METABOLISM

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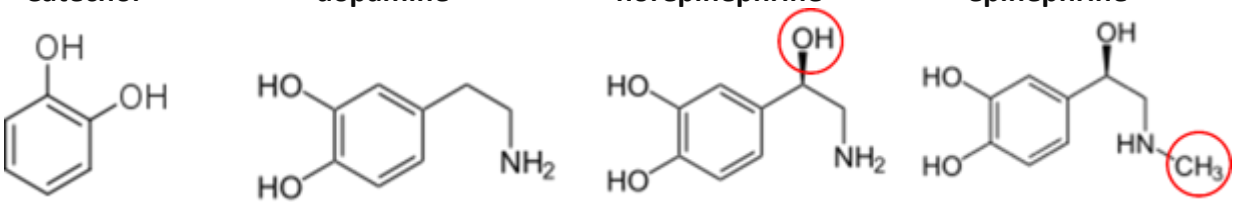
NITROGEN CONTAINONG COMPOUNDS

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:

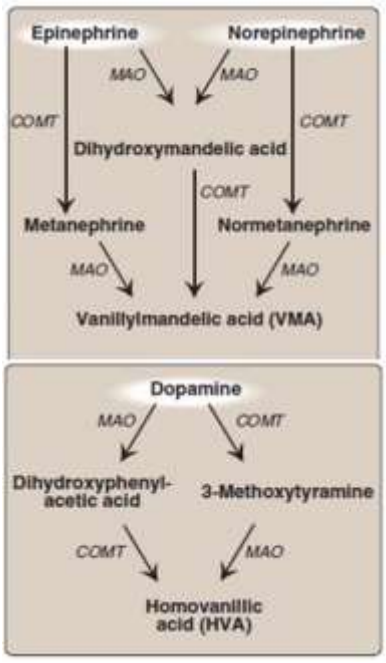
Catecholamines are degraded by to mechanisms:

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.

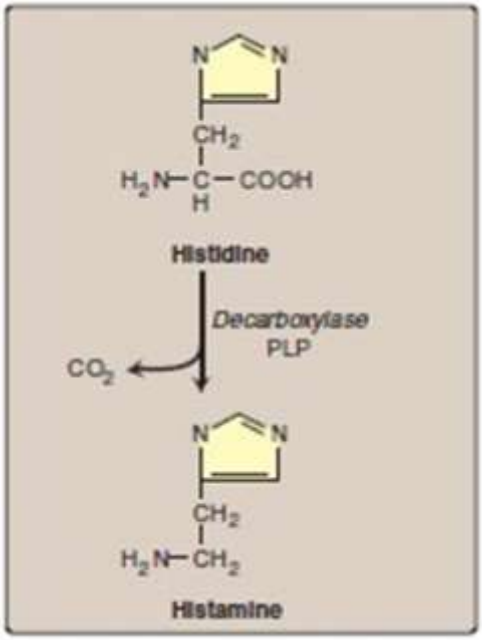
VMA is increased with pheochromocytomas (adrenal tumor with increased catecholamine production).

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.

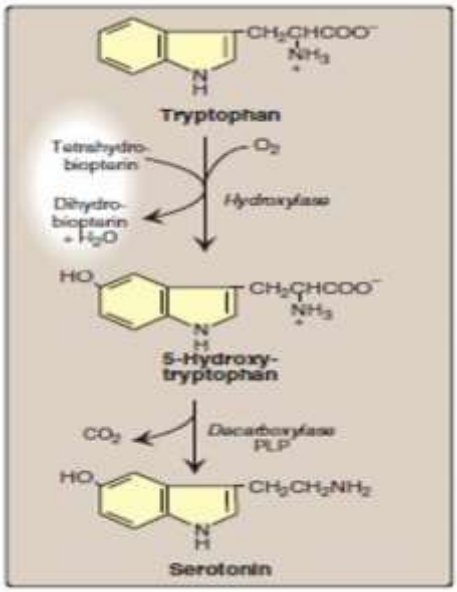
Histamine:

- **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.



