Metabolism

فريق طوفان الأقصى

Modified N: 20

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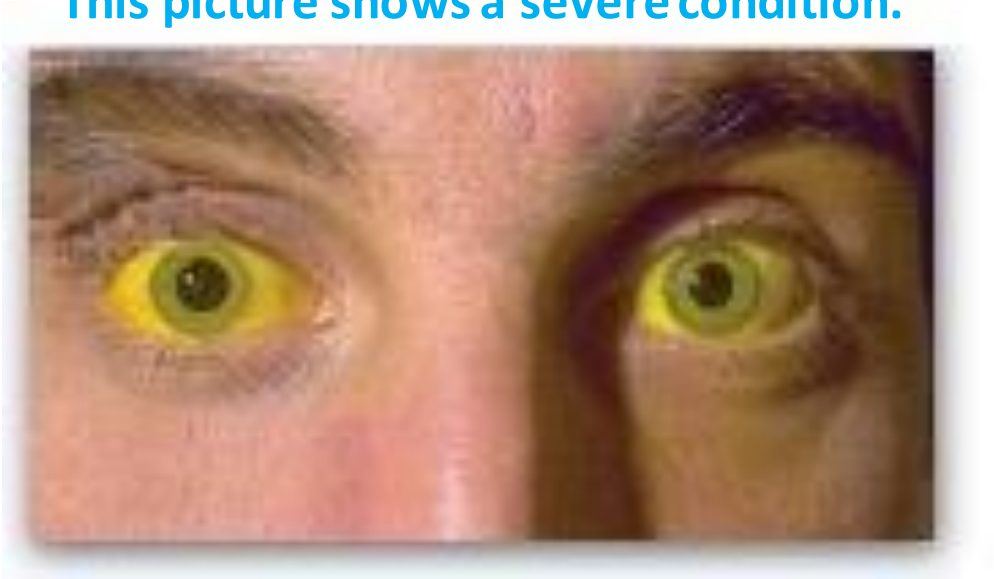
Jaundice

This picture shows a severe condition.

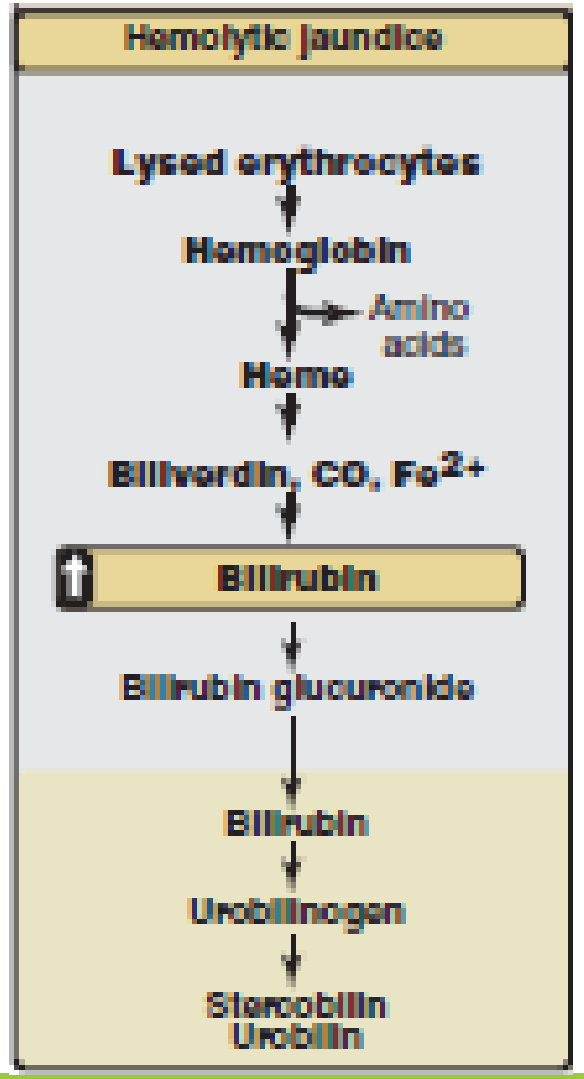


Jaundice (or icterus) is the yellow color of skin, nail beds, and sclera due to bilirubin deposition secondary to hyperbilirubinemia

Jaundice is a symptom not a disease, **related to the metabolism of heme group bilirubin specifically.**

Types of Jaundice

NOTE: different types of jaundice based on the causes of this symptom.

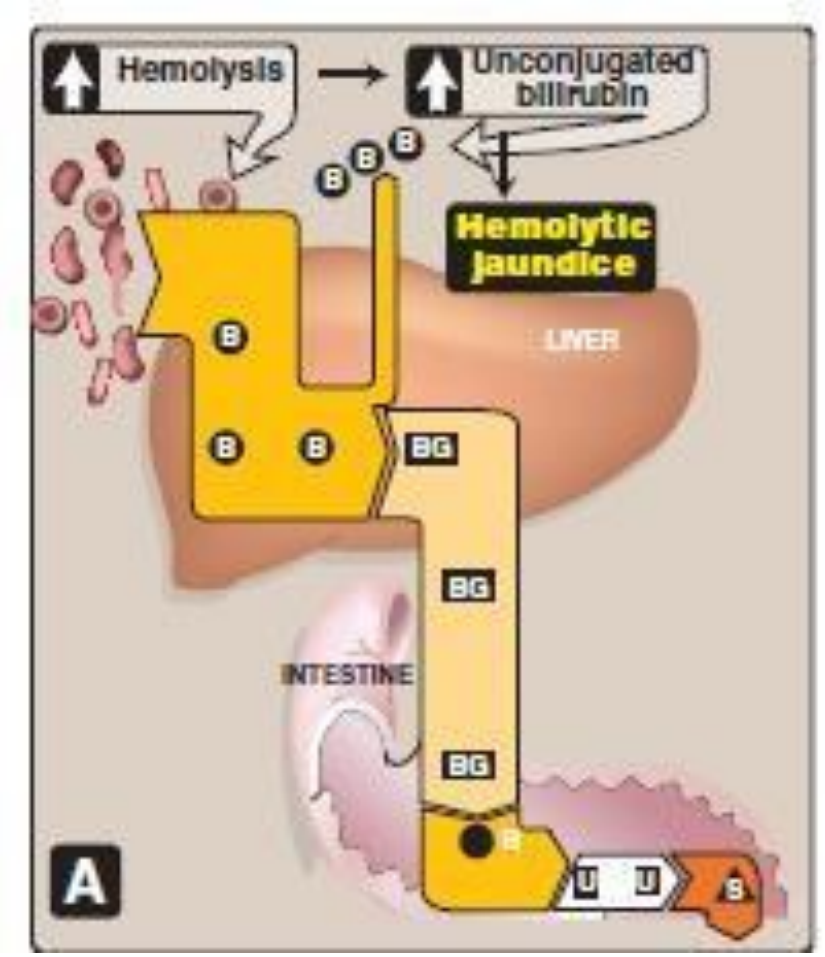


1. Hemolytic jaundice:

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. **Anything that can cause hemolytic anemia or more hemolysis**



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

The complement in this slide:

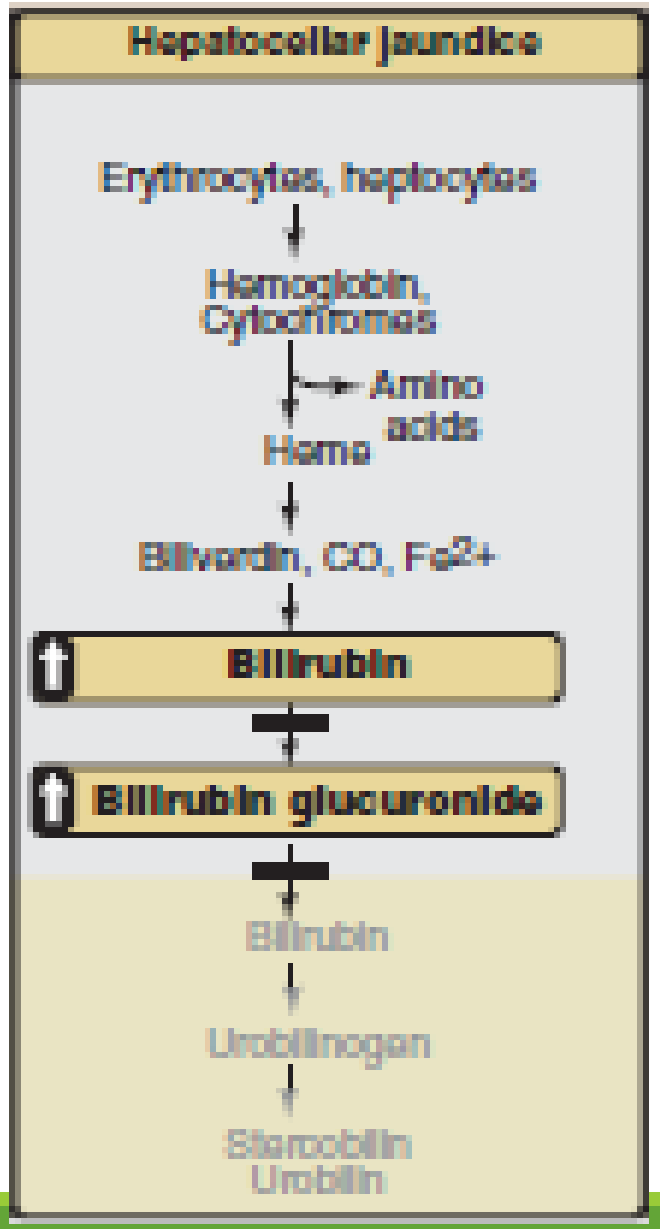
- Normally, the body conjugates about 300 mg of bilirubin each day. If the amount of bilirubin exceeds this level, the body will still only conjugate 300 mg, and any excess bilirubin will remain unconjugated.
- And this is what happening in hemolytic type of jaundice, we have hemolytic anemia(more degradation of RBCs than the degradation that is happening in normal individuals) the liver will perform its function to the conjugation 300mg and the rest will stay as is. (Beyond the capacity of hepatocytes) so there will be an accumulation of unconjugated bilirubin occurs resulting in jaundice.

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.



- **NOTE:** Hepatocellular jaundice due to damage to liver cells like:
- Hepatic cancer اصفر الي عندهم سرطان كبد بالأخير بصير
- Hepatitis: causes cirrhosis and fibrosis (type B and C specially processed into chronic disease like cirrhosis and hepatic cancer.)

Viro Lec 1 xD

NOTE: Depending on the amount of distraction in the hepatocytes:

- We expect that the capacity of the liver as an organ decreases.
- Liver will produce less than 300mg depending on the amount of distraction it has.
- may result in the accumulation of both conjugated and unconjugated bilirubin .
- Dark and bile color of their feces depending on destruction of the cell that perform the conjugation.

Types of Jaundice-cont

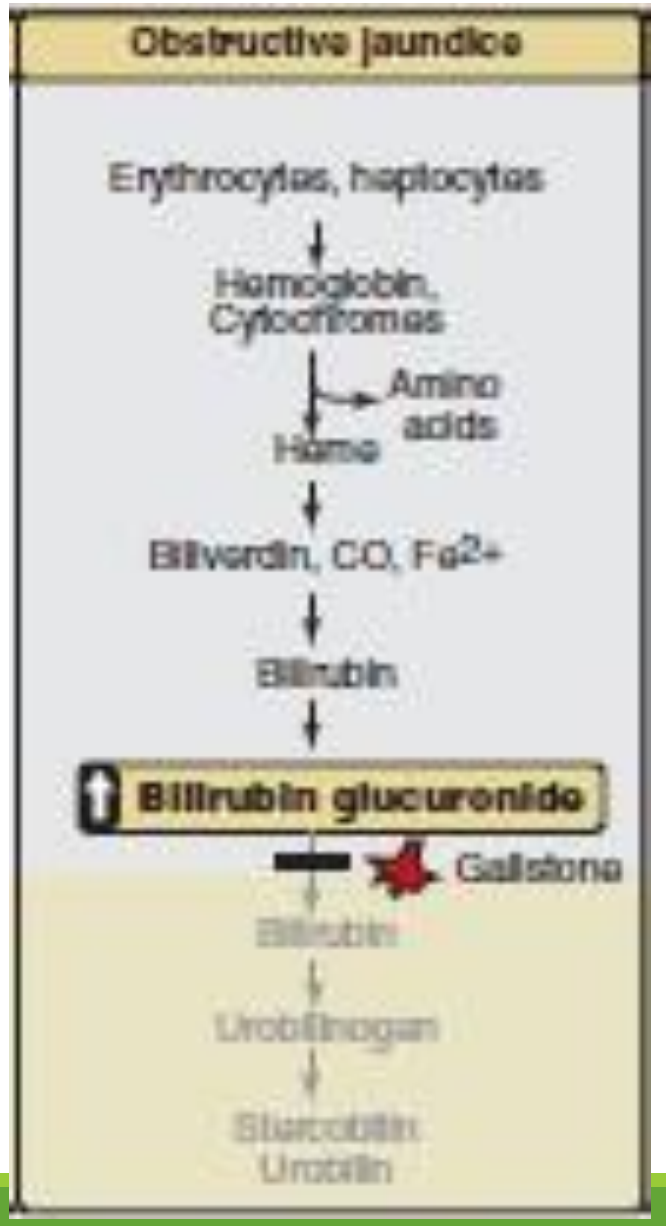
3. Obstructive (يعني في اشي مسكر) **jaundice:** Obstruction of the bile duct (extrahepatic cholestasis) due to a tumor or bile stones, preventing bilirubin passage into the intestine.

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.

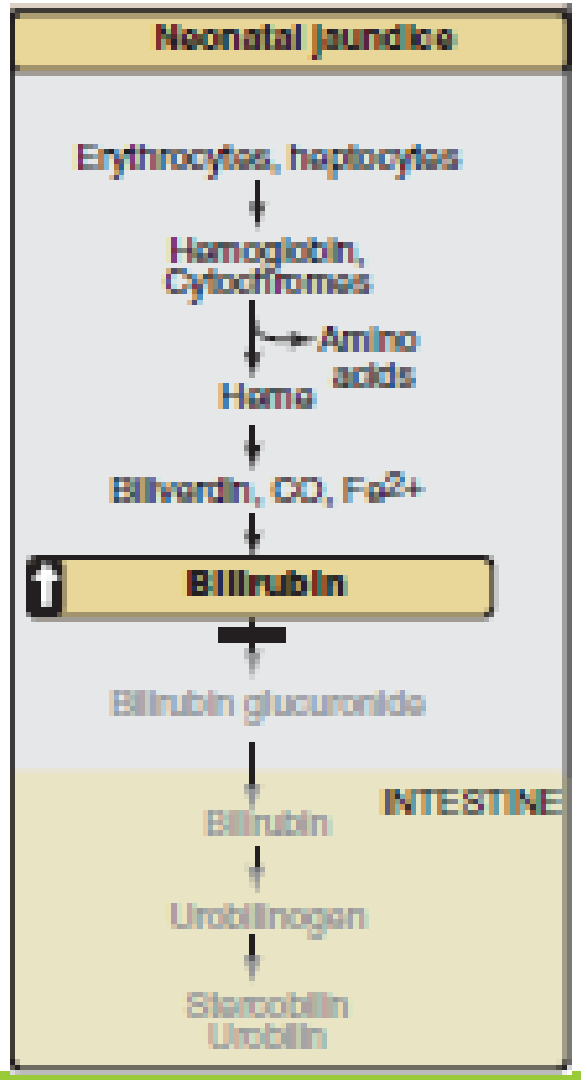
Prolonged obstruction of the bile duct can damage the liver and increase unconjugated bilirubin



- **The complement in this slide:**
- The function of the liver is normal, the capacity of the liver is normal.
- The problem is in the secretion of conjugated bilirubin.
- Conjugate bilirubin goes to the biliary system, so it needs to be secreated with the bile.
  أو اشي ضاغط عليها من الخارج فمسكرها (Stones) لكن تخيل انه القناة مسكرة اما من الداخل
- Accumulation of conjugated bilirubin.

