Review Article

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Urate Transporters in the Kidney: What Clinicians Need to Know

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Urate is produced in the liver by the degradation of purines from the diet and nucleotide turnover and excreted by the kidney and gut. The kidney is the major route of urate removal and has a pivotal role in the regulation of urate homeostasis. Approximately 10% of the glomerular filtered urate is excreted in the urine, and the remainder is reabsorbed by the proximal tubule. However, the transport of urate in the proximal tubule is bidirectional: reabsorption and secretion. Thus, an increase in reabsorption or a decrease in secretion may induce hyperuricemia. In contrast, a decrease in reabsorption or an increase in secretion may result in hyperuricosuria. In the proximal tubule, urate reabsorption is mainly mediated by apical URAT1 (*SLC22A12*) and basolateral GLUT9 (*SLC2A9*) transporter. OAT4 (*SLC22A11*) also acts in urate reabsorption in the apical membrane, and its polymorphism is associated with the risk of hyperuricemia. Renal hypouricemia is caused by *SLC22A12* or *SLC2A9* loss-of-function mutations, and it may be complicated by exercise-induced acute kidney injury. URAT1 and GLUT9 are also drug targets for uricosuric agents. Sodium-glucose cotransporter inhibitors may induce hyperuricosuria by inhibiting GLUT9b located in the apical plasma membrane. Urate secretion is mediated by basolateral OAT1 (*SLC22A6*) and OAT3 (*SLC22A8*) and apical ATP-binding cassette super-family G member 2 (*ABCG2*), NPT1 (*SLC17A1*), and NPT4 (*SLC17A3*) transporter in the proximal tubule. NPT1 and NPT4 may be key players in renal urate secretion in humans, and deletion of *SLC22A6* and *SLC22A8* in mice leads to decreased urate excretion. Dysfunctional variants of *ABCG2* inhibit urate secretion from the gut and kidney and may cause gout. In summary, the net result of urate transport in the proximal tubule is determined by the dominance of transporters between reabsorption (URAT1, OAT4, and GLUT9) and secretion (ABCG2, NPT1, NPT4, OAT1, and OAT3).

Key Words: Gout, Hyperuricosuria, Hypouricemia, Proximal tubule, Uric acid transport

Urate Homeostasis

Uric acid or urate homeostasis in humans is determined by the balance between hepatic production and renal and intestinal excretion[1)]. Purines are metabolized to urate in the liver, and their sources are both exogenous (dietary intake) and endogenous (cellular metabolism of nucleic acids). The enzyme xanthine oxidase (XO) acts on the final step of purine metabolism from xanthine to urate, and XO inhibitors such as allopurinol and febuxostat are clinically useful as urate-lowering therapy. In most mammals, urate is converted by uricase or urate oxidase into allantoin, which is water-soluble and easily excreted in urine. In humans and apes, however, urate is the end product of purine metabolism because of nonsense mutations in uricase, and plasma urate levels are three to ten times higher than in other mammals[2)].

Uric acid has two dissociable protons with an aqueous

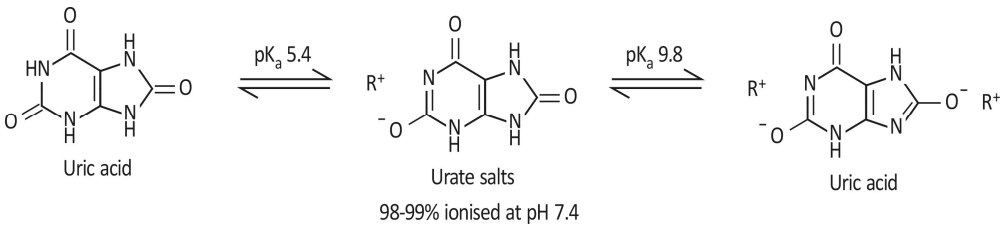

Fig. 1. Uric acid pKa and formation of urate salts. At physiological pH, uric acid is predominantly found as the deprotonated urate anion. Adapted from Reference 3.

pKa1 of 5.4 and pKa2 of 9.8 (Fig. 1). Consequently, at the physiological pH of 7.4, uric acid in the extracellular fluid is predominantly (98-99%) found as a deprotonated urate anion[3]. The divalent urate anion is practically nonexistent in the body because of the very high pKa2, and thus the term urate is generally used to refer to monovalent urate in the biomedical literature. Because the ratio of urate-to-uric acid in the circulation remains constant with constant pH, the terms urate and uric acid are often used interchangeably to refer to the total pool of uric acid, dissociated and undissociated[1].

