Purine Metabolism

Dr.Abrar Albadr
M.B.Ch.B FIBMS (Chem.Pathology)

Nucleotides

Nucleotides are the building blocks of the nucleic acids, and essentials for all cells, without them neither DNA nor RNA can be produced and therefore protein cannot be synthesized or cell proliferate.

•The nitrogen- containing bases belong to two families of compounds: the purines and the pyrimidines.

•Both DNA and RNA contain the same purine bases: adenine (A) and guanine (G) , Both DNA and RNA contain the pyrimidine cytosine (C), but they differ in their second pyrimidine base: DNA contains thymine (T), whereas RNA contains uracil (U).

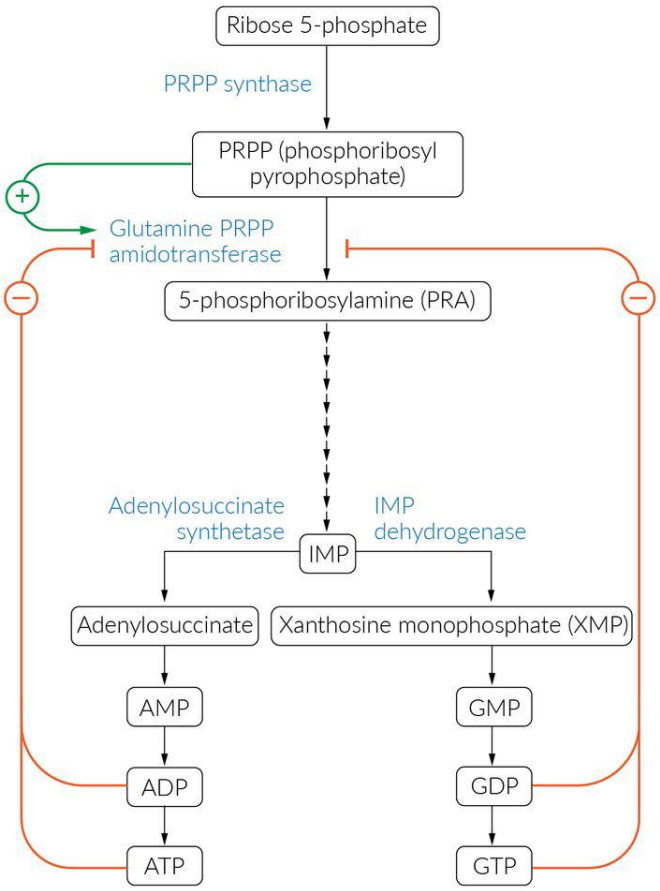
•The addition of a pentose sugar to a base produces a nucleoside.
•The addition of one or more phosphate groups to a nucleoside produces a nucleotide.

Synthesis of purine nucleotides :

The purine bases found in the nucleotides can be synthesized by:
De Novo: from the beginning, occurs primarily in the liver .

Salvage (saving) pathway: allow the reuse of the preformed bases resulting from normal cell turnover or from the diet.
It accounts for 90% of daily purine biosynthesis and it require less energy than de novo pathway, occurs primarily in the extrahepatic tissues

De Novo pathway



Synthetic inhibitors

Sulfonamides

- Structural analogs of para-aminobenzoic acid that competitively inhibit bacterial synthesis of folic acid .
- Because purine synthesis requires THF as a coenzyme, the sulfa drugs slow down this pathway in bacteria.
- Humans cannot synthesize folic acid, and must rely on external sources of this vitamin. Therefore, sulfa drugs do not interfere with human purine synthesis.

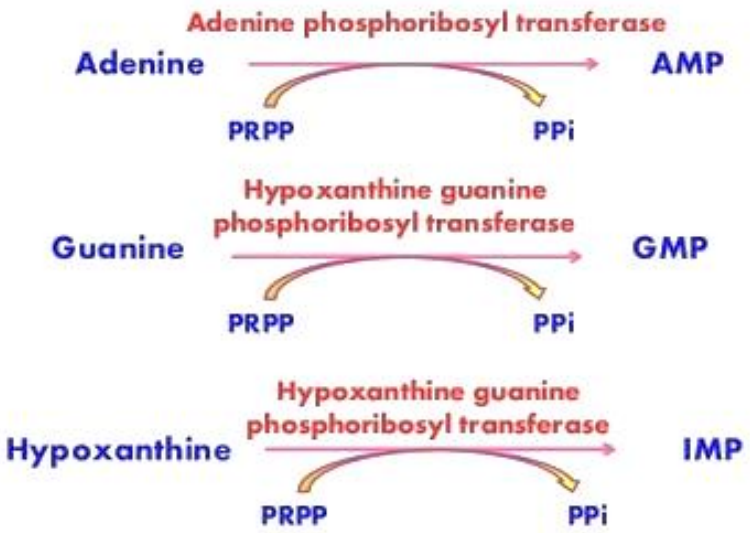
Trimethoprim: is another structural analog of folic acid ,act as a competitive inhibitor of dihydrofolate reductase in bacteria thus inhibit THF.

