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Urate Transport in Health and Disease

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Abstract

Circulating urate levels are determined by the balance between urate production and excretion, a homeostasis regulated by the function of urate transporters in key epithelial tissues and cell types. Our understanding of these physiological processes and identification of the genes encoding the urate transporters has advanced significantly, leading to a greater ability to predict risk for urate associated diseases and identify new therapeutics that directly target urate transport. Here we review the identified urate transporters and their organization and function in the renal tubule, the intestinal enterocytes, and other important cell types to provide a fuller understanding of the complicated process of urate homeostasis and its role in human disease. Further, we provide a review of the genetic tools that have provided the unbiased catalyst for transporter identification as well as a discussion of the role of transporters in determining the observed significant sex differences in urate associated disease risk.

Keywords

gout; urate; hyperuricemia; ABCG2; SLC2A9; SLC22A12; URAT1

I. Introduction

Uric acid is a weak organic acid with a pK_a of 5.75, and at physiological pH exists primarily in its protonated form, urate. Urate has peak solubility at pH 5.5[1], and is less soluble at more alkaline, including physiological, pH[2]. Urate is the terminal metabolite of purine metabolism in humans and the other great apes, due to accumulation of three mutations in the uric acid oxidase (uricase) gene (*UOX*) resulting in complete loss of function[3]. The pseudogenization of *UOX* in humans is the culmination of a diminishing gradient of uricase activity in all primates[3], supporting strong selective pressure for the loss of uricase function and the increase of circulating urate levels[4]. Urate is produced from the degradation of purine nucleotides and amino acids, mediated by xanthine oxidase.

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Without uricase activity, humans have serum urate (SU) levels 5 to 6 times higher than other mammals[5]. The gradual loss of uricase activity likely permitted adaptation to increased urate load in humans, mitigating many pathophysiological consequences associated with uricase silencing, including the acute urate nephropathy renal failure observed in uricase knock-out mice[6]. The possible benefit of elevated SU is still hotly debated, however the disadvantages for human health are clear: increased SU results in hyperuricemia (>6.8 mg/dL), a condition which increases the risk of precipitation of monosodium urate crystals and gout, as well as a risk factor for cardiometabolic diseases[7].

The number of affected individuals with hyperuricemia in the United States is estimated to be 47.2 million (20%); with 27.9 million individuals (11.9%) having severe hyperuricemia (>7mg/dL), and men (20.2%) are affected five times more often than women (4.2%)[7]. These large numbers of hyperuricemic individuals result in an equally high prevalence of gout of approximately 4% in the United States, Europe, and Southeast Asia[7, 8]. In addition to a causal role in gout, hyperuricemia is independently associated with major drivers in human health including renal diseases, hypertension, cardiovascular disease, and metabolic syndrome[7–10]. Beneath each of these pathologies is a derangement in the careful balance between urate production and excretion with significant biological consequences. This urate homeostasis, predominantly determined by urate excretion, is maintained by epithelial transport systems of the liver, kidney, and intestine[11], but is mirrored by similar systems at the tissue and cell layer in the blood brain barrier, placenta, and in chondrocytes[12, 13]. Here we will review the molecular mechanisms of urate transport in an effort to understand urate homeostasis and the consequences of its disruption, and the role of genetics in determining risk of urate related pathologies.

II. Genome-wide association study evidence

Several approaches have been utilized to attempt to identify urate transporter machinery. Gout risk and SU levels display a strong heritable component, estimated between 40–70%[14, 15], making SU a strong candidate for genomic exploration. Initial studies examined families with pathological SU levels using a labor-intensive comparative and candidate based cloning approach. This led to the identification of urate transporter URAT1, encoded by *SLC22A12*[16]. Subsequent work proved that other members of the SLC22 gene family (the Organic Anion Transporters or OATs) have affinity for urate[17, 18]; however, physiological relevance of these transporters has been difficult to substantiate[19]. Frustratingly, the candidate approach failed to identify secretory urate transporters or transporters linked to increased disease risk. Fortunately, the advent of genome-wide association studies (GWAS) provided an unbiased approach to identify urate associated genes. GWAS find correlations between a given condition and common single nucleotide polymorphisms (SNPs), which serve as markers for genomic space[20]. After identification of these genomic regions, additional analyses can then be performed to identify those genes most likely to underlie the associated SNP, in some cases identifying novel causal variants that contribute to disease risk.

