Amino Acid Metabolism: Conversion of Amino Acids to Specialized Products

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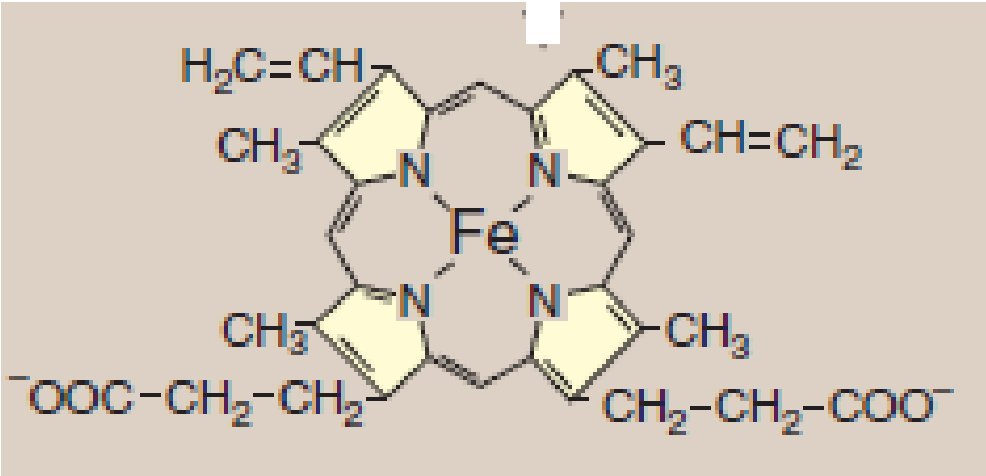
All images are taken from Lippincott's Biochemistry textbook except where noted

PORPHYRIN



Porphyrins are cyclic compounds that readily bind metal ions (Fe2+ or Fe3+)

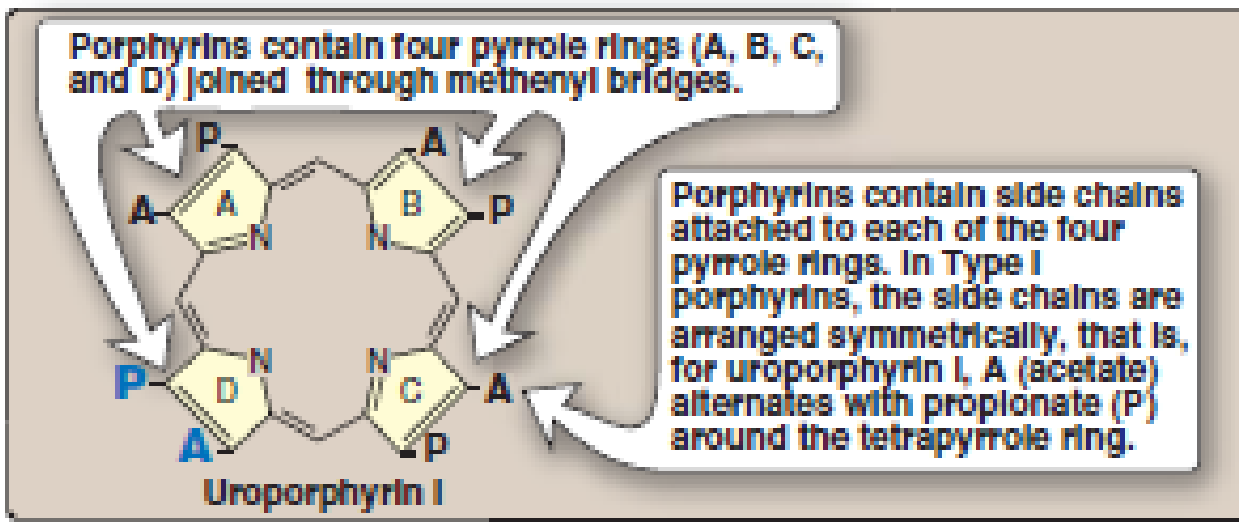
The most prevalent metalloporphyrin in humans is heme

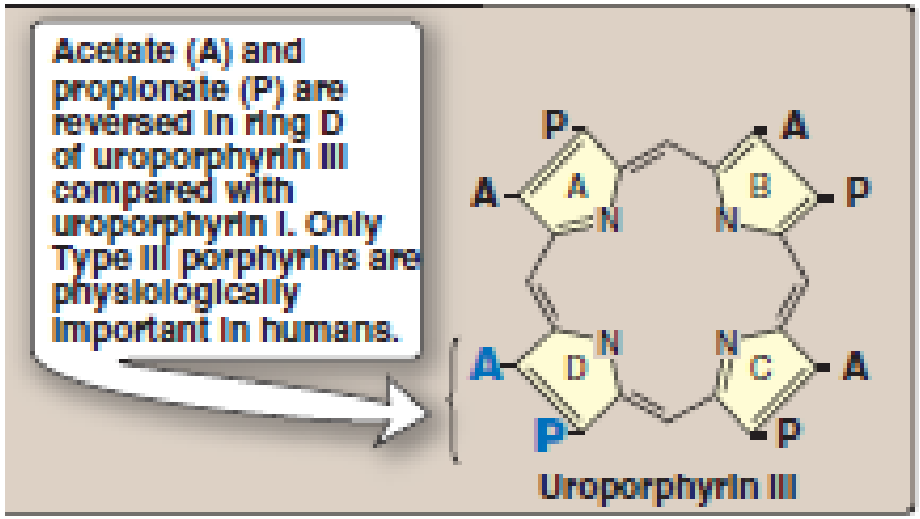
Heme is found in hemoglobin, myoglobin, the cytochromes, catalase, nitric oxide synthase, and peroxidase.

Hemeproteins are rapidly synthesized and degraded

6–7g of hemoglobin are synthesized each day to replace heme lost through the normal turnover of erythrocytes.

Structure of porphyrins

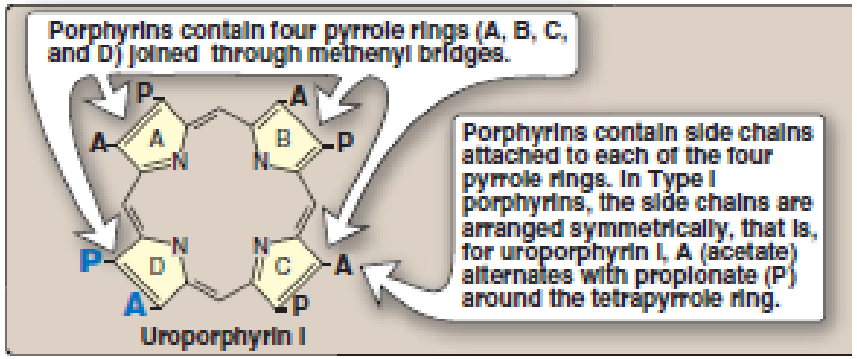


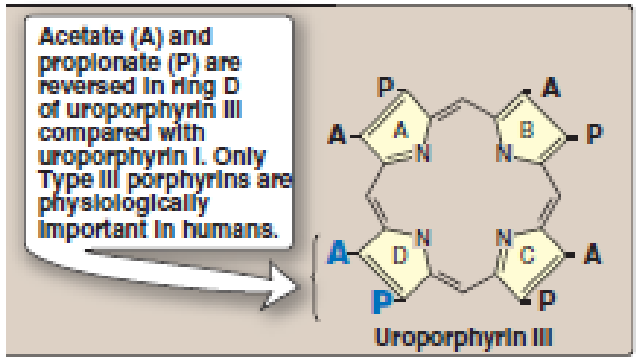


The medical significance of porphyrins is related to the following structural features of these molecules:

1. Nature of the side chains that are attached to each of the four pyrrole rings.
Uroporphyrin contains acetate (–CH2–COO–) and propionate (–CH2–CH2–COO–)
Coproporphyrin contains methyl (–CH3) and propionate groups
Protoporphyrin IX (and heme) contains vinyl (–CH=CH2), methyl, and propionate groups.

Structure of porphyrins





The medical significance of porphyrins is related to the following structural features of these molecules:

2. Distribution of side chains around the tetrapyrrole nucleus. Four different ways (I to IV) Only Type III porphyrins (asymmetric substitution on ring D) are physiologically important in humans.

3. Porphyrinogens (porphyrin precursors) exist in a chemically reduced, colorless form, and serve as intermediates between porphobilinogen and the oxidized, colored protoporphyrins in heme biosynthesis.

Biosynthesis of heme

The major sites of heme biosynthesis are:

1. Liver (cytochrome P450), variable rate depending on demands for heme proteins

2. Erythrocyte-producing cells of the bone marrow (hemoglobin), more than 85% of all heme synthesis

The initial and last steps in porphyrins formation occur in mitochondria
The intermediate steps occur in the cytosol

