SHEET NO. 24

METABOLISM

DOCTOR 2019 | MEDICINE | JU

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Heme degradation

- Approximately 85% of heme destined for degradation comes from senescent RBC. The remainder is from the degradation of hemeproteins other than Hb.

1.Bilirubin formation:

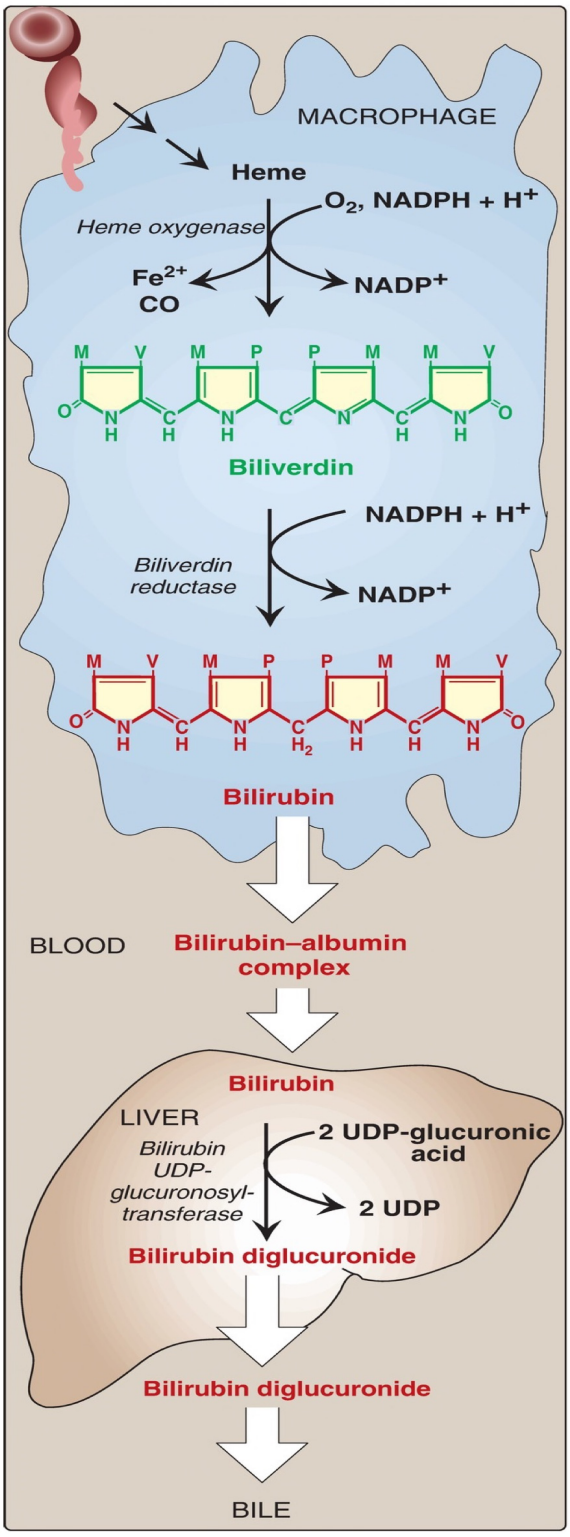
- The first step in the degradation of heme is catalyzed by microsomal **heme oxygenase** in macrophages .
- the enzyme degrade heme in three successive oxygenations (using NADPH as reducing agent and O2 as oxidising agent) that result in :

1- opening of the porphyrin ring (converting cyclic heme to linear **biliverdin**)
2- production of carbon monoxide (CO) and release of Fe2+

- Biliverdin, a green pigment, is reduced (using NADPH and biliverdin reductase) forming the **red-orange bilirubin**.

- Note: The changing colors of a bruise reflect the varying pattern of intermediates that occurs during heme degradation.

- this reaction occurs in both directions, and it is an oxidation reduction reaction, so Bilirubin functions at low levels as an antioxidant. In this role, it is oxidized to biliverdin, which is then reduced by biliverdin reductase, regenerating bilirubin.



Formation of bilirubin from heme and its conversion to bilirubin diglucuronide.

