Purine and Pyrimidine metabolism

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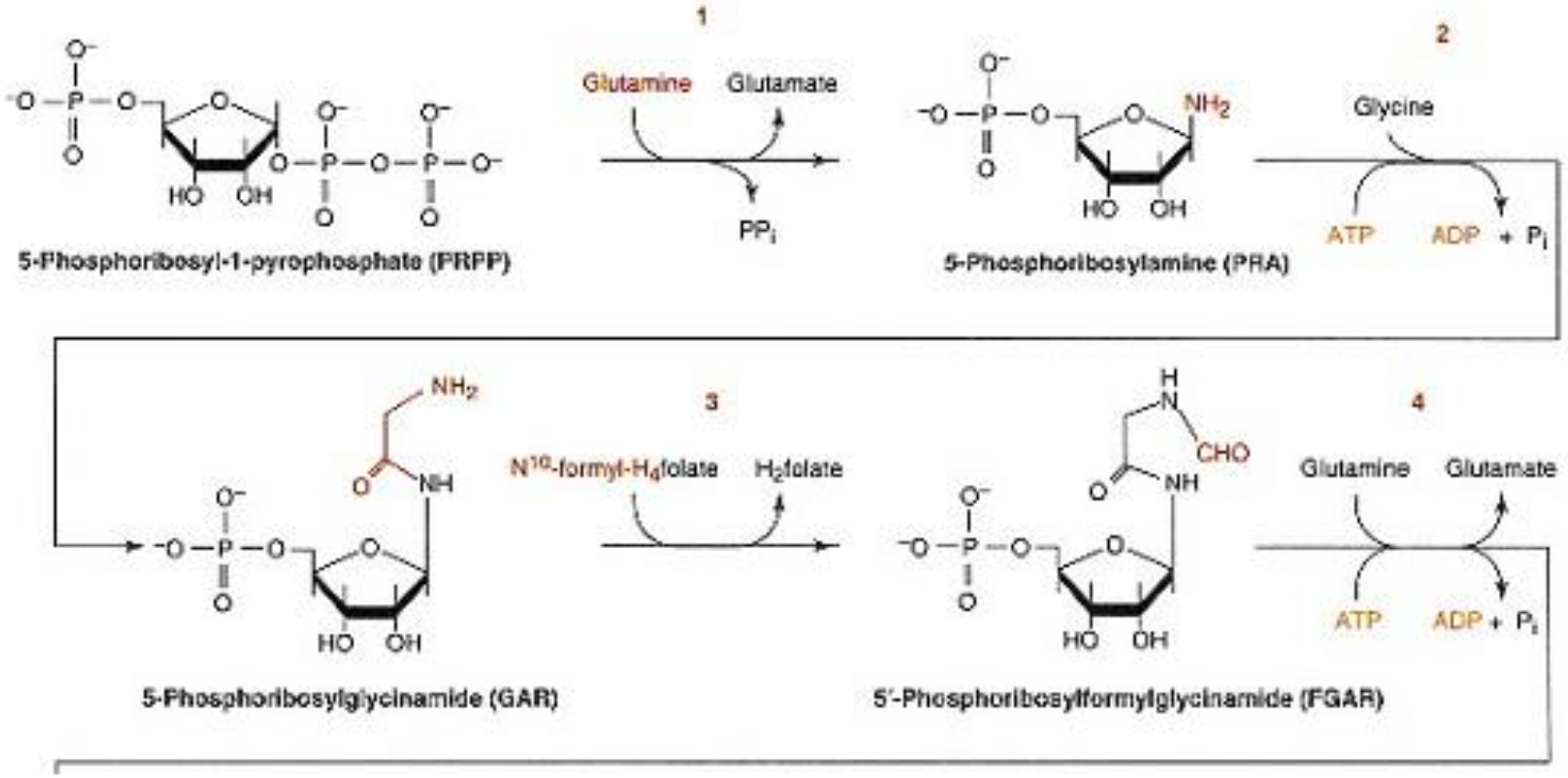
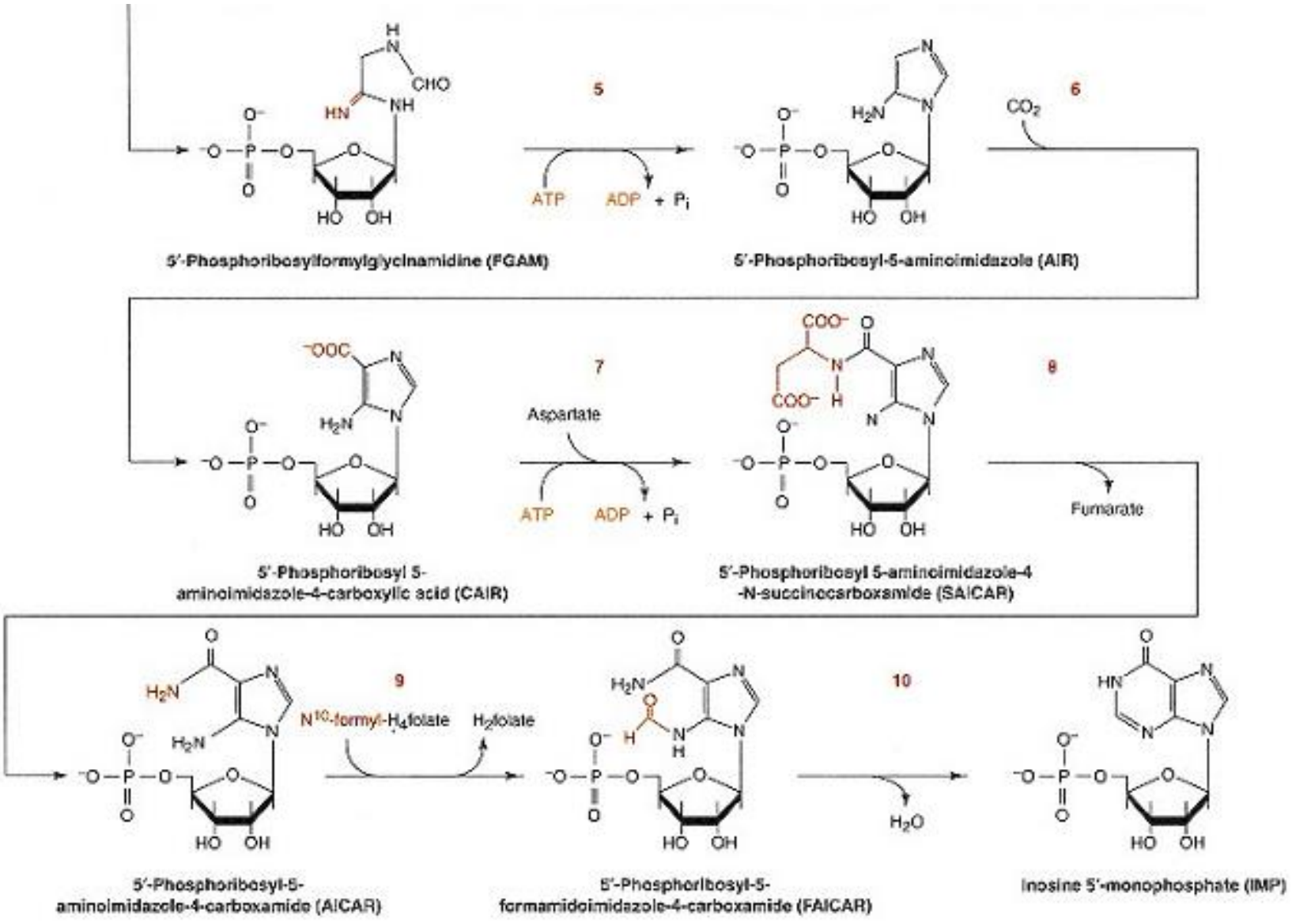
Lecture 1

