The Molecular Physiology of Uric Acid Homeostasis

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Abstract

Uric acid, generated from the metabolism of purines, has proven and emerging roles in human disease. Serum uric acid is determined by production and the net balance of reabsorption or secretion by the kidney and intestine. A detailed understanding of epithelial absorption and secretion of uric acid has recently emerged, aided in particular by the results of genome-wide association studies of hyperuricemia. Novel genetic and regulatory networks with effects on uric acid homeostasis have also emerged. These developments promise to lead to a new understanding of the various diseases associated with hyperuricemia and to novel, targeted therapies for hyperuricemia.

INTRODUCTION

Hyperuricemia is both causative and protective in disease. The causative link between hyperuricemia and disease is clearest for gout, a common and excruciatingly painful inflammatory arthritis (1). The prevalence of gout is substantial and increasing, with some 8.3 million Americans affected (2). Gout is independently associated with higher medical and arthritic comorbidity, in addition to greater primary care utilization and more frequent hospitalization (3). The burden of the major comorbidities of gout and hyperuricemia (e.g., hypertension, chronic kidney disease, diabetes) is also considerable (4). Hyperuricemia has also been linked with varying degrees of certainty to the pathogenesis of several gout-associated comorbidities, particularly hypertension (5–7) and diabetic renal disease (8). Hyperuricemia is also a well-recognized concomitant of the metabolic syndrome, which also encompasses abdominal obesity, glucose intolerance, insulin resistance, dyslipidemia, and hypertension. Serum uric acid concentration (SUA) can thus be considered a marker of the metabolic syndrome (9), with a high prevalence of metabolic syndrome in patients with gout (10).

Hyperuricemia has a dramatically different, protective effect in neurodegenerative disease, including Parkinson's disease (PD), multiple sclerosis (11), and Alzheimer's disease/dementia (12). For example, higher uric acid levels reduce the risk of PD (13) and reduce the risk of disease progression (14). Although the associated mechanisms are likely heterogeneous, most theories incorporate some role for the well-described antioxidant effect of uric acid (15).

In a series of dramatic bedside-to-bench developments, the genetic epidemiology of uric acid has had an enormous impact on the relevant molecular physiology, identifying several key urate transporters and a host of intriguing genetic networks that influence uric acid homeostasis (16). These developments can be integrated into an increasingly detailed understanding of the molecular physiology of uric acid homeostasis.

URATE METABOLISM

Uric acid is a weak acid (pK_a 5.8) that exists largely as urate at physiological pH. Urate is generated from the metabolism of purines (see **Figure 1**), both endogenous and exogenous (17). The last two steps in purine metabolism are catalyzed by xanthine oxidoreductase (also known as xanthine oxidase), which generates urate from hypoxanthine and xanthine. Purines can be reutilized through a salvage pathway involving the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT); genetic deficiency of HPRT in Lesch-Nyhan syndrome is associated with hyperuricemia and gout. The de novo synthesis of purines begins with the production of 5′-phosphoribosyl 1-pyrophosphate (PRPP) from adenosine triphosphate (ATP) and ribose 5′-phosphate. This step is catalyzed by PRPP synthetase; genetic overreactivity of this enzyme is also associated with hyperuricemia and gout (18). Finally, ATP degradation leads to ADP and AMP, with subsequent metabolism to urate (see **Figure 1**); conditions associated with net degradation of ATP can also be associated with hyperuricemia (1).

The cumulative analysis of multiple genome-wide association studies (GWAS) within the Global Urate Genetics Consortium recently led to the identification and replication of 28 genes associated with variation in SUA (16) (**Figure 2**). Of these genes, pathway analyses indicate a handful of genes that influence glucose homeostasis, including genes encoding GCKR (glucokinase regulator) and the regulatory subunit γ2 of AMPK (AMP-activated protein kinase). Increased flux of glucose through the pentose phosphate pathway is expected to increase the level of ribose 5′-phosphate, thus increasing purine generation (see **Figure 1**). Increased anaerobic glycolysis

