Ουρική νόσος

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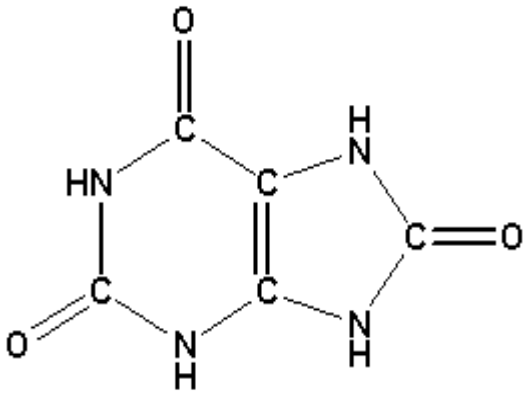
ρευματολόγος

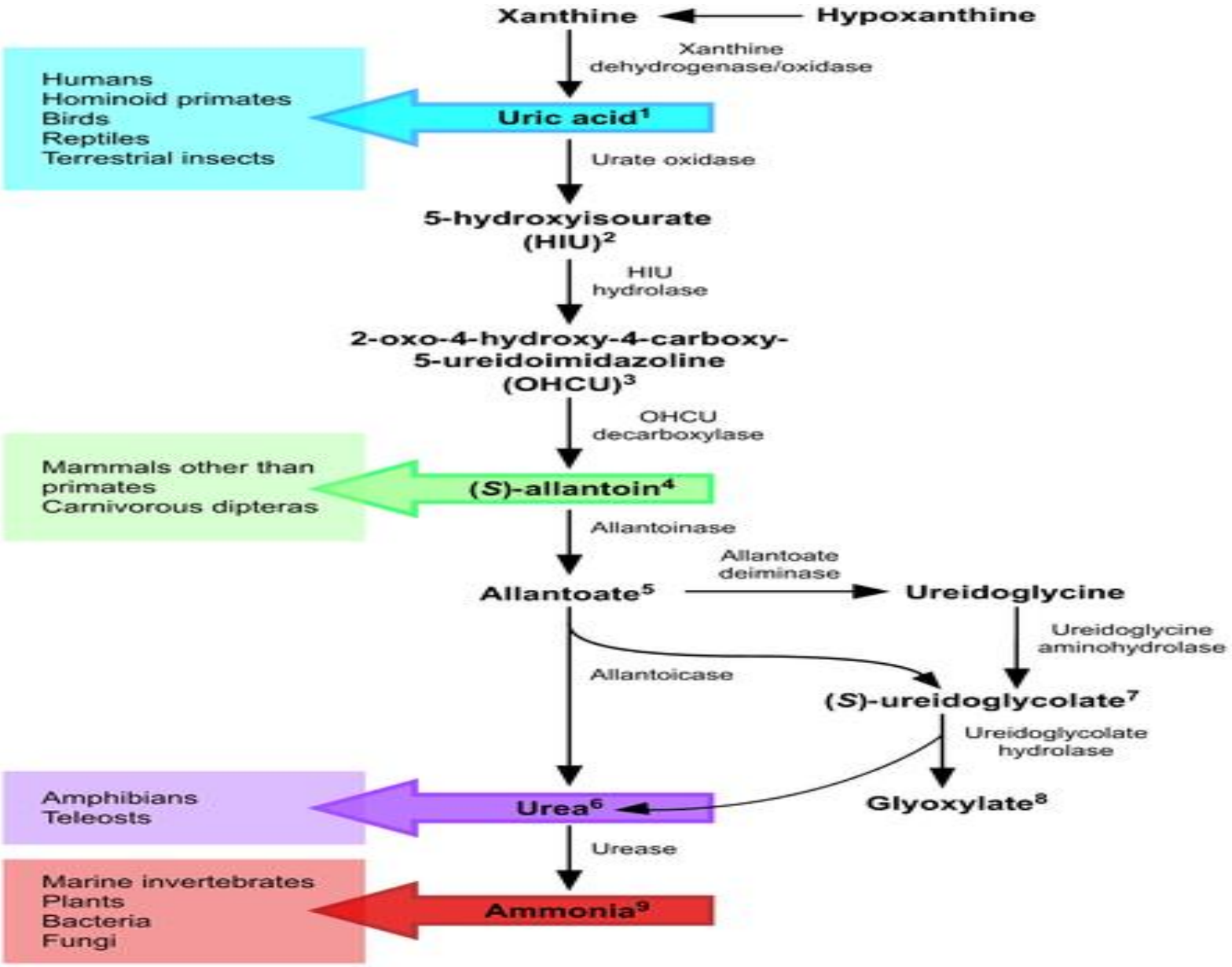
Disclosure Statement

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any cooperate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Βιολογική σημασία Ουρικού οξέος



Uric Acid


Xanthine
Hypoxanthine
Xanthine dehydrogenase/oxidase
Humans
Hominoid primates
Birds
Reptiles
Terrestrial insects
Uric acid[1]
Urate oxidase
5-hydroxyisourate (HIU)[2]
HIU hydrolase
2-oxo-4-hydroxy-4-carboxy-5-ureidoimidazoline (OHCU)[3]
OHCU decarboxylase
Mammals other than primates
Carnivorous dipteras
(S)-allantoin[4]
Allantoinase
Allantoate deiminase
Allantoate[5]
Ureidoglycine
Ureidoglycine aminohydrolase
Allantoicase
(S)-ureidoglycolate[7]
Ureidoglycolate hydrolase
Amphibians
Teleosts
Urea[6]
Glyoxylate[8]
Urease
Marine invertebrates
Plants
Bacteria
Fungi
Ammonia[9]

Ουρικό οξύ

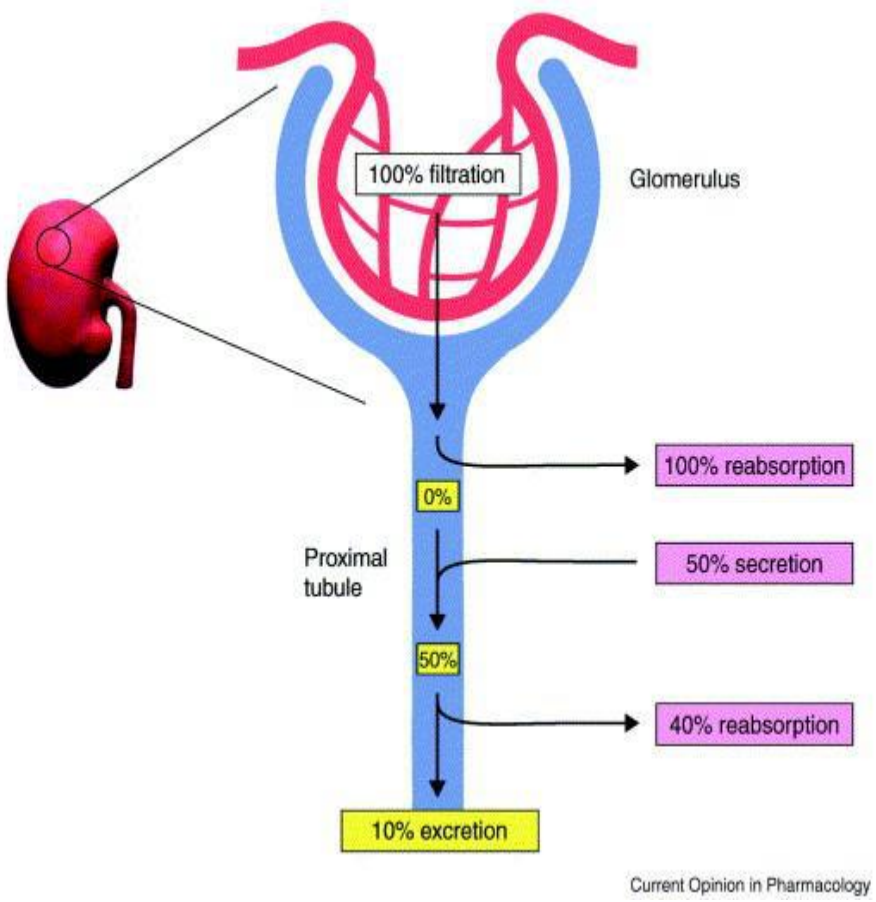
- Τελικό προϊόν καταβολισμού των πρωτεϊνών στον άνθρωπο
- Θεωρείται προγνωστικός δείκτης μεταβολικών και αιμοδυναμικών διαταραχών
- Αποβάλλεται κατά τα 70% από τους νεφρούς και 30% από το έντερο
- Προέλευση ουρικού οξέως: 2/3 ενδογενές, 1/3 διατροφική προέλευση

Ουρικό οξύ

- Διαλυτότητα ουρικού οξέος σε συνήθεις συνθήκες 6.4-6.8 mg/dl μέγιστη 7.0 mg/dl

(σε φυσιολογικό ph καιθερμοκρασία)

- Το ουρικό οξύ ελευθέρα φιλτράρεται στο σπείραμα , επαναρροφάται , απεκκρίνεται και εκ νέου επαναρροφάται στο εγγύς εσπειραμένο σωληνάριο



Ποιος ο ρόλος του ουρικού οξέος στον οργανισμό?

