Invited Review Article

Renal Organic Solute Transporters: Relation to Serum Urate Disorder

Naohiko Anzai[*], Promsuk Jutabha, Hitoshi Endou

Abstract

Hyperuricemia is associated with an increased risk of developing gout, hypertension, cardiovascular diseases such as myocardial infarction and stroke, and renal diseases such as acute urate nephropathy and nephrolithiasis, despite its beneficial role, e.g. antioxidative activity. The urate transport system of the kidney is an important determinant of the serum urate level, but clarification of its molecular mechanism remains incomplete. In 2002, our group identified URAT1, a kidney-specific urate transporter, leading to the accumulation of information concerning individual molecules involved in urate transport in the kidney. In 2008, we functionally characterized facilitatory glucose transporter family member GLUT9 as a voltage-driven urate efflux transporter URATv1 and analysis of a renal hypouricemia patient with a genetic defect in URATv1/GLUT9 gene *SLC2A9* have established the main route of the urate reabsorption pathway, where urate in the urinary lumen is taken up via URAT1 and intracellular urate exits from the cell to the interstitium/blood space via GLUT9. Therapeutics designed to modify urate transport activities of these proteins might be useful in treating pathologies associated with hyperuricemia. In this review, recent findings concerning these molecules are presented.

Introduction

Urate (uric acid), the final metabolic product of purine nucleotides in humans and higher primates, is produced primarily in the liver, and it is mainly excreted by the kidneys. The serum urate concentration is determined by the balance between urate production and elimination.

Hyperuricemia can develop when urate production is greater than elimination and/or when elimination of a normal amount of produced urate is inadequate. Therefore, in humans, reduction in urate excretion by the kidney causes hyperuricemia, leading to diseases such as

Department of Pharmacology and Toxicology, Kyorin University School of Medicine, 6-20-2, Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan
[*]Corresponding author: Naohiko Anzai, M.D., Ph.D. Department of Pharmacology and Toxicology, Kyorin University School of Medicine, 6-20-2, Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan Tel. +81 4224 7551 1 ext. 3452 Fax. +81 4227 9132 1
E-mail: anzai@ks.kyorin-u.ac.jp, nhanzai@hotmail.com

cardiovascular diseases and renal failure, as well as gout and urolithiasis. Also, renal hypouricemia is considered to be caused by increased urate excretion of the kidney, and this suggests that the urate transport system of the renal proximal tubules plays an important role in the determination of the serum urate level.

In the body, urate, existing as an organic anion, needs membrane proteins called transporters to be transported into the cell across the plasma membrane. The results of classical urate transport studies using renal tubular membrane vesicles suggest the presence of transcellular urate reabsorption and secretion mechanisms in renal proximal tubular epithelial cells (bidirectional, Figure 1), but the responsible protein for these functions long remained unknown. In 2002, Enomoto *et al.* first identified the kidney-specific urate transporter URAT1 *(SLC22A12)* (Enomoto et al., 2002) through human genome database analysis using the nucleotide sequence of organic anion transporter OAT4, and demonstrated that this protein is the target of drugs that alter the urate level and causes idiopathic (familial) renal hypouricemia.
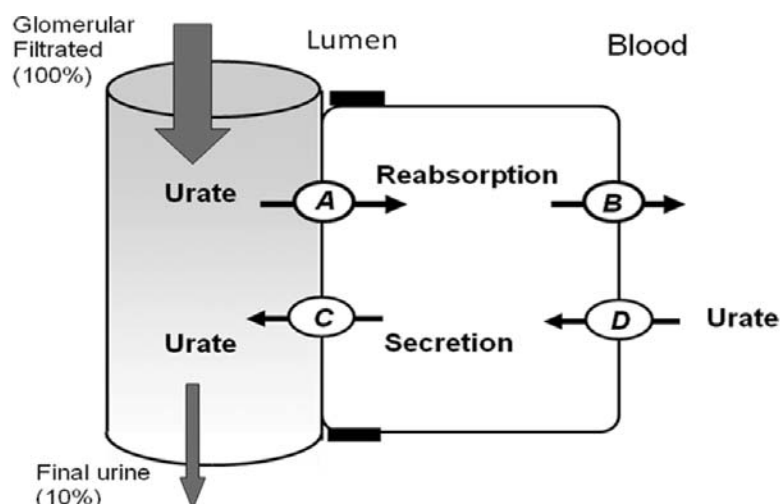

Figure 1 Model of bidirectional renal urate handling. A, influx pathway of urate in reabsorption. B, efflux pathway of urate in reabsorption. C, efflux pathway of urate in secretion. D, influx pathway of urate in secretion. Thick arrow, the flow of glomerular filtrated urate. Thin arrow, the flow of urate into final urine (Anzai et al., 2007)

The identification of URAT1 has contributed to advances in the evaluation of the roles of organic anion transporters OAT1 (SLC22A6) to OAT4 (SLC22A11) in urate transport (Anzai et al., 2007), identification of new molecules (Anzai et al., 2007; Anzai et al., 2006; Gopal et al., 2004; Gopal et al., 2007; Bahn et al., 2008; Vitart et al., 2008; Anzai et al., 2008; Woodward et al., 2009) (pOATv1, MRP4, SMCT1 and SMCT2, OAT10, URATv1/GLUT9, BCRP, etc.) and related protein (Anzai et al., 2004) (PDZK1) involved in urate transport, and the accumulation of information concerning molecules related to renal urate handling. In this review, recent findings regarding renal urate transport are presented, focusing on points that have been clarified to date.

