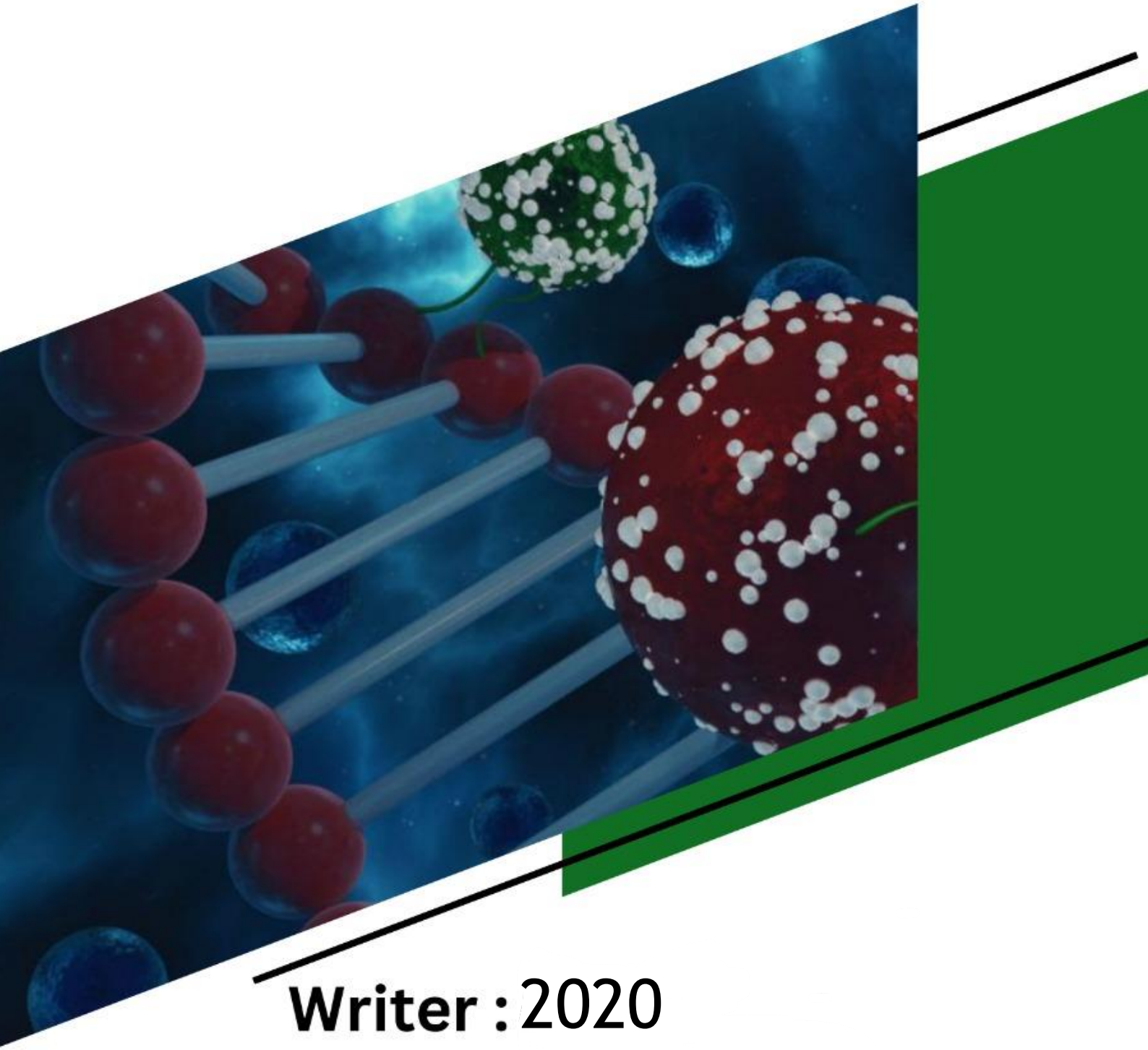
Doctor 021

# METABOLISM

## Sheet no.32



Writer : 2020

Corrector :2021

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# Jaundice

اليرقان **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**

**Jaundice has different types due to causes that result in this symptom:**

## -- Types of Jaundice

### 1. Hemolytic jaundice:

**More