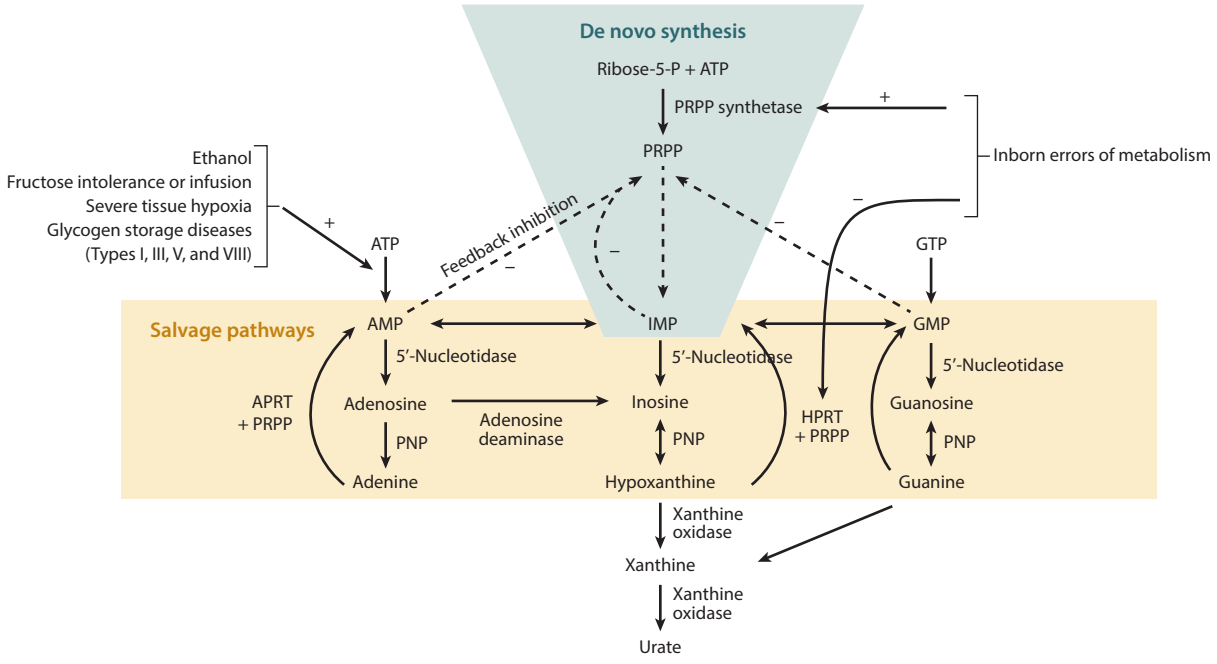

Figure 1

Urate production pathways. The de novo synthesis starts with 5′-phosphoribosyl 1-pyrophosphate (PRPP), which is produced by addition of a further phosphate group from adenosine triphosphate (ATP) to the modified sugar ribose 5′-phosphate (ribose-5-P). This step is performed by the family of PRPP synthetase enzymes. In addition, purine bases derived from tissue nucleic acids are reutilized through the salvage pathway. The enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT) salvages hypoxanthine to inosine monophosphate (IMP) and guanine to guanosine monophosphate (GMP). Only a small proportion of patients with urate overproduction have the well-characterized inborn errors of metabolism such as superactivity of PRPP synthetase and deficiency of HPRT. Furthermore, conditions associated with net ATP degradation lead to the accumulation of adenosine diphosphate and adenosine monophosphate (AMP), which can be rapidly degraded to uric acid. These conditions are displayed in the upper left corner. The plus sign denotes stimulation, and the minus sign denotes inhibition. Other abbreviations: APRT, adenine phosphoribosyltransferase; GTP, guanosine triphosphate; PNP, purine nucleotide phosphorylase. From Reference 1.

also generates increased circulating lactate, which increases renal reabsorption of filtered urate (see below).

In most mammalian species, uric acid generated from purine metabolism undergoes oxidative degradation via the uricase enzyme, producing the more soluble compound allantoin. In humans, the uricase gene is crippled by two mutations that introduce premature stop codons (19). The absence of uricase, combined with extensive reabsorption of filtered urate, results in urate levels in human plasma that are approximately ten times those of most other mammals. Whereas primates such as the chimpanzee share the same truncating mutations in uricase, independent loss-of-function mutations in gibbon apes suggest that this gene was subject to significant negative pressure during the evolution of *Homo sapiens* and other hominoids (20). Highly speculative advantages conferred by the relative hyperuricemia in these species include reduced oxidant stress and a decreased incidence of cancer (21), complexation of circulating iron and inhibition of iron-catalyzed oxidation (22), an enhanced ability to survive under conditions of low dietary salt (23), and even increased intelligence (24). The purported benefits of an increase in uric acid

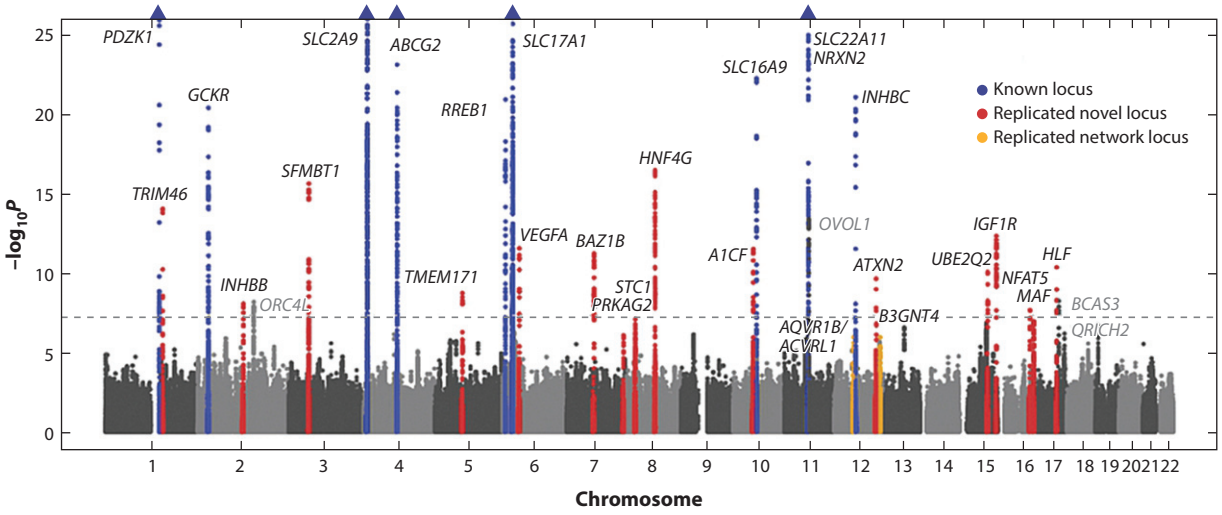

Figure 2

At least 28 genes affect the risk of hyperuricemia. A truncated Manhattan plot shows $-\log_{10}P$ values for all single-nucleotide polymorphisms (SNPs) of the urate discovery GWAS ordered by chromosomal position. The gene closest to the SNP with the lowest *P* value at each locus (index SNP) is listed. The loci in gray met one but not both replication criteria. Blue triangles represent loci containing SNPs with *P* values of less than 10^{-25}. From Reference 16.

are offset in part by the risk of gout (1), nephrolithiasis (25), and other hyperuricemia-associated comorbidities.

The risk of hyperuricemia in humans is genetically mitigated by comparative repression of the human xanthine oxidoreductase gene (26, 27), the enzyme that mediates the last two steps of purine metabolism (28); transcription of this gene is considerably more widespread and robust in mice (26, 27). This is a recurrent theme in the genomics of urate homeostasis; several other genes that are variably conserved or preserved in different species underscore the divergent evolutionary pressures on these pathways.

Approximately one-third of urate elimination occurs in the gastrointestinal tract, with the remainder excreted in the urine (29). In plasma, urate is freely filtered by renal glomeruli. Subsequent bidirectional transport along the nephron results in either net reabsorption (for humans, primates, rats, and dogs) or secretion (for pigs and rabbits); pigs and rabbits (30, 31) appear to lack the apical urate-anion exchanger that is found in all the reabsorptive species, presumably due to inactivation of the *SLC22A12* gene, which encodes URAT1 (see below). The fractional excretion of urate differs considerably in mammals: 10% in humans versus ~40% in rats (32) and 200% in pigs (33). *Cebus* monkeys also exhibit a fractional excretion of ~10% (34); however, unlike other New World monkeys, *Cebus* monkeys possess an active uricase enzyme and have a uric acid level that is approximately half that of humans (35). In contrast, chimpanzees lack uricase activity, exhibit a fractional excretion for urate of ~10%, and have circulating uric acid levels that are roughly equal to those of humans (36). Therefore, the evolutionary loss of uricase and the development of highly efficient reabsorptive mechanisms for urate appear to be separate, additive events that result in relative hyperuricemia in humans and related hominoids.