- Θετική βιολογική δράση

- Διατήρηση φυσιολογικής αρτηριακής πίεσης σε δίαιτες με χαμηλό νάτριο
- Αντιοξειδωτικό
- Νευροπροστατευτική δραστηριότητα
- Συσχέτιση με το IQ

Higher antioxidant capacity and greater longevity

- It is thought that UA contributes to >50% of the antioxidant capacity of blood. For this reason, Ames *et al.* proposed that the loss of **uricase** expression and the subsequent increase in UA levels had the **evolutionary benefit** of increasing antioxidant capacity, increasing the life expectancy of hominids and decreasing age-specific cancer rates. The loss of **uricase** could be associated with the previous loss of capacity to synthesize vitamin C which occurred 40–50 million years ago
- B Álvarez-Lario, J Macarrón-Vicente - Rheumatology, 2010

Ποιος ο ρόλος του ουρικού οξέος στον οργανισμό?

- Αρνητική δράση

- Ουρική αρθρίτις
- Νεφρολιθίαση
- Μεταβολικό σύνδρομο
- Υπέρταση
- Νεφρική νόσος
- Καρδιαγγειακή νόσος

Epidemiological Studies-Hyperuricemia

- Cerebrovascular disease
- Preeclampsia
- Metabolic syndrome
- Stroke
- Hypertension
- Vascular dementia
- Coronary artery disease
- Renal disease
- This relationship with cardiovascular disease is especially high in those at risk for CVD and in women
- Johnson, RJ. N. Engl J. Med 359 2008


The GOUT

Βιολογικη δραση ουρικου

- gout
- **uric** lithiasis,
- association with hypertension, metabolic syndrome, renal disease and cardiovascular disease

Hypotheses on **evolution**ary advantages of the loss of **uric**ase

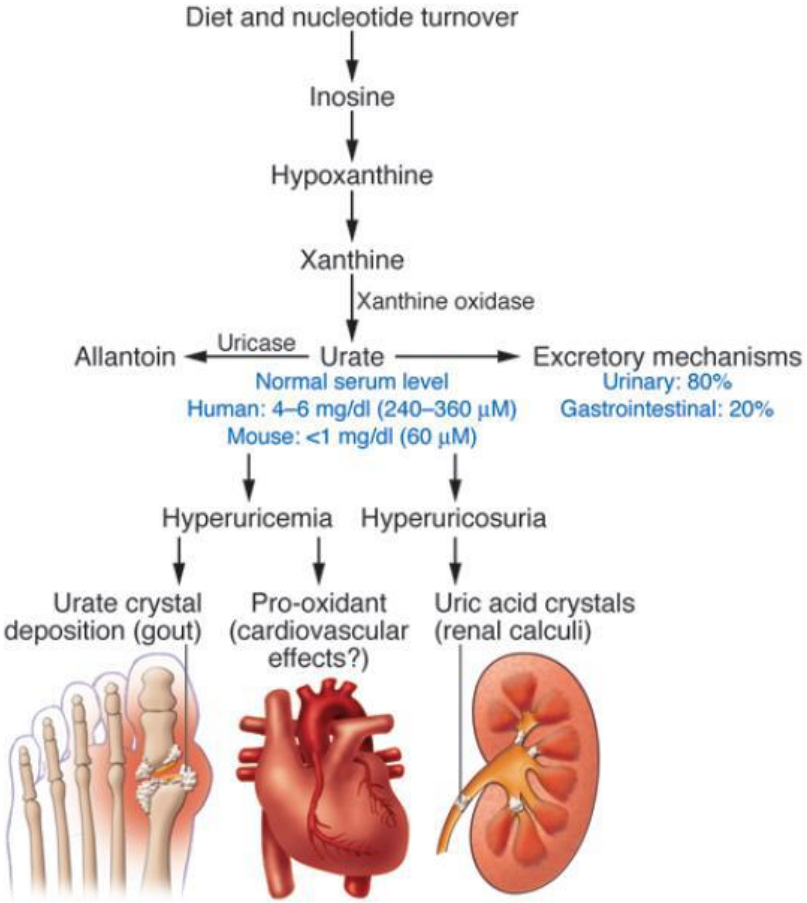
- Higher antioxidant capacity and greater longevity
- To maintain blood pressure during low salt ingestion
- UA and intelligence
- UA and neuroprotection

- B Álvarez-Lario, J Macarrón-Vicente - Rheumatology, 2010

- 84
- Pegloticase: Mechanism of Action
- Reprinted from Baraf HSB, Matsumoto AK. *Int J Clin Rheumatol*. 2012;7(2):143-154. **Hypoxanthine**
- **Xanthine**
- **Uric Acid**
- **Allantoin**
- Xanthine Oxidase Inhibitors
- **Tophaceous Deposits**
- **Pegloticase**
- ++ Uricosuric Agents
- Cell Breakdown Diet
- Purines **Urinary Excretion**
- **Urinary Excretion**

- Theory lL-1 B blockade - reduces acute gout flares when initiating chronic treatment
- Anakinra (Kineret), Rilonacept(Arcalyst)
- Canakinumab (Ilaris)
- May lead to improved adherence

