35

carbohydratesisomersketone starchlipidproteinamine

Bio chemistry

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

DONE BY

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DOCTOR

Diala

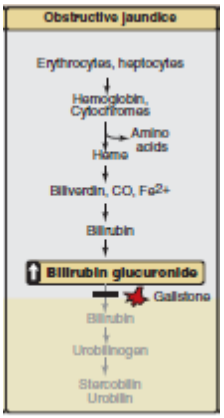
last sheet we talked about heme synthesis and degradation also we discussed 2 types of jaundice today we will finish what we started

quick recap:1- hemolytic jaundice is due to increased hemolysis

2- hepatocellular jaundice is due liver damage

3- Obstructive jaundice: in this type there is **NO** increased hemolysis "overproduction of bilirubin" **OR** decreased conjugation **but** what actually happens is accumulation of conjugated bilirubin in the biliary system due to obstruction in the transport of conjugated bilirubin within the bile duct (extrahepatic cholestasis) .SO WHAT IS THE REASON BEHIND BILIARY OBSTUCTION ?

** ANSWER: it may be gallbladder stones OR the presence of a tumor in the canal or the duct itself narrowing it and decreasing bile secretion **leading to saturation and the formation of bilirubin gallstones**



Exception: we may have hepatocellular jaundice and obstructive jaundice together due to a tumor in the liver which lowers the liver's functionality and applies pressure on the duct thereby narrowing it.

*Signs and symptoms: GI pain and nausea, pale clay color stool, and urine that darkens upon standing. "because bilirubin can reach the kidneys through the blood"
Hyperbilirubinemia, bilirubin excretion in the urine, no urinary urobilinogen

Obstruction in the biliary system → Accumulation of conjugated bilirubin → Obstructive jaundice → Bilirubin gallstones

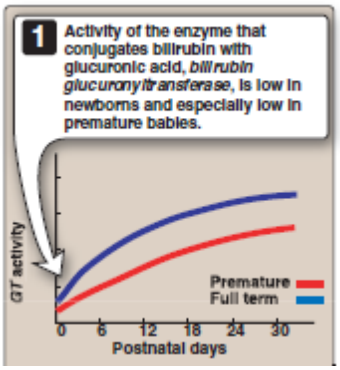
4- jaundice in newborns: occurs particularly in prematures, often accumulation in bilirubin because the activity and amount of hepatic bilirubin glucuronyltransferase is low at birth and not enough to conjugate bilirubin efficiently.

Full term infants may also have low amount of the enzyme which is due to uncompleted development "not a genetic mutation" so we need a short period of time (4 weeks) to get the problem completely solved by the body.

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

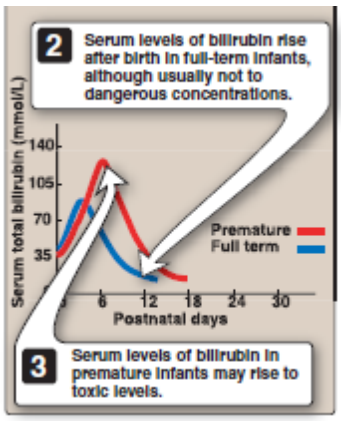
Newborn screening include jaundice tests (bilirubin screening) if there is low increase in bilirubin conc. we advice the mom to expose her baby to the sun or to give the baby powdered milk .

But if the levels of bilirubin are high the baby needs incubation under **blue florescent light** which converts bilirubin to a more water soluble photoisomers that can get excreted into the bile without conjugation to glucuronate.



Note: we measure bilirubin levels in the blood to check liver status and function.

In modern labs bilirubin tests are automated so ***how* does the lab's device **measure bilirubin's** conc.?**



It indicates bilirubin levels by a reaction between blood sample and diazotized sulfanilic acid 'DSA" forming red azodipyrrols (van den bergh reaction) The color change is measured colorimetrically.
First step is: performing the reaction on an aqueous solution so conjugated bilirubin in blood will be detected by reacting with (DSA) we call this **"direct reacting bilirubin test"** which is a rapid rxn (within 1 minute).

NOTE: we detected conjugated bilirubin ***because it is soluble in aqueous solutions*** .