hemolysis→more unconjugated bilirubin in the liver→hemolytic jaundice**

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

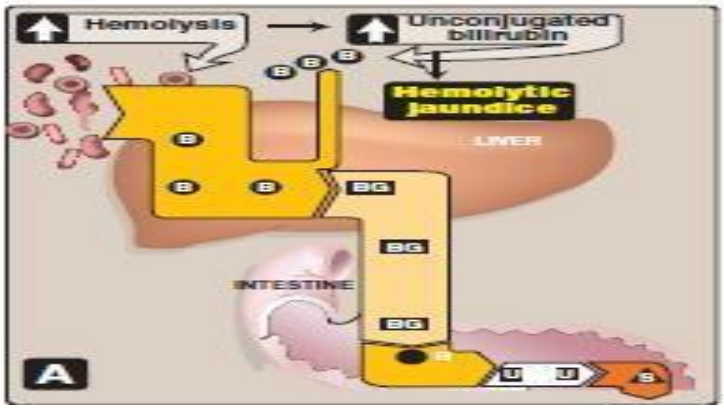
**If there is more bilirubin, this will result in accumulation of unconjugated ones.**

**300 mg/day of bilirubin produced**

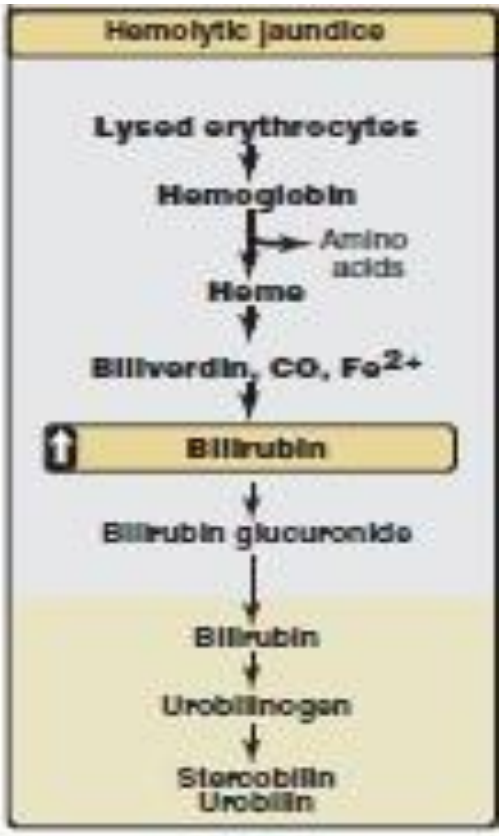
**Diseases that are related to this type of jaundice:**

