BHARATHIDASAN UNIVERSITY

Tiruchirappalli – 620024

Tamil Nadu, India.

Programme: Biochemistry

Course Title: Intermediary Metabolism

COURSE CODE: BC201CR

Unit: 3

Amino acid Metabolism

Dr. A. Antony Joseph Velanganni

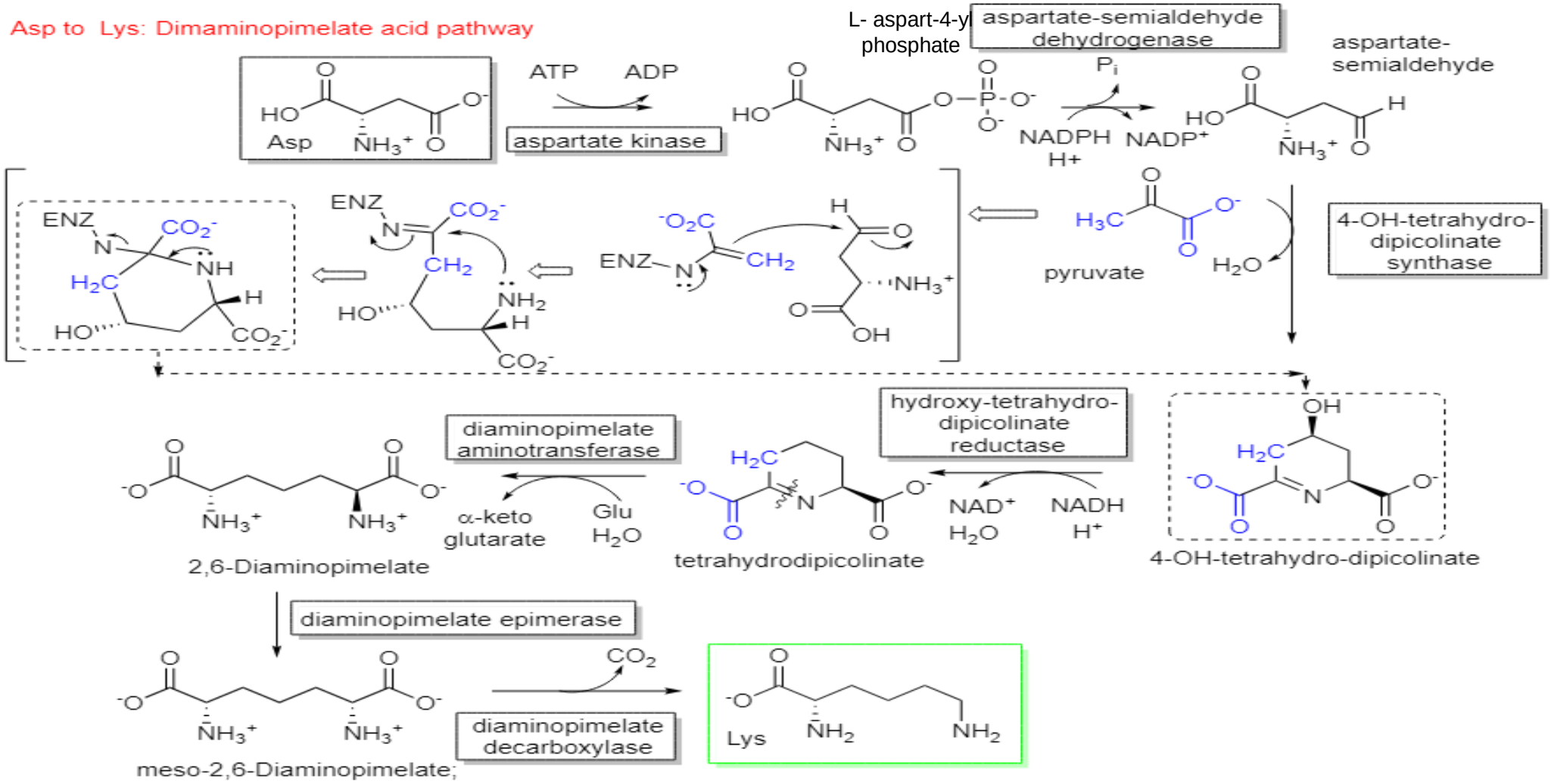
Associate Professor

Department of Biochemistry

LYSINE :

- *Lysine is an essential basic amino acid. It is one of the four common a-amino acids to have a nitrogen atom in its side chain.*
- *Lysine was first isolated by the German biological chemist Ferdinand Heinrich Edmund Drechsel in 1889 from hydrolysis of the protein casein, and thus named it Lysin, from λύσις lysis "loosening".*
- *In 1902, the German chemists Emil Fischer and Fritz Weigert determined lysine's chemical structure by synthesizing it.*
- *The one-letter symbol K was assigned to lysine for being alphabetically nearest, with L being assigned to the structurally simpler leucine.*
- *It does not undergo transamination.*
- *Lysine is predominantly ketogenic.*

BIOSYNTHESIS OF LYSINE:



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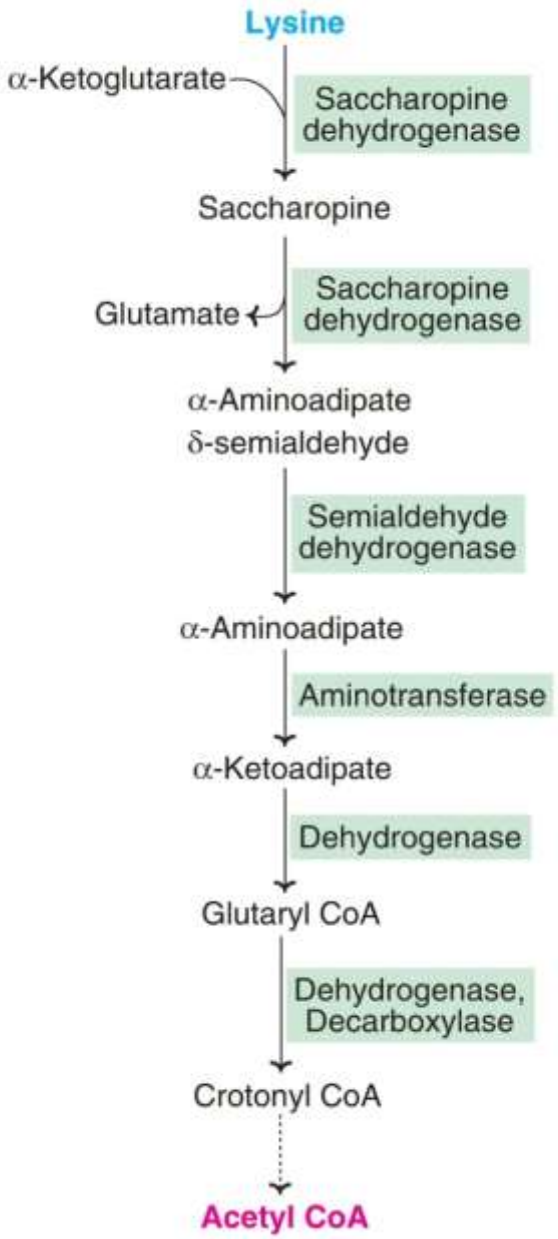
DEGRADATION OF LYSINE:



Hyperlysinemia (238700*)	Lysine:alpha-ketoglutarate reductase	**Biochemical profile:** Hyperlysinemia **Clinical features:** Muscle weakness, seizures, mild anemia, intellectual disability, joint and muscular laxity, ectopia lentis; sometimes benign **Treatment:** Limited lysine intake
2-Ketoadipic acidemia (245130*)	2-Ketoadipic dehydrogenase	**Biochemical profile:** Elevated urine 2-ketoadipate, 2-aminoadipate, and 2-hydroxyadipate **Clinical features:** Benign **Treatment:** None needed
Glutaric acidemia type I (231670*)	Glutaryl CoA dehydrogenase	**Biochemical profile:** Elevated urinary glutaric acid and 2-hydroxyglytaric acid **Clinical features:** Dystonia, dyskinesia, degeneration of the caudate and putamen, frontotemporal atrophy, arachnoid cysts **Treatment:** Aggressive treatment of intercurrent illness, carnitine Protein, lysine, and tryptophan restriction
Saccharopinuria (268700*)	Alpha-aminoadipic semialdehyde-glutamate reductase	**Biochemical profile:** Elevated urine lysine, citrulline, histidine, and saccharopine **Clinical features:** Intellectual disability, spastic diplegia, short stature, electroencephalographic abnormality **Treatment:** No clear treatment

Source:principles of biochemistry- lehninger 4th edition

Regulation Mechanism:

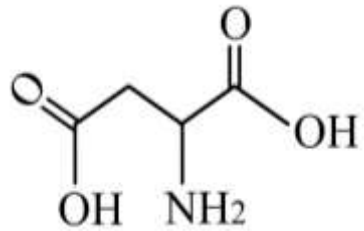
- The pathway is tightly regulated to ensure the appropriate balance of lysine synthesis.
- Feedback mechanisms and allosteric regulation play pivotal roles in modulating the expression and activity of enzymes involved in lysine biosynthesis.
  - Transcriptional Control

    Transcription factors play a crucial role in regulating the expression of genes involved in lysine biosynthesis, responding to the cellular demands for this essential amino acid.
  - Metabolic Feedback:

    Intricate feedback loops and metabolite concentrations exert significant control over the rate and effectiveness of lysine biosynthetic pathways.
  - Enzymatic Regulation

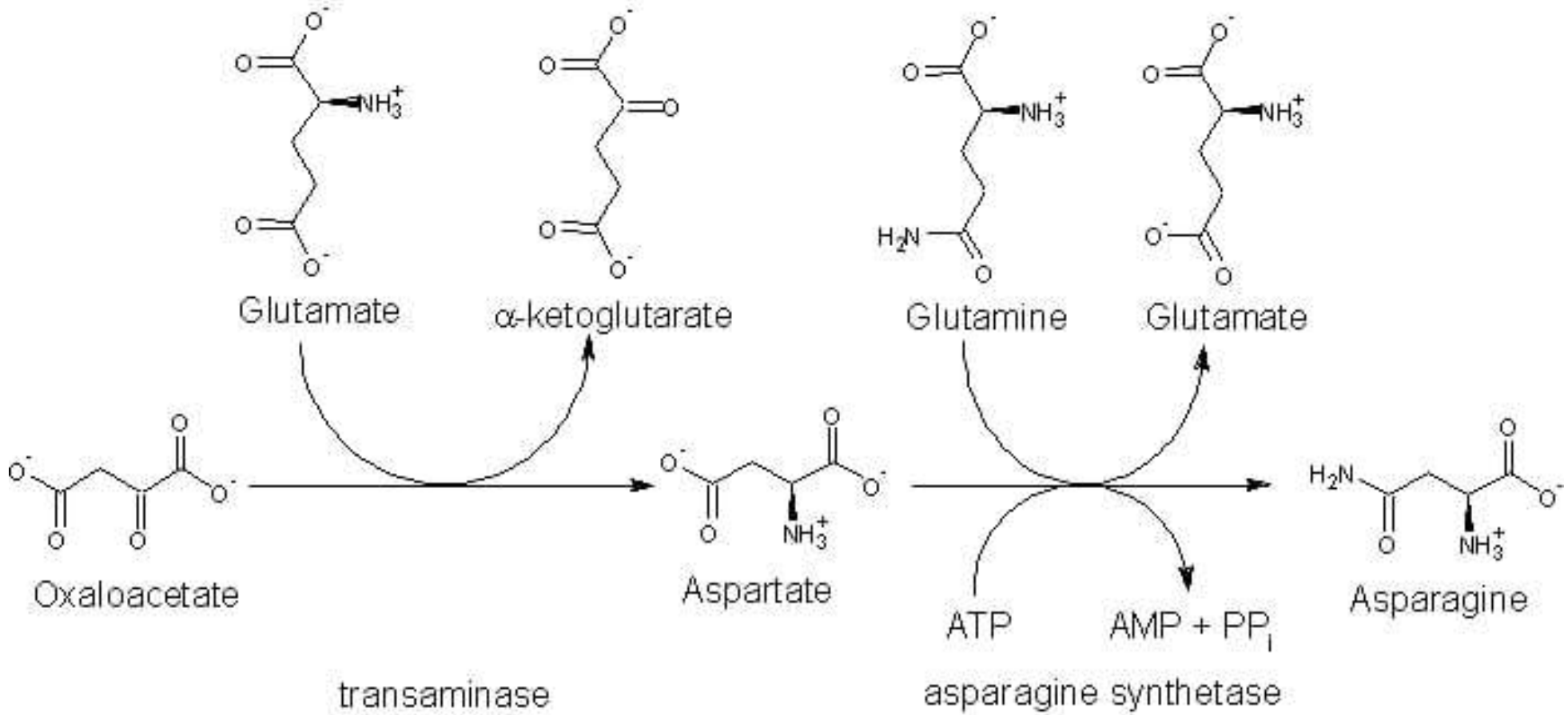
    Allosteric enzyme play a pivitol role in controlling the pace of lysine catabolism responding to metavolic cues and energy demands within the cell.

ASPARTATE:



- Aspartic acid was first discovered in 1827 by Auguste-Arthur Plisson and Étienne Ossian Henry by hydrolysis of asparagine, which had been isolated from asparagus juice in 1806. (Swedish chemist Jons Jacob Berzelius in 1827)
- Aspartate also known as aspartic acid which is non-essential amino acid that plays a crucial role in protein synthesis and energy production.
- It is involved in the urea cycle which helps remove ammonia from the body and is also a precursor for the synthesis of other amino acids.
- It is important for maintain overall health and proper functioning of the nervous system.

BIOSYNTHESIS OF ASPARTATE:



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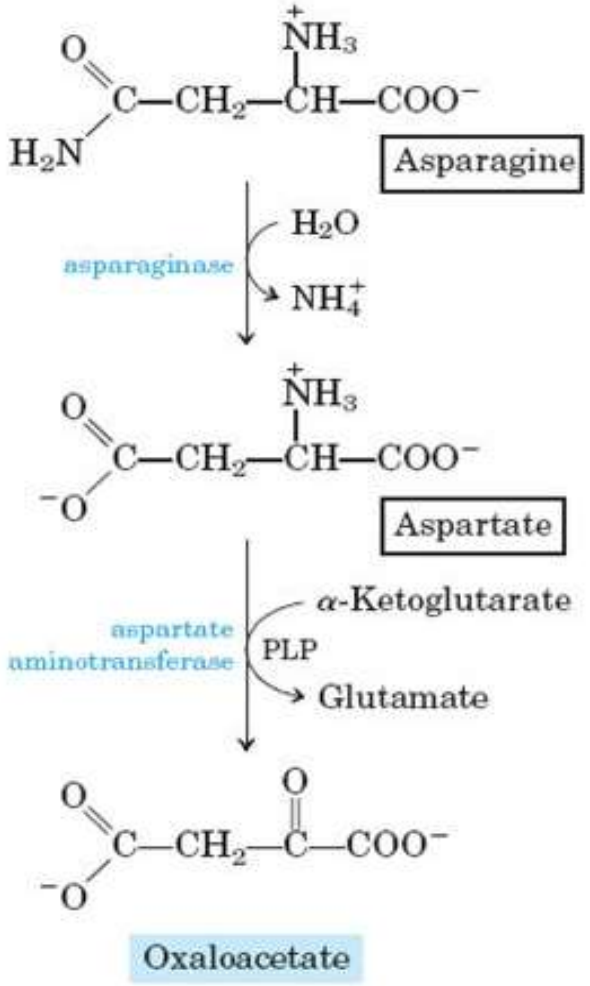
- In the human body, aspartate is most frequently synthesized through the transamination of oxaloacetate.
- The biosynthesis of aspartate is facilitated by an aminotransferase enzyme: the transfer of an amine group from another molecule such as alanine or glutamine yields aspartate and an alpha-keto acid.
- In plants and microorganisms, aspartate is the precursor to several amino acids, including four that are essential for humans: methionine, threonine, isoleucine, and lysine.
- The conversion of aspartate to these other amino acids begins with reduction of aspartate to its "semialdehyde", O2CCH(NH2)CH2CHO.
- Asparagine is derived from aspartate via transamination.