I. Transporters related to urate reabsorption

1. Kidney-specific urate transporter URAT1 (SLC22A12)

1) Characteristics of urate transport by URAT1

The transporter encoded by the SLC22A12 gene (urate transporter 1, URAT1) is a molecule with twelve transmembrane domains that is compatible with the OAT family member, and is expressed in the apical (luminal) membrane of the renal proximal tubules. In Xenopus oocyte expression system, URAT1 shows a time-dependent increase in urate uptake with a Km 370 μM, and its urate transport is not dependent on the Na$^+$ concentration, membrane potential, or pH (Enomoto et al., 2002).

Since URAT1 interacts with various drugs that affect the serum uric acid level (probenecid, benzbromarone, sulfinpyrazone, losartan, furosemide, salicylate, etc.), these drugs have been suggested to promote urate excretion by

inhibiting its reabsorption through the luminal side of the renal proximal tubules. Moreover, mutation of the SLC22A12 gene causes hereditary renal hypouricemia, but, as no increase in urate excretion is observed in patients with this disease on the benzbromarone test (Ichida et al., 2004), benzbromarone was shown to promote urate excretion by inhibiting URAT1-mediated urate transport in vivo.

Since urate uptake is stimulated by preincubation of monocarboxylates such as lactates, nicotinates, and pyrazinoate (PZA), a metabolic product of pyrazinamides, and since nicotinate excretion was stimulated when, after the injection of nicotinate into oocytes, urate was added to their medium, URAT1 was found to be a urate transporter that mediates the exchange of these organic anions with urate (Enomoto et al., 2002). Since no decrease in urate excretion is observed in the in vivo pyrazinamide test in patients with hereditary renal hypouricemia with SLC22A12 gene mutation (Ichida et al., 2004), the inhibition of urate excretion by pyrazinamide is considered to be due to the enhancement of urate reabsorption by URAT1 rather than the inhibition of urate excretion in the renal tubules, and URAT1 was shown to be the target molecule of pyrazinamide in its induction of hyperuricemia.

2) URAT1 and drug transport

Imaoka et al. reported that mouse Urat1 (RST1) transports drugs such as para-aminohippurate (PAH), benzylpenicillin, and mycotoxin ochratoxin A (Imaoka et al., 2004). Iwanaga et al. reported that oxypurinol, the metabolite of the urate production inhibitor allopurinol, is transported in oocytes expressing human URAT1 (Km: 800 μM) and is suppressed

by benzbromarone (Iwanaka et al., 2005). We previously reported that urate transport by URAT1 is inhibited by salicylate (1 mM), which is most frequently prescribed as an antipyretic, but we have recently found that salicylate is transported by URAT1 (Ohtsu et al., 2010). Salicylate is known to have "paradoxical effects" on renal urate transport, i.e., it inhibits urate excretion in the renal tubules at low concentrations (5–10 mg/dl) but inhibits urate reabsorption in the renal tubules at high concentrations (≥15 mg/dl). Salicylate is speculated to show these paradoxical effects by serving as a transport substrate of URAT1, and is expected to contribute to the understanding of urate-related phenomena with the involvement of salicylate and some other drugs, which have long been known.

3) Other roles of URAT1

We have recently found that orotate (orotic acid), an intermediate metabolite of pyrimidine synthesis, is a substrate of URAT1 (Miura et al., 2009). Orotate is converted to UTP, which is known not only to be important in RNA synthesis, but also to be used for the synthesis of sugar nucleotides such as UDP-Glc and UDP-Gal that play an important role in the glycosylation of basement membrane collagen in renal hypertrophy of diabetic nephropathy. The uptake of orotic acid has been reported in the liver and kidney, but its molecular mechanism has not been clarified. When we studied the uptake of RI-labeled orotate using cells stably expressing URAT1, Km of orotate was 5.2 μM, which is interestingly about 100 times higher than that of urate. It is obvious that URAT1, whose genetic defect causes familial renal hypouricemia, clearly contributes to renal urate transport *in vivo* in humans, but it is considered to

have roles other than urate transport in other species in physiological condition.

2. Voltage-dependent urate efflux transporter URATv1/GLUT9

In 2007, Li *et al.* performed a genome-wide association study (GWAS) of a genetically isolated population in Sardinia, and identified GLUT9 of the glucose transporter family as a gene correlated with the serum uric acid level (Li et al., 2007). Similar results have been reported from 2 other facilities (Vitart et al., 2008; Doring et al., 2008). Particularly, Vitart et al. simultaneously reported that GLUT9 *(SLC2A9)*, originally reported as a fructose transporter, transports urate (Vitart et al., 2008). Human GLUT9 has 2 isoforms (GLUT9 and GLUT9ΔN) depending on the splicing of the intracellular part of the N-terminal, and GLUT9 and GLUT9ΔN are expressed on the basal and luminal sides, respectively, in polarized MDCK cells (Augustin et al., 2004).