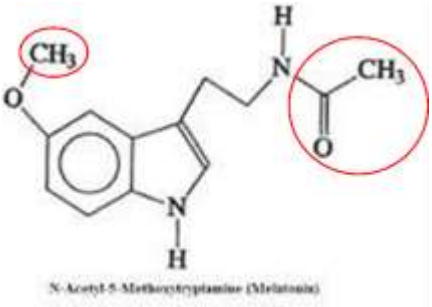
Serotonin, or 5-hydroxytryptamine (5HT):

- 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).

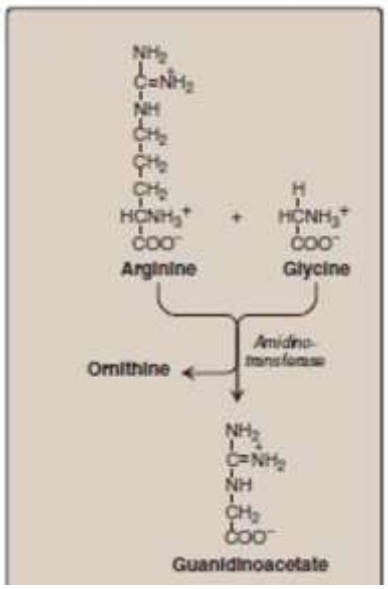


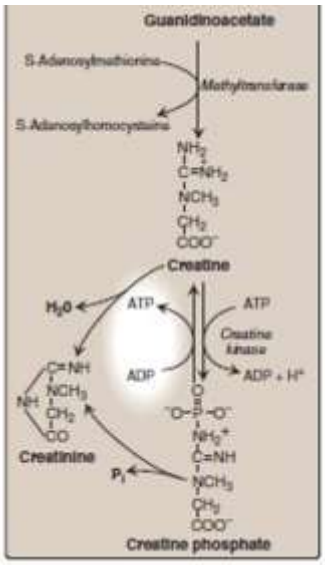
Melatonin Hormone (Sleep Hormone):

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



Creatine:





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:

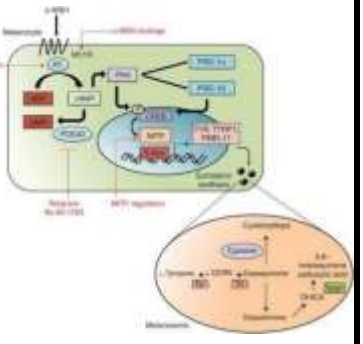
Creatine is converted to **creatinine** in a **cyclization** reaction to be excreted in urine. (A typical adult male excretes ~15 mmol of creatinine per day).

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

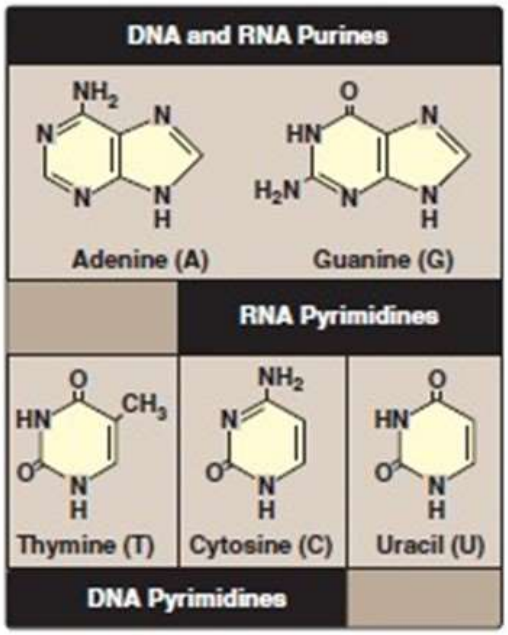


In the melanocytes of the epidermis specifically melanosomes melanin is produced. Melanin gives the eyes hair and skin their colors as well as it protects the underlying cells from the harmful effects of sunlight. Defect in melanin production results in albinism (the most common form is due to defects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

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).