**Sickle cell anemia→more hemolysis process beyond the capacity of the liver**

**pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency**




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



## 2. Hepatocellular jaundice

**due to damage to liver cells**

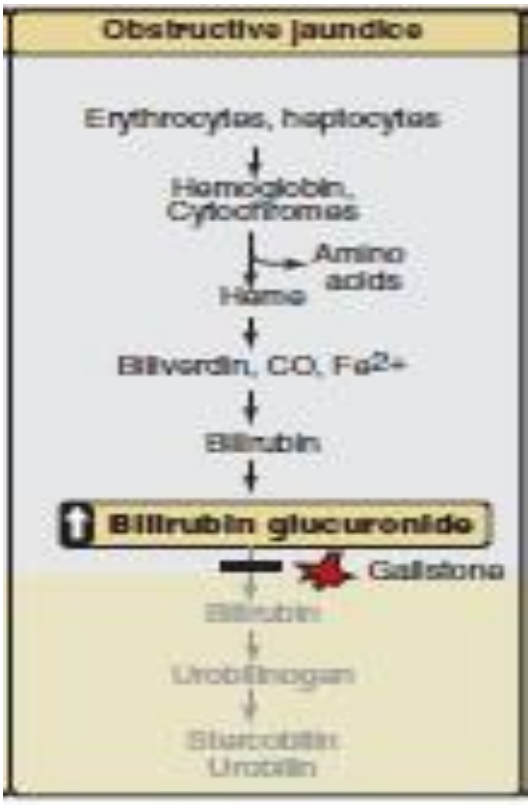

**more destruction of the liver→**

**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.**

## 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.**

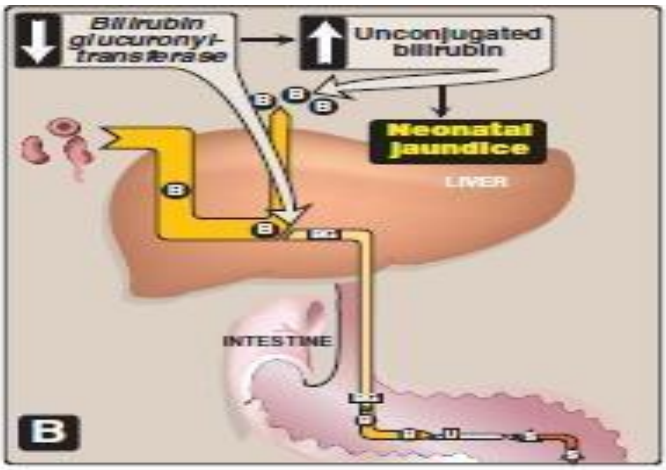
**Hyperbilirubinemia, bilirubin execretion in the urine, no urinary urobiloinogen.**

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

***Note: conjugated and unconjugated bilirubin can cause jaundice.**

## Jaundice in newborns especially in preterm newborns

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




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

**Enzyme adult levels are reached in ~4 weeks (so it is just a time issue)**

**It depends on degree or level of bilirubin,**

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

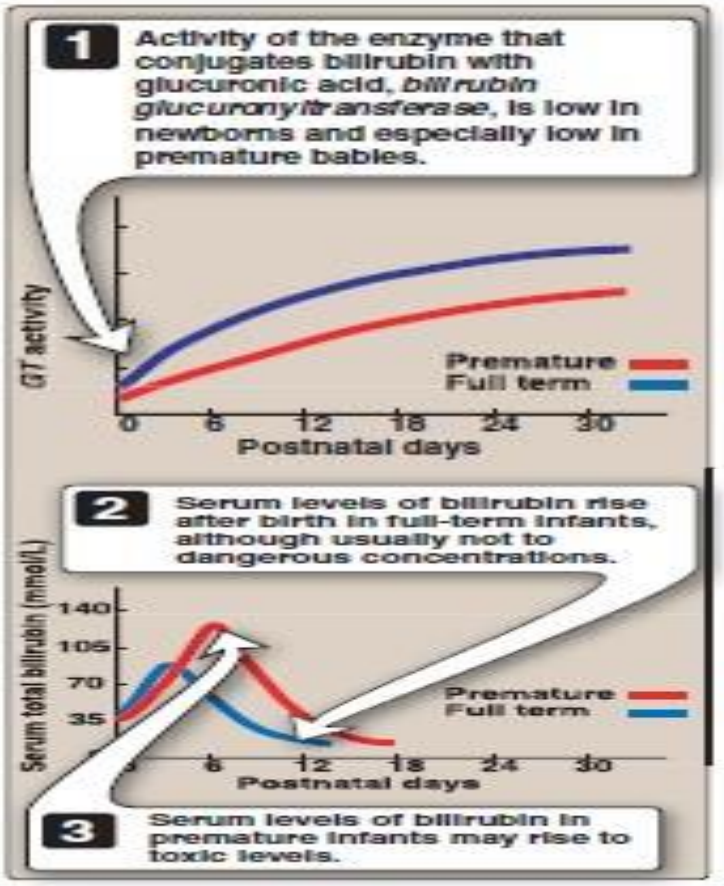

**So, our concern about newborns is not to pass their BBB by bilirubin.**

صلِّ على النبي

**In incubator, blue fluorescent light is used that converts unconjugated bilirubin to more polar water-soluble isomers.**