DEGRADATION OF ASPARTATE:



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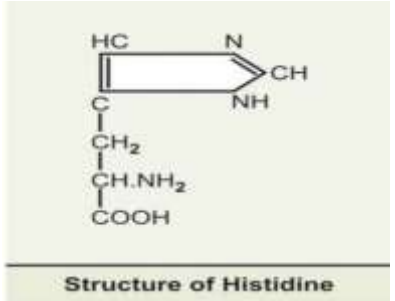
REGULATION OF ASPARTATE:

- **Feedback Inhibition:** Aspartate biosynthesis is regulated by feedback inhibition mechanisms, where the end products of its metabolic pathways can inhibit the activity of key enzymes involved in its synthesis. For example, high levels of downstream metabolites like fumarate or arginine can inhibit enzymes in the urea cycle or citric acid cycle, leading to decreased production of aspartate.
- **Hormonal Regulation:** Hormones such as insulin, glucagon, and cortisol can influence the metabolism of amino acids, including aspartate. These hormones can modulate the activity of enzymes involved in aspartate metabolism, affecting its utilization for energy production or protein synthesis
- **Genetic Regulation:** Gene expression and regulation play a crucial role in controlling the enzymes involved in aspartate metabolism. Transcription factors and epigenetic modifications can influence the expression levels of genes encoding enzymes that synthesize or degrade aspartate.

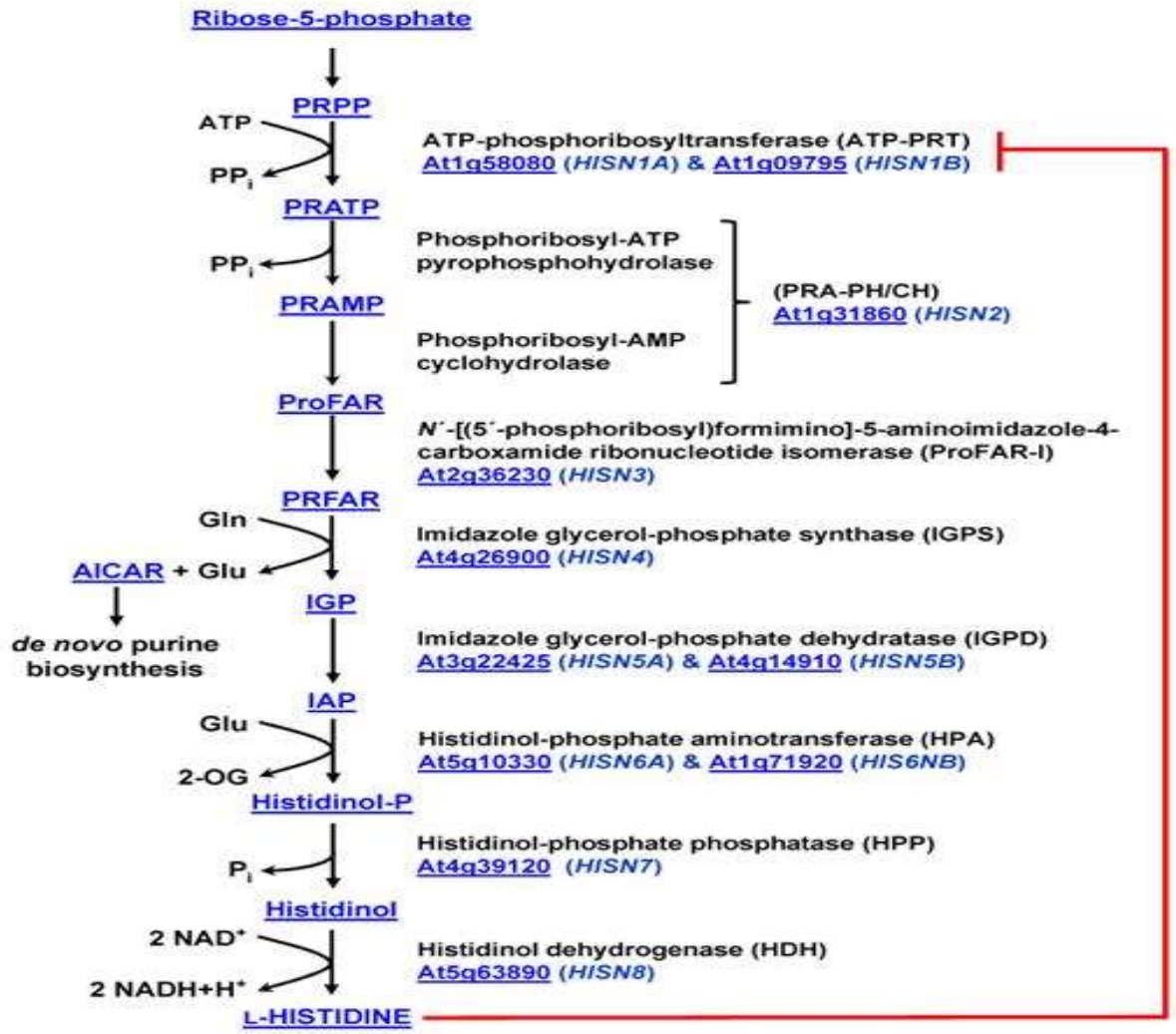
HISTIDINE



Structure of Histidine

- It’s a semi-essential amino acid.
- It is **glucogenic** through formation of glutamate to alpha ketoglutarate.
- The amino acid L-histidine (His) was discovered independently by Kossel and Hedin in 1896.
- Histidine, on decarboxylation, gives the corresponding amine—histamine. Histamine regulates HCl secretion by gastric mucosa,
- Excessive production of histamine causes asthma and allergic reactions.
- **Histidinemia :** The frequency of histidinemia is 1 in 20,000. It is due to a defect in the enzyme histidase. Histidinemia is characterized by elevated plasma histidine levels and increased excretion of imidazole pyruvate and histidine in urine. Most of the patients of histidinemia are mentally retarded and have defect in speech. No treatment will improve the condition of the patients.

BIOSYNTHESIS OF HISTIDINE:



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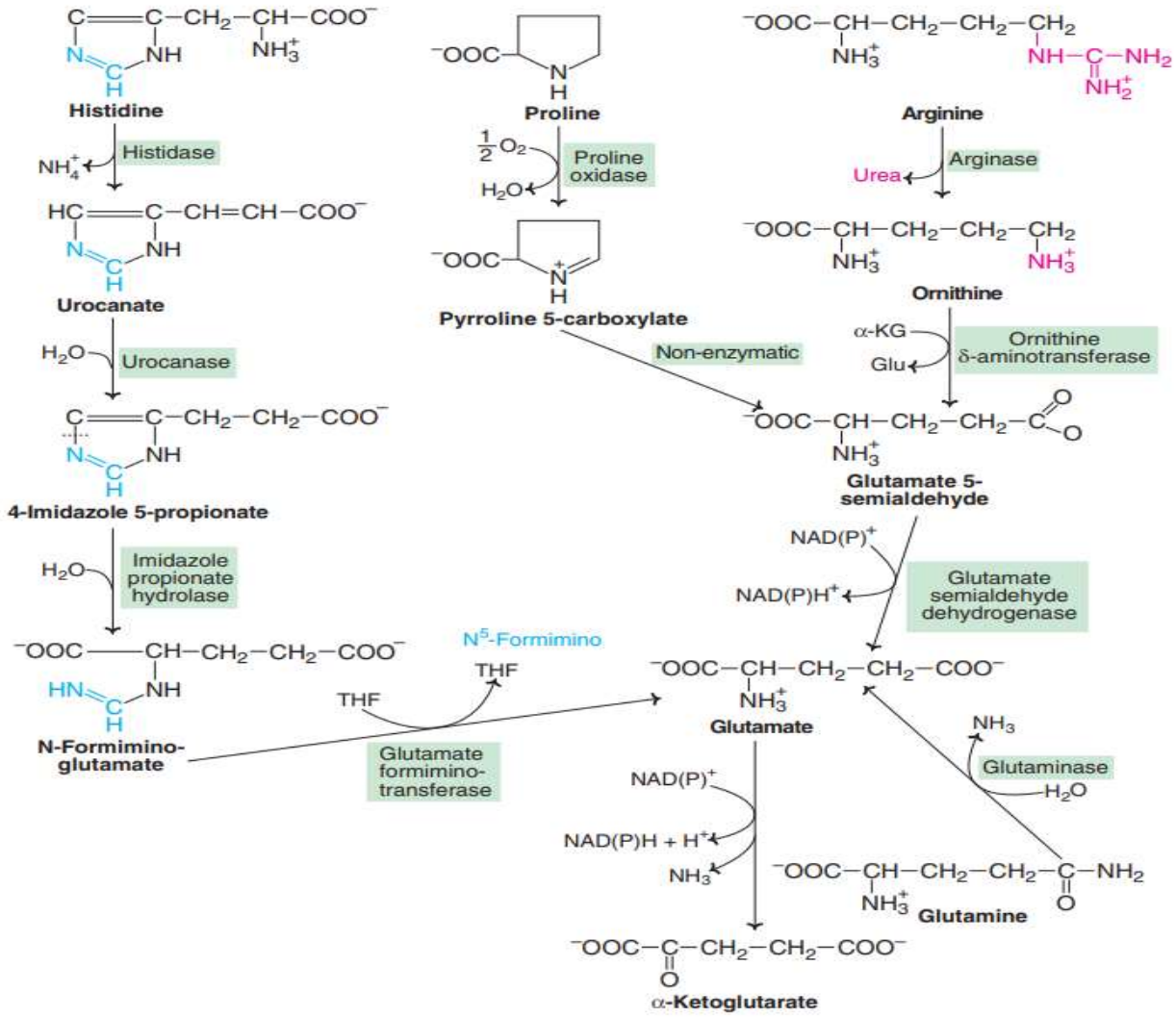


Source:Biochemistry,4th edition by sathyanarayanan

REGULATION OF HISTIDINE:

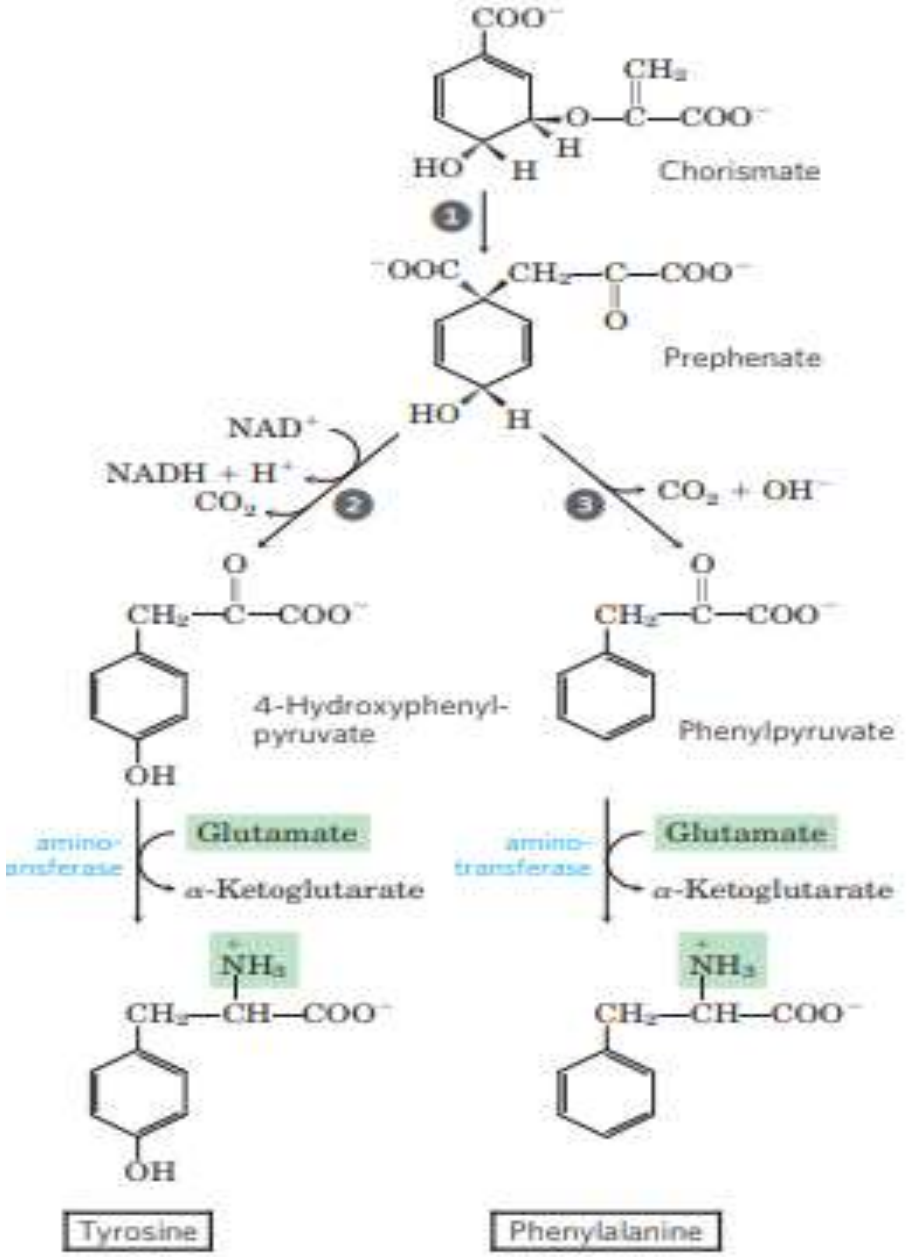
- **Neurotransmitter Regulation**
- Histidine is involved in the synthesis of histamine, a neurotransmitter with various physiological functions.
- **Gene Regulation**
- Transcriptional regulation controls the expression of enzymes in the biosynthesis pathway.
- **Feedback Inhibition**
- Accumulation of histidine acts as a feedback inhibitor, modulating enzyme activity.
- **Coordination with Other Amino Acids**
- Histidine biosynthesis coordinates with the overall regulation of amino acid metabolism.
- Enzyme regulation: The biosynthesis of histidine is regulated by a series of enzymes in the histidine biosynthetic pathway. Feedback inhibition mechanisms control the activity of these enzymes to prevent overproduction of histidine.
- Hormonal regulation: Hormones such as growth hormone and insulin can influence histidine metabolism and utilization in the body. For example, growth hormone stimulates the expression of enzymes involved in histidine metabolism, while insulin regulates the uptake of histidine into cells.

Phenylalanine Biosynthesis

- Plants and bacteria synthesize all 20 common amino acids. Mammals can synthesize about half the others are required in the diet (essential amino acids).

- Among the nonessential amino acids, glutamate is formed by reductive amination of alpha ketoglutarate and serves as the precursor of glutamine, proline, and arginine

- The amino acid biosynthetic pathways are subject to allosteric end-product inhibition; the regulatory enzyme is usually the first in the sequence. Regulation of the various synthetic pathways is coordinated.



