



NUCLEIC ACID METABOLISM AND RELATED DISEASES II

Ass. Prof. Dr. Jaafaru Sani Mohammed
Advance Clinical Biochemistry II (MA 416)

Spring Semester

Lecture 2

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Outlines

- Objectives
- Pyrimidine catabolism
- Defect in purine metabolic enzyme
- Salvage pathway and Lesch Nyhan syndrome.
- Uric acid and gout diseases
- Summary
- Activities

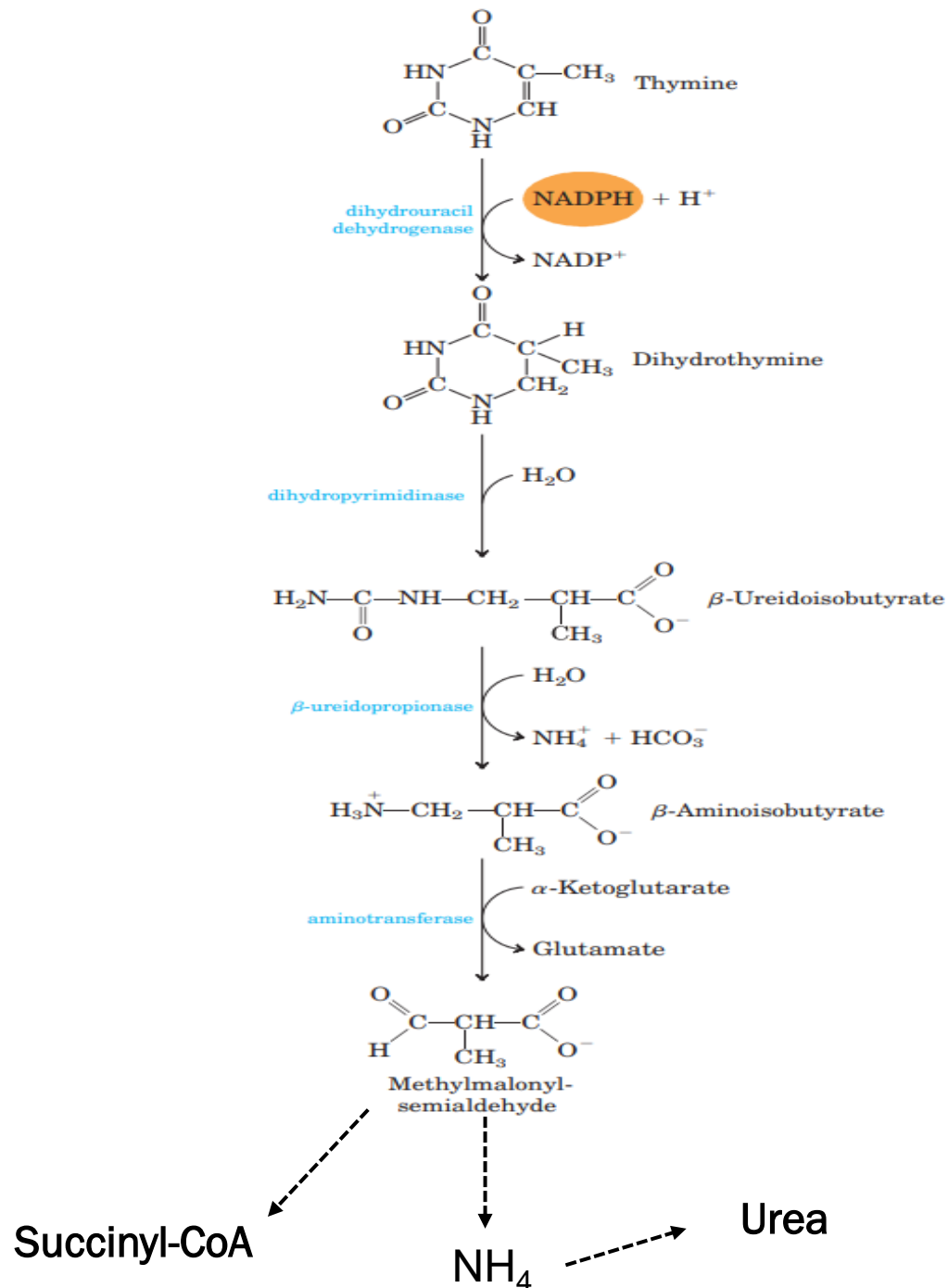
Objectives

- **At the end of this lesson, the students should be able to:**
- Understand the catabolic process of pyrimidines.
- Understand the impact of a genetic defect on certain enzymes in the purine metabolic pathway.
- Be acquainted with the knowledge of the salvage pathway.
- Understand the biochemical basis of gout disease development and possible treatment approaches.



