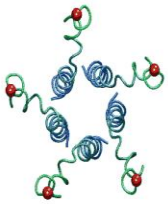
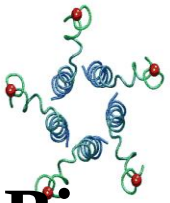


Protein metabolism

Lec 2

By

Dr.Anwar J almzaiel

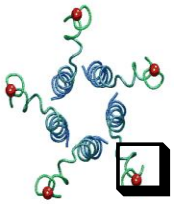


Introduction

Biosynthetic (anabolic) pathways share common intermediates with the degradative (catabolic) pathways.

The amino acids are the building blocks for proteins and other nitrogen-containing Compounds

- **Nitrogen Fixation**
- **Reducing atmospheric N2 to NH3**
- **Amino acid biosynthesis pathways**
- **Regulation of amino acid biosynthesis.**
- **Amino acids as precursors to other biological molecules.*e.g.*, Nucleotides and porphoryns**



- **The ammonium ion is assimilated into an amino acid through glutamate and glutamine**

- **Most amino acids obtain their α–amino group from glutamate by transamination.**

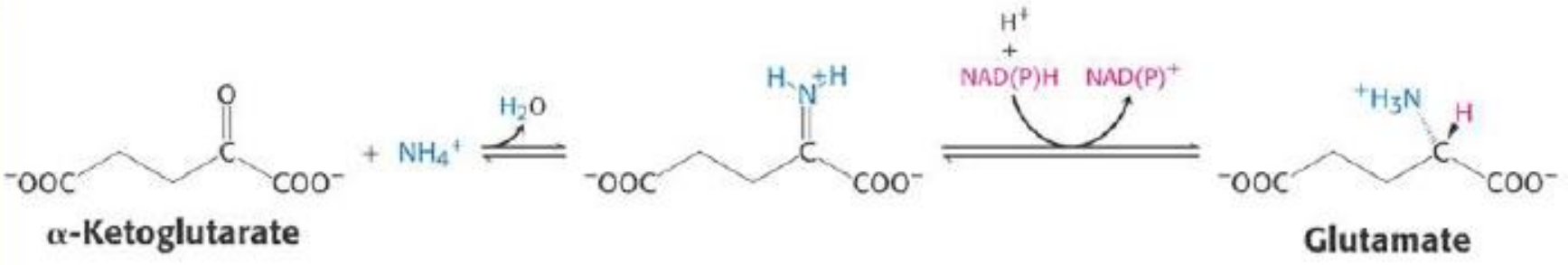
- **The side chain nitrogen of glutamine is the nitrogen source for the side chain nitrogens of tryptophan and histidine.**

Assimilation of Ammonium Ion

Glutamate dehydrogenase

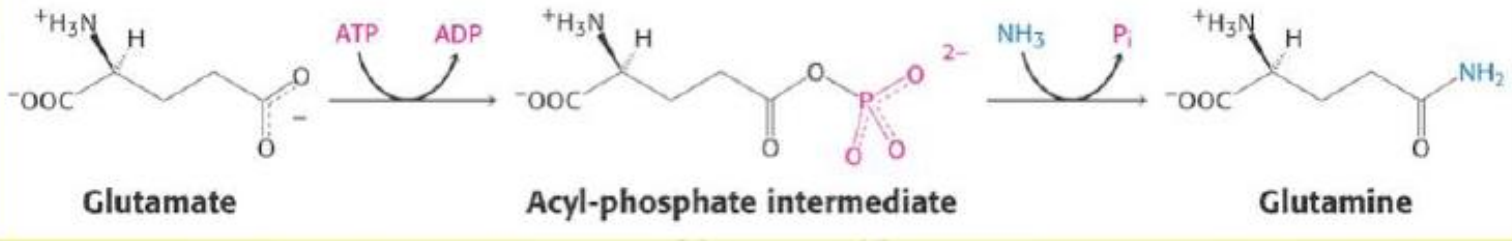
$NH_4^+ + \alpha$–ketoglutarate + NADPH + H^+ ⇌

glutamate + $NADP^+$ + H_2O



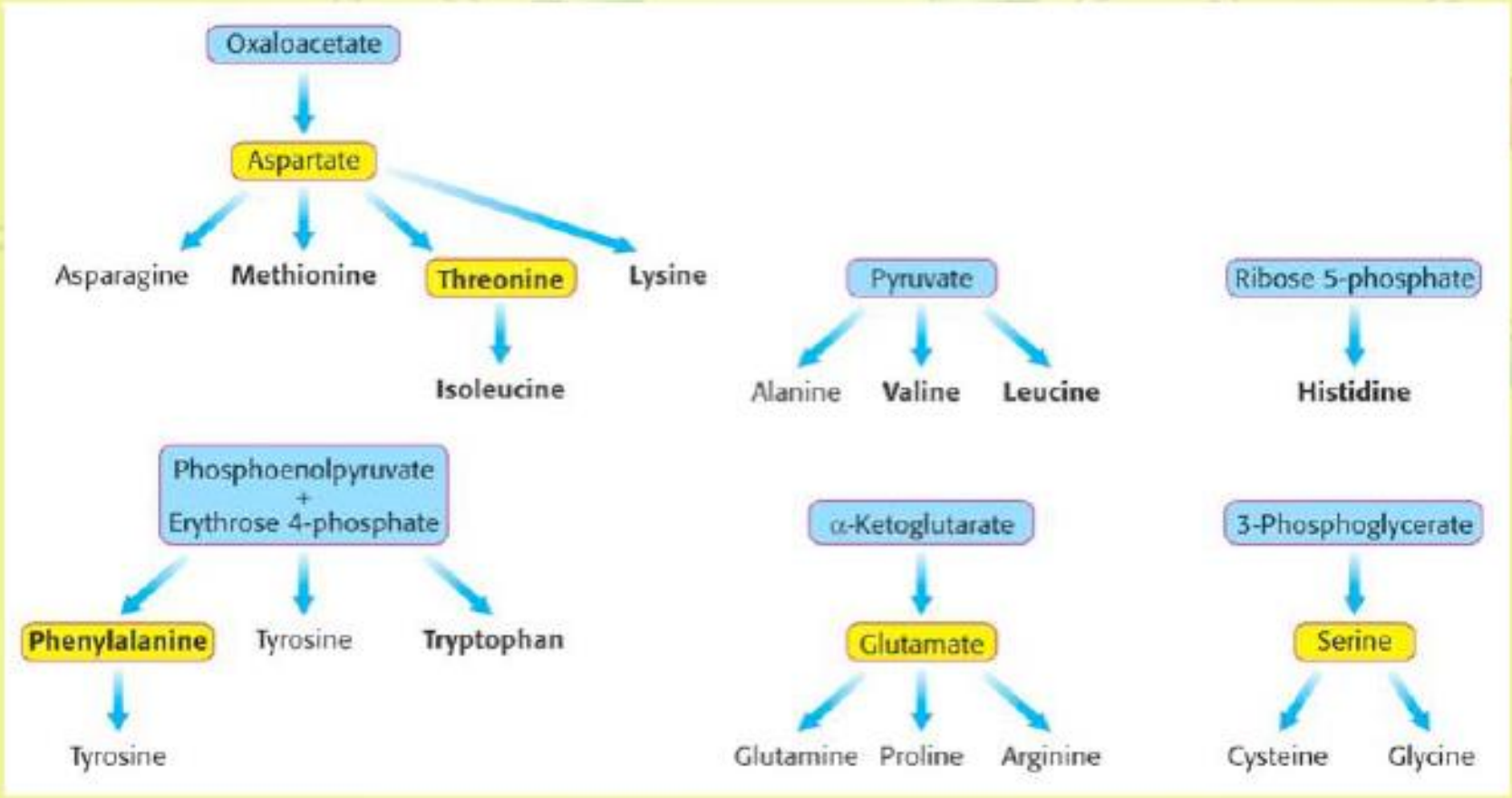
Glutamine synthetase

NH_4^+ + glutamate + ATP ⇌ glutamine + ADP + P_i



BIOSYNTHESIS OF NONESSENTIAL AMINO ACIDS

The biosynthetic pathways can be grouped into families:



Transaminations

A. Synthesis from α-keto acids

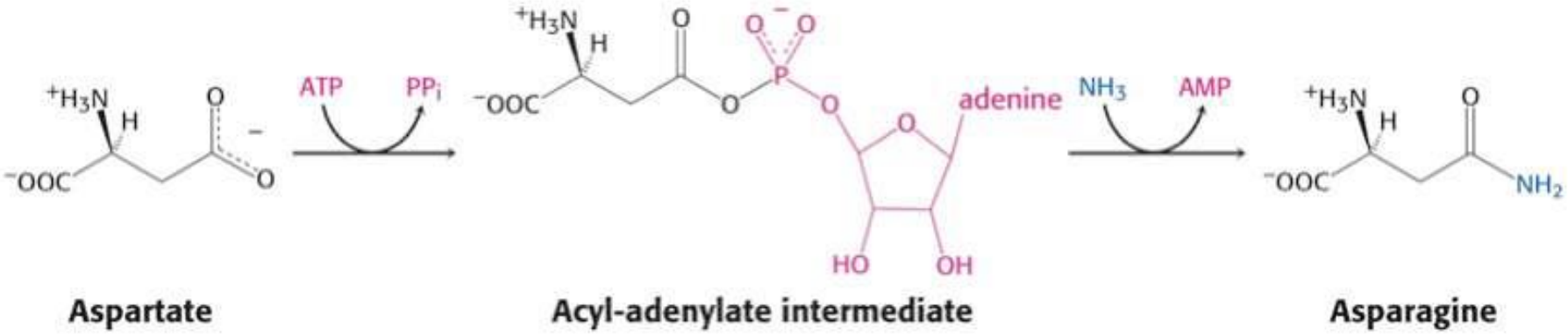
Aspartate, glutamate and Alanine

Oxaloacetate + glutamate ⇌ aspartate + α-ketoglutarate

Pyruvate + glutamate ⇌ alanine + α-ketoglutarate

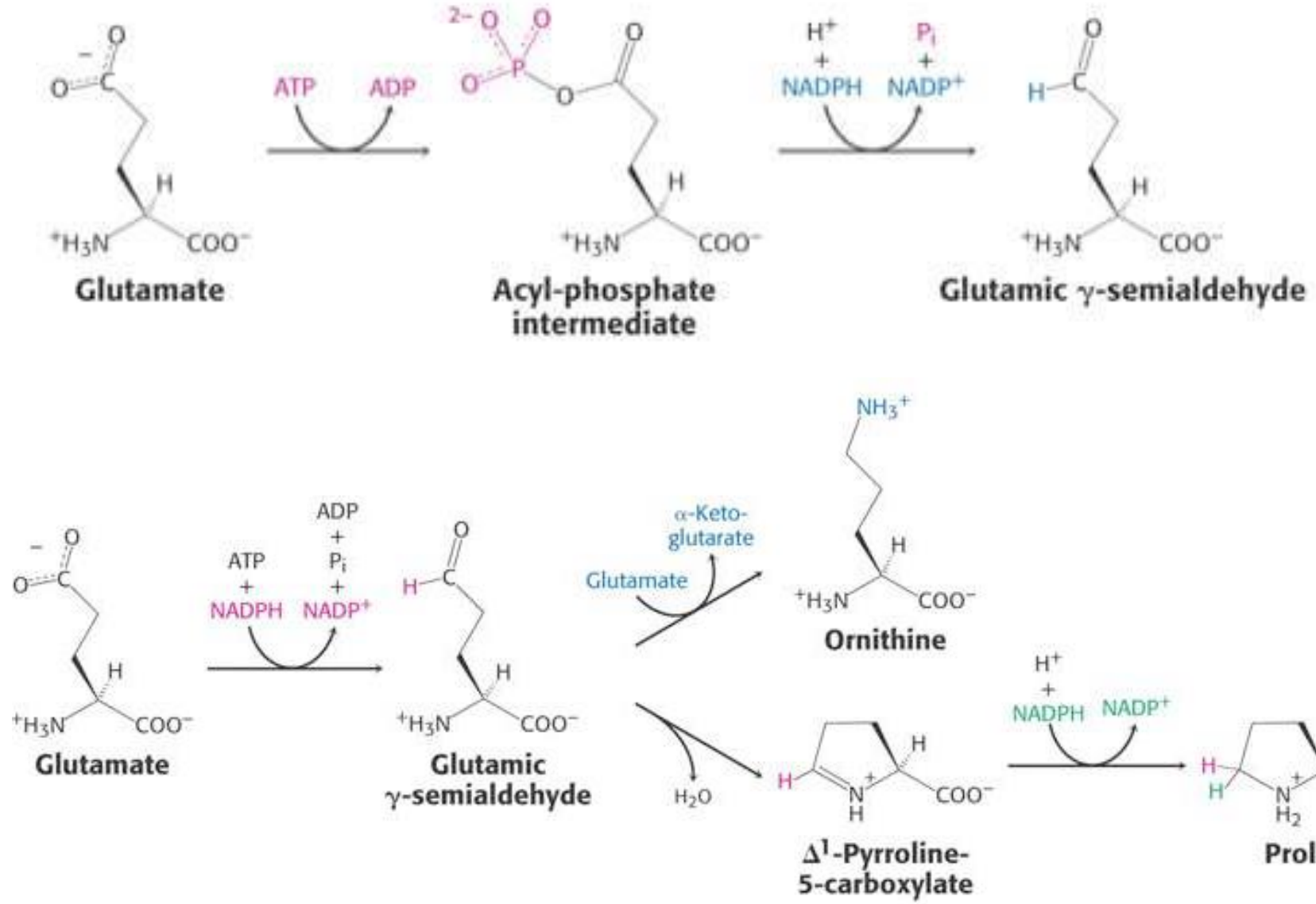
B-. Synthesis by amidation

Asparagine and glutamine



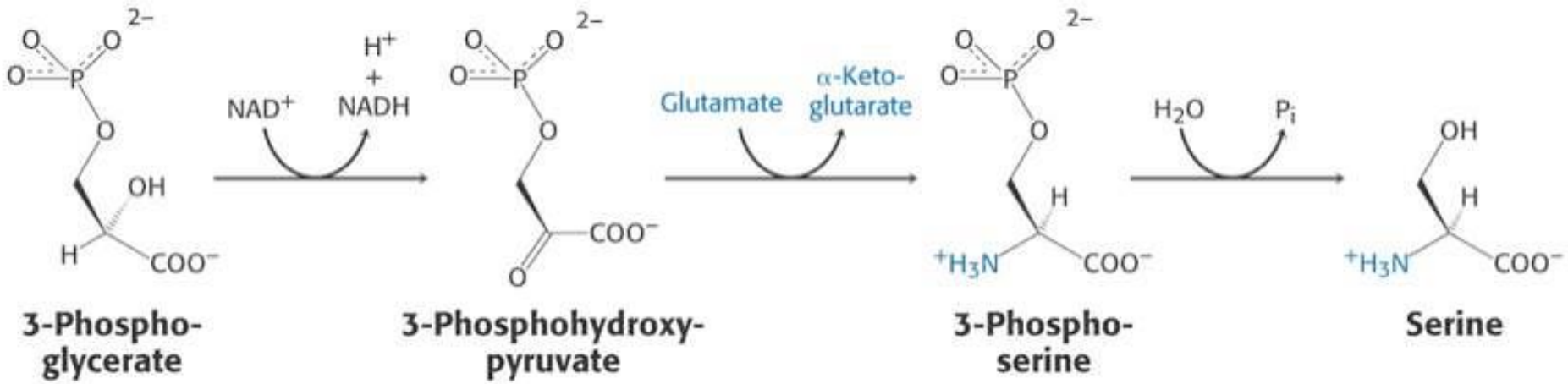
C-Proline and Arginine

By cyclization and Reduction of Glutamate



D- Serine, Glycine and cystiene

From Oxidation of 3–phosphoglycerate

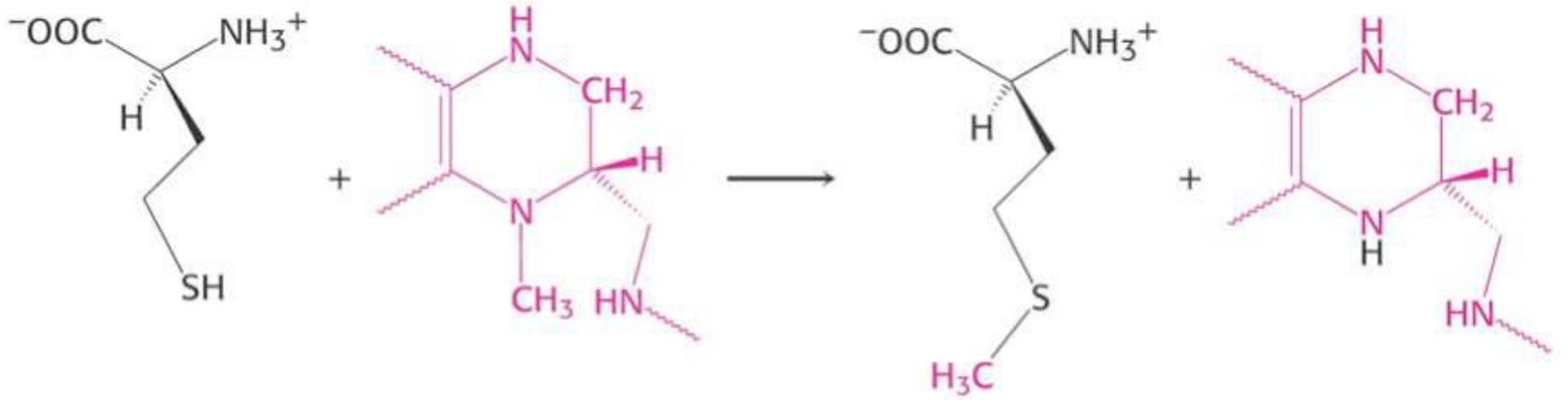


Serine transhydroxymethylase produces glycine from serine

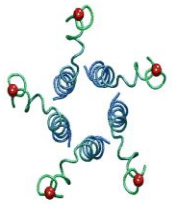
serine + tetrahydrofolate → glycine +methylenetetrahydrofolate + H2O