Abnormal urate homeostasis can be classified into hyperuricemia and hypouricemia. Hyperuricemia may be induced by increased urate production in the liver or decreased urate excretion through the kidney and/or gut. Although a purine-rich diet may increase hepatic production of uric acid, diet alone is generally insufficient to cause hyperuricemia. Lesch-Nyhan syndrome is caused by hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency and resultant uric acid overproduction and is presented with dystonia, gout, intellectual disability, and self-mutilation[4]. HGPRT is an enzyme catalyzing the conversion of hypoxanthine to inosine monophosphate and guanine to guanosine monophosphate, generating purine nucleotides through the purine salvage pathway[5]. Urate underexcretion through the gut and/or kidney is the other important etiology of hyperuricemia, and intestinal and renal urate transporters may be involved in these pathological conditions. Diet and genetic polymorphisms in the renal transporters of urate seem to be the main causal factors of primary gout[6].

Theoretically, hypouricemia can be caused by decreased urate production in the liver or increased urate excretion through the kidney and/or gut. Malnutrition may be associated with hypouricemia because of low dietary purine

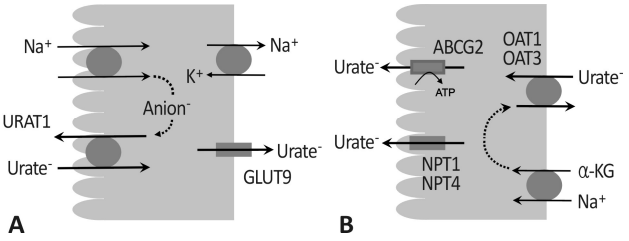

Fig. 2. Major urate transporters for bidirectional pathways in the proximal tubule. (**A**) Na^+-dependent anion transport by SMCT1 and SMCT2 increases intracellular concentrations of anions that exchange with luminal urate by URAT1. GLUT9 acts as the basolateral exit for urate reabsorption. (**B**) OAT1 and OAT3 transport urate through the basolateral membrane in exchange with α-ketoglutarate (α-KG). At the apical membrane, urate is secreted via ABCG2, NPT1, and/or NPT4.

intake. Molecular defects in critical pathways involving urate synthesis in the liver or urate reabsorption in the kidney may cause hypouricemia. Medications affecting urate production in the liver (e.g., allopurinol, febuxostat) and urate transport through the gut and kidney (e.g., probenecid, benzbromarone) may lower serum uric acid levels.

Urate Transporters in the Kidney

The kidney is the major route of urate removal, typically responsible for 70-80% of daily urate excretion, and the remainder is eliminated by intestinal secretion[7]. Plasma urate is freely filtered at the glomeruli, and fractional excretion of urate is approximately 10% in adult humans[1]. Thus, 90% of the glomerular filtrates are normally reabsorbed along the nephron, but this is the net result of reabsorption and secretion in the proximal tubule.

Figure 2 illustrates major urate transporters in the proximal tubule. Considering the usual ranges of fractional excretion of urate, transporters mediating urate reabsorption

may be more influential than those mediating urate secretion. The former includes apically located urate transporter 1 (URAT1), organic anion transporter 4 (OAT4), and OAT10, and basolaterally located glucose transporter 9 (GLUT9). URAT1, encoded by the *SLC22A12* gene, is the primary urate/anion exchanger responsible for luminal urate reabsorption. For the exchange of urate with organic anions, it is coupled with sodium monocarboxylate cotransporter 1 (SMCT1) and SMCT2 at the apical membrane of the proximal tubule. With URAT1, organic anions such as nicotinate and pyrazinoate have a higher affinity than other anions such as lactate, β-hydroxybutyrate, acetoacetate, chloride, and nitrate[8].