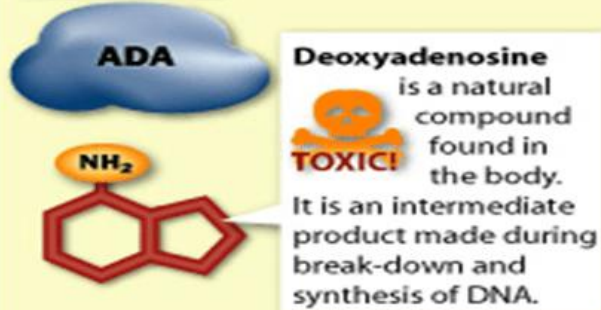
Catabolism of pyrimidines

- The pathways for degradation of pyrimidines generally lead to NH_4 production.
- Since NH_4 cannot be removed from the human body, urea is produced.
- Thymine, for example, is degraded to methyl malonyl semialdehyde (Figure) an intermediate of valine catabolism.
- It is further degraded through propionyl-CoA and methyl malonyl-CoA to succinyl-CoA



ADA Converts Deoxyadenosine to a Non-toxic Substance

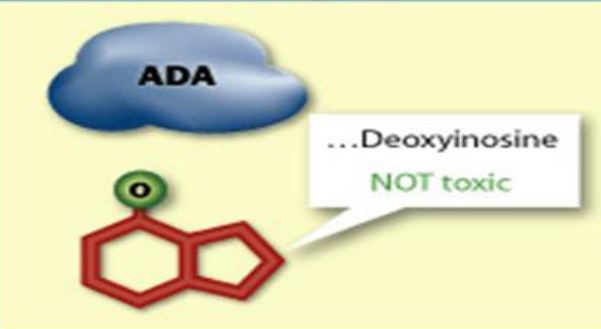
Normal



ADA Deficiency



- High levels of deoxyadenosine kill B and T cells of the immune system
- The body is open to infection by bacteria and viruses

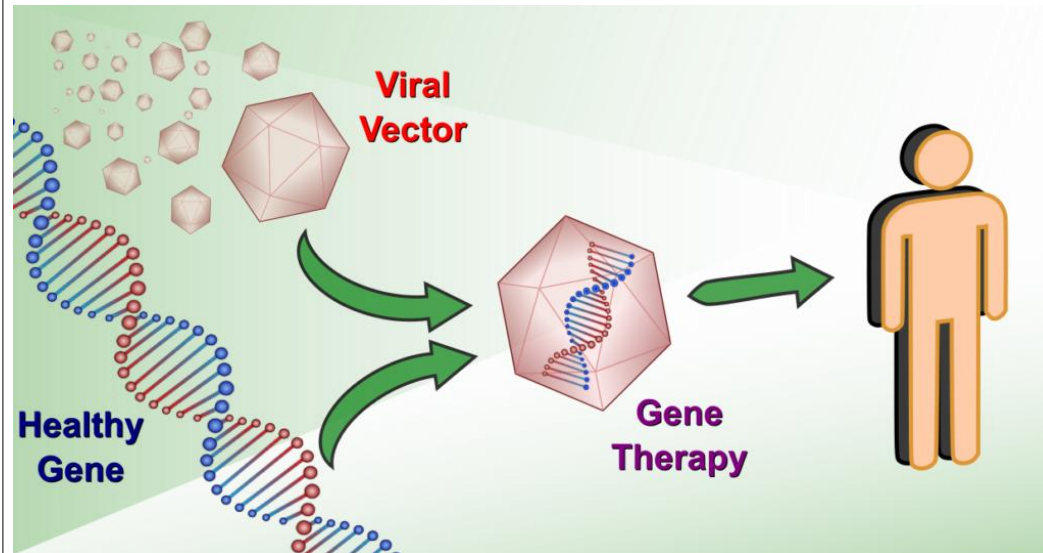


Defect in purine metabolism enzyme

- Genetic defects in human purine metabolism have been found with consequences.
- Adenosine deaminase (ADA) deficiency is one of the examples of the consequences.
- It leads to severe immunodeficiency disease due to improper development of T-lymphocytes and B lymphocytes.
- Lack of ADA leads to a 100-times increase in the cellular conc. of dATP, which inhibits ribonucleotide reductase.

Cont.

