CATABOLISM OF PURINE NUCLEOTIDES

The end product of purine metabolism in humans is uric acid.

The nucleotide monophosphates (AMP, IMP & GMP) are converted to their respective nucleoside forms (adenosine, inosine & guanosine) by the action of nucleotidase.

The amino group, either from AMP or adenosine, can be removed to produce IMP or ionosine. Inosine & guanosine are converted to hypoxanthine & guanine (purine bases) by purine nucleoside phosphorylase.

Adenosine is not degraded by this enzyme, it has to be converted to inosine. Guanine undergoes deamination by guanase to form xanthine.

Xanthine oxidase converts hypoxanthine to xanthine & xanthine to uric acid. This enzyme contains FAD, molybdenum & iron. It is exclusively found in liver & small intestine. Xanthine oxidase liberates H2O2 which is harmful to the tissues. Catalase cleaves H2O2 to H2O & O2.

URIC ACID (2,6,8- tri oxy purine)

It is final excretory product of purine metabolism in humans.

It is excreted as uric acid is very little in humans, as humans are ureotelic (nitrogen is excreted as urea).

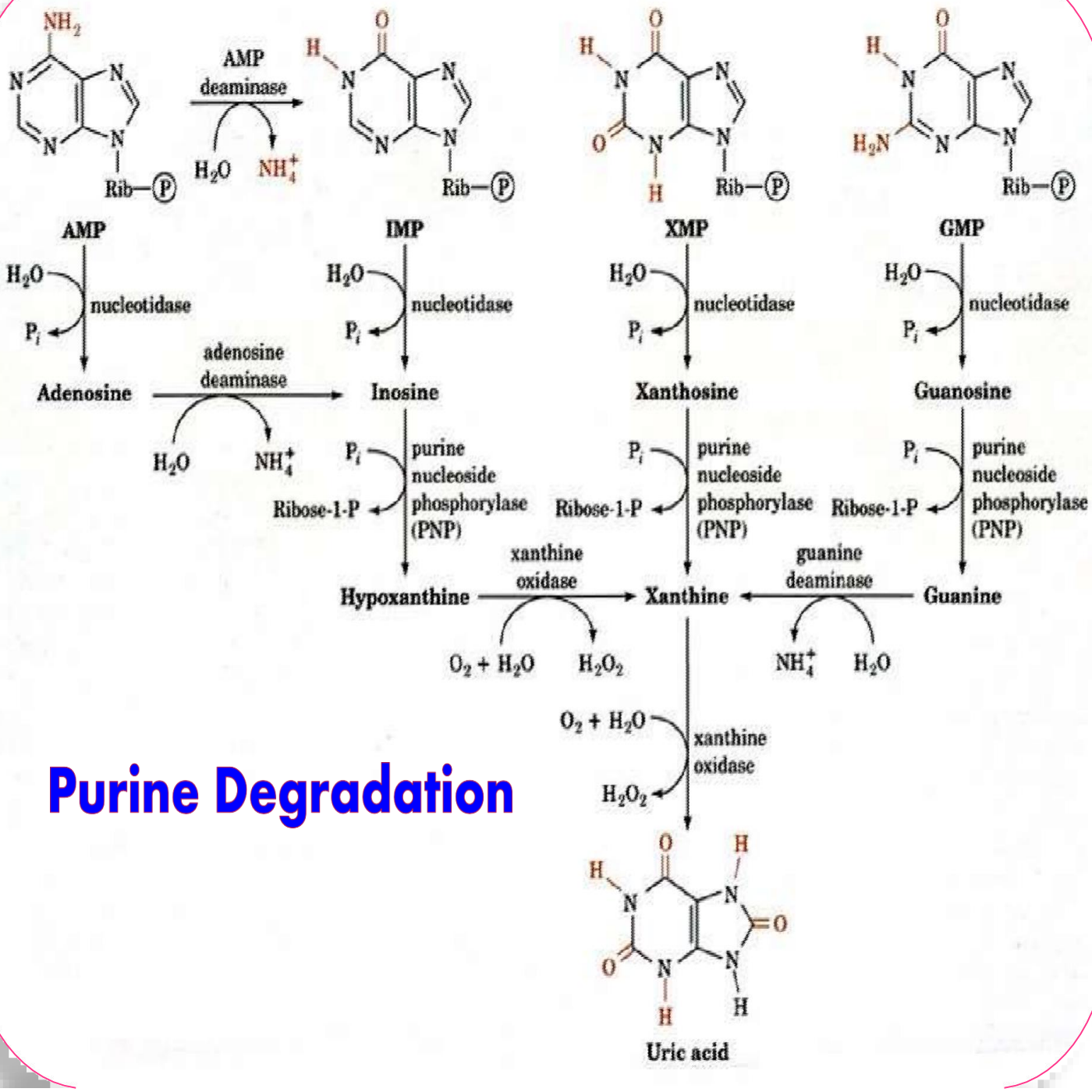
In birds, amphibians and reptiles are uricotelic – they excrete uric acid as major end product of purine and amino acid catabolism.