OAT4 and OAT10 may act as urate/anion exchangers like URAT1. OAT10, encoded by *SLC22A13*, is expressed at the messenger RNA (mRNA) level in the human kidney, but not at the protein level[9]. Its function as a urate/monocarboxylate exchanger was demonstrated only in vitro with a lower affinity for urate than URAT1[10]. Human OAT10 is also expressed to a weak extent in the intestine but its function remains unclear[11]. Unlike URAT1 and OAT10, OAT4, encoded by *SLC22A11*, mediates urate/dicarboxylate exchange, with a lower estimated affinity for urate compared with URAT1[12]. Thus, URAT1 appears to play the most important role in apical entrance for urate reabsorption.

Interestingly, URAT1 was also localized to the cell membrane of human vascular smooth muscle cells. This finding is compatible with the role of uric acid in cardiovascular disease, suggesting that uric acid enters the human vascular smooth muscle cell via URAT1[13].

GLUT9, encoded by the *SLC2A9* gene, functions as the major mechanism for the basolateral exit of urate, allowing for its reabsorption into the blood[10]. Human GLUT9 has two splice variants with distinct N-terminal isoforms; GLUT9a is expressed in multiple tissues including the small intestine and colon, while GLUT9b (also termed GLUT9ΔN) is highly expressed in the kidney, and to a lesser extent in the liver[14]. Their unique N-termini are responsible for differential localization, with GLUT9a localizing to the basolateral membrane of the proximal tubule and GLUT9b located in the apical membrane of the proximal tubule[14] or collecting duct[15]. In the murine kidney, Glut9a is expressed weakly in the proximal tubule whereas Glut9b is present in the distal convoluted tubule[16]. Physiologic action and species-specific intrarenal localization of GLUT9b remain to be confirmed.

Another set of transporters mediate urate secretion in the proximal tubule. ATP-binding cassette super-family G member 2 (ABCG2), also known as the breast cancer-resistant protein (BCRP), was initially identified as a transporter of drugs but has a role in the ATP-dependent urate efflux[17]. It is located in the apical membrane of the proximal tubule for secretion of urate, along with other ABC transporters such as multidrug resistance protein 2 (MRP2) and MRP4[18]. ABCG2 is also highly expressed in intestinal tissue, where it excretes up to one-third of all uric acid and is thus thought to be the main extrarenal site of uric acid elimination[19]. To a lesser extent, MRP2 also called ATP-binding cassette sub-family C member 2 (ABCC2) and MRP4 also called ATP-binding cassette sub-family C member 4 (ABCC4) are expressed in the intestine to efflux organic anions including urate[11].

NPT1, encoded by *SLC17A1*, is a sodium-phosphate cotransporter located in the apical membrane of the proximal tubule in the human kidney and was identified as a candidate protein in mediating the electrogenic exit of urate[20]. The highly related NPT4, encoded by *SLC17A3*, is located at the apical membrane of the proximal tubule and mediates voltage-dependent urate transport[21]. It was also reported to exist in the intestines and liver[22]. On the other hand, NPT5, encoded by *SLC17A4*, is expressed in the intestinal mucosae but not in the kidney[23]. These findings may indicate a possible involvement of the NPT homologs in urate efflux from the kidney and intestinal tract.

OAT1 and OAT3, encoded by *SLC22A6* and *SLC22A8*, respectively, are located in the basolateral membrane of the proximal tubule for urate uptake and overall function in renal urate secretion. They exchange urate and other organic anions for intracellular dicarboxylates such as α-ketoglutarate, coupled to intracellular sodium transport through the sodium-dicarboxylate cotransporter 3 (NaDC-3) encoded by *SLC13A3*[5]. OAT2, encoded by *SLC22A7*, similarly is located in the basolateral membrane of the proximal tubule[24], and its activity as a low-affinity urate transporter was found in transfected HEK293 cells[25].