After the identification of URAT1, we also noted that some orphan transporters belonging to the glucose transporter family SLC2 have a low sequence homology with organic anion transporters through searching human databases on the basis of the amino acid sequence of OAT4. We focused our attention on GLUT9 *(SLC2A9)*, the isoform expressed in the kidney, and analyzed urate transport on this molecule. As a result, we found that SLC2A9 is URATv1, the voltage-dependent urate efflux transporter, which transports urate in a voltage-dependent manner (Anzai et al., 2008). In addition, as SLC2A9 is expressed on the basolateral membrane of tubular cells in the human kidney (Augustin et al., 2004), we suggested that URATv1 *(SLC2A9)* is involved in the urate efflux toward the blood side at the same site (Anzai et

al., 2008). Recently, we confirmed the voltage-dependency of URATv1 by employing the two-electrode voltage clamp method (Anzai et al., 2010), as other facility has also reported that mouse Glut9 is involved in voltage-dependent urate transport (Bibert et al., 2009). In addition, we detected P412R mutation of *SLC2A9* in patients with renal hypouricemia with no mutation of URAT1 *(SLC22A12)* and clarified its reduced urate transport activity in such mutant by analysis using *Xenopus* oocytes. We concluded that renal hypouricemia can be induced by the mutation of not only URAT1, apical urate influx transporter, but also URATv1, basolateral urate efflux transporter Therefore, at least 2 types of renal hypouricemia, i.e., URAT1 and URATv1 types, are believed to exist (Figure 2). Another group subsequently reported the induction of renal hypouricemia by the mutation of URATv1 *(SLC2A9)* (Matsuo et al., 2008), supporting our hypothesis.

Moreover, the results of Glut9 knockout (KO) mice analysis have recently been reported, and liver-specific KO mice develop severer hyperuricemia than generalized KO mice (Preitner et al., 2009). Since mice have uricase, urate taken up by cells is rapidly degraded into allantoin. Therefore, as this group suggested, Glut9 may well be an influx transporter of urate in the liver, but this process is unlikely to be present in the human kidney lacking uricase, and further evaluation is necessary to determine whether the results in mice can be directly related to humans.
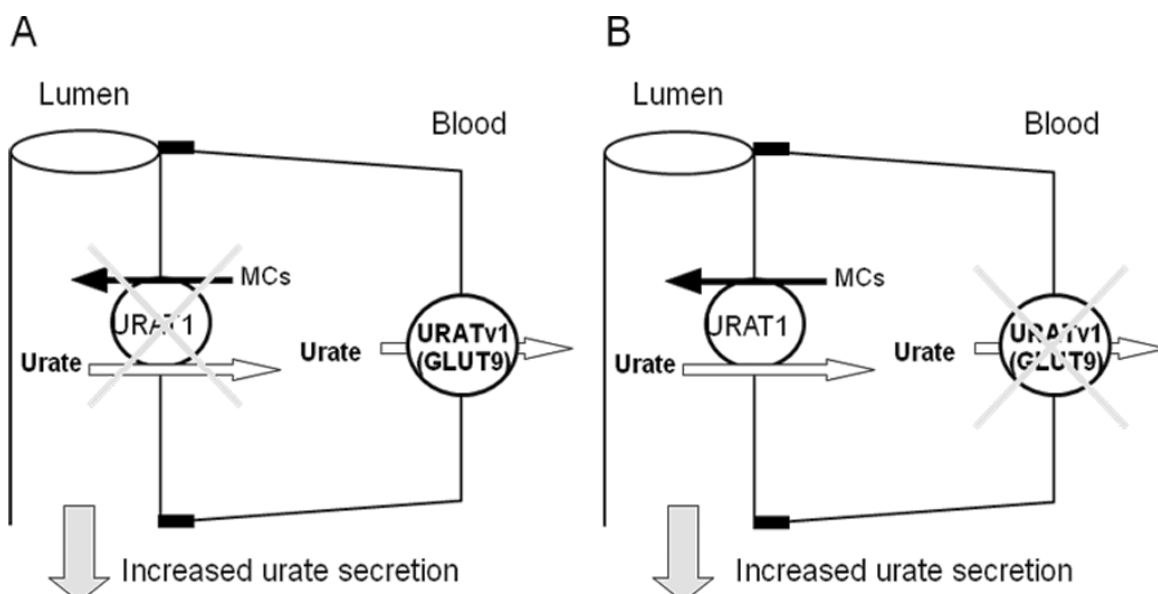

Figure 2 Novel idea concerning the onset of familial renal hypouricemia. A, URAT1 type mutation. B, URATv1 type mutation. MCs: monocarboxylates such as lactate (Anzai et al., 2008)

3. Apical organic anion transporters OAT4 and OAT10

1) OAT4 (*SLC22A11*)

It was first reported by Kimura *et al*. that OAT4 present on the luminal side transports urate in the kidney (Kimura et al., 2001). Recently, Hagos *et al*. reported that OAT4 takes up urate by exchanging OH^-, and suggested an involvement of OAT4 as a cause of hydrochlorothiazide-induced hyperuricemia, because urate uptake increases when cells are pretreated with thiazide diuretics (Hagos et al., 2007). Also, Sato *et al.* showed that urate transport by OAT4 is inhibited by angiotensin II receptor blockers (ARBs), and suggested that hyperuricemia may also be caused by ARBs through the exchange of ARBs with urate (Sato et al., 2008). So far, there has been no *in vivo* evidence that OAT4 is involved in renal urate transport, and further analysis is anticipated.