Mature RBCs lack mitochondria and are unable to synthesize heme

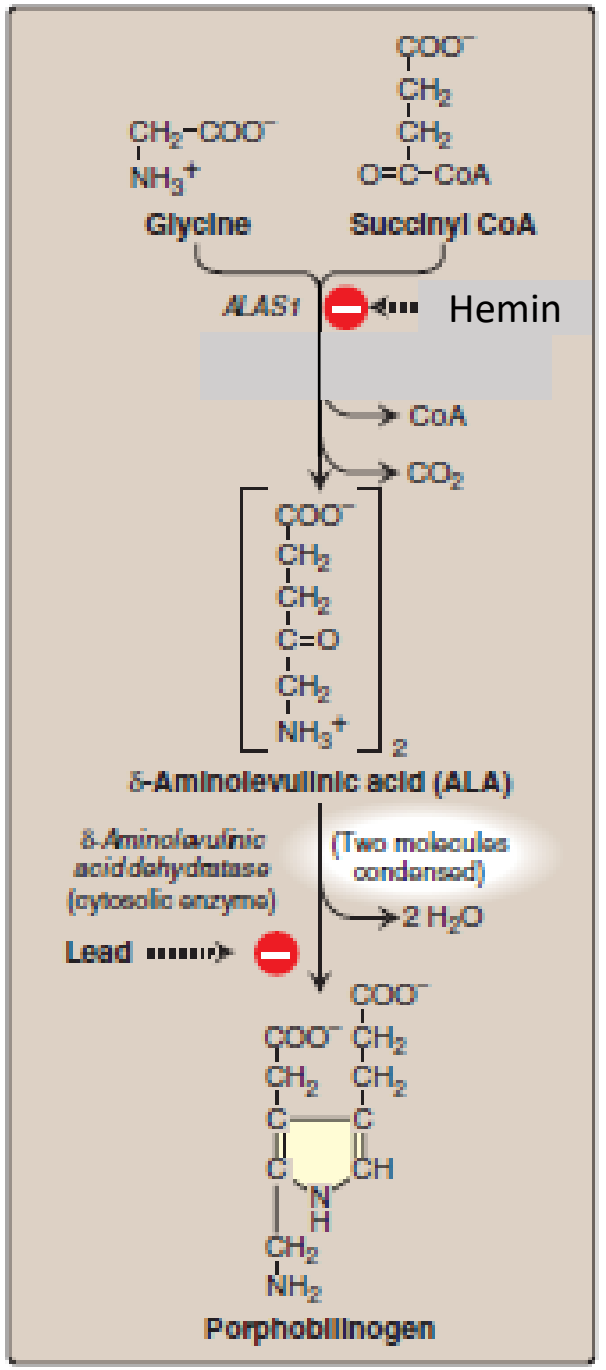
Biosynthesis of Heme

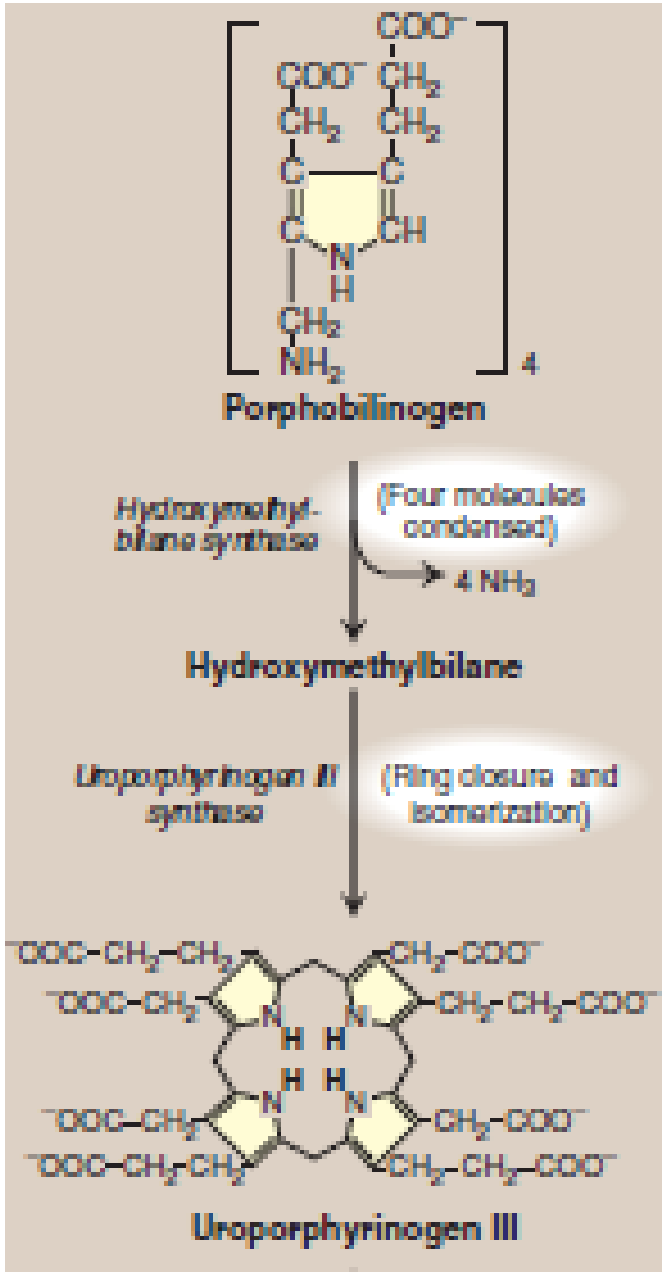
1. **Formation of δ-aminolevulinic acid (ALA)**

The rate-limiting step in porphyrin synthesis

2. Formation of porphobilinogen

ALA is elevated in the anemia seen in lead poisoning.





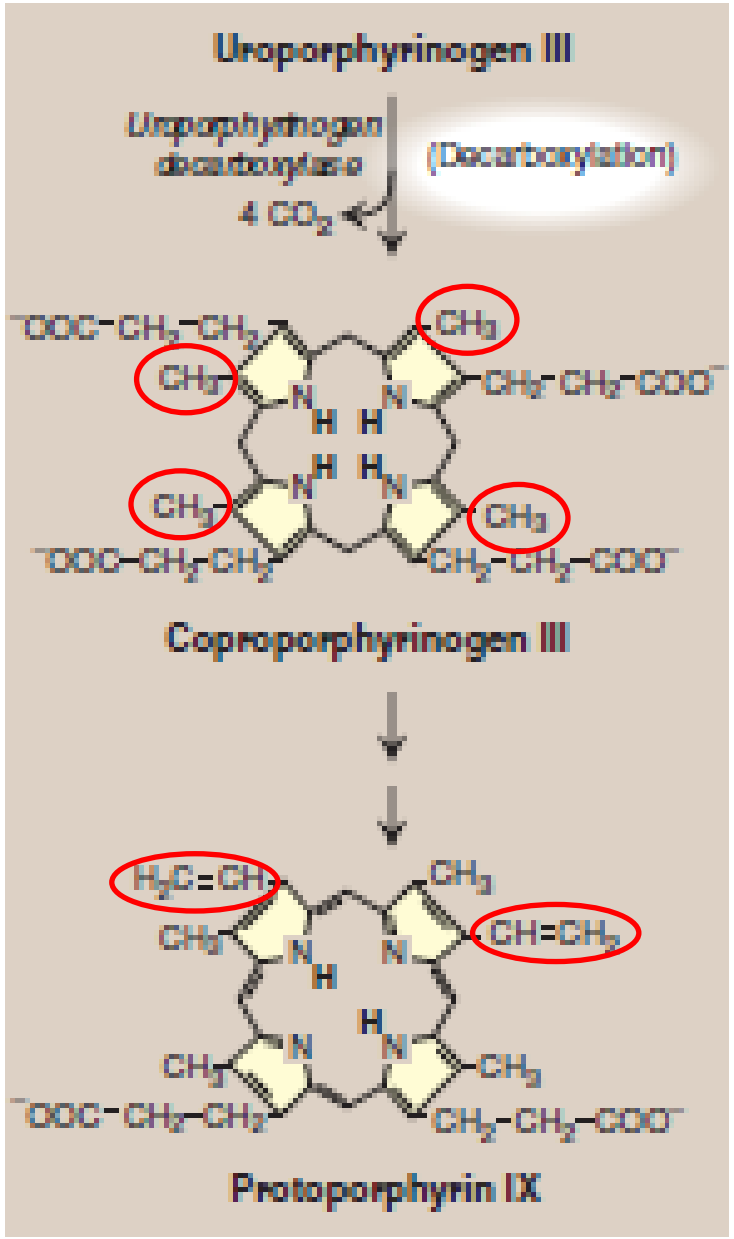
Synthesis of Heme

3. Formation of uroporphyrinogen: The condensation of four porphobilinogens produces the linear tetrapyrrole, hydroxymethyl bilane

Hydroxymethyl bilane is isomerized and cyclized by uroporphyrinogen III synthase to produce the asymmetric uroporphyrinogen III.

These reactions occur in the cytosol.

Synthesis of Heme



Cytosol

The cyclic hydroxymethyl bilane is decarboxylated (of its acetate groups) generating coproporphyrinogen III

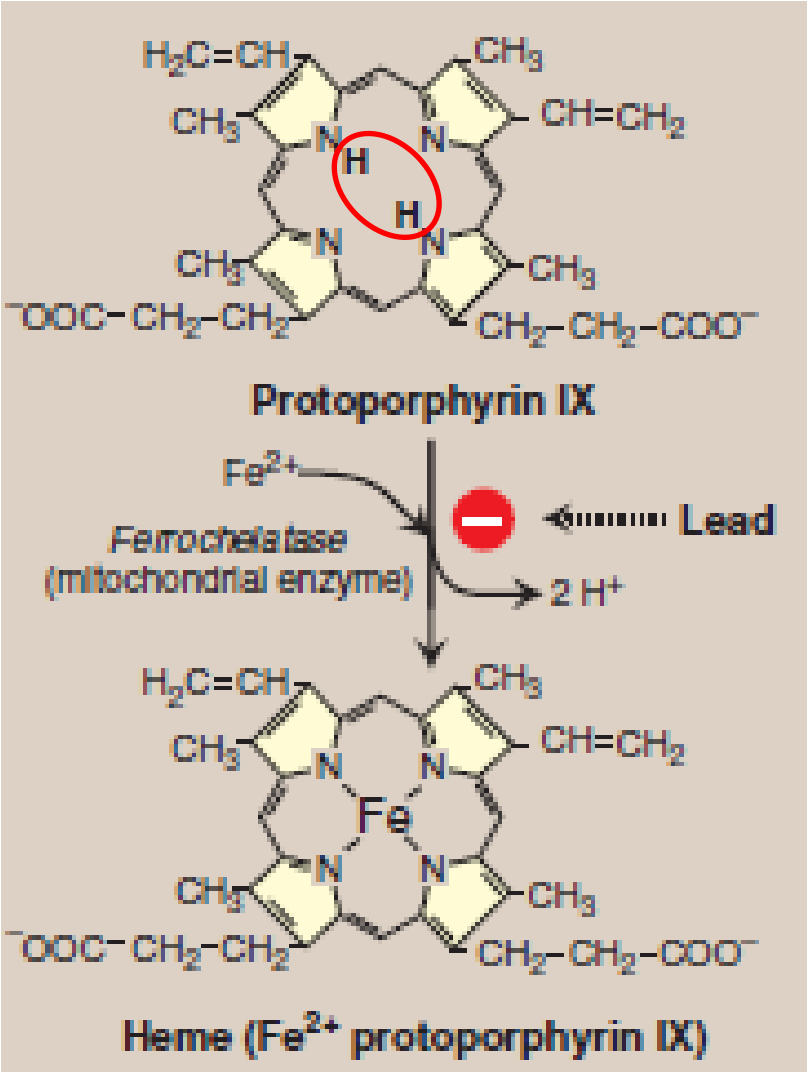
These reactions occur in the cytosol.