De novo synthesis of purine ribonucleotides

- Purine nucleotides that occur in DNA include adenine and guanine. Synthesis of purine nucleotides takes place in the cytosol of the cell.
- Ribose-5-phosphate (from pentose pathway) reacts with ATP to form 5-phosphoribosyl-1-pyrophosphate (PRPP). This reaction is catalyzed by **ribose phosphate pyrophosphokinase**
- In the de novo pathway, a stepwise series of reactions leads to synthesis of IMP which serves as a common precursor of AMP and GMP.
- Defects in the metabolic pathway that lead to loss of regulatio n of purine nucleotide synthesis result in overproduction of purine nucleotides and the end product, uric acid

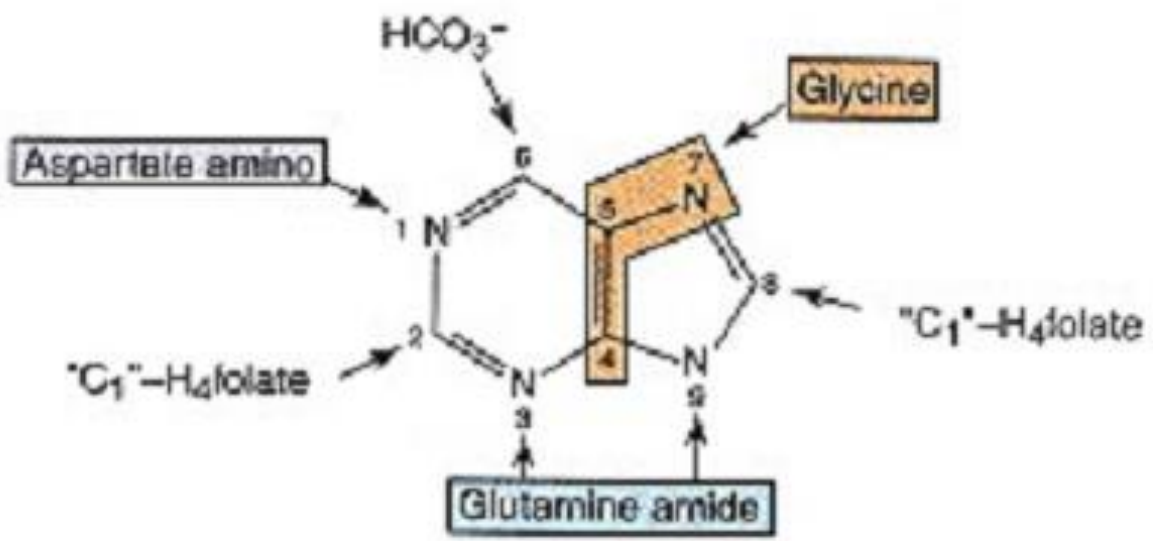


1= glutamine PRPP amidotransferase
2= GAR synthetase;
3= GAR transformylase
4= FGAM synthetase