2) OAT10 (*SLC22A13*)

Bahn *et al*. analyzed the orphan transporter hORCTL3 (human organic cation transporter-like 3: OCTL1) that is highly expressed in the kidney using a *Xenopus* oocyte expression system, confirmed the transport of nicotinate, PAH and urate, and renamed OAT10 (Bahn et al., 2008). Since the IC_{50} of non-labeled urate on OAT10-mediated nicotinate transport is 759 μM, they reported that OAT10 is a low-affinity urate transporter. They suggested that OAT10 is the molecule responsible for cyclosporine A-induced hyperuricemia. There is also no evidence that OAT10 is involved in renal urate transport *in vivo*, and further studies are necessary.

4. Na⁺-dependent monocarboxylate transporter SMCT1 and SMCT2 (*SLC5A8* and *SLC5A 12*)

As mentioned above, URAT1 mediated urate transport in exchange for endogenous substrates such as lactate and nicotinate and organic anions such as PZA. The presence of a Na^+-dependent transporter that takes up these monocarboxylates in the luminal membrane of renal proximal tubules was functionally suggested. In 2004, Li *et al*. showed that it is *SLC5A8*, a protein and tumor suppressor gene inactivated by methylation in colon cancer (Li et al., 2003). The product of this *SLC5A8* gene is SMCT1, the Na^+-dependent monocarboxylate transporter, which transports monocarboxylates such as lactate and nicotinate in addition to short-chain fatty acids including butyrate and propionate in a Na^+-dependent manner (Gopal et al., 2004; Miyauchi et al., 2004). Subsequently, the product of SLC5A12 gene was also shown to mediate Na^+-dependent transport of monocarboxylates such as lactate, nicotinate, and short-chain fatty acids, and was named SMCT2 (Gopal et al., 2007).

The urate transport activity was reported to be enhanced by PZA and nicotinate in oocytes expressing both SMCT1 and URAT1 (Mount et al., 2006). This suggests that SMCT1 (and probably SMCT2) enhances renal urate uptake by taking up monocarboxylates, which are the exchange substrates for urate transport by URAT1 (Figure 3), so these molecules may also be new targets for the treatment of hyperuricemia.

II. Transporters related to urate secretion

1. Basolateral organic acid transporters OAT1, OAT2 and OAT3

1) OAT1 (*SLC22A6*)

Urate transport by OAT1, which exists in the basolateral membrane of renal proximal tubules and mediates the transport of organic anions such

as PAH in exchange for dicarboxylates in the kidney, has been analyzed by Ichida et al. using cells stably expressing OAT1 (Ichida et al., 2003). Km of urate transport by human OAT1 was 943 μM. Since OAT1 uses outward gradient of dicarboxylates as a driving force, it is considered to be the influx of urate in the basolateral membrane in the urate secretion.

Also, on the basis of the results of analysis using OAT1 knockout mice, Eraly et al. showed a decrease in urate secretion, and speculated that OAT1 contributes to the influx of urate in the basolateral membrane in the urate secretion (Eraly et al., 2008).

2) OAT2 (*SLC22A7*)

Recently, we confirmed that porcine and mouse Oat2 transports urate, and suggested that it is a new route of urate transport in the liver and kidney in these species (Anzai et al., 2006). Moreover, human OAT2 was also confirmed to transport urate employing an experimental system using *Xenopus* oocytes (Sato et al., 2010). In the human kidney, OAT2 is present in the basolateral membrane of proximal tubules, and its driving force has been reported not to be the same as OAT1 and OAT3, so that OAT2 may serve as another influx pathway on the basolateral side of renal urate secretory pathway independent of OAT1 and OAT3.

3) OAT3 (*SLC22A8*)

In the human kidney, OAT3 is present in the basolateral membrane of the proximal renal tubules, and mediates the transport of organic anions such as steroid-sulfate conjugate in exchange for dicarboxylates. Urate transport by OAT3 has been analyzed by Kimura et al. using

cells stably expressing OAT3 (Kimura et al., 2000). The Km of urate transport by human OAT3 was 2.9 mM. OAT3 is also considered to be the influx for urate in the basolateral membrane in the urate secretion.

Eraly *et al.* also observed a decrease in urate secretion on OAT3 knockout mice analysis, as in OAT1 knockout mice, and suggested that OAT3 also contributes to an influx of urate in the basolateral membrane in the urate secretion (Eraly et al., 2008).