An abundant number of urate associated GWAS have been conducted with large and diverse populations, greatly expanding our knowledge of the key urate transporters in

humans[21, 22]. The three most commonly associated genes are *ABCG2*, *SLC2A9*, and *SLC22A12*[21–27], and variants in these three genes have been shown to contribute to the largest portion of the measured variability in SU levels (~5%)[22]. In addition, a recent targeted study demonstrated the common *ABCG2* variant rs2231142 is the only locus strongly associated with early onset gout in both European and Polynesian individuals[28]. Some additional urate associated transporters include *SLC16A9*[22, 24, 25], *SLC17A1–4*[21, 22, 24–26], *SLC22A6*[22], *SLC22A7*[22, 27], and *SLC22A11*[24, 25], with some evidence for *SLC22A9* in East Asian populations[29], as well as *SLC22A8*, *SLC22A13*, and *ABCC4* in populations with chronic renal insufficency of either European or African ancestry[30] and in Māori and Pacific Island populations of New Zealand[31]. In addition to genes coding for transport proteins, more than one hundred other loci have associated with either serum urate levels, gout risk, or both, providing an extremely rich genetic understanding of networks of associated genes, including genes that modify transporters. For example, a recent comprehensive trans-ancestry GWAS, Tin et al[22] attempted to identify common variants causal for alterations in urate levels. They identified both well-established urate transporter gene variants in *ABCG2*[32], as well as in the transcription factor genes *HNF1A* and *HNF4A*[22], both of which have been shown to affect expression of several urate transporters[22, 33–38]. Finally, computational approaches can be added to trans-ancestral meta-analyses to improve fine mapping of candidate causal variants to single SNP resolution, and have recently identified causal variants in *SLC2A9* for both urate (rs3775948) and gout (rs4697701), and another variant in *ABCG2* (rs2622621) in gout along with the previously established rs2231142[39].

A second genetic methodology that has aided in our understanding of the mechanisms of urate transport is whole exon association studies. These use whole exon or whole exome sequencing of patient populations again compared to phenotypes, specifically powered to discover both common and rare causal variants associated with SU or gout risk. Tin et al[40] found a large number of exclusively rare variants in *SLC22A12* and demonstrated a select few were loss of function variants, illustrating key functional components of the URAT1 transporter. They also found a large number of both common and rare variants in *SLC2A9*, helping better understand the structure and function of the SLC2A9 (GLUT9) urate transporter protein[40]. Thus, genetic studies provide valuable information into the identification of various urate associated genes, including urate transporters themselves, variations in allele frequency in populations of different ethnicities, and sex differences. In addition, this work has illuminated, through the identification of functional variants, the structure and function of the key transport proteins providing insights into the unique human handling of urate and road maps to future therpautic targets.

III. Urate handling in the kidney

Urate homeostasis is the balance between urate production and excretion, a dynamic process that requires physiological adaptation and flexibility. Urate excretion occurs primarily through the normal excretion pathways for all metabolites and waste products: the kidney and the gastrointestinal tract. Of these two, the kidneys are responsible for 70% of the total urate excretion (Figure 1), joining the other primary human nitrogenous waste product, urea, expelled in the urine[41, 42]. Like our understanding of urea handling in

the human kidney, urate excretion appears more complicated than necessary for simply waste elimination. After urate is freely filtered at the renal glomerulus, transporter proteins within the convoluted S1 segment of the proximal tubule facilitate the reabsorption of urate as part of the initial bulk reabsorption of many organic anions[19, 43, 44] (Figure 1C). This early proximal urate reabsorption may be influenced by either sodium or volume status. Clinical studies showed that increased dietary sodium and the resulting increases in volume, blood pressure, and renin, correlated with decreased serum urate, consistent with decreased tubule reabsorption[45]. In rats, decreases in extracellular fluid volume increases urate reabsorption in the proximal tubule and decreases urate excretion, while increases in extracellular fluid volume have the opposite effect[46], similar to what has been reported in humans[45]. Overall, the majority of the filtered urate (estimated as high as 95%)[19] is reabsorbed, an odd fate for a waste product, but may be a result of efficient but low specificity general anion capture in the early proximal tubule. The next step is avid and energetically costly secretion of urate back into the tubule lumen, as much as 50% of the original filtered load[44]. This may occur in the next 2 segments of the proximal tubule (S2, S3), the segments with the highest expression of secretory transporters (Figure 1D). The process is completed with a second phase of reabsorption in the latter S2 and S3 segments resulting in a dynamic fractional excretion of urate (FE_{UA}) ranging from 5 to 15%[19, 43, 44]. This model of urate handling is based largely on experiments in animal models and *in vitro* assays and remains somewhat controversial[19]. The recent identification of many key human urate transporters, their functional assessment, and expression along the human nephron, has supported the functionally distinct phases of urate handling along the tubule. However, confirmatory protein localization in human tissue is often missing and so testing this hypothesis remains a driving force in urate research.