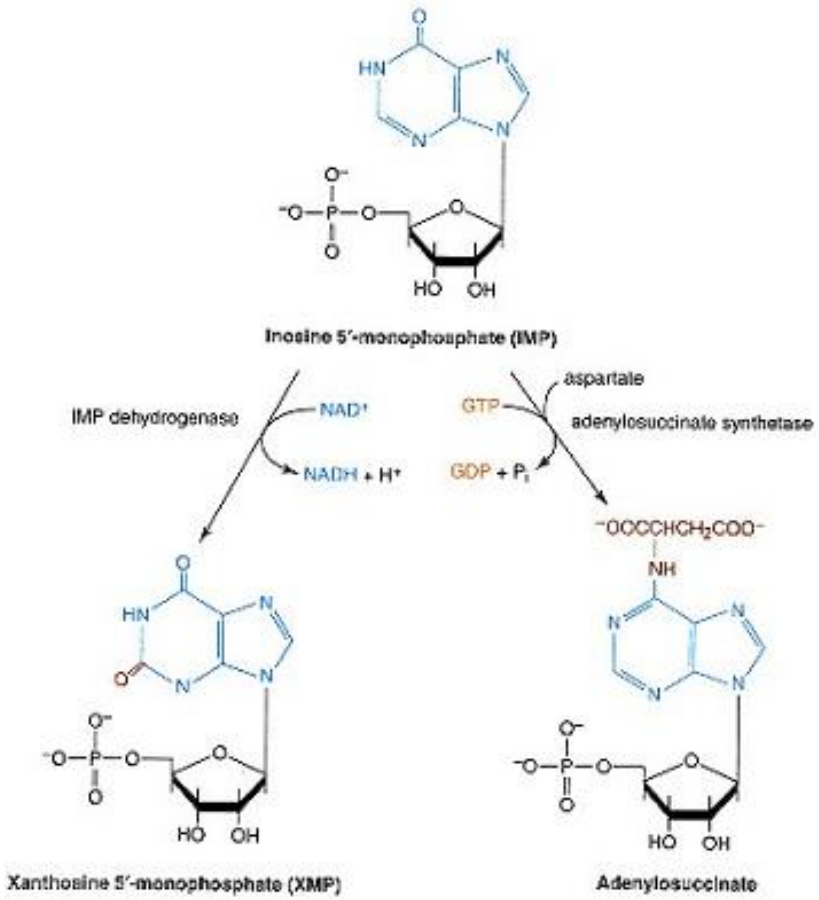


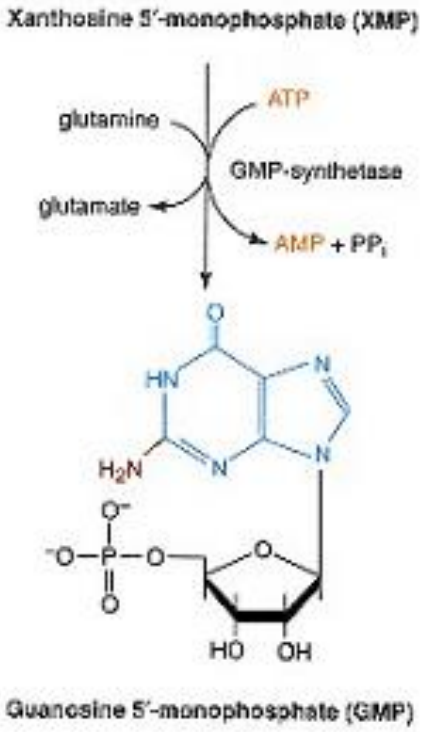
5=AIR synthetase; 6=AIR carboxylase; 7=SAICAR synthetase; 8= adenylosuccinate lyase; 9= AICAR transformylase; and 10= IMP cyclohydrolase.

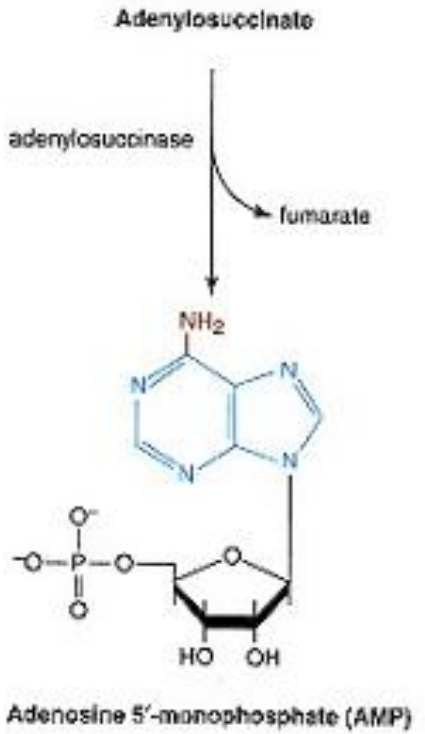
Sources of carbon and nitrogen atoms in the purine ring