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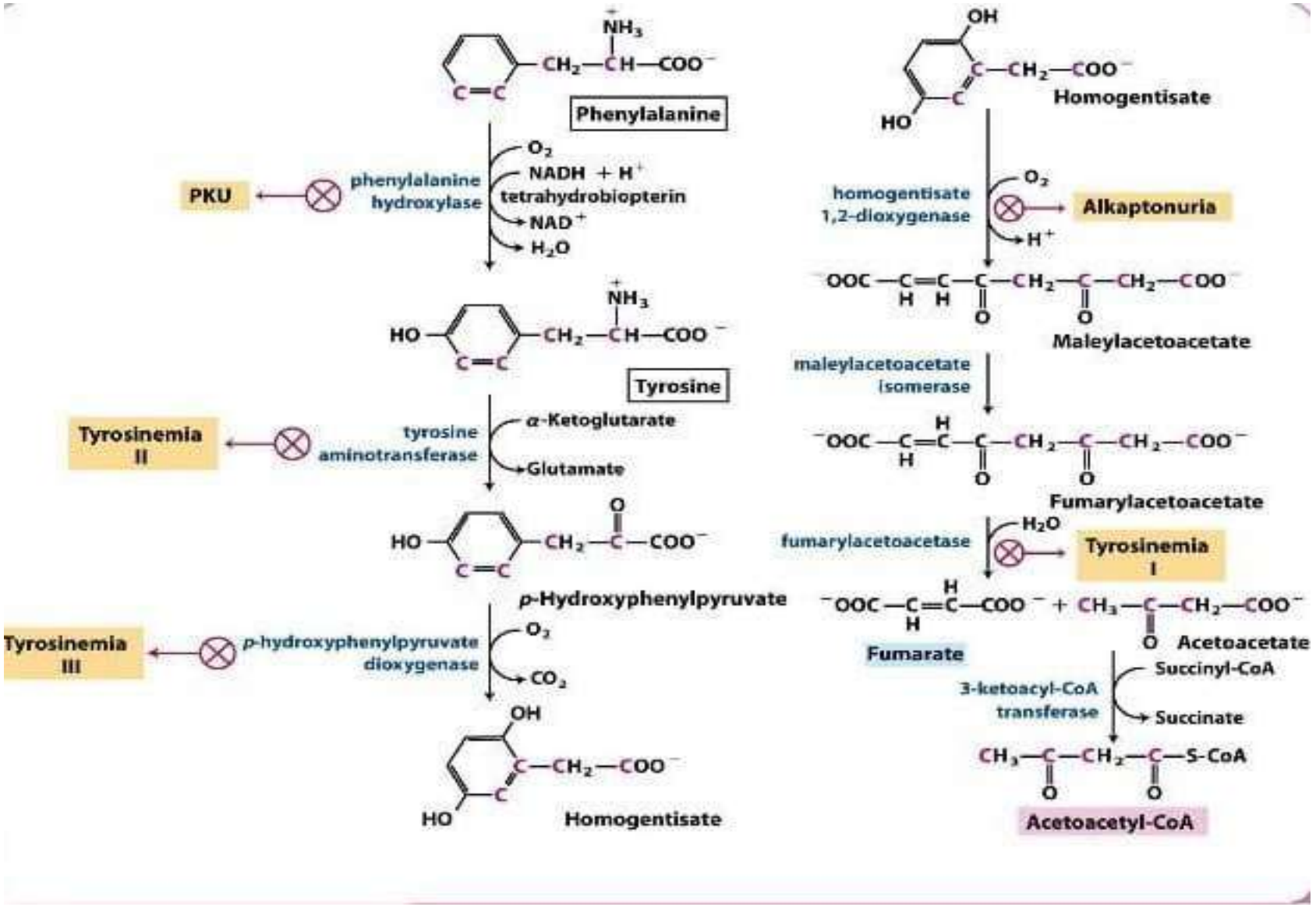
Degradation



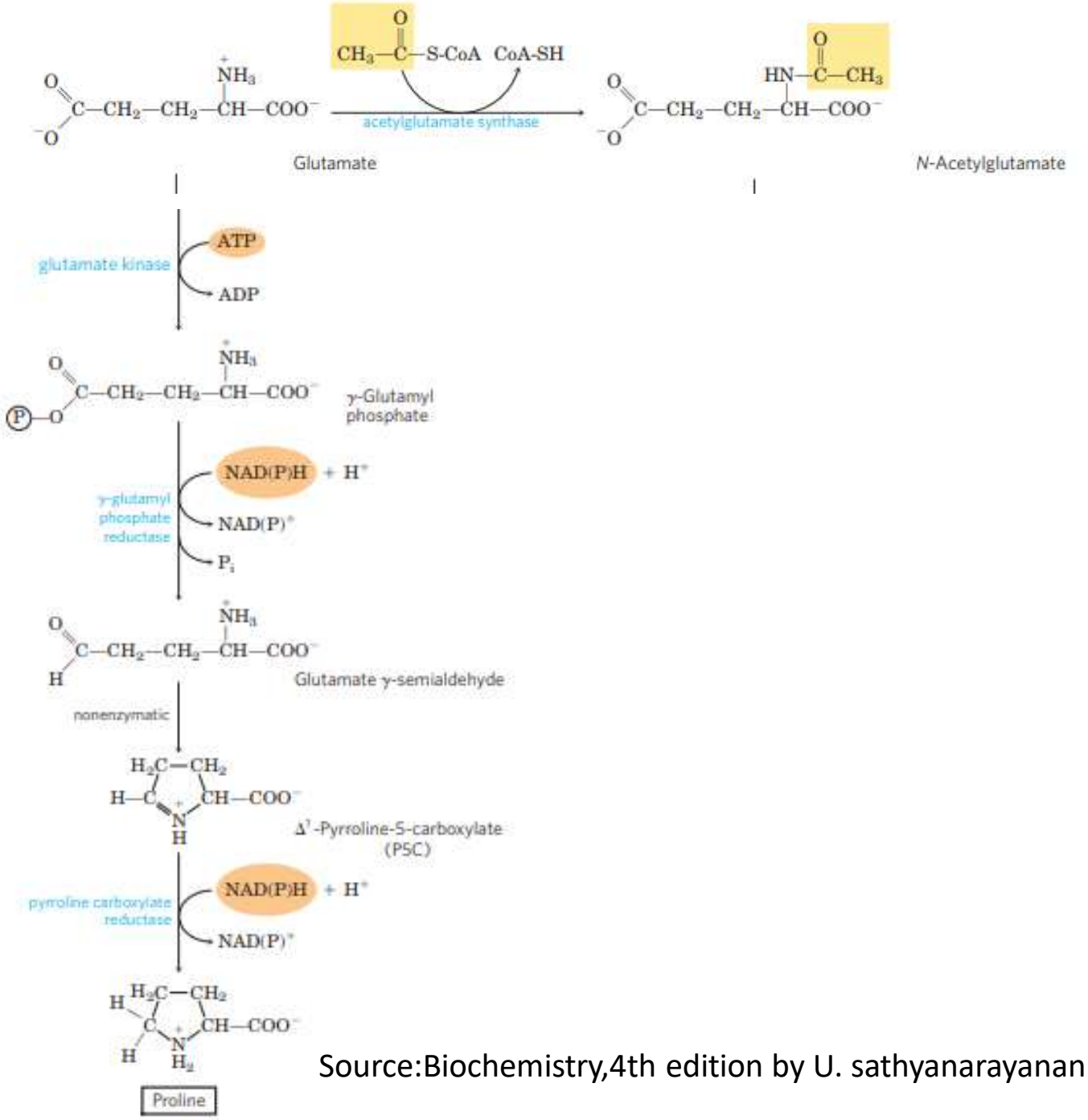
Source:Biochemistry,4th edition by Sathyanarayanan

Regulation:

- The regulation of phrnylalanine metabolism is primarily mediated by the enzyme phenylalanine hydroxylase (PAH), which catalyzes the conversion of phenylalanine to tyrosine.
- PAH activity is tightly regulated at the transcriptional ,post-transcriptional and allosteric levels.
- Notably, mutations in the PAH gene can lead to phenylketonuria (PKU), a metabolic disorder characterized by the accumulation of phneylalanine and its metabolites, which can cause severe neurological impairment if left untreated.

Proline Biosynthesis

- Biosynthesis of proline and arginine from glutamate in bacteria. All five carbon atoms of proline arise from glutamate
- In many organisms, glutamate dehydrogenase is unusual in that it uses either NADH or NADPH as a cofactor
- The r-semialdehyde in the proline pathway undergoes a rapid, reversible cyclization to D 1 -pyrroline-5-carboxylate (P5C), with the equilibrium favoring P5C formation.



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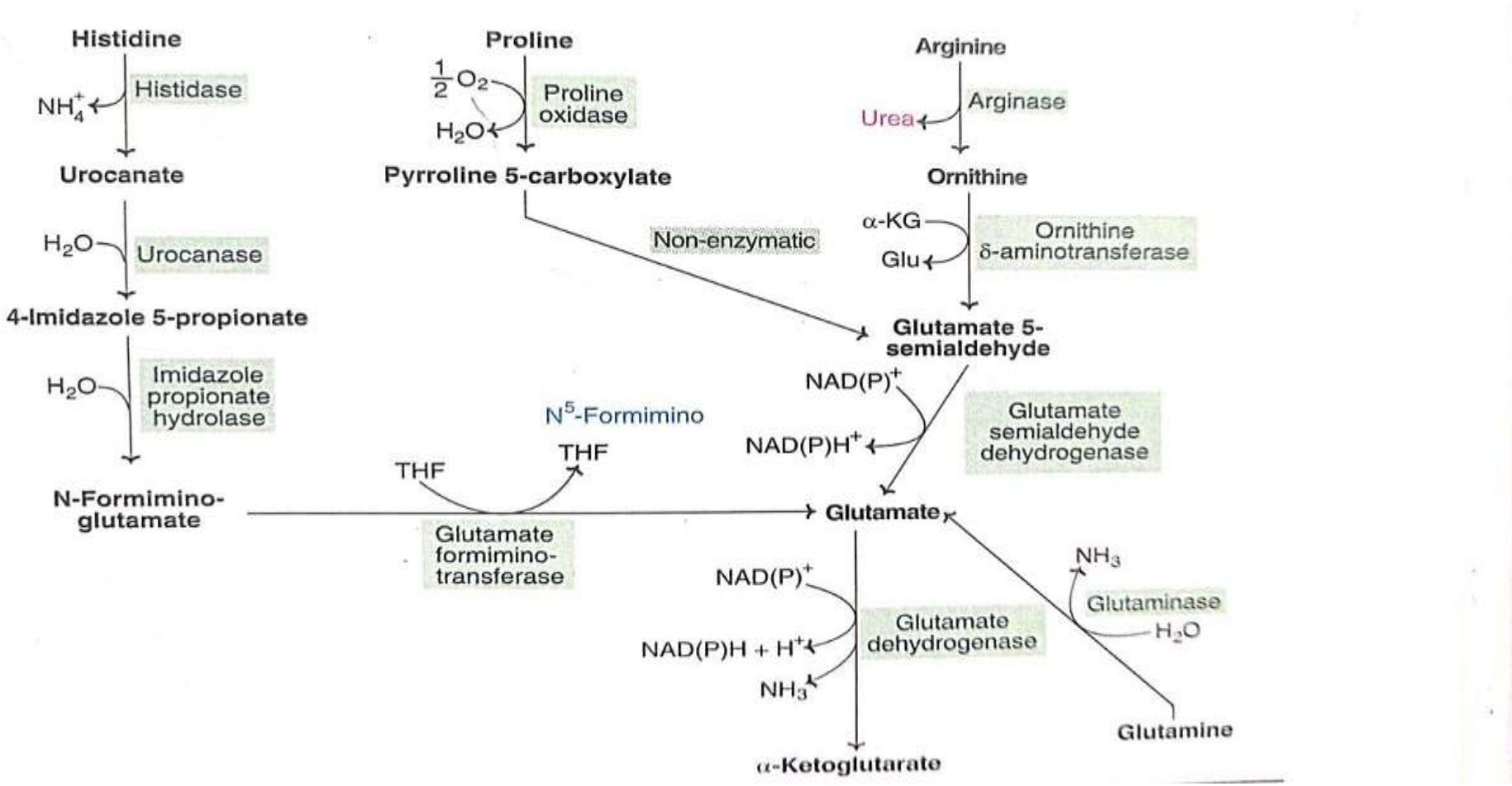
Degradation



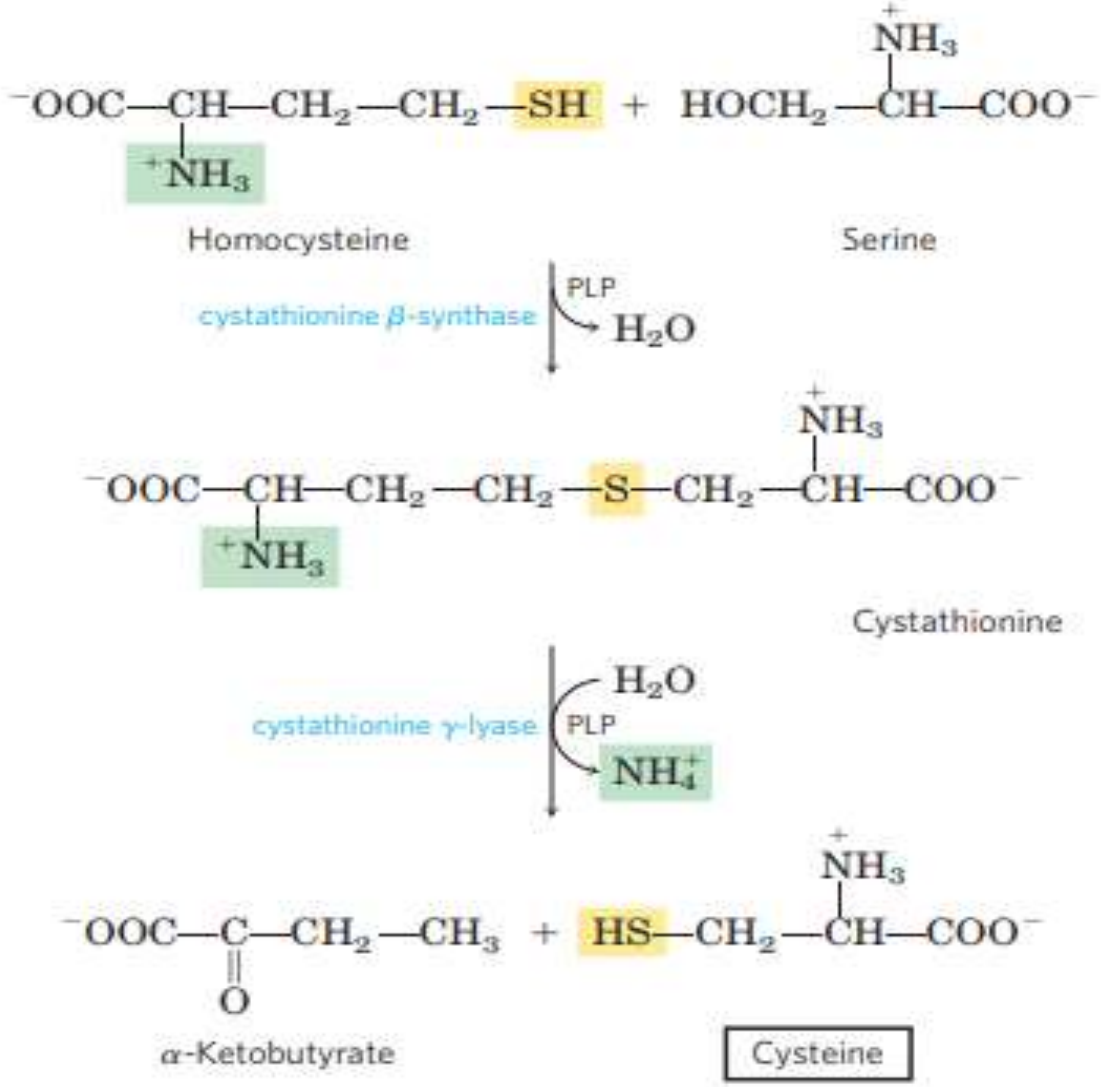
Source:Biochemistry,4th edition by U.Sathyanarayanan

Regulation

- Glutamate: The main source of proline biosynthesis and the end product of its catabolism.
- Target of rapamycin (TOR) kinase: A factor that regulates proline metabolism
- Sucrose non-fermenting 1 (SNF1)-related protein kinase 1 (SnRK1) signaling pathways: A factor that regulates proline metabolism
- PKA signaling: A factor that negatively regulates proline utilization in yeast
- Msn2 and Msn4: Stress-responsive transcription factors that partially inhibit proline utilization in yeast
- Lactate: Inhibits proline oxidase, the first enzyme in the proline degradative pathway

Cysteine Biosynthesis

- Biosynthesis of cysteine from serine in bacteria and plants.
- Biosynthesis of cysteine from homocysteine and serine in mammals. The homocysteine is formed from methionine