- High levels of dATP produce a general **deficiency of other dNTPs** in T & B lymphocytes.
- Individuals with ADA deficiency lack an effective immune system and **do not survive unless isolated** in a sterile environment.
- ADA deficiency is corrected through **human gene therapy**. (One of the first targets for the trial)



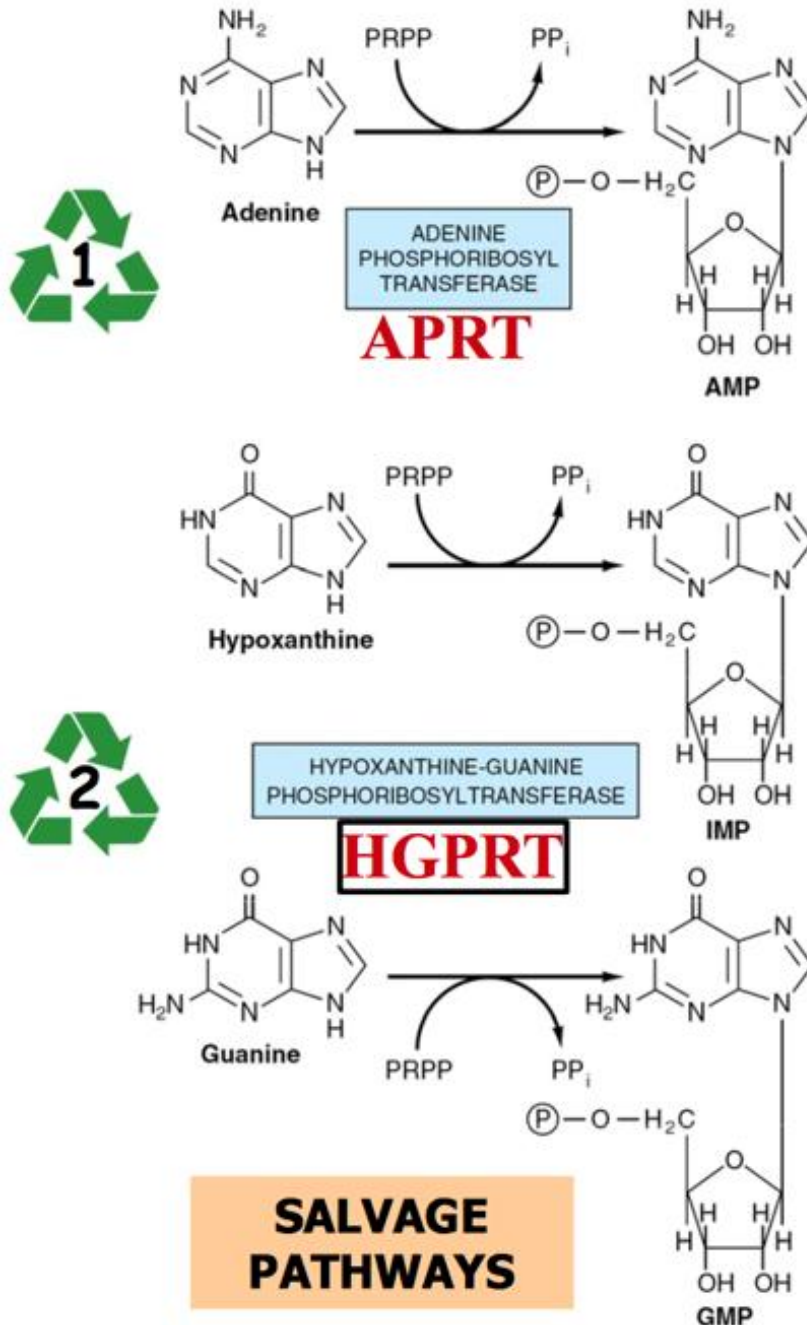


Interaction

- What is the final waste product of pyrimidine catabolism, and can it be excreted from the body? Explain
- The common intermediate for thymine (Nitrogenous base) and valine (amino acid) catabolism is called.....
- What is the full meaning of ADA, and what could be the likely consequences of its deficiency/defect?
- What are the consequences of an increased level of dATP in the cells?