Mitochondria

Coproporphyrinogen III enters the mitochondrion

Two propionate side chains are decarboxylated to vinyl groups generating protoporphyrin IX

Synthesis of Heme



4. Formation of heme:

Protoporphyrinogen IX is oxidized to protoporphyrin IX.

The introduction of iron (as Fe2+) into protoporphyrin IX occurs spontaneously

The rate of Fe addition is enhanced by ferrochelatase (an enzyme that is inhibited by lead)

Heme Degradation

RBCs are degraded by the reticuloendothelial system (liver and spleen)

~85% of degraded heme comes from senescent RBCs
~15% of degraded heme comes from immature RBCs turnover and cytochromes of nonerythroid tissues.

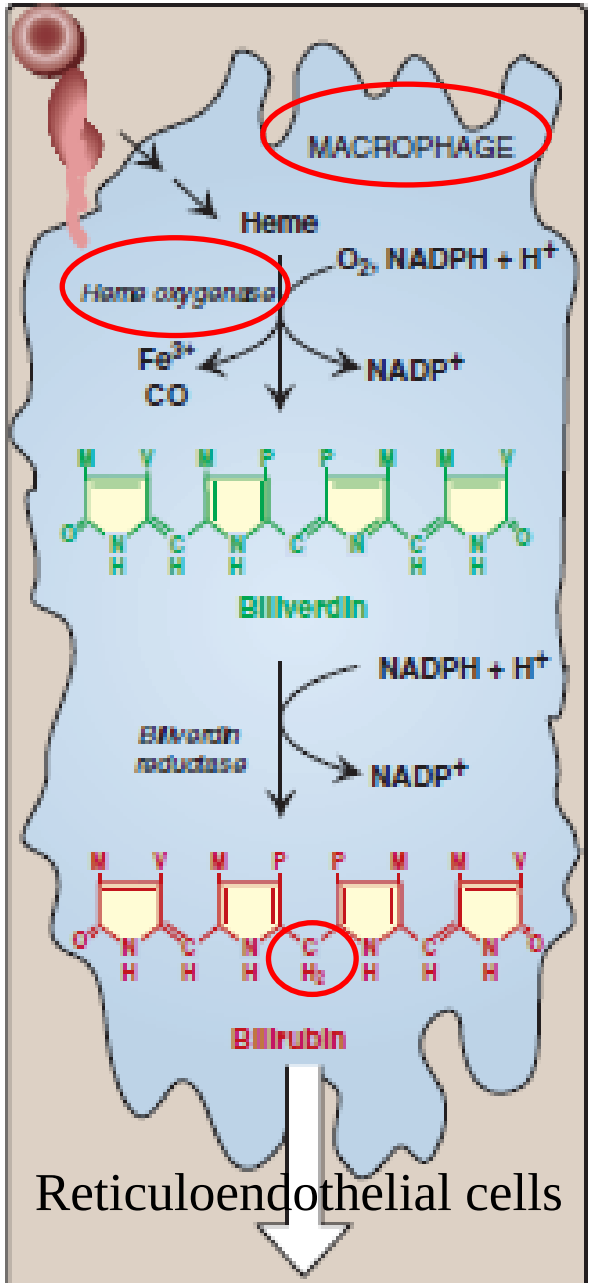
1. **Formation of bilirubin:**

A. Biliverdin formation by the addition of an OH to the methenyl bridge between two pyrrole rings, and then a second oxidation by the same enzyme system to cleave the porphyrin ring.

Products: the green pigment biliverdin, ferric iron (Fe3+) and CO

B. Biliverdin reduction to bilirubin (redorange)

Bilirubin and its derivatives are called bile pigments.
Bilirubin functions as an antioxidant (oxidized to biliverdin)



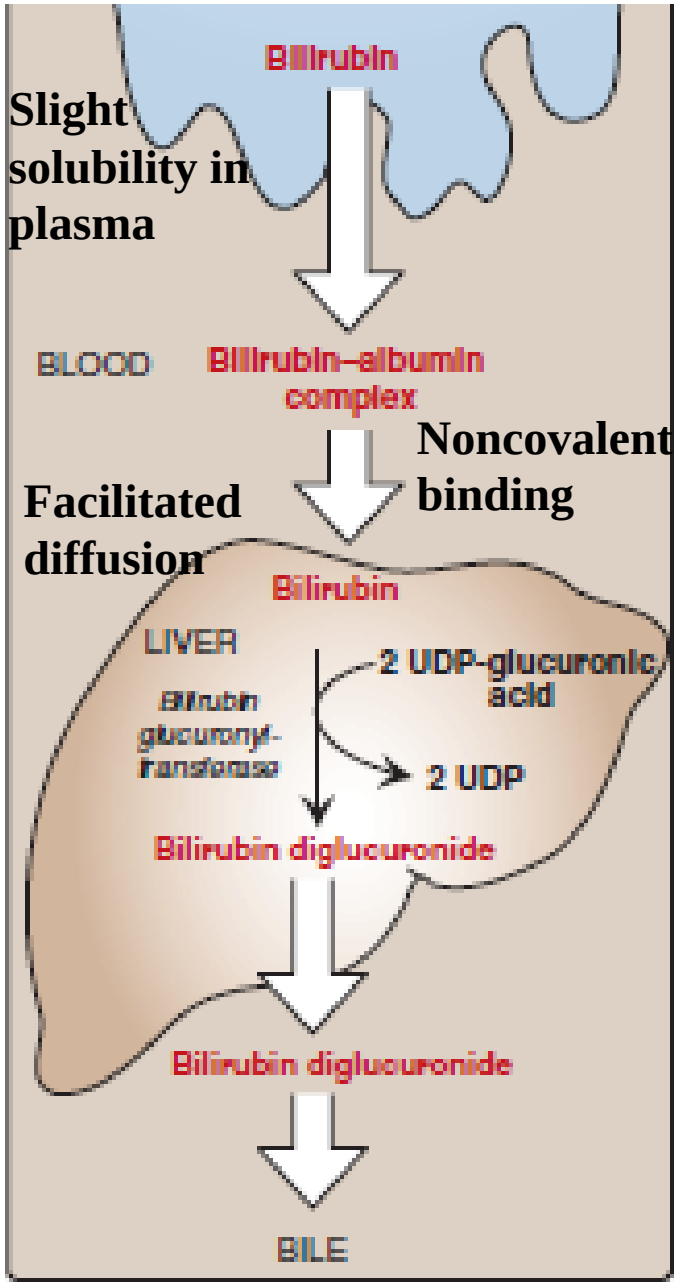
Heme Degradation

2. Uptake of bilirubin by the liver:

In hepatocytes, bilirubin binds to intracellular proteins, such as, ligandin.

3. Formation of bilirubin diglucuronide: two molecules of glucuronic acid are added to increase solubility (conjugation) by bilirubin glucuronyl-transferase

Deficiency of this enzyme results in Crigler-Najjar I and II (more severe) and Gilbert syndrome.



Heme Degradation

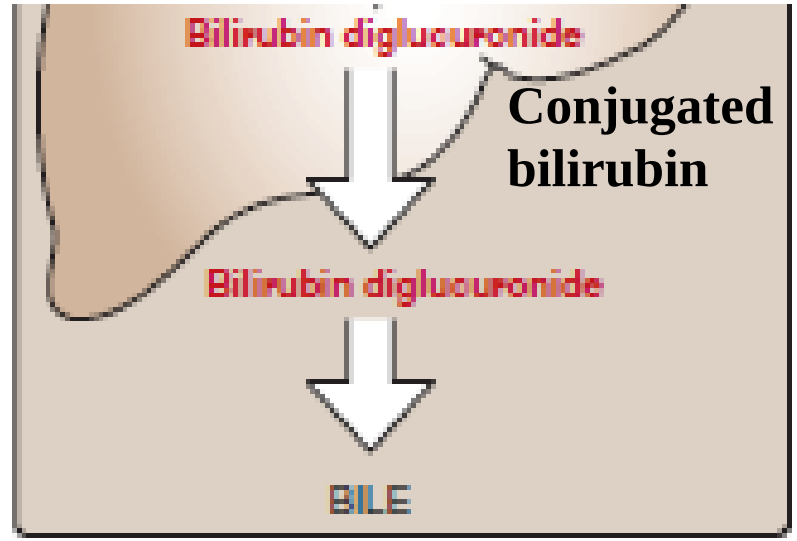
4. Secretion of bilirubin into bile:

Conjugated bilirubin is **actively transported** into the bile canaliculi and then into the bile.

The rate-limiting step (energy-requiring step).

Dubin-Johnson syndrome results from a deficiency in the transport protein of conjugated bilirubin.

Unconjugated bilirubin is normally not secreted.



Heme Degradation

5. Formation of urobilins in the intestine:

Bilirubin diglucuronide is hydrolyzed and reduced by bacteria in the gut to yield urobilinogen (colorless).

