Molecular Physiology of Urate Transport

Humans excrete uric acid as the final breakdown product of unwanted purine nucleotides. Urate scavenges potential harmful radicals in our body. However, in conjunction with genetic or environmental (especially dietary) factors, urate may cause gout, nephrolithiasis, hypertension, and vascular disease. Blood levels of urate are maintained by the balance between generation and excretion. Excretion requires specialized transporters located in renal proximal tubule cells, intestinal epithelial cells, and vascular smooth muscle cells. The recently identified human urate transporters URAT1, MRP4, OAT1, and OAT3 are thought to play central roles in homeostasis and may prove interesting targets for future drug development.

Purine nucleotides are the principle constituents of cellular energy stores such as ATP and components of DNA and RNA. In humans, urate is the final breakdown product of unwanted purines because higher primates lack the enzyme uricase that, in other species, converts urate into allantoin (58, 59) (FIGURE 1). The biosynthesis of urate is catalyzed by xanthine oxidase (XO) and/or its isoform, xanthine dehydrogenase. Approximately two thirds of the daily turnover of urate is accounted for by urinary excretion, with the remaining one third being excreted into the gut as feces (48). In the setting of oxidative stress, some urate may also be oxidized to allantoin or other breakdown products, such as parabanic acid and alloxan (13, 56). In the human kidney, urate is reabsorbed and secreted via recently identified urate transporters.

Although urate may have beneficial effects, since it scavenges potential harmful radicals in our body (1, 5), in conjunction with genetic or environmental factors it can cause significant health problems, including complications associated with urate crystals such as kidney stones and gout. There is also increasing evidence that subjects with elevated uric acid may be at increased risk for cardiovascular and renal disease and that this may be mediated by uric acid via a crystal-independent mode of action. The levels of urate in the blood are dependent on the balance of generation and excretion. Normally, the body eliminates enough urate in the kidney and in part also in the intestines, keeping its blood concentration between 240 and 350 μM (FIGURE 1). In people with gout or kidney stone disease, however, the body either produces excessive amounts of urate or its ability to eliminate urate is disturbed.

Gout and Hyperuricemia

Although the mechanism of gout has not been completely elucidated, the likelihood of developing gout increases with increased serum urate levels. Serum concentrations of urate are higher in men than in women, and gout is therefore more common in men. However, only a small proportion of individuals with hyperuricemia (defined by serum urate concentrations >7 mg/dl (>420 μM) in men and >6 mg/dl (>300 μM) in women) develop gout. It is estimated that 5–10% of adult Americans have hyperuricemia, whereas only 20% of this population develop gout (51, 52). In some cases, gout is even observed with “normal” uric acid levels. Therefore, hyperuricemia is often not sufficient for expression of gout, and additional genetic or environmental risk factors are involved, including hypertension, the use of thiazides and loop diuretics, obesity, and a high alcohol intake (7).

Gout emerged as an epidemic in 18th and 19th century England, where it was considered a disease of the wealthy because it seemed to be caused by eating rich foods and drinking too much alcohol. Indeed, purine content in the diet is one of the factors that affect the body load of urate. The magnitude of this contribution depends on the amount and type of purine in the diet, but it is often considerable. Foods high in purine include anchovies, sardines, herring, trout, organ meats (liver, heart, kidney), meat gravies, broths, asparagus and mushrooms. The effect of alcohol is in part related to increased urate synthesis, which is due to enhanced turnover of ATP during the conversion of acetate to acetyl-CoA as part of the metabolism of ethanol (16). Also, acute alcohol consumption causes lactate production, and because lactate is an antiuricosuric agent, it will reduce renal urate excretion and exacerbation of hyperuricemia (see Identification and characterization of URAT1). In addition, part of the association of alcohol intake with gout is likely related to the high lead content in drinking wine.
Gout may be either primary (e.g., genetic) or secondary (due to a condition known to cause hyperuricemia). The pathogenesis of gout is characterized by sodium urate crystal precipitation in tissues, in particular in the joints of hyperuricemic patients. This is followed by phagocytosis of the crystals by neutrophils and macrophages and activation of acute inflammation and tissue injury. The solubility of urate decreases with decreasing temperature, explaining the increased incidence of gout in peripheral joints, which are cooler. However, what exactly initiates crystallization of urates in joints and why certain peripheral joints are preferentially involved is still unknown.