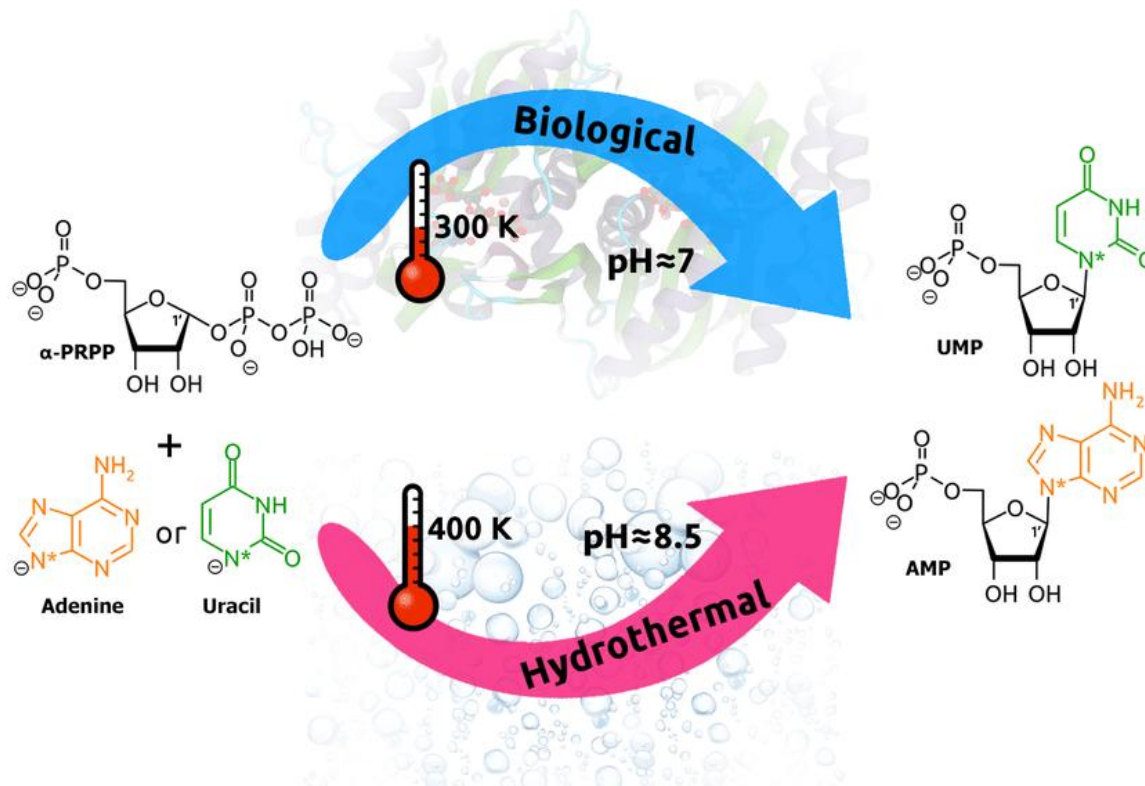
Salvage (Recycle) Pathways for Purine and Pyrimidine Bases

- Free purine and pyrimidine bases are constantly released in cells during the **metabolic degradation of nucleotides**.
- Large parts of free purine are **salvaged and reused** to make nucleotides.
- The **salvage pathway** is much simpler than the **de novo synthesis** of purine/pyrimidine nucleotides.



Cont.

- Purine salvage pathway is primarily important due to the involvement of a crucial reaction catalysed by **adenosine phosphoribosyl-transferase (APRT)**.
- In this case, free adenine reacts with **phosphoribosyl pyrophosphate (PRPP)** to yield the corresponding adenine nucleotide:
- Adenine + PRPP → AMP P_i



Cont.

- Free guanine and hypoxanthine are salvaged in the same way by **hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)**.
- A genetic lack of that enzyme activity is seen almost exclusively in **male children**, resulting in a strange set of symptoms called **Lesch-Nyhan syndrome (LNS)**.



48) Lesch Nyhan Syndrome

❖ Clinical features

- ✓ Self-injury (Most distinctive behavioral problem)
 - Fingers & mouth biting
 - Head banging
- ✓ Dystonia
- ✓ Chorea
- ✓ Hypotonia
- ✓ Ballismus
- ✓ Developmental delay



❖ Laboratory finding ?

- ✓ Hyperuricemia

❖ Complications :

- ✓ Gouty arthritis
- ✓ Kidney & bladder stones
- ✓ Renal failure

❖ Most common cause of death?

- ✓ Renal failure

❖ Mode of inheritance?

- ✓ X-linked recessive
- ✓ HPRT1 gene
- ✓ Defect in purine metabolism

❖ Treatment :



- ✓ Allopurinol
- ✓ High fluid intake
- ✓ Behavioral therapy

Cont.

- **Lesch-Nyhan syndrome** usually manifests in children at 2 years.
- The victims sometimes become poorly coordinated and mentally retarded.
- In addition, they are extremely hostile and show compulsive self-destructive tendencies.
- They mutilate themselves by biting off their fingers, toes, and lips.





Cont.

- The devastating effects of **Lesch-Nyhan syndrome** illustrate the importance of the salvage pathways.
- Hypoxanthine and guanine arise constantly from the breakdown of nucleic acids in the absence of **the enzyme**.
- PRPP levels rise, and purines are overproduced by the de novo pathway.