Second step is: performing this reaction with methanol (**CH3 OH)** which can mix conjugated and unconjugated bilirubin**" cuz it has polar OH and non-polar CH3"** and interact with (DSA) detecting total blood bilirubin, we call this **"indirect reacting bilirubin test"**

Now we have the amount of total and conjugated bilirubin we can measure unconjugated bilirubin by the following equation:

Unconjugated bilirubin= total bilirubin - conjugated bilirubin

In normal plasma, only about **4%** of the total bilirubin is conjugated or direct-reacting, because most is secreted into bile.

Van den bergh rxn on aqueous solution **"direct reacting bilirubin test"** **conjugated** → Van den bergh rxn on methanol media **"indirect reacting bilirubin test"** ***TOTAL*** → Calculate unconjugated bilirubin using the equation

Let's talk about the last part of amino acid metabolism which is utilizing AAs to synthesize other nitrogen containing compounds

Catecholamines

as the name implies they contain "**catechol + amine group**"

catechol: is composed of a **benzene ring** with **two adjacent OH** groups, it is similar to tyrosine structure which has one OH group ,so if we add an OH to tyrosine we will get a catechol structure in the molecule which is called dopa.

** so hydroxylation of tyrosine by tyrosine hydroxylase which uses the **COenzyme BH4** produces dopa "amino acid"

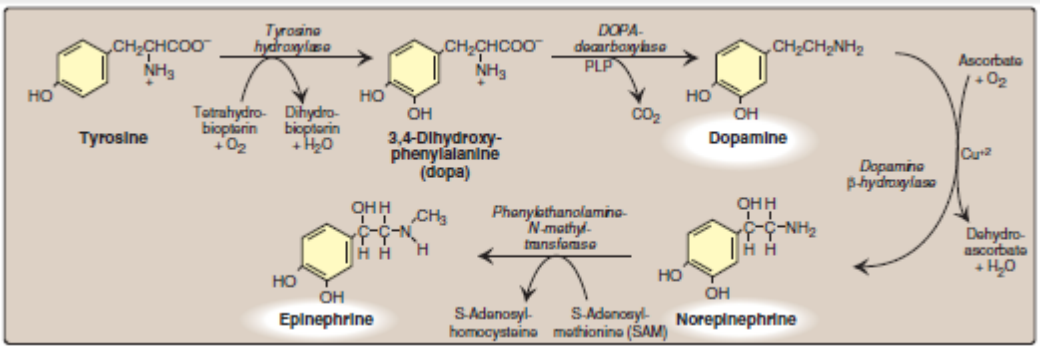
AND decarboxylation of dopa by dopa decarboxylase which needs the **COenzyme PLP produces dopamine "amine"

NOTE:Parkinson disease, a neurodegenerative movement disorder, is due to insufficient dopamine production due to an idiopathic loss of dopamine-producing cells in the brain. Administration of L-DOPA (levodopa) is the most common treatment.

AND hydroxylation of dopamine by dopamine β-hydroxylase which uses **CO enzyme ascorbic acid (vitamin C) produces NE

-Vitamin C usually works as an anti-oxidant-

AND methylation of NE by phenyl ethanolamine n- transferase which uses **S-adenosyl methionine(SAM) as a methyl donor produces epinephrine



Dopamine and norepinephrine are synthesized in the brain and function as neurotransmitters.

Norepinephrine and epinephrine are also synthesized in the adrenal medulla

Outside the nervous system, norepinephrine and epinephrine, are hormone regulators of **carbohydrate and lipid metabolism**.

Norepinephrine and epinephrine are released from storage vesicles in the adrenal medulla in response to fright, exercise, cold, and low levels of blood glucose to increase

the degradation of glycogen and TAG, they also increase blood pressure and the output of the heart (to prepare for "**fight-or-flight**" reactions).

