

AMINO ACID METABOLISM

PHL-285

Biochemistry-2

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- **Overview of amino acid metabolism.**
- **Classification of amino acids.**
- **Biosynthesis of nonessential amino acids.**
- **Amino acid catabolism.**
 1. **Fate of amino groups and urea cycle.**
 2. **Fate of carbon skeletons.**
- **Genetic defects of amino acid metabolism**
- **Biosynthesis of some important molecules.**
- **Integration of metabolism**

Overview of amino acids metabolism:

- a) Amino acids serve as substrates for the synthesis of protein,
- b) Amino acids provide nitrogen for the synthesis of other nitrogen-containing compounds,
- c) Amino acids are catabolized as fuels.

Classification of amino acids:

1. Chemical classification.

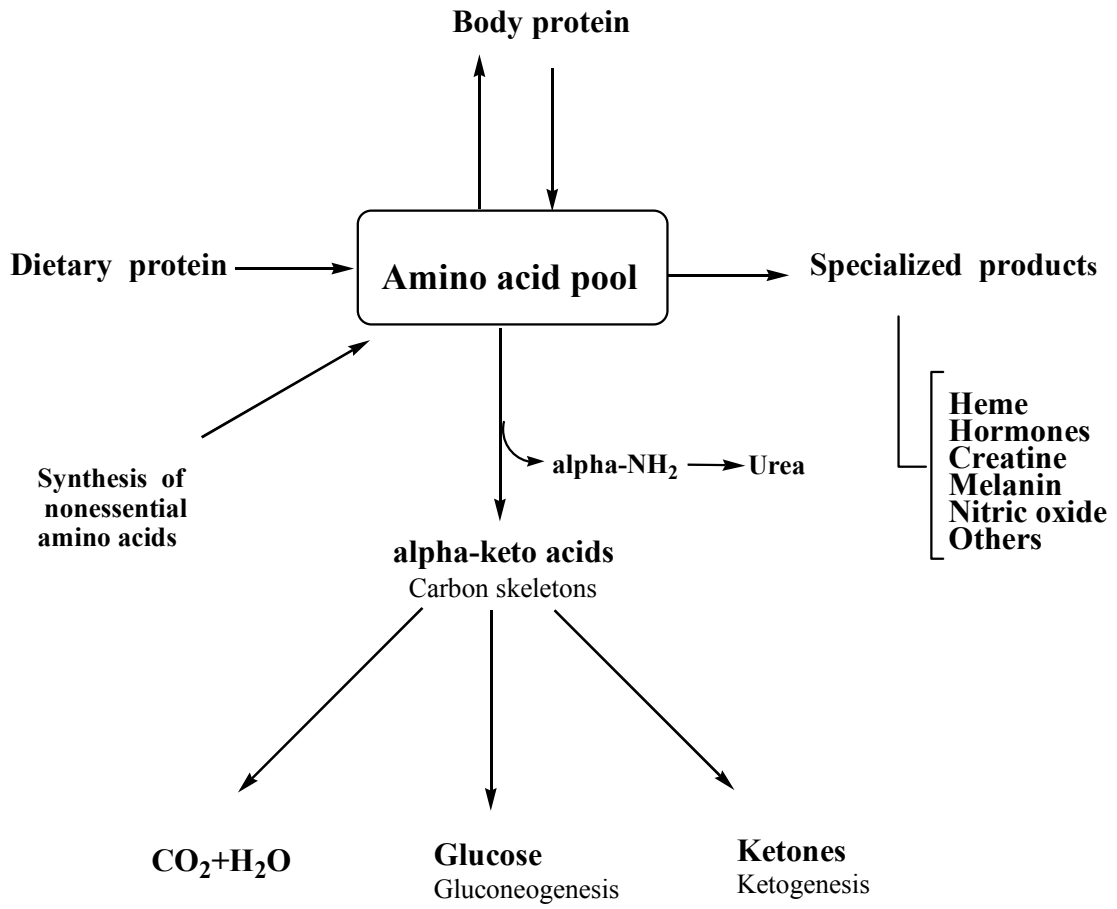
- a. According to the **chemistry** of the side chains.
- b. According to **polarity** of side chains.