Renal Hypouricemia

Hypouricemia caused by a renal tubular defect was termed

'renal hypouricemia'. The apical URAT1 and the basolateral GLUT9 are the main reabsorptive urate transporters, and loss-of-function mutations of the *SLC22A12* and *SLC2A9* gene can cause type 1 and type 2 renal hypouricemia, respectively[26]. Patients with renal hypouricemia can present with hematuria, urolithiasis, or exercise-induced acute kidney injury (AKI), and their fractional excretion of urate is much higher than 10% despite a very low level of serum urate. Among different mutations in the *SLC22A12* gene, W258X (*rs121907892*) was predominant in patients with type 1 renal hypouricemia reported from both Japan[27] and Korea[28].

Whereas type 1 renal hypouricemia mainly occurs in Asian children, cases of type 2 renal hypouricemia were reported from various parts of the world, including Asia, Middle East, and Europe. Different mutations were clustered according to the regions, and patients with type 2 renal hypouricemia were often diagnosed during their adulthood[29].

The reason why exercise-induced AKI can occur in patients with renal hypouricemia is unclear. One explanation could be that uric acid is a powerful antioxidant that scavenges singlet oxygen, oxygen radicals, and peroxynitrite[7]. The absence of uricase occurred approximately 30 million years ago in hominid evolution and was associated with the loss of the ability to synthesize ascorbic acid de novo[30], suggesting that uric acid may have replaced ascorbic acid as an antioxidant[31]. Interestingly, uric acid may function as an antioxidant in plasma and may act as a pro-oxidant within the cell (in cardiovascular disease)[32]. In patients with hypouricemia, the antioxidant activity of uric acid is overwhelmed by the massive reactive oxygen species produced by strenuous exercise. Thus, loss of antioxidant activity may lead to vascular constriction and endothelial damages, progressing to AKI[33].

Urate Transporters and the Risk of Hyperuricemia

1. URAT1

In addition to renal hypouricemia type 1, single nucleotide polymorphisms (SNPs) in the *SLC22A12* gene may be associated with hyperuricemia or gout. A meta-analysis showed that the *rs475688* polymorphism in the *SLC22A12* gene was associated with gout susceptibility[34]. The *rs559946* polymorphism was associated with increased hyperuricemia risk and might also contribute to gout development in Han Chinese men[35]. In the Vietnamese population, the *rs11231825* polymorphism was associated with gout[36]. The *rs3825017* polymorphism was associated with the risk of gout in a Czech population[37]. In the Korean Cancer Prevention Study-II cohort, the *rs75786299*, *rs7929627*, and *rs3825017* SNPs were associated with hyperuricemia[38].

2. GLUT9

In addition to renal hypouricemia type 2, the *SLC2A9* gene may also be associated with hyperuricemia or gout. In particular, the nonsynonymous Arg265His (*rs3733591*) variant of *SLC2A9* increases the risk for gout in some populations[39]. When a genome-wide association study (GWAS) was conducted in 6,881 Korean individuals, *rs16890979* polymorphism was associated with hyperuricemia[40]. In Croatian, German, and UK populations, three different *SLC2A9* variants, *rs1014290*, *rs6449213*, and *rs737267* were associated with gout[41]. Meta-analysis studies showed that the *rs3733591* polymorphism in the *SLC2A9* gene was associated with gout susceptibility[42] whereas the *rs12510549*, *rs16890979*, and *rs1014290* polymorphisms protect against the development of gout in Caucasians and/or Asians[43].

Hyperuricemia is frequently accompanied by chronic kidney disease (CKD), but its causal relationship with CKD is unclear. Testa et al. reported that the *rs734553* SNP in the *SLC2A9* gene was not only associated with serum uric acid levels in 211 healthy individuals but also predicted the risk of CKD progression in a cohort of 755 patients, supporting the hypothesis that the link between uric acid and CKD progression is causal in nature[44].