Treatment of gout

There are three main types of drugs used in treating gout and hyperuricemia. Allopurinol (Lopurin, Zyloprim), which is readily absorbed after oral intake, is used effectively for treatment of patients with primary hyperuricemia and gout. Allopurinol acts as a competitive inhibitor of XO, blocking the synthesis of urate in the liver and other organs and reducing the amount of urate in the body. Nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine help relieve the symptoms.
of gout by reducing inflammation. Probenecid (Benemid, Probalan), sulfipyrazone (Anturan), and benzboromarone (Urinorm) are uricosuric drugs (see Identification and characterization of \textit{URAT1}) that help the body to get rid of excess urate in the kidneys. In addition, rasburicase (Elitek; Sanofi-Synthelabo) is a genetically derived urate oxidase. Administration of rasburicase rapidly converts poorly soluble urate into highly soluble allantoin, which is readily excreted by the kidneys and prevents acute hyperuricemia and renal failure. This product has been approved by the US Food Drug Administration for the initial management of plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis.

\textbf{Uric Acid Stones}

Uric acid stones account for 5–10\% of urinary stones. Uric acid stones may contain pure uric acid or a combination of calcium and urate. Hyperuricosuria, which is defined as urinary excretion of urate >800 mg/day in men and >750 mg/day in women, can be a cause of stone formation. It may be due to either excessive dietary intake of purine-rich foods or endogenous urate overproduction. Approximately 15–20\% of patients with calcium stones have hyperuricosuria. Uric acid may initiate calcium oxalate stone formation by the induction of heterogeneous nucleation. Also, hyperuricosuria may be associated with hyperuricemia, and up to 20\% of patients with gout develop urate stones. However, uric acid stones may also occur in patients with normal urinary and serum levels of urate. Uric acid stones can generally be managed with alkalinization of the urine to pH 6.0–6.5, for example with oral potassium citrate. Urate is far more soluble than uric acid. Only the first proton dissociation (\(pK_1 = 5.75\)) need be considered here, since \(pK_2\) for the second proton is 10.3, a value well above the physiological range (see \textit{FIGURE 1, INSET}). The pH of the fluid in the proximal tubule is approximately the same as that of plasma, and this compound will therefore be mostly in the monovalent urate form. Acidification is a distal tubular function, and the pH of normal urine typically is below 5.8. Thus stones of the urinary collecting system are uric acid stones whose formation can be reduced by alkalinization of the urine.

\textbf{Acute Urate Nephropathy}

In addition to purine derived from dietary sources, there is extensive de novo purine synthesis in the body, primarily in the liver, which involves synthe-sis of inosine from ribose-1-phosphate. The catabolism of inosine then results in hypoxanthine via purine nucleoside phosphorylase and then xanthine and urate via XO, a flavoprotein that contains iron and molybdenum. In humans, XO is found to be highly expressed in the liver and also to a lesser extent in the mucosa of the small intestine. On the basis of its tissue distribution, urate synthesis appears to be largely a hepatic process in humans. When there is massive tissue breakdown, there may be a substantial release of DNA and RNA, resulting in a large purine load to the liver, followed by a marked rise in serum urate levels. The most common cause is accelerated cell turnover or cell lysis resulting from chemotherapy or radiation therapy, especially in leukemia and lymphoma. This condition, termed “tumor lysis syndrome,” results in a rapid increase of urate plasma levels, followed by a marked increase in urinary urate concentrations. This in turn results in intratubular crystallization with obstruction and acute renal failure (ARF). Local inflammation (including giant cell formation) and interstitial fibrosis may result if the obstruction is prolonged. Treatment may require acute hemodialysis as well as hydration and alkalinization of the urine to improve urate solubility. Rasburicase is also commonly used to acutely lower urate levels.

ARF may also accompany idiopathic renal hyperuricemia. This is a rare condition due to a defect in renal urate reabsorption (see \textit{Identification and characterization of \textit{URAT1}}) and has been particularly observed in the Japanese population. Although the pathogenesis of ARF has not been entirely elucidated, it has been reported to be precipitated by strenuous exercise. It remains possible that the mechanism involves exercise-induced rhabdomyolysis leading to increased urate generation that then results in high urinary urate levels with intratubular crystallization and obstruction.

