431e Disorders of Purine and Pyrimidine Metabolism

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Purines (adenine and guanine) and pyrimidines (cytosine, thymine, uracil) serve fundamental roles in the replication of genetic material, gene transcription, protein synthesis, and cellular metabolism. Disorders that involve abnormalities of nucleotide metabolism range from relatively common diseases such as hyperuricemia and gout, in which there is increased production or impaired excretion of a metabolic end product of purine metabolism (uric acid), to rare enzyme deficiencies that affect purine and pyrimidine synthesis or degradation. Understanding these biochemical pathways has led, in some instances, to the development of specific forms of treatment, such as the use of allopurinol and febuxostat to reduce uric acid production.

URIC ACID METABOLISM

Uric acid is the final breakdown product of purine degradation in humans. It is a weak diprotic acid with pK_a values of 5.75 and 10.3. Urates, the ionized forms of uric acid, predominate in plasma, extracellular fluid, and synovial fluid, with ~98% existing as monosodium urate at pH 7.4.

Plasma is saturated with monosodium urate at a concentration of 405 μmol/L (6.8 mg/dL) at 37°C. At higher concentrations, plasma is therefore supersaturated—a situation that creates the potential for urate crystal precipitation. However, plasma urate concentrations can reach 4800 μmol/L (80 mg/dL) without precipitation, perhaps because of the presence of solubilizing substances.

The pH of urine greatly influences the solubility of uric acid. At pH 5.0, urine is saturated with uric acid at concentrations ranging from 360 to 900 μmol/L (6–15 mg/dL). At pH 7, saturation is reached at concentrations from 9840 to 12,000 μmol/L (158–200 mg/dL). Ionized forms of uric acid in urine include monosodium, disodium, potassium, ammonium, and calcium urates.

Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. Urate production varies with the purine content of the diet and with rates of purine biosynthesis, degradation, and salvage (Fig. 431e-1). Normally, two-thirds to three-fourths of urate is excreted by the kidneys, and most of the remainder is eliminated through the intestines.

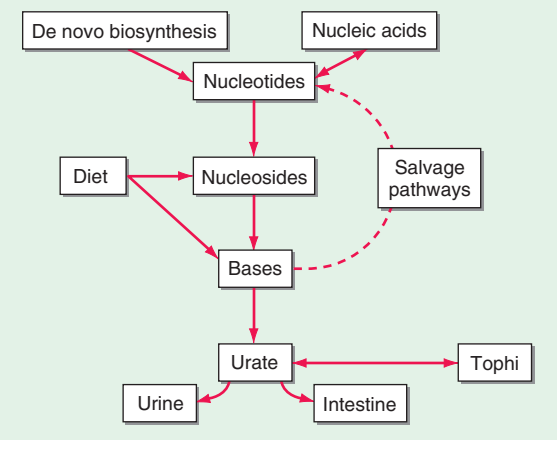

FIGURE 431e-1 The total-body urate pool is the net result between urate production and excretion. Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors, nucleic acid turnover, and salvage by phosphoribosyltransferase activities. The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can result from increased production, decreased excretion, or a combination of both mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs), including urate transporter 1 (URAT1, SLC22A12) (Fig. 431e-2). In humans, OAT1 (SLC22A6), OAT2 (SLC22A7), and OAT3 (SLC22A8) are located on the basolateral membrane of renal proximal tubule cells. OAT4 (SLC22A11), OAT10 (SLC22A13), and URAT1 are located on the apical brush-border membrane of these cells. The latter transporters carry urate and other organic anions into the tubular cells from the lumen in exchange for intracellular organic anions. Once inside the cell, urate must pass to the basolateral side of the lumen in a process controlled by voltage-dependent carriers, including glucose transporter 9 (GLUT9, SLC2A9). *Uricosuric* compounds (Table 431e-1) directly inhibit URAT1 on the apical side of the tubular cell (so-called *cis*-inhibition). In contrast, *antiuricosuric* compounds (those that promote hyperuricemia), such as nicotinate, pyrazinoate, lactate, and other aromatic organic acids, serve as the exchange anion inside the cell, thereby stimulating anion exchange and urate reabsorption (*trans*-stimulation). The activities of URAT1, other OATs, and sodium anion transporters result in excretion of 8–12% of the filtered urate as uric acid.

Most children have serum urate concentrations of 180–240 μmol/L (3–4 mg/dL). Levels begin to rise in males during puberty but remain low in females until menopause. The most recent mean serum urate values for men and premenopausal women in the United States are 415 and 360 μmol/L (6.14 and 4.87 mg/dL), respectively, according to National Health and Nutrition Evaluation Survey (NHANES) data for 2007–2008. After menopause, values for women increase to approximately those for men. In adulthood, concentrations rise steadily over time and vary with height, body weight, blood pressure, renal function, and alcohol intake.

HYPERURICEMIA

Hyperuricemia can result from increased production or decreased excretion of uric acid or from a combination of the two processes. Sustained hyperuricemia predisposes some individuals to develop clinical manifestations including gouty arthritis (Chap. 395), urolithiasis, and renal dysfunction (see below).

In general, hyperuricemia is defined as a plasma (or serum) urate concentration >405 μmol/L (>6.8 mg/dL). The risk of developing gouty arthritis or urolithiasis increases with higher urate levels and escalates in proportion to the degree of elevation. The prevalence of hyperuricemia is increasing among ambulatory adults and even more markedly among hospitalized patients. The prevalence of gout in the United States more than doubled between the 1960s and the 1990s. Based on NHANES data from 2007–2008, these trends continue, with an approximate prevalence of gout among men of 5.9% (6.1 million) and among women of 2.0% (2.2 million). Mean serum urate levels rose to 6.14 mg/dL among men and 4.87 mg/dL among women, with consequent hyperuricemia prevalences of 21.2% and 21.6%, respectively (with *hyperuricemia* defined as a serum urate level of >7.0 mg/dL [415 μmol/L] for men and >5.7 mg/dL [340 μmol/L] for women). These numbers represent a 1.2% increase in the prevalence of gout, a 0.15-mg/dL increase in the serum urate level, and a 3.2% increase in the prevalence of hyperuricemia over figures reported in NHANES-III (1988–1994). These rises are thought to be driven by increased obesity and hypertension and perhaps also by better medical care and increased longevity.

CAUSES OF HYPERURICEMIA

Hyperuricemia may be classified as primary or secondary, depending on whether the cause is innate or an acquired disorder. However, it is more useful to classify hyperuricemia in relation to the underlying pathophysiology—i.e., whether it results from increased production, decreased excretion, or a combination of the two (Fig. 431e-1, Table 431e-2).

Increased Urate Production Diet contributes to the serum urate concentration in proportion to its purine content. Strict restriction of purine intake reduces the mean serum urate level by ~60 μmol/L