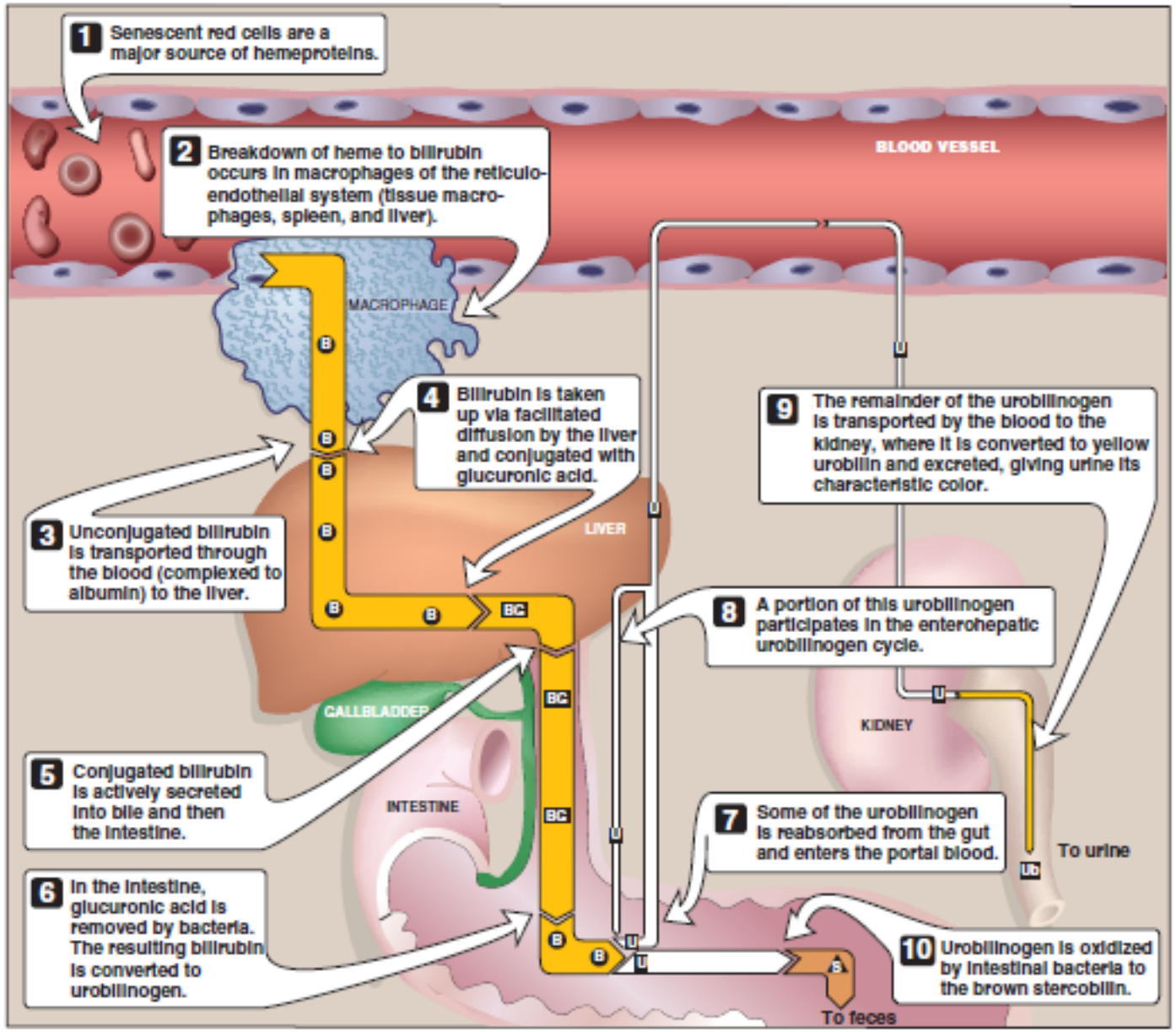
Urobilinogen fates:

1. Oxidation by intestinal bacteria to stercobilin (gives feces the characteristic brown color).

2. Reabsorption from the gut and entrance to the portal blood.

a. Some urobilinogen participates in the enterohepatic urobilinogen cycle where it is taken up by the liver, and then resecreted into the bile.
b. The remainder is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.

Catabolism of heme



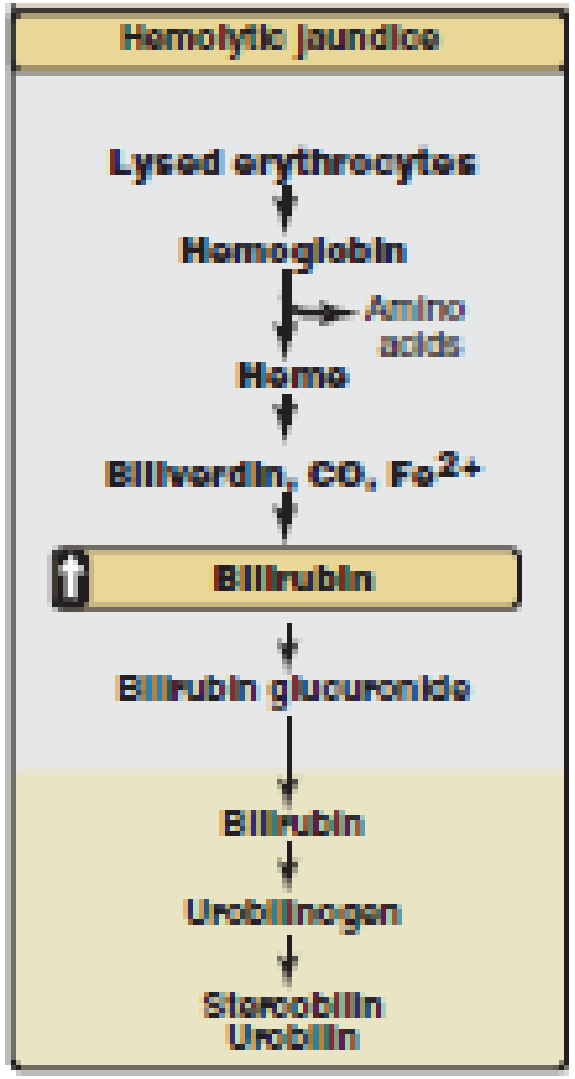
B = bilirubin; BC = bilirubin diglucuronide; U = urobilinogen; Ub = urobilin; S = stercobilin.

Jaundice

Jaundice (or icterus) is the yellow color of skin, nail beds, and sclera due to bilirubin deposition secondary to hyperbilirubinemia

Jaundice is a symptom not a disease

Types of Jaundice

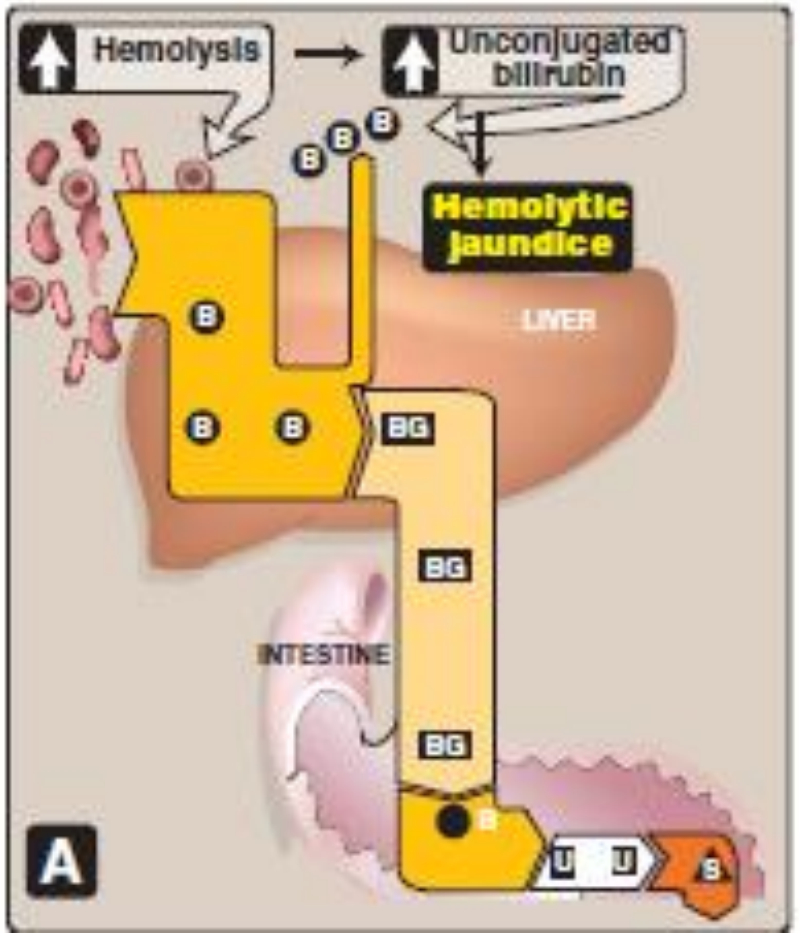


1. **Hemolytic jaundice:**

Bilirubin conjugation and execretion capacity of the liver is >3,000 mg/day

300 mg/day of bilirubin produced

Sickle cell anemia, pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency



BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

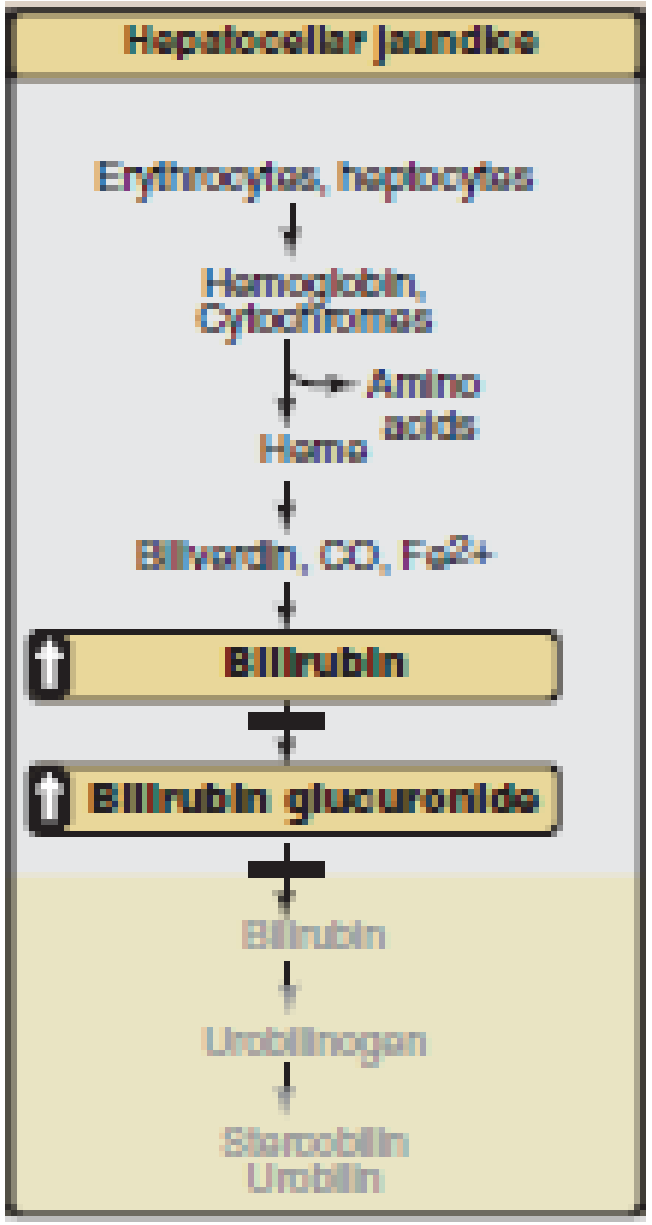
Types of Jaundice-cont

2. Hepatocellular jaundice due to damage to liver cells.

More unconjugated bilirubin levels in the blood

Urobilinogen is increased in the urine (the enterohepatic circulation is reduced) resulting in dark urine.