Jaundice in newborns

NOTE: premature infants are more susceptible to have jaundice.

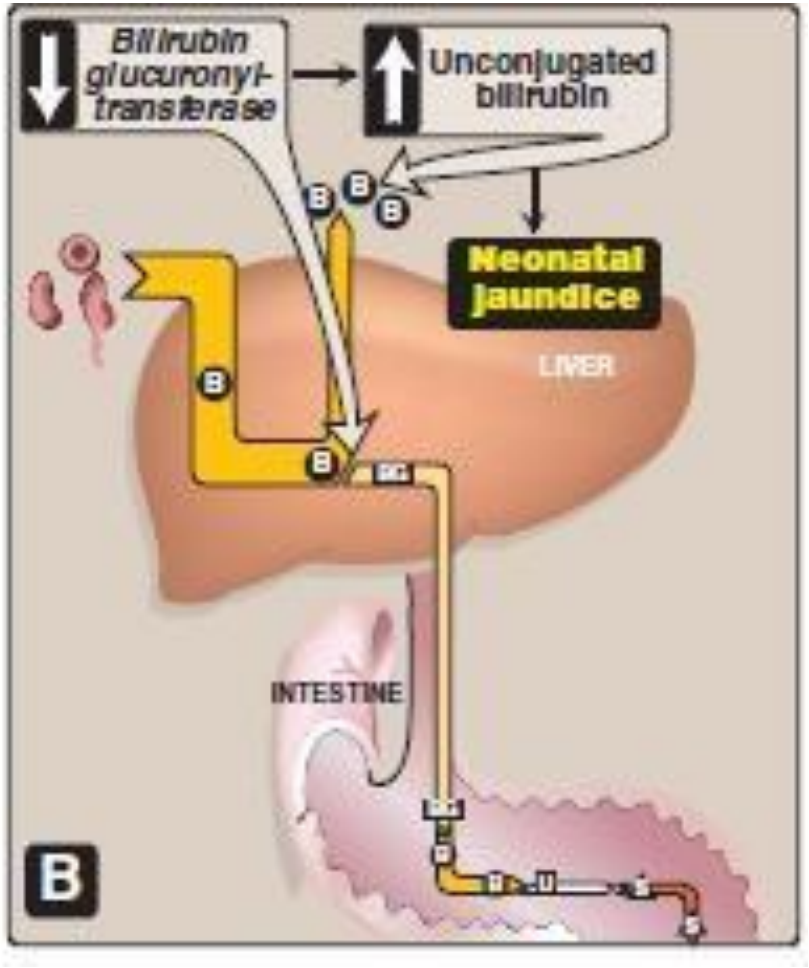


Newborn infants, particularly if premature, often accumulate bilirubin, because the activity of hepatic bilirubin glucuronyltransferase is low at birth

It's not a problem it is just a matter of time

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.

- **NOTE: not the babies with cirgler-Najjar or Glibert.**
- **The amount of Bilirubin glucuronyl-transferase is still less than what required (not deficiency, it is matter of development)**

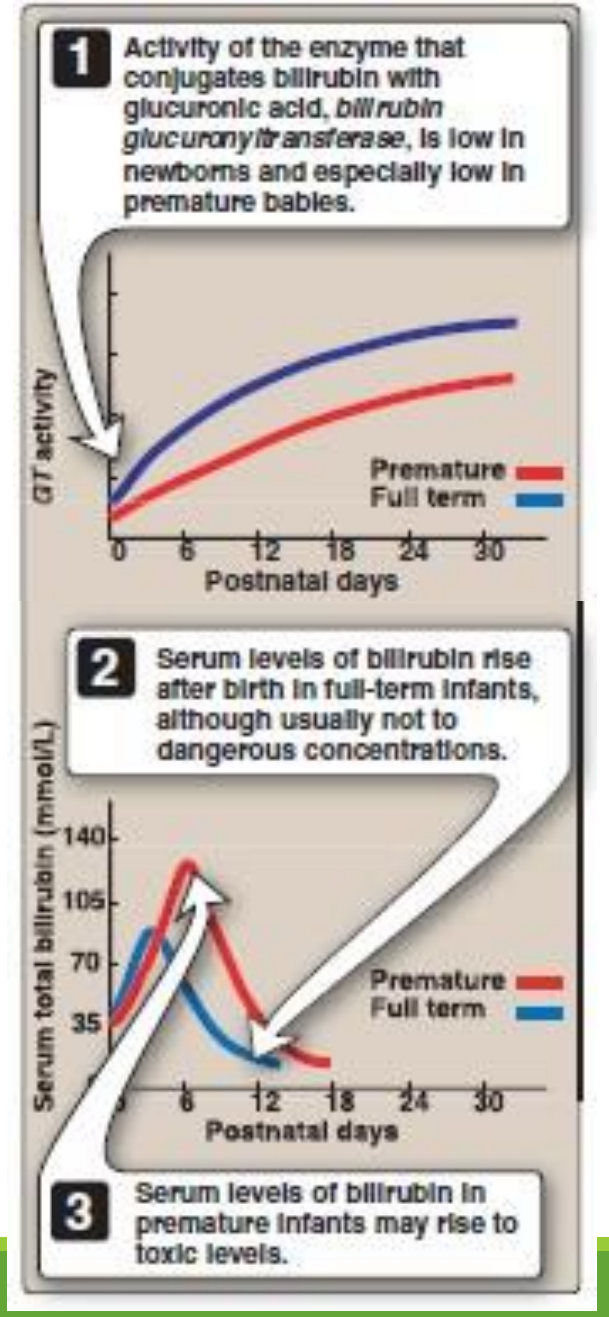
- **NOTE:**
- **But if the bilirubin exceed a certain limit then they have to be hospitalized, they incubated them(put them in an incubator) and their eyes are covered (like the picture in the next slide) and they have to be exposed to Blue fluorescent light that converts bilirubin to more polar water-soluble isomers.**
- **Unlike the body, we get rid of bilirubin in a different way but we have to because if it stays it would cause distraction to the CNS (to the brain) casuing kernicterus.**
- **They will be kept there until they catch up and their enzyme level goes up so they can do the conjugation normally without the need of this incubator.**

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.