New topic 😊

NEUCLOTIDES METABOLISIM



Purine and pyrimidine structures and functions:

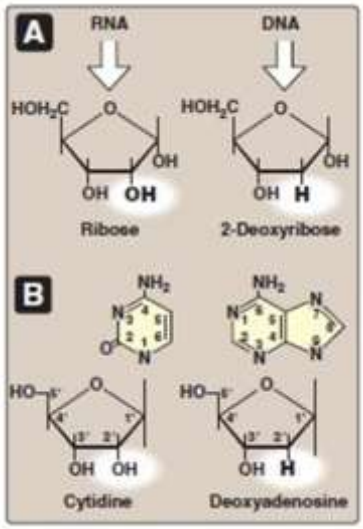
- Pyrimidines (thymine, cytosine, and uracil) composed from one ring made from 6 carbons while purines (adenine and guanine) composed from 2 rings → five membered ring and six membered ring fused to each other.
- Since nucleotides contain purines or pyrimidines (nitrogenous bases) therefore nucleotides considered as a one of the nitrogen containing compounds.
- Purines and pyrimidines are very important molecules that are found in nucleotides and serve different functions:
  1) Essential for RNA and DNA synthesis (deoxyribonucleic acid and ribonucleic acid).
  2) They serve as carriers of activated intermediates in the synthesis of some carbohydrates, lipids, and conjugated proteins, such as, UDP-glucose (glycogen synthesis) and CDP-choline (membrane lipid synthesis).
  3) They are structural components of several essential coenzymes, such as coenzyme A, FAD, NAD+, and NADP+.
  4) They serve as second messengers in signal transduction pathways, such as cAMP and cGMP.
  5) They are "energy currency" in the cell (ATP).
  6) They act as allosteric regulatory compounds for many metabolic pathways by inhibiting or activating key enzymes (eg: ADP, AMP ….).

Nucleosides:

- This method is used to name compounds that contain only sugar and a nitrogenous base, to indicate the number of phosphates that the compound contains.

  The main rule → (Nucleoside= Pentose sugar + Base).

  Eg: ATP can be named as adenosine Triphosphate, "sine" suffix is used to indicate the presence of nucleoside (sugar + nitrogenous base) as well as the number of phosphate groups attached to the nucleoside. However, ATP can be named as a "Nucleotide" with no indication for the number of phosphate groups.

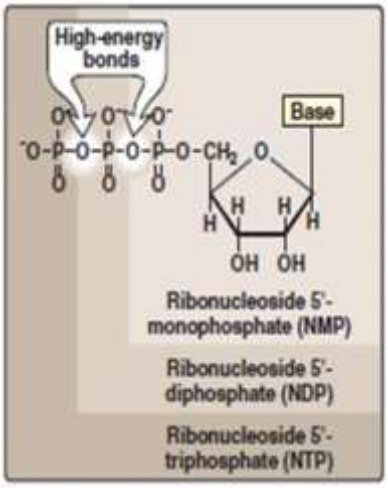


- (Ribose + base = Ribonucleoside).
  Eg: The ribonucleosides of A, G, C, and U are named **adenosine, guanosine, cytidine, and uridine**, respectively.

- (2-deoxyribose + base = deoxyribonucleoside.)
  Eg: The deoxyribonucleosides of A, G, C, and T are named **deoxyadenosine, deoxyguanosine, deoxycytidine, and deoxythymidine**, respectively. (Deoxy sugars are sugars that have had a hydroxyl group replaced with a hydrogen atom).

  Recall: the carbons in the sugar molecule are numbered with a prime 1', 2' while the carbons of the nitrogenous bases are named without prime (Observe the picture).