Functional characterization of several candidate transporters have revealed a number of proteins which have some affinity for urate (Figure 1). Based on renal tubular expression *in vivo*, the initial bulk reabsorption is likely conducted by apically expressed OAT4 (encoded by *SLC22A11*), and OAT10 (encoded by *SLC22A13*), and other still unindentified probable transporters with lower urate affinity, to remove urate from the tubular lumen, then transported basolaterally back into the interstitum via SLC2A9[11, 17, 47–50]. Interestingly, in mice the key urate reabsorption transporter SLC2A9 is not expressed in the proximal tubule[51] and kidney specific knock out of SLC2A9 results in mice with moderate hyperuricosuria, polyuria with no concentration defect, and no change in SU, urine pH, or renal structure[52]. In contrast, humans with loss of function mutations in SLC2A9 experience significant hypouricemia[23] as discussed below, demonstrating differences in the role of SLC2A9 between the two species, and suggesting renal urate handling in humans is an adaptation to the increases in filtered urate load resulting from the loss of uricase function. Urate in the peritubular capillary then re-enters the tubule though basolateral transporters OAT1 (encoded by *SLC22A6*) and OAT3 (encoded by *SLC22A8*) [17, 47, 53–55], where it is secreted through the primary secretory transporter, ABCG2 (BCRP), expressed on the apical brush border membrane, with further secretion contributed potentially by apically localized Na+ / phosphate co-transporters, NPT1 (encoded by *SLC17A1*) and NPT4 (encoded by *SLC17A3*)[32, 56–58]. Post secretory reabsorption is likely facilitated primarily by URAT1 (encoded by *SLC22A12*), which is expressed at the

apical brush border membrane, coupled with SLC2A9 on the basolateral membrane to transport urate to the peritubular capalaries[16, 23, 49, 59]. *SLC16A9* is also preferentially expressed in proximal tubule cells[60], however the precise localization and role in urate transport is not currently understood. Paradoxically, protein localization in human proximal tubules shows ABCG2 mediated secretion and URAT1 mediated reabsorption can occur in the same cell[61], begging the obvious question of why urate is secreted and reabsorbed simultaneously; could the nephron be using urate to perform other physiological work?

Recent advances in single cell RNA-Seq data have revealed that many of the urate associated transporters have different expression patterns along the nephron (Figure 1B). All of these transporters are expressed in the three segments of the proximal tubule, however *SLC17A1*, *SLC17A3*, *SLC22A6* and *SLC22A8* have highest mRNA expression in the S1 segment, *ABCG2*, *SLC2A9*, and *SLC22A12* have highest mRNA expression in the S3 segment, while *SLC22A11* and *SLC22A13* have similar mRNA expression levels in both the S1 and S3 segments[62]. Of note, some of these transporter proteins, including ABCG2, may be long lived within the cell[63], rendering mRNA levels deceptively low. Thus, different segments of the proximal tubule may have heterologous expression of a given set of transporters.

Further evidence supporting the involvement of URAT1 and SLC2A9 in urate reabsorption is found in patients with renal hypouricemia. Symptoms of hypouricemia may include hematuria and hypercalciuria, but more often include recurrent episodes of nephrolithiasis acute kidney injury (AKI) usually from dehydration due to intense or frequent exercise or gastroenteritis, or posterior reversible encephalopathy syndrome in patients with exercise associated AKI[64]. Hypouricemia type 1 (OMIM #220150) is the more common condition and associated with homozygous or compound heterozygous loss of function variants in *SLC22A12*, while hypouricemia type 2 (OMIM #612076) is caused by either heterozygous or homozygous defects in *SLC2A9*[64, 65]. These conditions have been best characterized in patients of East Asian ancestry, but additional evidence has shown that these variants are also found in a variety of ethnic groups including Arab Israelis, Ashkenazi Jews, Iraqi Jews, as well as individuals of various European ancestries[64]. Approximately 150 variants have been identified in the *SLC22A12* gene, and over 100 variants have been described in *SLC2A9*, some of which have known associations with gout[40, 64]. URAT1 expression and localization appears evolutionarily conserved, however, the human version of the URAT1 protein has a much higher affinity for urate than that of mice and rats. This is due to substitution of a few key amino acids within the primate transporter, which likely took place in the same timeframe as primates loss of uricase function, providing further evidence for a selection advantage to increased urate retention[66].

One possible explanation for the complexity in urate transport is that urate provides crucial driving forces for the movement of other critical anions and electrolytes along the nephron. For example, URAT1 is an exchanger, and thus reabsorbs urate when another counter-ion is secreted *in trans*. URAT1 has affinity for numerous metabolically active anions, including lactate, ketoglutarate (αKG) and β-hydroxybutyrate(βHB)[16]. OAT1/3 can also transport these citric acid cycle intermediates [47, 50, 54, 67]. Some of these anions are generated within the cell as a product of anaerobic (lactate) or aerobic (αKG and βHB) glucose catabolism, or these molecules can enter the cells through transporters. Lactate is freely