Formation of AMP and GMP from IMP







Salvage pathway for purines

- Purine bases (hypoxanthine, guanine and adenine) and preformed nucleosides can be used as substrates to reform nucleotides
- The salvage of bases requires the activity of phosphoribosyl transferases.
- Hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) catalyzes the reactions:

$$\text{Hypoxanthine} + \text{PRPP} \rightarrow \text{IMP} + \text{PP}_i$$

and

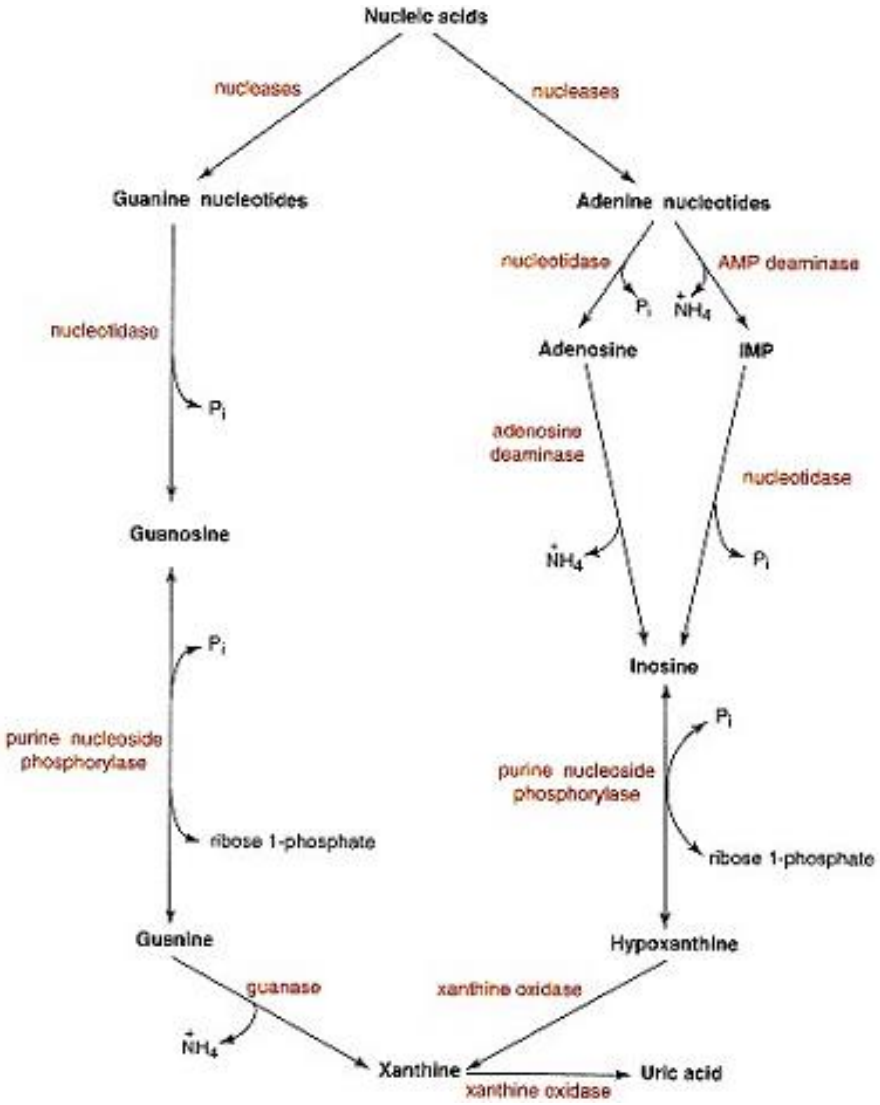
$$\text{Guanine} + \text{PRPP} \rightarrow \text{GMP} + \text{PP}_i$$

