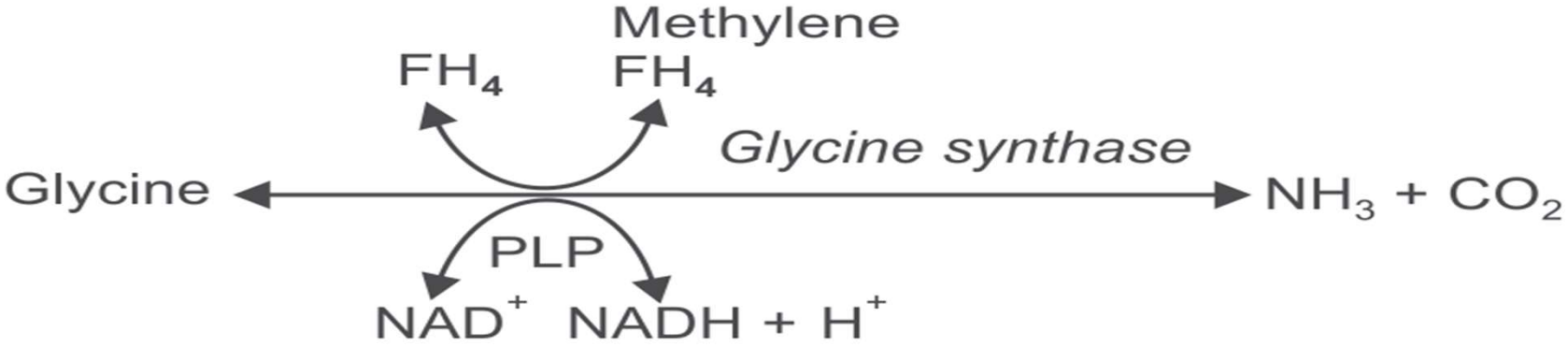
c. *Choline*

d. *Glyoxylate*

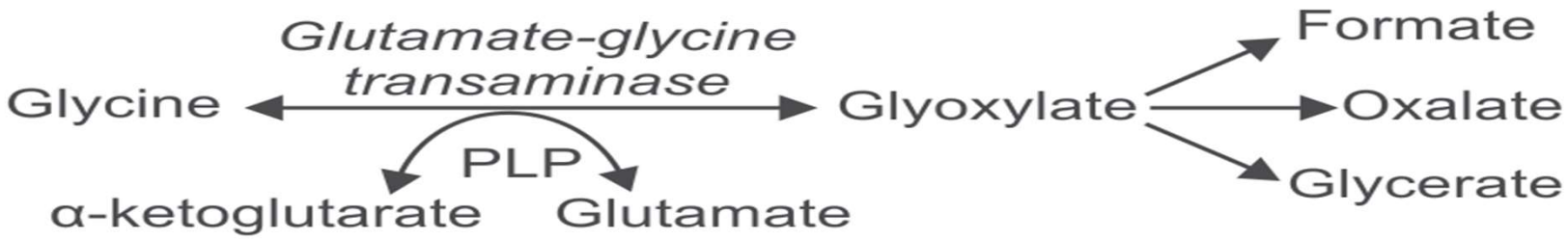
e. *Threonine*

Degradation of glycine

a. *Reversal of glycine synthase reaction:* Glycine is broken down to NH3 and CO2.



b. *Glycine transaminase:* Converts glycine to glyoxylate



Heme synthesis

• Glycine is starting material for heme synthesis