3. Nutritional classification :

- Essential
- Non-essential

3. Metabolic classification :

- Glucogenic,
- Ketogenic
- Both glucogenic and ketogenic



Overview of amino acid metabolism

Essential and nonessential amino acids

Essential	Nonessential
Arginine Histidine Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Trptophan Valine	Alanine Aspartate Asparagine Cysteine Glutamate Glutamine Glycine Proline Serine Tyrosine

Glucogenic and ketogenic amino acids

Glucogenic		Both Glucogenic and ketogenic	ketogenic
Alanine Asparagine Cysteine Glutamine Histidine Proline Threonine	Arginine Aspartate Glutamate Glycine Methionine Serine Valine	Isoleucine Phenylalanine Trptophan Tyrosine	Leucine Lysine

Biosynthesis of Nonessential Amino Acids:

Humans do not have the ability to synthesize 10 of the necessary 20 amino acids and must obtain them from the diet. These 10 are termed the nutritionally essential amino acids. The 10 nonessential amino acids are formed by 3 general mechanisms:

a) Transamination:

- **Alanine**, can be synthesized by transamination of the corresponding α -keto acid, pyruvate.
- **glutamate**, can be synthesized by transamination of the corresponding α -keto acid, α -ketoglutarate.
- **aspartate** can be synthesized by transamination of the corresponding α -keto acid, oxaloacetate
- **Serine** is synthesized by the transamination and dephosphorylation of 3-phosphoglycerate, an intermediate of glycolysis.

b) Assimilation of free ammonia:

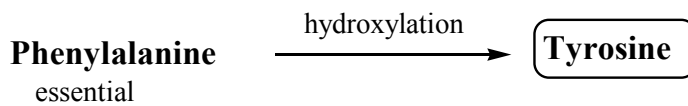
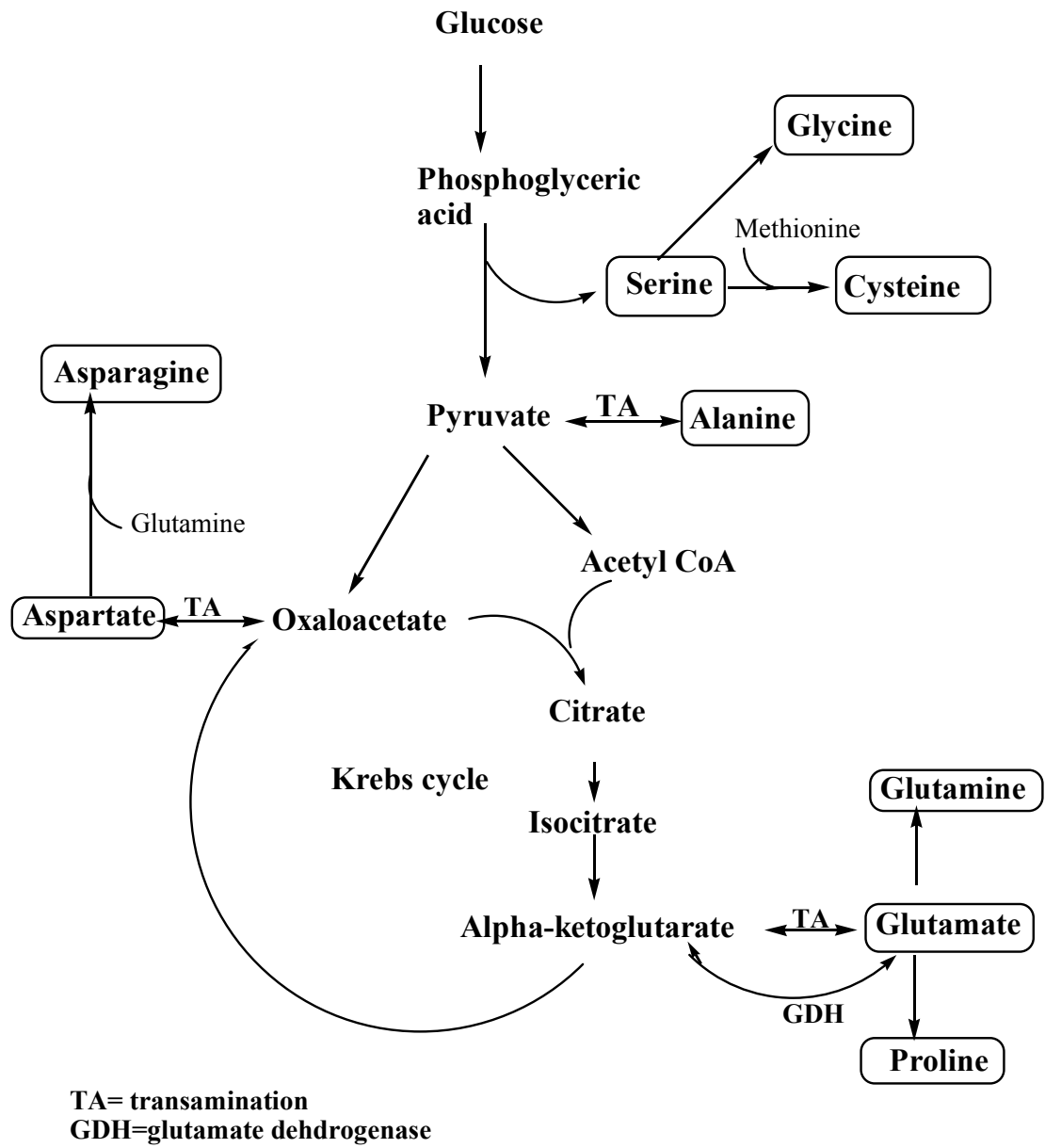
- **Glutamate:** Formation of glutamate from ammonia and α -ketoglutarate is catalyzed by glutamate dehydrogenase. This reaction is reversible and plays a role in both synthesis and breakdown of glutamate. Both NADPH and NADH can serve as the source of reducing equivalents used in this reaction.
- **Glutamine:** Glutamine synthetase catalyzes the ATP-dependent formation of glutamine, using glutamate and ammonia as substrates.