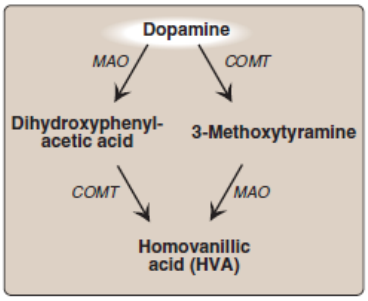
Catecholamines (CA) degradation

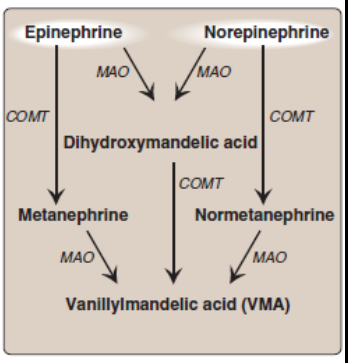
****whether it epinephrine, NE or dopamine the enzymes involved in degradation are the same but the final products differ

There are 2 types of enzymes involved in "CA" degradation:

1-**MonoAmine Oxidase (MAO)**: catalyzes the Oxidative deamination of CA
2- **catechol-O-methyltransferase (COMT)**: catalyzes the O-methylation by using SAM as the methyl donor

In CA degradation **either** MAO starts the pathway and COMT finishes **OR** vice versa "check the pictures"





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

**For a specific CA those 2 alternating pathways intermediates are different but the final products are the same.

Final product of **NE and epinephrine** degradation is **VMA** WHILE the final product of **dopamine** degradation is **HVA**

WHICH WILL BE EXCRETED IN THE URINE

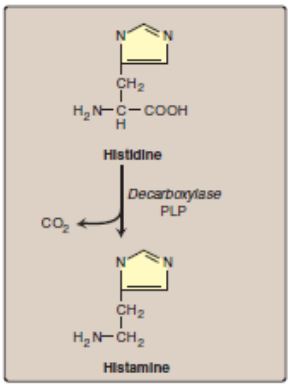
VMA is increased with pheochromocytomas (adrenal tumor with **increased catecholamine production)

CLINICAL APPLICATION: is the use of MAO inhibitors to increase or sustain excitation in the body by increasing CA concentrations, which improves the mood and is used as antidepressants but they have many side effects so they are not preferable ALSO they reduce metabolism of serotonin increasing its concentration consequently improve the mood.

TAKEAWAYS: MAO inhibitors inhibit CA degradation and serotonin→ increase their concentration→improve the mood by activation of NE and serotonin receptors.

Notes from the slides: *MAO INHIBITORS RXN IS :Irreversible or reversible MAO inactivation*
Neurotransmitter "WHEN a MAO inhibitor IS ADDED "escape degradation, accumulate within the presynaptic neuron and leak into the synaptic space.
MAO is found in neural and other tissues, such as the intestine and liver.

HISTAMINE



Which is an amine formed by decarboxylation reaction of histidine using **Coenzyme PLP.**

REMEMBER: to convert amino acid to an amine we need a decarboxylation reaction.

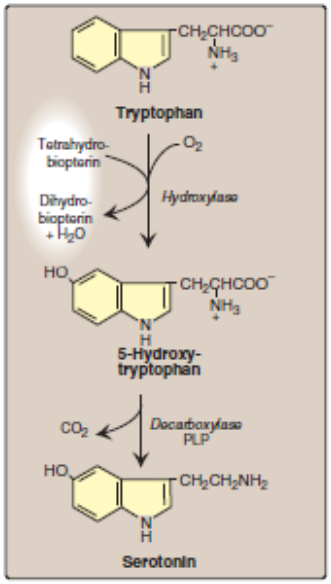
The Main function of histamine is **vasodilation** in allergic reactions, like spring allergies in which histamine is secreted by "**mast cells and eosinophils** "
**Vasodilation occurs which leads to edema that applies pressure on the airways making it hard to breathe we treat this case by using ANTI-HISTAMINE.

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

TAKEAWAYS: histamine formation reaction , histamine functions , histamine producing cells

Serotonin OR 5-hydroxytryptamine

*it's precursor is : **tryptophan** "amino acid" .



Steps of synthesis :1- hydroxylation of tryptophan using hydroxylase which use **BH4 as coenzyme** to produce 5-hydroxy tryptophan.