More recently, the results of human Mendelian genetics and GWAS have emphasized that renal and intestinal urate transport is bidirectional. **Figure 3** outlines the reabsorptive

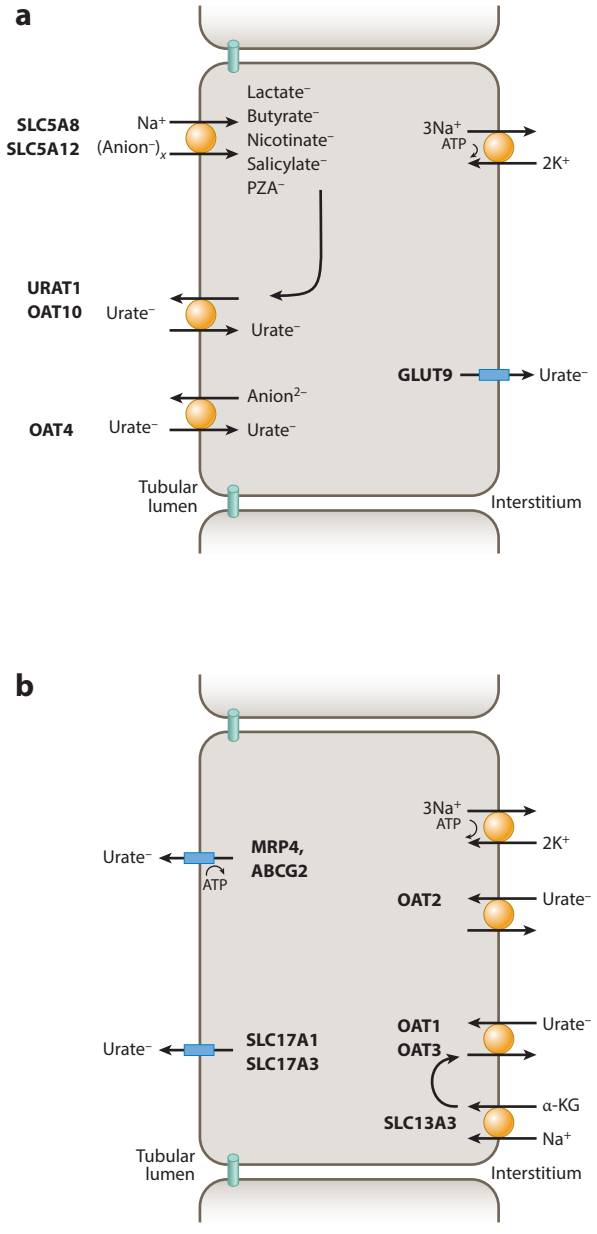

Figure 3

Transport pathways for urate in proximal tubule cells. (*a*) Urate reabsorption. Na^+-dependent anion transport by SLC5A8 and SLC5A12 increases intracellular concentrations of anions that exchange with luminal urate (URAT1/OAT10). OAT4 appears to exchange urate with divalent anions. GLUT9 acts as the exit pathway for urate at the basolateral membrane. PZA denotes pyrazinoate. (*b*) Urate secretion. Urate enters the cell at the basolateral membrane in exchange with α-ketoglutarate (α-KG), mediated by OAT1 and OAT3, or in exchange with unknown anions via OAT2; see text for details. At the apical membrane, urate is secreted via MRP4, ABCG2, NPT1, and/or NPT4.

and secretory transport pathways in renal proximal tubule cells. There are thus completely separate transport pathways for urate absorption and secretion across epithelia. Furthermore, loss of function in reabsorptive (37) or secretory (38–40) pathways results in hypouricemia or hyperuricemia, respectively, underscoring the bidirectional nature of transepithelial urate flux.

REABSORPTIVE URATE TRANSPORT

The Four-Component Model

The dominant physiological model of renal urate excretion has for decades consisted of four steps: glomerular filtration, reabsorption from the glomerular ultrafiltrate, subsequent secretion, and then postsecretory reabsorption (41). Elements of this four-component model appear in the current editions of leading physiology and nephrology textbooks such that the long-apparent flaws in this model (29, 42) necessitate a critical review.

The four-component model evolved in the 1960s and 1970s from an interpretation of the competing effects of uricosuric and antiuricosuric agents. The key assumption underlying this model is that the antiuricosuric agent pyrazinamide inhibits proximal tubule urate secretion. In the typical pyrazinamide suppression test (43), the oral administration of 2–3 g results in a marked decrease in the fractional excretion of urate; this effect is mediated by pyrazinoate (PZA), the deamidated metabolite (44). Dog experiments from the mid-1960s revealed that pyrazinamide abolished the secretory peak of ^{14}C-labeled urate injected into the renal artery; given that the initial urinary bolus of radioactive urate preceded that of ^{14}C-inulin, the primary source of this urinary ^{14}C-urate peak was thought to be tubule secretion rather than glomerular ultrafiltration. By extension, the antiuricosuric effect of pyrazinamide was attributed to an inhibition of urate secretion (45). The pyrazinamide suppression test was thus adopted as a pharmacological method to quantify tubule urate secretion (43).

The three-component model of renal urate handling was originally proposed by Gutman & Yu (46) in 1961, encompassing glomerular filtration, probenecid-sensitive tubular reabsorption, and pyrazinamide-sensitive tubular secretion. The full four-component model subsequently evolved to explain the interactions between pyrazinamide and uricosuric agents, including probenecid (41, 47), chlorothiazide (47), benzbromarone (48), and sulfinpyrazone (41). When these drugs are administered after pyrazinamide, there is a striking attenuation of their uricosuric effect (29). To explain this phenomenon, uricosuric agents were postulated to have a dominant effect on postsecretory reabsorption because their ability to increase urate excretion was blunted when putative upstream secretion was inhibited with pyrazinamide. It follows that these processes would occur serially, in anatomically separate segments of the proximal tubule; indeed, such a progression is incorporated into current textbook models of renal urate transport. However, physiological studies in reabsorptive species typically indicate a coexistence of reabsorption and secretion along the entire length of the proximal tubule.

The alternative possibility, that PZA does not inhibit secretion but instead stimulates urate reabsorption, was considered “rather awkward” (49) and “extremely unlikely” (43) during the initial formulation of the four-component model. However, a seminal observation in 1985 by Guggino & Aronson suggested that PZA does indeed stimulate tubule reabsorption (42); the same investigators had previously reported analogous data for lactate (30). Through the use of brush-border membrane vesicles (BBMV) from renal cortex, it was demonstrated that sodium (Na^+)-dependent uptake of PZA or lactate markedly stimulated vesicular urate uptake via brush-border urate-anion exchangers (see **Figure 4**); these and subsequent insights are discussed below.