\textbf{Purine and Nitrogen Metabolism}

In certain species, purines assume the additional function of secreting nitrogen waste. Organisms that excrete urate are called “uricotelic” (e.g., birds, terrestrial reptiles, insects). In contrast, organisms that excrete urea are called “ureotelic” (e.g., elasmobranch fish, mammals), and organisms that excrete ammonia are called “ammonotelic” (e.g., most aquatic invertebrates). Although more energy is required to produce urate compared with urea and ammonia, the benefit of urate is that less water is needed to excrete this compound. Birds, terrestrial reptiles, and insects use urate both as a nitrogen waste product and as a purine metabolism end product. Most mammals use urea as their major nitrogen end
Mechanisms of Renal Urate Reabsorption

In the kidney, filtered urate is greatly reabsorbed in the proximal tubules in humans but is secreted into the tubule fluid in other species. The reabsorption and secretion processes depend on specific transporter molecules that reside in these membranes. Based on membrane vesicle studies, the existence of two transporters, a voltage-sensitive pathway and a urate/anion exchanger, have been predicted in the renal proximal tubules (45).

Identification and characterization of URAT1

The transporter that reabsorbs urate has been recently identified by Enomoto et al. and was named URAT1 (SLC22A12) (15). URAT1 belongs to the organic ion transporter family (SLC22) (35) (see http://www.bioparadigms.org/slc/SLC22.htm). URAT1 consists of 555 amino acid residues and 12 predicted putative transmembrane domains (TMs), with large hydrophilic loops between the first and second as well as the sixth and seventh TMs and intracellular NH2 and COOH terminals (FIGURE 2). Similar to other SLC22 members, several PKA and PKC phosphorylation sites are predicted in the large intracellular hydrophilic loop between the first and second as well as the sixth and seventh TMs and intracellular NH2 and COOH terminals (FIGURE 2). The transporter that reabsorbs urate has been recently identified by Enomoto et al. and was named URAT1 (SLC22A12) (15). URAT1 belongs to the organic ion transporter family (SLC22) (35) (see http://www.bioparadigms.org/slc/SLC22.htm). URAT1 consists of 555 amino acid residues and 12 predicted putative transmembrane domains (TMs), with large hydrophilic loops between the first and second as well as the sixth and seventh TMs and intracellular NH2 and COOH terminals (FIGURE 2).

Beneficial Effects of Urate

Urate accumulation in man and higher primates has been proposed to have evolutionary advantages. Similar to vitamin C, urate is a potent antioxidant (1, 5). Based on the fact that birds are very long-lived for their body size—despite high metabolic rates, high body temperatures, and high blood glucose levels—it has been suggested that urate could contribute to the increased lifespan of primates compared with other vertebrates (11, 47). Also, urate can maintain blood pressure under low-salt conditions via stimulation of the renin-angiotensin system through a mechanism that is still poorly understood (37, 38, 40, 46, 57). Furthermore, recent studies (49, 53) suggest that urate may help arrest multiple sclerosis through scavenging the toxic compound peroxynitrite in the central nervous system. Humans reabsorb urate very efficiently to maintain relatively high blood levels of urate. The enhanced mechanism for urate reabsorption via the URAT1 transporter (see Identification and characterization of URAT1), the decrease in renal urate secretion, and the loss of uricase during hominoid evolution account for the higher levels of urate in human blood (180–720 μM) compared with mammals that have uricase (30–120 μM) (28).

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FIGURE 2. Proposed membrane topology model of the urate/anion exchanger URAT1 (SLC22A12).

The transporter has 12 putative transmembrane domains and a PDZ binding motif at the COOH terminus. PKA and PKC, protein kinases A and C, respectively.

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moves across the basolateral membrane into the blood by another organic anion transporter. URAT1 is presumably absent in other mammals such as rabbits and pigs, as these species predominantly secrete urate. But in humans, urate secretion is probably negligible and URAT1 is thought to be the major mechanism for regulating blood urate levels.