2. Bilirubin uptake by the liver

- Because bilirubin is only slightly soluble in plasma, it is transported through blood to the liver by binding **noncovalently to albumin**.

Note: Certain drugs such as aspirin can displace bilirubin from albumin, permitting bilirubin to enter the central nervous system (CNS). This causes the potential for neural damage in infants

- Bilirubin dissociates from the carrier albumin molecule, enters a hepatocyte via facilitated diffusion, and binds to intracellular proteins, particularly the protein ligandin.

3. Bilirubin diglucuronide formation:

• In the hepatocyte, bilirubin solubility is increased by the sequential addition of **two** molecules of **glucuronic acid** in a process called **conjugation**.

• The reactions are catalyzed by microsomal bilirubin UDP-glucuronosyltransferase (bilirubin UGT) using uridine diphosphate (UDP)-glucuronic acid as the glucuronate donor.
• The **bilirubin diglucuronide** product is referred to as **conjugated bilirubin** (CB)

• Note: Varying degrees of **deficiency of bilirubin UGT** result in Crigler-Najjar I and II and Gilbert syndrome, with Crigler- Najjar I being the most severe

4. Bilirubin secretion into bile:

- CB is **actively transported** against a concentration gradient into the bile canaliculi and then into the bile.
- this is **the rate limiting step.**

- Note: A rare deficiency in the protein required for transport of CB out of the liver results in Dubin-Johnson syndrome.

- Unconjugated bilirubin (UCB) is normally not secreted into bile.

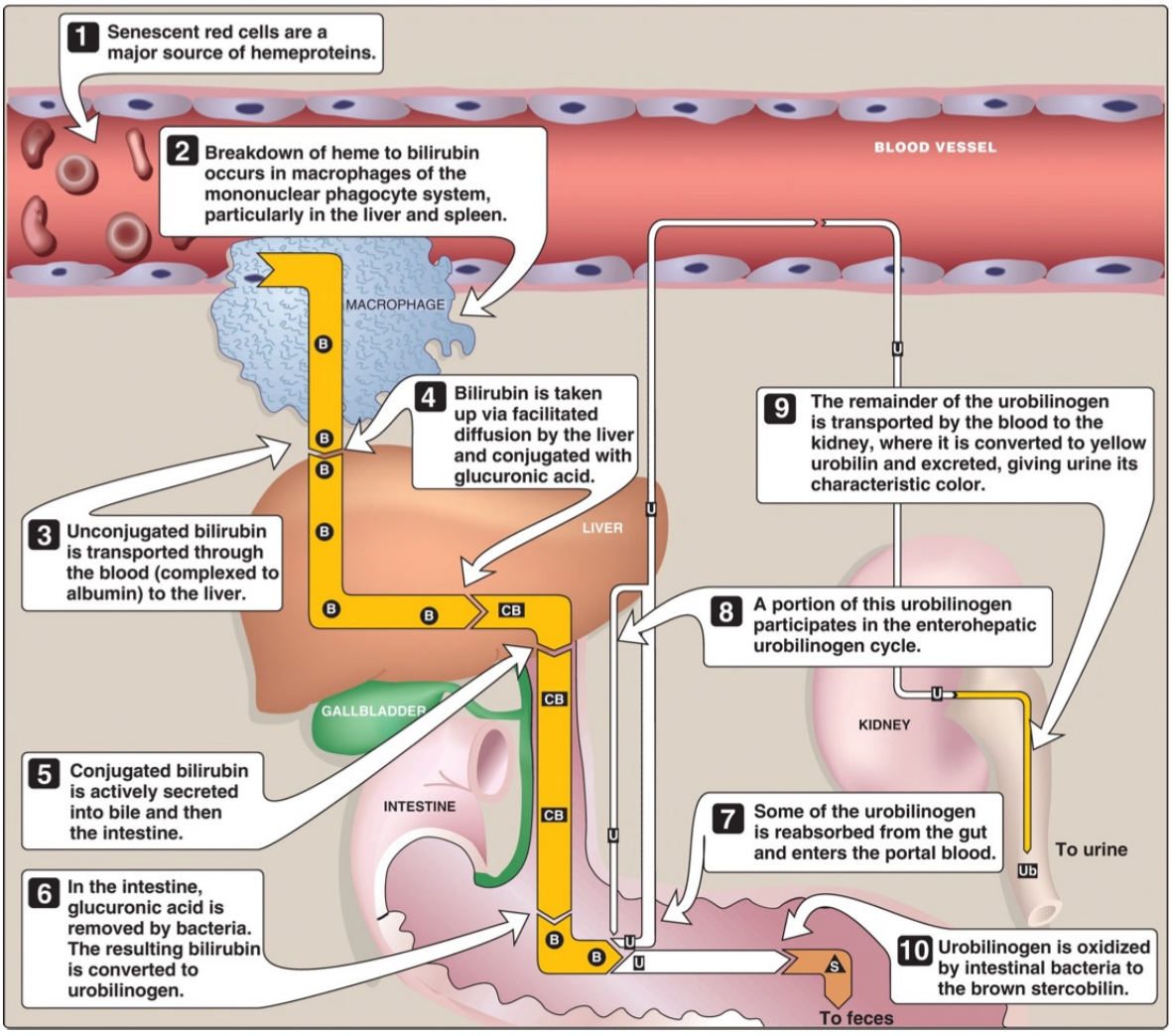
5. Urobilin formation in the intestine:

- CB is hydrolyzed and reduced by gut bacteria to yield urobilinogen, a colorless compound.
- bacteria will hydrolyse the glycosidic bond between bilirubin and glucuronic acid.

- Most of the urobilinogen is further oxidized by bacteria to stercobilin, which gives feces the characteristic brown color.

- However, some urobilinogen is reabsorbed from the gut and enters the portal blood reaching the liver again and then resecreted into the bile. (the enterohepatic urobilinogen cycle)

- The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted (by oxidation) to yellow urobilin and excreted, giving urine its characteristic color.

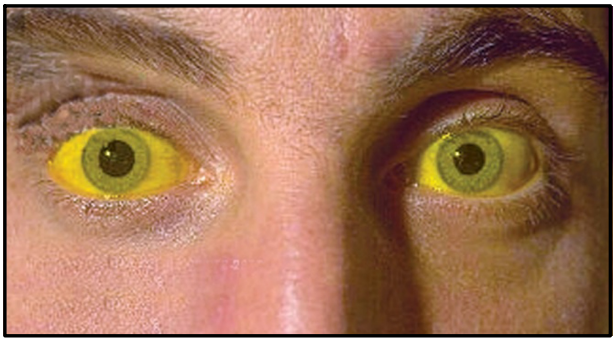


Catabolism of heme

Porphyrin metabolism

Jaundice

• Jaundice (or, icterus) refers to the yellow color of skin, nail beds, and sclerae (whites of the eyes) caused by bilirubin deposition .
• caused by increased bilirubin levels in the blood (hyperbilirubinemia).
• jaundice is not a disease, however it is usually a symptom of an underlying disorder
• Blood bilirubin levels are normally ≤1 mg/dl
• Jaundice is seen at 2–3 mg/dl.



Jaundiced patient with the sclerae of his eyes appearing yellow

Types

• jaundice can be classified into three major types

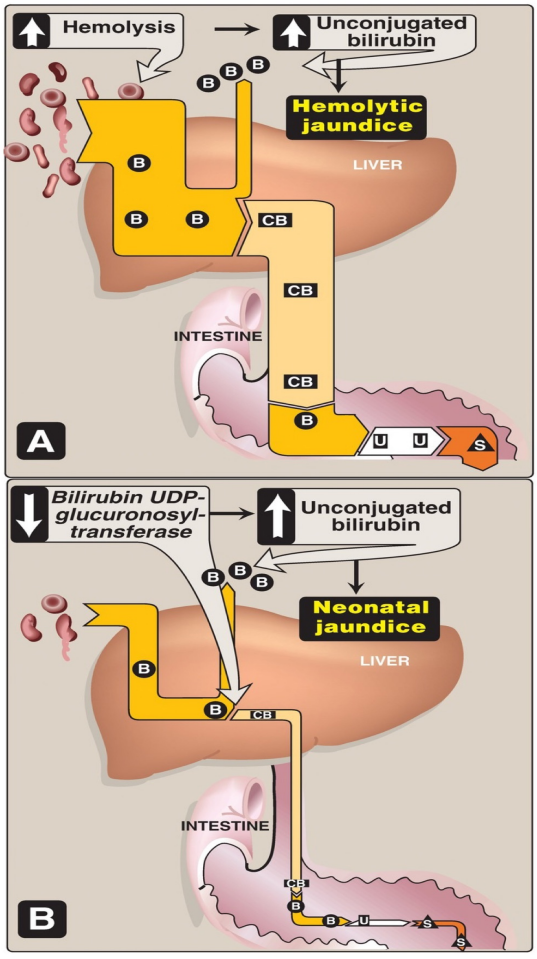
a. Hemolytic (prehepatic)