- c) **Modification of the carbon skeletons of existing amino acids.**
- **Cysteine:** Cysteine contains atoms donated by both methionine and serine.
 - **Glycine:** Serine is also converted to glycine by the removal of its hydroxymethyl group.
 - **Tyrosine:** Phenylalanine is hydroxylated to form tyrosine.
 - **Proline:** Glutamate is reduced and cyclized to form proline.
 - **Asparagine:** Asparagine is synthesized by the transfer to the amide group of glutamine to the β -carboxyl group of aspartate

Pyridoxal Phosphate:

In a transamination reaction, i.e. reactions involving the transfer of the α -amino group of an amino acid to the α -carbon of a keto acid, thereby forming a new amino acid and a new keto acid.

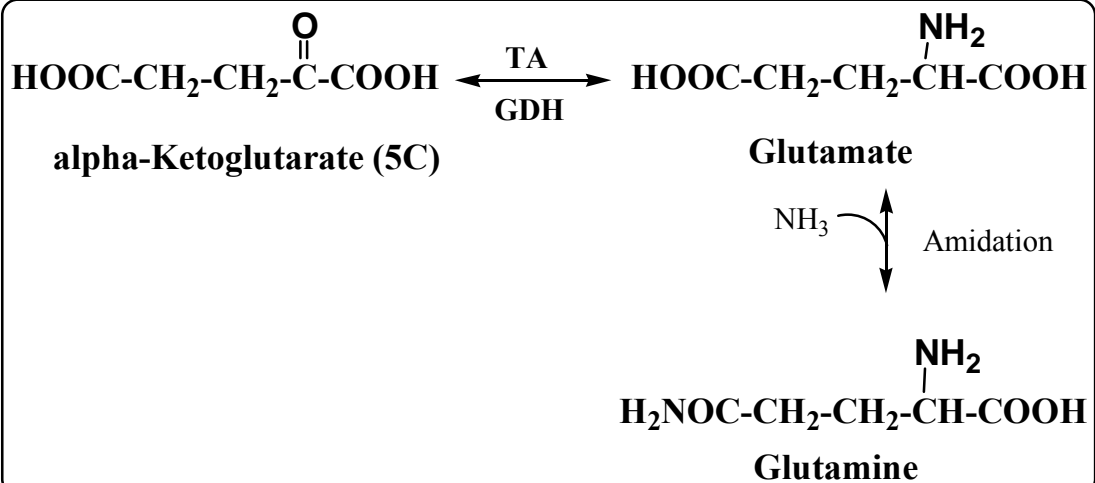
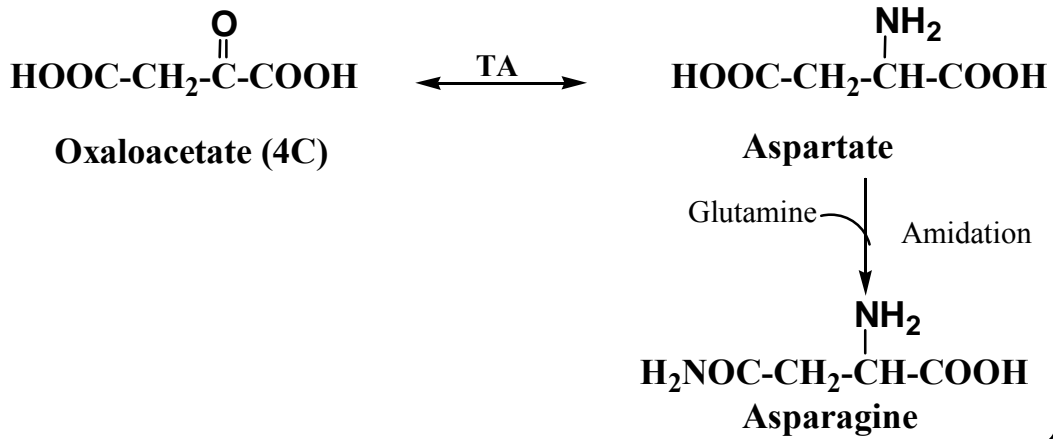
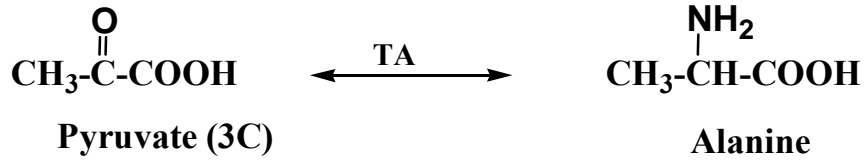
Pyridoxal phosphate (**vitamin B6**) acts as an intermediate carrier of the amino group that is being transferred.