3. ABCG2

Dysfunction of ABCG2 causes hyperuricemia and raises the risk of gout because ABCG2 has a role in urate secretion in both proximal tubule and intestinal mucosa[17]. The intestinal excretion of urate is responsible for approximately 30% of total urate excretion[45].

A common ABCG2 variant, Q141K (*rs2231142*), was associated with an increase of uric acid levels in multiple pop-

ulations, including African Americans, Asians, Caucasians, and Pacific Islanders[1]. Sequencing of the ABCG2 gene in 90 hyperuricemia patients revealed several nonfunctional ABCG2 mutations, including Q126X[46]. When a GWAS was conducted with data from a Korean cohort (3,647 subjects recruited by the Korean National Institute of Health), *rs2054576* in ABCG2 was associated with hyperuricemia[47].

4. Other urate transporters

OAT4 (*SLC22A11*) is localized in the apical membrane of the proximal tubule, mediating urate reabsorption. In a Japanese population, the *rs17300741* polymorphism in the *SLC22A11* gene was associated with renal underexcretion type gout[48].

NPT1 (*SLC17A1*) and NPT4 (*SLC17A3*) may be key players in renal urate secretion because SNPs in NPT1 and NPT4 weakly to moderately correlated with altered uric acid levels[17]. Gain-of-function variants of *SLC17A1* may protect against gout, and loss-of-function mutations of *SLC17A3* may be associated with hyperuricemia or gout[10].

Multidrug-resistant proteins MRP2 (ABCC2) and MRP4 (ABCC4) transport urate in vitro, but there is no evidence at present for such a role in the kidney *in vivo*[1]. SNPs in these genes generally have a weak association with hyperuricemia[17].

URAT1 and GLUT9 as Drug Targets

Pharmacologic agents for urate-lowering therapy can be classified into XO inhibitors, uricosuric agents, and uricases. Among these, uricosuric agents may act on urate transporters in the proximal tubule to increase urinary urate excretion. Both the inhibition of urate-reabsorbing transporters and stimulation of urate-secreting transporters might be conceivable, but the former is the known mechanism of action of uricosuric agents.

The apical URAT1 is the main target of uricosuric action. Probenecid and benzbromarone remarkably inhibit urate transport by URAT. Basolateral GLUT9 is also downregulated by probenecid and benzbromarone[49]. Lesinurad is a recently introduced uricosuric drug that may be used in combination with allopurinol or febuxostat. Its mechanism of action derives from the inhibition of URAT1, although OAT4 inhibition could also be associated[3].

Losartan has a uricosuric action because of the inhibition of URAT1 and GLUT9[8]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors also have a uricosuric effect, probably induced by the inhibition of GLUT9b in the collecting duct[50]. On the other hand, pyrazinamide may induce hyperuricemia via the stimulation of URAT1[1].

Regulation of Urate Transporters in the Gut and Kidney

Serum uric acid levels are different between men and women, and the prevalence of hyperuricemia in adult males is higher than in females[51]. Sex hormones may play a role in regulating the expression or activity of urate transporters because *SLC2A9* may have a stronger association with lower serum uric acid levels in females, whereas ABCG2 may have a stronger association with higher serum uric acid levels in males[52]. The *ABCG2* Q140K+/+ knock-in mouse model is orthologous to the human *ABCG2* Q141K variant. The Q140K+/+ mice showed hyperuricemia in males but not in females. Urinary urate excretion decreased in association with reduced renal ABCG2 protein abundance in male Q140K+/+ mice. However, urinary urate excretion and renal ABCG2 protein abundance were unaltered in female Q140K mice[53].

The regulation of renal urate transporter expression by female hormones was investigated using ovariectomized mice with or without hormone replacement. Takiue et al. reported that estradiol suppressed the protein levels of URAT1, GLUT9, and ABCG2 in mouse kidneys[54]. On the other hand, the effect of testosterone was investigated in orchiectomized mice with or without testosterone replacement. Testosterone enhanced mRNA and protein levels of sodium-coupled monocarboxylate transporter 1 while those of GLUT9 were attenuated. Although the mRNA level of *URAT1* was enhanced by testosterone, the corresponding levels of URAT1 protein remained unaffected[55].