2- decarboxylation " to form an amine" by decarboxylase using **PLP** to form serotonin

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)

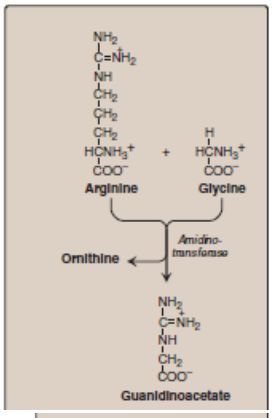
Melatonin

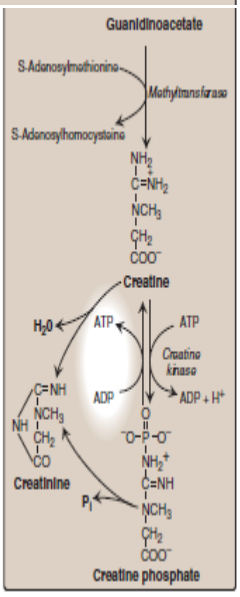
Melatonin is formed and secreted by the **pineal gland** which is found in the brain via acetylation and methylation of serotonin.

Melatonin's main function → Circadian rhythm (**night-day regulation of sleep**),in the night → high melatonin levels… during the day→ low melatonin levels

When you travel over a large distance your body still needs to accommodate to the new day and night cycle known as "Jet lag". You will need 2 or 3 weeks until the hormones are secreted at the right time (for the new country). Melatonin can also be bought over the counter so you use it to reduce the time needed for accommodation.

Creatine





Source of energy especially for muscles BUT must be phosphorylated to provide energy in this phosphate group.

Creatine is made up of two amino acids: Glycine & Arginine

The carbon with two nitrogen atoms on arginine is given to glycine (similar to urea cycle) to produce Guanidinoacetate.The rest of the arginine will be released as **ornithine**

Guanidinoacetate will be converted to creatine by a methylation reaction using SAM as a methyl group donor and the enzyme methyl transferase.

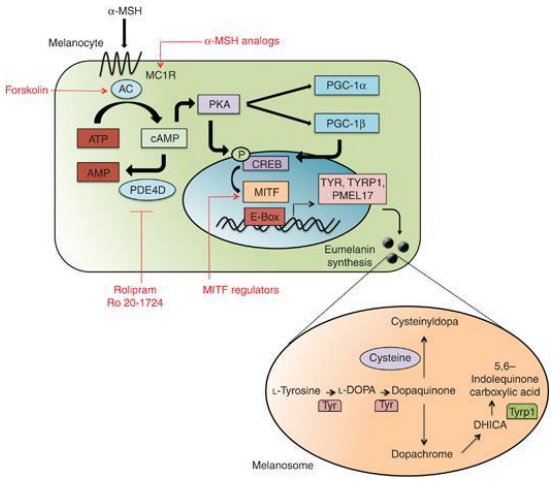
Creatine will be converted to creatine phosphate by action of the enzyme creatine kinase which uses up one ATP.

Creatine is phosphorylated giving it a high energy bond which gets hydrolyzed to provide energy.

<u>The presence of creatine kinase in the plasma indicates heart damage, and is used in the diagnosis of MI.</u>

The amount of creatine phosphate is proportional to the muscle mass.Creatine phosphate or phosphocreatine which is a high-energy compound found in muscle and provides a small but rapidly mobilized reserve of high energy phosphates.

Creatine degradation : Conversion of creatine molecule to a Cyclic compound (cyclization reaction producing a 3 membered ring). The compound produced is called creatinine.



Creatinine

Which is Sensitive indicator for **kidney function**. As its going to be excreted through **urine**.

Excreted creatinine amount is proportional to the total creatine phosphate content of the body, thus can be used to estimate muscle mass.when muscle mass decreases (paralysis or muscular dystrophy), the creatinine content of the urine falls.

a typical adult excretes about 15 mmol of creatinine per day."A healthy person's blood sample contains very LOW creatinine".

If the person has a problem with his kidney -> creatinine will remain in blood as it is not excreted therefore the level in blood will be Very HIGH.

It is a LATE marker of Kidney failure so it does not detect a problem in kidneys early on, the person will most likely need dialysis.

Melanin

Melanin is a pigment produced by melanocytes which are found in the *skin, hair and the eyes*.melanin protects the underlying cells from the harmful effects of sunlight ,a defect in melanin production results in albinism (most common form is due to defects in copper-containing tyrosinase)

They produce melanin specifically in a small particle called melanosome. It starts with Tyrosine → DOPA (like catechol amines)→ DOPA quinone which undergoes a series of reactions to produce two types of melanin:Eumelanin (real melanin) AND Pheomelanin.