Nucleotides:



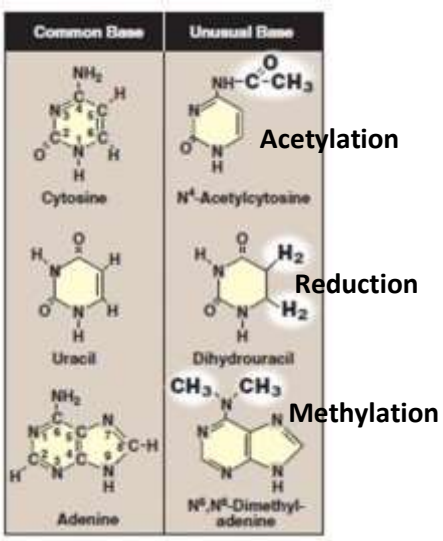
- This method is used to name compounds that contain sugar, nitrogenous base and phosphate without any indication for the number of phosphates that the compound contain.

  (Nucleoside + one or more phosphate groups= Nucleotide).

- The first P group is added by an ester linkage to the 5'-OH of the pentose forming a **nucleoside 5'-phosphate** or a **5'-nucleotide**. The second and third phosphates are each connected to the nucleotide by a "high-energy" bond.
  (Nitrogenous base is added to the pentose on the 1' carbon and the phosphate group is added on the 5' carbon).

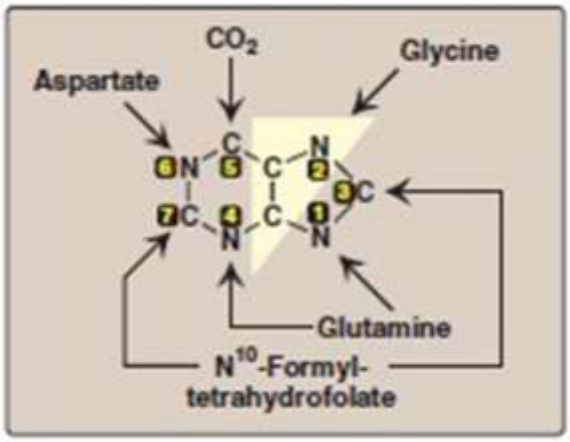
  Recall: The phosphate groups are negatively charged causing DNA and RNA to be nucleic acids.

Base modification:



- Nitrogenous bases specifically in the DNA or RNA structures are more susceptible for further covalent epigenetic modifications. Therefore, nucleotide sequences are more able to be recognized by specific enzyme or to be protectable from degradation from certain nucleases.
- *__Methylation__ for nitrogenous bases is important in gene silencing → preventing transcription factors from binding accordingly no gene expression occur.
  *__Acetylation__ for nitrogenous bases is usually associated with gene activation → allowing for transcription factors to bind accordingly more activation for gene expression. `
  *__Reduction__ is important in URICIL.
  *__Glycosylation__ by adding sugars.

Nucleotides (IMP) and Purine synthesis:



The purine and pyrimidine bases are synthesized in well fed state (excess of energy) in two ways: 1) **de novo** (From A to Z). 2) **salvage pathways** (reuse of the preformed bases resulting from normal cell turnover).

Little of the purines and pyrimidines supplied by diet are utilized, and are degraded instead

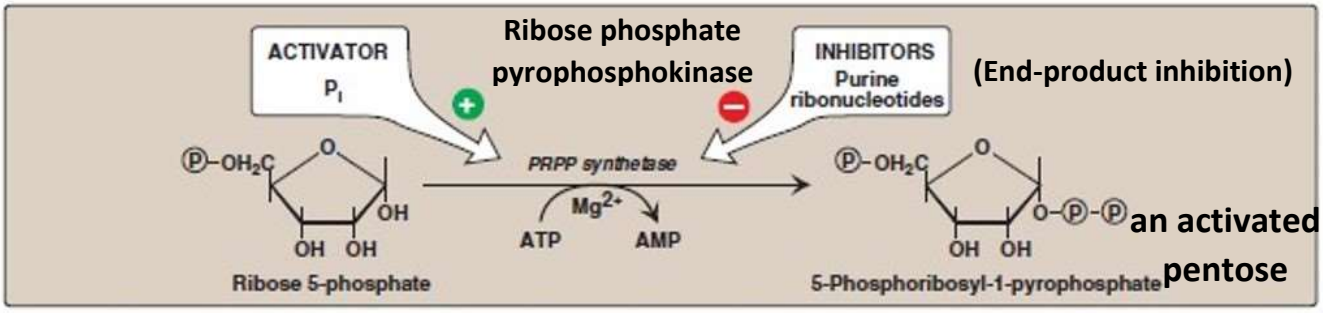
The contributing compounds in purine synthesis are:

1) Amino acids (aspartate, glycine, and glutamine) the major component in purine synthesis used as a source of carbons as well as nitrogen.
2) CO_2.
3) N10-formyltetrahydrofolate.

The purine ring is constructed primarily in the liver by a series of reactions that add the donated carbons and nitrogens to a preformed ribose 5-phosphate.

STEPS OF THE REACRIONS (de novo synthesis of purines):

STEP1:

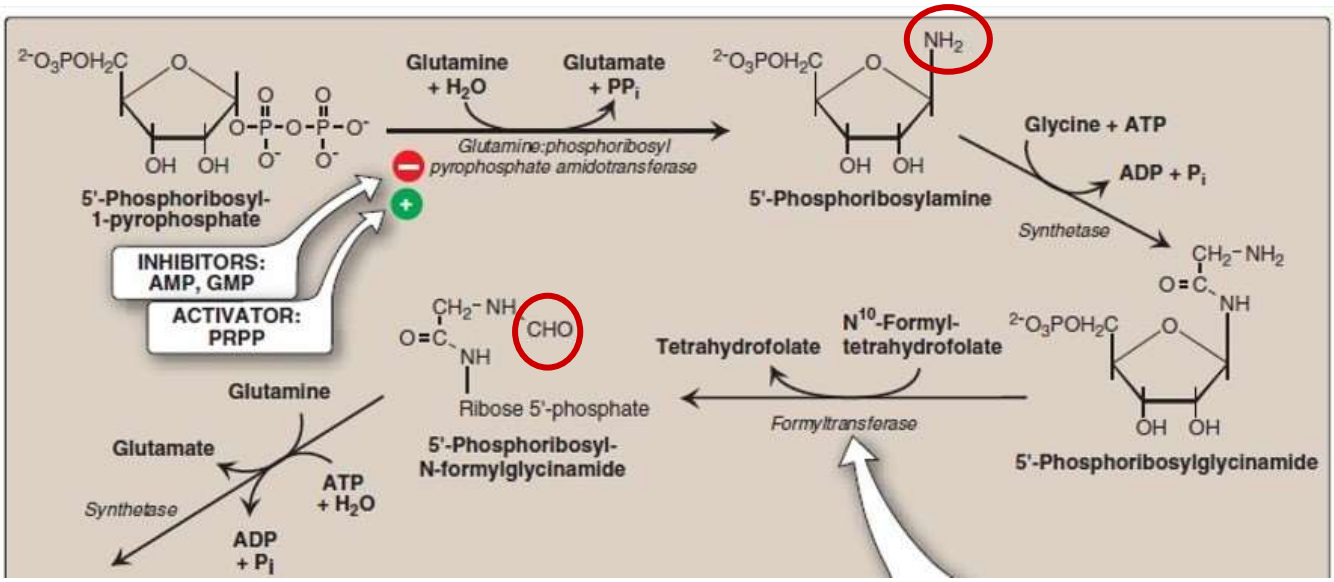


Ribose-5-phosphate that comes from pentose phosphate pathway is activated by adding pyrophosphate on the carbon no.1 in a phosphorylation reaction converting ATP to AMP. The product of this activation reaction is **5-phosphoribosyl-1-pyrophosphate (PRPP).** This step is catalyzed by **Ribose phosphate pyrophosphokinase (PRPP synthetase).**

-Notice that pyrophosphate is added on carbon no. 1 where purine synthesis will take place. Therefore, pyrophosphate works as a sign to complete the reaction in nucleotide synthesis-

Regulation:

Inorganic phosphates are considered as allosteric activators for PRPP synthetase enzyme. While excess of purine ribonucleotides the final product produced considered as an allosteric inhibitor.