Stools may have a pale, clay color.



Types of Jaundice-cont

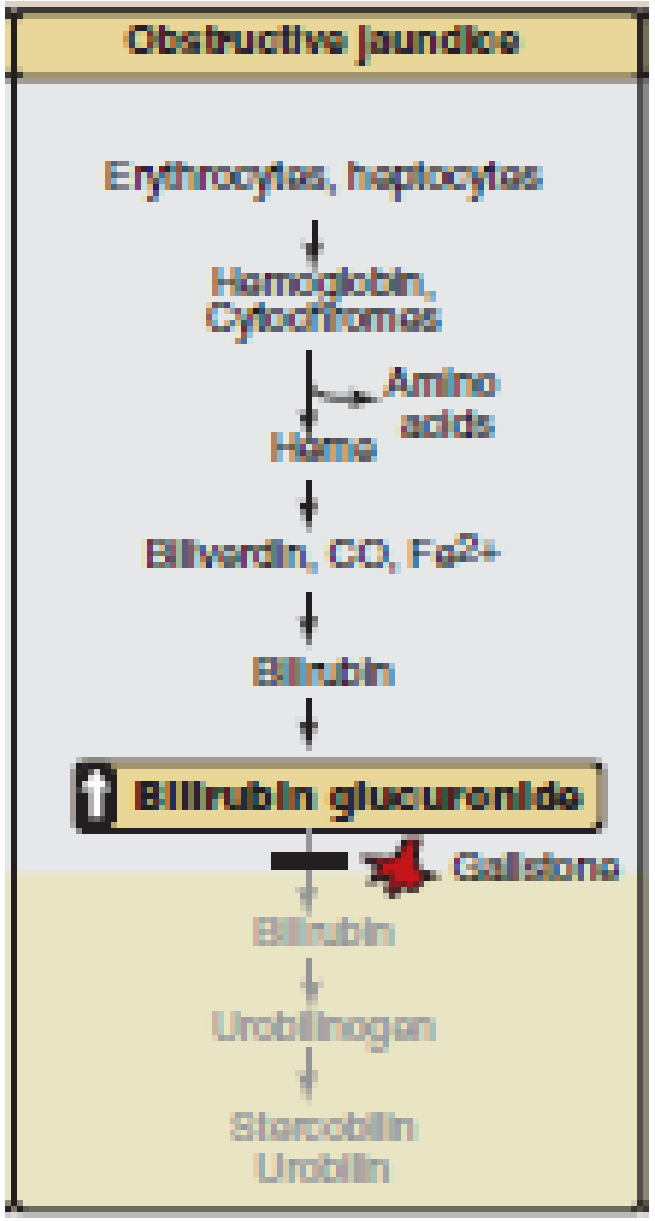
3. Obstructive jaundice: Obstruction of the bile duct (extrahepatic cholestasis) due to a tumor or bile stones, preventing bilirubin passage into the intestine.

No overproduction of bilirubin or decreased conjugation

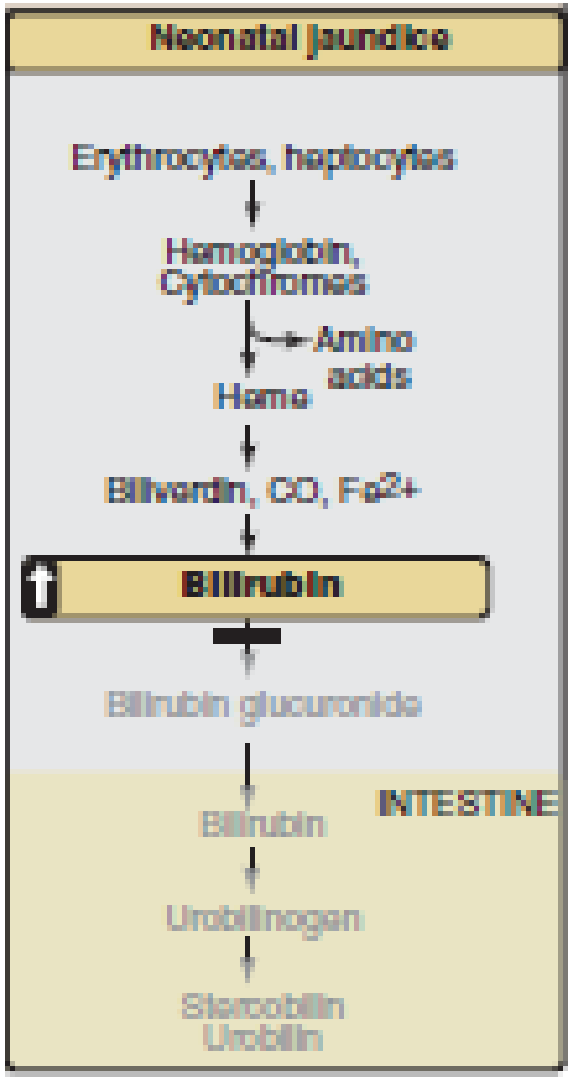
Signs and symptoms: GI pain and nausea, pale clay color stool, and urine that darkens upon standing.

Hyperbilirubinemia, bilirubin execretion in the urine, no urinary urobiloinogen.

Prolonged obstruction of the bile duct can damage the liver and increase unconjugated bilirubin



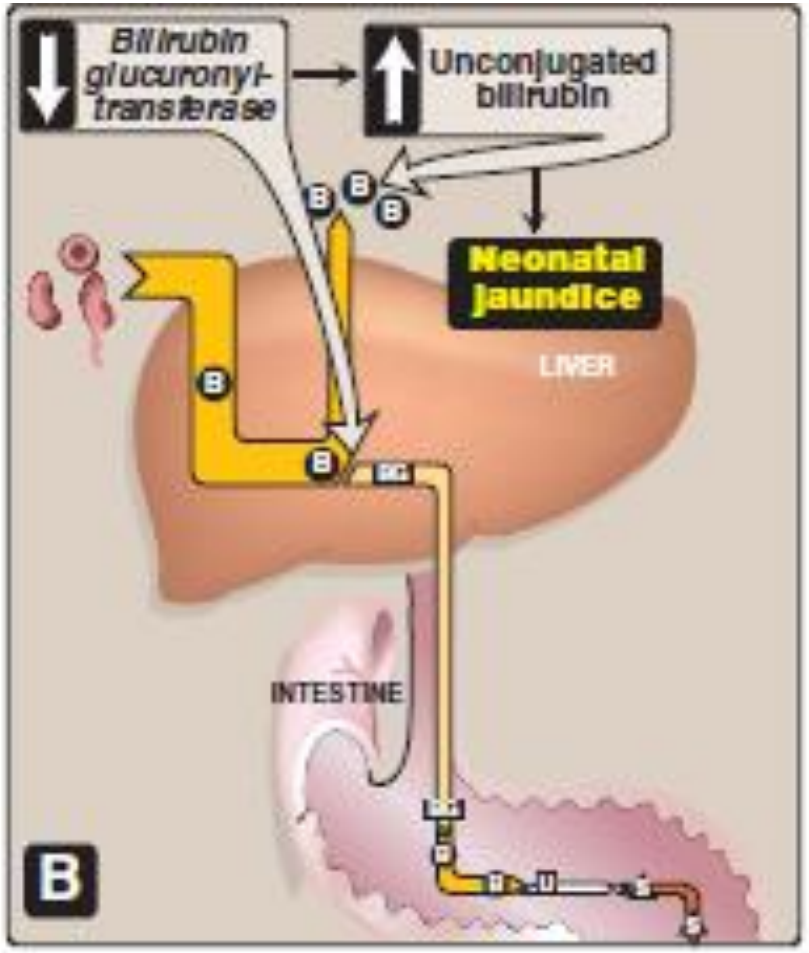
Jaundice in newborns



Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic bilirubin glucuronyltransferase is low at birth

Enzyme adult levels are reached in ~4 weeks

High bilirubin above the binding capacity of albumin, can diffuse into the basal ganglia and cause toxic encephalopathy (kernicterus).



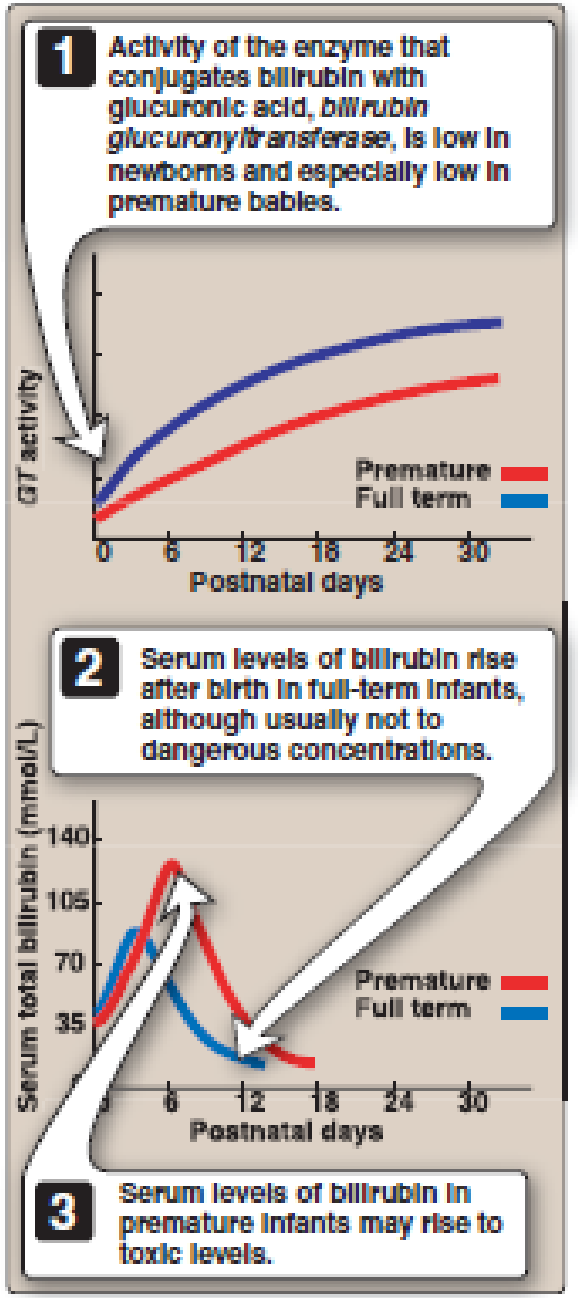
BG = bilirubin glucuronide; B = bilirubin; U = urobilinogen; S = stercobilin.