Eumelanin is found in everyone in varying degrees.

Increase in concentration of eumelanin ➔ Darker hair, skin and eyes

Decrease in concentration of eumelanin ➔ lighter hair, skin and eyes ➔ blond like Western countries.

Red haired individuals (Gingers) have Pheomelanin which gives the red color (so it's not varying degrees but rather a **different type of melanin**).

*When you go outside to tan (sunlight) your skin color becomes darker. In winter you skin color returns to normal when there is less sunlight. SO What actually happens?

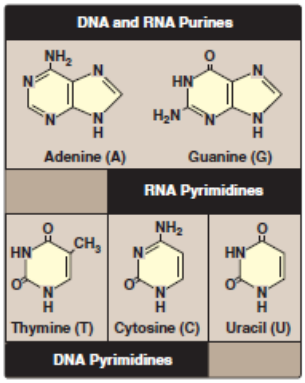
Melanin is produced in melanocytes but it doesn't have to stay in them, melanin moves to the skin cells. The transportation of melanin to the skin cells (superficial Cells) from melanocytes (which are deep in the skin) **is light sensitive**. When you are exposed to the sunlight it acts as a stimulus making them move up the layers giving you the darker color since it has moved to the superficial layer also the **production of melanin** ↑

When there is no sunlight➔ no stimulus ➔ they move back down the layers ➔ giving you the lighter color

~Done with Amino Acids~

Nucleotide Metabolism

Nucleotides are found in :**DNA and RNA** & **ATP and GTP** & Coenzymes /election carriers such as **NAD+, FAD and NADP+** & Carriers of activated intermediates in the synthesis of some carbohydrates, lipids and conjugated proteins, such as **UDP-glucose and CDP-choline** & Second messengers in signal transduction pathways such as **cAMP and cGMP** & they act as ***regulatory compounds*** for many metabolic pathways by inhibiting or activating key enzymes.



Classified into 2 major groups : **purines & pyrimidines** which share structural features

little of purines and pyrimidines supplied by the diet are utilized, and are degraded instead " from the slides"

Purines: Have two rings (a 5 membered ring connected with 6 membered ring) …they include adenine and guanine.

Pyrimidines: They have a 6 membered ring with different modifications to produce each different pyrimidine including :Cytosine (C) & Uracil (U) &Thymine (T) "CUT"

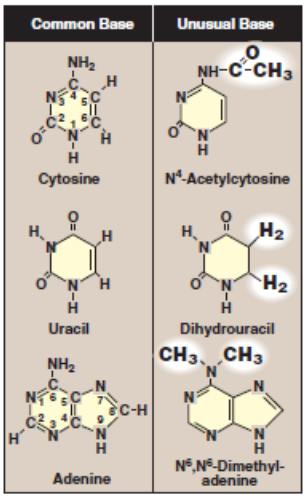
Synthesis of nucleotides (purines and pyrimidines) occurs in two ways in cells:
1- De Novo synthesis (from scratch): Start collecting the atoms that are present within

the ring from different sources such as sugar and phosphate and then add them together to form the nucleotide.

2-Salvage pathways: Which are faster and somewhat easy. **Examples on salvaged things : like salvaged cars or PC's

Nucleotides Structure: The nitrogenous bases can be modified , which can occur normally in aging or through normal regulatory processes

Examples on modifications : Acetylation** ➔ addition of ch3-c=o group especially to Cytosine, **Reduction**, **Methylation**,**Glycosylation**. The main purpose for modification is for Gene Silencing and Gene activation



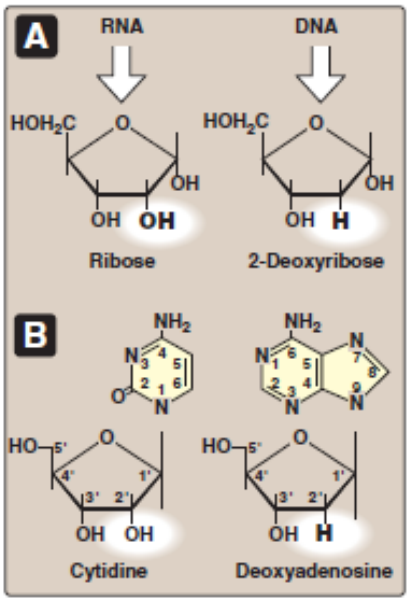
The presence of an unusual base in a nucleotide sequence may aid in its recognition by specific enzymes, or protect it from being degraded by nucleases.