**(notice that their eyes are covered)**

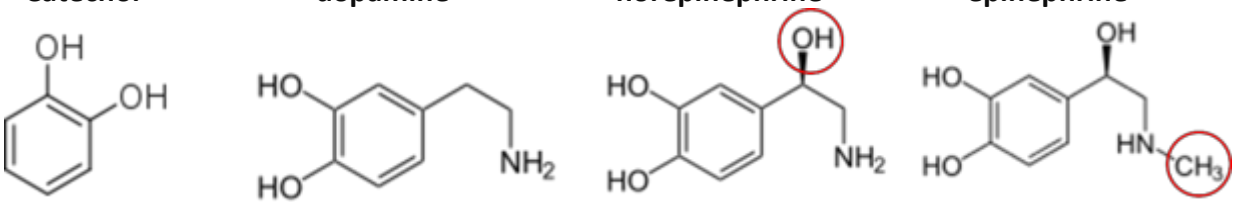
**The resulting photoisomers can be excreted into the bile without conjugation to glucuronic acid.**



# NITROGEN CONTAINONG COMPOUNDS

## Catecholamines:

**Catechol** **dopamine** **norepinephrine** **epinephrine**




- Includes dopamine, norepinephrine, and epinephrine. They are all derived from AA tyrosine and contain amine group.
- Dopamine and norepinephrine considered as neurotransmitters while epinephrine considered as a hormone.

**SYNTHESIS OF CATECHOLAMINES**: They are produced by several successive reactions so that each substance produced is the reactant for the reaction that follows. Starting with a **tyrosine AA** that is hydroxylated by **tyrosine hydroxylase** enzyme producing **the catechol ring** (benzene ring with tow hydroxyl group in tow adjacent carbons). Further reactions occur to the catechol ring by adding ethylamine producing **dopamine**. Dopamine is hydroxylated on the ethylamine sidechain producing **norepinephrine**. Finally, norepinephrine is methylated by **methyl transferase** producing **epinephrine.**

**DEGRADATION OF CATECHOLAMINES:**

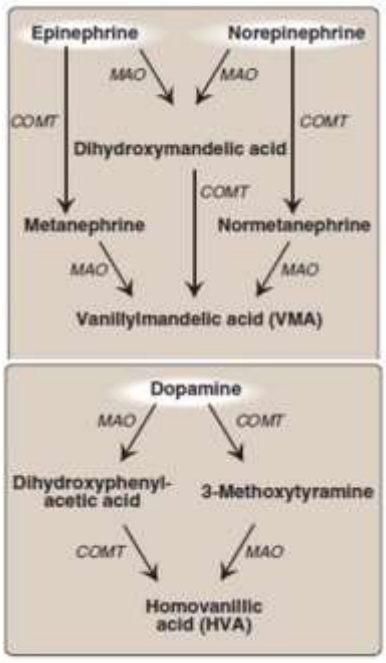
Catecholamines are degraded by to mechanisms:

1) Oxidative deamination catalyzed by **monoamine oxidase (MAO)**

2) O-methylation by **Catechol-O-methyltransferase (COMT)** using **SAM** as the methyl donor. (MAO and COMT work in complementary way to each other).

Further explanation: If we start degradation of Epinephrine by COMT it we give us Metanephrine, after that MAO will work and give us VMA, but if we start the degradation by MAO we will have Dihydoxymandelic Acid as an intermediate, then COMT will give us VMA.