• The liver has the capacity to conjugate and excrete >3,000 mg of bilirubin/day whereas the normal production of bilirubin is only 300 mg/day.

• This excess capacity allows the liver to respond to increased heme degradation with a corresponding increase in conjugation and secretion of Conjugated bilirubin .

• However, extensive hemolysis (for example, in patients with sickle cell anemia or deficiency of pyruvate kinase or glucose 6-phosphate dehydrogenase) may produce bilirubin faster than it can be conjugated (exceeding the liver capacity)

• unconjugated bilirubin levels in the blood become elevated (unconjugated hyperbilirubinemia), causing **jaundice** .
• the conjugation process is efficient but the amount of bilirubin is large



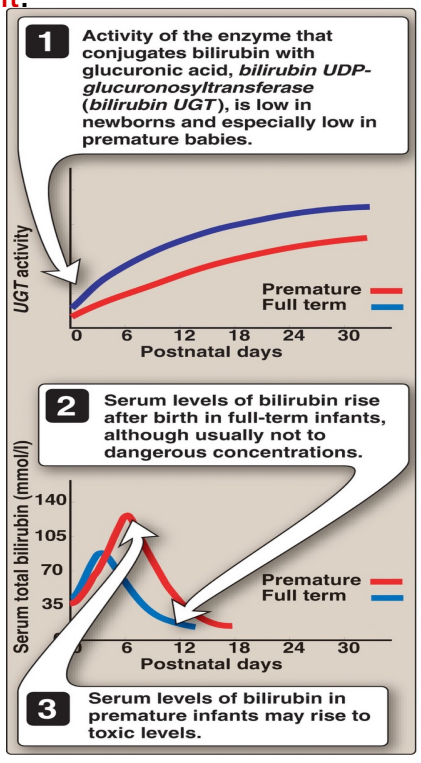
Note: With hemolysis, more Conjugated bilirubin is made and excreted into the bile, the amount of urobilinogen entering the enterohepatic circulation is increased, and urinary urobilinogen is increased

b. Hepatocellular (hepatic):

• Damage to liver cells (for example, in patients with cirrhosis or hepatitis) can cause unconjugated hyperbilirubinemia as a result of decreased conjugation.
• Urobilinogen is increased in the urine because hepatic damage decreases the enterohepatic circulation of this compound, allowing more to enter the blood, from which it is filtered into the urine
• The urine consequently darkens, whereas stools may be a pale, clay color.
• Plasma levels of alanine and aspartate transaminases (ALT and AST) respectively are elevated.
• If CB is made but is not efficiently secreted from the liver into bile (intrahepatic cholestasis), it can leak into the blood (regurgitation), causing a conjugated hyperbilirubinemia.

c. Obstructive (posthepatic):

• In this instance, jaundice is not caused by overproduction of bilirubin or decreased conjugation but, instead, results from obstruction of the common bile duct (extrahepatic cholestasis).
- For example, the presence of a tumor or bile stones may block the duct, preventing passage of CB into the intestine.
• Patients with obstructive jaundice experience GI pain and nausea and produce stools that are a pale, clay color.
• The CB regurgitates into the blood (conjugated hyperbilirubinemia).
• The CB is eventually excreted in the urine (which darkens over time) and is referred to as urinary bilirubin. Urinary urobilinogen is absent.