Jaundice in newborns

Treatment:

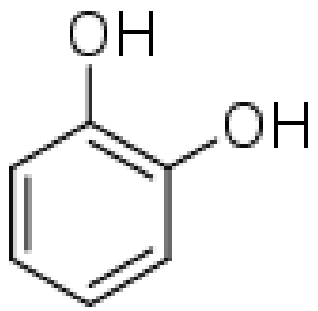
Blue fluorescent light that converts bilirubin to more polar water-soluble isomers.

The resulting photoisomers can be excreted into the bile without conjugation to glucuronic acid.

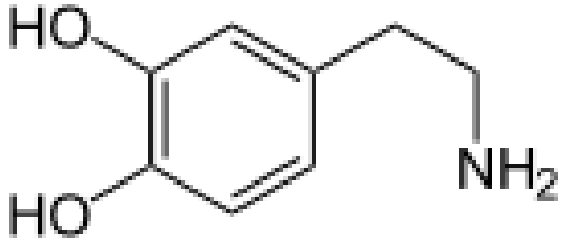


OTHER NITROGEN-CONTAINING COMPOUNDS

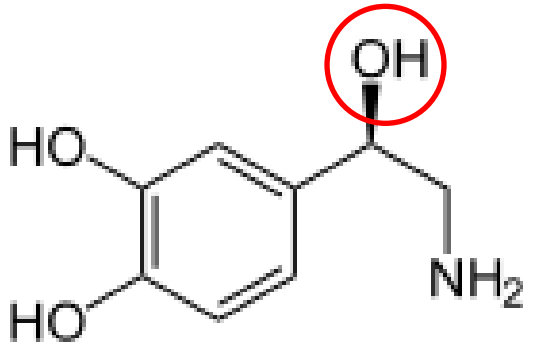
Catecholamines
(Dopamine, norepinephrine, and epinephrine)



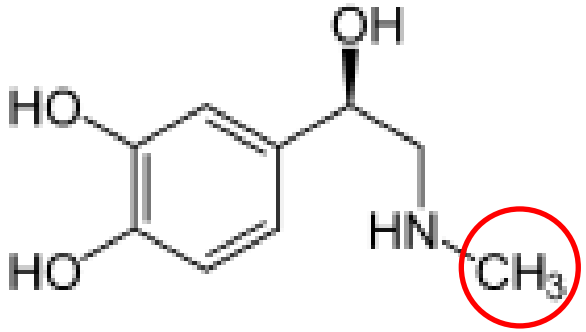
Catechol



Dopamine



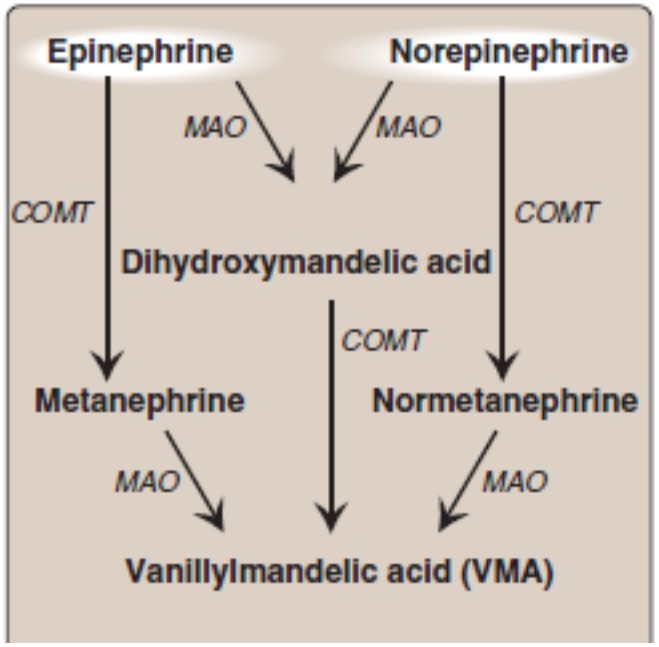
Norepinephrine

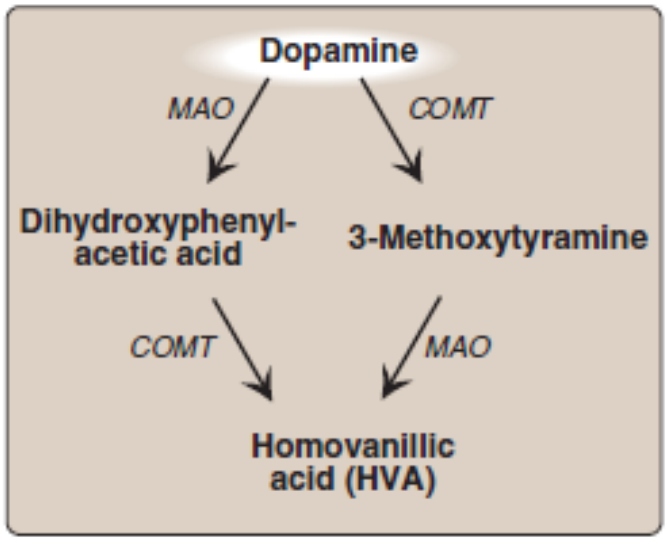


Epinephrine

From Tyrosine AA

Degradation of catecholamines





Catecholamine inactivation by:

A. Oxidative deamination catalyzed by monoamine oxidase (MAO)

A. O-methylation by catechol-O-methyltransferase (COMT) using SAM as the methyl donor

The aldehyde products of the MAO reaction are oxidized to the corresponding acids.

The metabolic products of these reactions (VMA, HVA) are excreted in the urine

VMA is increased with pheochromocytomas (adrenal tumor with increased catecholamine production).

Clinical Hint: MAO Inhibitors Antidepressants

MAO is found in neural and other tissues, such as the intestine and liver.

Neuron

MAO oxidatively deaminates and inactivates any excess neurotransmitters (norepinephrine, dopamine, or serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

MAO inhibitors

Irreversible or reversible MAO inactivation
Neurotransmitter molecules escape degradation, accumulate within the presynaptic neuron and leak into the synaptic space.

Activation of norepinephrine and serotonin receptors leads to the antidepressant action of MAO inhibitors

Histamine

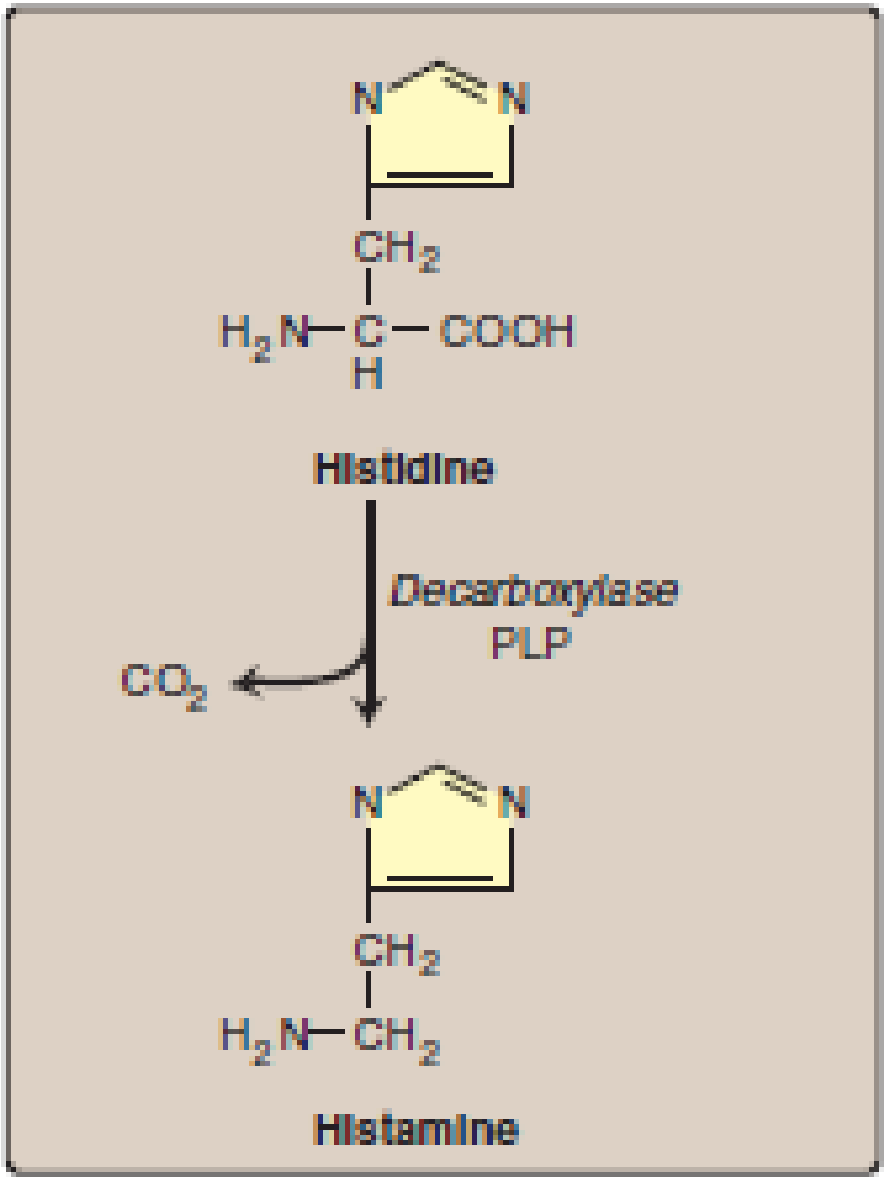
Histamine is a chemical messenger that mediates a wide range of cellular responses