5-Methionine

Methylation of homocysteine

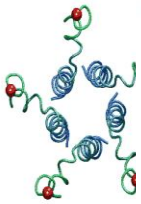


Homocysteine **N^5-Methyl-tetrahydrofolate** **Methionine** **Tetrahydrofolate**

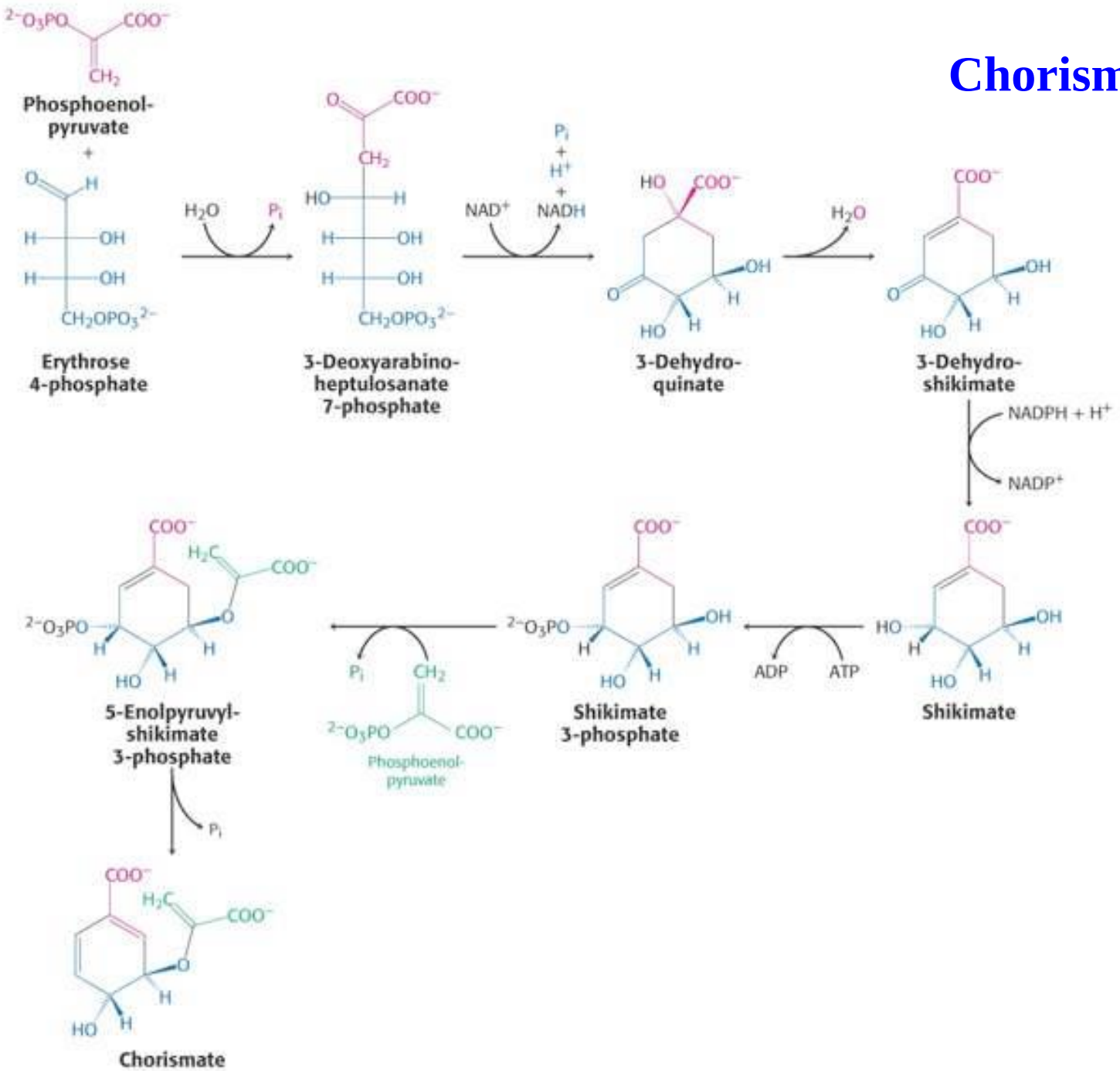


6-Aromatic Amino Acids

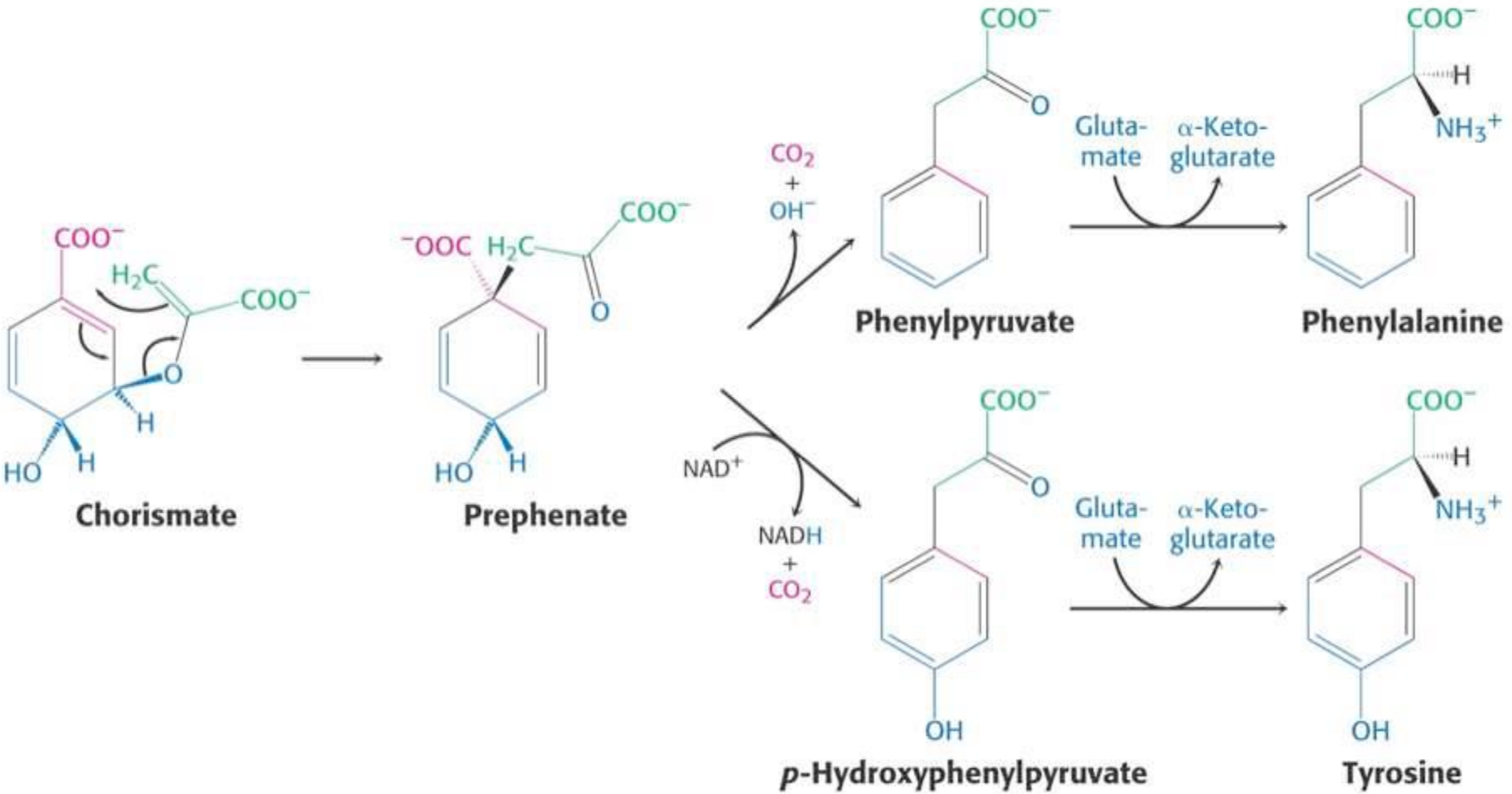
Example of essential amino acid synthesis
Involve Shikimate and Chorismate intermediates



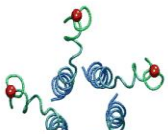
Chorismate:

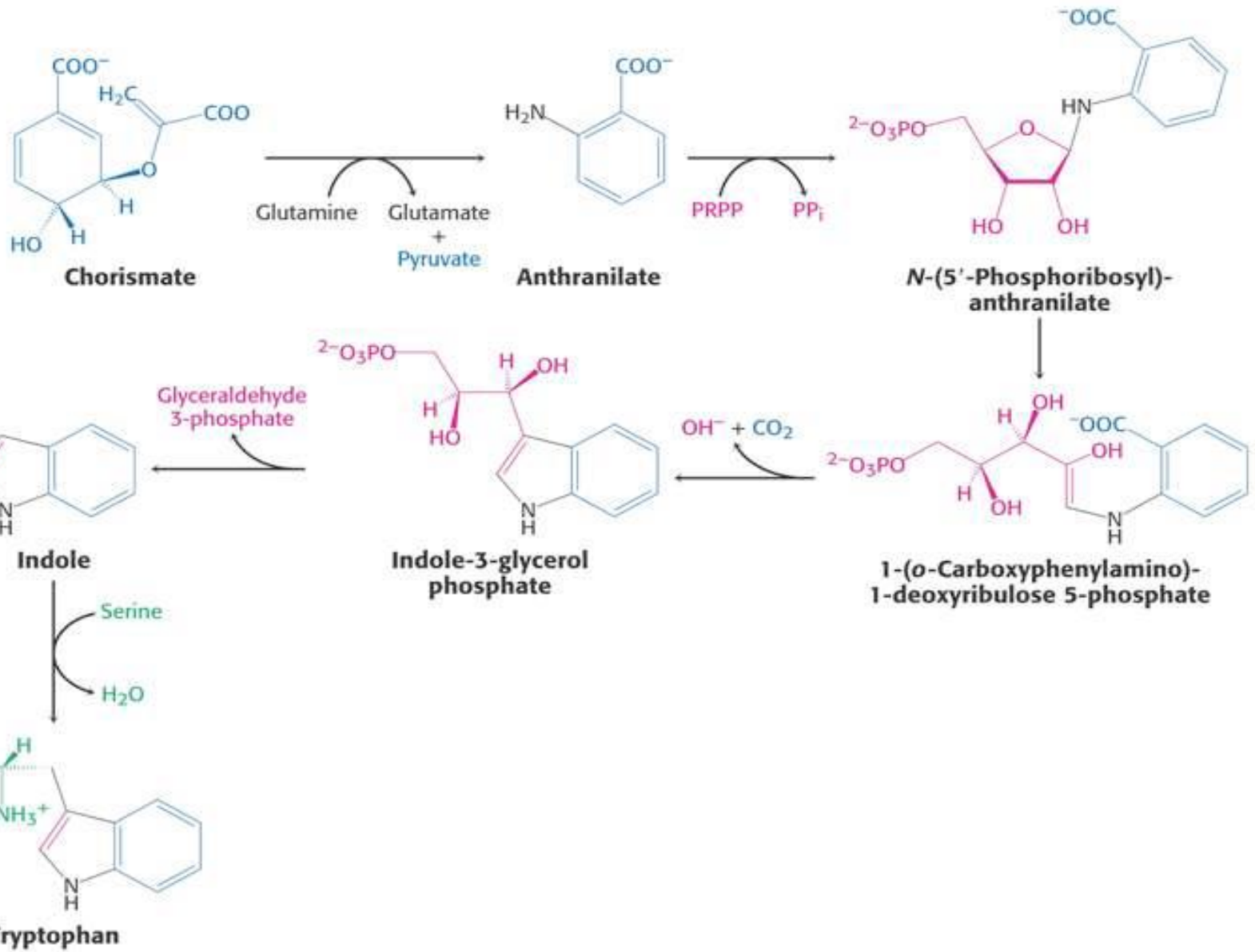

Phosphoenol-pyruvate
Erythrose 4-phosphate
3-Deoxyarabino-heptulosanate 7-phosphate
3-Dehydro-quinate
3-Dehydro-shikimate
Shikimate
Shikimate 3-phosphate
5-Enolpyruvyl-shikimate 3-phosphate
Chorismate
Phosphoenol-pyruvate
NADPH + H+
NADP+
ADP
ATP
NAD+
NADH
H2O
Pi

Tyrosine and Phenylalanine



Tryptophan

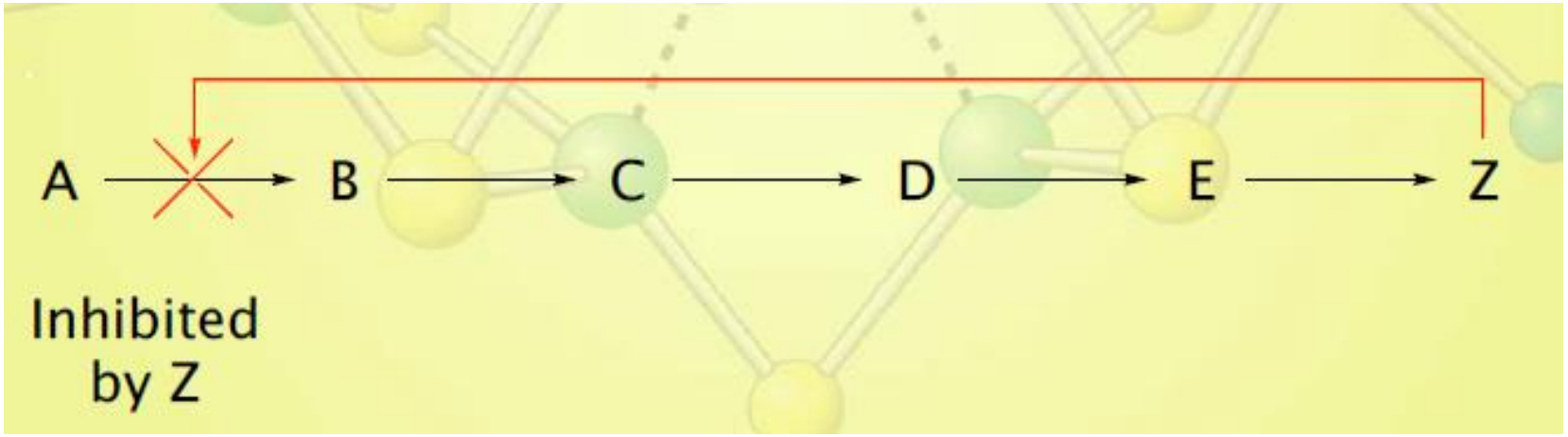



Chorismate
Glutamine
Glutamate
+
Pyruvate
Anthranilate
PRPP
PPi
N-(5'-Phosphoribosyl)-anthranilate
1-(o-Carboxyphenylamino)-1-deoxyribulose 5-phosphate
OH⁻ + CO2
Indole-3-glycerol phosphate
Glyceraldehyde 3-phosphate
Indole
Serine
H2O
Tryptophan