Biosynthesis of nonessential amino acids

alpha-Keto acid

alpha-Amino acid



Amino Acid Catabolism:

Fate of amino groups:

Step 1: transamination with α -ketoglutarate to form glutamate and new α -keto acid.

Step 2: glutamate is deaminated through oxidative process.

Step 3: formation of urea through urea cycle.

Synthesis of urea: (urea cycle)

The amino groups for urea synthesis are collected in the form of **aspartate** and **ammonia**.

Site: Partly in mitochondria and partly in cytosol (Liver).

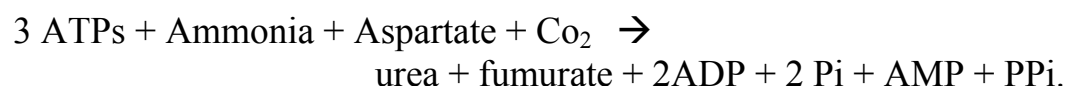
Reactions:

- 1) Ammonia enters the cycle by combining with CO_2 and ATP to form carbamoyl phosphate
- 2) Carbamoyl phosphate combines with ornithine to produce citrulline.
- 3) Aspartate, carrying the second nitrogen atom of urea, enters the cycle by condensing with citrulline to form argininosuccinate.
- 4) Argininosuccinate is cleaved to fumarate and arginine.
- 5) Arginine is further hydrolyzed to yield urea and regenerate the ornithine needed for the next round of the cycle.

Regulation of urea cycle:

- a) Glutamate dehydrogenase, which provides the bulk of the ammonia for urea synthesis, is activated by ADP and GDP and inhibited by ATP and GTP.
- b) The activity of carbamoyl phosphate synthase I is activated by N-acetylglutamate.

Energy of urea Cycle:



Clinical significance of blood urea:

- Elevated in renal insufficiency.
- Decreased in hepatic failure.

Why is ammonia toxic?



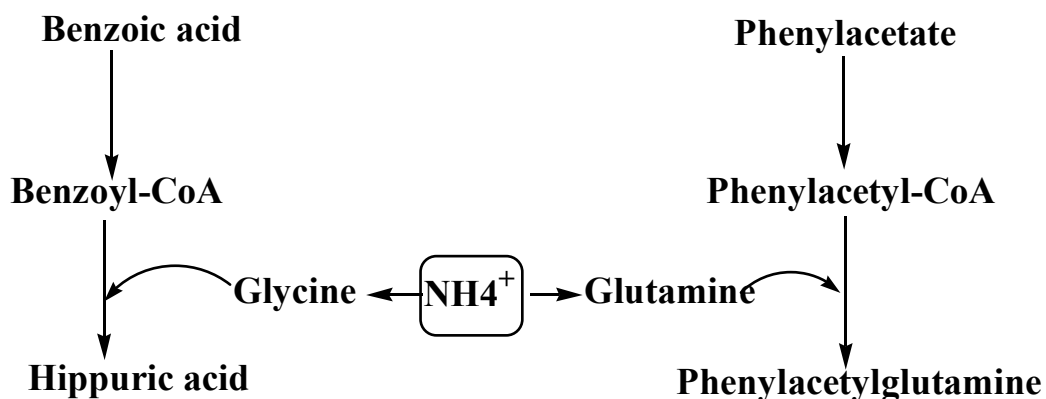
High ammonia depletes the TCA cycle of α -ketoglutarate \rightarrow low ATP \rightarrow COMA (a symptom of high ammonia levels).

Hyperammonemia:

1. **Acquired Hyperammonemia. e.g.** liver disease.
2. **Hereditary Hyperammonemia. e.g.** genetic deficiencies of Urea cycle enzymes.e.g.
 - a. Congenital hyperammonmia Type I:
carbamoyl phosphate synthetase deficiency
 - b. Congenital hyperammonmia Type II:
Ornithine transcarbamoylase deficiency

Treatment:

1. Limit protein intake.
2. Give carbon skeletons to provide the essential amino acids.
3. Use a trapping molecule (sodium benzoate, sodium phenylacetate) that bind covalently to amino acids and produce nitrogen containing molecules that are excreted.