Lower primates and some mammals have the enzyme uricase which converts uric acid to allantoin (which is more soluble)

Uric acid can serve as an important antioxidant by getting itself converted (non-enzymatically) to allantoin.

It is believed that the antioxidant role of ascorbic acid in primates is replaced by uric acid.

Normal blood level of uric acid.
Females: 2 - 5 mg/dl.
Males: 3 - 7 mg/dl.
The daily excretion varies from 500-700 mg.
Nucleic acid content is more in non- vegetarian diet.Uric acid is sparingly soluble inwater.



Purine Degradation

HYPERURICEMIA

Hyperuricemia refers to an elevation in the serum uric acid concentration. This is sometimes associated with increased uric acid excretion (uricosuria). Hyperuricemia – increased serum uric acid levels above 7 mg/dl in Men & above 6 mg/dl in women

Causes – Excessive Alcohol consumption, CRF (Chronic renal failure), inherited metabolic disorders, MalignanciesPre-eclampsia

It is a metabolic disease associated with overproduction of uric acid. At the physiological pH, uric acid is found in a more soluble form as sodium urate.
In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, particularly in the joints. Such deposits are commonly known as tophi.

This causes inflammation in the joints resulting in a painful gouty arthritis. Sodium urate or uric acid may also precipitate in kidneys & ureters that results in renal damage & stone formation.

Gout is of two types:

- Primary
- Secondary

Primary gout :

- ✧ Inherited - 90% ,due to an Inborn error of metabolism caused by defective enzymes of Purine synthesis.
- ✧ Idiopathic - 10 % cases

1. Variant form of PRPP(Phosphoribosyl pyrophosphate) synthetase- not subject to allosteric control.
2. Variant of PRPP glutamyl amidotransferase - not sensitive to feedback control.

3.Glucose 6 phosphatase deficiency - Von Gierke's disease

- ✧ G-6-P enters HMP shunt produces excess R-5-P & PRPP – purine overproduction.
- ✧ Lactic acidosis in Von Gierke's disease – impairs UA excretion.

3. Deficiency of enzymes of salvage pathway –HGPRT deficiency leading to Lesch-Nyhan syndrome.

Decrease utilization of purines by salvage pathway – diverts PRPP to purine synthesis

Decrease salvage pathway – decreases IMP & GMP – impairs feedback regulation of denovo synthesis of purine – leads to overproduction of purines.

5.Elevation of Glutathione reductase

It coverts oxidized Glutathione to reduced form by utilizing NADPH from HMP shunt.

Abnormal activity of GR - Inc. NADP+ - Inc. HMP shunt – which rises R-5-P and PRPP synthesis – overproduction of purines.

Secondary gout:

Due to various disease causing increased synthesis or decreased excretion of uric acid.

A)Overproduction of uric acid – due to enhanced turn over rate of nucleic acids

- ✓ Increased tissue turn over due to psoriasis.
- ✓ Rapidly growing malignant tissues - CANCER - Leukemias, polycythemia, lymphomas.
- ✓ Increased tissue break down – after treatment for large tumor masses –radiotherapy & chemotherapy, trauma and starvation.

B)Reduced excretion of uric acid

- ✓ Chronic Renal failure due to reduced GFR.
- ✓ Increased alcohol consumption leads to lactic acidosis - Lactic acid decreases tubular excretion of uric acid.
- ✓ Ketoacidosis – decreases the tubular excretion of uric acid
- ✓ Thiazide diuretics inhibits tubular secretion of uric acid.

Clinical features:

Due to the low solubility of uric acid.

More common in Males, post menopausal women.

Typical gouty arthritis affects first metatarso phalangeal joint (GREAT TOE) – Classical site

In Gout , serum urate levels exceed solubility limit, leading to formation of MSU crystals and get deposited in joints. These deposits are called Tophi.

- Inflammation of joints
- painful acute gouty arthritis