STEP 2: **Synthesis of 5'-phosphoribosylamine** (the committed step in purine nucleotide biosynthesis).

Glutamine donates its own amine group to **PRPP** in the presence of **H2O** producing

5'-phosphoribosylamine. Notice that pyrophosphate is removed, and glutamine converted to glutamate.

The first source of nitrogen in purine and pyrimidine synthesis is from glutamine AA

Regulation:

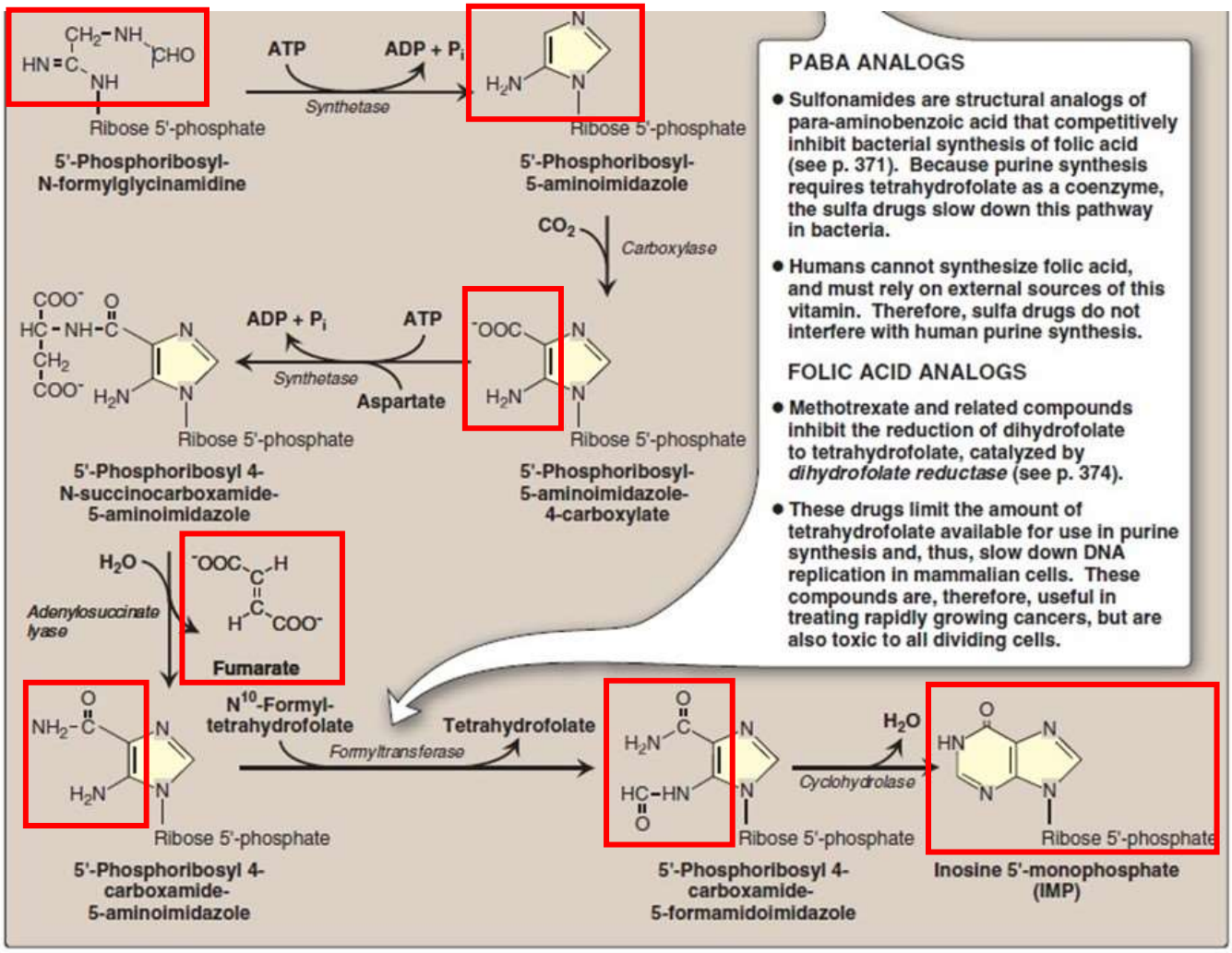
AMP and GMP are considered as allosteric inhibitors for this step while PRPP is an allosteric activator