- and adenine phosphoribosyl transferase (APRTase) catalyzes

$$\text{Adenine} + \text{PRPP} \rightarrow \text{AMP} + \text{PP}_i$$

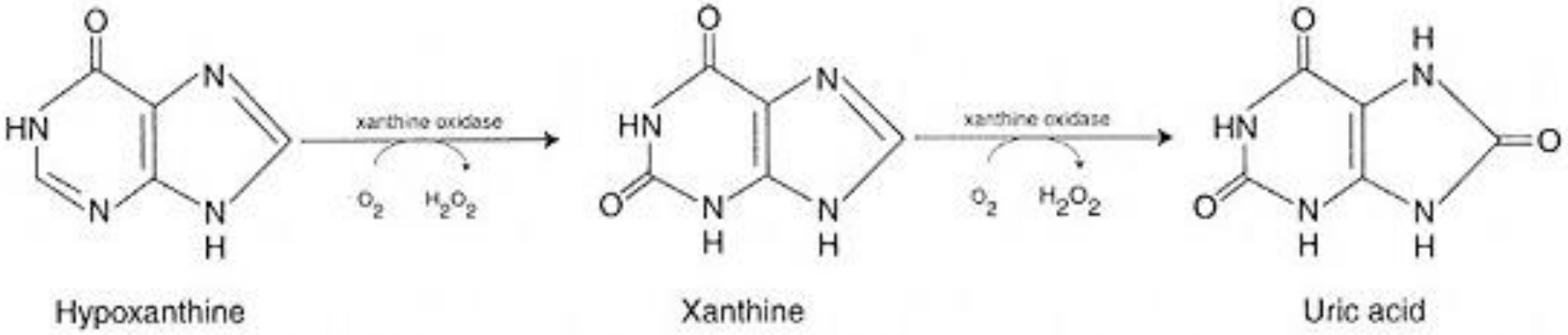
- The hypoxanthine and guanine for salvage arise from breakdown of endogenous and exogenous purine nucleotides.
- The source of adenine salvaged is mainly from the synthesis of polyamines.

Degradation of purine nucleotides



- Deoxyinosine and deoxyguanosine are excellent substrates for purine nucleoside phosphorylase.
- This is important for removal of deoxyadenosine to prevent uncontrolled accumulation of dGTP, which is toxic to cells at hi gh concentrations.
- The main function of the enzyme is the degradative rather tha n synthetic pathway.
- Adenine nucleotides end up as hypoxanthine while guanine n ucleotides are metabolized to xanthine.
- These purines are metabolized by xanthine oxidase to form uric acid, a unique end product of purine nucleotide degradati on in humans.
- Xanthine oxidase is an enzyme that contains FAD, Fe and Mo and requires molecular oxygen as a substrate.

Xanthine oxidase reaction



Gout

- Gout is characterized by elevated uric acid levels in blood and urine due to a variety of metabolic abnormalities that lead t overproduction of uric acid.
- Genetic or dietary factors promote increased production or retention of uric acid.
- Uric acid has low solubility and easily forms crystalline deposits, preferentially in joints and soft tissue
- Urate crystals promote inflammation and lead to arthritis that is painful and destructive
- Gout results from excess levels of uric acid, the end product of adenine and guanine degradation. The disease is not restricted to patients with mutations in a specific gene and can arise from different causes.