2. Type I sodium phosphate transporters (NPTs)
1) NPT1 (*SLC17A1*)

In 2003, we identified OATv1 in the kidney of the pig, a urate secretor species, as a transporter that performs the voltage-dependent excretion of organic anions in the luminal membrane of proximal tubules. Urate is one of the transport substrates of pOATv1 (Jutabha et al., 2003). pOATv1 is considered to be the voltage-sensitive pathway identified by the classical experiment using membrane vesicles. In humans, type I sodium-dependent phosphate transporter NPT1, which belongs to the SLC17 family showed highest homology. Human NPT1 has been reported to exhibit urate transport activity (Uchino et al., 2000). Recently, Urano *et al.* showed a significant association of I269T gene polymorphism with the occurrence of gout in obese gouty males (Urano et al., 2010). Further evaluation is necessary to clarify how NPT1 contributes to urate transport in the renal tubules.

2) NPT4 (*SLC17A3*)

In the GWAS performed by Dehghan *et al.* to search for causative genes of hyperuricemia, *ABCG2* (BCRP) and *SLC17A3* (NPT4) in addition to the above-mentioned *SLC2A9*

(URATv1／GLUT9) were regarded as candidates (Dehghan et al., 2008). We recently discovered that human NPT4, which belongs to the same family as human NPT1, is not only involved in voltage-dependent organic anion transport, similarly to porcine OATv1, but also mediates low-affinity urate efflux transport (Jutabha et al., 2010).

3. ABC (ATP-binding cassette) transporters

1) Multidrug-resistance associated protein MRP4 *(ABCC4)*

MRP4 was reported to be present in the luminal membrane of the renal proximal tubules and perform ATP-dependent urate excretion (Km: 1.5 mM) (van Aubel et al., 2005). Sato *et al.* also demonstrated that urate transport by MRP4 is inhibited by ARBs such as candesartan, losartan and telmisartan, similar to urate transport by OAT4, and suggested that this may be a cause of ARB-induced hyperuricemia (Sato et al., 2008). Recently, El-Sheikh *et al.* noted that the loop diuretics furosemide and thiazide inhibit urate transport by MRP4 and that allopurinol and oxypurinol promote urate excretion, and suggested that MRP4 is the target in both furosemide- and thiazide-induced hyperuricemia and an allopurinol-induced decrease in the uric acid level (El-Sheikh et al., 2008). Whether these observations can be reproduced *in vivo* is interesting.

2) Breast cancer resistance protein BCRP *(ABCG2)*

As noted in the previous section, Dehghan *et al.* found that *ABCG2* (BCRP) and *SLC17A3* (NPT4) are the causative gene of hyperuricemia, as well as *SLC2A9* (URATv1／GLUT9) (Dehghan et al., 2008). BCRP, which belongs to ABC transporters along with MRP4, has recently been reported to transport urate (Woodward et al., 2009). Since the gene polymorphism Q141K, which is related to gout, causes a decrease in the urate excretion ability, ABCG2 was suggested to be involved in urate excretion in the luminal membrane of renal proximal tubules. Figure 3 shows urate transporter molecules of the renal tubules that have been reported to date.
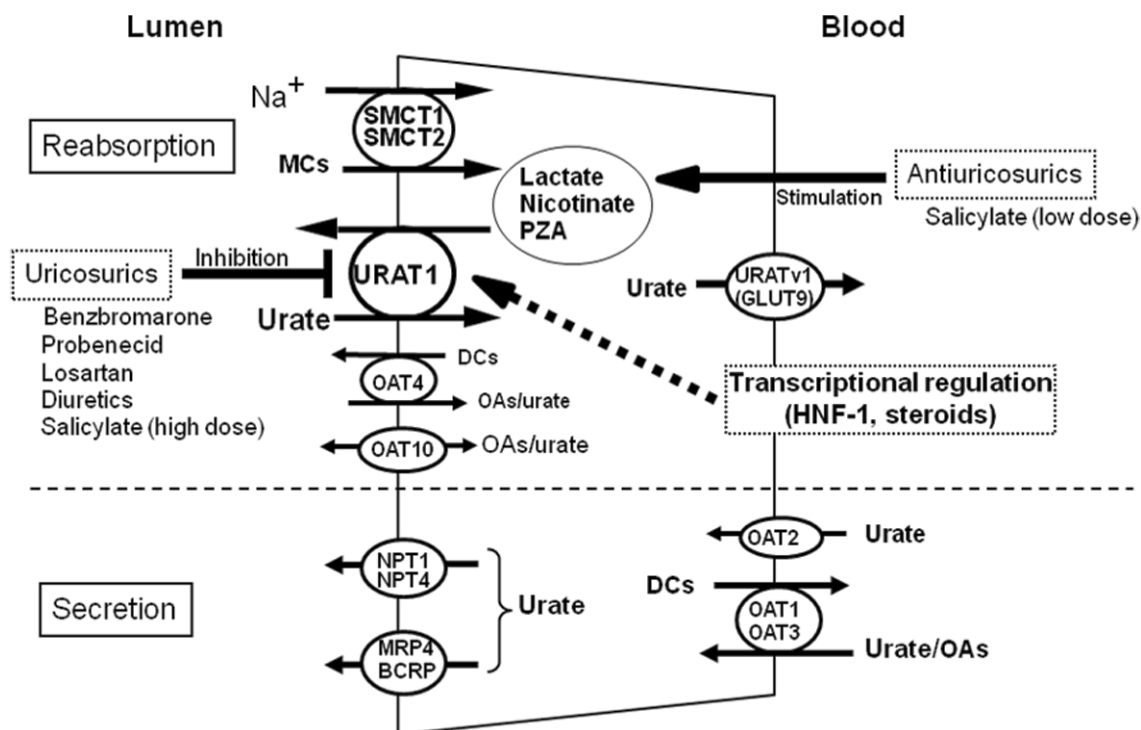
Figure 3 Model of transcellular transport of urate in renal proximal tubules. OAs: organic anions, MCs: monocarboxylates, DCs: dicarboxylates (Modified from Anzai et al., 2007).