Fate of carbon skeletons:

Following removal of their amino groups, the **carbon skeletons** of all amino acids are degraded to intermediates already encountered in fuel metabolism:

1. Acetyl-CoA.
2. Pyruvate.
3. Intermediates of the citric acid cycle:
 - α -ketoglutarate.
 - Oxaloacetate.
 - Succinyl-CoA.
 - Fumarate.

Glucogenic or ketogenic amino acids:

During fasting, those amino acids that are degraded to pyruvate or 4- or 5-carbon intermediates of the citric acid cycle can be used as substrates for gluconeogenesis.

Amino acids that are degraded to acetyl-CoA provide substrates for ketogenesis. This distinction has led to the classification of amino acids as glucogenic or ketogenic.

- Leucine and lysine are purely ketogenic i.e. their catabolism yields only acetyl-CoA.
- Four amino acids (isoleucine, phenylalanine, tryptophan, and tyrosine) are both glucogenic and ketogenic.
- The remaining 14 amino acids are glucogenic.

Genetic Defects of Amino Acid Metabolism:

Phenylketonuria: (PKU)

- Deficiency of **phenylalanine hydroxylase**.
- Tyrosine is an essential amino acid
- Phenylpyruvate, phenylacetate, and phenyllactate are produced in greater amounts and are spilled in the urine.
- The major manifestation of the disease is mental retardation.

Homocystinuria:

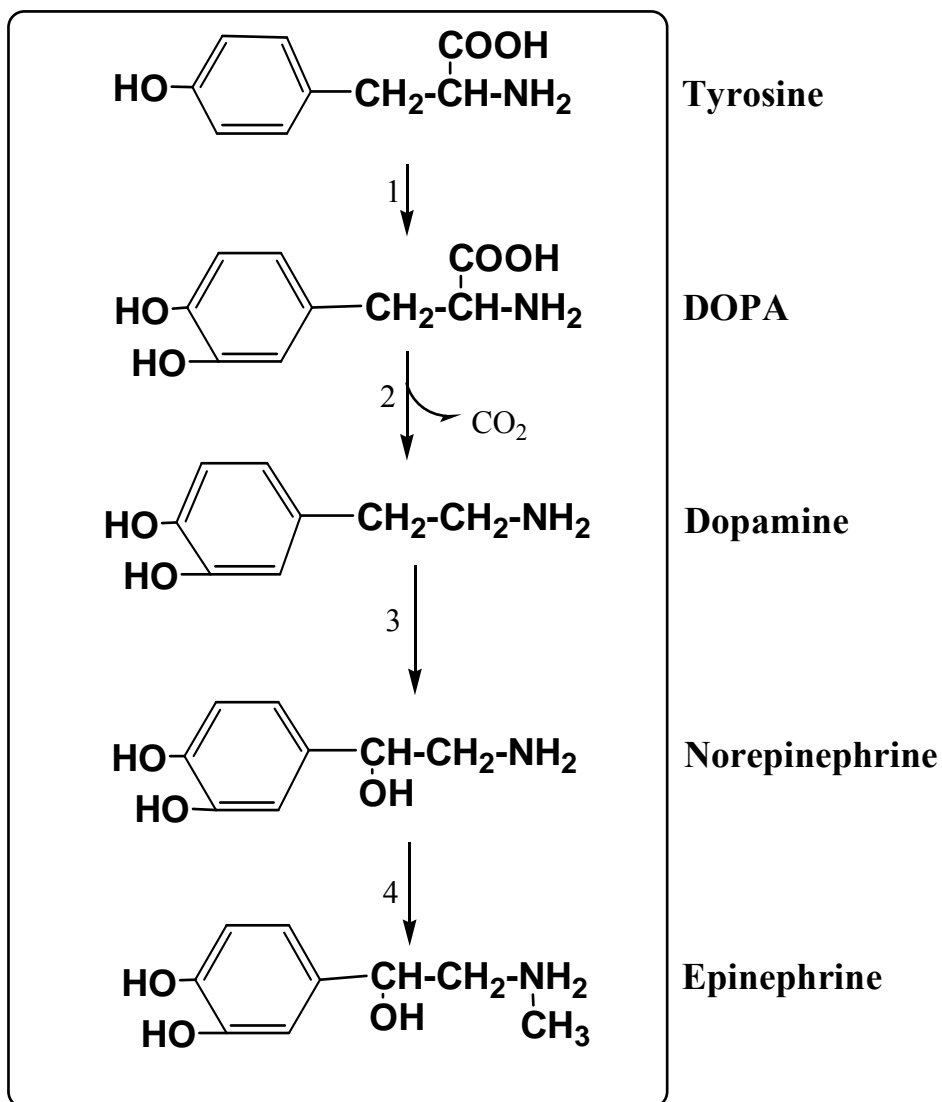
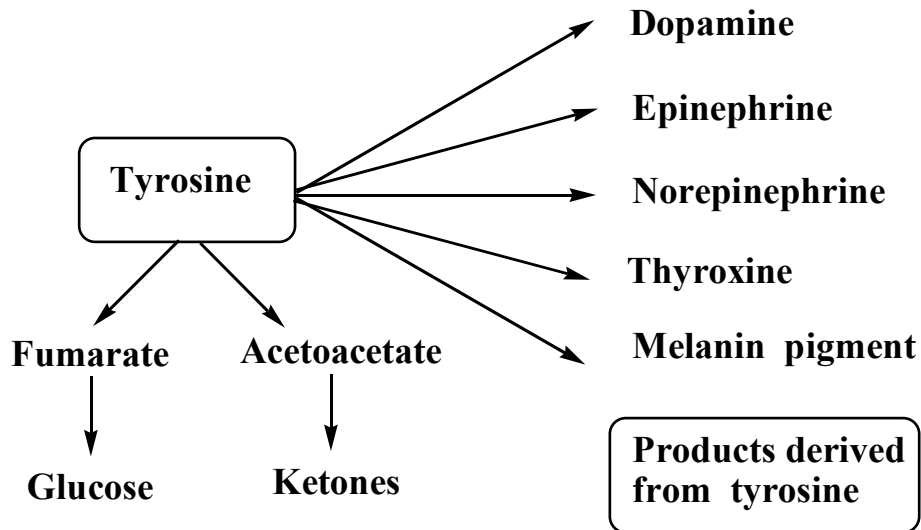
- Deficiency of **cystathionine synthase**, an enzyme that forms part of the pathway for cysteine synthesis, results in a disorder known as homocystinuria.
- High urinary levels of homocysteine, a substrate of the impaired enzyme.
- Two forms have been described, one of which can be treated by high doses of vitamin B6. This form of the disorder is due to the reduced affinity of cystathionine synthase for its coenzyme, pyridoxal phosphate.
- The other form is treated by limiting intake of methionine and by providing cysteine in the diet.