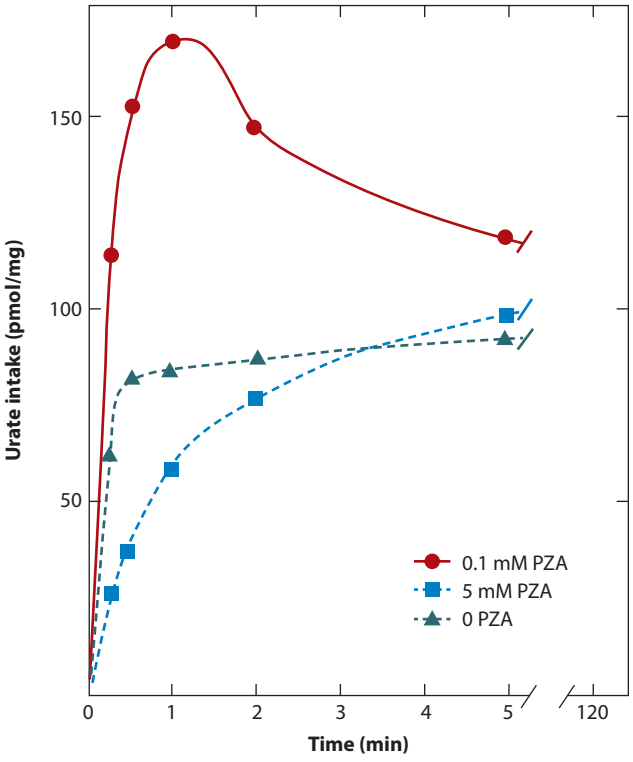

Figure 4

The antiuricosuric agent pyrazinoate (PZA), a metabolite of pyrazinamide, has dual effects on urate transport by the proximal tubule. Urate uptake by brush-border membrane vesicles isolated from canine kidney cortex is shown in the presence of 100 mM Na^+ with 0.1 mM PZA, 5 mM PZA, or 0 PZA. The concentration results in Na^+-dependent uptake of PZA and in the potentiation of urate uptake via URAT1 or OAT10; in contrast, the higher concentration *cis*-inhibits urate exchange, thus reducing urate uptake by the membrane vesicles.

Reabsorptive Urate-Anion Exchangers

An apical urate-anion exchange activity was first described in nonprimate, urate-reabsorbing species, i.e., rats and dogs (30, 50–52). This anion exchanger accepts various monovalent organic anions, including urate, *p*-aminohippurate (PAH), lactate, chloride (Cl^-), and hydroxyl (OH^-); divalent anions are not substrates (30). Apical urate-anion exchange activity is evidently absent in species with net urate secretion (30, 53), whereas it is present and highly sensitive to uricosuric agents in urate-reabsorbing species (50, 51); these observations suggested a significant role for urate-anion exchange in proximal tubular reabsorption. A similar uricosuric-sensitive urate exchanger has been demonstrated in BBMV from the human kidney, albeit with some important distinctions; notably, PAH and OH^- are not substrates for the human exchanger (54). This observation is reflected in the relatively modest effect of PAH infusion on urate excretion in humans; moreover, PZA does not affect PAH homeostasis, suggesting that the absorptive mechanisms for PAH and urate are distinct in this species (55).

The molecular identification of URAT1 as the dominant apical urate exchanger of the human proximal tubule (56) was a landmark event in the physiology of urate homeostasis. The URAT1 protein is encoded by the *SLC22A12* gene, part of the large SLC22 family of organic ion

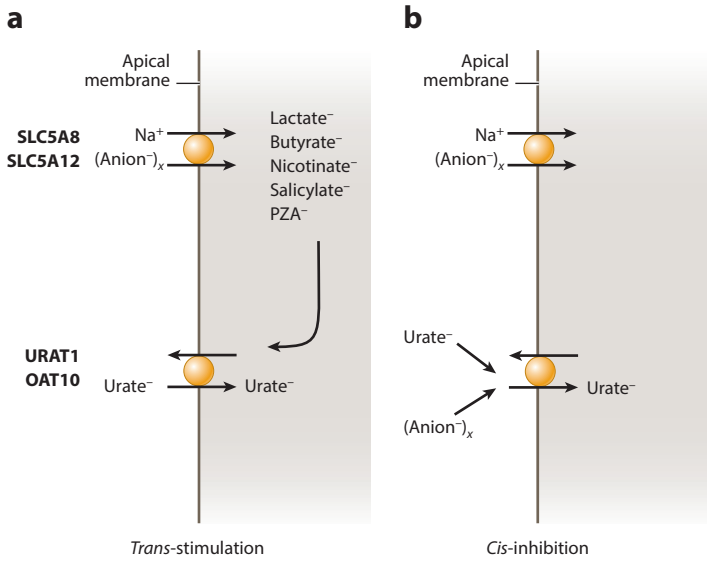

Figure 5

Cis- and *trans*-interactions of anions with apical urate-anion exchange. (*a*) At lower luminal concentrations, anions that exchange with urate on URAT1 +/− OAT10 are reabsorbed at the apical membrane by Na^+-dependent transport and are concentrated within proximal tubule cells. These events result in *trans*-activation of apical urate exchange and in hyperuricemia. (*b*) At higher luminal concentrations, the same anions can *cis*-inhibit urate exchange, thus resulting in uricosuria and in a reduction in serum uric acid concentration.

transporters. URAT1 is a member of the organic anion transporter (OAT) branch of this gene family; other subgroups include organic cation transporters and organic cation transporter novel type/carnitine transporters. Although not initially acknowledged as such (56), URAT1 is the human ortholog of RST (renal-specific transporter), which was cloned from the murine kidney many years ago (57). URAT1/RST is in point of fact not renal specific, with detectable transcript in many tissues other than the kidney. Regardless, immunohistochemistry reveals the URAT1 protein at the apical membrane of proximal tubules in both human (56) and mouse (58) kidneys. Heterologous expression in *Xenopus* oocytes indicates that human URAT1 is capable of urate transport (^{14}C-labeled urate uptake), with a K_m of 371 ± 28 μM. Uricosuric drugs such as probenecid, benzbromarone, fenofibrate (59), and losartan (60) are potent inhibitors of URAT1. Thus, their effect on SUA is mediated through inhibition of urate reabsorption, rather than through activation of renal secretion. URAT1 has the highest affinity for aromatic organic anions, such as nicotinate and PZA, with lower affinities for lactate, β-hydroxybutyrate, acetoacetate, and inorganic anions such as Cl^- and nitrate. These relative affinities are manifest by a marked activation (*trans*-stimulation; see **Figure 5**) of ^{14}C-urate uptake in URAT1-expressing oocytes that were individually microinjected with PZA, nicotinate, or lactate (i.e., in *trans* to the ^{14}C-urate) and in the absence of Cl^-; the relative response fits with the *trans*-stimulation of urate exchange in human BBMV Na^+-dependent transport of these monovalent anions (61) (see also below). Notably, however, we have not been able to replicate the effects of microinjected lactate in *Xenopus* oocytes (101), perhaps reflecting the weaker affinity of this anion for URAT1 and/or intracellular metabolism of the injected lactate. The same anions except lactate (101), at higher concentrations, can *cis*-inhibit the uptake of ^{14}C-urate when present in the extracellular medium, another operative characteristic of the anion exchanger (**Figure 5**).