Notice from this example that if we start with different enzymes, we will get different intermediates, but because of the **complementary**



**between COMT and MAO** we will end up with the Same final product. (Intermediates aren't required only the final product).

**<u>The final product</u> for the degradation of epinephrine and norepinephrine via MAO and COMT is vanillylmandelic acid (VMA)**

**<u>The final product</u> for the degradation of dopamine via MAO and COMT is homovanillic acid (HVA).**

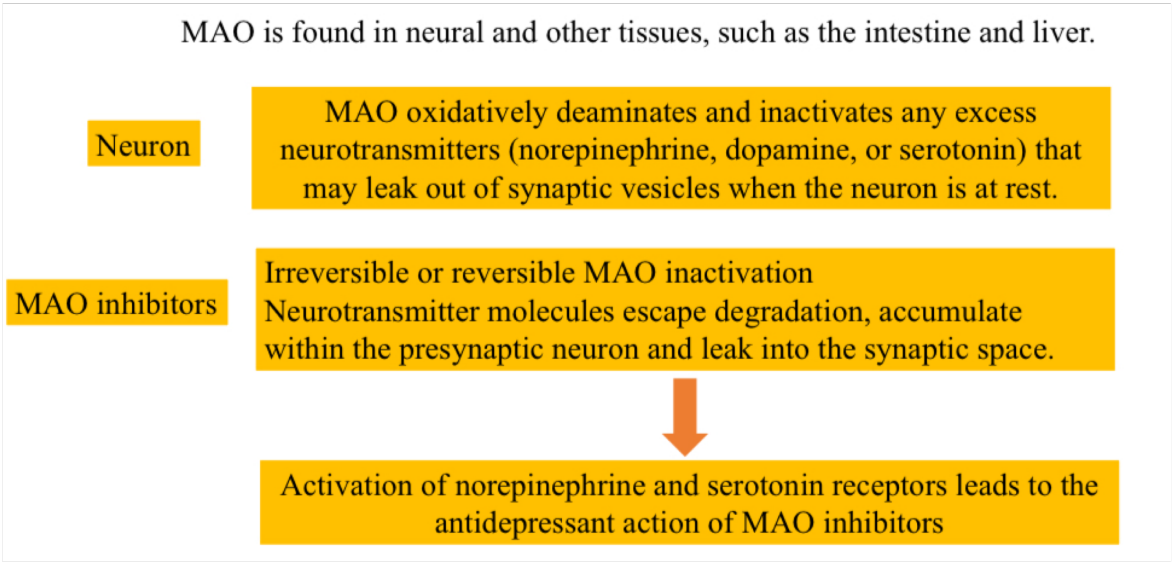
**The aldehyde products of the MAO reaction are oxidized to the corresponding acids.**

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

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

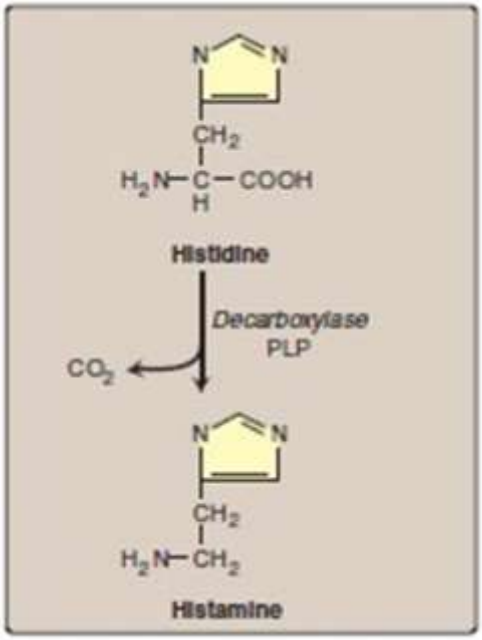
## CLINCAL HINT: MAO INHIBITORS ANTIDEPRESSENTS

The main function of MAO is to inactivate any excess neurotransmitters (norepinephrine, dopamine, or serotonin) that may leak out of synaptic vesicles when the neuron is at rest. Accordingly, MAO inhibitors inactivate MAO so excitatory Neurotransmitter molecules escape degradation, accumulate within the presynaptic neuron and leak into the synaptic space which leads to Activation of norepinephrine and serotonin receptors leads to the antidepressant action of MAO inhibitors.