Enzyme level

Bilirubin level

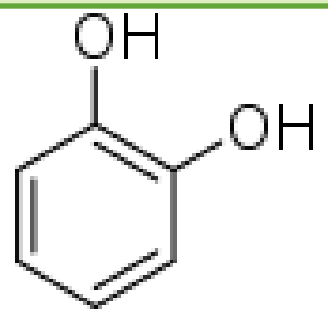
Notice that the level of bilirubin is higher in premature infants (red curve)

OTHER NITROGEN-CONTAINING COMPOUNDS

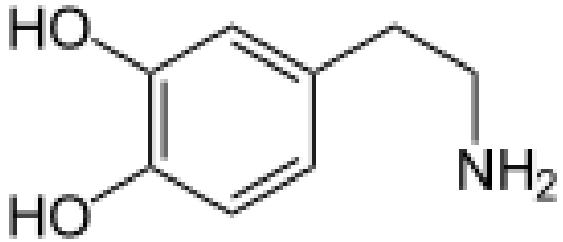
Catecholamines (Dopamine, norepinephrine, and epinephrine)

NOTE: they are produced one after one كل واحد بصنع الي قبله فعليا

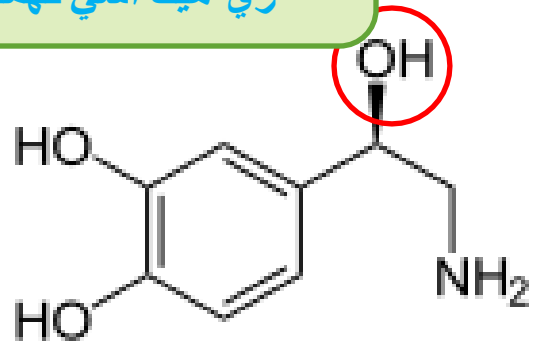
مسؤول عن المتعة(النشوة)مش السعادة .. السعادة ممكن نحكي شيء مستمر أما النشوة فجأة زي مثلا فرحتك بعلامتك التوجيهي او شغلة لحظية حلوة صارت زي هيك اشي فهمت من الدكتورة 😎



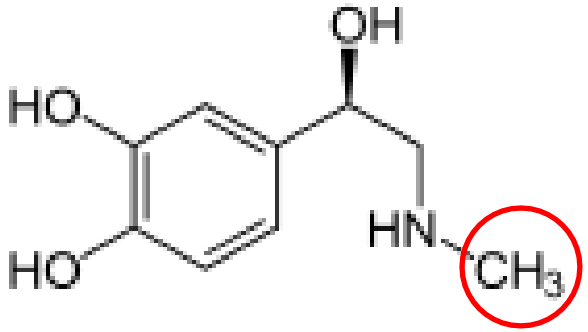
Catechol



Dopamine



Norepinephrine

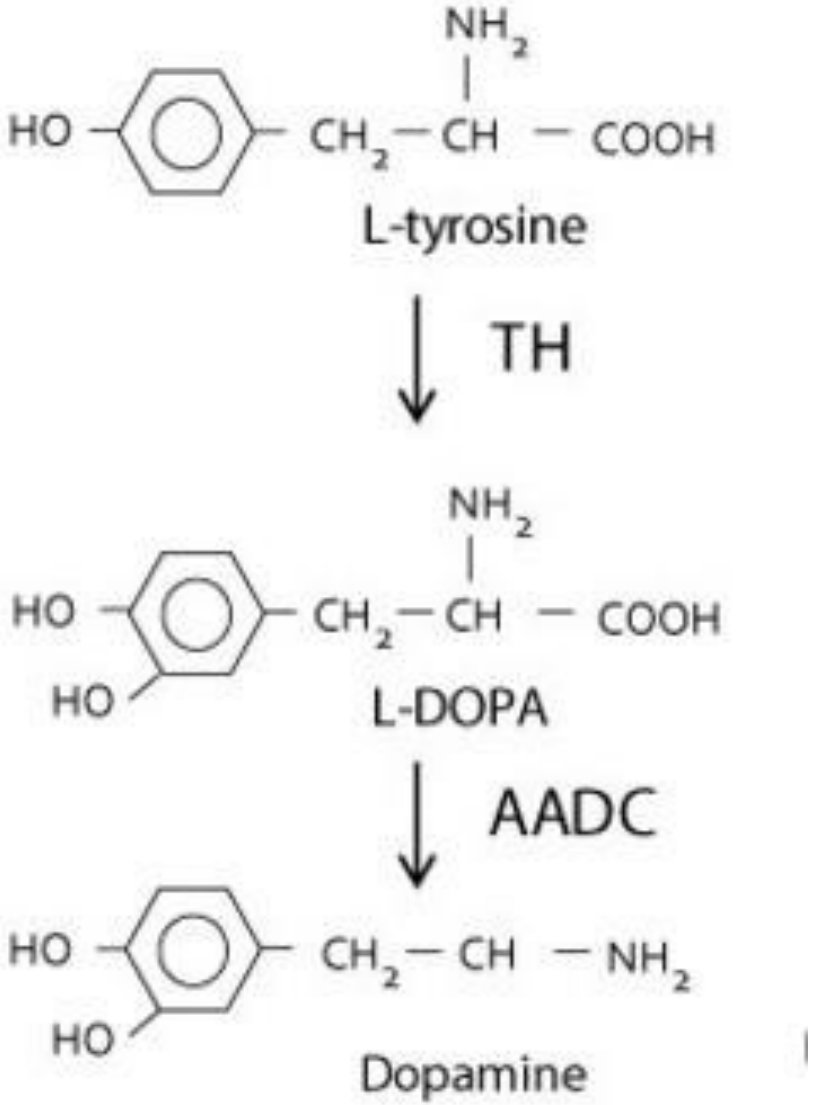


Epinephrine

Catechol are Benzene ring with 2 OH groups on adjacent carbon, the closet structure to this is Tyrosine

From Tyrosine AA

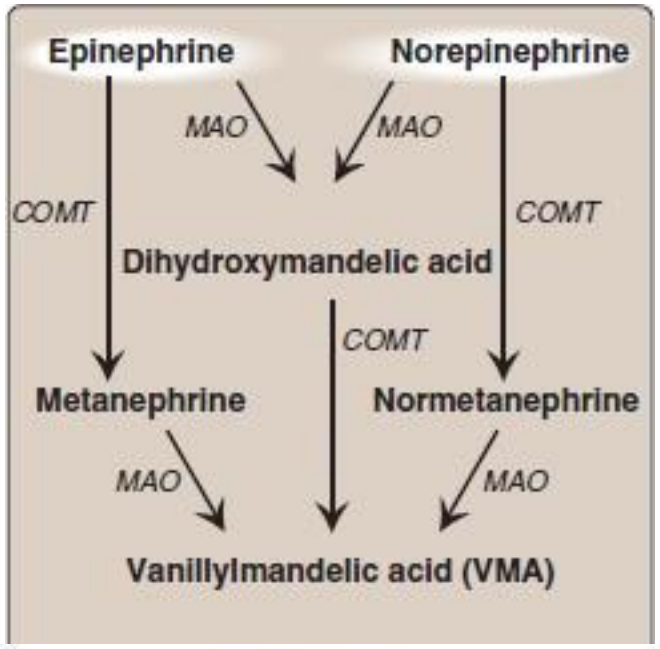
- **NOTE:** Norepinephrine and Epinephrine are hormones and can act as nurotransmitters, but dopamine mainly neurotransmitter
- Norepinephrine and Epinephrine in fight and flight conditions

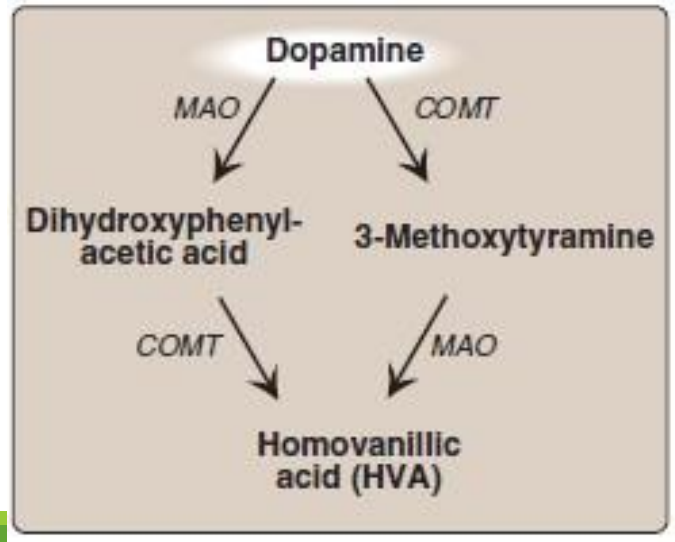


- **NOTE:** this picture is only for understanding
- TH= tyrosine hydroxylase will add the second OH group.
- To convert it to amine we have to remove the carboxyl, so decarboxylation occur resulting in the formation of dopamine.
- Then hydroxylation of dopamine produces Norepinephrine.
- Methylation of Norepinephrine produces epinephrine.