Pathways of urate homeostasis



Prevalence of Gout According to Age

Gonzalez EB. Clin Rheumatol(2012)31:13-21

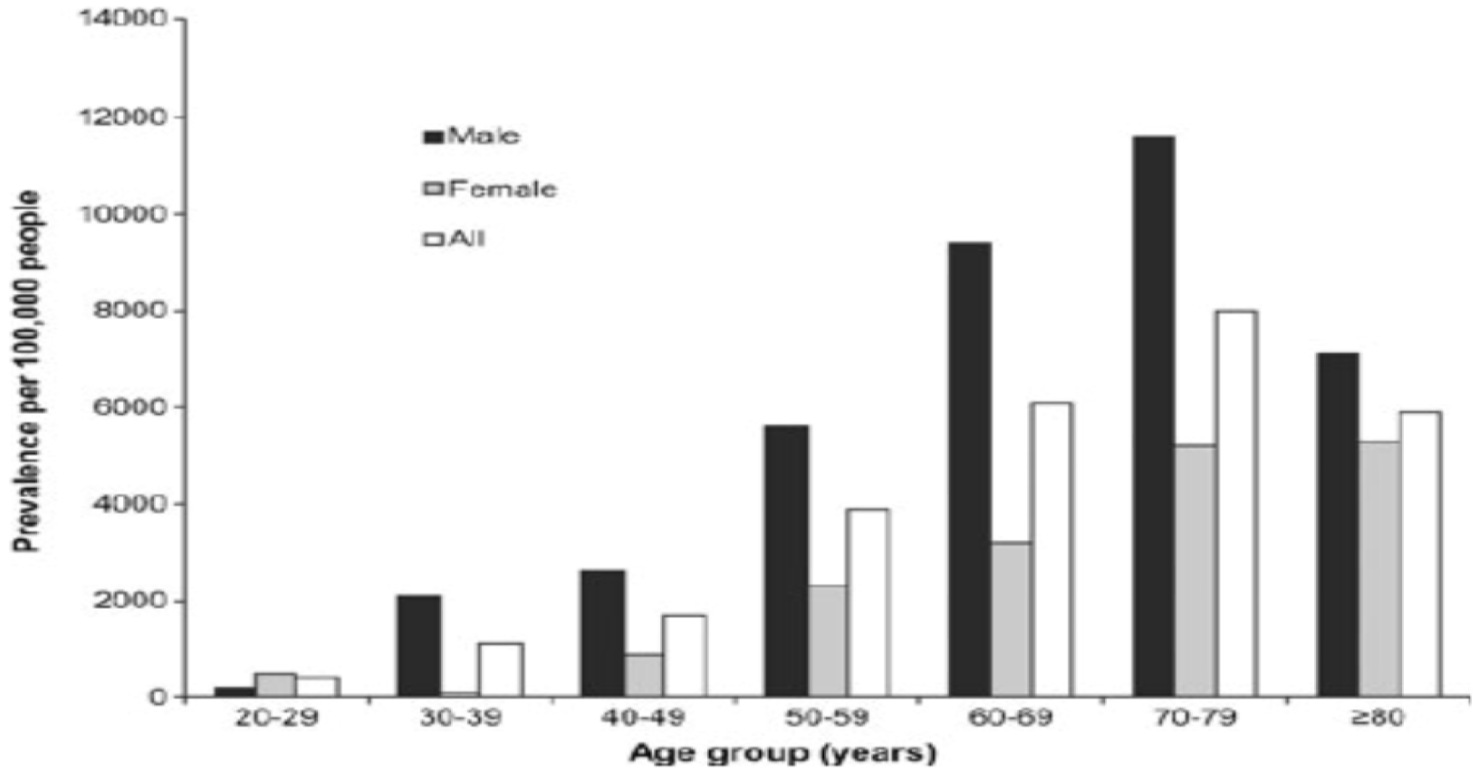


Fig. 1 Prevalence of gout in the USA according to age [1, 2]

Epidemiology

- One of the most common rheumatic diseases of adulthood
- Prevalence
- 3.9% of adults in the US
- ~8.3 million people
- Increases with age
- Peaks at 30 to 50 years of age
- Affects men about 7-9 times more often than women
- Men 40-44 y/o: 1 in 1,000
- Men 55-64 y/o: 1.8 in 1,000
- Young women: 0.8 cases per 10,000 patient-years
- Among those age ≥45: higher in African Americans than in whites
- Incidence and prevalence of gout are increasing worldwide
- Increased longevity, dietary habits, obesity and the metabolic syndrome

- Lawrence RC, et al. Arthritis Rheum. 2008 January ; 58(1): 26–35 Kramer HM, et al. Am J Kidney Dis 2002;40:37–42. Mikuls TR, et al. Ann Rheum Dis 2005;64:267–272

Overproduction of Uric Acid

- Enzyme abnormalities
- Increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase
- Increased concentration of PRPP
- PRPP is a key determinant of purine synthesis and uric acid production
- Deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT)
- increased metabolism of guanine and hypoxanthine to uric acid
- Increased breakdown of tissue nucleic acids
- Myeloproliferative and lymphoproliferative disorders
- Polycythemia vera
- Psoriasis

- Ernst ME, et al. Pharmacotherapy: A Pathophysiologic Approach. 8th ed. New York: McGraw-Hill; 2011.

Βιολογική σημασία Ουρικού οξέος

- προϊόν καταβολισμού -αποβολή αζώτου από τον οργανισμό

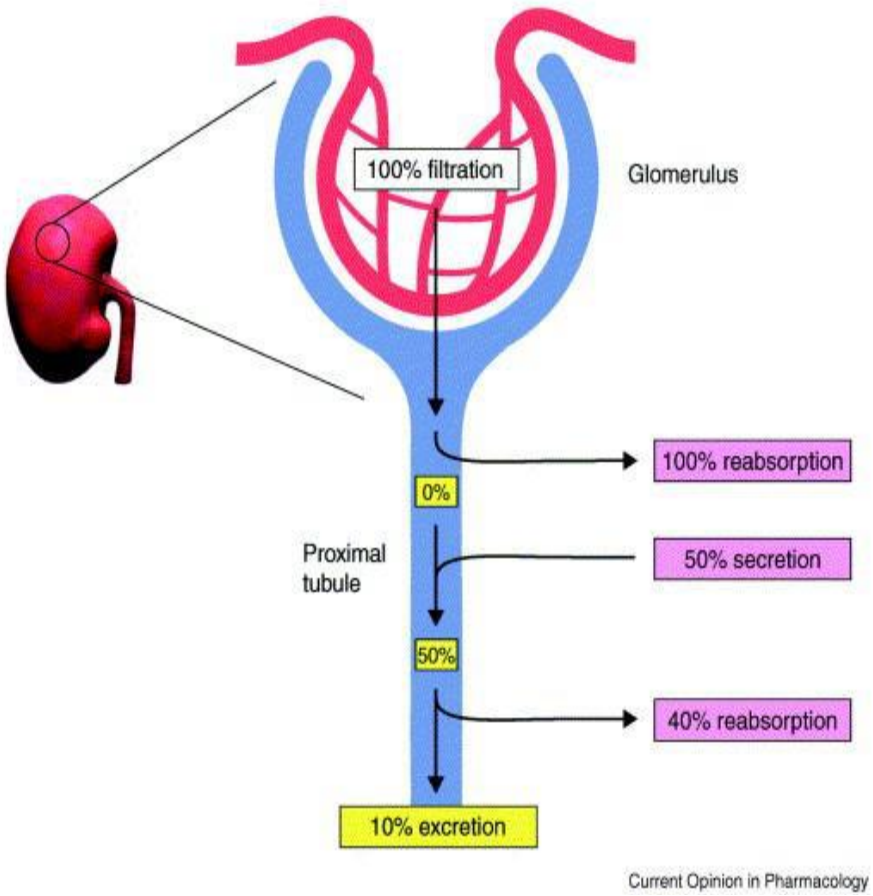
Uric Acid

- Uric acid: waste product
- Humans do not express the enzyme uricase
- Accumulated uric acid
- 1,200 mg in men
- 600 mg in women
- Uric acid is produced from purines (3 sources)
- Dietary purine
- Conversion of tissue nucleic acid to purine nucleotides
- De novo synthesis of purine bases
- Normal production: 600 to 800 mg of uric acid each day

- Terkeltaub RA. Gout. N Engl J Med 2003;349:1647–1655. Choi HK, et al. Pathogenesis of gout. Ann Intern Med 2005;143:499–516.

Underexcretion of Uric Acid

- Excretion of Uric Acid
- 2/3rds : urine
- 1/3rd: GI tract after enzymatic degradation by colonic bacteria
- Primary Idiopathic Hyperuricemia (80%-90 %)
- Relative decrease in the renal excretion of uric acid for an unknown reason



- Alderman MH. Current Opinion in Pharmacology, Volume 2, Issue 2, 1 April 2002, P126-130

Θέματα προς συζήτηση

- Σχέση μεταξύ υπερουριχαιμίας , ουρικής αρθρίτιδας και καρδιοαγγειακού κινδύνου
- Θεραπευτική αντιμετώπιση
- νεώτερα φάρμακα
- Θεραπευτικά πρωτόκολλα

Discussion Points

- Myths and Realities regarding gout
- Interaction between gout, hyperuricemia and CVD
- Recognizing the necessity for a multidisciplinary approach to treatment of gout
- Review of newer urate lowering therapies

Gout Facts

- Asymptomatic hyperuricemia is common but under recognized
- Risk of developing gout associated with the extent and chronicity of hyperuricemia. Increases significantly with uric acid levels >9.0 mg dL
- Only a minority actually develop gout
- Tophi not completely understood
- undervascularized tissue milieu leads to cool temperatures of joints.
- Low grade inflammation in and around tophi

Gout is a new age disease

- Reality:
- First description - Egyptians in 2640 BC
- Podagra recognized by Hippocrates in the fifth century BC - referred to it as 'the unwalkable disease'.
- Gout is derived from the Latin word gutta *(or 'drop')*

Gout is a disease of indulgence

- Reality:
- Estimated 6 million Americans have gout
- Last 20 years gout has doubled in in USA
- Large increase in gout prevalence in those individuals over age 65
- Striking increase in those aged over 75
- Unlikely this is secondary to indulgence
- Wallace, K. L. et al J. Rheumatology 31, 2004

Why the increase in the elderly?