Regulation of Amino Acid Biosynthesis

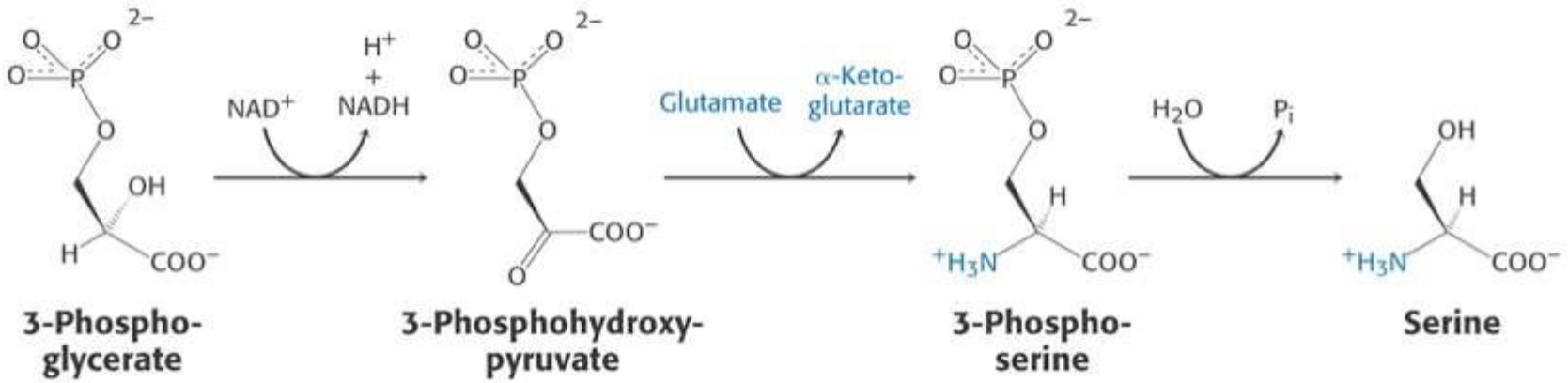
Amino acid biosynthesis is regulated by feedback inhibition.

The first committed step in a biosynthetic pathway is usually to the one that is regulated.



Regulation of Amino Acid Biosynthesis

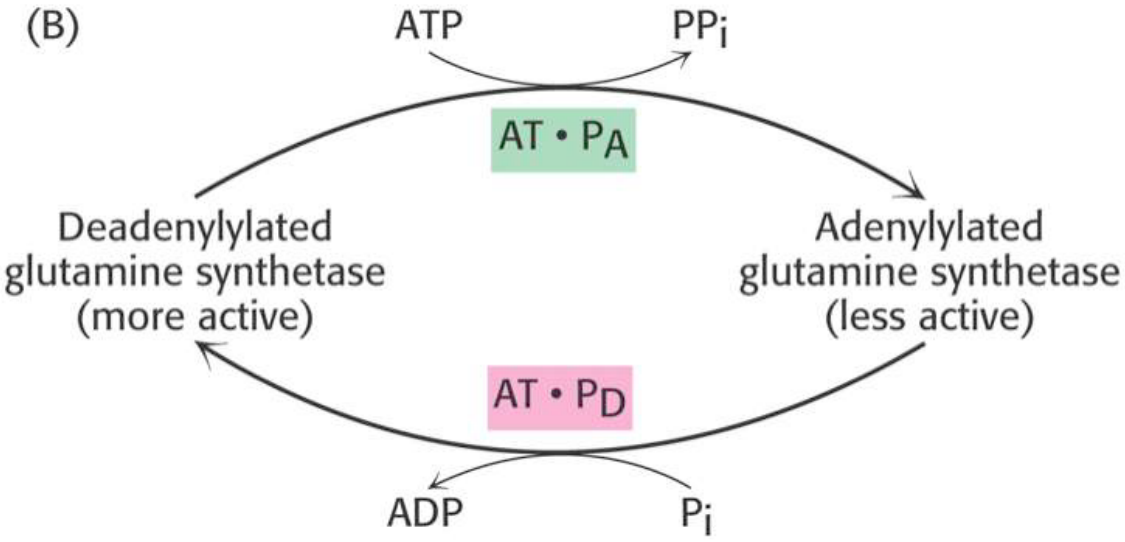
Example: Serine biosynthesis 3–Phosphoglycerate dehydrogenase is inhibited by serine.



Glutamine is the sources for nitrogen in the synthesis of

- tryptophan histidine
- carbamoyl phosphate
- glucosamine 6–phosphate
- cytidine triphosphate
- adenosine monophosphate

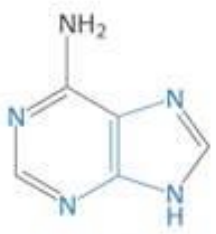
Glutamine Synthetase activity is also modulated by and enzymatic cascade



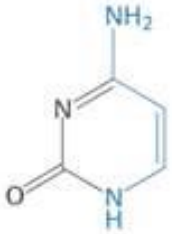
SPECIALIZED PRODUCTS DERIVED FROM AMINO ACIDS

Table 1 Products of Amino Acids

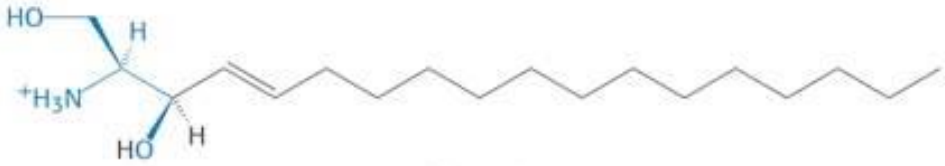
Amino Acid	Products
Tyrosine	Thyroid hormones T_3 and T_4 Melanin Catecholamines
Tryptophan	Serotonin NAD, NADP
Arginine	Nitric oxide (NO)
Glutamate	γ-Aminobutyric acid (GABA)
Histidine	Histamine



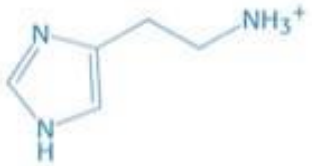
Adenine



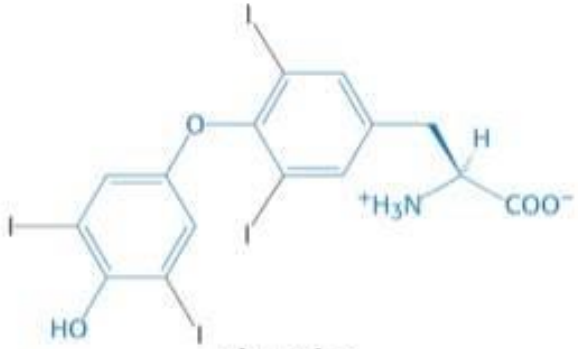
Cytosine



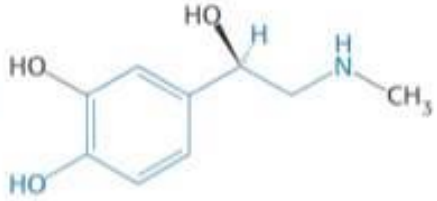
Sphingosine



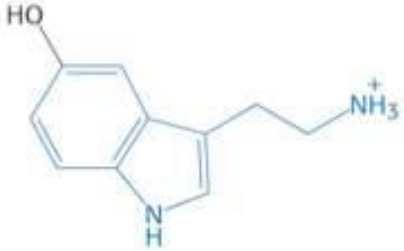
Histamine



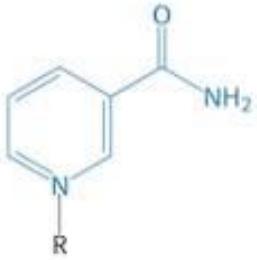
Thyroxine
(Tetraiodothyronine)



Epinephrine



Serotonin



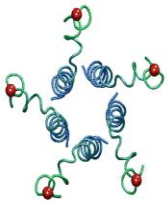
Nicotinamide
unit of NAD^+

Amino acids are precursors for many biomolecules

HEME SYNTHESIS

Heme synthesis occurs in almost all tissues because heme proteins include not only hemoglobin and myoglobin but all the cytochromes (electron transport chain, cytochrome P-450, cytochrome *b*5), as well as the enzymes catalase, peroxidase, and the soluble guanylate cyclase stimulated by nitric oxide.

The pathway producing heme, (Figure 1), is controlled independently in different tissues. In liver, the rate-limiting enzyme deleta δ-aminolevulinate synthase (δ-ALA) is repressed by heme