Degradation of catecholamines

Intermediates is not for memorizing just the final products





Catecholamine inactivation by:

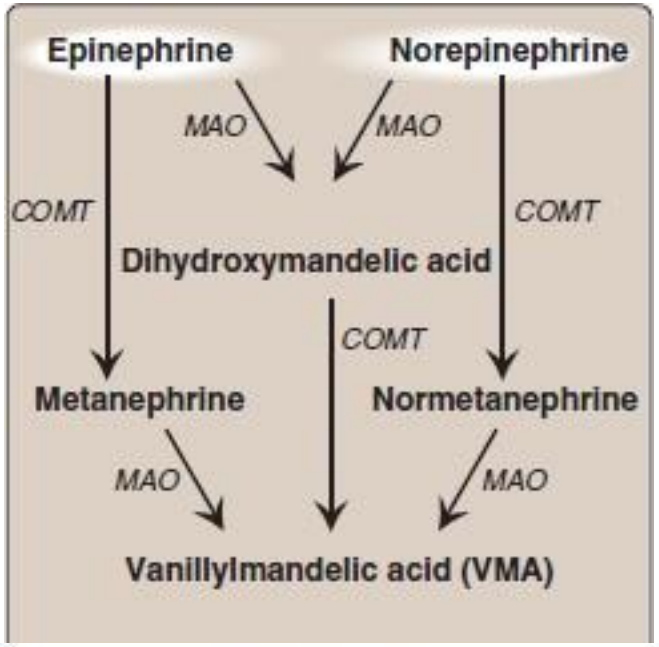
A. Oxidative deamination catalyzed by monoamine oxidase (MAO)

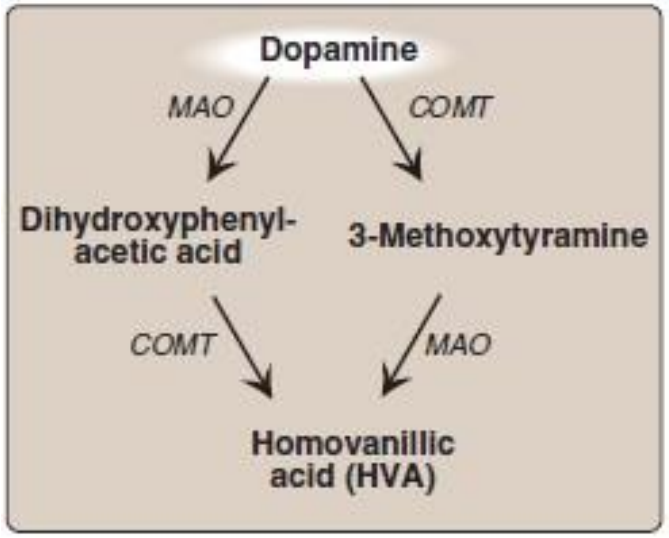
A. O-methylation by catechol-O-methyltransferase (COMT) using SAM as the methyl donor

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).





- **The complement in this slide:**
- Generally speaking, to finish the action of neurotransmitter we can degrade it.
- Degradartion of catecholamines occurs by 2 enzyme **MAO**(monoamine oxidase) and **COMT**(catechol-O-methyltransferase).
- One of them starts the pathway and the other one finishes it (anyone of them can start) and they end up with the same final product **VMA** (Vanillylmandelic) **(epinephrin and norepinephrine metabolised to it)** but with different intermediates **(you don't have to memorize the intermediates just the final product)**
- Dopamine degradatoin using the same enzymes, and it can be metabolised to **HVE** (Homovanillic acid).
- These enzymes work on serotonin too even if it is coming from another amino acid.

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.

لما اثبط عملية هدمهم رح يضلوا مرتبطين بالمستقبل فالاشارة تاعتهم هتضل شغالة مما يعني رح يقلّ الاكتئاب, وهذا مبدأ عمل antidepressant ولكن الها كثير اثار جانبية

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

Histamine

NOTE: As it appears from its name, it's the Amino Acid " Histidine " but without carboxyl group

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

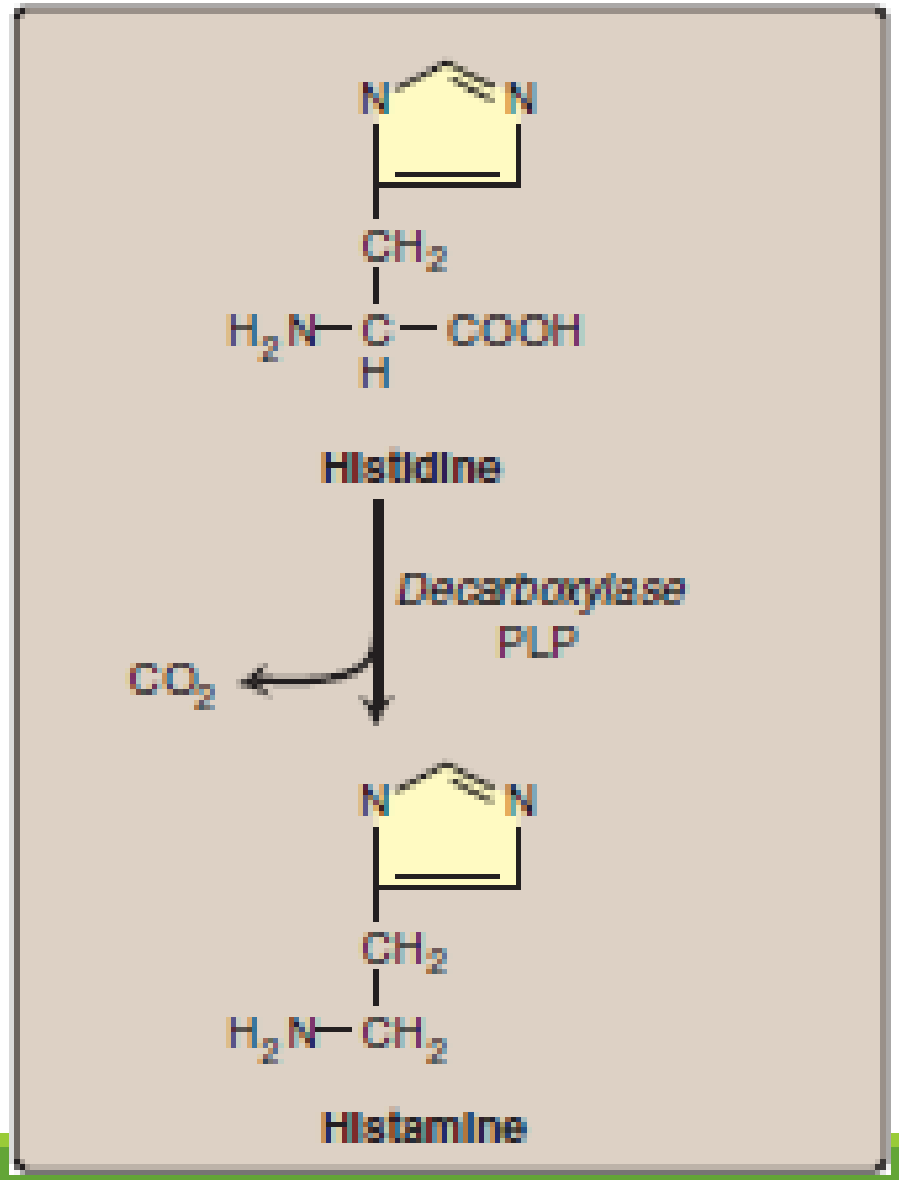
Roles include mediation of:

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**

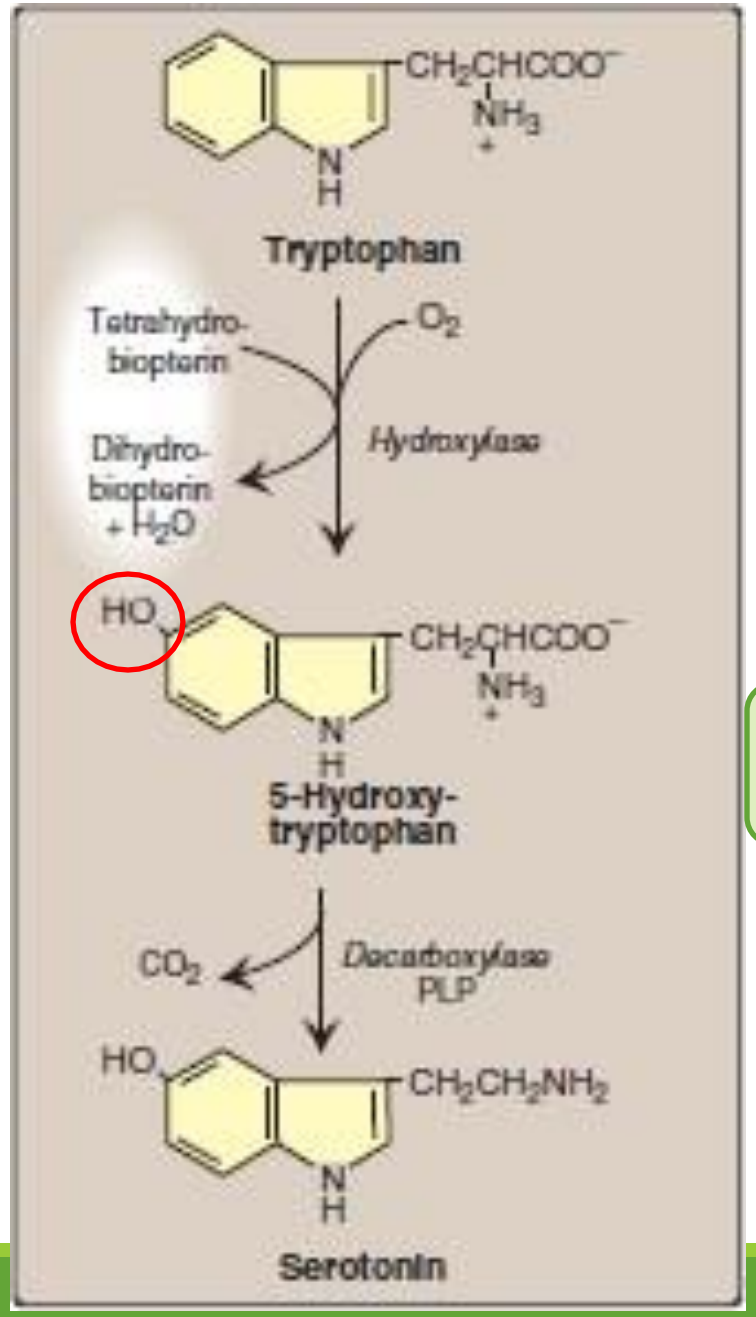
Histamine is formed by decarboxylation of **histidine** in a reaction requiring PLP



The complement in this slide: the amino acid Histidine can be converted to histamine by decarboxylase enzyme and with the cofactor PLP, but what is histamine? Yes it's an allergic mediator which is released by basophils and mast cells, it results in vasodilation and other effects –related to pathology- It has different effects on allergic people, from such shortness of breath or a rash to a SHOCK! (Anaphylactic shock), in the latest one, it can develop into a coma if the patient is not given an epinephrine shot. Of course the severity of allergy depends on many factors such as how much the patient was exposed to the source. Allergy, Contrary to common belief, is not confined solely to the respiratory system. They can also arise due to accessories in hand or many places in body in general . Anyway, this RXN will lead to vasodilation, increased permeability, and edema

- **Additional information:** referring back to the previous functions of histamine, we all know that it's involved in allergy but the second and third one are somehow strange right? so let's explain but keep in mind that it's not included now, we will take it in next semesters:
- Histamine has many receptors in body, one of them is " H2", when bind to it, it causes gastric acid secretions(this is why we give "anti H2" drugs for peptic ulcer patients"
- Histamine also plays a key role in CNS, it regulates alertness and sleep cycle, this is why anti histamine drugs have a common side effect which is Sleeping!

Serotonin, or 5-hydroxytryptamine (5HT)



NOTE:" tryptamine" means tryptophan without carboxyl group, it's hydroxylated in Carbon #5

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

NOTE: you can know the reactions just form the name 😁

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

NOTE: Serotonin can be produced in other locations in the body (but it can't cross the BBB) so what produced in CNS work in CNS and what produced outside work outside.

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

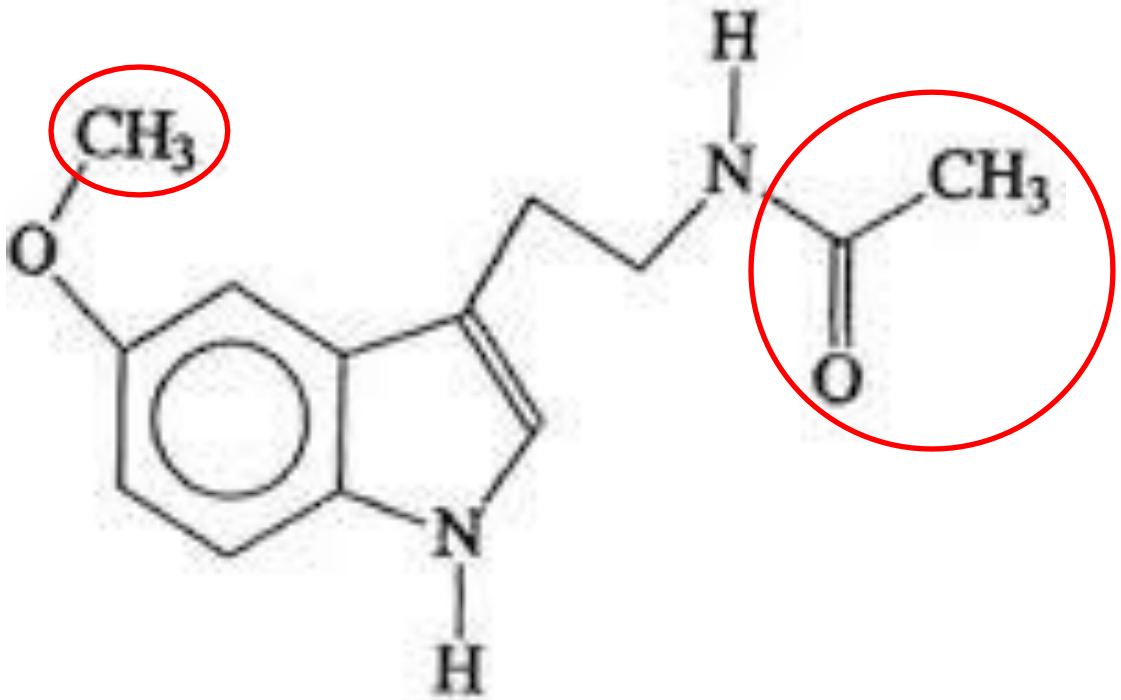
NOTE: although we call it " هرمون السعادة" it has other functions

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.