Other hormones might affect urate transporters in the kidney and gut for the regulation of urate homeostasis. Glucocorticoid was reported to increase urate excretion in mice by downregulating URAT1[56]. Hyperuricemia may be associated with secondary hyperparathyroidism in patients with CKD.

Sugimoto et al. reported that ABCG2 was downregulated by parathyroid hormone, increasing serum urate levels and these effects could be prevented by administration of the calcimimetic cinacalcet[57].

Kim et al. investigated responses of urate transporters to increased uric acid intake in rat kidneys. Whereas URAT1 protein abundance was not affected, OAT1 protein abundance was increased by uric acid supplementation[58]. The up-regulation of OAT1 would exert stimulation of urinary urate excretion and might contribute to protection from hyperuricemia.

The oral administration of oxonic acid can induce hyperuricemia in rats. In this rat model, Nagura et al. found an increase in *GLUT9* mRNA expression but no changes in *URAT1* and *ABCG2* mRNA in the kidney. Interestingly, *ABCG2* mRNA increased in the ileum of rats with oxonic acid-induced hyperuricemia[59]. The lack of valid antibodies for urate transporters has limited studies at the protein level.

Because ABCG2 is localized in both the kidney and gut, the relative contribution of intestinal urate secretion will be increased in patients with CKD. Consistent with this, Yano et al. showed that *ABCG2* mRNA expression increased in the ileum of rats with 5/6 nephrectomy[60]. In CKD, the role of intestinal urate transporters would be more important for maintaining urate homeostasis.

CONCLUSION

The kidney plays an important role in the maintenance of urate homeostasis because renal excretion of uric acid represents 70-80% of total uric acid excretion from the body. Approximately 10% of the glomerular filtered urate is normally excreted in urine after reabsorption and secretion in the proximal tubule. URAT1 (*SLC22A12*) is the major apical pathway for urate reabsorption, and GLUT9 (*SLC2A9*) is the principal pathway of basolateral urate exit from the proximal tubule cell in the human kidney. The loss-of-function mutation in either URAT1 or GLUT9 leads to renal hypouricemia. ABCG2, an apical ATP-driven efflux pump, functions in urate secretion by the proximal tubule and intestine, and ileal ABCG2 may be upregulated in CKD when renal urate transporters are downregulated. Genetic variations in *SLC2A9*, *ABCG2*, and *SLC22A12* are associated with serum uric acid levels or gout (Fig. 3). Regulation of urate homeostasis at the level of urate transporters needs to be elucidated.

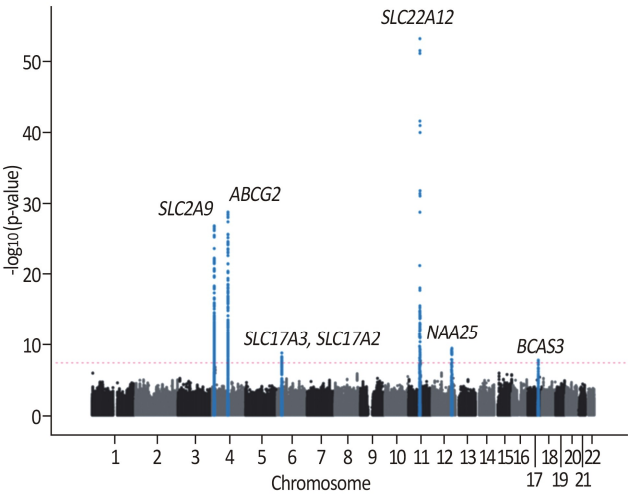

Fig. 3. A genome-wide association analysis of serum uric acid in 6,881 Korean individuals. Manhattan plot depicts that the major urate transporter genes *SLC22A12*, ABCG2, and *SLC2A9* are highly associated with hypouricemia or hyperuricemia. Adapted from Reference 40.

Conflict of Interest

The author declares no relevant financial interests.

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