- Declining mortality from cardiovascular disease
- Frequent comorbidities that promote hyperuricemia such as CKD, CHF, and hypertension
- Prescriptions of diuretics-loop and thiazides

- J.D. et al. Arthritis Rheum. 50 2004

Secondary Causes of Hyperuricemia

- Leukemia/lymphomas
- Psoriasis
- Tissue necrosis
- Seizures
- Renal insufficiency
- Dehydration
- Lead nephropathy
- Hypothyroidism
- Hyperparathyroidism
- Diuretics
- Ethambutol
- Pyrazinamide
- Aspirin
- Cyclosporine
- Niacin

Gout is common among men but rare among women

- Reality: Only true premenopausal
- Increases substantially after menopause and rises with age
- In kidney (URAT1)- Responsible for reabsorption of uric acid from proximal tubule
- Estrogen direct effect on expression

- Enomoto et al. Nature. 2002;417

Gout and women

- NHANES- prevalence of gout among women aged 60-69 was 3.5 %
- This increases to 5.6% for those 80 yrs and older

Women and Gout

- Even if true age–specific prevalence of gout was 50% lower, almost exceeds that of rheumatoid arthritis among women (3.3% in NHANES III).
- Take home: premenopausal – unlikely to be gout. Consider even without acute flares in postmenopausal with chronic joint pain.

- Rasch EK, et al. Arthritis Rheum. 48 2003
- Kramer HM. et al. Br J Nutr. 82 1999

The Uric acid is normal- It cannot be gout

- Reality:
- 339 patients (two studies) comparing treatment of etoricoxib or indomethacin for acute gout
- 14% uric acid less than 6.0 mg/dl at baseline
- 32% < than 8.0 mg/dL during acute attack

- Schiessinger et al. J Rheum 2009 Jun;36(6)

It’s just Arthritis

- Gout accounted for 2.2 million ambulatory visits annually
- 1.2% (11,064) of 922,000 hospitalizations for a diagnosis of arthritis
- Mean annual cost of employee with gout $6870 versus $3705 without gout
- Patients with gout miss 3-5 days/year
- Sacks et al Arthritis Care and Research 2010:62

- Kim et al Clin therap 2003:6, Brick et al Curr New Res Opin 2006: 7

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Does Gout cause or increase the risk of cardiovascular disease?

- Choi and Curhan (2007) :Those with gout have a higher risk of death from all causes
- At least three other studies have confirmed similar findings between gout and shortened longevity primarily through risk of coronary artery disease

- Choi and Curhan. Circulation. 2007b;116
- Krishnan et al Arch Intern me 2008;168

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- Anakinra (Kineret), Rilonacept(Arcalyst)
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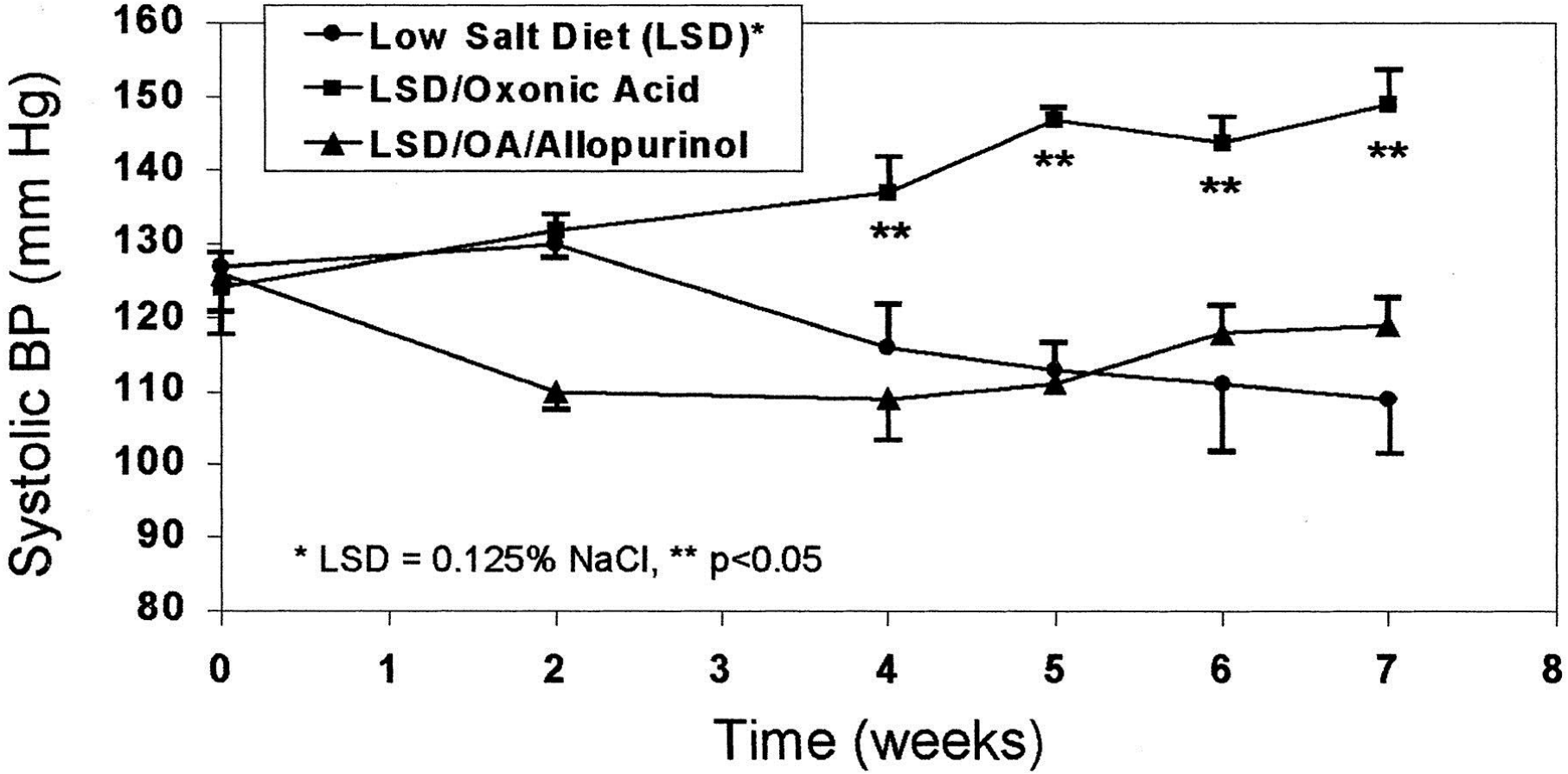
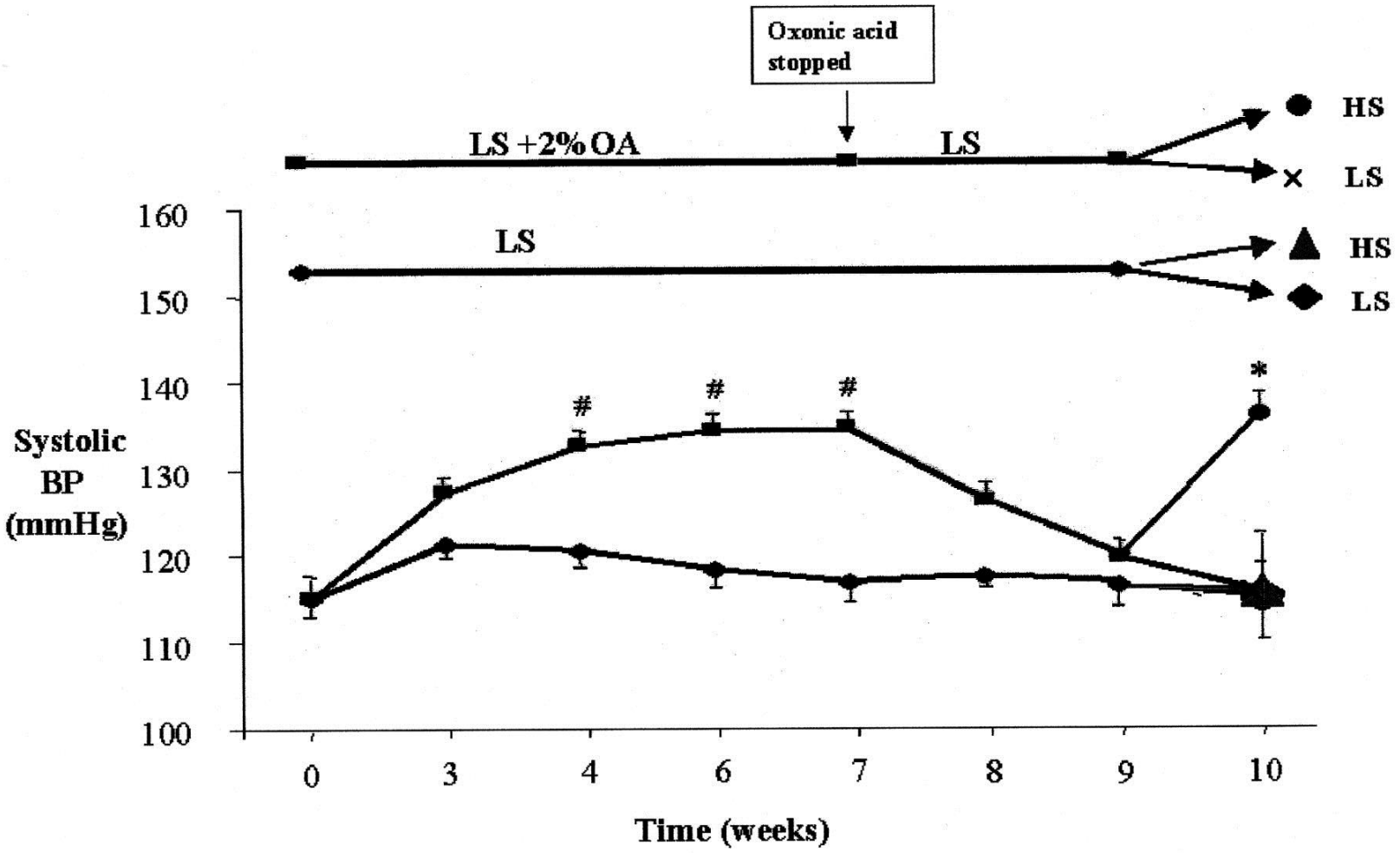
Secondary Causes of Hyperuricemia