Genetic factors

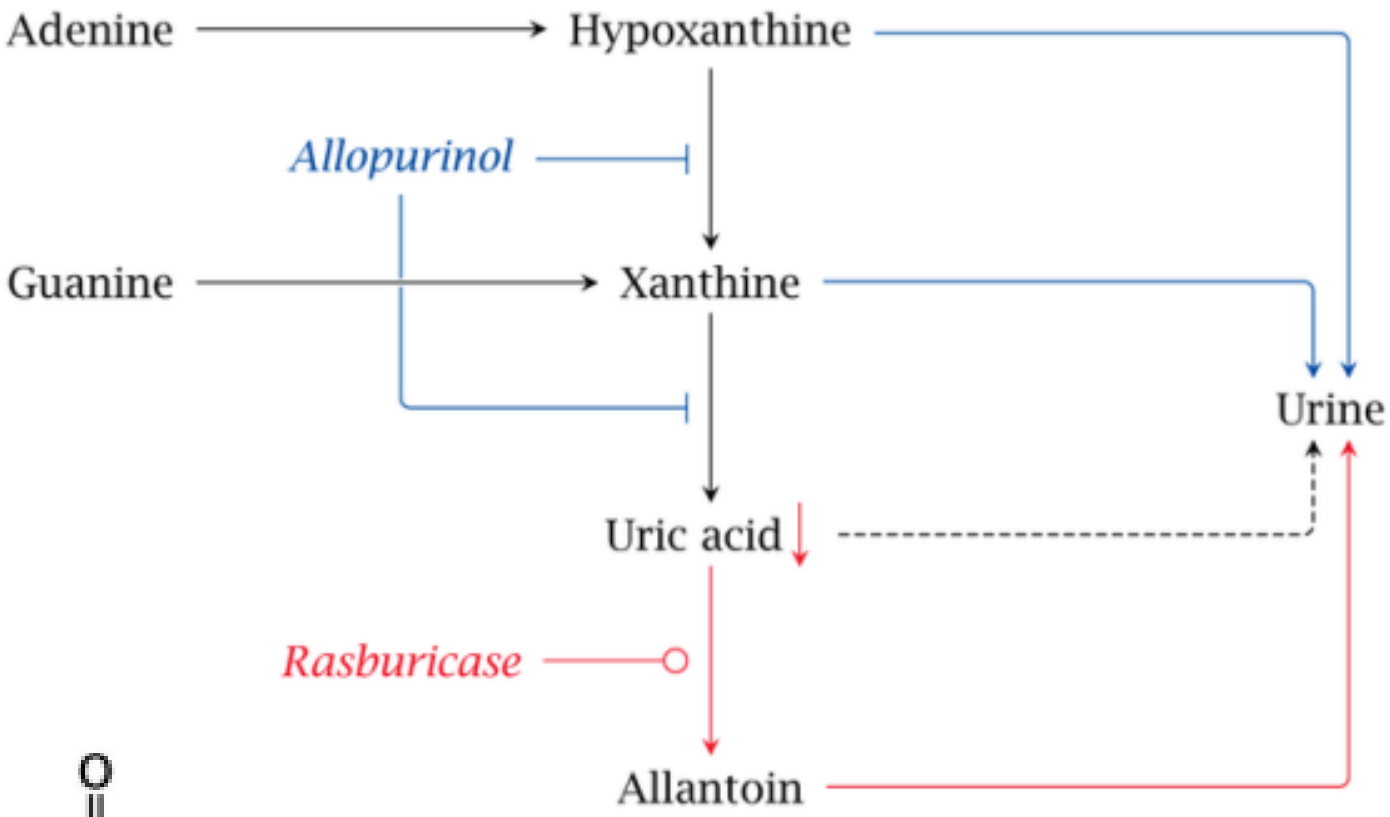
- Increased PRPP synthetase activity: Increased PRPP synthetas e activity results in increased intracellular levels of PRPP.
- Partial decrease in HGPRTase activity .
- Since there is decreased salvage of hypoxanthine and guanin, PRPP is not consumed by the HGPRTase reaction and PRPP ca n activate glutamine–PRPP amidotransferase activity.
- with decreased salvage of hypoxanthine and guanine, IMP an d GMP are not formed via this pathway so that regulation of t he PRPP amidotransferase step by IMP and GMP as negative e ffectors is compromised.
- Glucose 6phosphatase deficiency. Loss of glucose 6-phosphatase activity results in more glucose 6-phosphate being shunted to the HMP shunt. Hence more ribose 5-phosphate is generated and the intracellular level of PRPP is in