In their report describing the identification of URAT1, Enomoto et al. (56) provided unequivocal genetic proof that this anion exchanger is essential for normal urate homeostasis. Specifically, a handful of patients with renal hypouricemia (OMIM #220150) were shown to carry loss-of-function mutations in the human *SLC22A12* gene encoding URAT1, indicating that this exchanger is essential for the proximal tubule reabsorption of urate (56). Patients with homozygous loss-of-function mutations in *SLC22A12* do not respond to pyrazinamide and benzbromarone with urate retention and uricosuria, respectively (see below). However, a modest residual uricosuric response to probenecid and a fractional excretion of urate of ~70%—rather than 100% or greater—suggest that anion transporters other than URAT1 may participate in the luminal reabsorption of urate from the glomerular ultrafiltrate (62).

Two other apical urate-anion exchangers have been postulated to function in urate reabsorption by proximal tubule cells. OAT4, encoded by the *SLC22A13* gene directly adjacent to the *SLC22A12* gene encoding URAT1, exchanges urate and other anions for intracellular diacarboxylates such as glutarate (63, 64). Nicotinate and PZA are not substrates for OAT4, which furthermore seems to have asymmetrical preference for extracellular but not intracellular urate (64). OAT10, encoded by the *SLC22A13* gene, functions as a high-affinity nicotinate transporter and as a low-affinity urate transporter in *Xenopus* oocytes, mediating urate-PZA and urate-nicotinate exchange (65). Like OAT4 and URAT1, OAT10 is sensitive to uricosuric drugs. Transcript for OAT10 is reputedly detected in microdissected proximal tubules and in cortical collecting ducts (65). With a C-terminal PDZ (PSD95/discs large/ZO-1) interaction motif, as in the URAT1 and OAT4 proteins, OAT10 would be expected to traffic to the apical membranes of epithelial cells, and Western blots indicate exclusive reactivity with BBMV, but not with basolateral membrane vesicles (65). However, Schulz et al. (66) recently reported exclusive expression of OAT10 in rat kidneys at the basolateral membrane of type A intercalated cells; localization in human kidney has yet to be reported.

The *SLC22A11/SLC22A12* locus has been implicated in GWAS in determining SUA in a number of different populations (16, 67, 68). At the functional level, urate transport experiments show that one coding polymorphism, G65W, is a partial loss-of-function allele; each copy of this allele is associated with an ~1.0 mg/dL drop in SUA (67).

The Secondary Sodium Dependency of Urate Reabsorption

As discussed above, URAT1 reabsorbs urate from the glomerular ultrafiltrate by exchanging luminal urate with monovalent intracellular anions such as nicotinate and PZA. The intracellular concentration of these anions is determined largely by Na^+-dependent absorption from the same glomerular ultrafiltrate; this absorption generates a secondary Na^+ dependency of urate reabsorption since these anions increase proximal urate reabsorption via subsequent anion exchange. The nephron is thus primed for urate reabsorption by the Na^+-dependent loading of proximal tubule cells with antiuricosuric anions such as PZA.

Independent, overlapping studies many years ago suggested that a single cotransport activity in renal BBMV is responsible for the Na^+-dependent uptake of PZA, nicotinate, lactate, pyruvate, β-hydroxybutyrate, and acetoacetate (69–71). Urate is not a direct substrate; i.e., there is no evidence for direct Na^+-dependent urate uptake. Notably, all these anions are substrates for URAT1 and share a tendency to increase SUA in vivo. By extension from the BBMV data (42, 61), increased plasma concentrations of antiuricosuric anions result in increased glomerular filtration, in increased delivery to the proximal tubule, and in increased intracellular concentration in tubule epithelial cells. Increases in the intracellular concentration of these anions in turn induce urate

reabsorption and hyperuricemia via *trans*-stimulation (**Figure 5**) of URAT1 and OAT10 from inside the cell.

There are very clear clinical consequences for this physiology. Hyperuricemia is thus a well-recognized concomitant of the increased concentration of β-hydroxybutyrate and acetoacetate found in diabetic ketoacidosis (72, 73). Increases in lactic acid, such as those seen in alcohol intoxication (74), result in hyperuricemia due to increased urate reabsorption (75); transient increases in lactate and/or keto acids may contribute to the association between gout and alcohol (76). The effects of keto acids and lactate do not appear to be secondary to the respective acidoses, given that the experimental infusion or ingestion of these anions can also lead to urate retention (72, 77, 78). Hyperuricemia is also a long-appreciated complication of high-fat diet (79) and of starvation ketosis (80). Finally, the treatment of hypercholesterolemia with nicotinic acid (niacin) is frequently complicated by hyperuricemia (81), as is the treatment of tuberculosis with pyrazinamide (82, 83).

Patients with renal hypouricemia and loss-of-function mutations in *URAT1* lack a full response to both pyrazinamide and uricosurics (62). This finding provides genetic confirmation of the linkage between PZA and urate reabsorption; as predicted by the model shown in **Figure 3**, a functional urate exchanger is necessary for the antiuricosuric effect of PZA. Furthermore, BBMV urate exchange is not detectable in animal species that secrete urate in the absence of significant reabsorption (30); the *SLC22A12* gene is presumably inactivated in these species, much as the uricase gene is inactivated in humans and other hominoids. Again, PZA has no effect on urate transport in species in which secretion predominates (29). All these observations tend to refute the four-component model, showing that PZA requires a functioning reabsorptive transporter for its antiuricosuric effect.

The Na^+-dependent anion cotransporters that collaborate with URAT1 and possibly OAT10 are encoded by two paralogs from the *SLC5* gene family of Na^+-coupled solute transporters: *SLC5A8* and *SLC5A12*. Both proteins transport nicotinate and other monocarboxylates (84, 85); intrarenal localization of the murine Slc5a8 and Slc5a12 proteins indicate expression at the apical membrane of S2/S3 and S1 segments of the proximal tubule, respectively, such that the two cotransporters may serially contribute to Na^+-dependent anion transport within the proximal nephron. There is a residual question of molecular heterogeneity in proximal tubule Na^+-anion cotransport; prior evidence had suggested both electrogenic (86) and electroneutral (70, 87) modalities for BBMV Na^+-dependent monocarboxylate and/or nicotinate/PZA transport, whereas both SLC5A8 (85) and Slc5a12 (84) appear to be electrogenic cotransporters. Notably, the zebrafish orthologs clearly differ in this regard; zebrafish Slc5a12 is an electroneutral cotransporter (stoichiometry of one Na^+ to each monocarboxylate anion), whereas zebrafish Slc5a8 is electrogenic (stoichiometry of two Na^+ cations to each monocarboxylate anion) (88).