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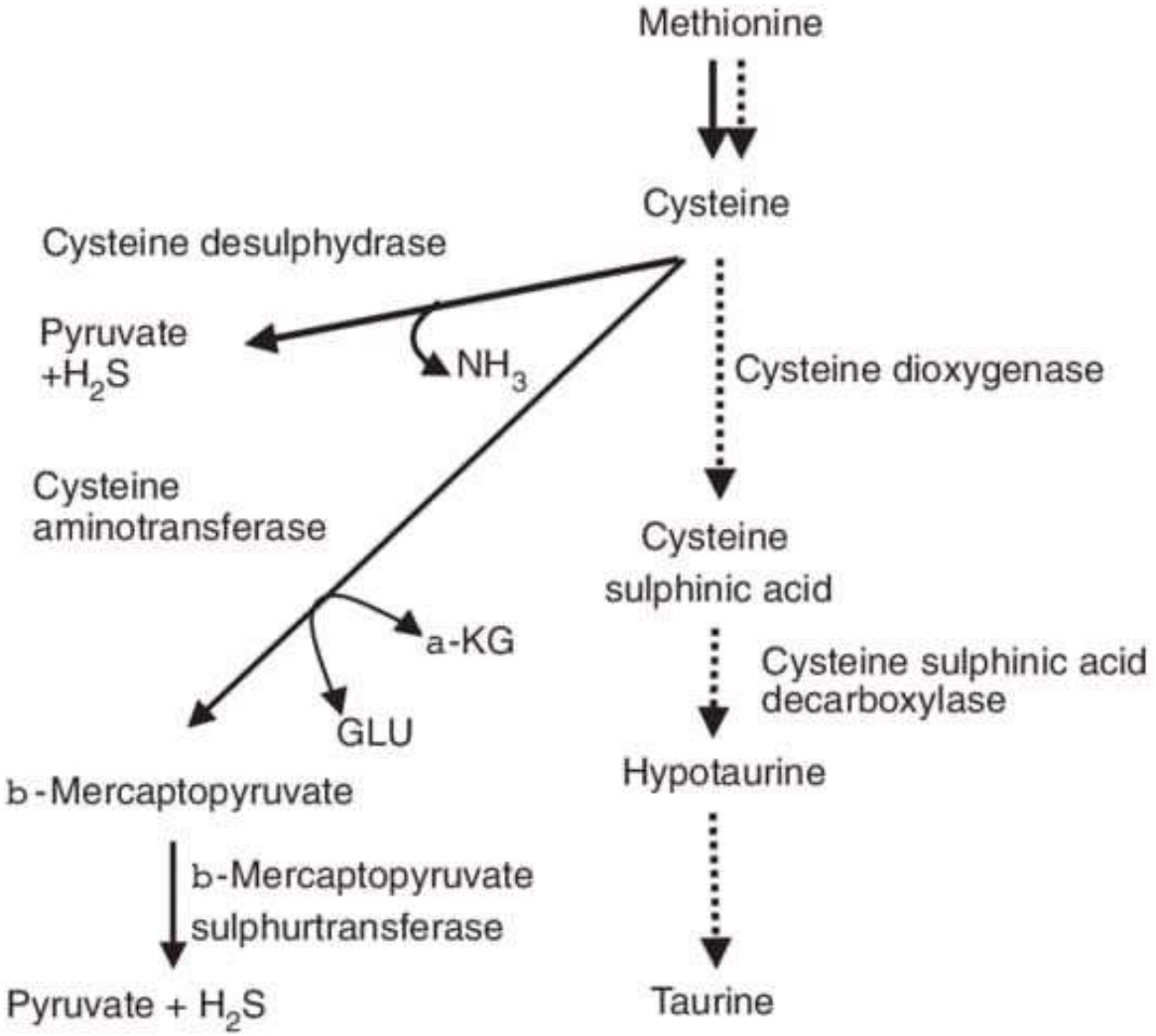
Degradation:



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Regulation:

- Cysteine is a highly reactive amino acid that is regulated in a number of ways, including:

In the liver

- The liver is the primary organ responsible for regulating cysteine homeostasis. It does this by:

  Maintaining cysteine levels within a narrow range

  Regulating the synthesis of glutathione (GSH)

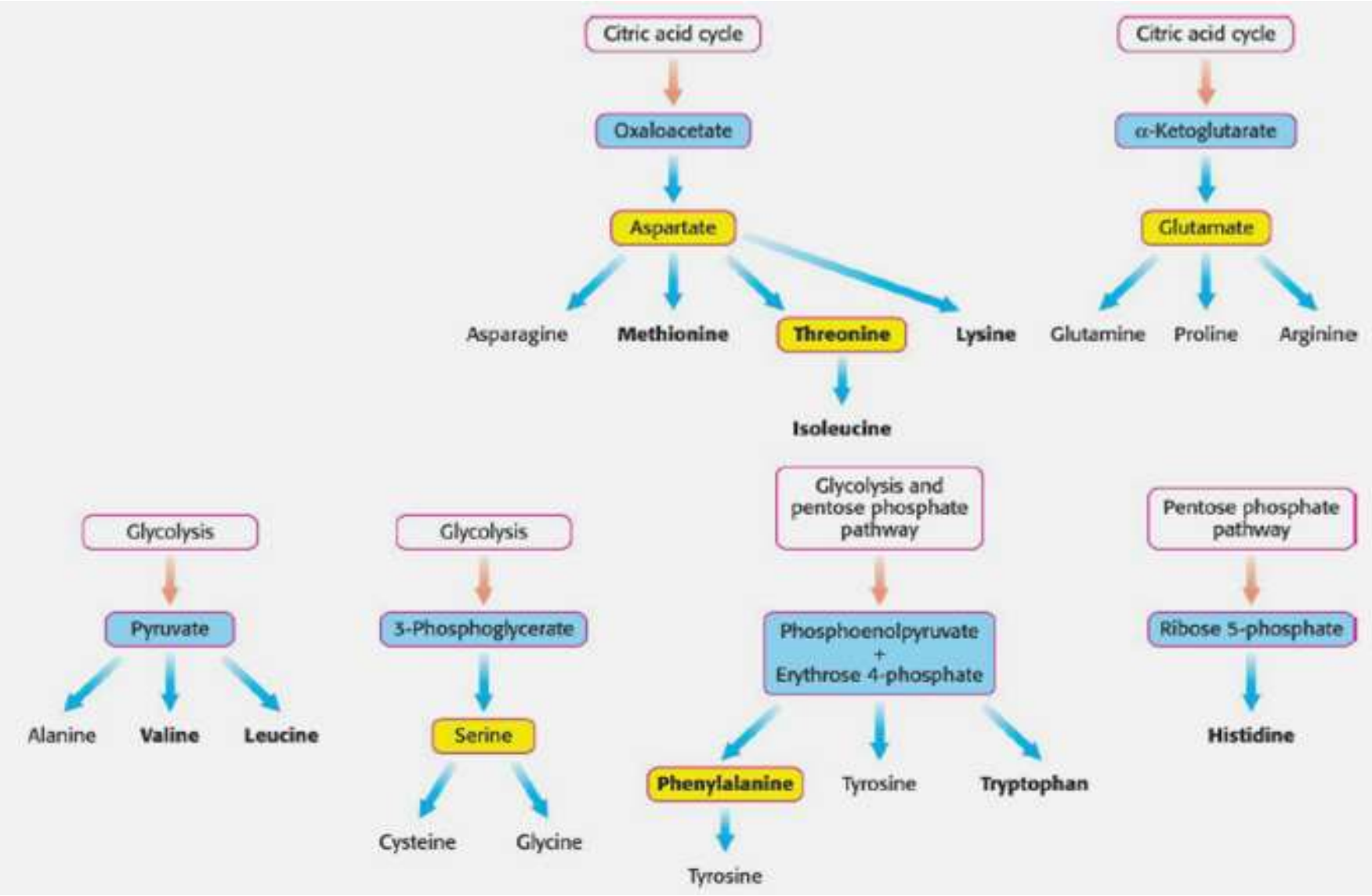
  Regulating the levels of cysteine dioxygenase (CDO)

  Increasing GCL activity when cysteine levels drop.

In mammals

- Cysteine catabolism is dependent on CDO, an enzyme that converts cysteine to cysteinesulfinic acid. CDO is highly responsive to changes in dietary protein and sulfur amino acids.

Biosynthetic families of amino acids in bacteria and plants.



Source;Biochemistry, 4 th edition ,by sathyanarayana and Chakrapani

- The amino acids that must be supplied in the diet are called essential amino acids, whereas the others, which can be synthesized if dietary content is insufficient, are termed nonessential amino acids.

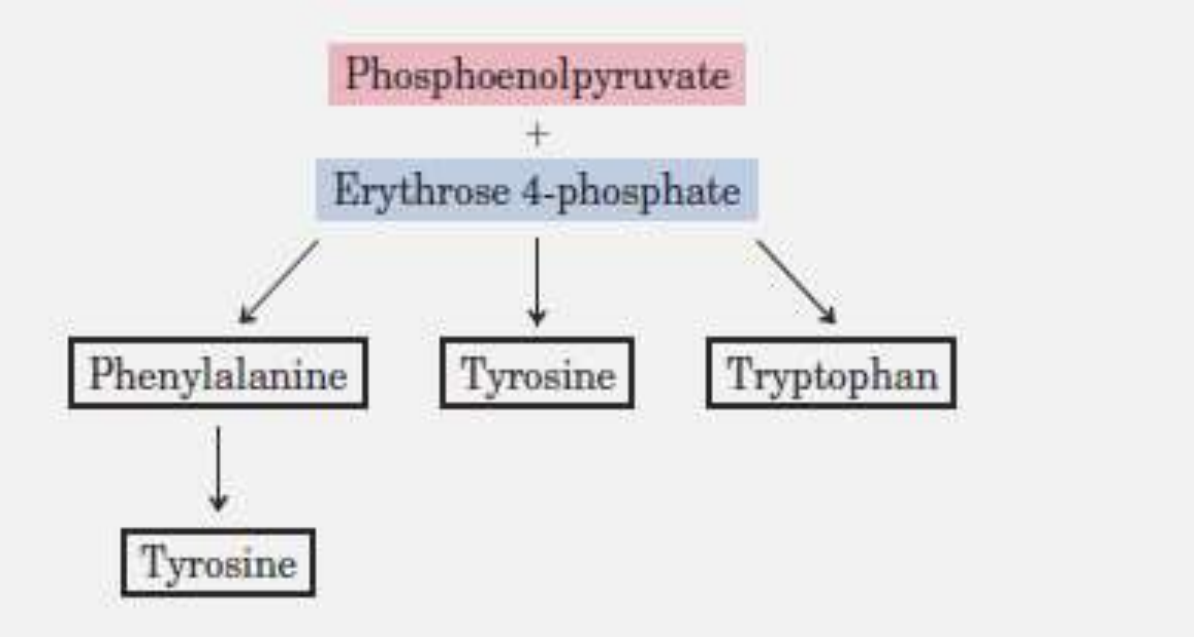
Metabolic classification of amino acids		
Glucogenic	*Ketogenic*	*Both ketogenic and glucogenic*
Glycine, alanine, serine, cysteine, aspartic acid, aspargine, glutamic acid, glutamine, proline, histidine, arginine, methionine, threonine, valine	Leucine Lysine	Isoleucine Phenylalanine Tyrosine Tryptophan

Source:Biochemistry, 4 th edition ,by sathyanarayana and Chakrapani

Biosynthesis of Aromatic Amino Acid

•Synthesis of the aromatic amino acids begins with the synthesis of chorismate – an important intermediate for many biosynthetic pathways.

•Phosphoenol pyruvate and erythrose 4-phosphate serve as beginning substrates for the pathway .



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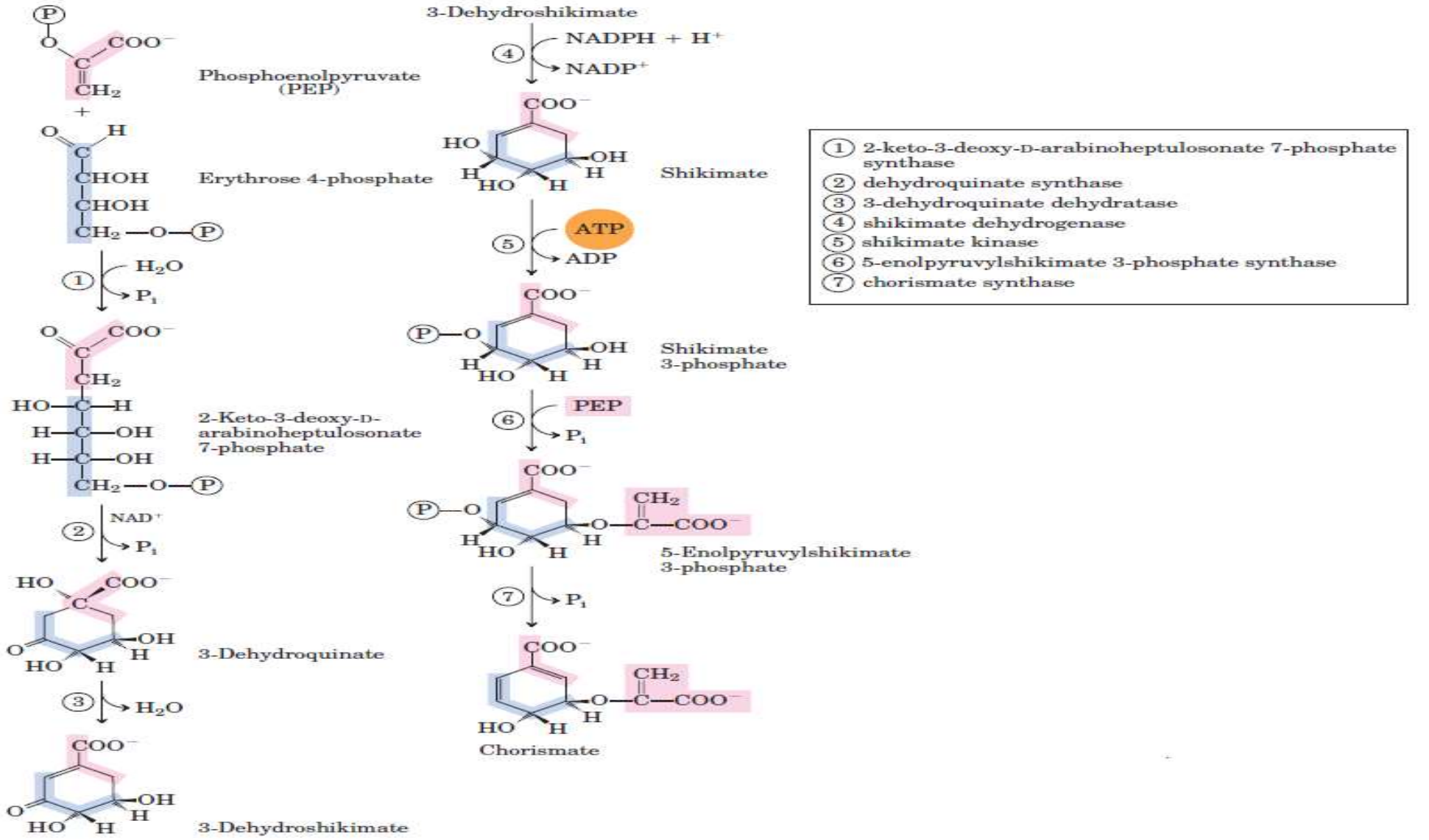

Synthesis of chorismate

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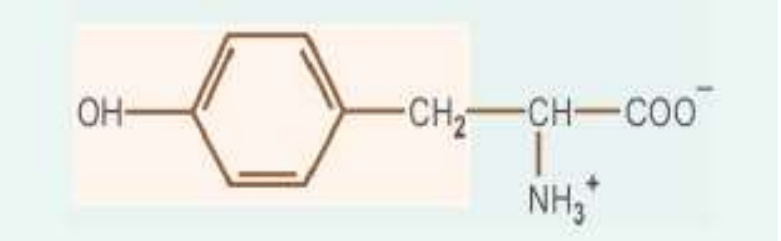
Tyrosine