filtered at the glomerulus and can be used for gluconeogenesis in the renal cortex [68], and uptake is increased by acidosis [69]. Lactate is primarily reabsorbed by sodium-coupled transporters encoded by *SLC5A8* and *SLC5A12*, whose protein products SMCT1 and SMCT2 are expressed on the apical side of proximal tubular cells [70, 71]. Interestingly, mice that are null for both *SLC5A8* and *SLC5A12* demonstrate increased urinary excretion of both lactate and urate indicating a functional coupling of lactate and urate transport *in vivo* [72]. The importance of sodium-dependent urate transport is further supported from data showing that healthy subjects administered the SGLT2 inhibitor phloridzin demonstrated increased FE_{UA}[73] and that mice deficient in SGLT1 demonstrate glucosuria and uricosuria with the addition of SLGT2 inhibitor canagliflozin, evidence that increased luminal glucose may induce uricosuria, and that URAT1 is required for this effect[74]. On the basolateral side, another sodium-dependent transporter NaDC3 (encoded by *SLC13A3*) also transports metabolic intermediates succinate, αKG, and citrate into the cell[75]. NaDC3 may couple with the basolateral OATs, in order to exchange αKG for urate[11]. Taken together, this data provides evidence for potential roles for urate in energy metabolism and sodium handling. Furthermore, the expression and activity of these transporters in the late proximal tubule seem to be conserved across species; however, further studies are required to elucidate the roles of these transporters in urate handling in humans.

Renal function may also contribute to hyperuricemia and gout susceptibility. Not only has hyperuricemia been reported as an independent risk factor for chronic kidney disease (CKD) [76], but patients with worsening kidney function may also be more likely to develop gout[77]. There is also evidence that mild hyperuricemia may correlate with kidney damage. Increased SU levels may predict development of end stage renal disease (CKD stage 5)[76], and overall prevalence of gout in CKD is 3 to 6 times higher than in the general population[7, 77]. However, urate lowering therapy (ULT) is currently only recommended for CKD patients with gout, and not asymptomatic hyperuricemia, as urate-lowering therapy with allopurinol does not alter progression of CKD in those without gout[78, 79]. Both allopurinol and febuxostat are xanthine oxidase inhibitors[80]. These and other ULT drugs, including uricosuric agents, have complex interactions with urate transporter proteins (reviewed in detail in [81], with selected examples in Table 1). For example, both allopurinol and oxypurinol are substrates of ABCG2 (Figure 1D)[82], and this interaction may cause reduced response to allopurinol urate lowering therapy, especially in patients with the ABCG2-Q141K variant[83, 84]. The primary target for most uricosurics is URAT1, with some drugs also inhibiting other reabsorptive transporters including OAT4 and OAT10 (Table 1a), thereby decreasing reabsorption and increasing urinary urate excretion. Other drugs used to treat kidney disease can also affect urate levels, including diuretics and SGLT2 inhibitors (Table 1b). Diuretics have been shown to increase SU levels, acting as competitive inhibitors for urate on OAT1 – 3[85]. Loop diuretics can also directly inhibit ABCG2[86] and NPT4[58], which leads to a decrease in urate secretion. The uricosuric effect of interactions between SGLT2 inhibitors and urate transporters is much less well characterized, with some evidence that SGLT2 inhibitor luseogliflozin (approved for use in Japan) does not affect reabsorptive urate transport activity of SLC2A9, URAT1, OAT4 or OAT10[87], indicating glucose may be influencing urate levels by some other mechanism, which remains unclear.

IV. Urate handling in the gut

Several of the urate transporters expressed in the kidney are also found in intestinal epithelial cells (Reviewed in [88]), including ABCG2, SLC2A9 and others. ABCG2 is localized to the apical compartment of the intestinal enterocytes[89]. SLC2A9 is expressed primarily on the basolateral side of enterocytes in mice[61, 90], poised to provide basolateral entry, coupled with ABCG2 on the apical side (Figure 1E). Disruption of this pathway in mice with the intestine specific knockout of SLC2A9 or the knock-in of the human gout variant ortholog Q140K ABCG2, leads to significantly reduced intestinal urate excretion, moderate hyperuricemia, and metabolic syndrome[61, 90]. However, the role of SLC2A9 in human intestine is less clear. Other urate associated transporter genes expressed in the intestine include *SLC17A4*[91] expressed on the apical brush border, *SLC22A13*[92] and *SLC16A9*[93], but where these proteins localize and how they contribute in intestinal excretion remains to be confirmed.

The most well characterized intestinal urate transporter is ABCG2. Matsuo et al demonstrated that patients with end stage renal disease who had severely reduced renal urate excretion were highly dependent upon ABCG2 mediated secretion in the gut [94]. Thus, patients with loss of function variants in ABCG2 activity displayed a higher degree of hyperuricemia compared with those without. A recent human interventional trial measured urate handling in individuals with the common Q141K variant (rs2231142) of ABCG2 compared to a control cohort. They showed in the control cohort that extrarenal (intestinal) excretion of urate was the primary driver of variation in SU levels during a urate loading test, whereas for Q141K ABCG2 individuals, renal excretion was the primary source of variation in SU, and there was a significant loss of extrarenal excretion. To understand the mechanism, in the same study, Hoque et al created a mouse ortholog model of the Q141K ABCG2 variant. These animals replicated the human phenotype: hyperuricemia, moderate reduction in renal excretion, and significant loss to intestinal urate excretion[61]. ABCG2 is expressed in the brush border of the villi cells in the jejunum and ileum in mice, and mice with the ABCG2 variant showed a complete loss of ABCG2 mediated intestinal excretion correlated with a severe reduction in ABCG2 abundance. Interestingly, the Q141K mouse model also confirmed the role of ABCG2 in renal excretion, but they found that, in contrast to the intestines, the variant showed only a moderate decline in abundance and function. Similar results were observed in ABCG2 whole body knockout mice, which demonstrate increased SU levels and decreased intestinal excretion of urate[95].