The bimodal interactions found in BBMV many years ago (42) between Na^+-dependent urate exchange and urate-anion exchange (see **Figure 4**) have yet to be reproduced for the cloned SLC5A8/SLC5A12 cotransporters coexpressed with URAT1 and OAT10. However, mice with double deficiency of Slc5a8/Slc5a12 exhibit lacturia and increased urate excretion, emphasizing the role of these proteins in urate reabsorption (89). The Na^+-dependent loading of proximal tubule cells by transporters that do not directly participate in urate transport drives urate uptake while bypassing the *cis*-inhibitory effects of competition for exchanged anions on URAT1/OAT10 (see **Figure 5**). The renal tubule reabsorption of filtered lactate and keto acids by SLC5A8 and SLC5A12 also has substantial implications for the Cori cycle and for fatty acid metabolism, respectively. In this regard, given the genetic linkages between glucose metabolism and SUA (16), it is somewhat surprising that variation within the human *SLC5A8* and *SLC5A12* genes does not contribute to the risk of hyperuricemia.

The GLUT9 Urate Transporter

Multiple GWAS of SUA variation have implicated genetic variability in the *SLC2A9* (solute carrier gene family 2, member 9) gene (90–92). *SLC2A9* encodes a urate transporter known as GLUT9 (glucose transporter 9, a member of the GLUT family of hexose transporters). Despite the ever-increasing list of hyperuricemic genes, variation in *SLC2A9* remains the major single genetic determinant of SUA (92, 93), followed closely by the effects of variation in the ABCG2 (ATP-binding cassette subfamily G, member 2) gene (see below). GLUT9 acts as the major urate exit mechanism at the basolateral membrane of the proximal tubule, functioning in transepithelial urate reabsorption. The separate basolateral urate transporters OAT1 and OAT3 function in urate secretion (94) by the proximal tubule, transporting urate into the cell from the interstitium (**Figure 3**).

Two distinct N-terminal isoforms, GLUT9a (540 residues) and GLUT9b [511 residues; also known as GLUT9ΔN (95)], are generated by alternative 5′ ends within *SLC2A9* transcripts. GLUT9a and GLUT9b differ in membrane targeting, with human GLUT9a trafficking to the basolateral membrane and GLUT9b to the apical membrane of MDCK cells (95). Although their unique N termini determine membrane trafficking, mutagenesis has failed to identify a specific sorting signal in either GLUT9a or GLUT9b (96, 97). In human kidneys, GLUT9a is expressed at the basolateral membrane of proximal tubule cells with GLUT9b at the apical membrane of collecting ducts, without more detailed localization in intercalated cells versus principal cells (96). In mouse kidneys, Glut9a protein is expressed weakly within proximal tubule, with Glut9b expressed in distal convoluted tubule cells (98, 99).

GLUT9 shares a conserved motif in transmembrane domain 7 with the other three class II GLUT paralogs, GLUT5, GLUT7, and GLUT11; this motif appears to confer the ability to transport fructose, reportedly a substrate for GLUT9 (100). GLUT9 functions as a robust urate transporter in *Xenopus* oocytes and is sensitive to benzbromarone and tranilast (101). Although GLUT9 is reportedly a fructose-urate exchanger (92, 102), we and others (103, 104) have not been able to confirm that fructose is a substrate. GLUT9 certainly does not function as a typical urate-anion exchanger, given the lack of *cis*-inhibition or *trans*-activation by PZA and related anions (104); rather, given the evident activation by membrane depolarization (high extracellular $[K^+\text{-}Cl^-]$ in the uptake media), it appears to function as a urate uniporter or as an electrogenic exchanger. Urate- and voltage-dependent currents can thus be demonstrated in *Xenopus* oocytes expressing GLUT9 (105). The interior-negative membrane potential of proximal tubule cells is thought to favor basolateral exit of urate from the cell via electrogenic GLUT9.

The complete absence of renal reabsorption of filtered urate in hypouricemic patients with GLUT9 loss-of-function mutations is dramatic evidence of the role of this protein in renal tubule urate reabsorption; the fractional excretion of urate is ~150% in affected individuals, indicating a predominance of tubule urate secretion in the absence of reabsorption (37). Common variation in the *SLC2A9* gene that encodes GLUT9 is in turn the single most significant genetic determinant of SUA and hyperuricemia (92, 93). Notably, however, the causal variant(s) within *SLC2A9*, i.e., the specific polymorphic variation, that is associated with hyperuricemia has not been identified. The overall expectation is that these causal variants impact *SLC2A9* transcription to the extent that the transcript expression level of *SLC2A9* correlates with hyperuricemia (91), and many single-nucleotide polymorphisms (SNPs) associated with GWAS signals for disease and/or endophenotypes such as SUA localize to regulatory elements (106). However, there is no obvious peak for SNP associations within the *SLC2A9* gene, with high-scoring SNPs extending over much of the gene; only in African American subjects has the signal been fine-mapped to a relatively short 37-kb section of the gene (107). The two N-terminal isoforms of GLUT9 are widely referred to as splice variants (91, 92, 95, 102, 108). This is partially a semantic issue (95),

but the architecture of the *SLC2A9* gene suggests that these isoforms are generated by transcriptional initiation at alternative promoters (95), which was recently confirmed (104). Analysis of ENCODE (106) data for *SLC2A9* also indicates a number of intragenic enhancer elements. The full characterization of these transcriptional elements and their interactions will likely shed light on the genetic mechanisms underlying the association between this gene and variation in SUA. This transcriptional analysis will also potentially explain the association between gender and the effect of *SLC2A9* genotype on SUA (91).

Sequence variation within *SLC2A9* is also much higher than average for human genes (91), with almost 25 nonsynonymous coding SNPs within the gene. There is also substantial heterogeneity in the genetics of *SLC2A9* in various human populations, with consistent association between *SLC2A9* and SUA but different associations for the same SNP within different populations (109). These observations are reflected in the heterogeneous effect of coding SNPs. So, for example, the R265H variant has been linked with a protective effect in hyperuricemia (110, 111) and with the severity of gout (111, 112), but not in all populations (113).