Jaundice in newborns

• Most newborn infants (60% of full term and 80% of preterm) show a rise in Unconjugated bilirubin in the first postnatal week because the activity of hepatic bilirubin UGT is low at birth .

• it is and a transient, physiologic jaundice

• the activity of hepatic bilirubin UGT reaches adult levels in about 4 weeks

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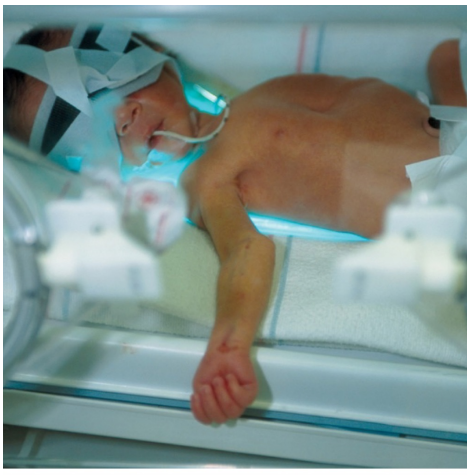
• Elevated unconjugated bilirubin , in excess of the binding capacity of albumin (20–25 mg/dl), can diffuse into the basal ganglia, causing toxic encephalopathy (kernicterus) and a pathologic jaundice
• Therefore, newborns with significantly elevated bilirubin levels are treated with blue fluorescent light (phototherapy),which converts bilirubin to more polar and, therefore, water-soluble isomers.
• These photoisomers can be excreted into the bile without conjugation to glucuronic acid.
• Note: Because of solubility differences, only Unconjugated bilirubin crosses the blood–brain barrier, and only conjugated bilirubin appears in urine.



Phototherapy in neonatal jaundice

❃ Bilirubin measurement

• Bilirubin is commonly measured by the van den Bergh reaction, in which diazotized sulfanilic acid reacts with bilirubin to form red azodipyrroles that are measured colorimetrically

• In aqueous solution, the water-soluble CB reacts rapidly with the reagent (within 1 minute) and is said to be direct reacting .The UCB (unconjugated bilirubin), which is much less soluble in aqueous solution, reacts more slowly. However, when the reaction is carried out in methanol, both CB and UCB are soluble and react with the reagent, providing the total bilirubin value. The indirect- reacting bilirubin, which corresponds to the UCB, is obtained by subtracting the direct-reacting bilirubin from the total bilirubin.

Note: In normal plasma, only ~4% of the total bilirubin is conjugated, or direct reacting, because most is secreted into bile.

Other nitrogen-conataining compounds

A. Catecholamines

• Dopamine, norepinephrine (NE), and epinephrine (or, adrenaline) are biologically active (biogenic) amines that are collectively termed catecholamines.

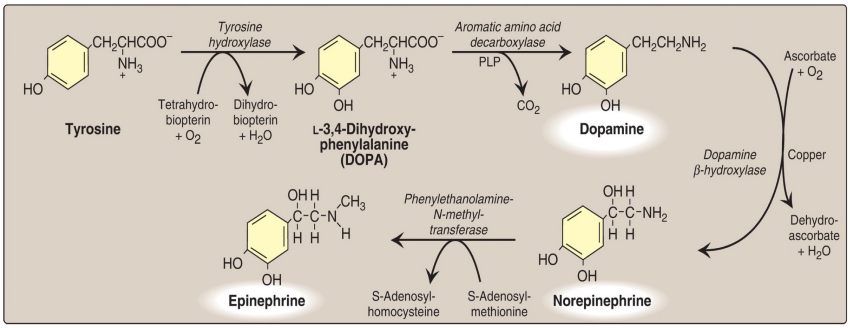
• Dopamine and NE are synthesized in the brain and function as neurotransmitters.
• Epinephrine is synthesized from NE in the adrenal medulla.

1.Function:
- Outside the CNS, NE and its methylated derivative, epinephrine, are hormone regulators of carbohydrate and lipid metabolism.
- NE and epinephrine are released from storage vesicles in the adrenal medulla in response to fright, exercise, cold, and low levels of blood glucose.