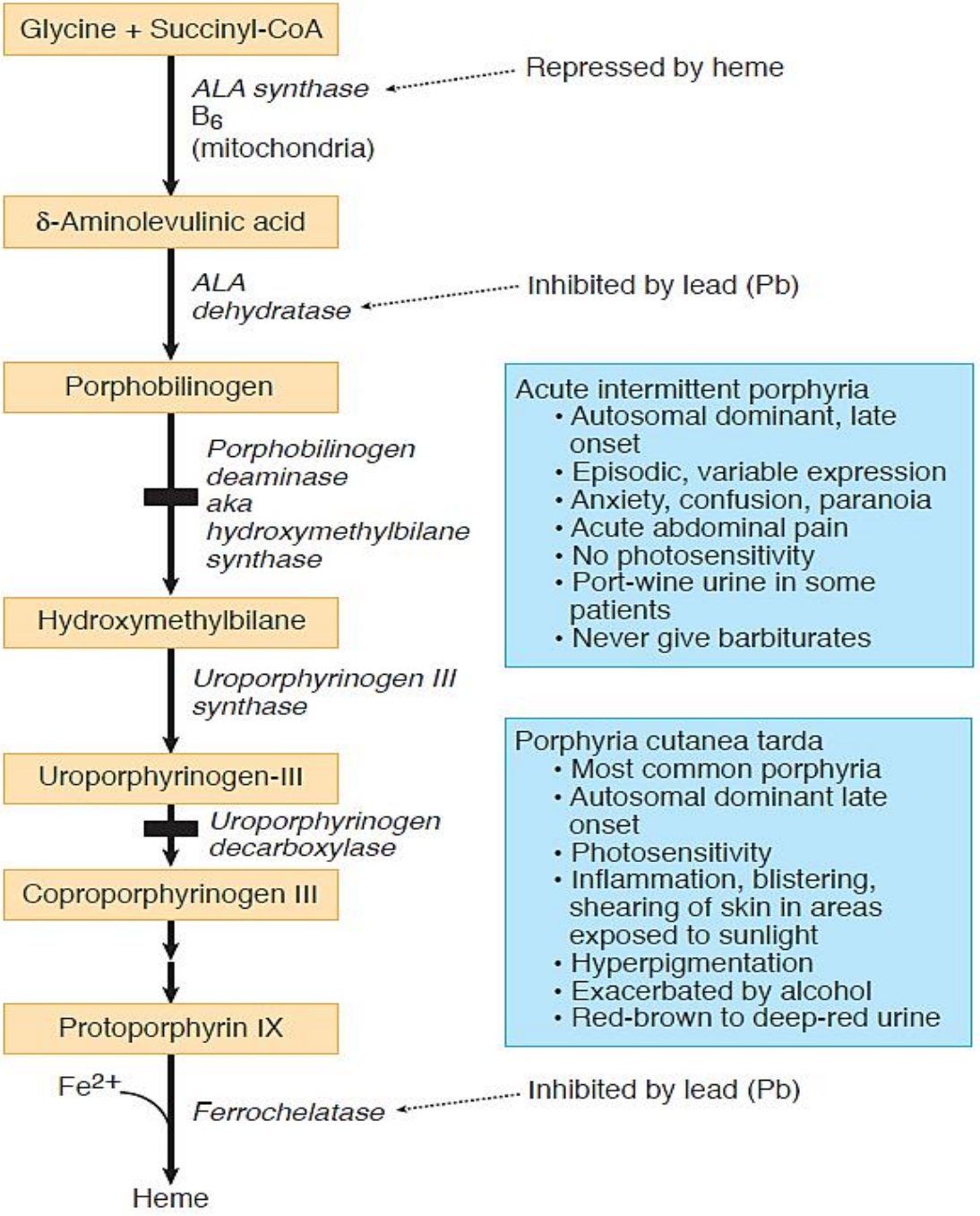


Figure 1 :Heme Synthesis

Other Porphyrias

Deficiencies of other enzymes in the heme pathway produce porphyrias in which photosensitivity is a common finding. Chronic inflammation to overt blistering and shearing in exposed areas of the skin characterize these porphyrias. The most common is porphyria cutanea tarda (deficiency of uroporphyrinogen decarboxylase), an autosomal dominant condition with late onset. b-Carotene is often administered to porphryia patients with photosensitivity to reduce the production of reactive oxygen species.

Vitamin B6 Deficiency

ALA synthase, the rate-limiting enzyme, requires pyridoxine (vitamin B6). Deficiencyof pyridoxine is associated with isoniazid therapy for tuberculosis and may cause sideroblastic anemia with ringed sideroblasts

Acute Intermittent Porphyria: Porphobilinogen Deaminase (Hydroxymethylbilane Synthase) Deficiency

This late-onset autosomal dominant disease exhibits variable expression. Many heterozygotes remain symptom-free throughout their lives. Signs and symptoms, when present, include:

- ❑ **Abdominal pain, often resulting in multiple laparoscopies (scars on abdomen)**
- ❑ **Anxiety, paranoia, and depression**
- ❑ **Paralysis**
- ❑ **Motor, sensory or autonomic neuropathy**
- ❑ **Weakness**
- ❑ **Excretion of ALA (δ-aminolevulinic) and PBG (porphobilinogen) during episodes**
- ❑ **In severe cases, dark red color to urine on standing**

Iron Deficiency

The last enzyme in the pathway, heme synthase (ferrochelatase), introduces the Fe2+ into the heme ring. Deficiency of iron produces a microcytic hypochromic anemia.

Lead Poisoning

Lead inactivates many enzymes including ALA dehydrase and ferrochelatase (heme synthase), and can produce a microcytic sideroblastic anemia with ringed sideroblasts in the bone marrow. Other symptoms include:

- **Coarse basophilic stippling of erythrocytes**
- **Headache, nausea, memory loss**
- **Abdominal pain, diarrhea (lead colic)**
- **Lead lines in gums**
- **Lead deposits in abdomen and epiphyses of bone seen on radiograph**

- **Neuropathy (claw hand, wrist-drop)**
- **Increased urinary ALA**
- **Increased free erythrocyte protoporphyrin**

Vitamin B6 deficiency, iron deficiency, and lead poisoning all can cause anemia.
These three conditions are summarized and compared in Table

Table 2. Comparison of Vitamin B6 Deficiency, Iron Deficiency, and Lead Poisoning

Vitamin B_6 (Pyridoxine) Deficiency	Iron Deficiency	Lead Poisoning
Microcytic	Microcytic	Microcytic Coarse basophilic stippling in erythrocytes
Ringed sideroblasts in bone marrow		Ringed sideroblasts in bone marrow
Protoporphyrin: ↓	Protoporphyrin: ↑	Protoporphyrin: ↑
δ-ALA: ↓	δ-ALA: Normal	δ-ALA: ↑
Ferritin: ↑	Ferritin: ↓	Ferritin: ↑
Serum iron: ↑	Serum iron: ↓	Serum iron: ↑
Isoniazid for tuberculosis	Dietary iron insufficient to compensate for normal loss	Lead paint Pottery glaze Batteries (Diagnose by measuring blood lead level)

IRON TRANSPORT AND STORAGE

Iron (Fe^{3+}) released from hemoglobin in the histiocytes is bound to ferritin and then transported in the blood by transferrin, which can deliver it to tissues for synthesis of heme.

Important proteins in this context are:

- **Ferroxidase (also known as ceruloplasmin, a Cu^{2+} protein) oxidizes Fe^{2+} to Fe^{3+} for transport and storage**
- **Transferrin carries Fe^{3+} in blood**
- **Ferritin itself oxidizes Fe^{2+} to Fe^{3+} for storage of normal amounts of Fe^{3+} in tissues. Loss of iron from the body is accomplished by bleeding and shedding epithelial cells of the mucosa and skin. The body has no mechanism for excreting iron, so controlling its absorption into the mucosal cells is crucial.**

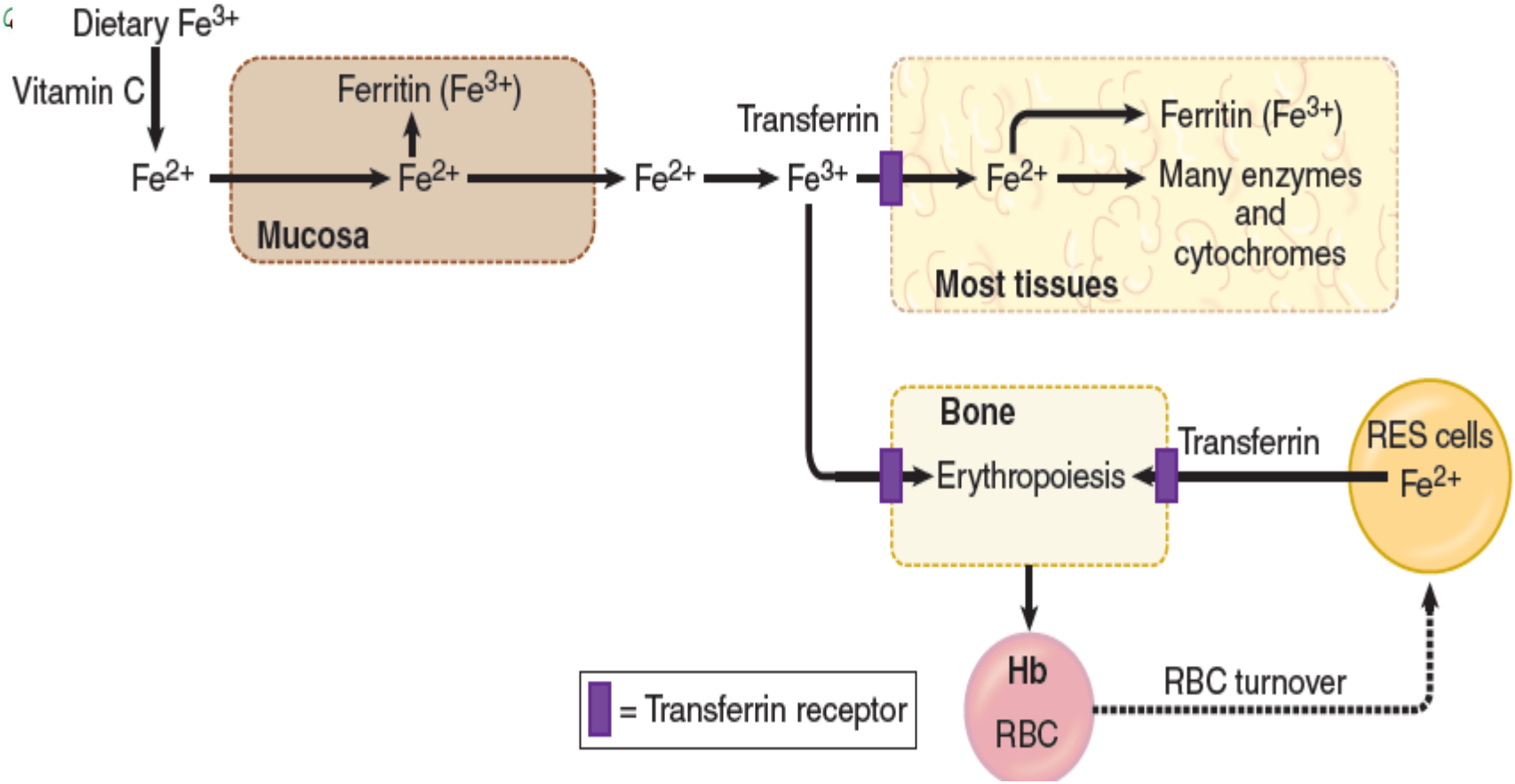


Figure2: Iron Metabolism

BILIRUBIN METABOLISM

Subsequent to lysis of older erythrocytes in the spleen, heme released from hemoglobin is converted to bilirubin in the histiocytes.