Branched-chain ketonuria (maple syrup urine disease):

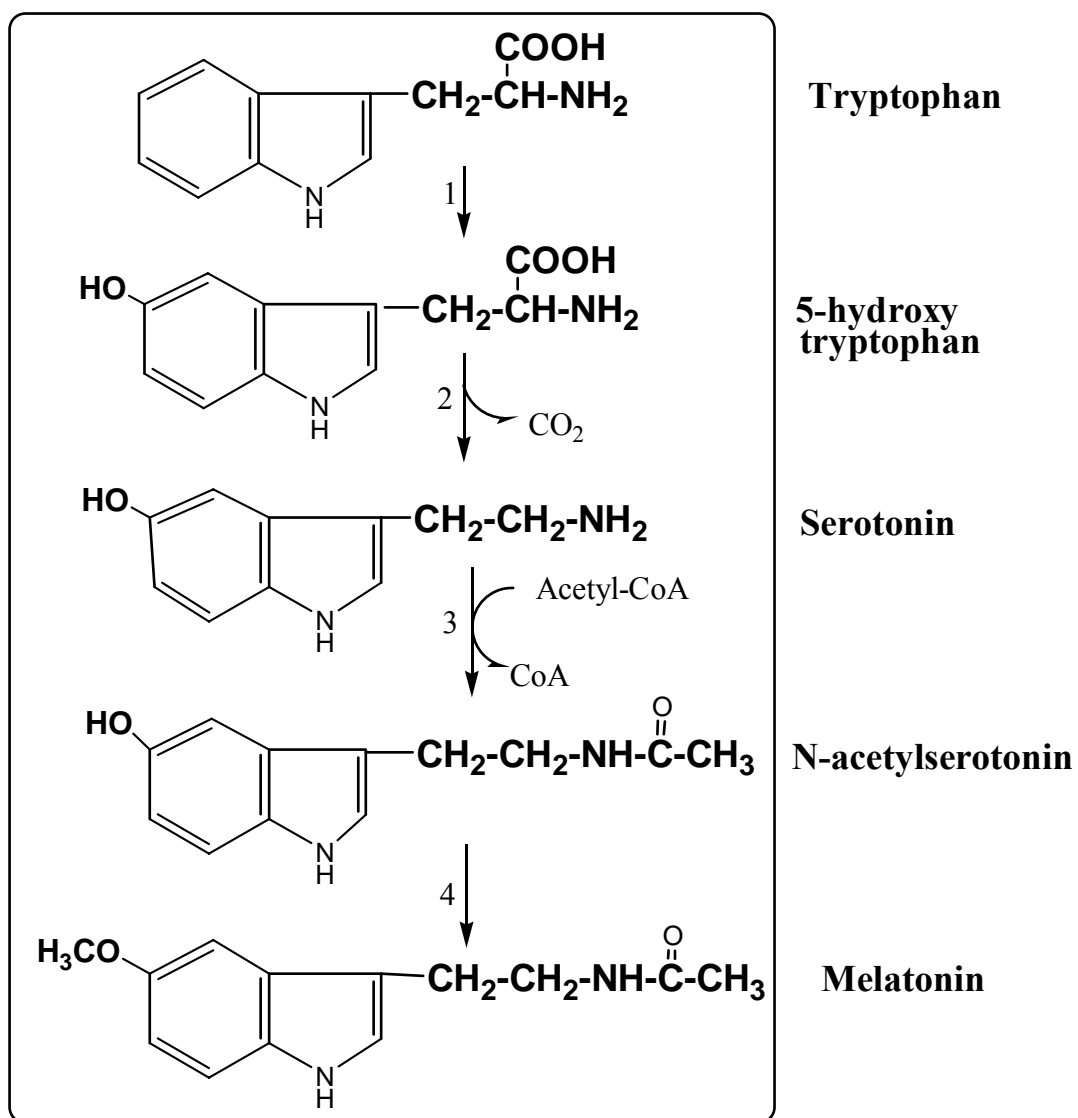
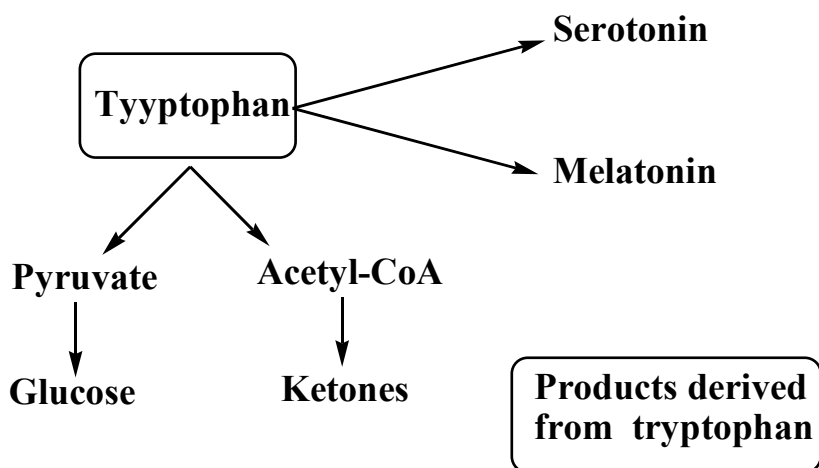
- Defect in **α keto acid decarboxylase**
(**α keto acid dehydrogenase**) an enzyme involved in the catabolism of leucine, valine, and isoleucine.
- The disease is manifested by severe brain damage.
- Urine smells like maple syrup.