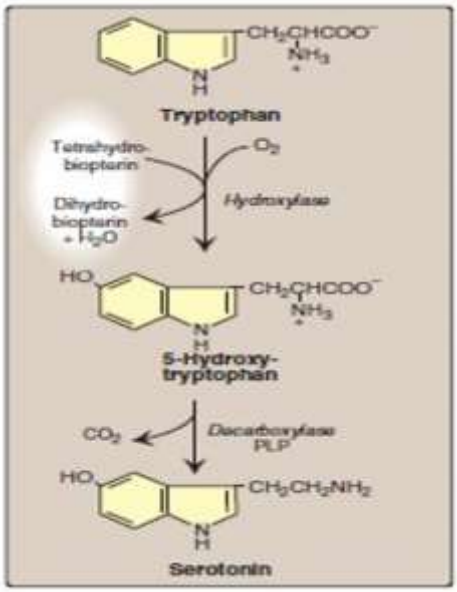
## Histamine:

- **Histamine** is formed by **decarboxylation** of **histidine AA** in a reaction requiring **PLP**.
- Histamine is a chemical messenger that mediates a wide range of cellular responses includes:
  1) Vasodilator that is secreted by mast cells during allergic and inflammatory reactions. Symptoms resulting from an allergy may range from small itchy rash to shortness of breath and may lead to anaphylaxis the most dangerous form of allergy. In inflammation histamine mediate the efflux of inflammatory mediators to the site of action which explains the occurrence of redness, edema, hotness, and congestion.
  2) Gastric acid secretion.
  3) Neurotransmission in parts of the brain.



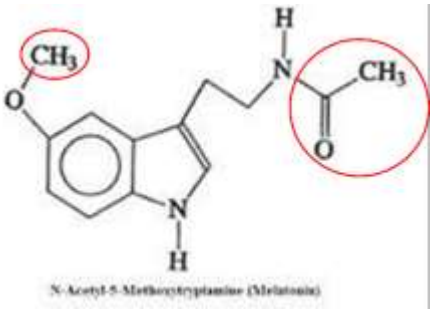

## Serotonin, or 5-hydroxytryptamine (5HT):

- Serotonin is derived from **Tryptophan AA.** Tryptophan is hydroxylated in the presence of $BH_4$ **to 5-hydroxy-tryptophan.** Then decarboxylation reaction occur converts 5-**hydroxy-tryptophan** to **serotonin (5-hydroxytryptamine).**
- Is synthesized and stored at several sites in the body, mostly in intestinal mucosal cells.
- Serotonin functions as neurotransmitter in the CNS and platelets and responsible for many physiologic roles such as pain perception, regulation of sleep, temperature, blood pressure, cognitive functions, and mood (causes a feeling of well-being).




## Melatonin Hormone (Sleep Hormone):

- **Serotonin** is converted to **melatonin** in the pineal gland via **acetylation** and **methylation**.
- Regulation of sleep wake cycle.
- Secreted in evening darkness.