- They increase the degradation of glycogen and triacylglycerol as well as increase blood pressure and the output of the heart. These effects are part of a coordinated response to prepare the individual for stress and are often called the “fight-or-flight” reactions.

2. Synthesis

• The catecholamines are synthesized from tyrosine
• Tyrosine is first hydroxylated by tyrosine hydroxylase to form L-3,4-**dihydroxyphenylalanine** (DOPA)
• The tetrahydrobiopterin (BH4)-requiring enzyme catalyzes the rate- limiting step of the pathway.
• DOPA is decarboxylated to form dopamine, which is hydroxylated by dopamine β-hydroxylase to yield NE in a reaction that requires ascorbic acid (vitamin C) and copper.
• Epinephrine is formed from NE by an N-methylation reaction using S-adenosylmethionine (SAM) as the methyl donor



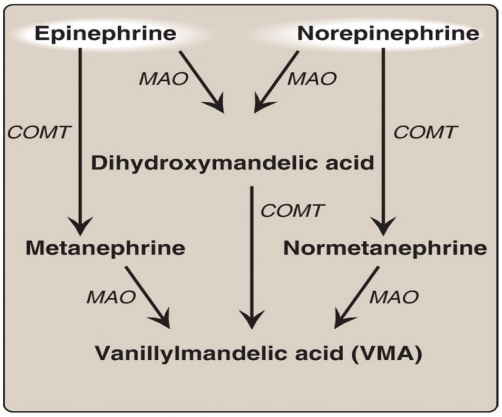
Synthesis of catecholamines

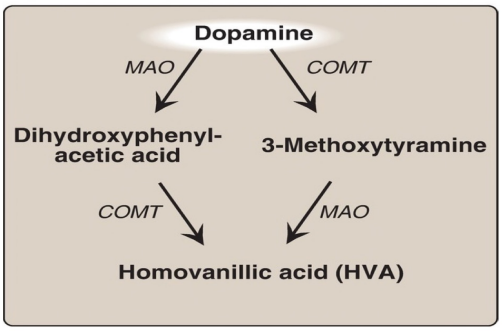
Parkinson disease
• a neurodegenerative movement disorder.
• occurs due to insufficient dopamine production as a result of the idiopathic loss of dopamine-producing cells in the brain.
• Administration of L-DOPA (levodopa) is the most common treatment, because dopamine cannot cross the blood–brain barrier.

3. Degradation

• The catecholamines are inactivated by oxidative deamination catalyzed by **monoamine oxidase (MAO)** and by O- methylation catalyzed by **catechol-O-methyltransferase (COMT)** using SAM as the methyl donor.
• The reactions can occur in either order.
• The aldehyde products of the MAO reaction are oxidized to the corresponding acids.
• The products of these reactions are excreted in the urine as vanillylmandelic acid (VMA) from epinephrine and NE and homovanillic acid (HVA) from dopamine.

Pheochromocytomas:
- rare tumors of the adrenal gland characterized by excessive production of catecholamines.
- VMA and the metanephrines are increased with pheochromocytomas





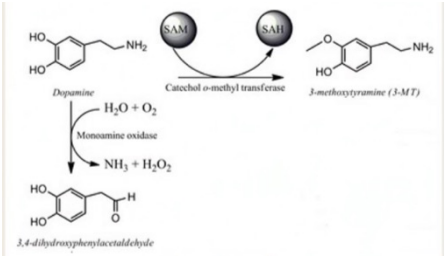
Metabolism of the catecholamines by catechol-O-methyltranferase (COMT) and monoamine oxidase (MAO).

Monoamine oxidase inhibitors :

• MAO inhibitors (MAOI) may irreversibly or reversibly inactivate the enzyme

• this permits neurotransmitter molecules to escape degradation and, therefore, they accumulate within the presynaptic neuron and to leak into the synaptic space.

• This causes activation of NE and serotonin receptors and may be responsible for the antidepressant action of MAOI.