The *SLC2A9* gene is widely expressed, with substantial transcript levels in the liver, kidney, brain, placenta, lung, and peripheral leucocytes (114). The cytokine-induced expression of GLUT9 in chondrocytes (115, 116) is particularly intriguing, given the role of Na^+-urate crystallization within the joint space in gout. The phenotypic analysis of mice with targeted deletion of *Slc2a9* is complicated by the widespread expression pattern of this gene because the entry of urate via the Glut9 protein at the basolateral membrane of murine hepatocytes facilitates uricase-catalyzed metabolism to allantoin (98). Transgenic mice with overexpression of Glut9 in the proximal tubule, driven by the URAT1 promoter, develop mild hyperuricemia that is not statistically significant from that of littermates, likely due to the mitigating effect of murine uricase on hyperuricemia; however, urinary urate excretion is reduced in these mice (117), indicating a potential renal mechanism for the effect of GLUT9 activation in human hyperuricemia and gout.

A loss-of-function mutation in *SLC2A9* has also been implicated in Dalmatian hyperuricosuria and hyperuricemia (118), a long-standing mechanistic problem in comparative physiology (119). Like humans and other hominoids, Dalmatians do not convert uric acid to allantoin. As a result, this breed is predisposed to form urinary calculi composed of Na^+-urate, with urine that readily forms a crystallized precipitate when cooled. Dalmatians and other affected breeds share a coding SNP or missense mutation (C188F) within transmembrane domain 5; although functional characterization has not been reported, the mutation is expected to be deleterious. This mutation in *SLC2A9* and the hyperuricemic phenotype are closely linked to a modifier of coat spot size such that they were fixed in the breed by selection for a more distinctive spotting pattern.

Loss of function in canine *SLC2A9* explains the combined hepatic and renal phenotype of Dalmatian hyperuricemia and hyperuricosuria. In the absence of functional GLUT9 at the basolateral membrane of hepatocytes, urate is not converted to allantoin by uric acid oxidase; the absence of renal tubule urate reabsorption in Dalmatians (118) is explained in turn by the loss of basolateral urate exit in proximal tubule cells.

SECRETORY URATE TRANSPORT

OAT1, OAT2, and OAT3

The basolateral entry of urate into renal proximal tubule cells is driven at least partially by the outwardly directed gradient for dicarboxylates such as α-ketoglutarate (α-KG), which in turn is generated by Na^+-dependent uptake via SLC13A1 (**Figure 3**). Thus, in renal basolateral membrane vesicles, urate exchange is not affected by lactate or PZA but is significantly *trans*-stimulated

by α-KG (120, 121). OAT1 and OAT3 appear to exchange urate with divalent anions such as α-KG (122–124), suggesting that they are suited to basolateral entry of urate, driven by intracellular α-KG, during urate secretion. This prediction is borne out by the characterization of OAT1/OAT3 double-knockout mice, in which renal urate secretion is impaired (94).

More recently, OAT2 has emerged as another candidate for the basolateral entry site of urate in renal tubule secretion. The OAT2 protein is expressed at the basolateral membrane of human proximal tubule cells (125). OAT2 has a more restricted substrate specificity than do OAT1 and OAT3 (126). OAT2 is also less sensitive to benzbromarone and probenecid than are other urate transporters. Urate transport in OAT2-expressing HEK293 cells is *cis*-inhibited, but not *trans*-activated, by both monocarboxylates and dicarboxylates, including PZA (126); this analysis leaves uncharacterized the endogenous anions that exchange with urate on OAT2 in vivo. However, a significant role of OAT2 in human urate homeostasis is indicated by a small but measurable effect on SUA due to variation in the *SLC22A7* gene, which encodes human OAT2 (16).

SLC17A1, SLC17A3, and SLC17A4

In addition to urate-anion exchange mechanisms, renal BBMV preparations from human (54) and other species contain a voltage-sensitive efflux mechanism driven by the cell-negative membrane potential. This transporter also appears to mediate apical exit of PAH. The NPT1 (Na^+-phosphate transporter) protein, encoded by the *SLC17A1* gene, was identified in 2000 as a candidate for this electrogenic exit pathway (127), with previous immunolocalization at the apical membrane of the rat proximal tubule (128). Interest in NPT1 was piqued considerably by the evidence that genetic variation in *SLC17A1* contributes to hyperuricemia (129). Mutant NPT1 (T269I), corresponding to a coding SNP (cSNP) associated with increased risk of hyperuricemia, mediates vesicle urate transport that is 32% lower than that of wild-type NPT1. Therefore, the reduction in apical urate secretion associated with this cSNP is presumed to lead to a dominance of reabsorption across the proximal tubule, leading to hyperuricemia.

Genetic variation in *SLC17A3*, which encodes human NPT4, also contributes to hyperuricemia (130). Heterologous expression of NPT4 in *Xenopus* oocytes reveals electrogenic PAH and urate transport (40); again, point mutations associated with risk of hyperuricemia exhibit a loss-of-function phenotype (40), consistent with an imbalance between urate secretion and reabsorption. The NPT4 protein is also detected at the apical membrane of human proximal tubule cells (40). NPT4 is inhibited by the loop diuretics furosemide and bumetanide, suggesting a possible contribution from reduced urate secretion to diuretic-associated hyperuricemia, a common clinical problem.

Another SLC17 paralog, SLC17A4, has been identified at the luminal membrane of human small intestine (131). Heterologous expression reveals functional characteristics similar to those of NPT1 and NPT4, indicating that this paralog may play a role in intestinal urate secretion.

ABCG2 and MRP4

The apical ATP-driven efflux pumps MRP4 (multidrug resistance protein 4) and ABCG2 function in urate secretion by the proximal tubule and intestine. Human MRP4, but not MRP2, expressed in HEK293 cells mediates ATP-dependent efflux of urate (132). The MRP4 protein is apically expressed in human proximal tubule cells (133). In cultured avian proximal tubules, which lack reabsorptive urate transport, knockdown of MRP4 expression reduces urate secretion by 65% (134). Human MRP4 is strongly inhibited by benzbromarone and probenecid, with a novel activation by the xanthine oxidase inhibitor allopurinol and its active metabolite, oxypurinol (135).

Genetic variation in human MRP4 has not been reported to affect SUA. In contrast, genetic variation in human ABCG2, another ATP-driven efflux pump, has emerged as a major factor in human hyperuricemia, rivalled only by variation in *SLC2A9*. GWAS first indicated a role for ABCG2 in 2008 (130). ABCG2 was subsequently found to mediate urate efflux in *Xenopus* oocytes, leading to a statistically significant reduction in the very modest ^{14}C-urate retention of oocytes; this effect was blocked by a loss-of-function mutation in ABCG2 and by pharmacological inhibition by fumitremorgin C, a specific ABCG2 inhibitor (39). A common nonsynonymous SNP in ABCG, Q141K, reduced ABCG2 function by 53% in this system. Subsequent work in mammalian cells (38, 136) and *Xenopus* oocytes (136) revealed a temperature-dependent expression defect in Q141K-ABCG2, linked to instability of the nucleotide-binding domain (136). There are similarities in the biochemical phenotype of Q141K-ABCG2 and ΔF508 CFTR proteins such that small-molecule therapies designed for cystic fibrosis can rescue the expression defect of Q141K-ABCG2 (136).