III. Urate transportsome (urate-transporting molecular complex)

Since Ichida et al. reported that a decrease in the urate transport activity of a URAT1 mutant with a 5-base insertion in the C-terminal of the URAT1 gene detected in patients with familial renal hypouricemia (Ichida et al., 2004), we noticed that the intracellular C-terminal part of URAT1 has an amino acid sequence specific to protein-protein interactions called the PDZ motif. We suspected that the urate transport function of URAT1 is regulated by the protein-protein interactions via PDZ motif, and employed the yeast two-hybrid method to screen a human kidney cDNA library using the C-terminus of URAT1 as bait. As a result, we discovered that PDZ domain protein PDZK1 is the binding partner for urate transporter

URAT1 (Anzai et al., 2004).

Since PDZK1, whose expression was detected on the luminal side of the proximal tubules, binds with some other transporters, we speculated that membrane transport proteins are tethered by intracellular scaffolding proteins such as PDZ protein and constitute a molecular complex at the plasma membrane involved in transport, acting as a functional unit in substrate transport through the plasma membrane (membrane transportsome).

Here, we propose "urate transportsome" (the urate-transporting molecular complex) as a model of urate transport in the luminal membrane of renal proximal tubules. According to this idea, renal urate transport should be evaluated not only from the viewpoint of URAT1, but from a functional unit composed of URAT1 and other molecules

supported by protein-protein interactions mediated by PDZK1. We believe that this concept is appropriate to consider the physiological function of urate transport in the kidney. For example, we can apply this idea to the link between SMCTs and URAT1 because we have already confirmed by a yeast two-hybrid method that Na+-dependent monocarboxylate transporters SMCT1 and SMCT2 (SMCTs) bind with PDZK1 (Srivastava et al., 2009). We propose that SMCTs enhance urate transport via URAT1 by supplying its exchange substrates such as lactate by coupling two transporters by PDZK1. This may be a physiological role of "urate transportsome" (Figure 4). Indeed, Thangaraju et al. reported an increase in urinary urate excretion and a significant decrease in the serum urate level in addition to a decrease in the serum lactate level due to increased urinary lactate excretion in c/ebp δ

knockout mice, in which the expression of both SMCT1 and SMCT2 in the kidney is lost, indicating the physiologic linkage of URAT1 and SMCT1 and SMCT2 via lactate (Thangaraju et al., 2006) so intracellular scaffolding proteins such as PDZK1 may provide a background for the relationship between them. Particularly, urate transportsome including SMCTs are expected to lead to the clarification of an Na+-dependent urate transport system that explains changes in the serum urate level associated with alterations in the volume of extracellular fluid, a phenomenon known for decades and hyperuricemia in the patients with metabolic syndrome, one of the famous complication with this syndrome, induced by upregulation of proximal tubular Na+ reabsorption due to hyperinsulinemia caused by insulin resistance (Anzai et al., 2007).
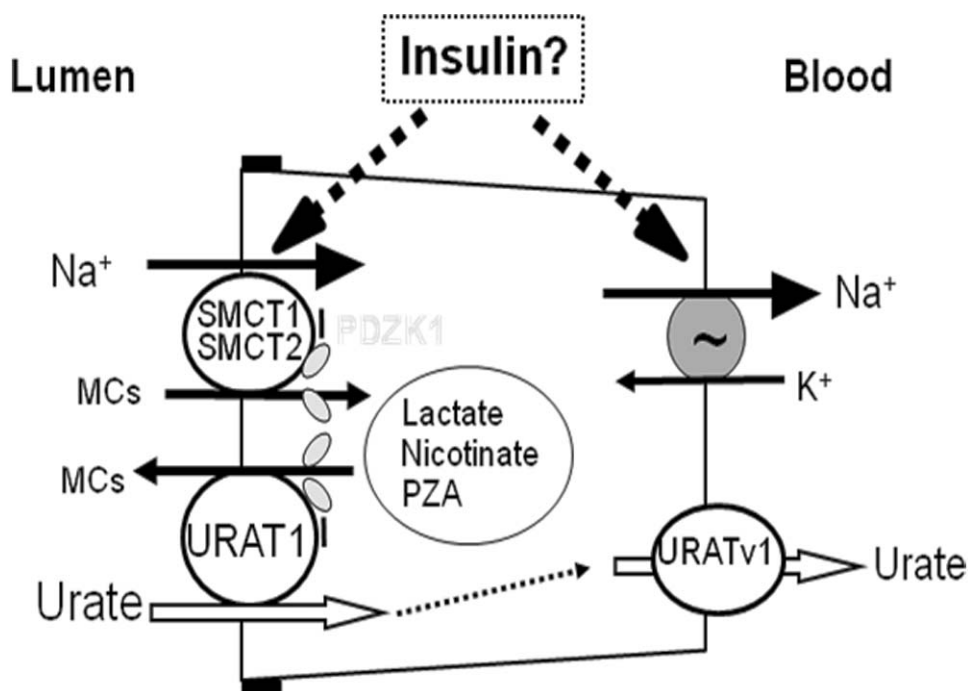