- **Bilirubin is not water soluble and is therefore transported in the blood attached to serum albumin.**
- **Hepatocytes conjugate bilirubin with glucuronic acid, increasing its water solubility.**
- **Conjugated bilirubin is secreted into the bile.**
- **Intestinal bacteria convert conjugated bilirubin into urobilinogen.**
- **A portion of the urobilinogen is further converted to bile pigments (stercobilin) and excreted in the feces, producing their characteristic red-brown color. Bile duct obstruction results in clay-colored stools.**
- **Some of the urobilinogen is converted to urobilin (yellow) and excreted in urine.**

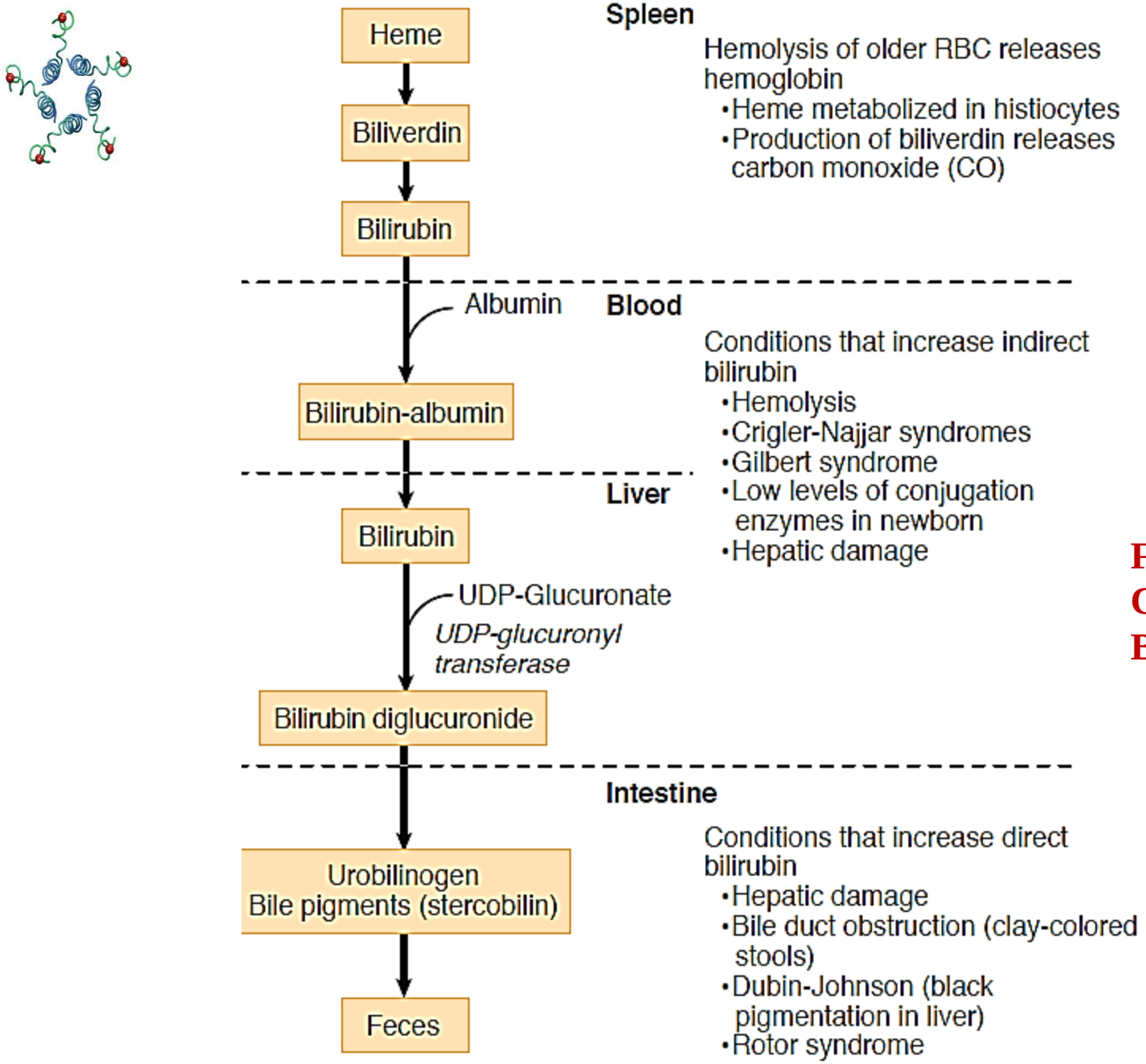


Figure. 3: Heme Catabolism and Bilirubin

Bilirubin and Jaundice

Jaundice (yellow color of skin, whites of the eyes) may occur when blood levels of bilirubin exceed normal (icterus). Jaundice may be characterized by an increase in unconjugated (indirect) bilirubin, conjugated (direct) bilirubin, or both.

Accumulation of bilirubin (usually unconjugated) in the brain (kernicterus) may result in death. When conjugated bilirubin increases, it may be excreted, giving a deep yellow-red color to the urine.

Examples of conditions associated with increased bilirubin and jaundice include hemolytic crisis, UDP-glucuronyl transferase deficiency, hepatic damage, and bile duct occlusion.

Figure 4 Jaundiced patient, with the sclerae of his eyes appearing yellow.

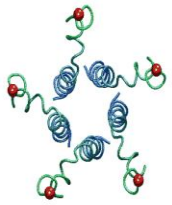
Types of jaundice:

a. Hemolytic jaundice
b. Hepatocellular jaundice
c. Obstructive jaundice

Hemolytic crisis

With severe hemolysis, more bilirubin is released into the blood than can be transported on albumin and conjugated in the liver. Unconjugated and total bilirubin increase and may produce jaundice and kernicterus. Examples include:

- **Episode of hemolysis in G6PDH deficiency**
- **Sickle cell crisis**
- **Rh disease of newborn**



	haemolytic jaundice	hepato-cellular jaundice	obstructive jaundice
	Pre-hepatic jaundice	**Hepatic jaundice**	**Post-hepatic jaundice**
Cause	➢ Due to increase in RBCs breakdown due to hemolytic anemia. ➢ The rate of RBCs lysis and bilirubin production more than ability of liver to convert it to the conjugated form.	➢ Due to liver cell damage (cancer, cirrhosis or hepatitis) ➢ Conjugation of bilirubin decreased (ID.Bil. ↑). ➢ Blilirubin that is conjugated is not efficiently secreted into bile but leaks to blood (D.Bil. ↑)	➢ Due to obstruction of bile duct which prevents passage of bilirubin into intestine. ➢ D.Bil will back to liver and then to circulation elevating its level in blood and urine.
Type of Bil.	ID.Bil > D.Bil	D.Bil, ID.Bil, T.Bil all (High)	D.Bil (High)
Conformational test	K^+ (High) Hematology: Complete blood count(CBC) (low Hb)	ALT, AST (High)	ALP (High)

Hemolytic crisis may be confirmed by low hemoglobin and elevated reticulocyte counts.

UDP-glucuronyl transferase deficiency

When bilirubin conjugation is low because of genetic or functional deficiency of the glucuronyl transferase system, unconjugated and total bilirubin increase.

Examples include:

- **Crigler-Najjar syndromes (types I and II)**
- **Gilbert syndrome**
- **Physiologic jaundice in the newborn, especially premature infants (enzymes may not be fully induced)**

Hepatic damage

Viral hepatitis or cirrhosis produces an increase in both direct and indirect bilirubin. Aminotransferase levels will also be elevated.

- **Alcoholic liver disease, AST increases more than ALT**
- **Viral hepatitis, ALT increases more than AST**

Bile duct occlusion

Occlusion of the bile duct (gallstone, primary biliary cirrhosis, pancreatic cancer) prevents conjugated bilirubin from leaving the liver.

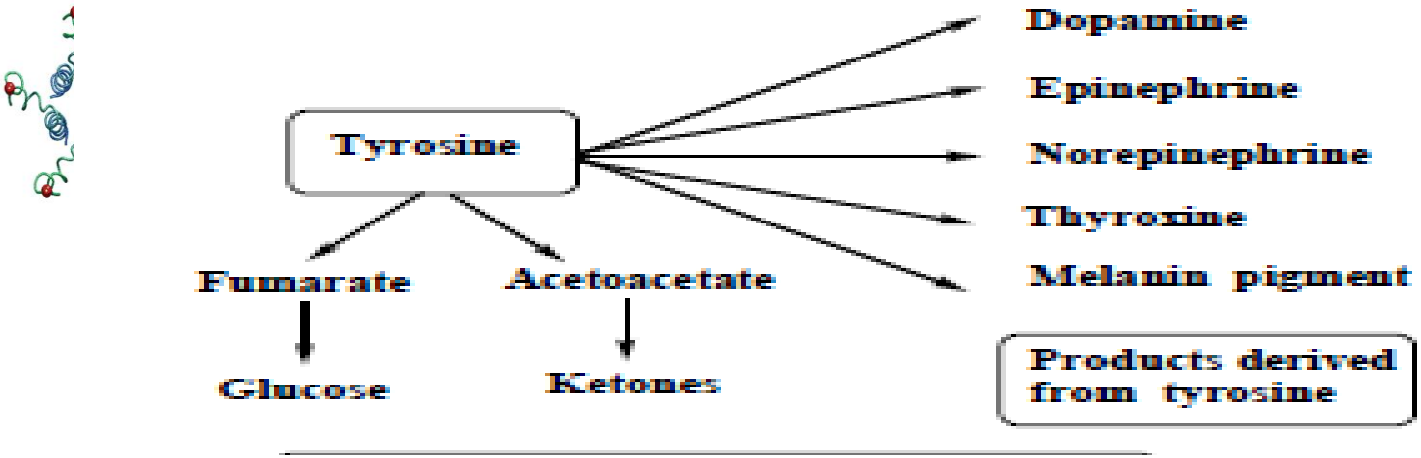
Conjugated bilirubin increases in blood and may also appear in urine. Feces are light-colored.

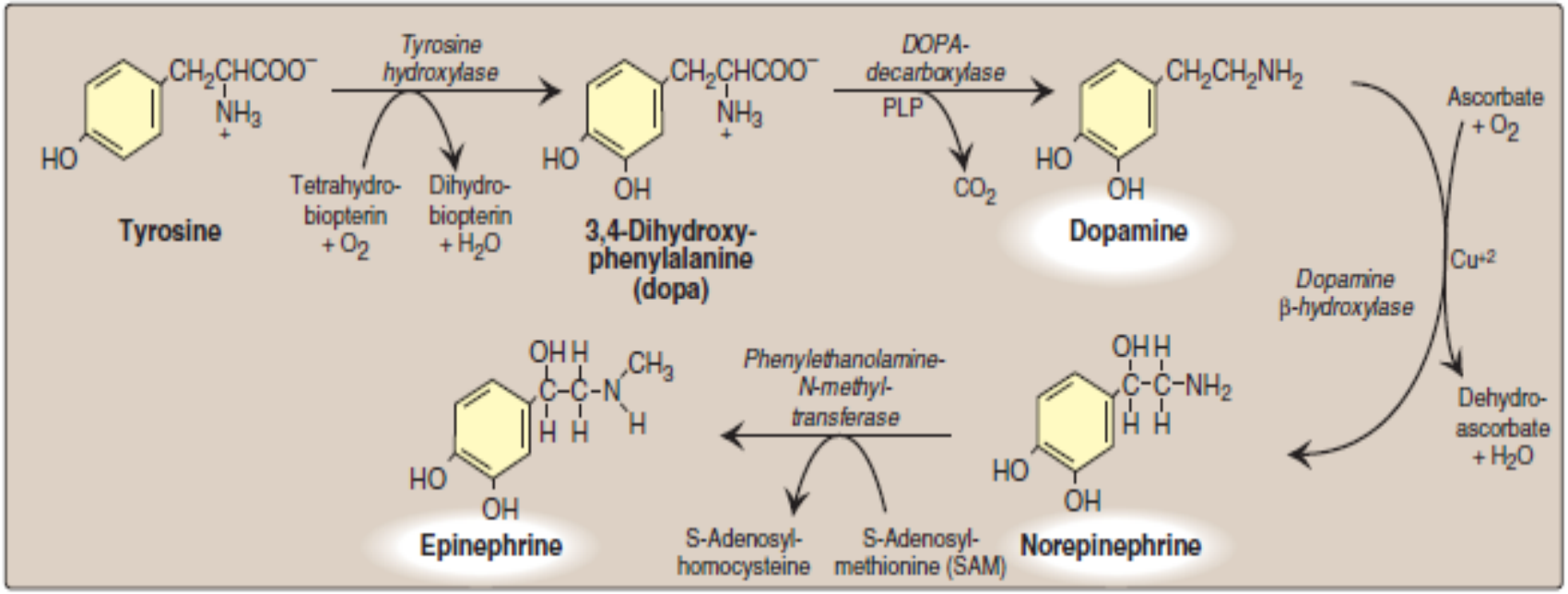
Biologically important compounds derived from Tryptophan

1- Vitamin niacin (vitamin B3)
2- Neurotransmitter serotonin

Hormone melatonin : is a hormone produced by the pineal gland which has effects on the hypothalamic pituitary system .Synthesis of melatonin is regulated by light –dark cycle and blood levels of melatonin rise at night.