A more robust transport assay, using membrane vesicles from HEK293 cells expressing ABCG2, verified its role as a high-capacity urate transporter (38). An additional five nonsynonymous mutations and cSNPs were detected by sequencing ABCG2 in 90 Japanese patients with hyperuricemia; all but one of these mutations dramatically reduced ABCG2 function (38).

An underlying assumption was that a loss of or reduction in ABCG2-mediated renal urate secretion would lead to increased renal urate reabsorption, given that reduced renal excretion of urate (137) is considered to be the underlying hyperuricemic mechanism in the vast majority of gout patients (138, 139). Surprisingly, however, hyperuricemic patients with graded levels of ABCG2 dysfunction, grouped on the basis of genotype for dysfunctional SNPs, have what superficially appears to be overproduction hyperuricemia, with elevated urinary urate excretion and fractional excretions of >5.5% (140). Intestinal urate excretion is reduced by more than 50% in ABCG2 knockout mice. Hence, by extension, what would appear to be overproduction hyperuricemia in hyperuricemic humans with ABCG2 dysfunction is more accurately characterized as renal overload hyperuricemia due to reduced intestinal secretion of urate (140). ABCG2 dysfunction also appears to cause renal underexcretion of urate in patients with lesser degrees of functional impairment, classified again on the basis of genotype (141).

In a cohort of 5,005 Japanese participants, the *ABCG2* genotype had a greater effect on SUA than did other epidemiological risk factors for hyperuricemia, such as body mass index and alcohol intake (142). This observation needs to be repeated in other populations; however, it suggests a broad utility for small-molecule therapies capable of correcting the expression defects in specific *ABCG2* mutations (136).

REGULATION OF URATE HOMEOSTASIS

The Role of PDZ Domain Proteins

The extreme C termini of all apical absorptive and secretory urate transporters except for ABCG2 end with typical PDZ domain interaction motifs. URAT1 interacts with PDZK1 (143, 144) and NHERF1 (144), well-characterized PDZ domain proteins that regulate trafficking and activity of multiple transport proteins in the proximal tubule. PDZK1 is a genetic determinant of serum urate levels (145), and targeted deletion of NHERF1 reduces renal urate reabsorption in mice (146). URAT1 proteins are thus retained in intracellular vesicles in NHERF1 knockout mice, indicating a critical role for NHERF1 in brush-border membrane targeting of the protein (146). MRP4 also interacts with NHERF1 (147, 148), but NHERF1 appears to have the opposite effect as that on URAT1, stimulating MRP4 internalization (148). However, MRP4 also interacts with PDZK1, which increases membrane expression and activity of the protein in HEK293 cells; apical

expression of the MRP4 protein in the proximal tubule is also downregulated in PDZK1 knockout mice (149). Therefore, how PDZ proteins assist in the specific and separate regulation of apical reabsorptive and secretory urate transporters awaits full characterization.

Neurohumoral Influences

There is considerable evidence for regulated homeostasis of urate. In bacteria, direct transcriptional regulation of urate homeostasis occurs via repression of uricase expression by urate-binding transcription factors (150); this and related operons are hypothesized to affect the ability of bacteria to respond to oxidative stress (150) and/or to respond to urate levels in plants colonized by the bacteria (151). In humans, oxidative stress induced by exposure to high altitude increases serum urate (152), indicating the ability to modulate urate production and/or excretion in response to changes in oxidative stress and/or other stimuli. Nigam and colleagues (153) have argued that tight regulation of ABC transporters and SLC22 transporters plays a key role in regulating urate acid homeostasis such that this transporter network coordinates the regulation of circulating urate concentration.

Volume status also influences urate excretion and the risk of acute gout such that volume-depleted patients can become hyperuricemic (154); this physiology underlies in large part the association between diuretic therapy and acute gout (155). In rats, hypovolemia increases proximal tubule urate absorption (156); in humans, there is a direct linkage between proximal tubule salt and urate transport (157). Short- and long-term salt restriction (158) causes significant hyperuricemia, which is dramatically reversed by salt loading (159–163). Thus, the SUA of subjects on a strict low-salt diet (~20–50 mEqu/day) is higher than the SUA of subjects on a high-salt diet (~170–214 mEqu/day) (159–163). The magnitude of these differences depends on the degree of salt restriction or salt loading, with a 1.8–2.0 mg/dL difference in SUA between 29–38 mEqu/day and 258 mEqu/day (160). These short-term changes in dietary salt affect SUA via changes in renal urate excretion (160). Potential mediators include angiotensin II (Ang II) (165, 166) and epinephrine (165, 167). Thus, the acute infusion of Ang II at 8 ng/min/kg over 120 min results in (*a*) a drop in fractional excretion of urate from $9.3 \pm 1.3\%$ to $4.5 \pm 1.0\%$ and (*b*) a drop in urate excretion from 0.16 ± 0.03 mmol/h to 0.07 ± 0.02 mmol/h (166). Hyperuricemia also predicts a blunted renal vascular response to infused Ang II, indicative of an activated intrarenal renin-angiotensin system (168), and plasma renin activity correlates with SUA (169).

Several other hormones regulate SUA. In particular, insulin-stimulated renal urate retention may play an important role in the associations between the metabolic syndrome, hyperuricemia, and gout (157, 170–174). Pathway analysis of GWAS data also indicates a role for genes in the inhibin-activin growth factor system, a pleiotropic signaling system with no single clear functional link to urate metabolism (16). Excessive parathyroid hormone (PTH) also reduces urate excretion in primary hyperparathyroidism (175) and during pharmacological therapy for osteoporosis (176, 177); this effect may be particularly relevant to the association between gout and chronic kidney disease (4, 178). Finally, SUA is typically lower during acute gout flares compared with baseline SUA (179), due to cytokine-stimulated uricosuria (179, 180).

CONCLUSIONS

In the years since the identification of URAT1 (56), what appears to be a complete picture of the major secretory and reabsorptive urate transporters has emerged. Recent advances notwithstanding, there are major gaps in the understanding of urate homeostasis. In particular, although insulin (171, 172), Ang II (165, 166), epinephrine (165, 167), and PTH (176–178) stimulate renal urate

retention, the mechanisms involved are uncharacterized. Another major challenge will be the full integration of urate homeostasis with the genetic networks identified by GWAS analysis (16).

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