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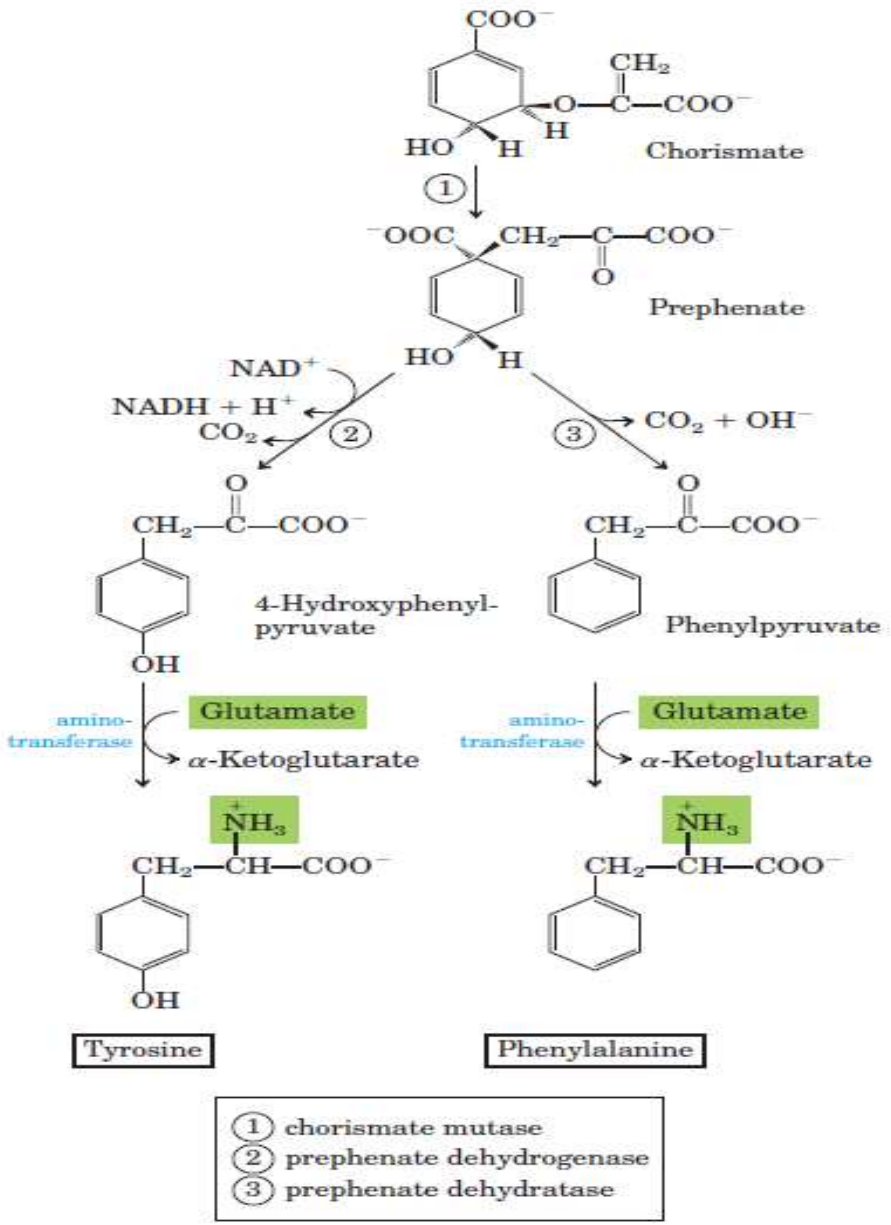
- Tyrosine is structurally aromatic amino acid.
- It is a non essential amino acid .

- Tyrosine is incorporated into proteins and is involved in the synthesis of a variety of biologically important compounds—**epinephrine, norepinephrine, dopamine (catecholamines), thyroid hormones—** and the pigment **melanin.**
- During the course of degradation, phenylalanine and tyrosine are converted to metabolites which can serve as precursors for the synthesis of glucose and fat. Hence, these amino acids are both **glucogenic and ketogenic.**

Biosynthesis of Tyrosine



- In plants and bacteria, **phenylalanine and tyrosine** are synthesized from chorismate in pathways much less complex than the tryptophan pathway.
- The common intermediate is prephenate .The final step in both cases is transamination with glutamate.
- Animals can produce tyrosine directly from phenylalanine through hydroxylation at C-4 of the phenyl group by **phenylalanine hydroxylase;** this enzyme also participates in the degradation of phenylalanine.

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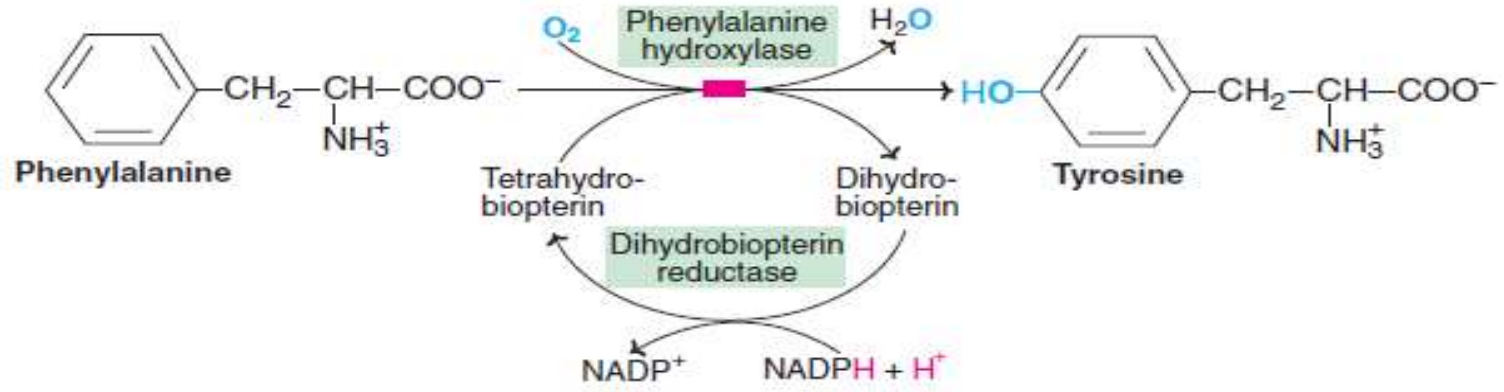

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Synthesis of tyrosine from phenylalanine

•This is an irreversible reaction and requires the participation of a specific coenzyme **biopterin** (containing pteridine ring).

•The active form of biopterin is tetrahydrobiopterin (H4-biopterin).

•In the phenylalanine hydroxylase reaction, tetrahydrobiopterin is oxidized to dihydrobiopterin (H2-biopterin).

•Tetrahydrobiopterin is then regenerated by an NADPH-dependent dihydrobiopterin reductase

Biosynthesis of Tyrosine

•In the conversion of phenylalanine to tyrosine, the reaction involves the incorporation of one atom of molecular oxygen (O2) into the para position of phenylalanine while the other atom of O2 is reduced to form water.

•It is the **tetrahydrobiopterin** that supplies the reducing equivalents which, in turn, are provided by NADPH.

•Tyrosine is considered a conditionally essential amino acid, or as nonessential insofar as it can be synthesized from the essential amino acid phenylalanine.

Degradation of tyrosine:

1. Conversion of Phenylalanine to Tyrosine

- ***Phenylalanine hydroxylase (PAH)*** converts phenylalanine to tyrosine .
- Phenylalanine hydroxylase is tetrahydrobiopterin (BH4) requiring enzyme.
- Dihydrobioteridine reductase catalyzes the conversion of dihydrobiopteridine to tetrahydrobiopterin.
- Deficiency of enzyme caused phenylketonuria .

2. Transamination of Tyrosine

- ***Tyrosine aminotransferase*** catalyzes the conversion to tyrosine to p-hydroxyphenylpyruvate.
- Tyrosine aminotransferase is a Pyridoxal-5-phosphate requiring enzyme .
- In the process, alpha-ketoglutarate is converted into glutamate .
- Deficiency of the enzyme causes neonatal tyrosinemia (Type III) .

Degradation of tyrosine

3. Hydroxylation of p-hydroxyphenylpyruvate to homogentisate

- The reaction is catalyzed by an enzyme ***p-hydroxyphenylpyruvate hydroxylase (dioxygenase)***

- Requires Vit C (ascorbate) for its activity

- Deficiency of the enzyme causes Tyrosinemia Type II

4. Oxidation of Homogentisate to 4-maleylacetoacetate

- Catalyzed by an enzyme ***homogentisate oxidase***

Deficiency of the enzyme causes Alkaptonuria

5. Conversion of Maleylacetoacetase to 4-fumarylacetoacetate

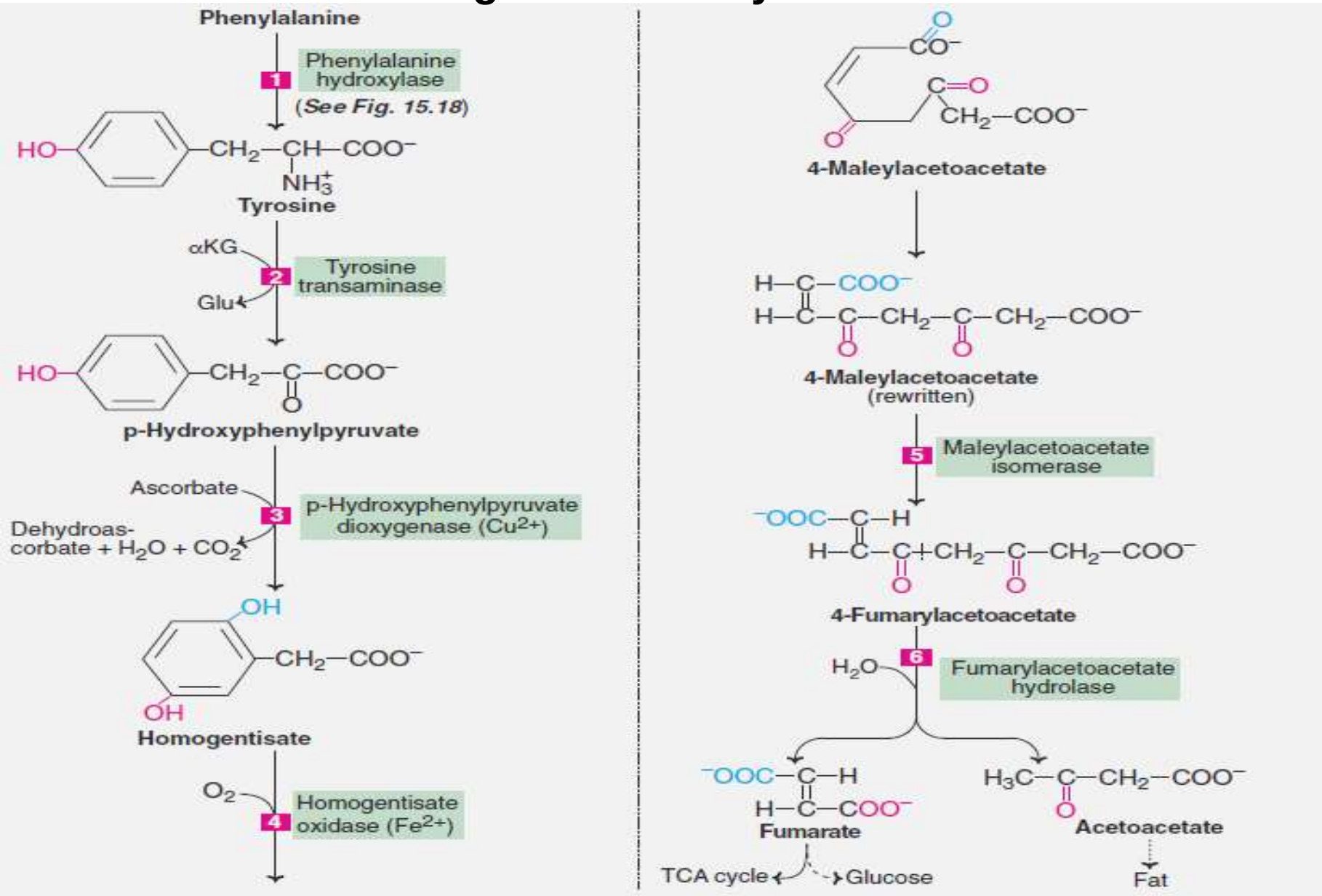
- Catalyzed of by an enzyme isomerase

- Conversion of 4-fumarlyacetoacetate to acetoacetate and fumarate

- Catalyzed of by an enzyme ***4-fumarlyacetoacetate hydrolase***

- Deficiency of the enzyme causes Tyrosinemia Type-I

Degradation of tyrosine



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Regulation of Tyrosine Metabolism

•The regulation of tyrosine metabolism is essential for maintaining cellular homeostasis and ensuring proper functioning of the body.

1. Regulation of Tyrosine Biosynthesis:

•Tyrosine biosynthesis is regulated by feedback inhibition. The enzyme that catalyzes the final step in tyrosine biosynthesis, tyrosine hydroxylase, is inhibited by high levels of tyrosine. This negative feedback mechanism helps to prevent the overproduction of tyrosine when it is not needed.

2. Regulation of Tyrosine Catabolism:

•Tyrosine catabolism involves multiple enzymes and pathways, including the tyrosine aminotransferase pathway and the homogentisate pathway. The rate-limiting step in tyrosine catabolism is the conversion of tyrosine to 4-hydroxyphenylpyruvate by the enzyme tyrosine aminotransferase. This enzyme is regulated by factors such as substrate availability, co-factor availability, and allosteric regulation.

Regulation of Tyrosine Metabolism

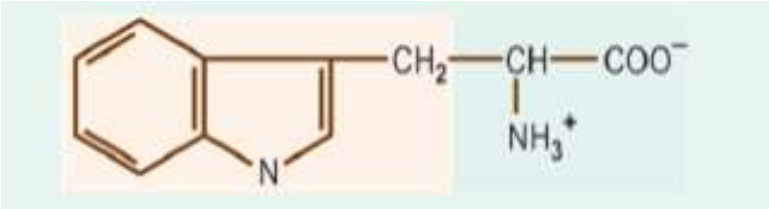
3. Regulation of Tyrosine-Derived Metabolites:

•Tyrosine-derived metabolites, such as dopamine, adrenaline, and melanin, are regulated by enzymes involved in their synthesis and degradation pathways. For example, the synthesis of dopamine from tyrosine is regulated by the enzyme tyrosine hydroxylase, while the degradation of dopamine is regulated by enzymes such as monoamine oxidase.

4. Hormonal Regulation:

•Hormones such as insulin, glucagon, and cortisol can also regulate tyrosine metabolism. Insulin promotes the uptake of tyrosine into cells, while glucagon stimulates the release of stored tyrosine from tissues. Cortisol can modulate the activity of enzymes involved in tyrosine metabolism, depending on the physiological state of the body.