Figure 4 Model of urate transportsome in renal proximal tubules. UA: uric acid (urate), MCs: monocarboxylates. Luminal entrance of urate is enhanced by the parallel Na$^+$-coupled uptake of lactate via SMCTs (SMCT1 and SMCT2). (Anzai et al., 2007)

Future perspectives

Identification of the urate transporter URAT1 in 2002 stimulated clarification of the urate transport system of the renal proximal tubules, leading to the proposal of the concept of the "urate transportsome". However, among the molecules constituting the urate transportsome, their physiological and pathophysiological roles have not been determined except for URAT1 and URATv1, in which mutations have been demonstrated in patients with renal hypouricemia. Thus, at present, we must also continue to evaluate known molecules and search for unknown ones while evaluating the transportsome as a possible answer.

Also, the recent GWA study reported 5 new genes related to the serum urate level, and included PDZK1 (Kplz et al., 2009) as well as transporters of SLC17A1 (NPT1), SLC22A11 (OAT4), SLC22A12 (URAT1), and SLC16A9 (MCT9) in addition to SLC2A9 (URATv1/ GLUT9) and ABCG2 (BCRP), which had been known. Therefore, the understanding of renal urate transport must be advanced further through the introduction of the concept of the urate transportsome.

Acknowledgements

References

Anzai N, Ichida K, Jutabha P, et al. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. *J Biol Chem* 2008; 283: 26834-26838.

Anzai N, Jutabha P, Kaneko S, et al. Voltage-dependent urate transport on a urate efflux transporter URATv1 expressed in *Xenopus* oocytes. *J Pharmacol Sci* 2010; 112: 202.

Anzai N, Kanai Y, Endou H. Organic anion transporter family: current knowledge. *J Pharmacol Sci* 2006; 100: 411-426.

Anzai, N, Kanai Y, Endou H. New insights into renal transport of urate. *Curr Opin Rheumatol* 2007; 19: 151-157.

Anzai, N, Miyazaki H, Noshiro R, et al. The multivalent PDZ domain-containing protein PDZK1 regulates transport activity of renal urate-anion exchanger URAT1 via its C terminus. *J Biol Chem* 2004; 279: 45942-45950.

Augustin R, Carayannopoulos MO, Dowd LO, et al. Identification and characterization of human glucose transporter-like protein-9 (GLUT9): alternative splicing alters trafficking. *J Biol Chem* 2004; 279: 16229-16236.

Bahn A, Hagos Y, Reuter S, et al. Identification of a new urate and high affinity nicotinate transporter, hOAT10 (SLC22A13). *J Biol Chem* 2008; 283: 16332-16341.

Bibert S, Hess SK, Firsov D, et al. Mouse GLUT9: evidences for a urate uniporter. *Am J Physiol Renal Physiol* 2009; 297: F612-619.

Dehghan A, Köttgen A, Yang Q, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet* 2008; 372: 1953-1961.

Döring A, Gieger C, Mehta D, et al. SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* 2008; 40: 430-436.

El-Sheikh AA, Van den Heuvel JJ, Koenderink JB, et al. Effect of hypouricaemic and hyperuricaemic drugs on the renal urate efflux transporter, multidrug resistance protein 4. *Br J Pharmacol* 2008; 155: 1066-1075.

Enomoto A, Kimura H, =Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature* 2002; 417: 447-452.

Eraly SA, Vallon V, Rieg T, et al. Multiple organic anion transporters contribute to net renal excretion of uric acid. *Physiol Genomics* 2008; 33: 180-192.

Gopal E, Umapathy NS, Martin PM, et al. Cloning and functional characterization of human SMCT2 (SLC5A12) and expression pattern of the transporter in kidney. *Biochim Biophys Acta* 2007; 1768: 2690-2697.

Gopal E, Fei YJ, Sugawara M, et al. Expression of slc5a8 in kidney and its role in Na(+)-coupled transport of lactate. *J Biol Chem* 2004; 279: 44522-44532.

Hagos Y, Stein D, Ugele B, et al. Human renal organic anion transporter 4 operates as an asymmetric urate transporter. *J Am Soc Nephrol* 2007; 18: 430-439.

Ichida K, Hosoyamada M, Hisatome I, et al. Clinical and molecular analysis of patients with renal hypouricemia in Japan-influence of URAT1 gene on urinary urate excretion. *J Am Soc Nephrol* 2004; 15: 164-173.

Ichida K, Hosoyamada M, Kimura H, et al. Urate transport via human PAH transporter hOAT1 and its gene structure. *Kidney Int* 2003; 63: 143-155.