STEP 3: (consists of 9 sub-steps leads to the synthesis of inosine-5'-monophosphate (IMP)**).**

- **Glycine AA** is attached to the amine group (observe the picture above) forming the first 4 atoms of purine's first ring. -ATP dependent step-
- Carbonyl group is added from **N10-formyl-tetrahydrofolate** forming 5 atoms of purine's ring.
- Amine group is added from **glutamine** and **cyclization reaction** occur producing the first ring of purine structure and the first nitrogen atom in the second ring. -ATP dependent step-
- Adding **CO_2** molecule forming the first 4 atoms of the second ring. (2 atoms from the first ring in addition to the amine group and CO_2).
- **Aspartate AA** gives the 5^{th} atom (nitrogen) of the second ring and leaves the reaction as fumarate.
- A carbonyl group is added from **N10-formyltetrahydrofolat** (6^{th} atom of the second ring).

- **Cyclization reaction** occur and finally the two rings of purine are ready. This step produces **inosine 5'-monophosphate IMP** (Inosine-5'-monophosphate= purine ring + sugar + phosphate).

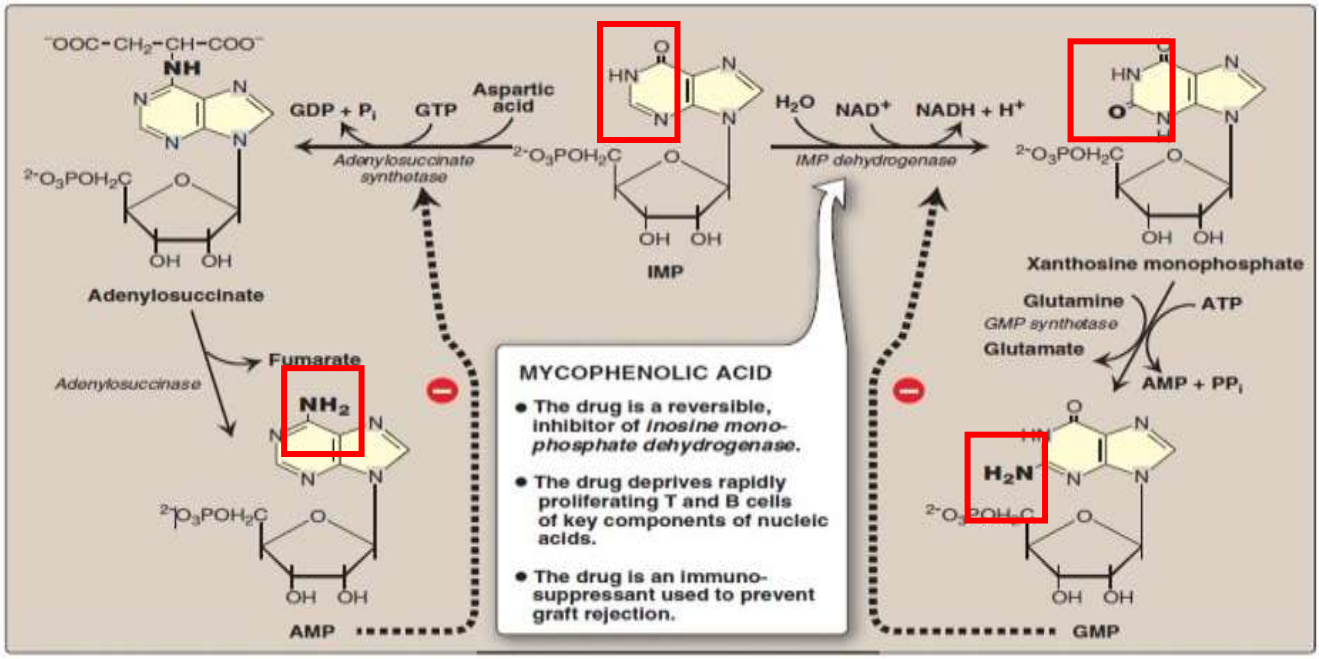
تبعوا مع الصور كل خطوة بخطوتها عشان تفهموا , التفاصيل المطلوب حفظها مكتوبة بالخطوات فوق و حاولوا احضرو مع الدكتورة لانها كانت تختصر الخطوات , فاحضروا المحاضرةعشان تفهموا مزبوط وين تركزوا.