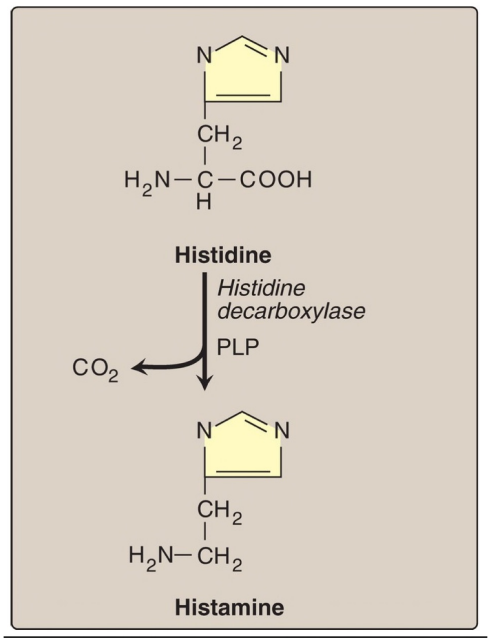


B. Histamine

• Histamine is a chemical messenger that mediates allergic and inflammatory reactions and gastric acid secretion.
• It is a powerful vasodilator.

• histamine is formed by decarboxylation of histidine in a reaction requiring PLP.

• Histamine has no clinical applications, but agents that interfere with the action of histamine have important therapeutic applications. (Antihistamines)



C. Serotonin

• Serotonin also called 5-hydroxytryptamine (5-HT)
• is synthesized and/or stored at several sites in the body.

• The largest amount by far is found in the intestinal mucosa. Smaller amounts occur in the CNS.

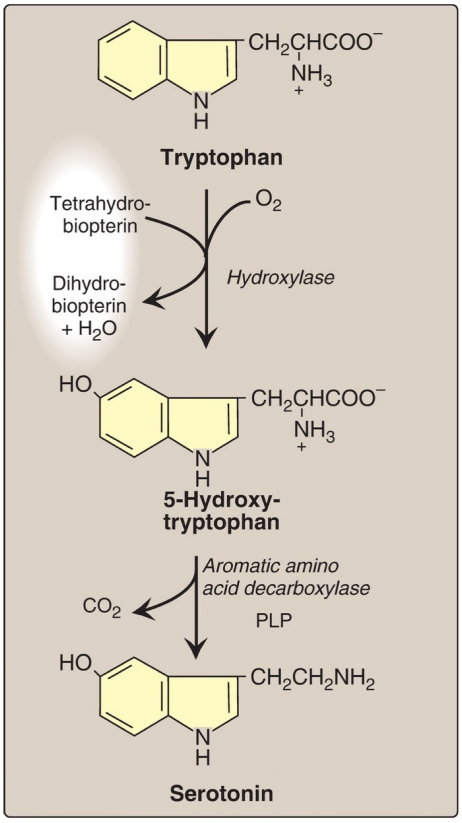
• Serotonin is synthesized from tryptophan, which is hydroxylated in a BH4-requiring reaction

• The product, 5-hydroxytryptophan, is decarboxylated to 5- HT (serotonin)

• Serotonin has multiple physiologic roles including pain perception and regulation of sleep.

• Note: Selective serotonin reuptake inhibitors (SSRI) maintain serotonin levels, thereby functioning as antidepressants.

• Serotonin is degraded by MAO to 5- hydroxy-3-indoleacetic acid (5-HIAA).



D. Creatine

• Creatine phosphate is also called phosphocreatine is :
- the phosphorylated derivative of creatine
- found in muscle
- a high-energy compound that provides a small but rapidly mobilized reserve of high-energy phosphates that can be reversibly transferred to adenosine diphosphate to maintain the intracellular level of 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.

1. Synthesis

- Creatine is synthesized in the liver and kidneys .
- it is synthesized from glycine and the guanidino group of arginine, plus a methyl group from SAM
- Creatine is reversibly phosphorylated to creatine phosphate by creatine kinase, using ATP as the phosphate donor.