Tryptophan



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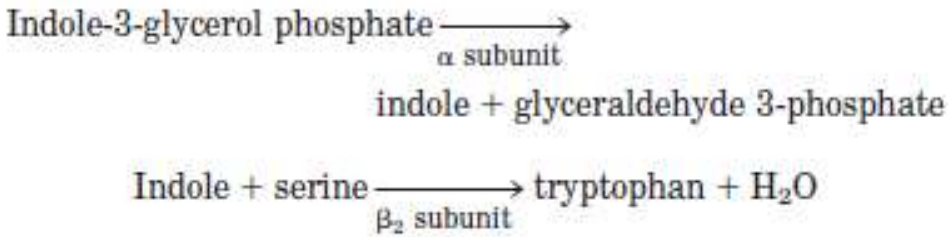
- Tryptophan is an aromatic amino acid.
- It is identified as an **essential amino acid.**
- It contains an indole ring and chemically it is alpha –amino beta -indole propionic acid.
- Tryptophan is both **glucogenic and ketogenic in nature.**
- It is a precursor for the synthesis of important compounds, namely **NAD+ and NADP+** (coenzymes of niacin), **serotonin and melatonin.**

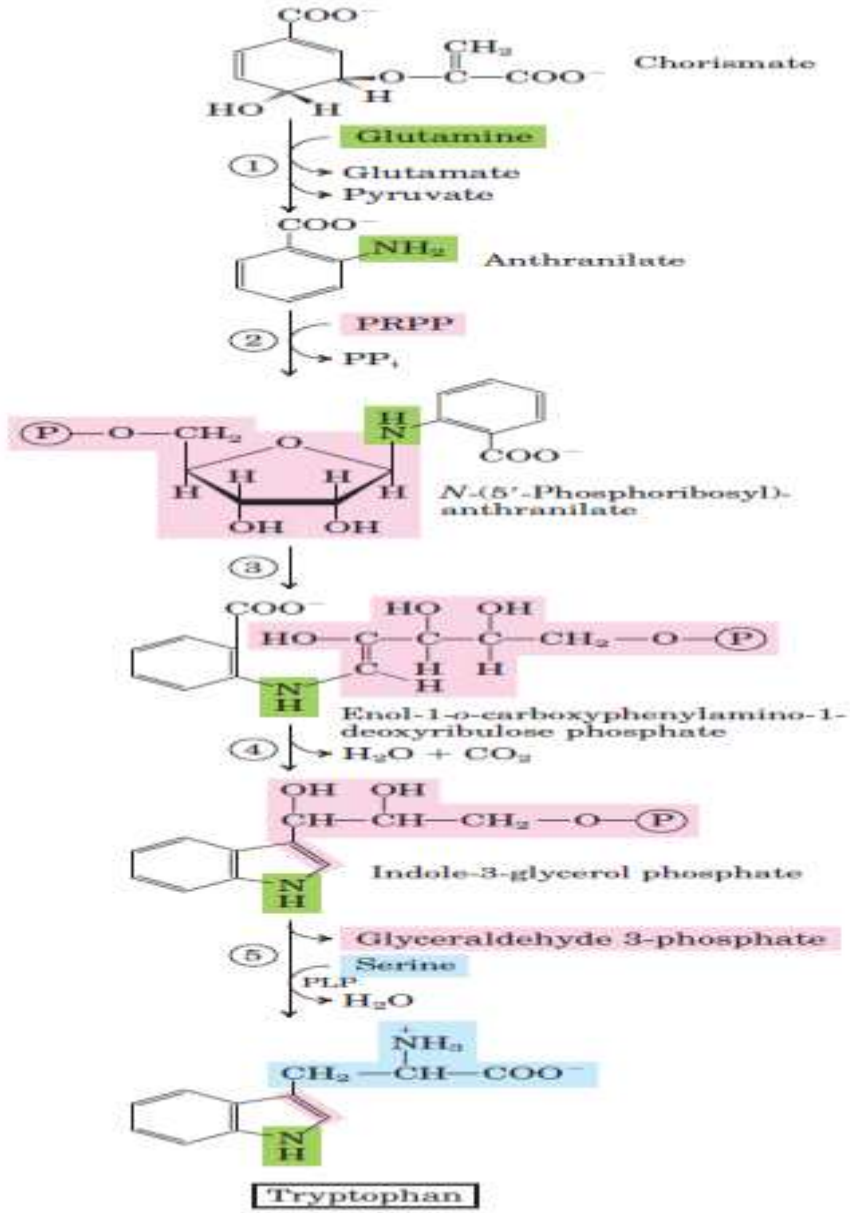
Biosynthesis of Tryptophan

- In the **tryptophan branch, chorismate** is converted to anthranilate in a reaction in which glutamine donates the nitrogen that will become part of the indole ring.
- Anthranilate then condenses with PRPP.
- The indole ring of tryptophan is derived from the ring carbons and amino group of anthranilate plus two carbons derived from PRPP.
- The final reaction in the sequence is catalyzed by **tryptophan synthase.**
- This enzyme has an 22 subunit structure and can be dissociated into two *subunits and a 2 subunit that* catalyze different parts of the overall reaction:



Biosynthesis of Tryptophan

1. anthranilate synthase
2. anthranilate phosphoribosyltransferase
3. *N*-(5'-phosphoribosyl)-anthranilate isomerase
4. indole-3-glycerol phosphate synthase
5. tryptophan synthase



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Degradation of Tryptophan

• Tryptophan is metabolized by two pathways:

1. Kynurenine pathway

2. Serotonin pathway.

Kynurenine Pathway:

•In this pathway tryptophan is oxidized to kynurenine and alanine. Kynurenine is then converted to either vitamin niacin or acetyl-CoA.

•The initial reaction is an oxidation of tryptophan to formylkynurenine, catalyzed by the enzyme ***tryptophan oxygenase*** *also called* ***tryptophan pyrrolase,*** *which is feedback inhibited by nicotinic* acid derivatives, e.g. NADH or NADPH.

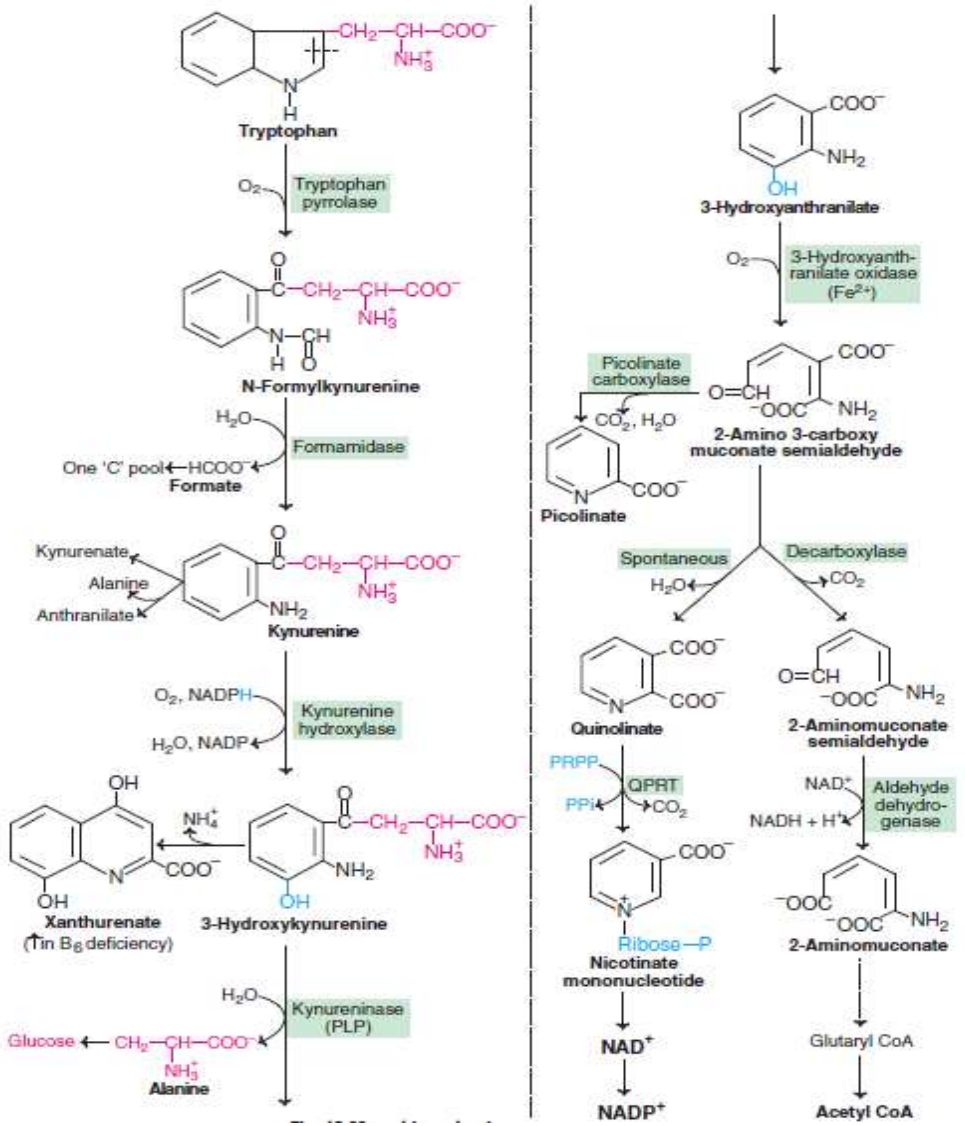
• Formylkynurenine is converted to kynurenine by removal of formyl group with the enzyme ***kynurenine formylase***.

Degradation of Tryptophan

•Kynurenine is then metabolized to 3-hydroxy kynurenine by ***kynurenine hydroxylase.***

•Next 3-hydroxykynurenine is converted to 3-hydroxyanthranilate and alanine by ***kynureninase,*** *a* PLP-dependent enzyme. A deficiency of vitamin B6 (pyridoxin) results in failure to catabolize the hydroxykynurenine, forming xanthurenate and excreted in urine in vitamin B6 deficiency.

• Next 3-hydroxyanthranilate undergoes decarboxylation forming vitamin *niacin which can be* converted to *NAD+ and NADP+ or 3-hydroxyanthranilate* can also be converted through a number of steps to acetyl-CoA.



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- The intermediate undergoes decarboxylation, catalysed by ***amino carboxysemialdehyde decarboxylase*** to produce 2-aminomuconate semialdehyde that enters glutarate pathway.
- The semialdehyde is converted to 2-aminomuconate by a dehydrogenase. The aminomuconate, in a series of reactions involving reduction, deamination, decarboxylation etc., is converted to glutaryl CoA and finally to acety CoA.
- The latter is either completely oxidized via TCA cycle or converted to fat (hence tryptophan is ketogenic).

Degradation of Tryptophan

Serotonin

• Serotonin is synthesized from tryptophan by neurons, pineal glands and intestinal argentaffin cells. In normal adult, about 1% of tryptophan is converted to serotonin.

Serotonin Pathway:

• Tryptophan is first oxidized to 5-hydroxytryptophan by ***tryptophan hydroxylase,*** *which* requires, tetrahydrobiopterin as a cofactor.

• 5-hydroxytryptophan undergoes decarboxylation to yield ***serotonin (5-hydroxytryptamine).***

• Acetylation of serotonin followed by methylation in the pineal gland forms a hormone ***melatonin.***

Functions of serotonin

• Serotonin is a **neurotransmitter and stimulates** cerebral activity. Therefore, serotonin deficiency causes a decrease in cerebral (brain) activity, which leads to depression.

• In humans, serotonin is involved in a variety of behavioral patterns, including sleep, body temperature and blood pressure.

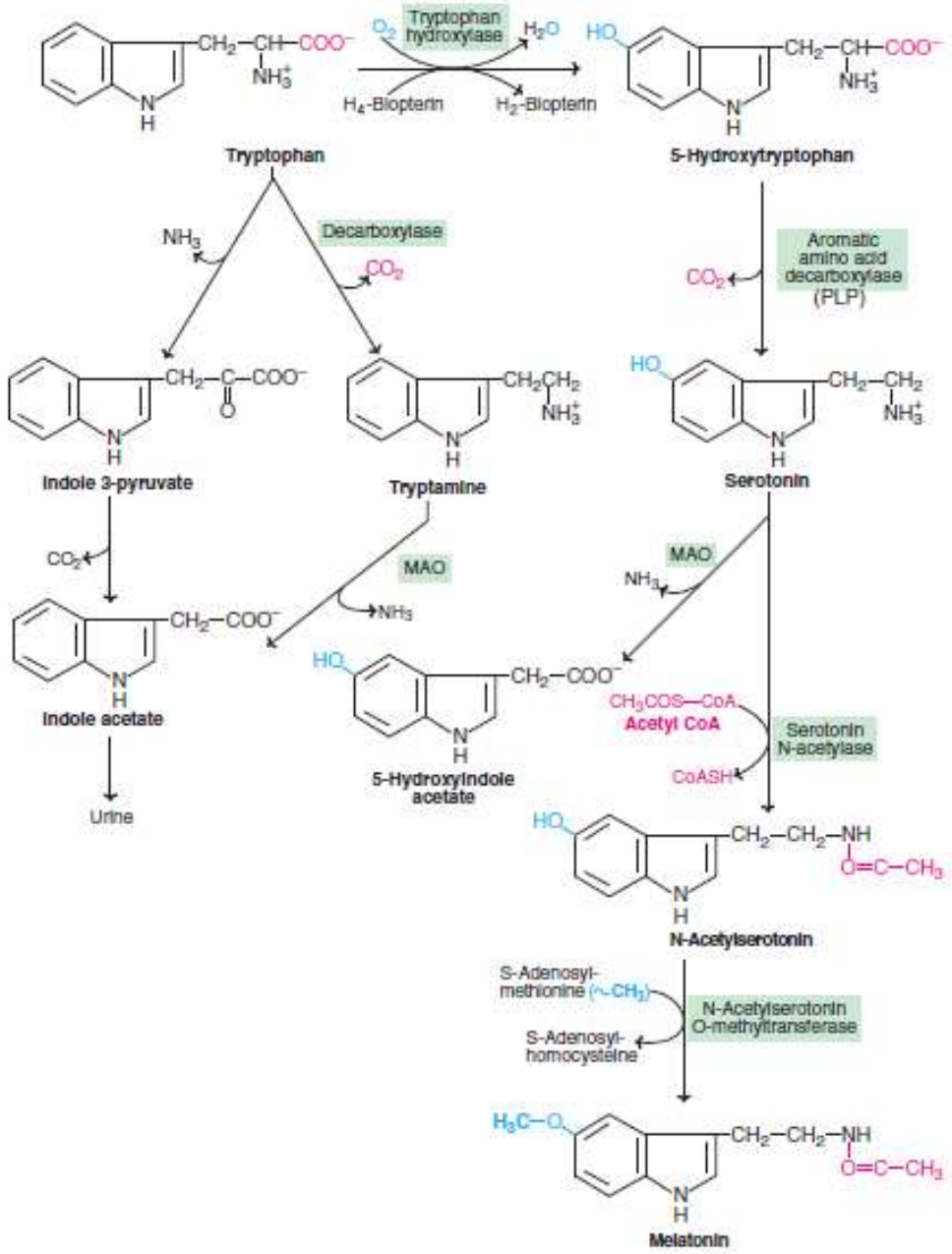
• Serotonin produced in intestinal cells stimulates the release of gastrointestinal peptide hormones.

• Serotonin serves as precursor of **melatonin in the** pineal gland.

• Serotonin is also a powerful **vasoconstrictor and** stimulator of smooth muscle contraction.

Conversion of tryptophan to indole acetate :

- Tryptophan undergoes deamination and decarboxylation to produce indolepyruvate and tryptamine, respectively.
- Both these compounds are converted to indoleacetate and excreted in urine.



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Regulation of Tryptophan

Tryptophan metabolism is tightly regulated in the body to maintain a balance between its role as a precursor for important molecules like serotonin and its catabolism into other metabolites. The regulation of tryptophan metabolism occurs at multiple levels and involves several enzymes and pathways.

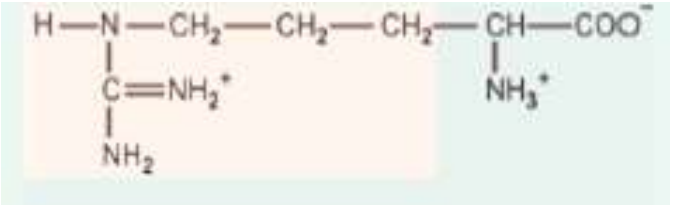
1. **Tryptophan uptake**: Tryptophan is an essential amino acid that cannot be synthesized by the body and must be obtained from the diet. The uptake of tryptophan into cells is regulated by specific transporters on the cell membrane.
2. **Tryptophan catabolism:** Tryptophan can be metabolized through two main pathways: the kynurenine pathway and the serotonin pathway. The kynurenine pathway is the major route for tryptophan catabolism and is regulated by the enzyme indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). These enzymes are induced by inflammatory signals, such as interferon-gamma, and regulate the rate of tryptophan degradation.

3. **Serotonin synthesis:** Tryptophan is also a precursor for serotonin, a neurotransmitter that plays a key role in mood regulation and other physiological functions. The enzyme tryptophan hydroxylase (TPH) catalyzes the rate-limiting step in serotonin synthesis and is regulated by various factors, including dietary intake of tryptophan, hormonal signals, and neurotransmitters.