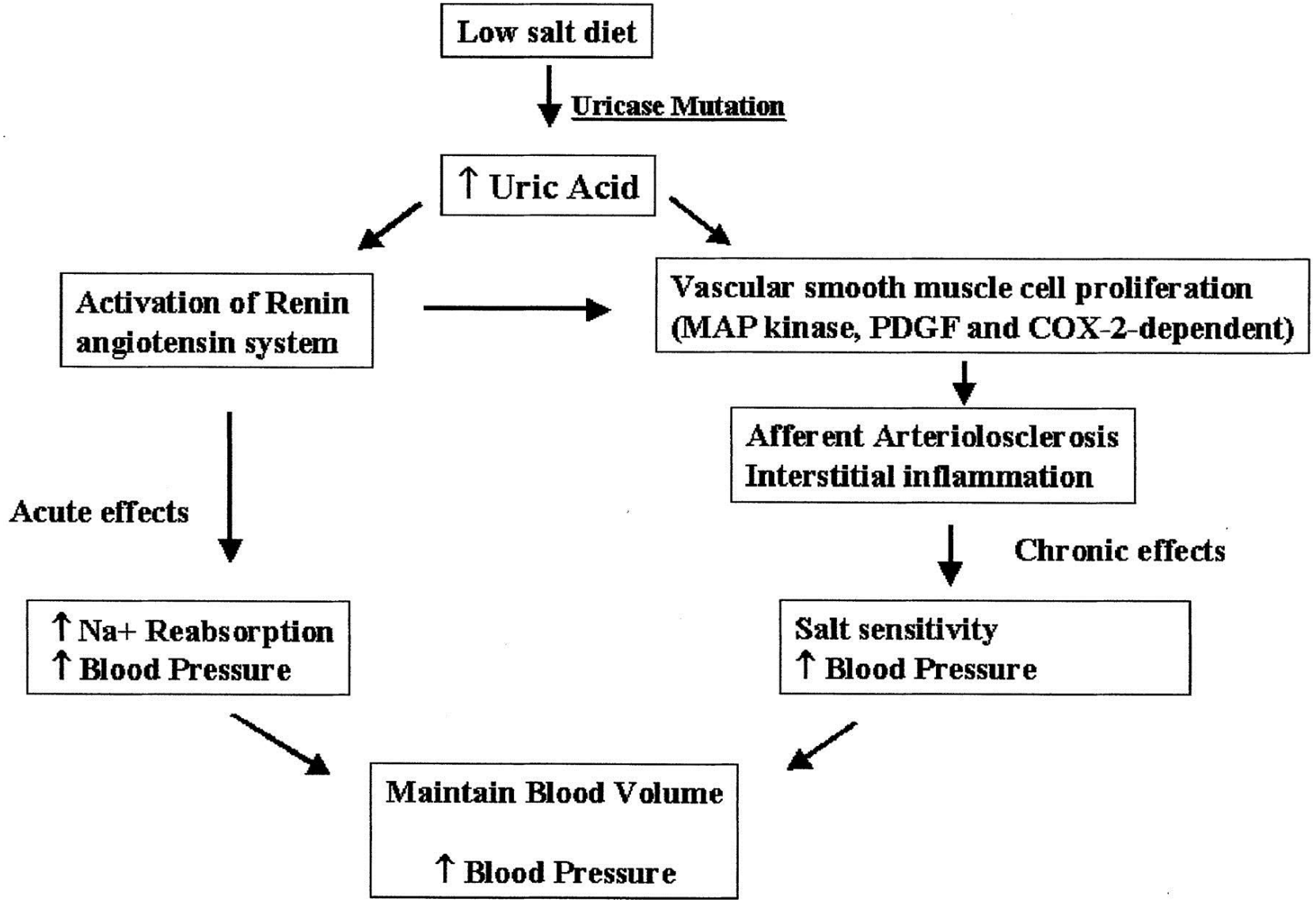
- **Uric Acid: Potential Role in Hypertension and Cardiovascular Disease in Industrialized Societies**
- **Uric Acid Stimulates Smooth Muscle Cell Proliferation**
- **Hyperuricemia Induces Salt Sensitivity in Rats**
- **Uric Acid Maintains Blood Pressure Under Low-Sodium Conditions**
- **Parallel Mutations in the Uricase Gene in Early Hominoids: Evolutionary Implications**