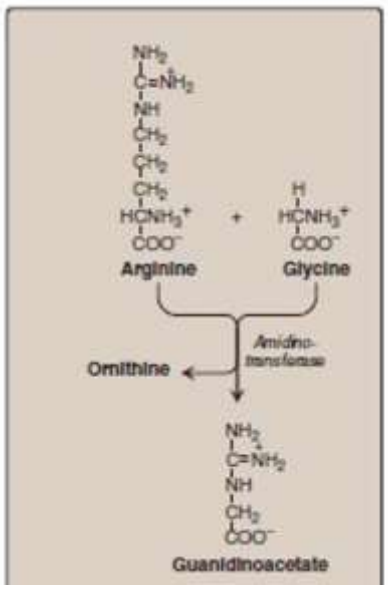


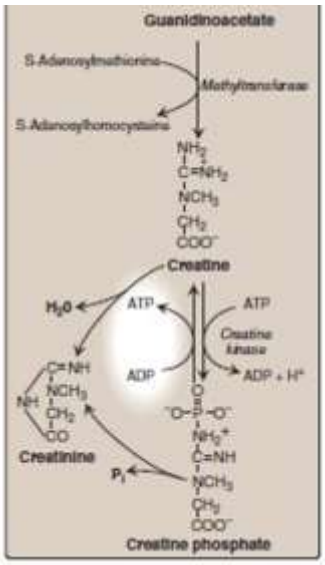
# Creatine:

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

Source of energy for muscle cells. (The amount of creatine phosphate in the body is proportional to the muscle mass).

Creatine is synthesized from 2 AAs arginine and glycine




## CREATINE SYNTHESIS:

- The fork like structure of the **arginine** (carbon attached with to amine groups) interacts with **glycine** producing **guanidinoacetate** and **ornithine** (urea cycle intermediate) as a side product.
  This step is catalyzed by **Amidino transferase**.
- **Guanidinoacetate is** methylated by **methyltransferase** using SAM (S-adenosylmethionine) forming **creatine**.
- **Creatine** then is phosphorylated forming **creatine phosphate**(phosphocreatine). phosphocreatine is high-energy compound found in muscle cells, rapidly mobilized and reserve of high-energy phosphates.

## CREATINE DEGRADATION:

**Creatine** is converted to **creatinine** in a **cyclization** reaction to be excreted in urine. (A typical adult male excretes ~15 mmol of creatinine per day).

Since creatine considered as source of energy in the muscles so When muscle mass decreases due to paralysis or muscular dystrophy→ the creatinine content of the urine falls.

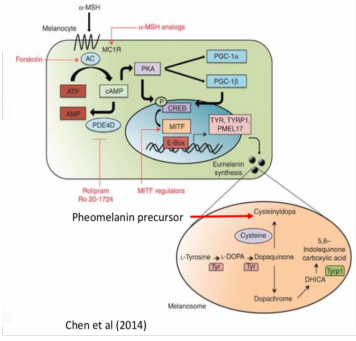
## CLINCAL AMPLICATION:

The presence of **creatine kinase** in the plasma indicates heart damage and is used in the diagnosis of MI (myocardial infarction). However, Rise in **blood creatinine** is a late sensitive indicator of kidney malfunction. Creatinine levels are tested through blood test called kidney function test KFT.

# Melanin Pigment

It is synthesized from tyrosine in the epidermis by melanocytes

In the melanocytes of the epidermis specifically melanosomes melanin is produced. Melanin gives the eyes hair and skin their colors as well as it protects the underlying cells from the harmful effects of sunlight. Defect in melanin production results in albinism (the most common form is due to defects in copper-containing tyrosinase)



Chen et al (2014)

**SYNTHESIS OF MELANINE: tyrosine** AA is converted into **L-dopa** by **tyrosinase** enzyme activity then to other materials lead to produce 2 main types of melanin 1) **eumelanine** (expressed in people with normal hair colors) 2) **pheomelanin** (expressed in people with red hair).

نسِيَ الطينُ ساعَةً أَنَّهُ طينٌ حَقيرٌ فَصالَ تيها وَعَربَد
وَكَسى الخَزُّ جِسمَهُ فَتَباهى وَحَوى المالَ كيسُهُ فَتَمَرَّد
يا أَخي لا تَمِل بِوَجهِكَ عَنّي ما أَنا فَحمَة وَلا أَنتَ فَرقَد
أَنتَ لَم تَصنَعِ الحَريرَ لَبَس وَاللُؤلُؤَ الَّذي تَتَقَلَّد

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# V1