V. Urate handling in the liver

Increased urate production is another potential cause of hyperuricemia. The liver is the major site of urate production[19, 96], where urate precursors enter hepatic cells, and are then metabolized to urate through xanthine oxidase. These precursors include endogenous nucleotide purines, including AMP and GMP, as well as dietary purines and fructose[97]. Fructose metabolism rapidly consumes ATP, stimulating AMP deaminase, leading to increased urate production[98]. Increased fructose intake through either sucrose or high fructose corn syrup can not only increase SU levels through increased ATP consumption, but can also increase risk for developing several urate associated co-morbidities including

metabolic syndrome, fatty liver disease, insulin resistance, and type 2 diabetes[99]. *In vitro* analyses of human hepatocytes have shown that increased urate, independent of fructose, can stimulate fructose metabolism through up-regulation of fructokinase (KHK)[100], and that inhibition of urate production blocked fructose-induced hepatocyte triglyceride accumulation in both human HepG2 cells and in male rats fed high fructose treated with allopurinol[100]. Thus, there is evidence that it is the increased urate as a result of higher fructose intake that plays a role in fructose associated co-morbidities.

The liver also expresses several urate transporters, including *ABCG2, SLC2A9, SLC22A7* and *SLC22A11*[49, 89, 101] supporting an important role for urate transport in the liver that has yet to be determined, particularly in humans. *SLC2A9* is expressed on the apical surface of hepatocytes in humans[49], as well as mice[102]. Interestingly, liver-specific SLC2A9 knock out mice (LG9KO) demonstrate higher SU than whole body SLC2A9 knock out mice (G9KO), with a lower increase in FE_{UA} (~25%) compared to G9KO mice (~100% for males, ~150% for females), implying SLC2A9 may be essential for urate uptake into murine livers[102]. In addition, ABCG2 is expressed in the liver, specifically at the bile canalicular membrane, oriented to efflux urate into the bile, leading to eventual deposition in the intestine[89]. However, oxonate-treated rats demonstrated only a 0.68% recovery of administered ^{14}[C] uric acid in the bile, compared to 42.58% in the urine and 8.90% in the intestinal lumen[103], supporting a lesser contribution to overall urate excretion from the liver. Human hepatic excretion of urate in the bile has yet to be determined[12], so the effect of common ABCG2 variants in the liver is unclear.

VI. Sex differences in urate handling

Sex differences in human physiology have recently come into focus in a variety of fields, including immunological[104–106] and renal diseases[107–111]. There is also substantial evidence that male sex is a significant risk factor for hyperuricemia and gout[112, 113], with men up to 4 times more likely to be affected than women[8]. This observation has recently been coupled to investigations of sex differences in urate handling in the kidney[61], as well as differential effects of pathogenic variants in urate transporter genes[22, 114]. A recent review[115] argued that even though SU levels tend to be lower in females[7], females with elevated SU levels have increased risk of associated co-morbidities, including hypertension[116–118], chronic kidney disease[117, 119, 120], and type 2 diabetes[117, 121]. GWAS evidence has shown almost 200 loci associated with SU levels[22, 29], but only three of these SNPs have sex specific effects; two in urate transporters ABCG2 and SLC2A9, and the third in gene encoding urate transporter scaffold protein PDZK1[22, 114]. Thus, the observed sex differences are more likely due to intrinsic differences in urate handling in males compared to females, with some evidence that estrogen may play a role in regulating either urate transporters themselves[122–124], or urate associated transcription factors[125, 126]. This is further supported by the fact that the chance of females becoming hyperuricemic increases 5-fold after menopause, and this risk can be mitigated by hormone replacement therapy[127–129]. However, further studies are required to elucidate the precise mechanisms for the differential regulation of urate handling between males and females.

VII. Summary

Urate homeostasis is a complicated process that involves several organ systems. Several urate transport proteins have been identified through genetic associations using GWAS and *in vitro* studies. Urate transport in the kidney has been the most well characterized; however, the purpose and regulation of this intricate process of reabsorption, secretion, and additional reabsorption has yet to be elucidated. This complex system implies the kidney may be using urate as a counter-ion to perform some other function that remains to be determined. Further study is also required to identify the full complement and subsequent roles of the urate and related transporters in both the intestine and the liver to better understand whole body urate homeostasis. This greater understanding could lead to insights into the mechanisms regarding sex differences in urate handling, as well as potential novel therapeutic targets and treatments to improve quality of life of patients afflicted with hyperuricemia, gout, and other related co-morbidities.