Conversion of IMP to AMP and GMP: (observe the picture below)

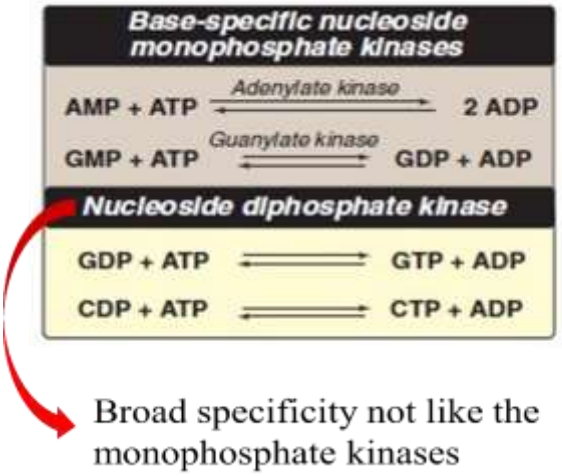
Recall that there are two types of purines; adenine and guanine → the difference between them is only in the position of amine group. In the previous pathway IMP is synthesized and ready to be modified into AMP or GMP.

- AMP:
  *__Aspartate__ is added to IMP as a source of nitrogen and **GTP** as a source of energy producing **adenylosuccinate**. This step is catalyzed by **adenylosuccinate synthetase**.
  *Fumarate is released producing AMP.
  Regulation: AMP is an allosteric inhibitor (feedback inhibition).
- GMP:
  *IMP got oxidized by **IMP dehydrogenase** producing **Xanthosine monophosphate** and NADH.
  *__Glutamine__ is added as a source of nitrogen and **ATP** as a source of energy producing GMP.
  Regulation: GMP is an allosteric inhibitor (feedback inhibition).



Conversion of AMP and GMP to ADP/ATP and GDP/GTP respectively:

Phosphate groups are added separately so that one phosphate group is added each time by different enzyme. Accordingly, the enzymes that is responsible for adding the first phosphate group are specific enzymes **"Base specific nucleoside monophosphate kinases"** for each nucleotide. While the enzymes that is responsible for adding the second phosphate group are not specific **"nucleoside diphosphate kinase".**



- AMP is phosphorylated to ADP by **adenylate kinase (AK)** and GMP is phosphorylated to GDP by **guanylate kinase**.
  Both AMP and GDP hydrolyze ATP as a source of phosphate since it is present in higher concentrations than the other nucleoside triphosphates.
- GDP and ADP are phosphorylated to GTP and ADP respectively by **nucleoside diphosphate kinase**. Both AMP and GDP hydrolyze ATP as a source of phosphate (the enzyme that catalyzes this step can phosphorylate any type of nucleotide, whether these nucleotides contain purines or pyrimidines).

  NOTE: Base-specific nucleoside monophosphate kinases do not discriminate between ribose or deoxyribose in the substrate and Adenylate kinase (AK) is particularly active in liver and muscle also AK maintains an equilibrium among AMP, ADP, and ATP

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