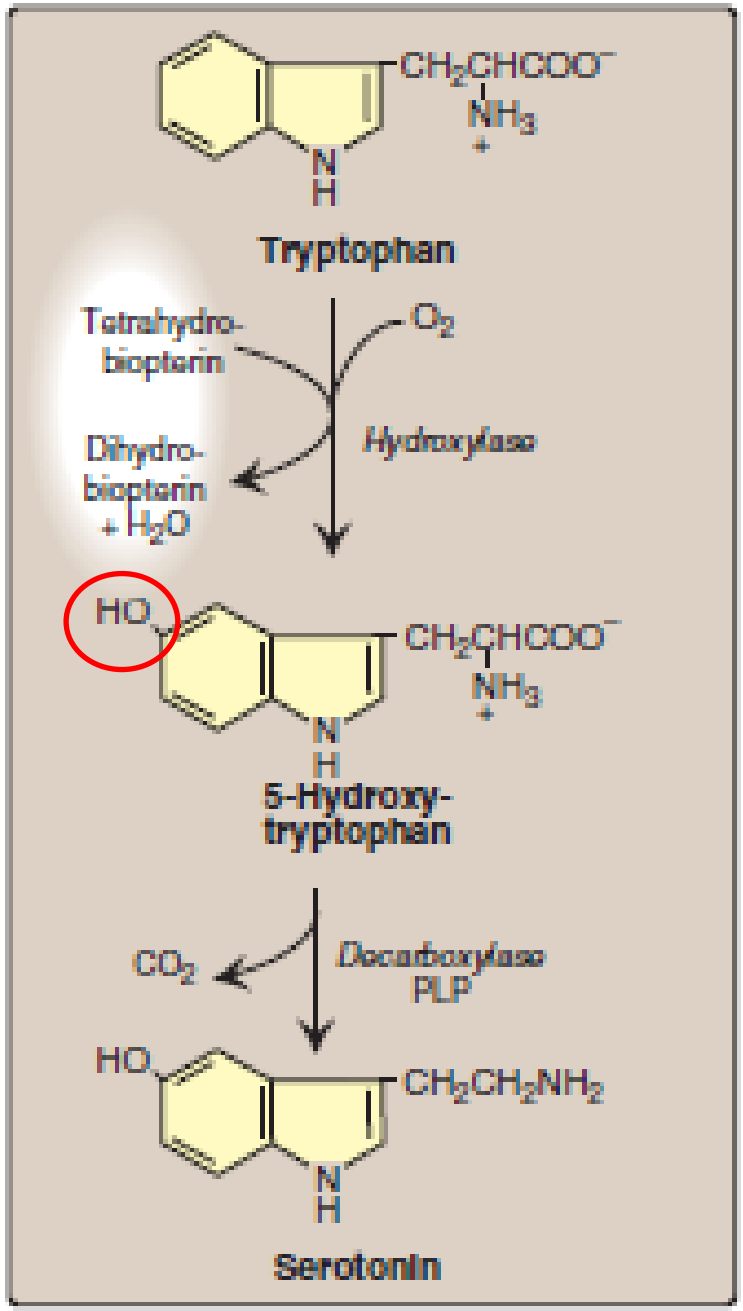
Roles include mediation of:
1. Allergic and inflammatory reactions
2. Gastric acid secretion
3. Neurotransmission in parts of the brain.

It is secreted by mast cells as a result of allergic reactions or trauma.

Histamine is a **vasodilator**

Histamine is formed by decarboxylation of **histidine** in a reaction requiring PLP





Serotonin, or 5-hydroxytryptamine (5HT)

Is synthesized and stored at several sites in the body, mostly in intestinal mucosal cells

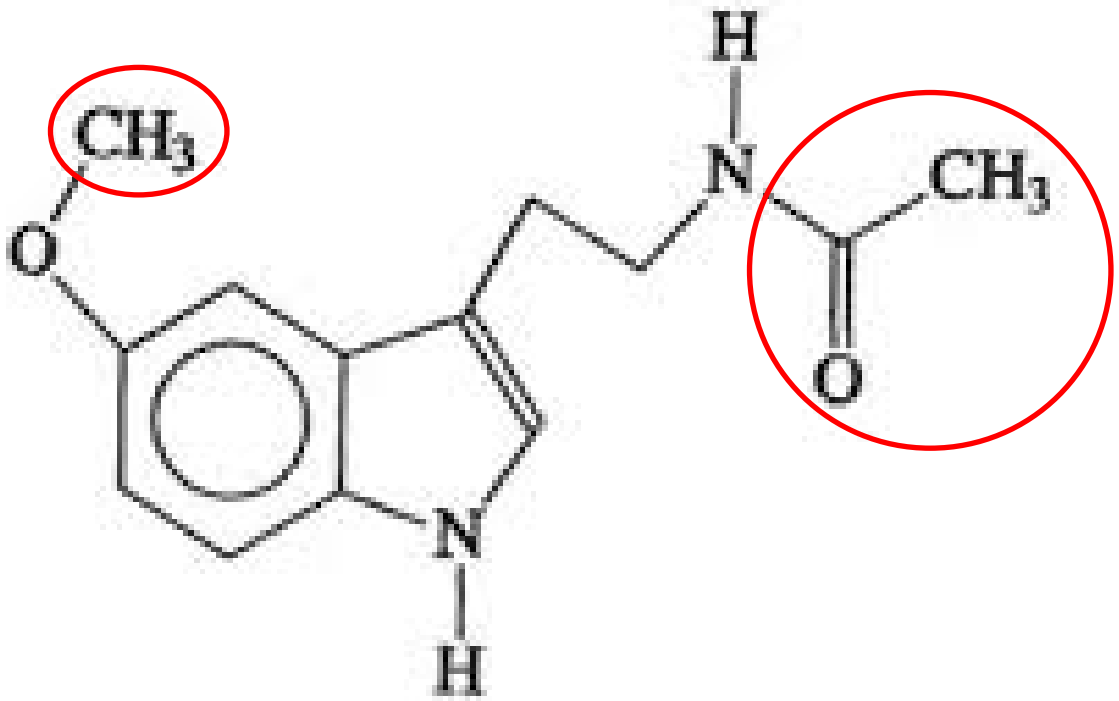
Smaller amounts in the CNS (functions as a neurotransmitter), and in platelets.

Physiologic roles are pain perception, regulation of sleep, appetite, temperature, blood pressure, cognitive functions, and mood (causes a feeling of well-being)

Melatonin Hormone (Sleep Hormone)

- ✓ Regulation of sleep wake cycle.
- ✓ Secreted in evening darkness.

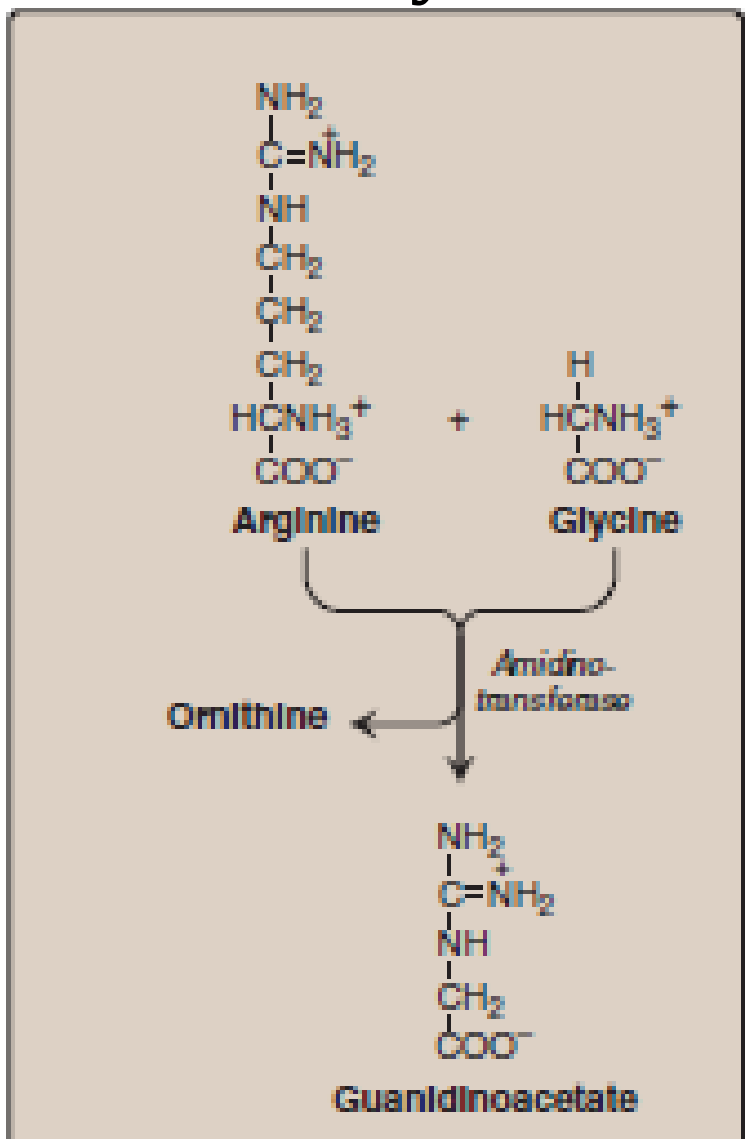
- ✓ Serotonin is converted to melatonin in the pineal gland via acetylation and methylation.