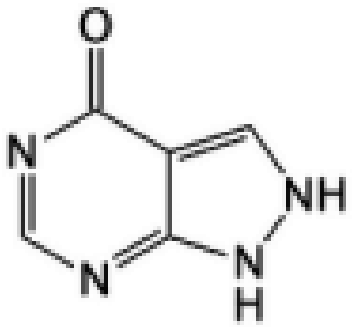
Dietary factors that promote gout

- Overly purine-rich food
- Drugs that contain purines: dideoxyadenosine
- Alcoholic beverages e.g. beer
- *Anorexia nervosa*
- Drugs that interfere with uric acid excretion: pyrazinamide, salicylic acid
- Excessive fructose or sucrose

- Dietary purines are mostly not utilized via salvage pathways but instead are converted to uric acid and excreted.
- Anorexia nervosa leads to gout probably due to the formation of ketone bodies, which as organic acids may also increase tubular reuptake of uric acid.
- Salicylic acid as well as pyrazinoic acid and hydroxypyrazinoic acid, which are formed in the metabolism of the tuberculostatic drug pyrazinamide, also act as exchange substrates for uric acid and thereby reduce its renal elimination.
- Fructose has been linked to increased uric acid production. Fructokinase produces fructose-1-phosphate more rapidly than it can be turned over by aldolase. Accumulating F-1-P ties up phosphate, which is then no longer available for the regeneration of ATP. ADP rises, and adenylate kinase causes AMP to rise in turn; the latter enters degradation to uric acid.

Treatment of gout





Allopurinol

- Allopurinol inhibits xanthine oxidase and thereby the formation of uric acid.
- Benzbromarone is a uricosuric drug i.e. it inhibits the tubular reuptake of uric acid by URAT1 (the key transporter in tubular reuptake which exchanges uric acid for other organic acids) and so increases its renal elimination.
- In gout inhibition of xanthine oxidase prevents the final oxidation steps, leading to the excretion of uric acid.
- Hypoxanthine and xanthine are somewhat more soluble than uric acid and therefore less prone to precipitation prior to excretion.
- Application of urate oxidase (uricase) comes in handy in treatment of gout.
- This enzyme, which occurs in animals other than primates and in many other organisms, converts urate to allantoin, which is considerably more soluble and forms the end product of purine degradation in these organisms.

- Rasburicase is a recombinant urate oxidase preparation used to cope with excess urate in chemotherapy patients.
- Rasburicase is an alternative to oral allopurinol for managing hyperuricemia in cancer patients (primarily lymphoma or leukemia)
- An acute increase in plasma levels (e.g., after cancer chemotherapy result in tumor lysis and subsequent elevation of plasma uric acid) results in acute renal failure due to the precipitation of urate in renal tubules.

Lesch-Nyhan syndrome

- The Lesch-Nyhan syndrome is characterized clinically by hyperuricemia (excesss uric acid production) and neurological problems which may include spasticity, mental retardation and self-mutilation.
- This disorder is due severe or complete deficiency of HGPRTase activity.
- Since HGPRTase gene is on X chromosome this deficiency is virtually limited to males.
- This defect also leads to excretion of hypoxanthine and xanthine.
- Hypoxanthine and guanine are not salvaged, leading to increa sed intracellular pools of PRPP and decreased levels of IMP or GMP. Both of these factors promote de novo synthesis of puri ne nucleotides without regard for proper regulation of this pathway.

- In the brain, lack of HGPRTase could lead to decreased levels of intracellular GTP due to decreased salvage of guanine.
- Since GTP is a precursor of tetrahydrobiopterin, a required cof actor in the biosynthesis of neurotransmitters, low levels of G TP during development could be the triggering factor in the o bserved neurological manifestations.
- Treatment of Lesch-Nyhan syndrome
- Treatment of Lesch-Nyhan syndrome patients with allopurinol will decrease the amount of uric acid formed, relie ving some of the problems caused by sodium urate deposits.
- However, since the Lesch-Nyhan patient has a marked reduction HGPRTase activity, hypoxanthine and guanine are not salvaged, PRPP is not consumed, and consequently de nov o synthesis of purine nucleotides is not shut down.
- There is no treatment for the neurological problems.

References

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