- Few infants survive beyond the first year of life.

Biosynthesis of some important molecules:

- Catecholamines.
- Serotonin and melatonin.
- Histamine.
- Gamma-aminobutyric acid.
- Nitric oxide.
- Glutathione.

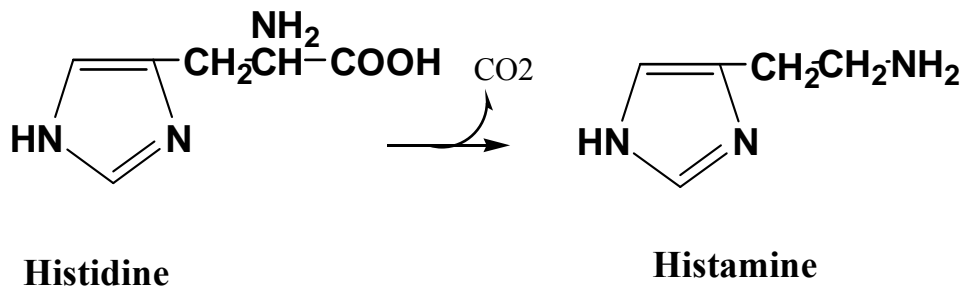


Biosynthesis of catecholamines



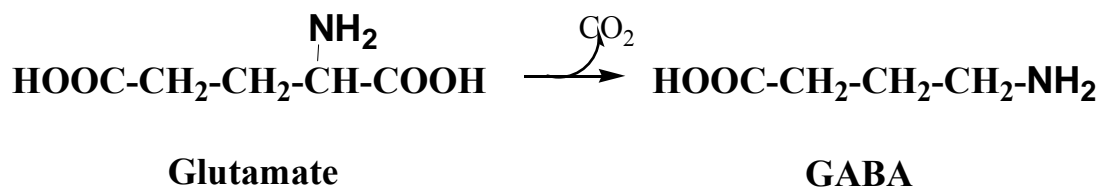
Biosynthesis of serotonin and melatonin

Biosynthesis of histamine:



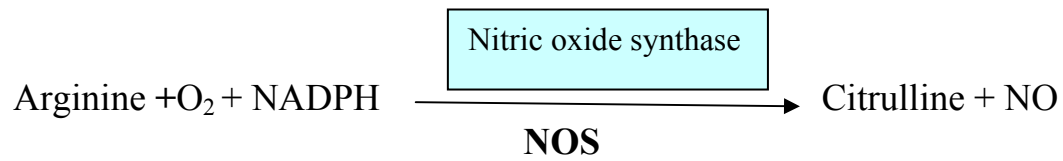
- Synthesized and released by mast cells
- Mediator of allergic response: (H₁ receptors)
 - H₁ blockers: Diphenhydramine (Benadryl)
Loratidine (Claritin)
- Stimulates secretion of gastric acid (H₂ receptors)
 - H₂ blockers: Cimetidine (Tagamet)
Ranitidine (Zantac)

Biosynthesis of γ -aminobutyric acid:



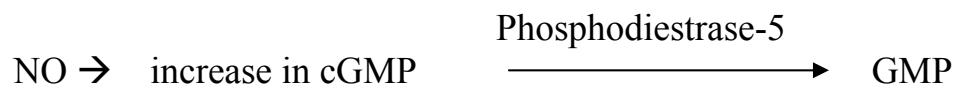
- GABA is an important inhibitory neurotransmitter in the brain

Nitric oxide:

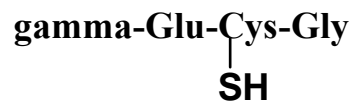


Functions:

- Neurotransmitter
- Prevents platelet aggregation.
- Bactericidal.
- Relaxes smooth muscle by activation of guanylyl cyclase \rightarrow cGMP \rightarrow relaxation.
 - Nitroglycerin \rightarrow Glycerin + NO
 - Sildenafil (Viagra): inhibits phosphodiesterase-5 in vascular smooth muscle \rightarrow increase in cGMP.



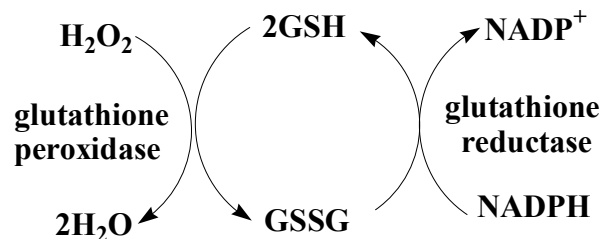
Glutathione: (GSH)



- It is three amino acids together. γ -Glutamylcysteinylglycine
- γ -glutamate – attached via the γ -carbon instead of the α -carbon
- The active part is the -SH group of cysteine (sulfhydryl group)
- The -SH is the reduced form. Two molecules can be bridged by a disulfide bond; which produces the oxidized form (GS-SG).
- These two reactions are catalyzed by **glutathione peroxidase** and **glutathione reductase**

Functions of GSH:

1. **RBCs – GSH peroxidase and GSH reductase scavenge for peroxide (free radicals).**



2. **Conjugation** : Lipophilic drugs can be converted to hydrophilic molecules for excretion by attaching it to glutathione
3. **Transport of amino acids** especially in the renal epithelium.

Integration of Metabolism

The average 70 kg man has fuel stores consisting of:

- 15 kg of triglyceride,
- 6 kg of protein and
- 0.2 kg of glycogen

FED STATE	
Signals:	Storage forms:
Insulin: Up	Glycogen: Up
Glucagon: Down	Fat: Up
	Protein: Up
FASTING STATE	
Signals:	Storage forms:
Insulin: Down	Glycogen: Down
Glucagon: Up	Fat: Down
	Protein: Down
STARVATION	
Signals:	Storage forms:
Insulin: Down	Glycogen: Exhausted
Glucagon: Up	Fat: Down
	Protein: Down

INSULIN:

- It is a signal for high blood glucose levels.
- It stimulates synthesis of glycogen, fat, and protein.
- It inhibits breakdown of glycogen, fat, and protein.
- It increases glucose transport into cells (muscle and adipose tissue).

GLUCAGON:

- It is a signal for low blood glucose levels.
- It stimulates breakdown of glycogen, fat, and protein.
- It inhibits synthesis of glycogen, fat, and protein.
- It increases protein phosphorylation.
It activates cAMP-dependent protein kinase.