Consistent with this, mutations of SLC22A12 cause idiopathic renal hypouricemia (15, 25). This is a rare disorder with a prevalence of 0.12% (with higher frequencies in Japanese and Iraqi Jews). As discussed above, it is primarily characterized by exercise-induced ARF triggered by the increased production of urate and reactive oxygen species that occurs in muscle during exercise (34). The lack of a functional URAT1 transporter results in lower blood levels of urate and high urinary urate levels, resulting in crystal formation within the kidney tubules. This, together with exposure of the kidneys to reactive oxygen species generated during exercise, causes death of tubule cells. Without exercise, however, these patients can live normally, except for an increased occurrence of kidney stones. Genetic examinations of SLC22A12 in Japanese patients with idiopathic renal hypouricemia revealed that 2 out of 32 patients did not have missense mutations in this gene (25). This suggests that additional genes related to urate transport or metabolism could be involved in the pathogenesis, although the possibility of altered promoter function of SLC22A12 has not yet been addressed.

URAT1 interacts with a wide variety of therapeutic drugs and pharmacological reagents. For example, drugs that are used to treat inflammation or high blood pressure have undesirable side effects on urate excretion (45). By definition, “uricosuric” drugs such as probenecid, benz bromarone, the anti-inflammatory drug sulfipyrazone, the anti-hypertensive drug losartan, and the loop diuretic furosemide increase urate secretion, whereas “antiuricosuric” drugs such as pyrazinamide, nicotinate, and lactate decrease urate secretion. In general, Enomoto et al. (15) found that uricosuric drugs directly inhibit URAT1 from the apical side, whereas anturicosuric drugs serve as the exchanging anion from inside tubule cells, thereby enhancing urate transport by URAT1 through trans-stimulation. The inhibitory (uricosuric) or stimulating (anturicosuric) effects of the different drugs was evaluated by using Xenopus oocyte expression analysis.

Regulation of URAT1

Because URAT1 controls the blood urate level, it is important to clarify the regulatory mechanisms of URAT1. One possibility is the regulatory system via phosphorylations. URAT1 possesses PKA and PKC phosphorylation sites, and thus studying the phosphorylation of URAT1 will be of great importance. It is also increasingly recognized that membrane transport proteins are regulated through protein-protein interaction modules that are composed of three amino acid residues, (S/T)-X-φ (where X is any amino acid and φ is a hydrophobic residue). PDZ motifs bind to PDZ domains, which are 80–90 amino acids in length and are typically expressed in multiple copies within PDZ proteins. These are multidomain proteins that not only target and provide scaffolds for protein-protein interactions but also modulate the function of the association proteins (24). Also, PDZ proteins are thought to cluster membrane proteins such as transporters, channels, and receptors within subcellular domains to coordinate their activity.

A recent study demonstrated that URAT1 interacts with the multivalent PDZ domain-containing protein PDKZ1 via its COOH terminus (FIGURE 2). PDZ motifs are protein-protein interaction modules that are composed of three amino acid residues, (S/T)-X-φ (where X is any amino acid and φ is a hydrophobic residue). PDZ motifs bind to PDZ domains, which are 80–90 amino acids in length and are typically expressed in multiple copies within PDZ proteins. These are multidomain proteins that not only target and provide scaffolds for protein-protein interactions but also modulate the function of the association proteins (24). Also, PDZ proteins are thought to cluster membrane proteins such as transporters, channels, and receptors within subcellular domains to coordinate their activity.

A recent study demonstrated that URAT1 interacts with the multivalent PDZ domain-containing protein PDKZ1 via its COOH-terminal PDZ motifs (2). PDZK1 was first identified from rat kidney in 1997 (10) and possesses four tandem PDZ domains. Immunohistochemical analyses revealed that URAT1 and PDZK1 are colocalized at the apical membrane of renal proximal tubular cells (2). This interaction required the PDZ motif and the first,
Mechanisms of Urate Secretion

Despite the recent progress in the understanding of urate transport, there are still many open questions. The identification of URAT1 only accounts for part of the urate transport system in the kidney. For example, the basolateral exit pathway of urate in proximal tubule is still unknown. The organic anion transporters OAT1 (SLC22A6) and OAT3 (SLC22A8) (9) probably mediate basolateral urate uptake, as both transporters function as organic anion/dicarboxylate exchangers (FIGURE 3) and both have been shown to transport urate (4, 26). Given the outwardly directed electrochemical dicarboxylate gradient that is maintained by the apical and basolateral sodium/dicarboxylate transporters SLC13A2 and SLC13A3, respectively, it is likely that OAT1 and OAT3 contribute to basolateral urate uptake rather than efflux.