4. **Feedback inhibition**: The enzymes involved in tryptophan metabolism are subject to feedback inhibition by their end products. For example, **serotonin can inhibit the activity of TPH**, leading to a decrease in serotonin synthesis when levels are high. Similarly, some metabolites of the kynurenine pathway can inhibit IDO and TDO, regulating the rate of tryptophan degradation.

5. **Regulation by hormones and signaling pathways:** Tryptophan metabolism is also regulated by various hormones and signaling pathways. For example, cortisol and glucocorticoids can induce the expression of IDO and TDO, promoting tryptophan degradation. Inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha, can also stimulate tryptophan catabolism through the kynurenine pathway.

Arginine



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- Arginine is an basic amino acid.
- It is a essential amino acid, but non-essential in others. Hence they are semi-essential amino acid.
- Premature infants cannot synthesize Arginine.
- Arginine is **glucogenic in nature.**
- Arginine is the substrate for the production of nitric oxide (NO).

Biosynthesis of Arginine

•**Arginine is synthesized from glutamate via ornithine** and the urea cycle in animals.

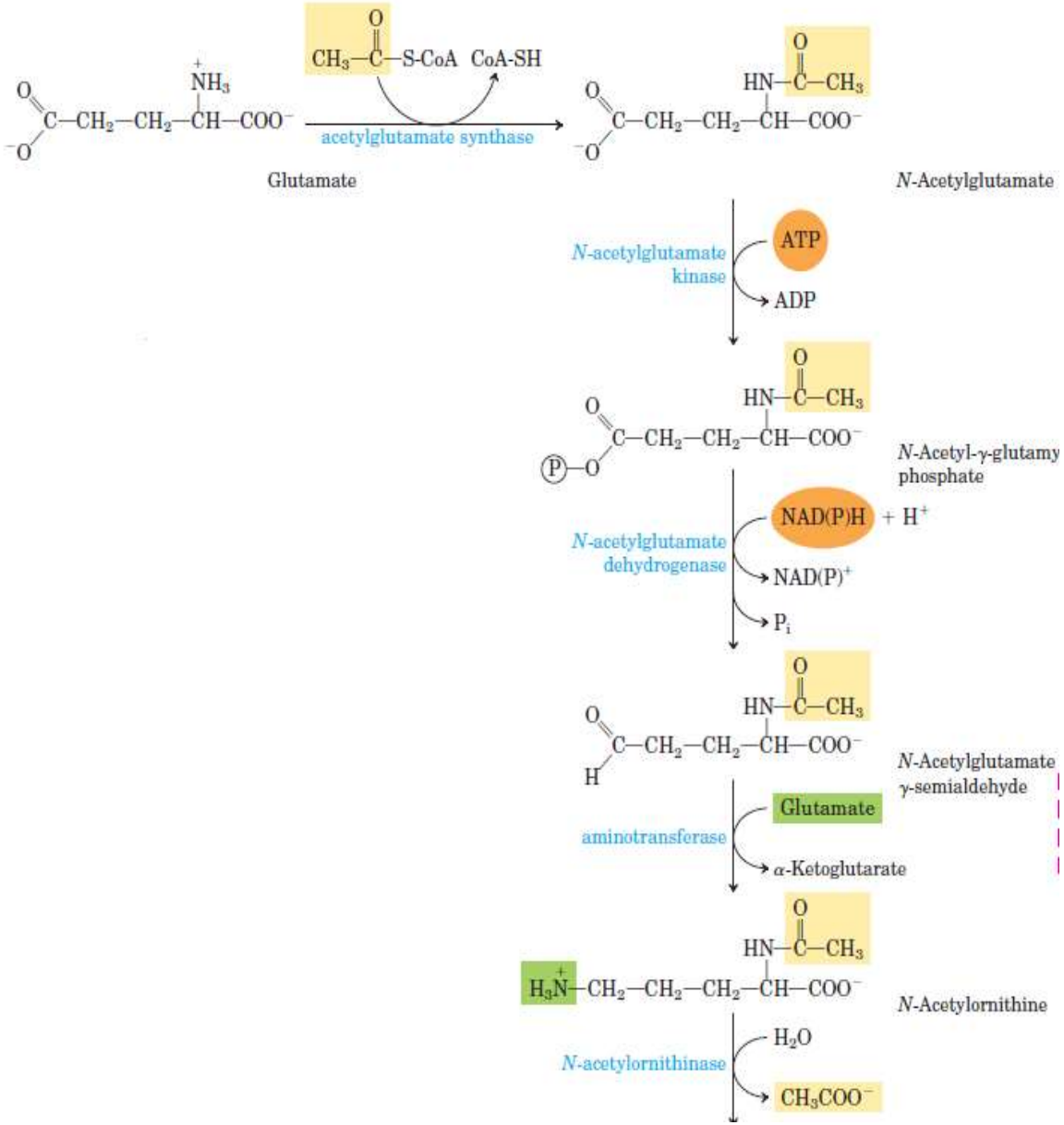
•In principle, ornithine could also be synthesized from glutamate gamma-semialdehyde by transamination, but the spontaneous cyclization of the semialdehyde in the proline pathway precludes a sufficient supply of this intermediate for ornithine synthesis.

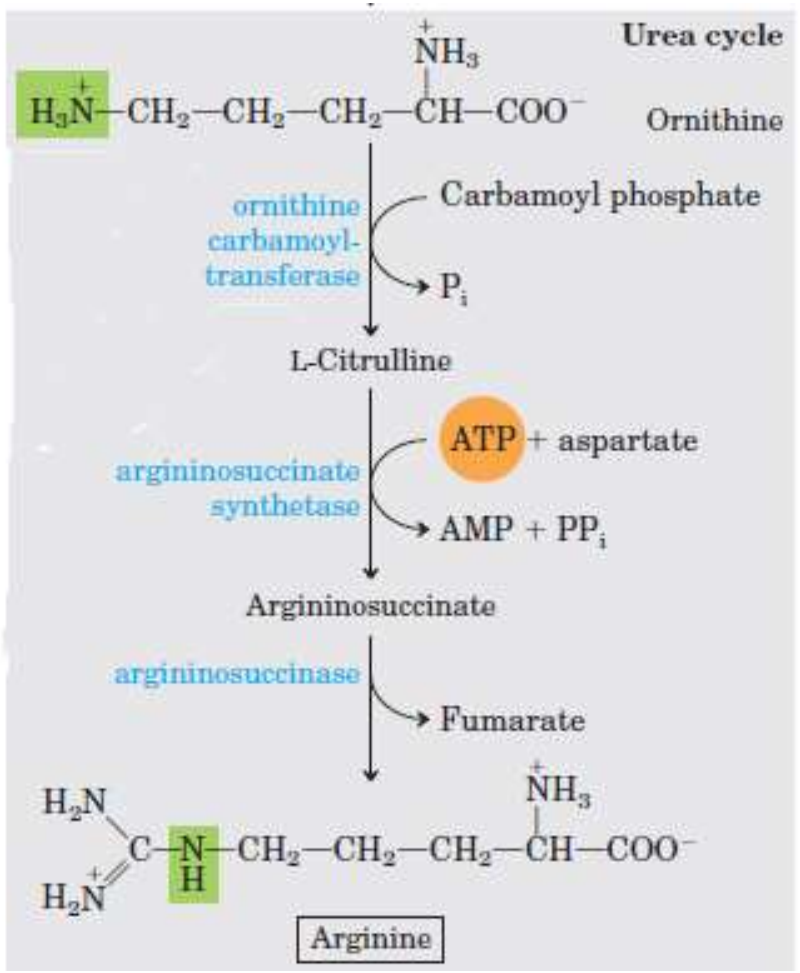
•It is also obtained from dietary or tissue protein.

•Arginase, a urea cycle enzyme, converts arginine to ornithine and urea.

• When arginine from dietary intake or protein turnover is insufficient for protein synthesis, the ornithine -aminotransferase reaction operates in the direction of ornithine formation. Ornithine is then converted to citrulline and arginine in the urea cycle.

Biosynthesis of Arginine





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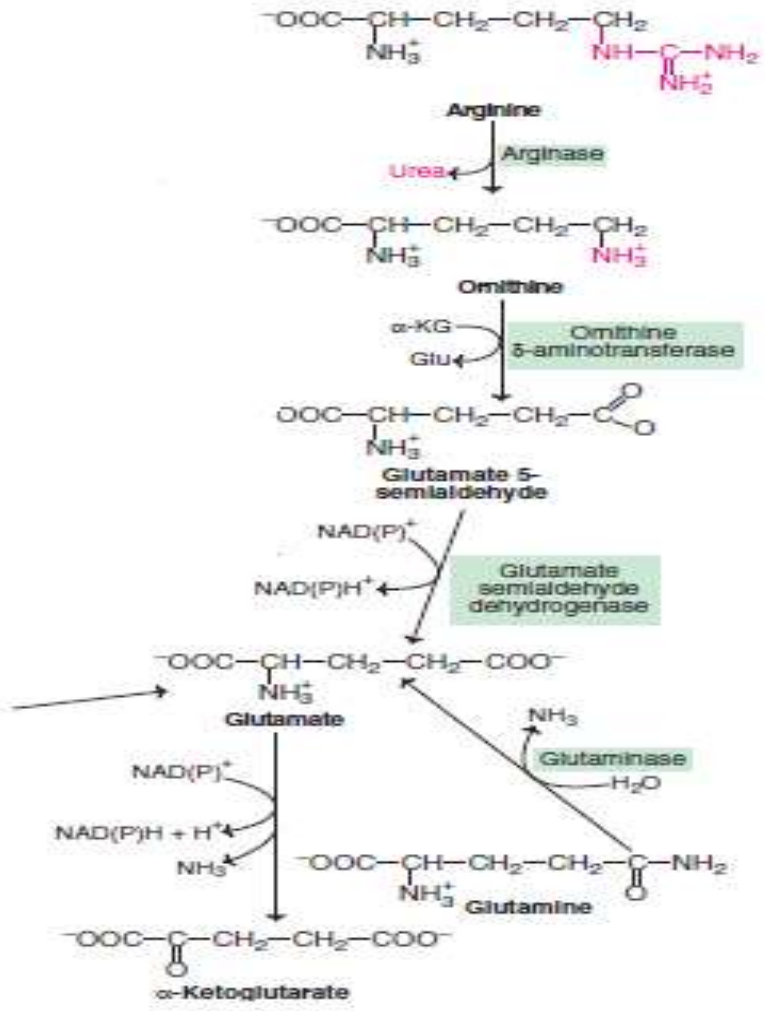
Degradation of Arginine

•Arginine is cleaved by arginase to liberate urea and produce ornithine. Ornithine undergoes transamination of delta -amino group to form glutamate gamma -semialdehyde which is converted to glutamate.

• **Hyperargininemia** is an inborn error in arginine metabolism due to a defect in the enzyme ***arginase.***



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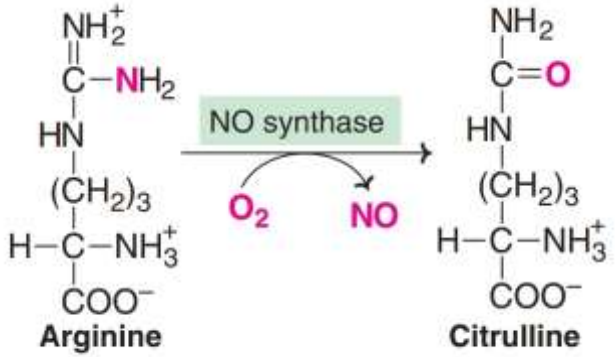
Formation of Nitric oxide

•Arginine is acted upon by an enzyme called nitrogen oxide synthase, a cytosolic enzyme and converts arginine to citrulline and nitric oxide.

•This reaction requires NADPH, FMN, FAD, heme and tetrahydrobiopterin.

•NO has a very short half-life (about 5 seconds).



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Regulation of Arginine

- The regulation of arginine metabolism is tightly controlled to maintain cellular homeostasis and meet the metabolic demands of the body.
- 1. **Arginine biosynthesis:** - Arginine can be synthesized from citrulline in the urea cycle, primarily in the liver. The enzyme argininosuccinate synthase (ASS) catalyzes the conversion of citrulline and aspartate into argininosuccinate. - The expression and activity of ASS are regulated by various factors, including dietary protein intake, hormonal signals (e.g., insulin and glucagon), and metabolites (e.g., citrulline levels). Regulation of ASS ensures the efficient synthesis of arginine to meet the body's needs.

2. **Arginine catabolism:** - Arginine can be catabolized through two main pathways: the NO synthase (NOS) pathway and the arginase pathway.

- The NOS pathway converts arginine into NO and citrulline, which plays a key role in regulating vascular tone, immune function, and neurotransmission.
- The activity of NOS enzymes (endothelial NOS, inducible NOS, neuronal NOS) is tightly regulated by calcium/calmodulin, cofactors (e.g., tetrahydrobiopterin), and post-translational modifications (e.g., phosphorylation).
- The arginase pathway converts arginine into ornithine and urea, which is important for the urea cycle and polyamine synthesis. The two isoforms of arginase (arginase I and arginase II) are regulated by various factors, including substrate availability, cellular localization, and inflammatory signals.

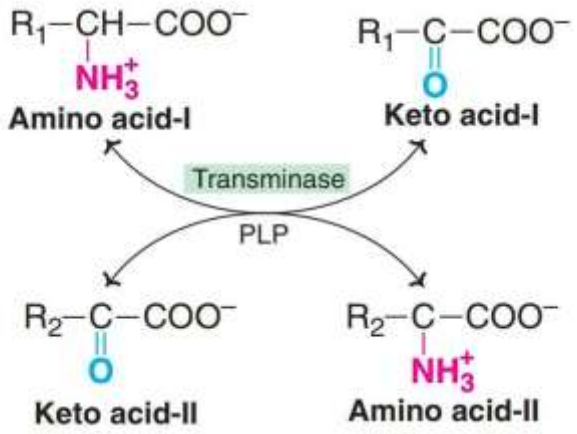
Regulation of Arginine

3. **Feedback inhibition:** Enzymes involved in arginine metabolism are subject to feedback inhibition by their end products or metabolites. For example, NO can inhibit arginase activity, leading to increased arginine availability for NO production. Conversely, high levels of ornithine can inhibit NOS activity, affecting NO synthesis.

4**. Regulation by hormones and signaling pathways:** - Hormones such as insulin, glucagon, growth factors, and cytokines can regulate arginine metabolism by modulating the expression and activity of key enzymes involved in biosynthesis and catabolism. For example, insulin can stimulate arginine uptake and utilization in muscle cells.

Transamination

- The transfer of an amino (NH2) group from an amino acid to a keto acid is known as transamination.
- This process involves the interconversion of a pair of amino acids and a pair of keto acids, catalysed by a group of enzymes called transaminases (recently, aminotransferases).



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Salient Features of Transamination

- All transaminases require pyridoxal phosphate (PLP).
- Specific transaminases exist for each pair of amino and keto acids.
- Aspartate transaminase and alanine transaminase—make a significant contribution for transamination.
- There is no free NH3 liberated, only the transfer of amino group occurs.
- Transamination is reversible .
- Transamination is very important for the redistribution of amino groups and production of non-essential amino acids, as per the requirement of the cell. It involves both catabolism (degradation) and anabolism (synthesis) of amino acids.
- Glutamate is the only amino acid that undergoes oxidative deamination to a significant extent to liberate free NH3 for urea synthesis.
- All amino acids except lysine, threonine, proline and hydroxyproline participate in transamination.