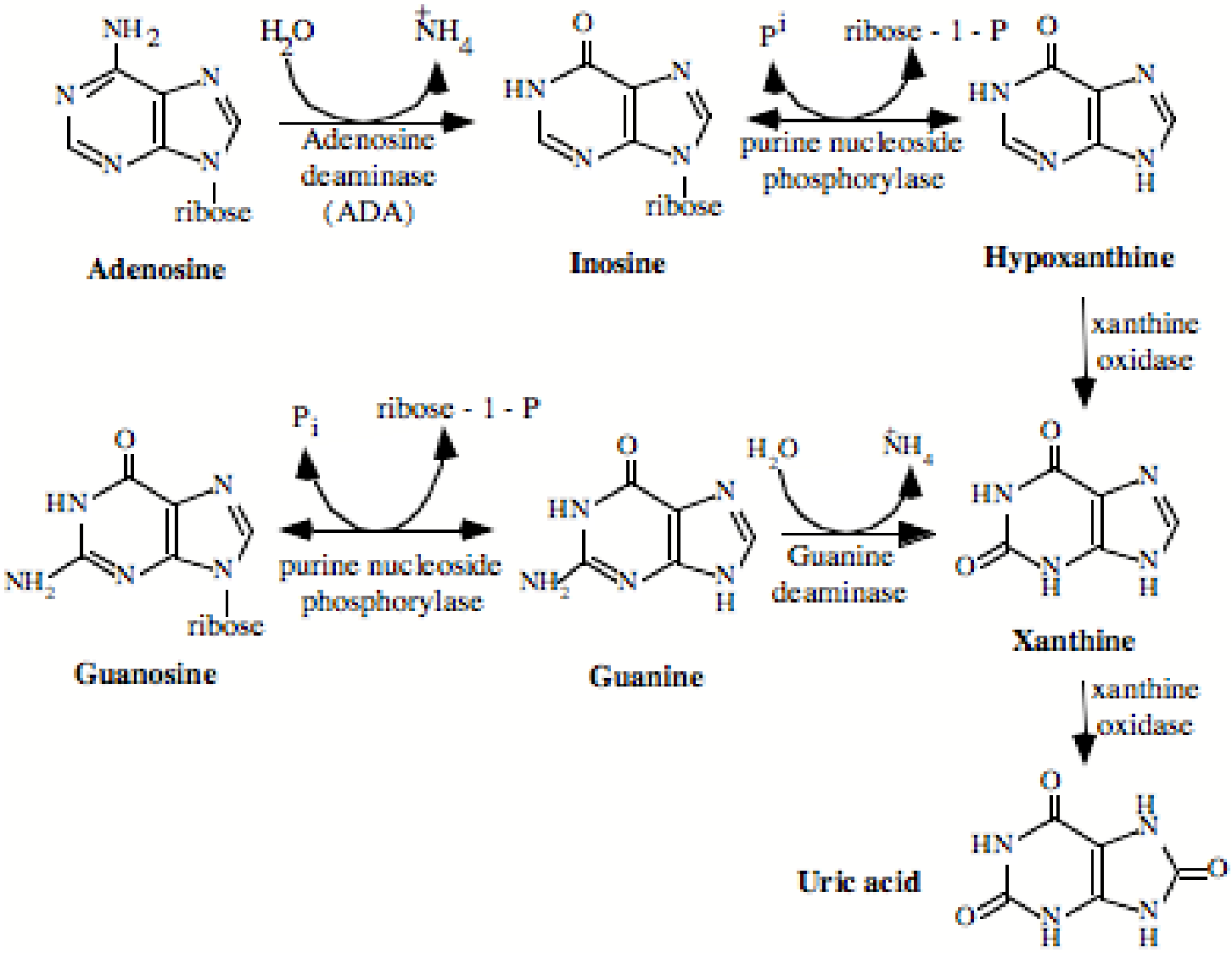
Humans have elevated serum uric acid as a result of a mutation in the urate oxidase (uricase) gene that occurred during the Miocene. We hypothesize that the mutation provided a survival advantage because of the ability of hyperuricemia to maintain blood pressure under low-salt dietary conditions, such as prevailed during that period. Mild hyperuricemia in rats acutely increases blood pressure by a renin-dependent mechanism that is most manifest under low-salt dietary conditions. Chronic hyperuricemia also causes salt sensitivity, in part by inducing preglomerular vascular disease. The vascular disease is mediated in part by uric acid-induced smooth muscle cell proliferation with activation of mitogen-activated protein kinases and stimulation of cyclooxygenase-2 and platelet-derived growth factor. Although it provided a survival advantage to early hominoids, hyperuricemia may have a major role in the current cardiovascular disease epidemic.


Low Salt Diet (LSD)*
LSD/Oxonic Acid
LSD/OA/Allopurinol
Systolic BP (mm Hg)
160
150
140
130
120
110
100
90
80
0
1
2
3
4
5
6
7
8
Time (weeks)
**
**
**
**
* LSD = 0.125% NaCl, ** p<0.05



Values are mean ± SE. # P < 0.05 vs LS (Student's t test); *P <0.05 vs all other groups (ANOVA with Fishers Exact Test)


Low salt diet
Uricase Mutation
↑ Uric Acid
Activation of Renin angiotensin system
Vascular smooth muscle cell proliferation (MAP kinase, PDGF and COX-2-dependent)
Afferent Arteriolosclerosis
Interstitial inflammation
Acute effects
Chronic effects
↑ Na+ Reabsorption
↑ Blood Pressure
Salt sensitivity
↑ Blood Pressure
Maintain Blood Volume
↑ Blood Pressure


Adenosine
Adenosine deaminase (ADA)
Inosine
purine nucleoside phosphorylase
Hypoxanthine
xanthine oxidase
Xanthine
xanthine oxidase
Uric acid
Guanosine
purine nucleoside phosphorylase
Guanine
Guanine deaminase