NOTE: sleep cycle also called circadian rhythm

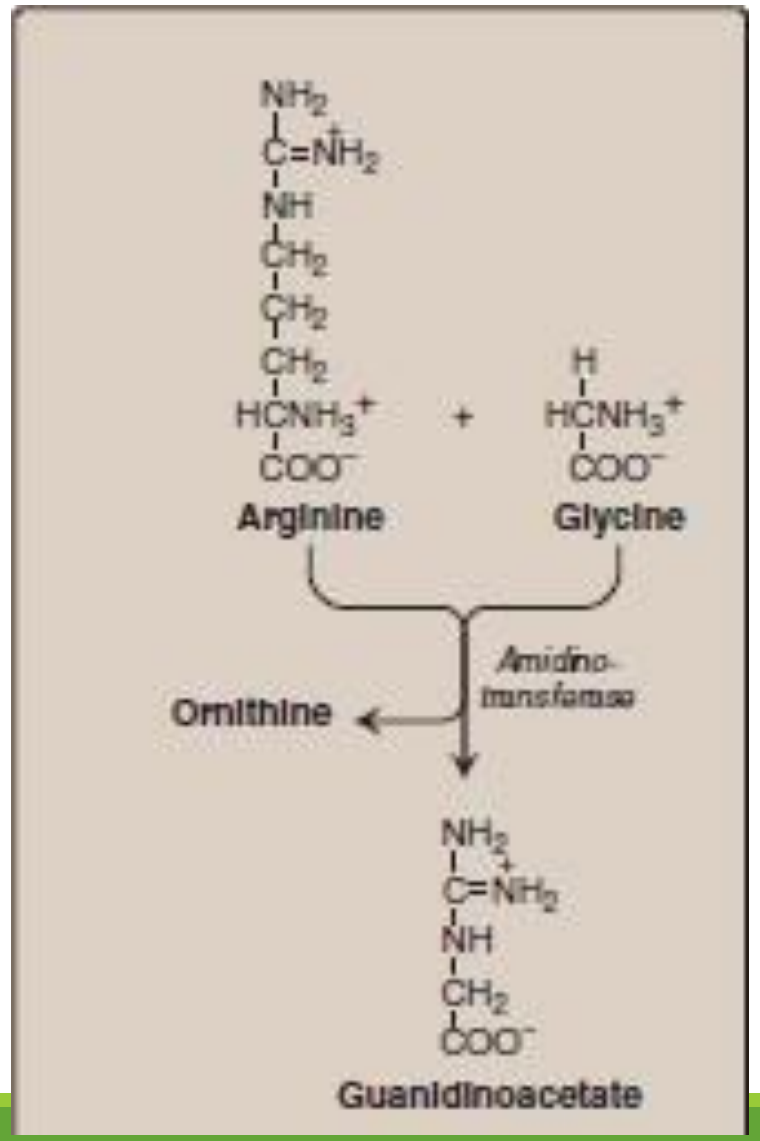
Additional information: it has several functions other than regulating sleep like: Antioxidant Properties, Eye Health, Mood Regulation, etc..

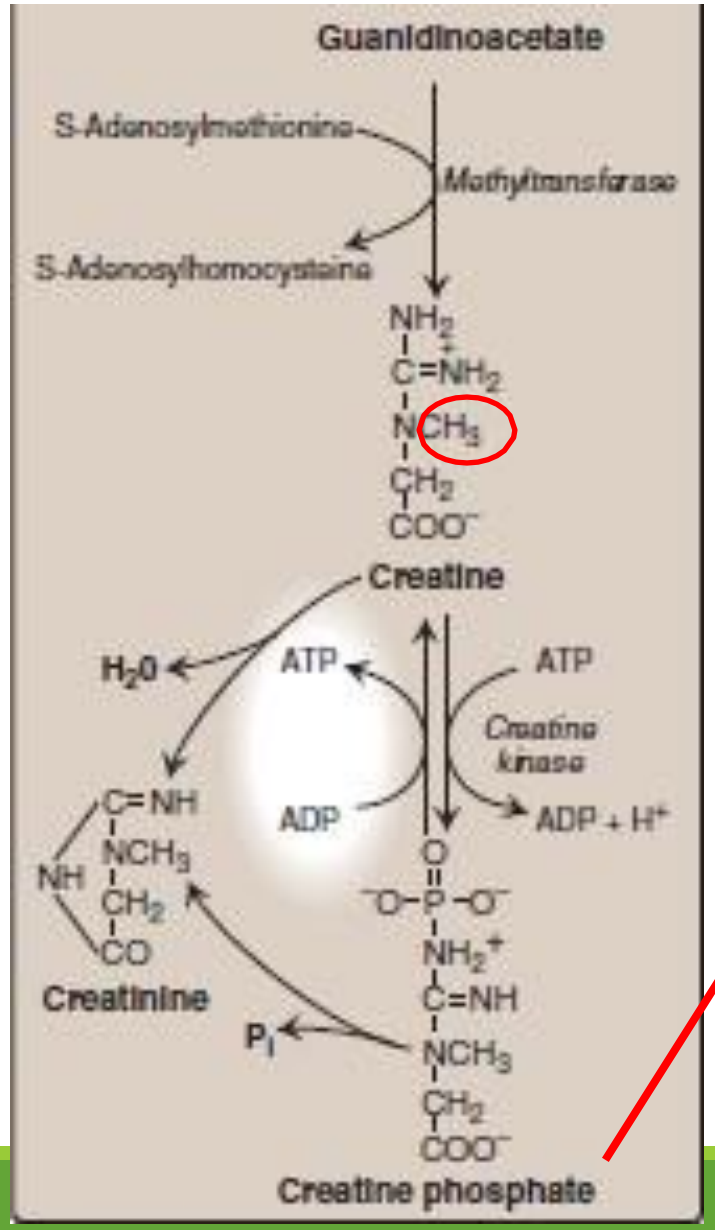


N-Acetyl-5-Methoxytryptamine (Melatonin)

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.

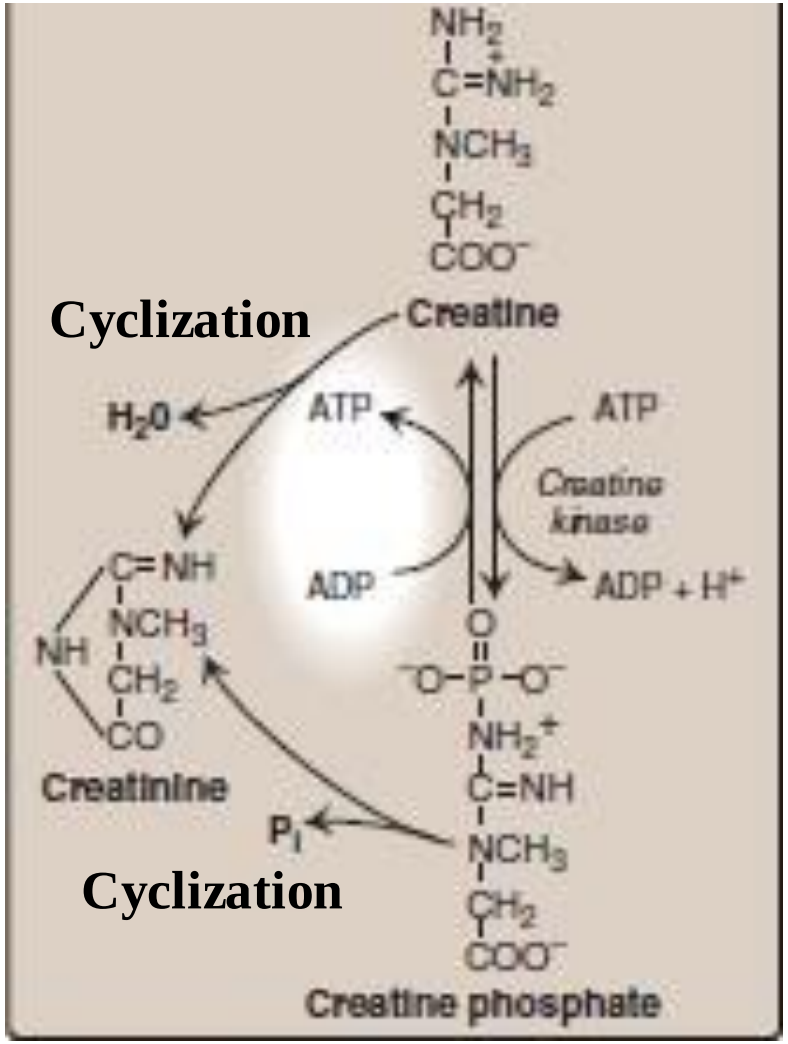
or phosphocreatine
a high-energy compound found in muscle and provides a small but rapidly mobilized reserve of high-energy phosphates