Efflux transporter OATv1

Recently, an apical, voltage-driven, organic anion efflux transporter termed OATv1 was isolated from a porcine kidney cDNA library (29). OATv1 is a new member of the SLC17 vesicular glutamate transporter family. The ability of OATv1 to transport urate was confirmed by Xenopus oocyte expression studies. OATv1 is thought to correspond to the voltage-sensitive luminal exit pathway that was predicted based on vesicle studies (45). However, a human ortholog of OATv1 has not been identified thus far. Also, OATv1 shares some similarity with human NPT1/SLC17A1 (see http://www.bioparadigms.org/slc/SLC17.htm). This transporter may play a primary role in species like rabbits and pigs that regulate their blood uric acid level mainly by secretion.

Species difference in renal handling of urate has always been an unsolved problem in renal physiology (12, 45). The molecular identification of urate transporters is beginning to provide answers and clues to this problem. Net reabsorption predominates in humans, dogs, and rats, which excrete less urate than is filtered at the glomerulus, and net secretion predominates in rabbits, pigs, and birds, which excrete more urate than is filtered at the glomerulus. It is not unexpected, therefore, that urate transporters involved in secretion are absent or expressed at low levels in urate “reabsorbers,” whereas urate transporters involved in reabsorption are present at low levels in urate “secretors.” This appears to be true for pig OAT1 and human URAT1, which mediate urate secretion and reabsorption, respectively. However, although filtered urate is almost completely reabsorbed in humans through URAT1, renal hypouricemic patients with defective URAT1 (which reabsorb <10% of filtered urate) were shown to exhibit urate excretion that exceeds the glomerular filtration rate (34). Given that proximal tubules hardly produce urate, this finding clearly indicates that there must be a urate secretion process in human kidney.

Efflux pump MRP4

Recently, a novel human renal apical organic anion efflux transporter, called MRP4, has been identified (54). MRP4 is a member of the ATP-binding cassette transporter family. It is proposed to mediate secretion of urate and other organic anions such as cAMP, cGMP, and methotrexate across the apical membrane of human renal proximal tubular cells. Human MRP4 is an ATP-dependent unidirectional efflux pump for urate with multiple allosteric substrate binding sites (55). MRP4 is furthermore expressed in the basolateral membrane of hepatocytes, where it is presumed to mediate hepatic export of urate into the circulation. Whether similar mechanisms are in place for the excretion of urate in the intestine (FIGURE 1) remains to be elucidated.

Other Proteins Involved in Renal Urate Handling

Tamm-Horsfall protein/uromodulin

Another gene involved in renal transport of urate is...
Tamm-Horsfall protein (THP), also known as uromodulin (43). THP is exclusively expressed in epithelial cells of the thick ascending limb. It is the most abundant protein in urine. Mutations in the human uromodulin gene result in hyperuricemia and reduced urinary concentrating ability. Such mutations are the cause of glomerulocystic kidney disease and medullary cystic disease/familial juvenile hyperuricemic nephropathy (6, 43). Many of the uromodulin mutations likely affect protein folding, resulting in intracellular aggregation and accumulation and thereby reducing the excretion of uromodulin in the urine. The exact mechanism by which uromodulin affects urate secretion is still unknown. One possibility is that mutations in THP affect sodium reabsorption in the thick ascending limb, because this part of the kidney is known to interact with the Na⁺-K⁺-2Cl⁻ cotransporter NKCC2. This could result in both a defect in water concentration and sodium conservation. A consequence of a defect of this nature would be an upregulation of proximal mechanisms for sodium reabsorption, which would be predicted to increase urate reabsorption (8). Recent studies of THP knockout mice revealed that these animals exhibit increased expression of major distal electrolyte transporters, whereas juxtaglomerular cyclooxygenase-2 (COX-2) and renin expression was decreased compared with wild-type mice (3). The THP knockout mice did not develop hyperuricemia, nor do they get renal failure. Whether fractional urate reabsorption is increased in these animals still remains to be determined.