Most of the time when methylation occurs in a certain gene it results in turning the gene off ➔ we don't want to produce mRNA and protein from it.

Most of the time when acetylation occurs in a certain gene it results in turning the gene on ➔ mRNA and Protein produced

Nucleotides are made up from: 1-**Pentose sugar** (which can be either **ribose or 2-deoxyribose**) ,2- **Phosphate/s** "can be 1 such as in DNA or RNA , can be 2 such as in ADP,can be 3 such as in ATP or GTP therefore, it is variable , **3- Nitrogenous base**

Pentose Sugar + Base = **Nucleoside** (no phosphate)



Ribose +base = ribonucleoside

the ribonucleosides of A, G, C, and U are named Adenosine, guanosine, cytidine, respectively.

2-deoxyribose + base = deoxyribonucleotide.

the deoxyribonucleosides of A, G, C and T are named deoxyadenosine, deoxyguanosine, deoxycytidine, and deoxythymidine, respectively.

numbering is separate and different (prime and on prime)

Underlined sentences are from the slides

Nucleoside + one or more Phosphates = Nucleotide

the first P group is attached by an ester linkage to the 5’-OH of the pentose forming a nucleoside 5’-phosphate or 5’-nucleotide

The type of pentose is denoted by the **prefix** in the names “5'-ribonucleotide” and “5'-deoxyribonucleotide.”

The second and third phosphates are each connected to the nucleotide by a “high-energy” bond.higher than the first , The phosphate groups are negatively charged causing DNA and RNA to be nucleic acids.

Note: having the -**sine** suffix means that it is a **nucleoside** ,An example is Adenosine Mono Phosphate (AMP) (a nucleotide)

Why is this naming scheme important?

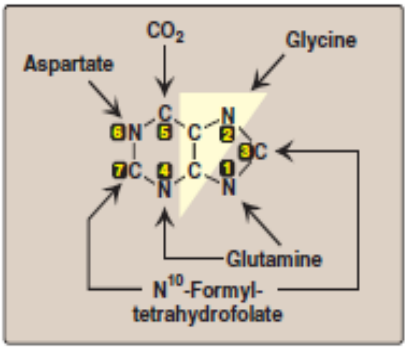
It allows us to distinguish the number of phosphates present in the nucleotide by first giving the nucleoside and then the number of phosphates.

Going back to De Novo synthesis …We will find out the source of each atom present in the purines and pyrimidines

Molecules that are used in purines and pyrimidines synthesis:

1-Amino acids : are used to provide Nitrogen atoms, EX: glutamine , aspartate , glycine

2- CO_2 coming from decarboxylation or Krebs cycle is used to provide carbon.

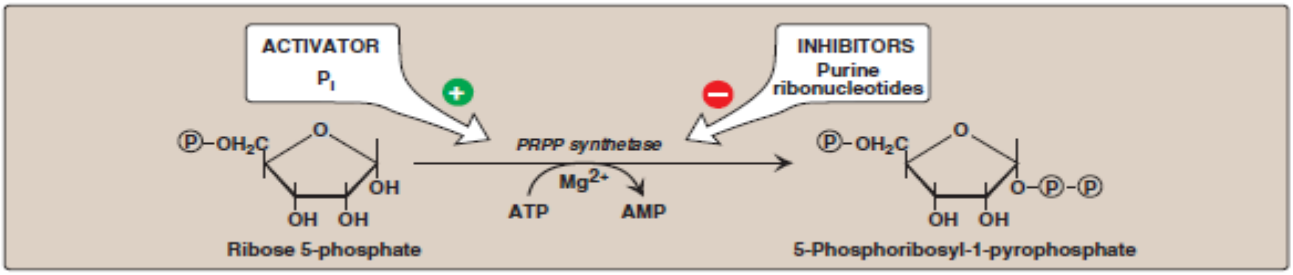


3- Tetrahydrofolate :Especially **N10-formyltetrahydrofolate** which provides carbon to the formation of purines

The purine ring is made primarily in the liver by a series of reactions that add the donated carbons and nitrogen atoms to a preformed ribose 5-phosphate. Ribose 5-phosphate is synthesized by the pentose phosphate pathway

Note : We will concentrate on the pathway as a whole since there are very hard intermediates that are difficult to memorize as they are long words, we will care about how the process occurs, we will however memorize specific intermediates which are important.