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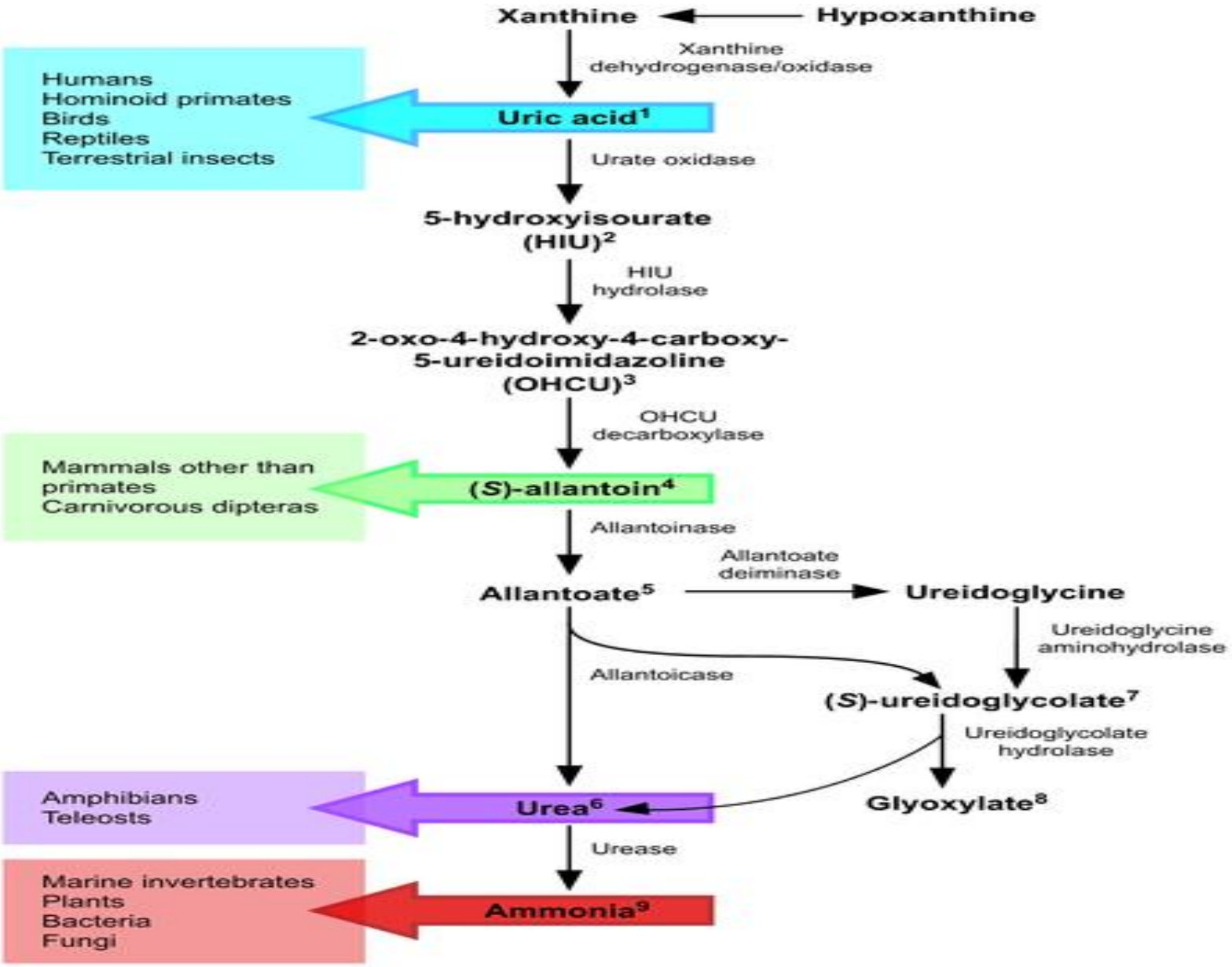
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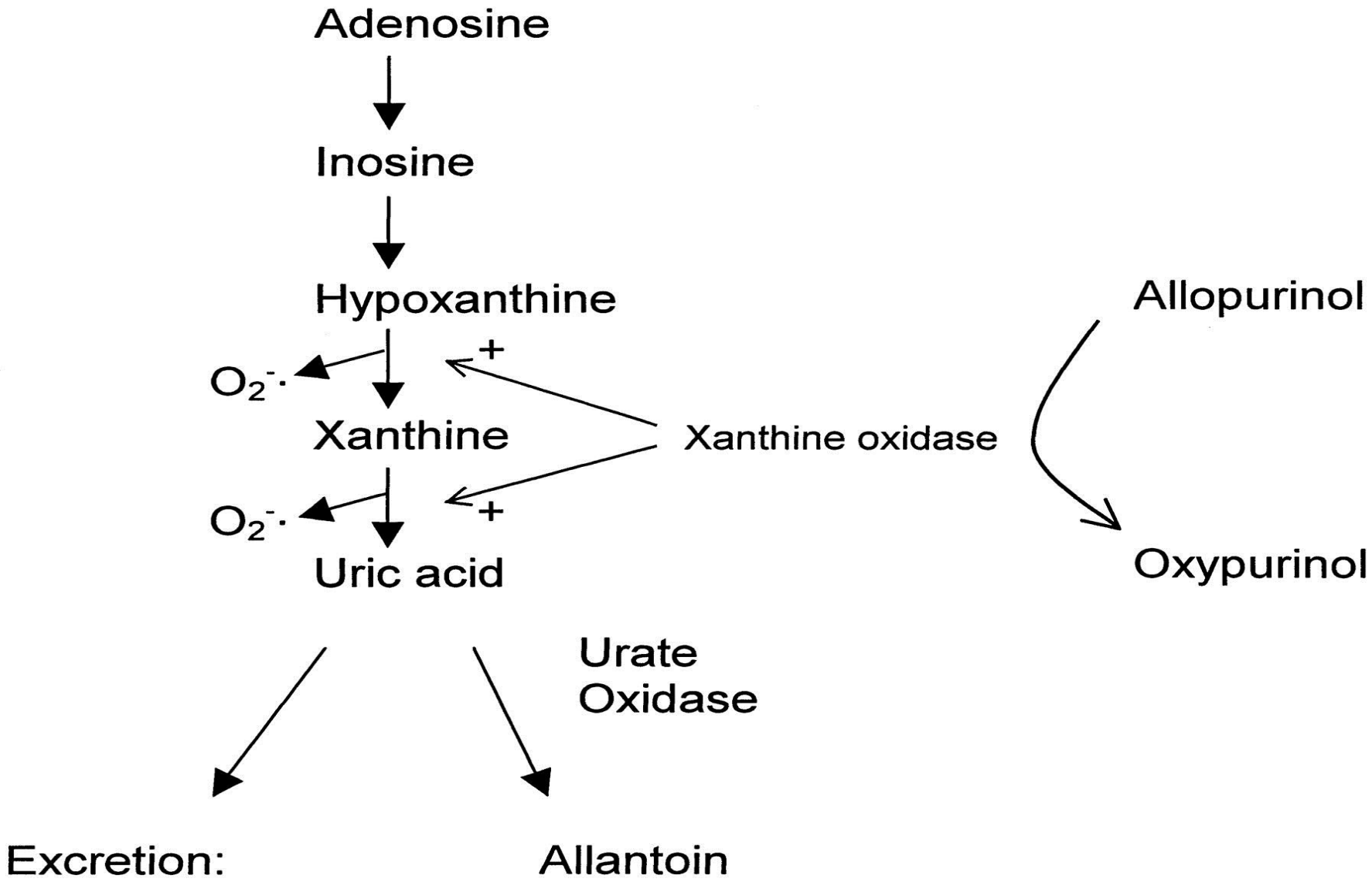
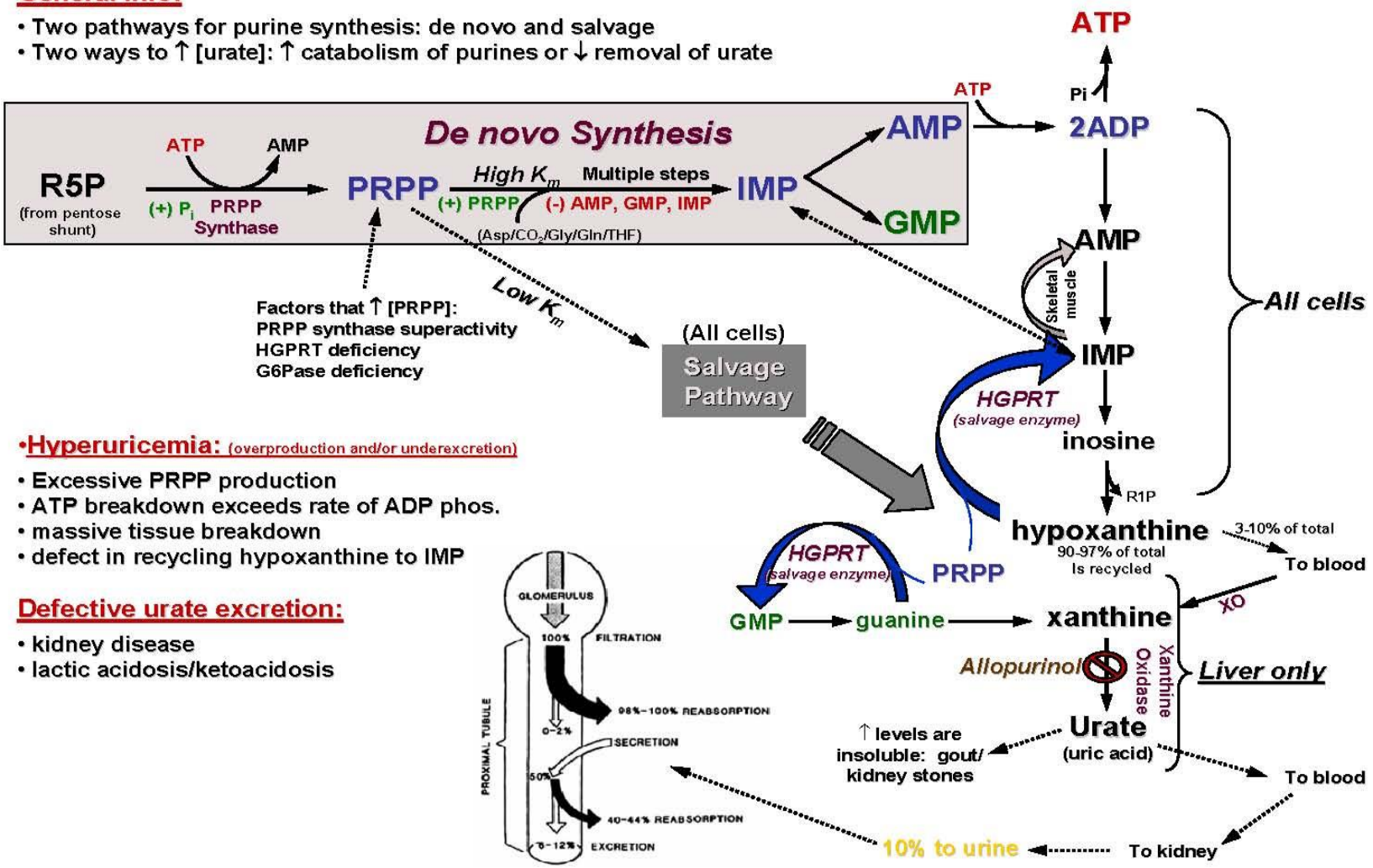