UAT/galectin 9

UAT has also been proposed to be involved in renal urate transport (36). UAT was identified by screening a rat kidney cDNA library with a polyclonal antibody to pig liver uricase, and its function was examined by using a reconstitution assay. UAT is expressed ubiquitously and localizes to the apical side of the proximal tubule in the kidney. It consists of 322 amino acid residues and contains 4 transmembrane-spanning domains, with a predicted urate binding site on the intracellular loop between membrane-spanning domains 2 and 3. Consequently, UAT is supposed to be a multimeric protein. Interestingly, UAT is identical to galectin 9, whose function has been related to various functions that, at a first glance, appear to be unrelated to urate transport. Further studies are needed to determine the precise role of UAT/galectin 9 in urate metabolism.

Urate, Hypertension, and Vascular Disease

Urate clearly has many beneficial effects. However, markedly elevated serum levels (>350–400 μM) due to a combination of genetic or environmental (especially dietary) factors may be detrimental. In addition to the risk for gout and nephrolithiasis, there is increasing evidence that hyperuricemia may also be involved in the pathogenesis of hypertension, vascular disease, and renal failure (27). Experimental hyperuricemia in rats has been shown to result in hypertension via a mechanism involving alterations in endothelial function, activation of the renin-angiotensin system, and the development of microvascular disease (27, 33, 37, 39, 57). Intrarenal arteriolar disease develops in these animals and appears to be mediated via a direct effect of urate on the vascular smooth muscle cell (39). Specifically, it has been shown that urate enters rat vascular smooth muscle cells via an organic anion transporter (21), where it then activates ERK1/2 (57) and p38 (30) MAP kinases, NF-κB and AP-1 nuclear transcription factors (30), PDGF A- and C-chain mRNA (44, 57), COX-2 mRNA, thromboxane (32), and monocyte chemoattractant protein-1 (MCP-1) (30). This results in proliferation of the vascular smooth muscle cell and the release of inflammatory mediators (especially MCP-1). Similarly, urate has been shown to activate human vascular smooth muscle cells and to induce cell proliferation, stimulating production and release of C-reactive protein and inducing upregulated expression of the angiotensin II type 1 receptor (31).

The specific transporter that mediates the uptake of urate into the vascular smooth muscle cell is not known, although the possibility that it is URAT-1 has been supported by the recent demonstration that both human aortic and renal afferent vascular smooth muscle cells express both the mRNA and the protein (42).

In addition to effects on vascular smooth muscle cells, urate also inhibits endothelial cell proliferation (18) and reduces endothelial nitric oxide levels (33). Thus, experimentally, uric acid may have both systemic effects (inhibition of systemic nitric oxide levels and activation of the renin-angiotensin system) and direct cellular effects (on vascular smooth muscle cells and endothelial cells) that may be responsible for causing both hypertension and renal microvascular disease (57). Interestingly, although the effect of experimental hyperuricemia to cause hypertension can be prevented by lowering uric acid, once significant renal microvascular disease is induced, the hypertension is then mediated by the kidney and becomes salt sensitive and uric acid independent (37, 57).

Studies in humans also show that elevated urate levels predict the development of hypertension (reviewed in Ref. 27). In new-onset essential hypertension in adolescents, the correlation between
urate levels and blood pressure is remarkable (r = 0.8, P < 0.01) with an elevated uric acid level pres- ent in 89% of subjects vs. 0% in 63 controls (17). In pilot studies, the lowering of uric acid in adoles- cents with new-onset hypertension resulted in nor- malization of blood pressure in four of five subjects (18). A placebo-controlled, double-blind study is now in progress to determine whether lowering urate will reduce blood pressure in this population. It thus appears that the mutation that caused the lack of the enzyme uricase in humans may have partially because in an increase in urate serum was protective against hypertension in low-salt situa- tions and because of the antioxidant effects of urate. However, in modern society, where the diet often consists of both high salt and high purine content, serum urate may rise to such an extent in some subjects that its benefits may be outweighed by an increased risk not only for gout and kidney stones but possibly for the development of cardio-vascular and renal disease.

References