Parkinson ’ s disease :
in Parkinson’ s disease , dopamine levels in the CNS are decreased because of a deficiency of cells that produce dopamine and depression is associated with low levels of serotonin.



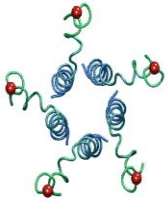


Synthesis of catecholamines. PLP = pyridoxal phosphate.

Other Nitrogen-Containing Compounds

A. Histamine

Histamine is a chemical messenger that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and possibly neurotransmission in parts of the brain. A powerful vasodilator, histamine is formed by decarboxylation of histidine in a reaction requiring pyridoxal phosphate. It is secreted by mast cells as a result of allergic reactions or trauma. Histamine has no clinical applications, but agents that interfere with the action of histamine have important therapeutic applications.



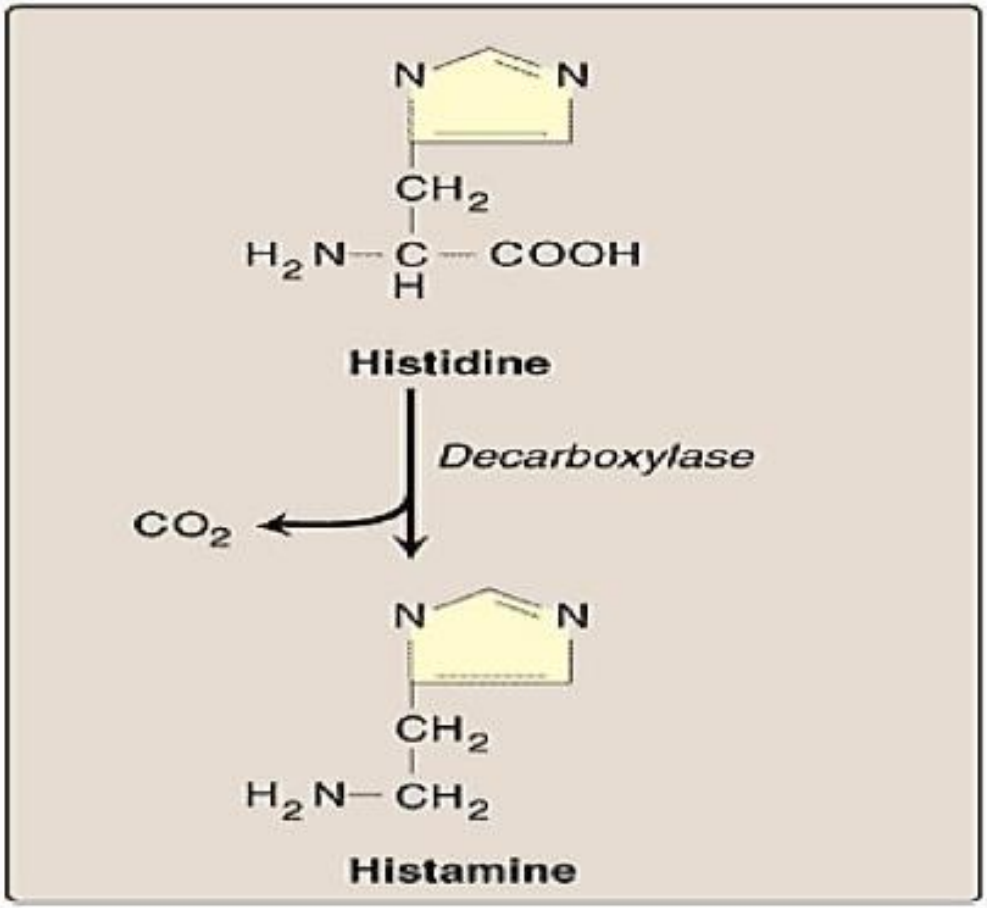


Figure 5:Biosynthesis of histamine

C. Serotonin

Serotonin, also called 5-hydroxytryptamine, is synthesized and stored at several sites in the body. By far the largest amount of serotonin is found in cells of the intestinal mucosa. Smaller amounts occur in the central nervous system, where it functions as a neurotransmitter, and in platelets.

Serotonin is synthesized from tryptophan, which is hydroxylated in a reaction analogous to that catalyzed by phenylalanine hydroxylase. The product, 5-hydroxytryptophan, is decarboxylated to serotonin. Serotonin has multiple physiologic roles, including pain perception, affective disorders, and regulation of sleep, temperature, and blood pressure.

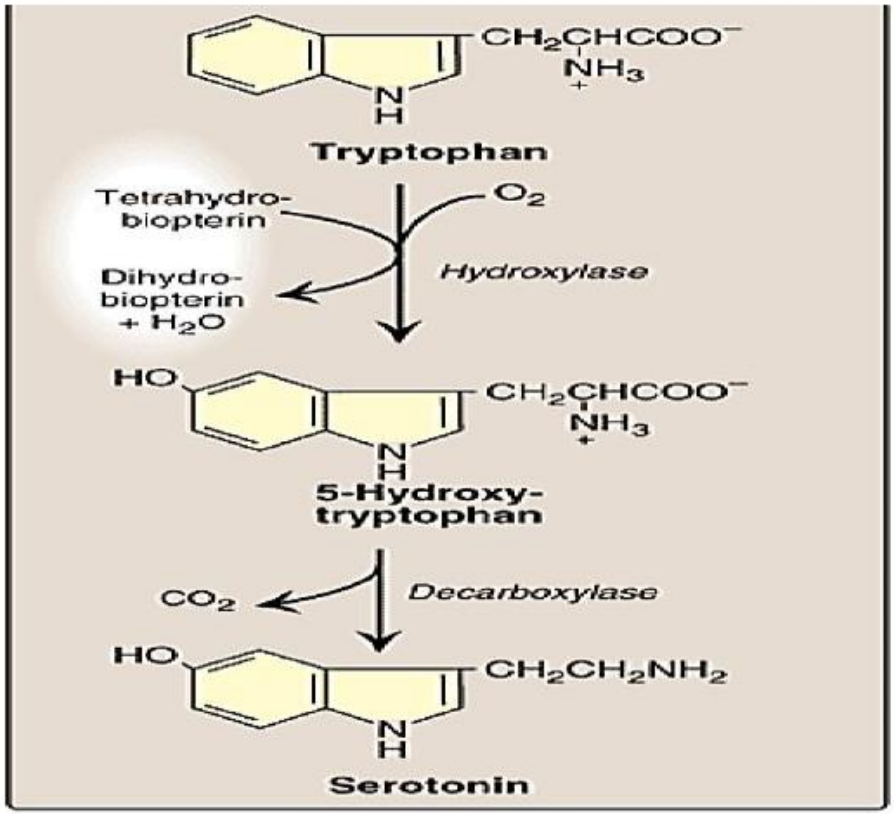


Figure 6:Synthesis of serotonin.

D. Creatine

Creatine phosphate (also called phosphocreatine), the phosphorylated derivative of creatine found in muscle, is a high-energy compound that can reversibly donate a phosphate group to adenosine diphosphate to form ATP).

Creatine phosphate provides a small but rapidly mobilized reserve of high-energy phosphates that can be used to maintain the intracellular level of adenosine triphosphate (ATP) during the first few minutes of intense muscular contraction.
[Note: The amount of creatine phosphate in the body is proportional to the muscle mass.