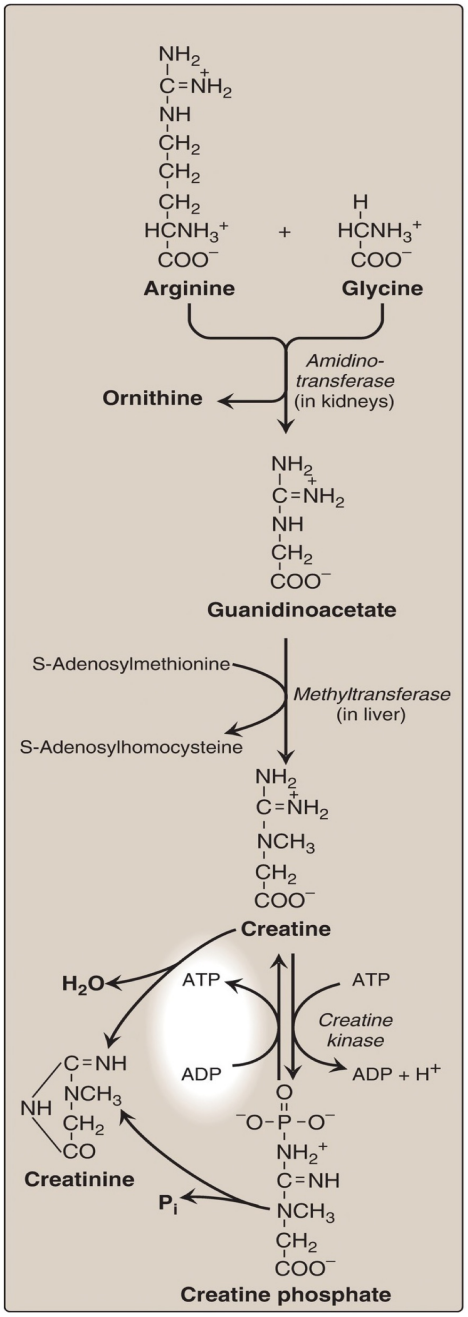
- Note: The presence of creatine kinase (MB isozyme) in the plasma is indicative of heart damage and is used in the diagnosis of myocardial infarction

2. Degradation

- Creatine and creatine phosphate spontaneously cyclize at a slow but constant rate to form creatinine, which is excreted in the urine .

- The amount excreted is proportional to the total creatine phosphate content of the body and, therefore, can be used to estimate muscle mass

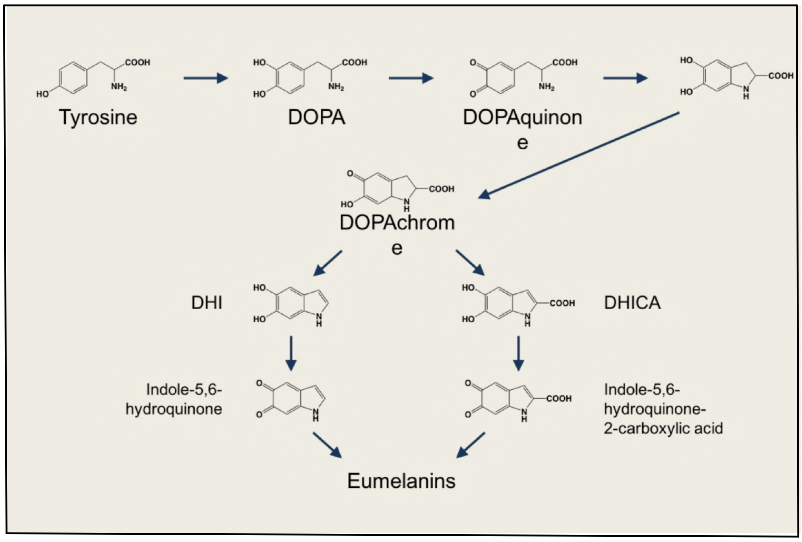
- A typical adult male excretes ~1–2 g of creatinine/day.



Synthesis of creatine

E. Melanin

- Melanin is a pigment that occurs in several tissues, particularly the eye, hair, and skin.
- It is synthesized from **tyrosine** in melanocytes (pigment- forming cells) of the epidermis.
- It functions to protect underlying cells from the harmful effects of sunlight



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استشعروا رقابة رب العالمين واتذكروا :

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