LESCH-NYHAN SYNDROME

DEFICIENCY IN HGPRT

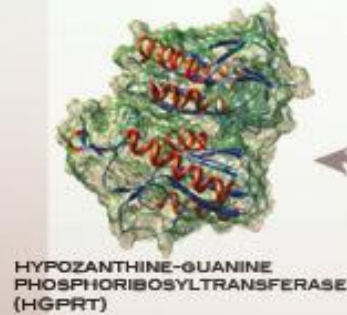
In the body purine base Guanine is recycled by converting it back to its nucleotide, guanosine monophosphate with the help of an enzyme HGPRT



Deficiency in HGPRT leads to accumulation of Guanine, which then breaks down into uric acid



The accumulation of uric acid causes a number of peculiar nervous system impairments. These manifest themselves in what is known as Lesch-Nyhan syndrome an inherited X-linked recessive disease



Symptoms

Neurologic dysfunction, cognitive and behavioral disturbances, as well as hyperuricemia. Some may also be afflicted with anemia. All affected individuals are male.

Behavior

Self-mutilating behavior characterized by fingerlip biting and head banging. Exacerbates in stressful moments!

Treatment

Aloprinolol is used to reduce the excessive amounts of uric acid. A number of drugs can be used to treat neurological symptoms, such as diazepam, phenobarbital, or haloperidol.



Cont.

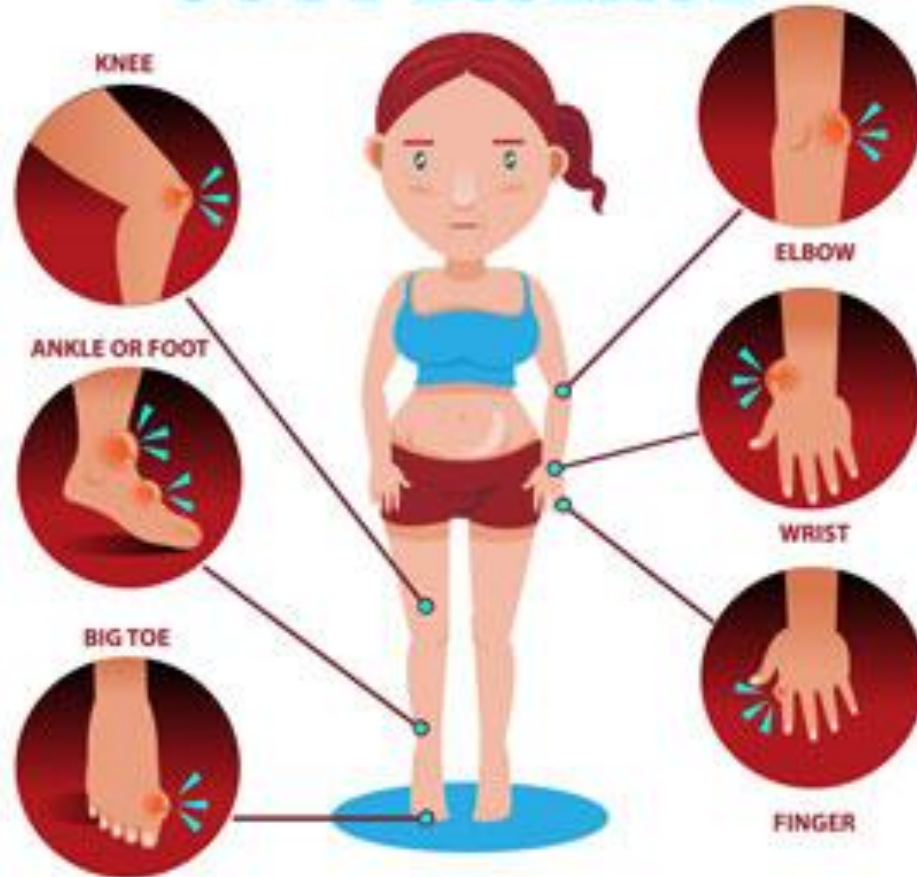
- Resulting in high levels of uric acid production and gout-like damage to tissue.
- The brain is especially dependent on the salvage pathways, and this may account for the central nervous system damage in children with Lesch-Nyhan syndrome.
- This syndrome is another target of early trials in gene therapy.



Interaction

- Synthesis of nucleotide from purine and pyrimidine bases is called _____
- The enzymes in the salvage biosynthetic pathway of purine base nucleotides are _____
- Genetic deficiency of the above enzymes leads to a disease condition called _____
- Briefly highlight the signs and symptoms of the disease condition.

