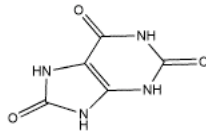


Disorders of Nucleotide Metabolism: Hyperuricemia and Gout

- Gout (also called urate crystal deposition disease) is a condition characterized by hyperuricemia - high levels of uric acid
- the deposition of monosodium urate and uric acid crystals in tissues as a result of supersaturation of extracellular fluids with urate
- gout is manifested by recurrent attacks of acute inflammatory arthritis, the development of uric acid stones and renal disease
- like PKU, gout has both genetic and environment contributions
- disease has been recognized for centuries (Henry VIII, Benjamin Franklin)

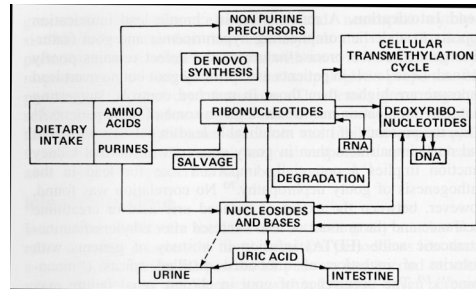


Uric acid

Clinical features of gout

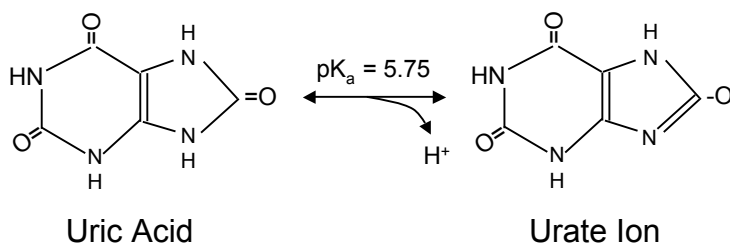
- symptomatic manifestations of gout only arise in a minority of persons with hyperuricemia, and usually only after 20-30 years of sustained hyperuricemia
- 1) Acute gouty arthritis: episodes of painful inflammatory arthritis, last hours to weeks and are usually monoarticular (affects only one joint); big toe is common site
 - " The patient goes to bed and sleeps quietly till about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, ankle or instep. The pain resembles that of a dislocated bone...and is immediately preceded by a chilliness and slight fever in proportion to the pain which is mild at first but grows gradually more violent every hour; sometimes resembling a laceration of ligaments, sometimes the gnawing of a dog, and sometimes the weight and constriction of the parts affected, which becomes so exquisitely painful as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein."
 - 2) Urate nephropathy: a renal disease caused by deposition of urate crystals in the interstitial space of the kidneys, can lead to kidney failure
 - 3) Uric acid urolithiasis: bladder stones

Overview of purine metabolism



- ATP is substrate for the cellular transmethylation cycle to form S-adenosylmethionine (SAM); during cellular transmethylation, adenosine is formed and feeds into the purine degradation pathway
- salvage of purines from dietary sources
- RNA degradation

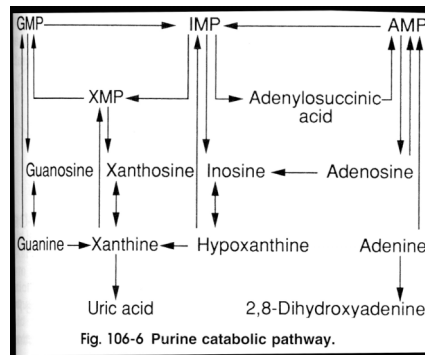
Uric Acid Homeostasis



- ionized forms of uric acid readily form salts
- in extracellular fluids in which sodium is the principal cation, 98% of the uric acid is found as the monosodium salt at pH 7.4
- crystals of monosodium urate monohydrate form in the synovial fluid when the solubility limits are exceeded

Why do we have any uric acid?

- uric acid is a breakdown product of purines (ATP, GTP, nucleic acids) and its excretion permits the necessary removal of nitrogen waste from the body



Overview of purine catabolism

Why do we have any uric acid - part 2?

- may also play a role in immunity as an adjuvant

vaccination of an organism with antigen alone is likely to induce tolerance rather than an immune response without the presence of an adjuvant

known adjuvants: mycobacterium, LPS (act via toll-like receptors and upregulation of co-stimulatory molecules such as CD86 to induce a full T-cell response)

mammalian cytosol from dying or damaged cells can be an adjuvant; in 2003 Shi and colleagues showed that uric acid is one of the cytosolic factors (only crystalline uric acid can serve as an adjuvant: fail-safe mechanism against presence of low [urate]s)

Why did evolution select for an endogenous adjuvant?