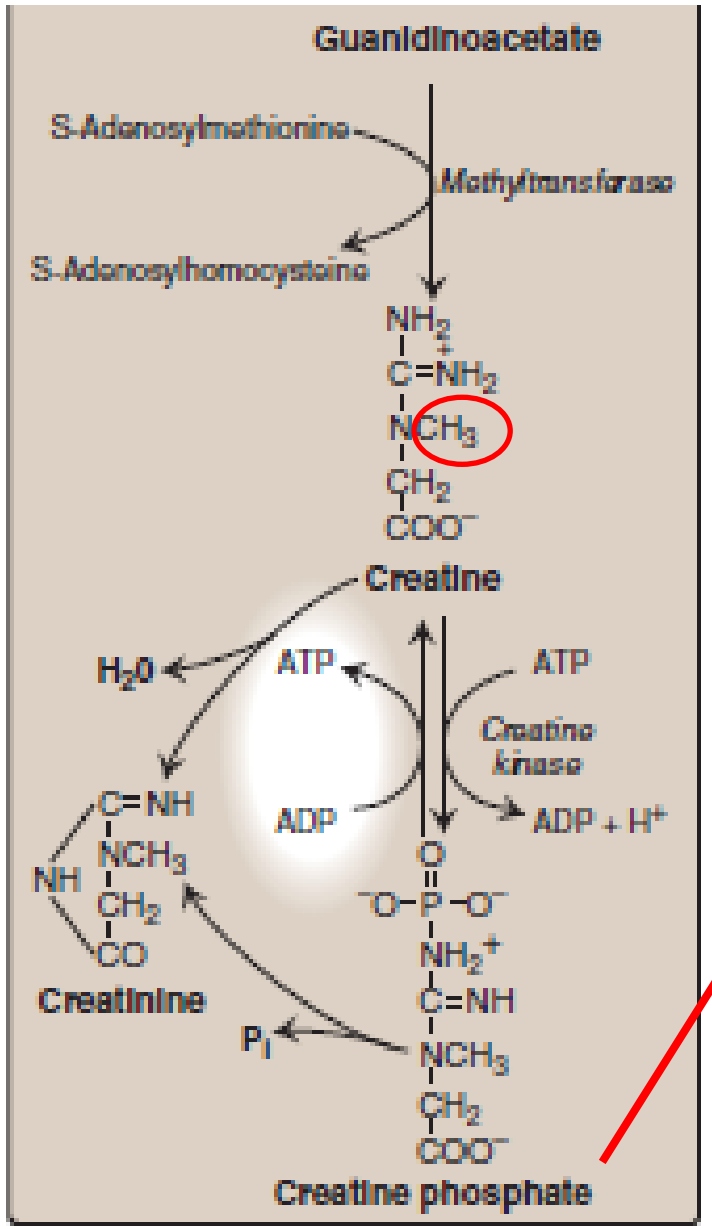


N-Acetyl-5-Methoxytryptamine (Melatonin)

Creatine

Creatine Synthesis





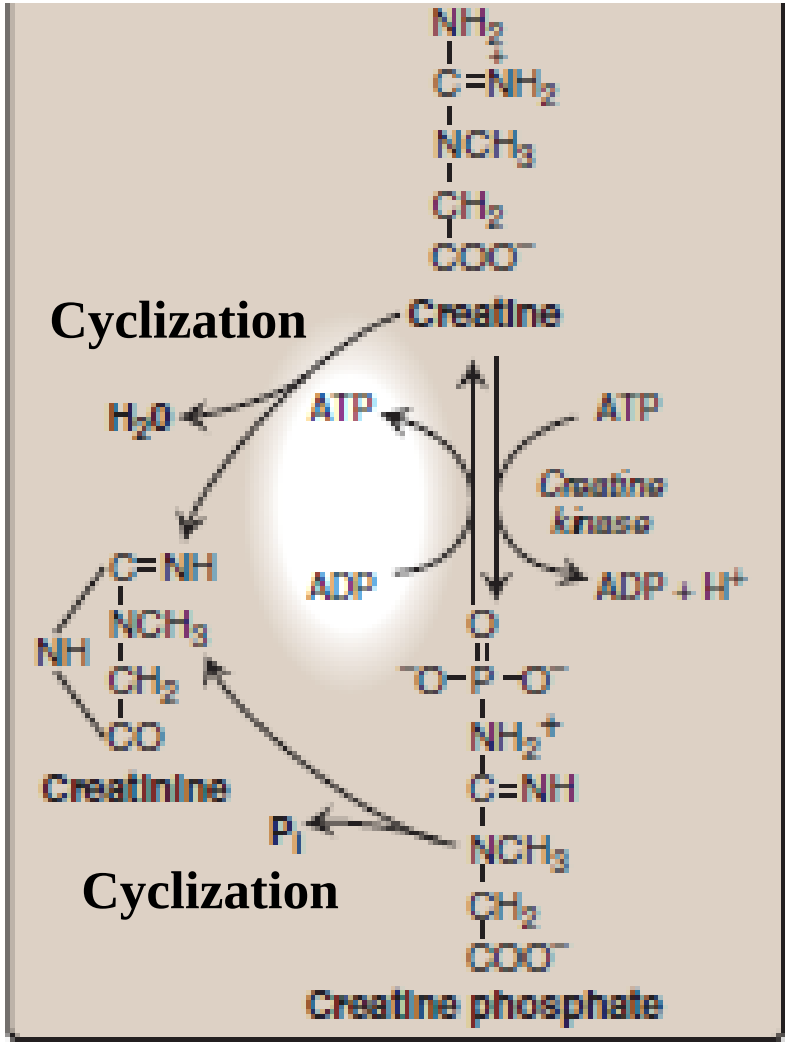
-The presence of creatine kinase in the plasma indicates heart damage, and is used in the diagnosis of MI

-The amount of creatine phosphate in the body is proportional to the muscle mass.

or phosphocreatine
a high-energy compound found in muscle and provides a small but rapidly mobilized reserve of high-energy phosphates

Creatine Degradation

- Creatinine is excreted in the urine.
- Excreted creatinine amount is proportional to the total creatine phosphate content of the body, and thus can be used to estimate muscle mass.
- When muscle mass decreases (paralysis or muscular dystrophy), the creatinine content of the urine falls.
- Rise in blood creatinine is a sensitive indicator of kidney malfunction
- A typical adult male excretes ~15 mmol of creatinine per day.



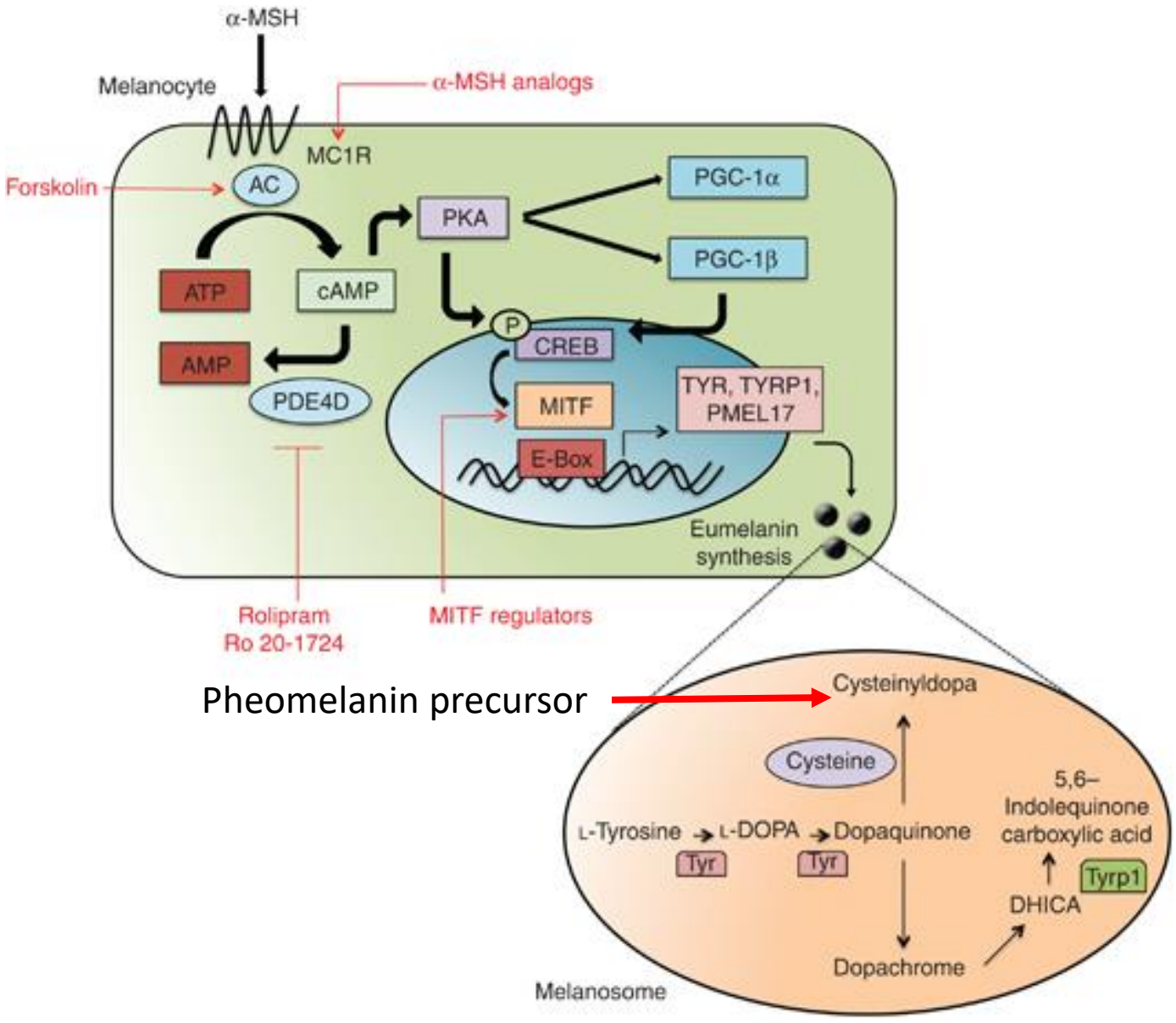
Melanin Pigment

A pigment in several tissues, particularly the eye, hair, and skin.

It is synthesized from tyrosine in the epidermis by melanocytes.

Melanin protects the underlying cells from the harmful effects of sunlight.

A defect in melanin production results in albinism (the most common form is due to defects in copper-containing tyrosinase)



Chen et al (2014)