GOUT DISEASE

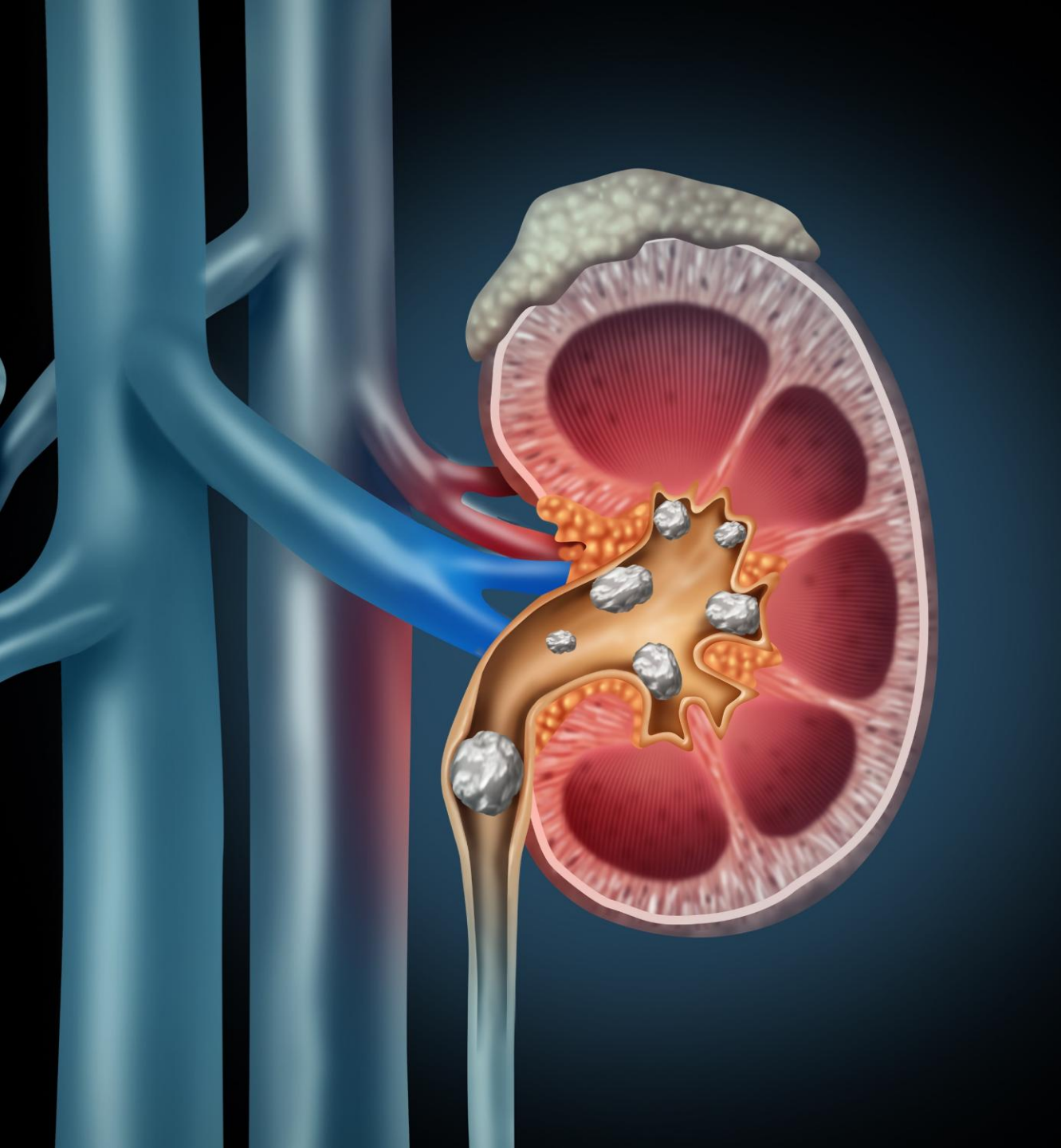


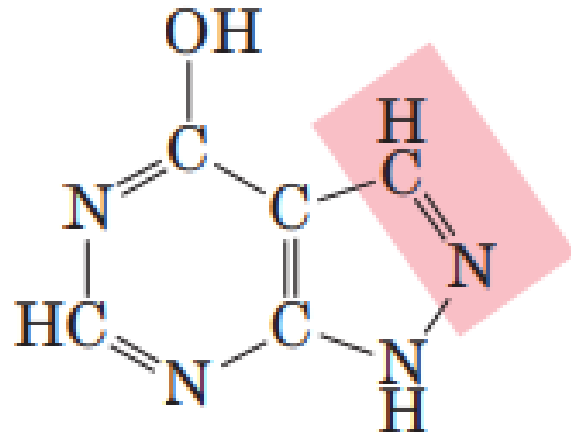
Excess Uric Acid Causes Gout

- Long thought, erroneously, to be due to “high living.”
- Gout is a disease of the joints caused by an elevated concentration of uric acid in the blood and tissues.
- The joints become inflamed, painful, and arthritic, owing to the abnormal deposition of sodium urate crystals.