VIII. Practice Points

- Serum urate levels are influenced by the urate transport mechanisms of the kidney and intestine excretion pathways.
- Pathological disruptions of these key excretory organs, as observed in CKD and intestinal infection, increases serum urate and risk for gout.
- Recent genetic analysis has revealed much of the heritability of hyperuricemia and gout risk is due to functional variants in the key urate transporter genes, *ABCG2*, *SLC22A12*, and *SLC2A9*.
- Understanding individuals genetic background may inform on risk for urate associated disease and point to patient centered treatment options.

IX. Research Agenda

- Additional research into the physiology and identities of urate transporters to better understand the counter intuitive nature of the kidney’s handling of urate
- Functional studies examining the role of urate as a counter-ion for some other physiologically important process, such as sodium or water balance
- Additional laboratory research examining the role of how urate and glucose each influence renal handling of the other, and mechanistic studies into the contributions of SGLT2
- Identification and characterization of additional urate transporters in the intestine and the liver
- Functional studies to determine the underlying mechanisms for the sex differences in urate handling

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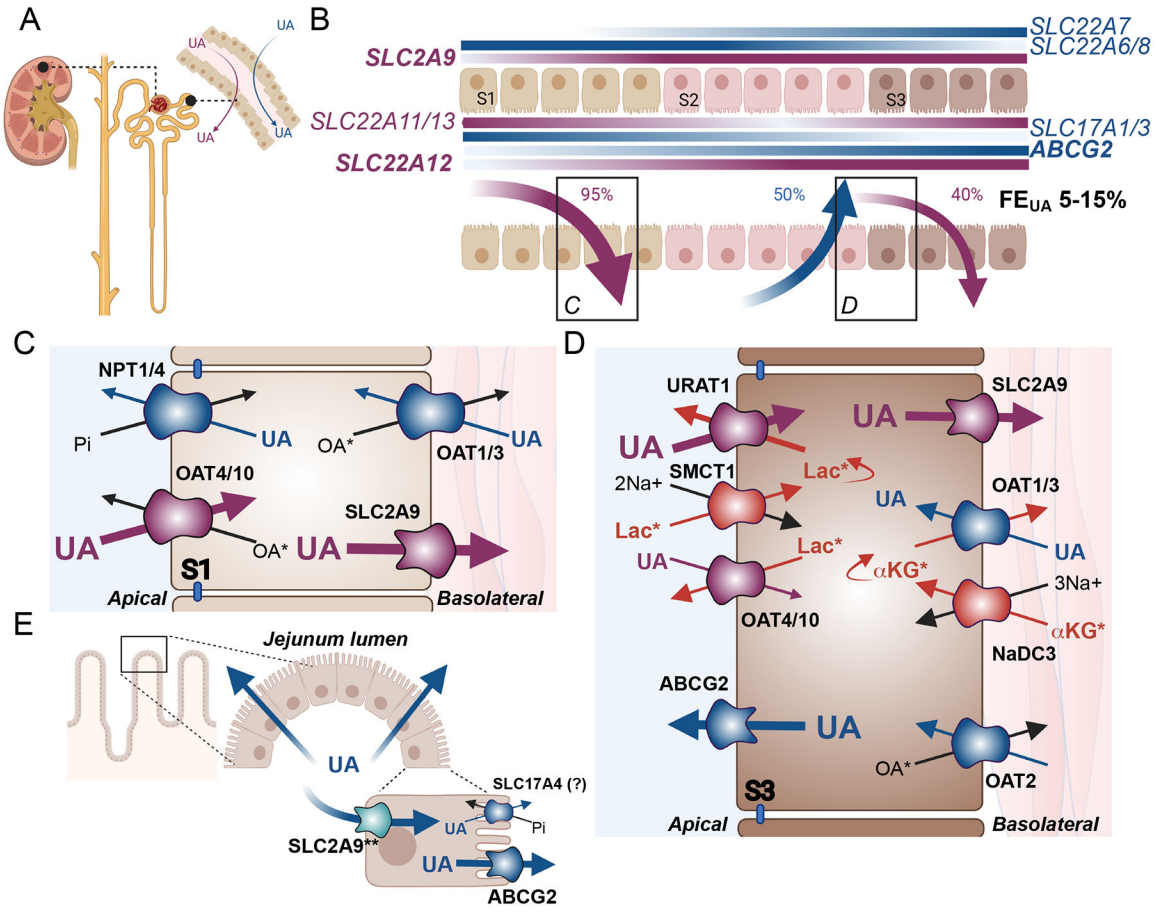