- The complement in this slide: " Creatine – p " is a high energy molecule (as you know it's the second source of energy to cell after ATP, so when ATP is low? This what happens
- Creatine Phosphate + ADP → Creatine + ATP look at the picture above while reading this
  - We start the RXN with Gly + Arg , then by the enzyme " Amidinotransferase " we transfer the carbon with two nitrogen " look at upper part of Arg " so congrats! We have guanidinoacetate but our story did not finish yet, it has just begun. The compound guanidinoacetate will be methylated by methyltransferase the source of methyl is SAM which will be converted to SAH , and our methylated compound here is (Creatine) . Now simply by creatine kinase using ATP we'll have creatine phosphate (can work as a source of energy in cells)

- Additional information: the enzyme CK (Creatine Kinase) has izozymes in the body, it is existed in skeletal muscles, heart, brain .. the one in heart is called (CK-MB) when heart cells are damaged (such as MI as it mentioned in the previous slide) the CK-MB will release into the blood , high concentration of it is a biomarker for MI !

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.



The complement in this slide: when(Creatine-p) is consumed to form ATP , it will return back to creatine , we will do cyclization ((formation of a cyclic compound called **creatinine** after removing the phosphate group)

Creatinine goes to the blood stream and then it will be excreted by the kidney through urine.

Anyways, as the kidney is responsible of excreting it, high levels of creatinine in blood indicates problem in function ! but it's a slow marker actually **(late)** .

Creatinine test is one of common kidney tests, it is a clinical information, remember that well, future doctor 😉

- **Additional information: The amount of creatinine produced in the body is directly related to muscle mass. Therefore, in conditions where muscle mass decreases, such as paralysis or muscular dystrophy, the production of creatinine also decreases as mentioned in the previous slide .**

Melanin Pigment

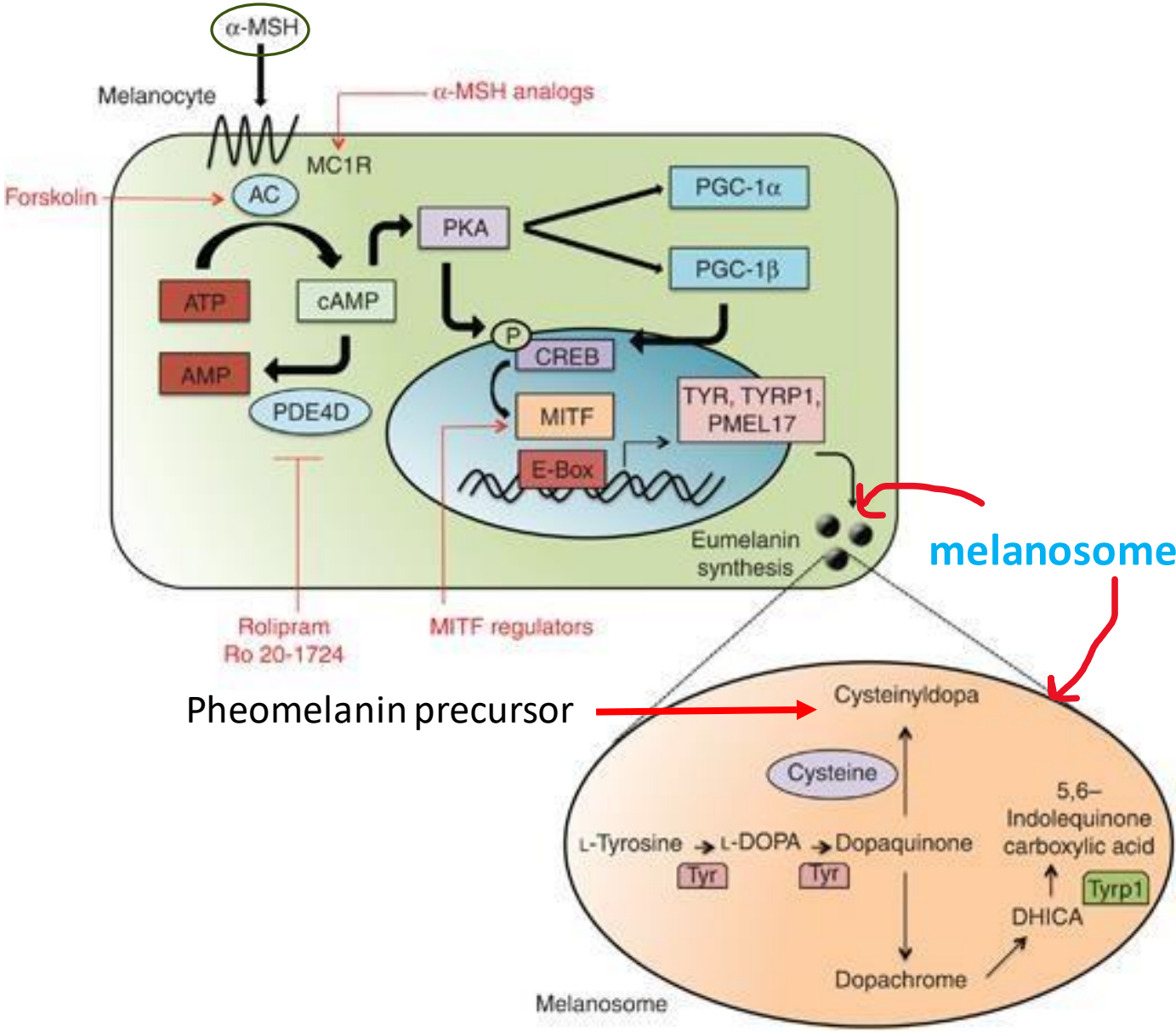
A pigment in several tissues, particularly the eye, hair, and skin.

It is synthesized from tyrosine in the epidermis by melanocytes.

Can u mention what is the molecules that is derived from tyrosin?

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)

- **The complement in this slide:** Melanin producing is stimulated by Melanocyte-stimulating (MSH in the previous pic)it's a hormone released by pituitary gland, anyways, Tyrosine is the precursor of the synthetic pathway of the melanin pigment which occurs in the melanocytes. Melanocytes have melanosome, where melanin is produced.
- Tyrosine --> L-DOPA --> Dopaquinone which act as branching point where we can make 2 types of melanin pigments which are:
- 1) Eumelanin (It provides brown to black pigments)
- 2) Pheomelanin (This type of melanin contributes to red and yellow pigments)
- Melanin is synthesized in melanocytes but to be able to give color it has to be released to the keratinocytes.

- **Additional information: Doctor has mentioned that when exposed to sunlight, more melanin move to skin surface, this movement is sensitive to UV light .. so we become darker (such as in summer).**
  To explain more : When skin is exposed to UV radiation, melanocytes are stimulated to produce more melanin. This is a protective mechanism to guard the skin against UV damage. This melanin is transfered from melanosome to keratinocyte (as it's movable)this Increased melanin production leads to the darkening of the skin, commonly known as tanning.