“danger signal” concept: in 1990s, Matzinger postulated that cells damaged by trauma or viral infection might need a way to signal the immune system

- programmed cell death initiates an active process of DNA fragmentation and purine degradation, leading to high urate production in the dying cell
- Hu and colleagues used a mouse model of immunologic tumor rejection to test this theory
- they observed that lowering levels of uric acid with either allopurinol or uricase led to delayed tumor rejection and treating the tumor mice with uric acid enhanced the rate of rejection

Why do humans and other primates have so much uric acid?

- unlike most mammals with serum urate levels below 2 mg/dL, primates tend to have serum urates in the range of 6 to 7 mg/dL, due to the lack of the uricase enzyme
- uricase breaks down uric acid to a more soluble component, allantoin prior to excretion
- uric acid is a weak acid that may exert antioxidant effects

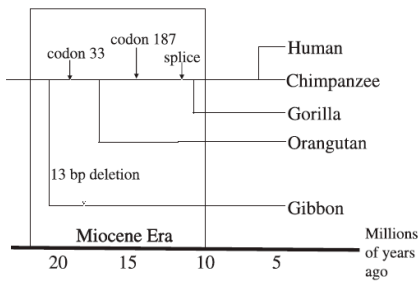
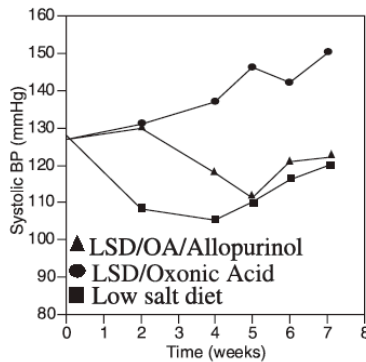


Figure 2 The loss of the uricase gene happened differently in different primates, but all in the same era.

- the fact that loss of uricase occurred in the same era suggests that it may have conferred a survival advantage during that period
- our ancestors in the Miocene era were mainly limited to a diet of fruits and grasses (low in sodium); this low sodium diet may have led to a hypotensive “crisis”
- loss of uricase and accumulation of uric acid might have compensated for Hypotension
- biped more dependent on blood pressure to maintain cerebral perfusion

the experiment...

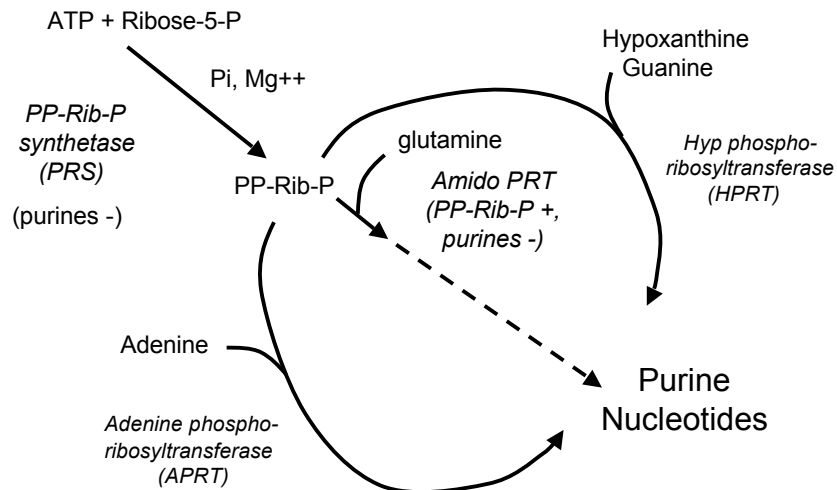
- rats fed a low-sodium diet then treated with oxonic acid, a uricase inhibitor
- this effect can be blocked by allopurinol, a xanthine oxidase inhibitor that reduces uric acid biosynthesis



Why do some human beings have too much uric acid?