Fig. 1. Renal and Intestinal Urate Physiology

(A) The proximal tubule of the renal nephron is the principal site of urate (UA) handling through both secretion (blue arrow) and reabsorption (purple arrow). (B) Expression patterns of human urate transporter genes. Secretory transporter genes are shown in blue, while reabsorptive transporter genes are shown in purple. Gradients are displayed on the membranes of expression, with *SLC22A6/7/8* and *SLC2A9* coding for basolateral proteins, and *ABCG2*, *SLC17A1/3*, and *SLC22A11/12/13* encoding apical transporters. The darker the color, the higher the expression, based on data from the Kidney Interactive Transcriptomics database[62]. Percentages delineate the amount of the original urate filtered load is either reabsorbed (purple arrows) or secreted (blue arrow) leading to a final fraction excretion of urate (FE_{UA}) shown in black. Transporter protein localization and transport patterns are shown for the S1 (C) and S3 (D) segments. (C) Transporters most abundantly expressed in the S1 segments include transporters of the secretory pathway: NPT1 (*SLC17A1*), NPT4 (*SLC17A3*), OAT1 (*SLC22A6*) and OAT3 (*SLC22A8*), shown in blue, and transporters of the reabsorptive pathway: OAT4 (*SLC22A11*), OAT10 (*SLC22A13*), and SLC2A9/GLUT9 (*SLC2A9*), shown in purple. (D) Transporters most abundantly expressed in the S3 segment include secretory pathway transporters ABCG2/BCRP (*ABCG2*), OAT1, OAT2 (*SLC22A7*) and OAT3 shown in blue, and reabsorptive pathway transporters URAT1 (*SLC22A12*), SLC2A9, OAT4, and OAT10, shown in purple. Additional transporters that are functionally coupled to urate transport include the sodium cotransporters SMCT1

(*SLC5A8*) and NaDC3 (*SLC13A3*) shown in red. Blue and purple arrows indicate the direction of urate transport, while black and red arrows indicate transport of counter ions. (E) Urate is also excreted through the jejunum segment of the small intestine, where urate may enter through basolateral SLC2A9 (**well established in mice, requires further confirmation in humans), and is then secreted into the lumen primarily through ABCG2 with some potential contribution from SLC17A4 (*SLC14A4*).. *Some transporters have many known endogenous substrates, with only the most relevant shown. Lac: lactate; αKG: alpha-ketoglutarate; OA: organic anion; Pi: inorganic phosphate. Endogenous OAs for the OATs may include the following: **OAT1**: medium chain fatty acids, citrulline, prostaglandin E2 prostaglandin F2, cyclic nucleotides (cAMP, cGMP), folate[47, 50, 53]; **OAT2**: cAMP, GMP, GDP, GTP, cGMP, glutamate, glutarate, α-ketoglutarate, L-ascorbate, orotic acid, trigonelline, hypoxanthine, prostaglandin E2, prostaglandin F2, estrone-3-sulfate, dehydroepiandrosterone sulphate[50, 67]; **OAT3**: cAMP, cortisol, glutarate, prostaglandin E2, prostaglandin F2α, dehydroepiandrosterone sulphate, estrone sulphate, estradiol-17β-glucuronide, taurocholate, cholate, indoxyl sulphate [47, 50, 54, 130]; **OAT4** estrone-3-sulfate, prostaglandin E2, prostaglandin F2, dehydroepiandrosterone sulphate[50, 67]; **OAT10**: lactate, nicotinate, glutathione, succinate[50, 92]. An additional endogenous OA for NPT1 and NP4 is inorganic phosphate co-transported *in cis* with Na+[57, 58]. SMCT1 mediates sodium dependent transport of monocarboxylates including short chain fatty acids, pyruvate and nicotinate[131], while NaDC3 mediates sodium coupled transport of di- and tri-carboxylates including, α-ketoglutarate, glutarate and its derivatives, citrate, succinate, and amino acid N-acetyl-L-aspartate[75].

Table 1a.