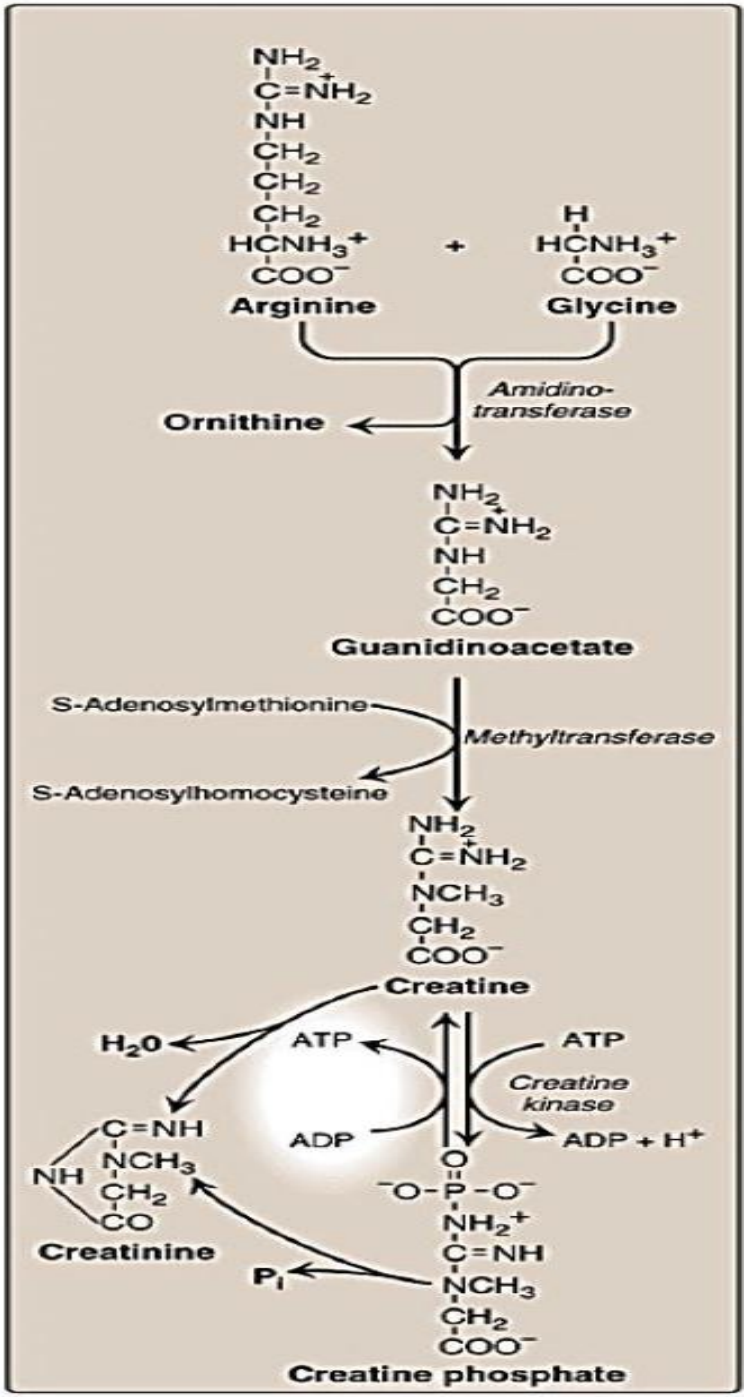
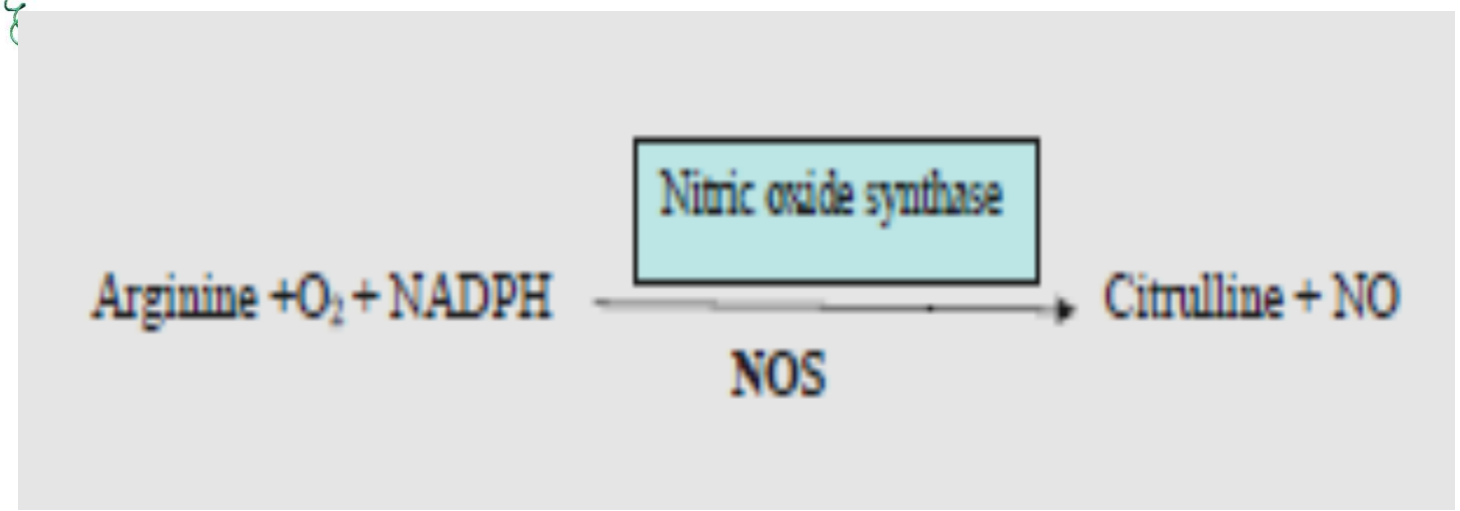


Figure 7: Synthesis of creatine

Nitric oxide:



Functions:

- **Neurotransmitter**
- **Prevents platelet aggregation.**
- **Bactericidal.**
- **Relaxes smooth muscle by activation of guanylyl cyclase cGMP**

Glutathione

Sulfhydryl buffer and antioxiidant

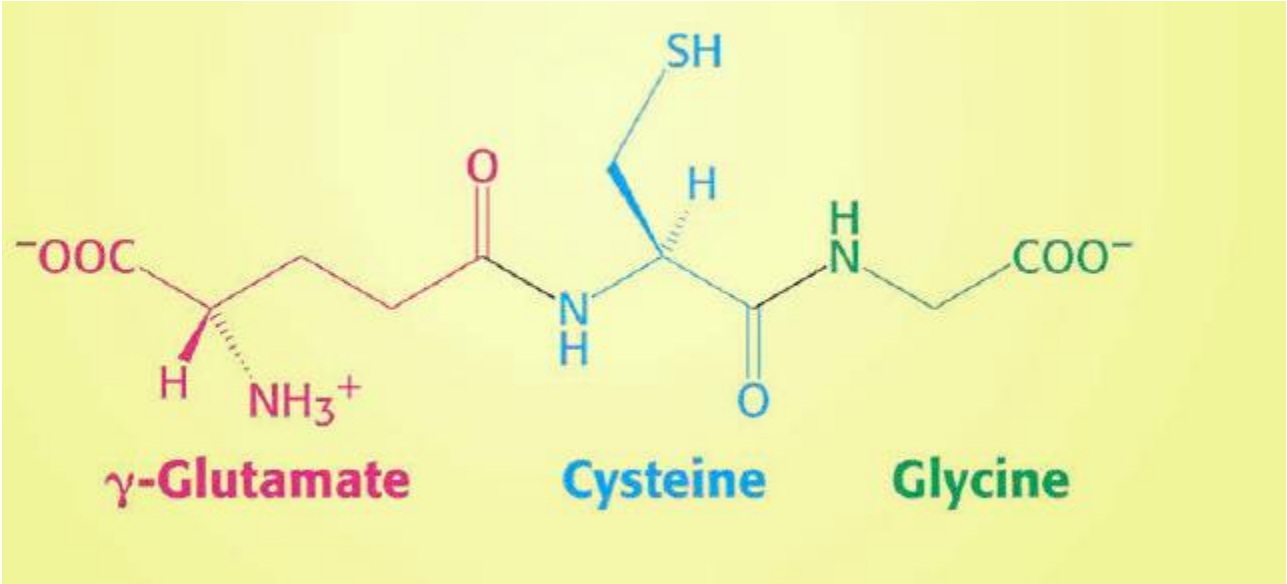


table 18–2

Some Human Genetic Disorders Affecting Amino Acid Catabolism

Medical condition	Approximate incidence (per 100,000 births)	Defective process	Defective enzyme	Symptoms and effects
Albinism	3	Melanin synthesis from tyrosine	Tyrosine 3-mono-oxygenase (tyrosinase)	Lack of pigmentation; white hair, pink skin
Alkaptonuria	0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	1.5	Urea synthesis	Argininosuccinate lyase	Vomiting, convulsions
Carbamoyl phosphate synthetase I deficiency	>0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy, convulsions, early death
Homocystinuria	0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development, mental retardation
Maple syrup urine disease (branched-chain ketoaciduria)	0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting, convulsions, mental retardation, early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting, convulsions, mental retardation, early death
Phenylketonuria	8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

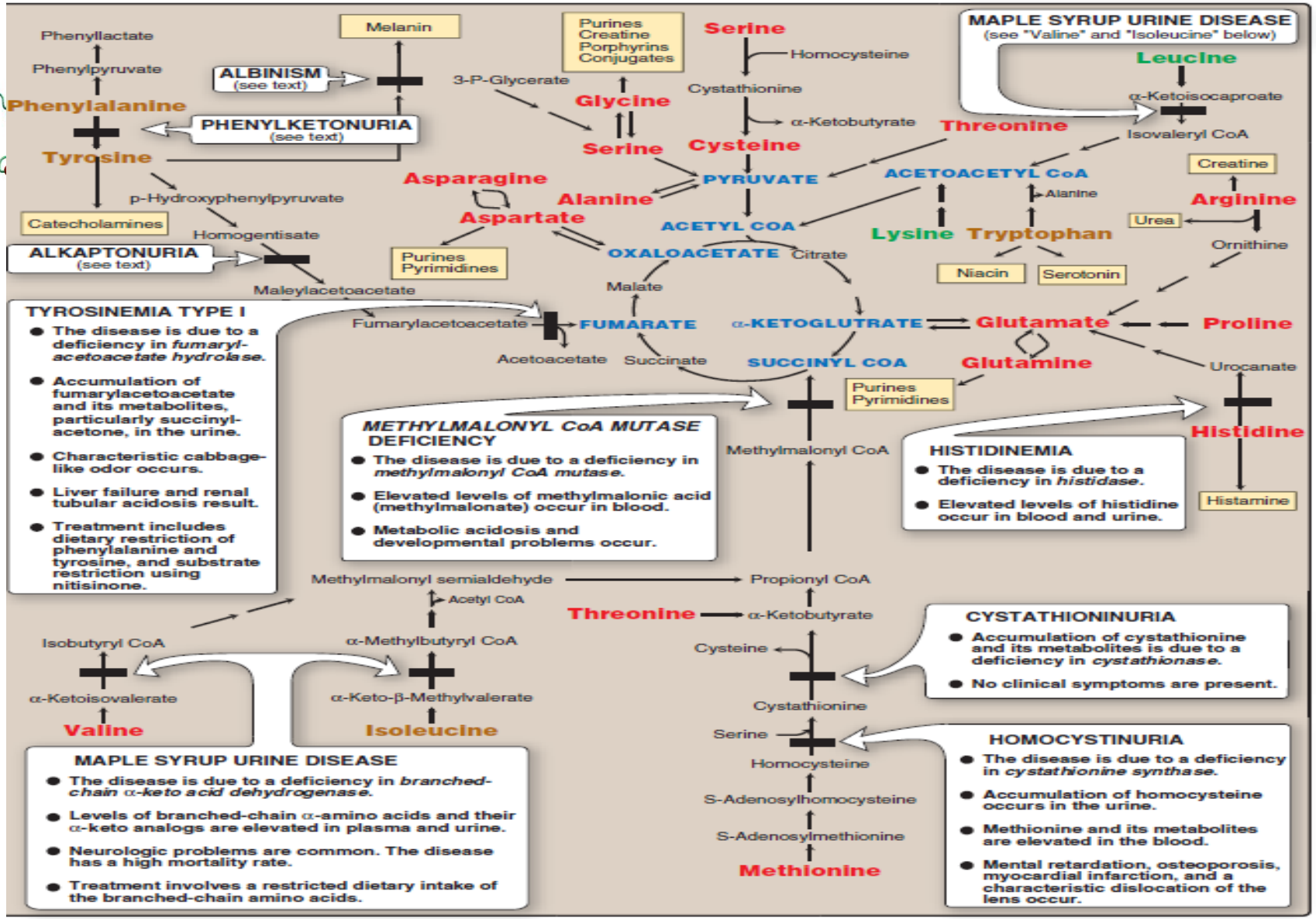


Figure 20.14
Summary of the metabolism of amino acids in humans. Genetically determined enzyme deficiencies are summarized in white boxes. Nitrogen-containing compounds derived from amino acids are shown in small, yellow boxes. Classification of amino acids is color coded: Red = glucogenic; brown = glucogenic and ketogenic; green = ketogenic. Compounds in **BLUE ALL CAPS** are the seven metabolites to which all amino acid metabolism converges.