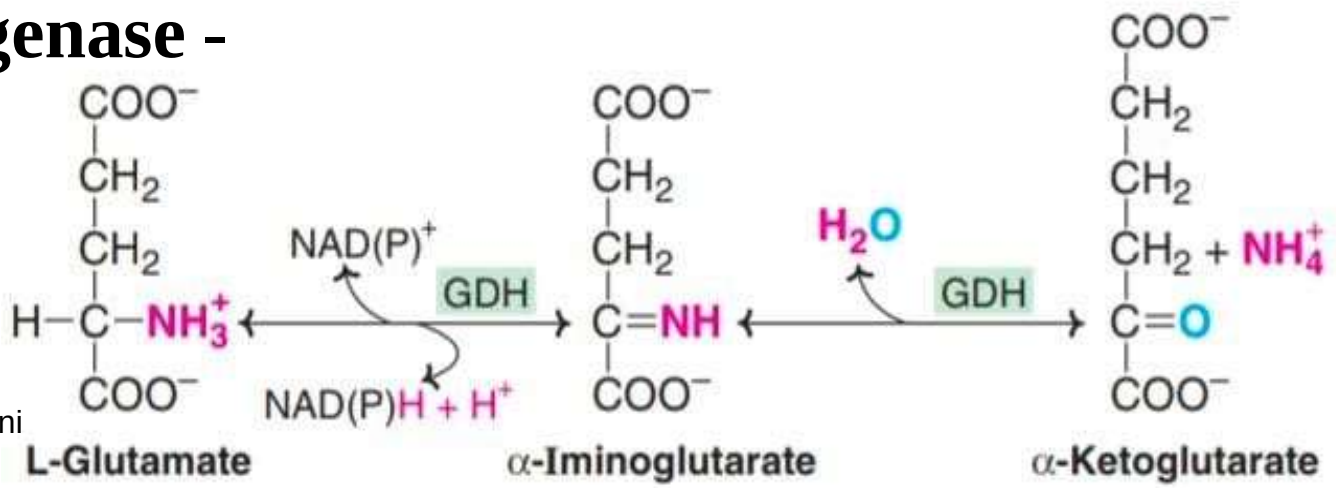
Deamination

- The removal of amino group from the amino acids as NH3 .
- Deamination results in the liberation of ammonia for urea synthesis.
- The carbon skeleton of amino acids is converted to keto acids

Oxidative Deamination

- Oxidative deamination is the liberation of free ammonia from the amino group of amino acids coupled with oxidation.
- It provide NH3 for urea synthesis and D-keto acids for a variety of reactions.

1.Role of Glutamate Dehydrogenase -



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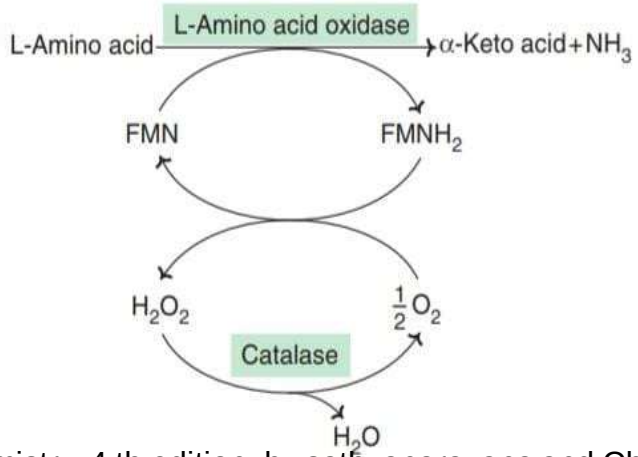
- In the process of transamination, the amino groups of most amino acids are transferred to D-ketoglutarate to produce glutamate.
- Thus, glutamate serves as a ‘collection centre’ for amino groups in the biological system.
- Glutamate rapidly undergoes oxidative deamination, catalysed by glutamate dehydrogenase (GDH) to liberate ammonia. This enzyme is unique in that it can utilize either NAD+ or NADP+ as a coenzyme
- Conversion of glutamate to D-ketoglutarate occurs through the formation of an intermediate, D-iminoglutarate .
- Glutamate dehydrogenase catalysed reaction is important as it reversibly links up glutamate metabolism with TCA cycle through D-ketoglutarate.
- GDH is involved in both catabolic and anabolic reactions.
- GDH is controlled by allosteric regulation. GTP and ATP inhibit— whereas GDP and ADP activate—glutamate dehydrogenase.

2.Oxidative deamination by amino acid oxidases :

- L-Amino acid oxidase and D-amino acid oxidase are flavoproteins, possessing FMN and FAD, respectively.
- They act on the corresponding amino acids (L or D) to produce D-keto acids and NH3.
- They act on the corresponding amino acids (L or D) to produce D-keto acids and NH3. In this reaction, oxygen is reduced to H2O2, which is later decomposed by catalase .The activity of L-amino acid oxidase is much low while that of D-amino acid oxidase is high in tissues (mostly liver and kidney).



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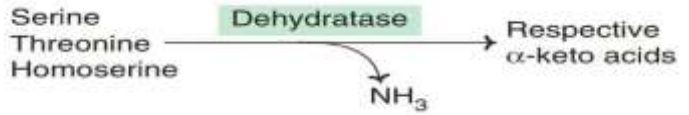
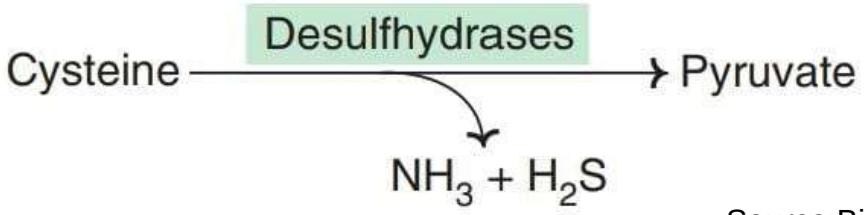
Non Oxidative Deamination:

- Some of the amino acids can be deaminated to liberate NH3 without undergoing oxidation.
- **Amino acid dehydrases-**



- Serine, threonine and homoserine are the hydroxy amino acids. They undergo non-oxidative deamination catalysed by PLP-dependent dehydrases (dehydratases).
- **Amino acid desulfhydrases –**
- The sulfur amino acids, namely cysteine and homocysteine, undergo deamination coupled with desulfhydration to give keto acids.



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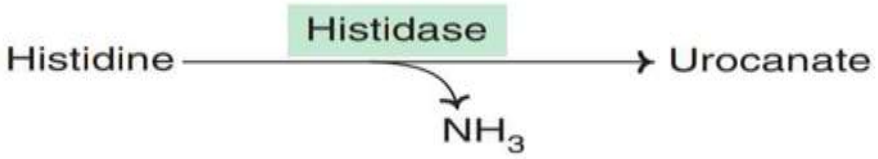
- **Deamination of histidine** : The enzyme histidase acts on histidine to liberate NH3 by a non-oxidative deamination process.



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METABOLISM OF AMMONIA

1. FORMATION OF AMMONIA:

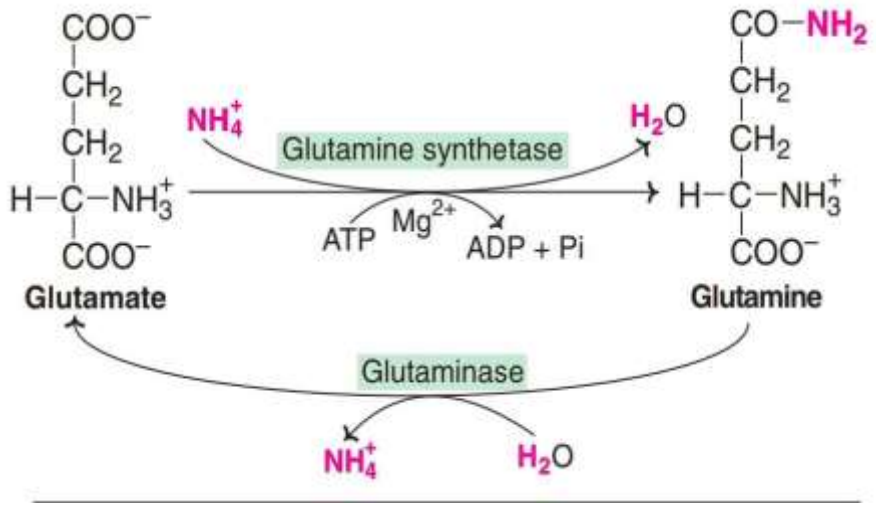
- The production of NH3 occurs from the amino acids (transamination and deamination), biogenic amines, amino group of purines and pyrimidines and by the action of intestinal bacteria (urease) on urea.

2. TRANSPORT AND STORAGE OF AMMONIA:

- The transport of ammonia between various tissues and the liver mostly occurs in the form of glutamine or alanine and not as free ammonia.

  Alanine is important for NH3 transport from muscle to liver by glucose-alanine cycle.

Role of Glutamine:

- It is a storehouse of NH3.
- It is present at the highest concentration (8 mg/dl in adults) in blood among the amino acids.
- Glutamine serves as a storage and transport form of NH3. Its synthesis mostly occurs in liver, brain and muscle.
- Glutamine synthetase (a mitoc  or the synthesis of glutamine from glutamate and a

3.FUNCTION OF AMMONIA

- It is involved (directly or via glutamine) for the synthesis of many compounds in the body.
- These include non- essential amino acids, purines, pyrimidines, amino sugars, asparagine etc.
- Ammonium ions (NH_4^+) are very important to maintain acid-base balance of the body.

4. DISPOSAL OF AMMONIA

- **Ammoniotelic**; The aquatic animals dispose off NH_3 into the surrounding water.
- **Uricotelic** : Ammonia is converted mostly to uric acid e.g. reptiles and birds.
- **Ureotelic** : The mammals including man convert NH_3 to urea. Urea is a non-toxic and soluble compound, hence easily excreted.

5.TOXICITY OF AMMONIA

- Even a marginal elevation in the blood ammonia concentration is harmful to the brain.
- Ammonia, when it accumulates in the body, results in slurring of speech and blurring of the vision and causes tremors.
- It may lead to coma and, finally, death, if not corrected.
- Hyperammonemia : Impairment in urea synthesis due to a defect in any one of the five enzymes is described in urea synthesis.
- All these disorders lead to hyperammonemia and cause hepatic coma and mental retardation.
- The acquired hyperammonemia may be due to hepatitis, alcoholism etc.
- where the urea synthesis becomes defective, hence NH3 accumulates.

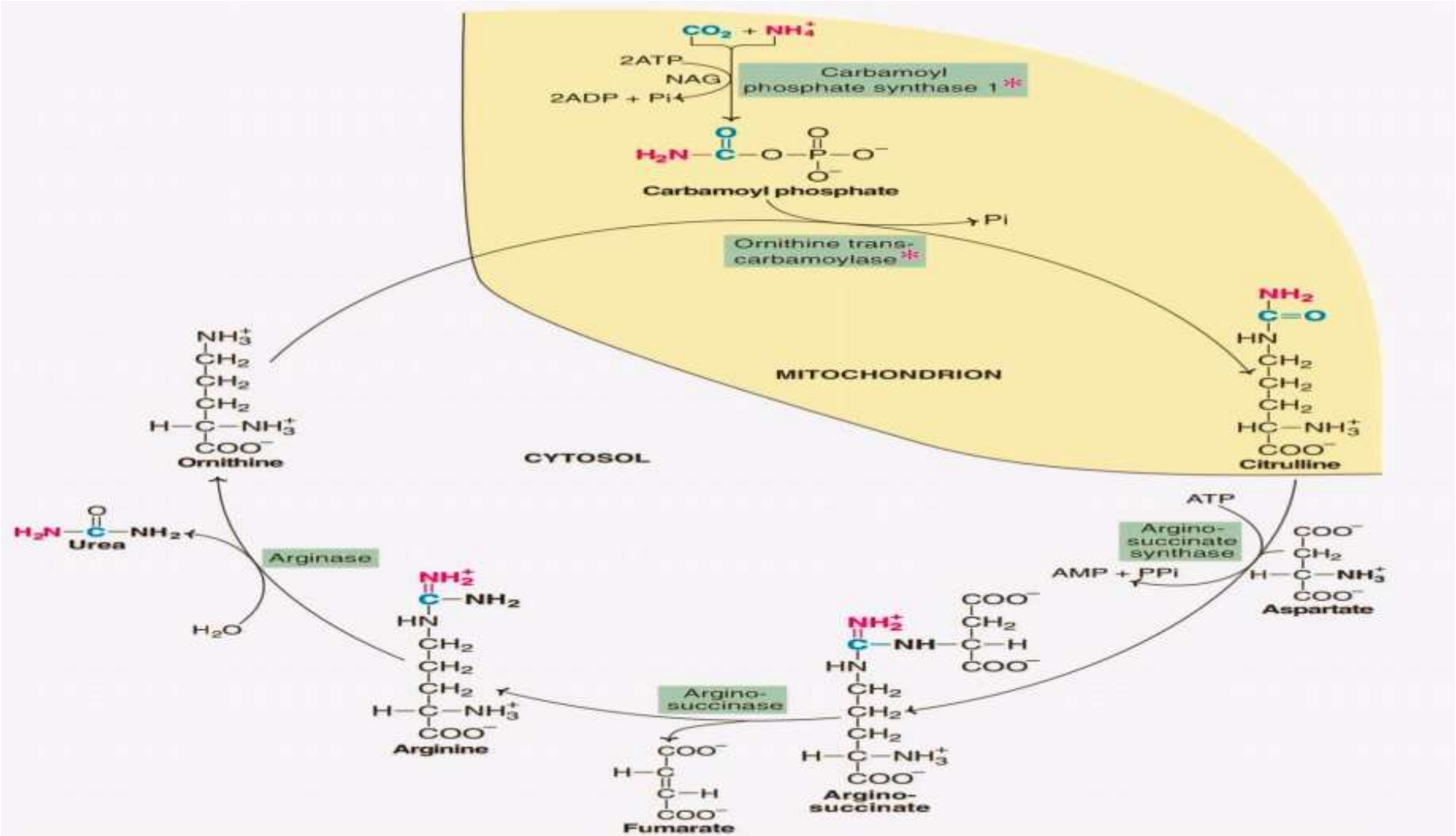
Urea Cycle

- Urea is the end product of protein metabolism .
- The nitrogen of amino acids, converted to ammonia, is toxic to the body.
- It is converted to urea and detoxified.
- Urea cycle is the first metabolic cycle that was elucidated by Hans Krebs and Kurt Henseleit (1932), hence it is known as Krebs-Henseleit cycle.
- Urea has two amino (NH_2) groups.
- The first two enzymes are present in mitochondria while the rest are localized in cytosol.

Reaction of Urea cycle

- Synthesis of Carbamoyl phosphate
- Formation of Citrulline
- Synthesis of arginosuccinate
- Cleavage of arginosuccinate
- Formation of urea

- 1.**Synthesis of carbamoyl phosphate** ; Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyses the condensation of NH ions with CO_2 to form carbamoyl phosphate. This step consumes two ATP and is irreversible, and rate- limiting. CPS I requires N-acetylglutamate for its activity.
- 2. **Formation of citrulline;** Citrulline is synthesized from carbamoyl phosphate and ornithine by ornithine transcarbamoylase. Ornithine is regenerated and used in urea cycle.
- 3. **Synthesis of arginosuccinate:** Argino- succinate synthase condenses citrulline with aspartate to produce arginosuccinate. The second amino group of urea is incorporated in this reaction.
- 4. **Cleavage of arginosuccinate**: Argino- succinase cleaves arginosuccinate to give arginine and fumarate
- 5. **Formation of urea:** Arginase is the fifth and final enzyme that cleaves arginine to yield urea and ornithine. Ornithine, so regenerated, enters mitochondria for its reuse in the urea cycle.



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Overall reaction

- The urea cycle is irreversible and consumes 3 ATP.

$$NH_4 + CO_2 + \text{Aspartate} + 3ATP \longrightarrow \text{Urea} + \text{Fumarate} + 2\,ADP + 2Pi + AMP + PPi$$

Regulation of Urea Cycle

- The first reaction catalysed by carbamoyl phosphate synthase I (CPS I) is rate-limiting reaction.
- CPS I is allosterically activated by N-acetylglutamate (NAG).
- It is synthesized from glutamate and acetyl CoA by synthase and degraded by a hydrolase.
- High concentrations of arginine increase NAG. The consumption of a protein-rich meal increases the level of NAG in liver, leading to enhanced urea synthesis
- Carbamoyl phosphate synthase I and glutamate dehydrogenase are localized in the mitochondria.
- They coordinate with each other in the formation of NH3, and its utilization for the synthesis of carbamoyl phosphate.
- The remaining four enzymes of urea cycle are mostly controlled by the concentration of their respective substrates.