Drugs that Increase Urinary Urate Excretion

Drug	Drug Action	Interactions with Urate Transporters (Secretion Pathway)	Interactions with Urate Transporters (Reabsorption Pathway)	Effects on Serum Urate
Primary Uricosuric Agents				
Probenecid	Renal tubule reabsorption inhibitor	High affinity inhibitor of OAT1[53] and OAT3[130], lower affinity inhibitor of OAT2[67] and NPT4[58]	Lower affinity inhibitor of URAT1[132] and OAT4[67]	Decreased SU due to decreased urate reabsorption at higher doses Increased SU due to inhibition of secretory transporters
Benzbromarone *	Renal tubule reabsorption inhibitor	OAT1 inhibitor[53]	Inhibitor of SLC2A9 [133] and URAT1[134]	Decreased SU due to increased urinary excretion with decreased urate reabsorption
Sulfinpyrazone	Renal tubule reabsorption inhibitor	---	URAT1 inhibitor [132, 135]	
Lesinurad	Renal tubule reabsorption inhibitor	Minimal effects on OAT1 and OAT3[136]	Inhibitor of URAT1 and OAT4[137]	
Verinurad †	Renal tubule reabsorption inhibitor	---	URAT1 inhibitor[138]	
Dotinurad †	Renal tubule reabsorption inhibitor	---	URAT1 inhibitor[139]	
Arhalofenate †	Renal tubule reabsorption inhibitor	---	Inhibitor of URAT1 and OAT4[140]	
Agents with Secondary Uricosuric Properties				
Tranilast †	Anti-inflammatory with pleiotropic effects	Moderate inhibition of NPT1, OAT1, and OAT3, with no inhibition of ABCG2[141]	High affinity inhibition of URAT1, SLC2A9, OAT4 and OAT10[141]	Preferential inhibition of urate reabsorption results in decreased SU
Losartan	Angiotensin II receptor antagonist (antihypertensive)	ABCG2 inhibitor[86]	Inhibitor of URAT1[134] and SLC2A9[133]	
Fenofibrate	PPARα activator (cholesterol lowering)	Inhibitor of ABCG2[86, 142] and OAT3 [143]	Moderate inhibition of URAT1 [144]	
Xanthine oxidase inhibitors (with net urinary urate excretion)				
Allopurinol	Xanthine oxidase inhibitor	Substrate of ABCG2 [83, 84] and OAT2[145]	---	Decreased urate production with potential decreased urate secretion
Febuxostat	Xanthine oxidase inhibitor	ABCG2 inhibitor[86]	---	
Topiroxostat †	Xanthine oxidase inhibitor	Inhibition of ABCG2[86], OAT1 and OAT3[81]	---	

SU: serum urate; ---: No known interactions;

†: clinical trials ongoing, drugs are not currently FDA approved in the US

* Benzbromarone has been withdrawn in the US due to concerns with hepatotoxicity [146]

Table 1b.

Drugs that Decrease Urinary Urate Excretion

Drug	Drug Action	Interactions with Urate Transporters (Secretion Pathway)	Interactions with Urate Transporters (Reabsorption Pathway)	Effects on Serum Urate
Loop Diuretics				
Furosemide	NKCC2 Inhibitor (loop diuretic)	Inhibitor of ABCG2[86] and NPT4[58]; substrate of OAT3[85]	---	Direct inhibition of urate secretion with competitive inhibition of urate transport, leads to increased SU due to decreased secretion;
Bumetanide	NKCC2 Inhibitor (loop diuretic)	NPT4 inhibitor[58]; substrate of OAT1[85], OAT2[67], OAT3[85],	Substrate of OAT4[67]	Competitive inhibition of urate transport, leads to increased SU due to decreased secretion
Ethacrynic acid	NKCC2 Inhibitor (loop diuretic)	NPT4 inhibitor[58]; substrate of oAt3[85]	---	
Torasemide	NKCC2 Inhibitor (loop diuretic)	Substrate of OAT1 and OAT3[147]	Substrate of OAT4[147]	Competitive inhibition of urate transport at the basolateral membrane, and increased urate uptake at the tubule lumen lead to increased SU
Thiazide Diuretics				
Bendroflumethiazide	NCC inhibitor (diuretic)	Substrate of OAT1 and OAT3[148]	---	Competitive inhibition of urate transport, leads to increased SU due to decreased secretion Increased SU due to increased reabsorption
Chlorothiazide Cyclothiazide Trichlormethiazide	NCC Inhibitor (diuretic)	Substrate of OAT1[85]	---	
Hydrochlorothiazide	NCC Inhibitor (diuretic)	Substrate of OAT1[85]	Substrate of OAT4[48]	
SGLT2 Inhibitors				
Canagliflozin	SLGT2 inhibitor (glucosuric)	Substrate of ABCG2, but not OAT1 or OAT3 [149]	URAT1 not inhibited but is required for uricosuric effect[74]	Uricosuric effects may be related to increased tubular glucose concentration[74, 87] or increased urate secretion, however the mechanisms are currently unknown
Dapagliflozin	SLGT2 inhibitor (glucosuric)	May improve OAT3 function[85]	Increased reduction in SU without influencing urate excretion in combination with febuxostat and verinurad [150]	
Empagliflozin	SLGT2 inhibitor (glucosuric)	Substrate of ABCG2[81]; may upregulate ABCG2 expression [151]; some interactions with OAT3 and minimally with OAT1[152]	---	
Ertugliflozin	SLGT2 inhibitor (glucosuric)	Substrate of ABCG2 [81]	---	
Other Drugs				
Aspirin	NSAID	Inhibition of OAT1 and OAT3 [153]	Substrate of URAT1[153]	Low does can increase SU due to increased reabsorption and decreased secretion High doses can cause inhibition of URAT1, with SU due to decreased reabsorption

SU: serum urate; NCC: Sodium Chloride Co-transporter; NKCC2: Sodium-Potassium-Chloride Co-transporter; PPARα: peroxisome proliferator-activated receptor alpha; SGLT2: sodium glucose cotransporter 2; NSAID: nonsteroidal anti-inflammatory drug; ---: No known interactions