- normal range in humans: 4-7 mg/dL; higher levels known to trigger attacks
- trauma, surgery, excessive ingestion of alcohol or purine-rich foods, starvation and administration of certain drugs (diuretics, cyclosporine, etc.)
- all the causes of gout are not extrinsic; this condition is associated with many genetic disorders
 - * handling of uric acid by the kidneys (URAT1 and UAT1)
 - * overproduction of uric acid can lead to hyperuricemic
- hereditary hyperactivity of the purine synthesis enzyme PRPP (5-P-D-ribose-1-pyrophosphate)
- partial deficiency of HGPR (hypoxanthine-guanine phosphoribosyl) transferase; the rate-limiting step in the purine salvage pathway

Mechanisms of Hyperuricemia: increased P-ribose-PP production



PRS superactivity and HPRT deficiency: two inborn errors associated with hyperuricemia and gout

- PRS superactivity; increased PP-Rib-P levels due to overproduction (no apparent decreases in purine nucleotide concentrations)
- HPRT deficiency: PP-Rib-P accumulates due to underutilization of this salvage reaction

Increased PP-Rib-P availability in both cases results in activation of AmidoPRT and acceleration of purine nucleotide and uric acid synthesis

Mechanisms of Hyperuricemia: increased ATP degradation

- Exercise
- Ethanol digestion
- Glucose-6-phosphatase deficiency (glycogen storage disease type I)
- Fructose-1,6-phosphatase deficiency
- Fructose infusion and hereditary fructose intolerance

Last three examples are noteworthy since they suggest that defects in carbohydrate metabolism may manifest themselves as hyperuricemia and gout

Mechanism of fructose-induced purine nucleotide degradation

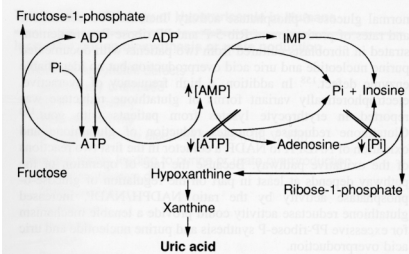


Fig. 106-12 Mechanism of fructose-induced purine nucleotide degradation. Fructose triggers rapid breakdown of purine nucleotides to uric acid in the liver. Phosphorylation of fructose to fructose-1-phosphate causes ATP to be degraded to ADP. Fructose-1-phosphate accumulates and thus traps inorganic phosphate. ADP is converted back to ATP by the mitochondrial electron transport system or glycolysis, which uses inorganic phosphate, or by adenylate kinase. The reaction with adenylate kinase also forms AMP. The net result is a diminution of intracellular ATP and inorganic phosphate and buildup of AMP. Elevated AMP concentrations also lead to increased IMP concentration. Dephosphorylation by 5-nucleotidase is triggered. If AMP and IMP concentrations are high enough, then the nonspecific phosphatase can be activated. Once dephosphorylation is activated, there is a cascade of nucleotide degradation through catabolic pathways leading to increased synthesis of uric acid. This accounts for the resultant hyperuricemia and elevated urinary excretion of inosine, hypoxanthine, xanthine, and uric acid. Interrupted arrows indicate enzyme inhibition. Bold arrows indicate changes in the levels of ATP, AMP and Pi, induced by fructose infusion. (Adapted with permission from Fox IH: *Metabolic basis for disorders of purine nucleotide degradation*. *Metabolism* 30:616, 1981.)

Treatments for gout

- acute gouty arthritis is most commonly treated with NSAIDs, steroids or colchicine
- lowering uric acid to prevent gouty attacks can be accomplished with allopurinol but there are contraindications for this therapy including diabetes, renal insufficiency and gastrointestinal pathology
- Febuxostat: nonpurine xanthine oxidase inhibitor that mimics the action of allopurinol
- Uricase infusion: lowers serum uric acid levels and insoluble urate crystal deposits (has same problems faced by PAL - highly immunogenic, poorly tolerated, short half-life)
- pegylation of uricase shown to be effective in improving pharmacological parameters

Pathophysiology of gout: How does hyperuricemia lead to an inflammatory response to urate crystals?

- presence of crystals stimulates a two-pronged inflammatory signal
 - * activation of complement results in chemoattractant generation which activates and attracts bloodstream neutrophils
 - * vascular endothelial cells must first be activated by cytokines generated by macrophages lining the synovium (IL-1, IL-6 and TNF- α)
- new evidence indicates a role for the inflammasome in the onset of gout
- inflammasomes are structures that mediate the production of IL-1 from its propeptide form proIL-1
- proteolysis of propeptide is carried out by caspase-1 which must first be aligned on a number of scaffolding complexes