Purine Synthesis



First step is :PRPP Production (5-phosphoribosyl-1-pyrophosphate)

Ribose-5-phosphate is converted to PRPP Using the enzyme PRPP Synthetase which is also known as Ribose phosphate pyrophosphate kinase which Uses an ATP molecule that is converted to AMP (2 phosphates removed) …Mg2+ needed

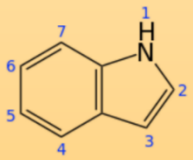
PRPP : Is an active compound in which you build upon the purine structure.

~Next steps will be explained in the next lectures~

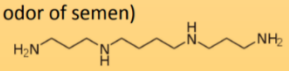
These slides were not mentioned by the doctor

Nitrogen-containing compounds synthesized from AA

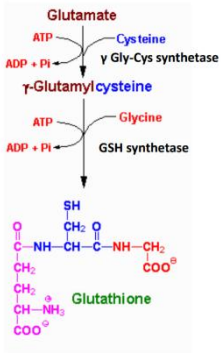
- Serine → ethanolamine + choline +Acetyl-CoA → Acetylcholine
- Gly + Succinyl-CoA → Heme
- Trp+ GI bacteria → Indoles
- Trp in the liver → Nicotinamide



- Glu → GABA (inhibitory neurotransmitter)
- Lys methylation → → → → Carnitine
- Ornithine → → → → Spermine (characteristic odor of semen)

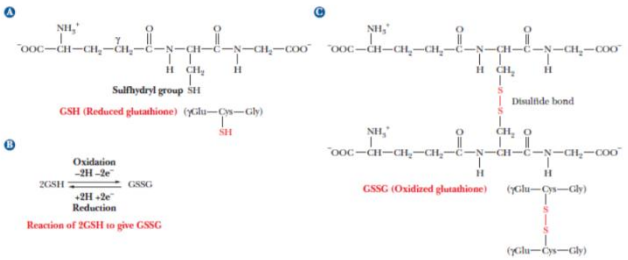


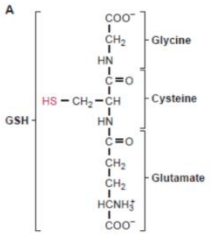
Glutathione



Glutathione

- Glu+Cys+Gly

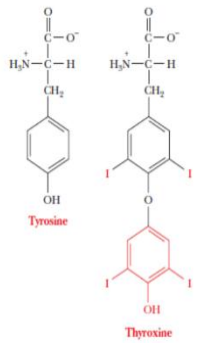




Functions:

- ✓ Reductant
- ✓ Conjugation of drugs (more polar)
- ✓ Transport of AA across cell membrane
- ✓ Cofactor
- ✓ Facilitate rearrangement of protein S-S bridges

Thyroxine



Test yourself

1-the reagent used in bilirubin tests is :

a) diazotized sulfanilic acid
b) ALA dehytratase
c) Glucurunate
d) Guanidinoacetate

2-serotonin is converted to melatonin by :

a) acetylation and methylation of serotonin in the parathyroid gland
b) acetylation and methylation of serotonin in the pineal gland
c) acetylation and hydroxylation of serotonin in the pineal gland
d) acetylation and methylation of cystine in the pineal gland

3- N10-formyltetrahydrofolate :

a) provides nitrogen to the formation of purines
b) provides carbon to the formation of pyrimidines
c) provides carbon to the formation of purines
d) provides nitrogen to the formation of pyrimidines

4-presence of creatine kinase in the plasma indicates

a) liver damage
b) kidney failure
c) arthritis
d) MI and heart damage

Special thanks to GJU's laith haddad , jamal alzu3bi from cyprus and fawzi radwan for their efforts in writing this sheet

FLIP YOUR SHEET FOR ANSWERS

ABCD