Methotrexate: is structural analog of folic acid interfere with synthesis of nucleotide, it inhibit the reduction of DHF to THF by dihydrofolate reductase so limit the amount of THF for purine synthesis and thus DNA replication.

Mycophenolic acid:

- It is a reversible inhibitor of IMP dehydrogenase
- It is an immunosuppressant used to prevent graft rejection.
- It block de novo synthesis of GMP ,so deprive the rapidly proliferating (T and B cells) of key components of nucleic acid.

Salvage pathway



Lesch–Nyhan syndrome

It is a rare X-linked recessive disorder associated with a virtually complete deficiency of HGPRT.

- This deficiency results in an inability to salvage hypoxanthine or guanine, from which excessive amounts of uric acid are produced .

- Hyperuricaemia occurs in young males.
- It is associated with mental deficiency, a tendency to self-mutilation, aggressive behavior and spastic paraplegia.

Synthesis of deoxyribonucleotides

DNA requires deoxyribonucleotides.

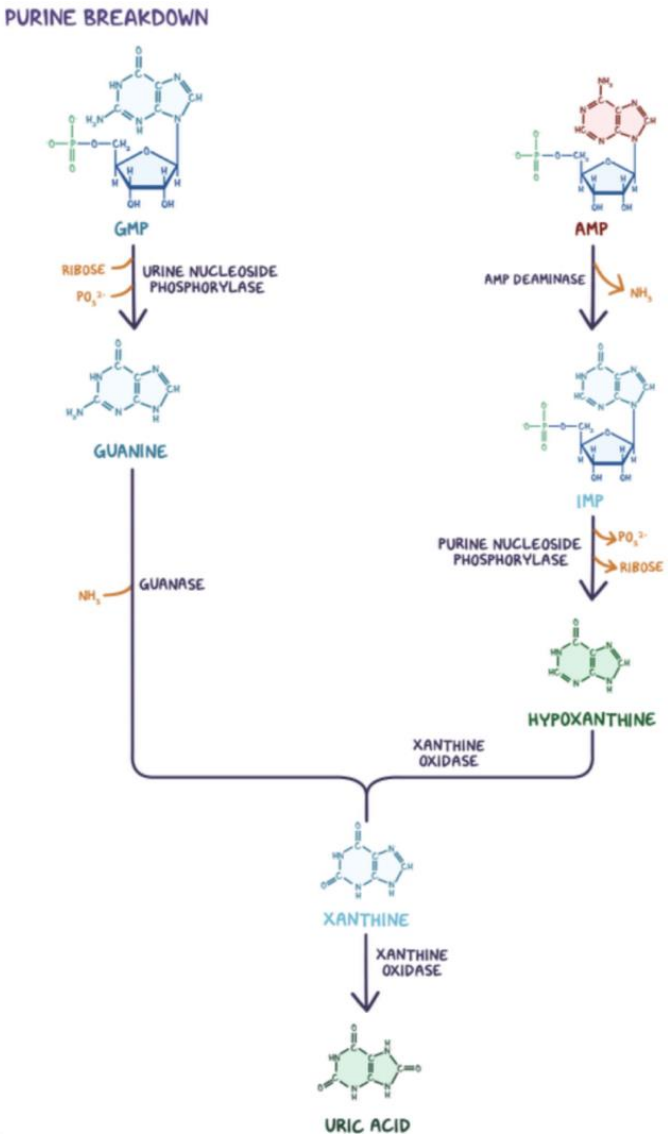
- Nucleoside diphosphates are reduced by ribonucleotide reductase formingdeoxyribonucleoside diphosphates .
- This enzyme active only when cells are synthesizing DNA preparing for cell division .

Ribonucleoside diphosphate —**Ribonucleotide reductase**→ **Deoxyribonucleoside diphosphate**

Degradation Of Purine Nucleotide:

Degradation of dietary nucleic acids occurs in the small intestine, where a family of pancreatic enzymes hydrolyzes the nucleic acids to nucleotides

Inside the intestinal mucosal cells, purine nucleotides are sequentially degraded by specific enzymes to nucleosides and free bases, with uric acid as the end product of this pathway.


PURINE BREAKDOWN
GMP
RIBOSE
PO_3^{2-}
URINE NUCLEOSIDE PHOSPHORYLASE
GUANINE
NH_3
GUANASE
AMP
AMP DEAMINASE
NH_3
IMP
PURINE NUCLEOSIDE PHOSPHORYLASE
PO_4^{3-}
RIBOSE
HYPOXANTHINE
XANTHINE OXIDASE
XANTHINE
XANTHINE OXIDASE
URIC ACID