Adenosine
Inosine
Hypoxanthine
$O_2^{-}\cdot$
+
Xanthine
Xanthine oxidase
Allopurinol
$O_2^{-}\cdot$
+
Uric acid
Oxypurinol
Urate
Oxidase
Excretion:
Allantoin
Renal (2/3)
Gastrointestinal (1/3)

Purine Metabolism/Hyperuricemia

Camire, Oct. 2005

General Info:

- Two pathways for purine synthesis: de novo and salvage
- Two ways to ↑ [urate]: ↑ catabolism of purines or ↓ removal of urate

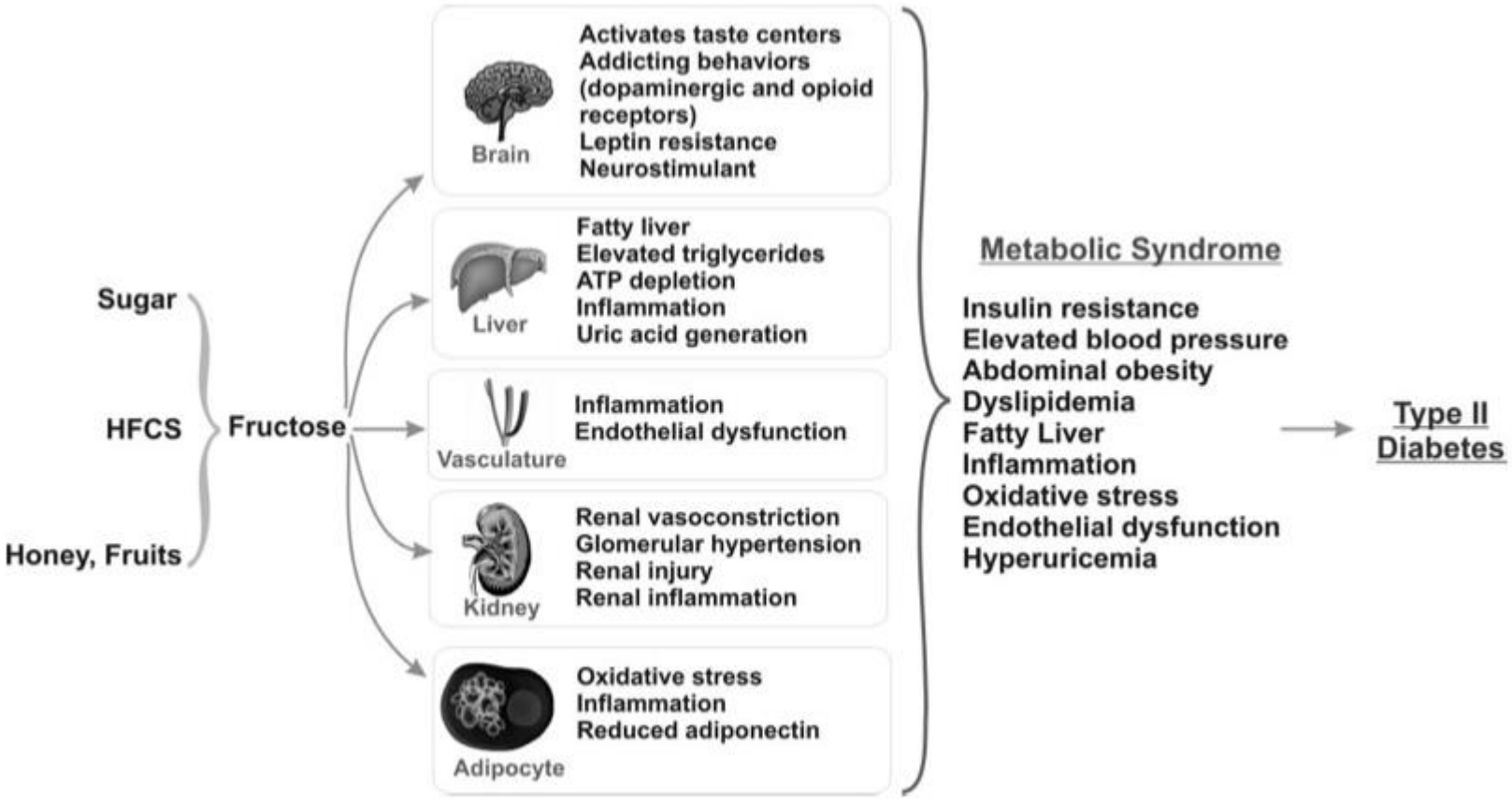


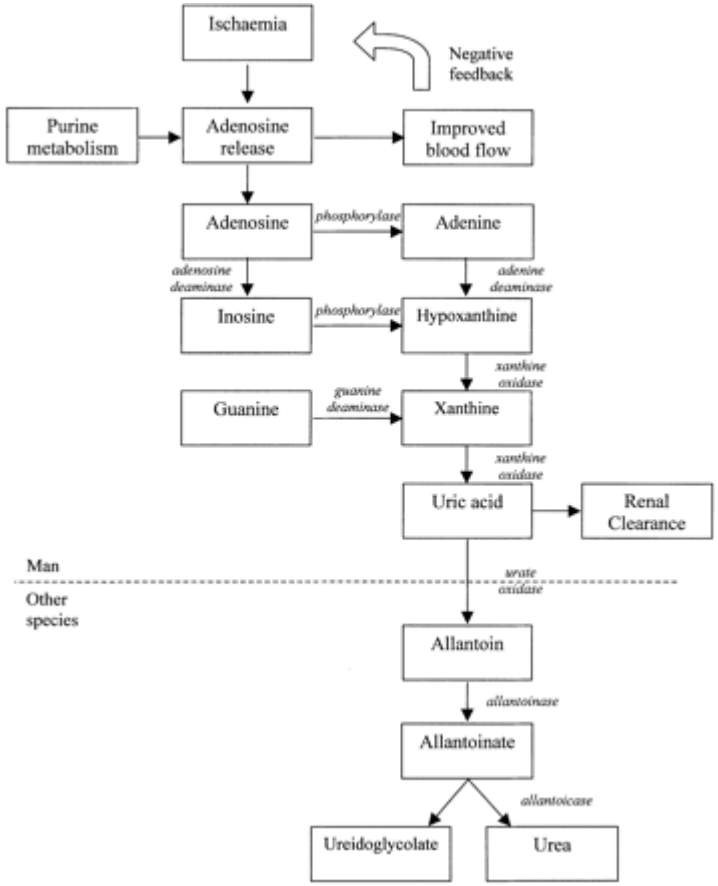
•Hyperuricemia: (overproduction and/or underexcretion)

- Excessive PRPP production
- ATP breakdown exceeds rate of ADP phos.
- massive tissue breakdown
- defect in recycling hypoxanthine to IMP

Defective urate excretion:

- kidney disease
- lactic acidosis/ketoacidosis


Sugar
HFCS
Honey, Fruits
Fructose
Brain
Activates taste centers
Addicting behaviors
(dopaminergic and opioid
receptors)
Leptin resistance
Neurostimulant
Liver
Fatty liver
Elevated triglycerides
ATP depletion
Inflammation
Uric acid generation
Vasculature
Inflammation
Endothelial dysfunction
Kidney
Renal vasoconstriction
Glomerular hypertension
Renal injury
Renal inflammation
Adipocyte
Oxidative stress
Inflammation
Reduced adiponectin
Metabolic Syndrome
Insulin resistance
Elevated blood pressure
Abdominal obesity
Dyslipidemia
Fatty Liver
Inflammation
Oxidative stress
Endothelial dysfunction
Hyperuricemia
Type II
Diabetes


Ischaemia
Negative feedback
Purine metabolism
Adenosine release
Improved blood flow
Adenosine
phosphorylase
Adenine
adenosine deaminase
adenine deaminase
Inosine
phosphorylase
Hypoxanthine
xanthine oxidase
Guanine
guanine deaminase
Xanthine
xanthine oxidase
Uric acid
Renal Clearance
Man
Other species
urate oxidase
Allantoin
allantoinase
Allantoinate
allantoicase
Ureidoglycolate
Urea