Imaoka T, Kusuhara H, Adachi-Akahane S, et al. The renal-specific transporter mediates facilitative transport of organic anions at the brush border membrane of mouse renal tubules. *J Am Soc Nephrol* 2004; 15: 2012-2022.

Iwanaga T, Kobayashi D, Hirayama M, et al. Involvement of uric acid transporter in increased renal clearance of the xanthine oxidase inhibitor oxypurinol induced by a uricosuric agent, benzbromarone. *Drug Metab Dispos* 2005; 33: 1791-1795.

Jutabha P, Anzai N, Kitamura K, et al. Mutations in renal drug efflux transporter hOATv1 cause hyperuricemia. *Endocrine J* 2010; 57: S563.

Jutabha P, Kanai Y, Hosoyamada H, et al. Identification of a novel voltage-driven organic anion transporter present at apical membrane of renal proximal tubule. *J Biol Chem* 2003; 278: 27930-27938.

Kimura H, Ichida K, Hosoyamada M, et al. Analysis of uric acid transport via hOAT3. *Gout and Nucleic Acid Metabolism (Japanese)* 2000; 24: 115-121.

Kimura H, Ichida K, Hosoyamada M, et al. Urate transport via hOAT4. *Gout and Nucleic Acid Metabolism (Japanese)* 2001; 25: 113–120.

Kolz M, Johnson T, Sanna S, et al. Meta-Analysis of 28,141 individuals identifies common-variants within five new loci that influence uric acid concentrations. *Plos Genet* 2009; 5: 1–10.

Li H, Myeroff L, Smiraglia D, et al. SLC5A8, a sodium transporter, is a tumor suppressor gene silenced by methylation in human colon aberrant crypt foci and cancers. *Proc Natl Acad Sci USA* 2003; 100: 8412–8417.

Li S, Sanna S, Maschio A, et al. The GLUT9 gene is associated with serum uric acid levels in Sardinia and Chianti cohorts. *PLos Genet* 2007; 3: e194.

Matsuo H, Chiba T, Nagamori S, et al. Mutations in glucose transporter 9 gene SLC2A9 cause renal hypouricemia. *Am J Hum Genet* 2008; 83: 744–751.

Miura D, Anzai N, Tsukada A, et al. *J Pharmacol Sci* 2009; 109: 134P.

Miyauchi S, Gopal E, Fei YJ, et al. Functional identification of SLC5A8, a tumor suppressor down-regulated in colon cancer, as a Na(+)-coupled transporter for short-chain fatty acids. *J Biol Chem* 2004; 279: 13293–13296.

Mount DB, Kwon CY, Zandi-Nejad K. Renal urate transport. Rheum. *Dis Clin North Am* 2006; 32: 313–331.

Ohtsu N, Anzai N, Fukutomi T, et al. Human renal urate transporter URAT1 mediates the transport of salicylate. *Nippon Jinzo Gakkai Shi* (Japanese) 2010 in press.

Preitner F, Bonny O, Laverrière A, et al. Glut9 is a major regulator of urate homeostasis and its genetic inactivation induces hyperuricosuria and urate nephropathy. *Proc Natl Acad Sci U S A* 2009; 106: 15501–15506.

Sato M, Iwanaga T, Mamada H, et al. Involvement of uric acid transporters in alteration of serum uric acid level by angiotensin II receptor blockers. *Pharm Res* 2008; 25: 639–646.

Sato M, Mamada H, Anzai N, et al. Renal secretion of uric acid by organic anion transporter 2 (OAT2/SLC22A7) in human. *Biol Pharm Bull* 2010; 33: 498–503.

Srivastava S, Anzai N, Miyauchi S, et al. Identification of the multivalent PDZ protein PDZK1 as a binding partner of sodium-coupled monocarboxylate transporter SMCT1 (SLC5A8) and SMCT2 (SLC5A12) by yeast two-hybrid assay. *J Pharmacol Sci* 2009; 109: 68P.

Thangaraju M, Ananth S, Martin PM, et al. c/ebpdelta Null mouse as a model for the double knock-out of slc5a8 and slc5a12 in kidney. *J Biol Chem* 2006; 281: 26769–26773.

Uchino H, Tamai I, Yamashita K, et al. p-aminohippuric acid transport at renal apical membrane mediated by human inorganic phosphate transporter NPT1. *Biochem Biophys Res Commun* 2000; 270: 254–259.

Urano W, Taniguchi A, Anzai N, et al. Sodium-dependent phosphate cotransporter type 1 (NPT1) sequence polymorphisms in male patients with gout. *Ann Rheum Dis* 2010; in press.

Van Aubel, RA, Smeets PH, van den Heuvel JJ, et al. Human organic anion transporter MRP4 （ABCC4） is an efflux pump for the purine end metabolite urate with multiple allosteric substrate binding sites. *Am J Physiol Renal Physiol* 2005; 288: F327–233.

Vitart V, Rudan I, Hayward C, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* 2008; 40: 437–442.

Woodward OM, Köttgen A, Coresh J, et al. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci USA* 2009; 106: 10338–10342.