Excess uric acid causes gout

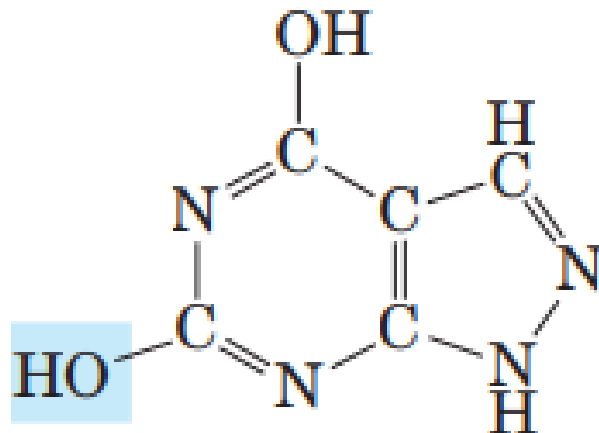
- The kidneys are also affected, as excess uric acid is deposited in the kidney tubules.
- Gout occurs predominantly in males. Its precise cause is not known, but it often involves an underexcretion of urate.
- A genetic deficiency of one or another enzyme of purine metabolism may also be a factor in some cases.



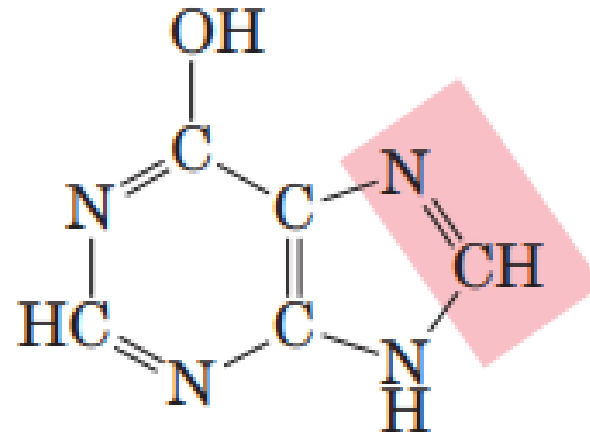


Allopurinol

xanthine
oxidase



Oxypurinol



Hypoxanthine
(enol form)

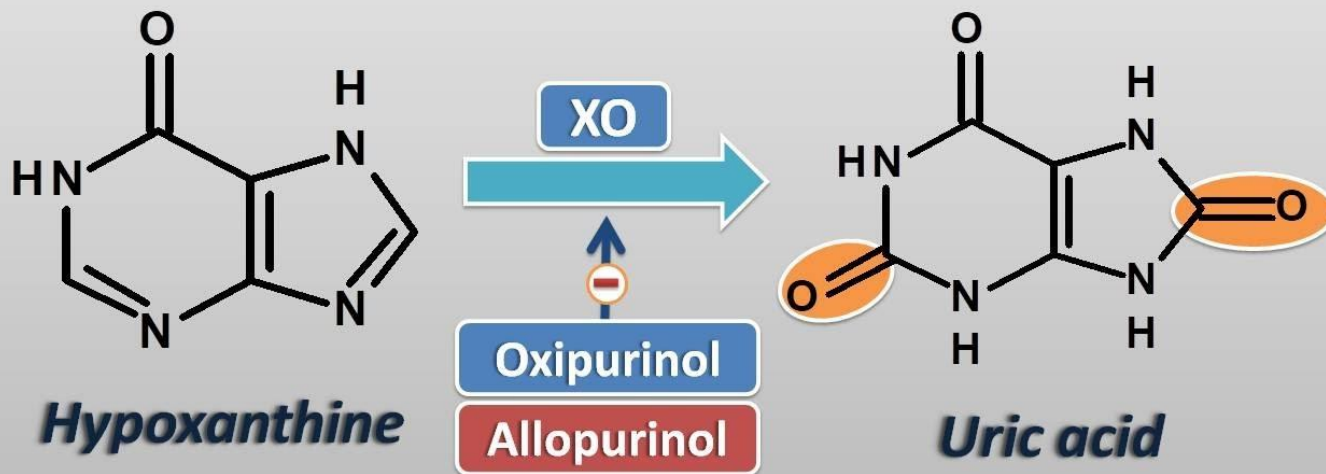
Cont.

- Gout is effectively treated by a combination of nutritional and drug therapies.
- Foods especially rich in nucleotides and nucleic acids, such as liver or glandular products, are suspended from the diet.
- Major alleviation of the symptoms is provided by the drug allopurinol.
- Allopurinol inhibits xanthine oxidase, the enzyme that catalyzes the conversion of purines to uric acid.

Cont.

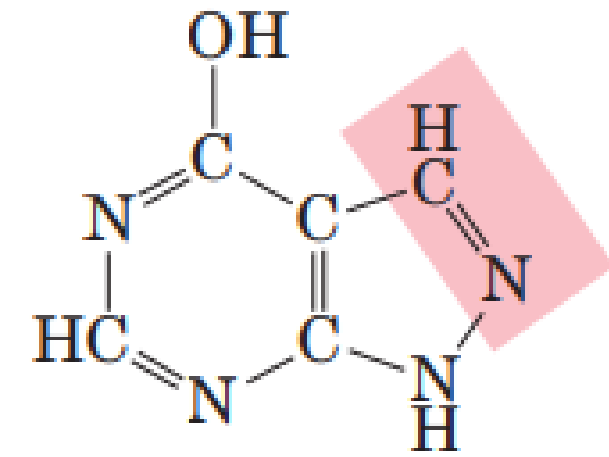
- Allopurinol is a substrate of xanthine oxidase, which converts allopurinol to oxypurinol (alloxanthine).
- Oxypurinol inactivates the reduced form of the enzyme by remaining tightly bound in its active site.
- When xanthine oxidase is inhibited, the excreted products of purine metabolism are xanthine and hypoxanthine.
- They are more water-soluble than uric acid and less likely to form crystalline deposits.

ALLOPURINOL – How it works in GOUT



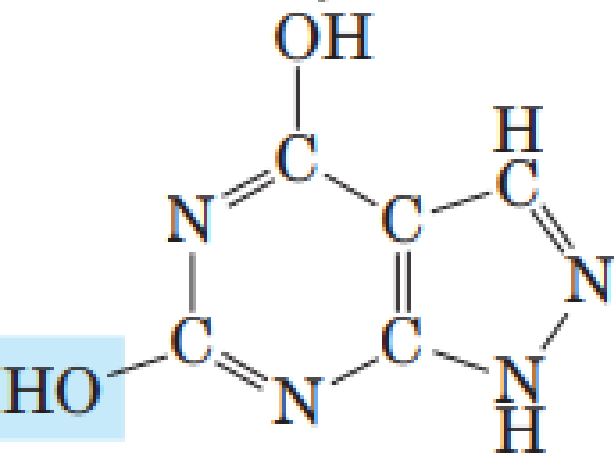
Treatment

- Allopurinol is an inhibitor of xanthine oxidase.
- Hypoxanthine is the normal substrate of xanthine oxidase.
- Only a slight change in the structure of hypoxanthine yields the medically effective enzyme inhibitor allopurinol.
- At the active site, allopurinol is converted to oxypurinol, a strong competitive inhibitor that remains tightly bound to the reduced form of the enzyme.

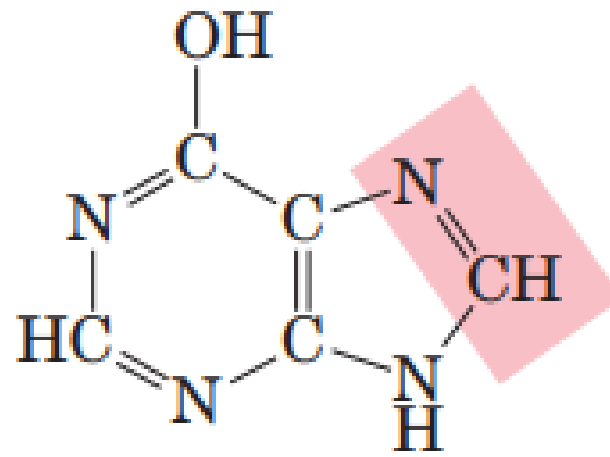


Allopurinol

xanthine
oxidase



Oxypurinol



Hypoxanthine
(enol form)

Summary

- Uric acid and urea are the end products of purine and pyrimidine degradation.
- Free purines can be salvaged and rebuilt into nucleotides.
- Genetic deficiencies in certain salvage enzymes cause serious disorders such as Lesch-Nyhan syndrome and ADA deficiency.
- Accumulation of uric acid crystals in the joints, possibly caused by another genetic deficiency, results in gout.
- Enzymes of the nucleotide biosynthetic pathways are targets for an array of chemotherapeutic agents used to treat cancer and other diseases.

Class activities

- The end product of Thiamine degradation is called _____
- Severe immunodeficiency disease could be caused by _____
- _____ leads to the underdevelopment of T- and B-lymphocytes.
- Differentiate between De novo and Salvage pathways.
- Discuss in detail the biochemical basis of the **Lesch Nyhan Syndrome** development.
- Describe the biochemical basis of gout disease development and its possible treatment.

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