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The Erythrocyte Urea Transporter UT-B

Serena M. Bagnasco
Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland 20187, USA

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Abstract. During the past decade significant progress has been made in our understanding of the role played by urea transporters in the production of concentrated urine by the kidney. Urea transporters have been cloned and characterized in a wide range of species. The genomic organization of the two major families of mammalian urea transporters, UT-A and UT-B, has been defined, providing new insight into the mechanisms that regulate their expression and function in physiological and pathological conditions. Beside the kidney, the presence of urea transporters has been documented in a variety of tissues, where their role is not fully known. Recently, mice with targeted deletion of the major urea transporters have been generated, which have shown variable impairment of urine concentrating ability, and have helped to clarify the physiological contribution of individual transporters to this process. This review focuses on the erythrocyte urea transporter UT-B.

Key words: Urea Transport — Kidney — Erythrocyte — Vasa recta — Colon — Urine concentration

Introduction

Urea is a small, water-soluble, organic molecule with a low permeability through lipid bilayers, which enables it to slowly cross cell membranes by passive diffusion. The existence of specific urea transporters is now well established, and several urea transporters have now been identified in mammals and other organisms, where they serve different purposes (reviewed in Bagnasco, 2005). In the mammalian kidney, high concentrations of urea in the inner medulla contribute to the cortico-medullary osmotic gradient required for proper concentration of urine. Maintaining high levels of urea in the medullary interstitium depends on the balance between urea excretion and reabsorption in the renal tubular segments, and on minimizing escape of urea from the medulla through the ascending vasa recta. This would not be possible if urea transfer across cells was solely determined by passive diffusion during the fast transit in the lumen of tubules and vasa recta. Earlier studies on water and urea transport in red blood cells showed that urea permeability across the erythrocyte was considerably higher (1.2×10^{-3} cm/s) compared to lipid bilayers (4×10^{-6} cm/s), that thiourea and other urea analogues competed with urea for transport, and could be inhibited by phloretin and mercurial compounds, which did not affect water permeability (Brahm, 1983; Mayrand and Levitt, 1983). These findings pointed to the presence of a specific urea transporter that could mediate rapid transfer of urea across the erythrocyte membrane. Based on these observations, a physiological role for urea facilitated diffusion was proposed by Macey and Yousef, who suggested that rapid transport of urea in erythrocytes would preserve their viability in the face of shifting extracellular osmolarity while passing through the medullary vasa recta, and could limit dissipation of the osmotic gradient in the renal medulla, by reducing the amount of urea carried by erythrocytes from the blood exiting the renal medulla into the systemic circulation (Macey & Yousef, 1988).

Structure-Function Relationship

The urea transporter expressed in human erythrocytes, HUT11, was first cloned by Olives et al. in 1994 from a human bone marrow cells library (GenBank ID L36121) (Olives et al., 1994). Following a proposal for a systematic nomenclature of urea transporters by Sands et al. (Sands, Timmer & Gunn, 1997), the erythrocyte transporter is now usually referred to as UT-B urea transporter. Based on

Correspondence to: S.M. Bagnasco; email: sbagnas1@jhmi.edu

sequencing of the genomic DNA of numerous blood donors, the L36121 cDNA, which encodes a predicted 391-aminoacid peptide, was later found to represent a mutated form of the true transporter (GenBank ID Y19039), which encodes a 389-amino-acid peptide (Sidoux-Walter et al., 1999). The presence of two UT-B transcripts of 4.4 and 2 kb has been detected by Northern analysis in human tissue, and their difference in size is thought to derive from use of alternative polyadenylation sites (Lucien et al., 1998). Although cDNA sequences of different length have been cloned for the human UT-B transporter, they appear to encode a single protein. The amino-acid sequence of the erythrocyte transporter shows more than 60% identity with the UT-A2 urea transporter, but the UT-B peptide has a distinctive "ALE" motif that has not been found in other urea transporters. According to the hydrophilicity profiles, the UT-B and UT-A2 proteins show similar topology, with ten trans-membrane domains, intracellular amino- and carboxy-terminals, and an extracellular loop bearing a consensus site for N-glycosylation (Olives et al., 1994).

The number of copies of UT-B has been estimated to be 14,000 per red blood cell (Masouredis et al., 1980). In a comprehensive review on urea transporters, Sands et al. estimated a high turnover rate of UT-B on the erythrocyte membrane, and suggested that this transporter may behave like a channel in physiological conditions (Sands et al., 1997).

There is no experimental evidence so far for short-term regulation of the UT-B transport activity in response to specific signaling pathways. High-stringency search for regulatory motifs in the UT-B polypeptide (http://scansite.mit.edu) shows the presence of a consensus site for tyrosine phosphorylation by FGR kinase in the human protein (Protein ID: AAX20112, Y282) and in the mouse protein (Protein ID: AAL47138, Y277), but not in rat UT-B (Protein ID: NP 062219). The FGR kinase is a member of the SRC kinase family, highly expressed in bone marrow and spleen (http://genecards.weitzman.ac). With less stringent criteria, the UT-B peptide shows potential consensus sites for Abl kinase (human, mouse, and rat), PKC kinase (rat and mouse), and ATM kinase in human UT-B. It is not clear whether the activity of the UT-B transporter might be affected by signals mediated by any of these kinases in physiological conditions.

The predicted molecular weight of the UT-B peptide is 42.5 kDa, with a single extracellular glycosylation site (Asn–211). In *in-vitro* translation assay the human UT-B cDNA gives rise to a 36 kDa protein, which, in the presence of microsomes, appears as a 40 kDa band (Olives et al., 1995). In human erythrocyte membranes, the UT-B protein shows a molecular size range of 45–65 kDa, which decreases to about 32–36 kDa after treatment with N-glycosidase F, consistent with its physiological expression as a glycoprotein (Timmer et al., 1999; Inoue et al., 2004). Lucien et al. used site-directed mutagenesis to delete the N-glycosylation site of human UT-B, and showed that, when expressed in *Xenopus* oocytes, lack of glycosylation in the mutant protein did not affect uptake of urea, compared to wild-type UT-B (Lucien et al., 2002). This observation indicates that glycosylation of UT-B may not be essential for its activity as urea transporter. In the same study, deletion of the first 59 amino-acids from the N-terminus, and combined mutation of Cys-25 and Cys-30 prevented membrane localization and urea uptake in oocytes, suggesting that these may be important domains for membrane targeting (Lucien et al., 2002). These findings have not been tested in other models of heterologous expression.

UTB transporter protein corresponds to the Kidd erythrocyte antigen (Olives et al., 1995), of which two alleles are known: Jk(a)/Jk(b). The Jk(a)/Jk(b) polymorphism was found to be caused by a transition (G838A), resulting in an Asp280 to Asn280 amino acid substitution, which does not result in different rates of urea uptake for the JK(a) and JK(b) protein, and does not affect their membrane localization when expressed in oocytes (Lucien et al., 2002). The UT-B protein in human erythrocytes also carries the blood ABO antigens (Lucien et al., 2002).

Rare individuals lacking the Kidd a and b antigens [JK(a-b-) or JK_{null}] have been identified, whose erythocytes show slower lysis in 2 M urea compared with those of JK-positive individuals, and were found to have significant reduction of urea permeability (Fröhlich et al., 1991). However, the permeability of JK_{null} erythrocytes to water was unaltered, indicating that the Kidd/UT-B protein mediates urea transport but not water transport in erythrocytes under physiological conditions. Such conclusion is supported by analysis of urea and water transport in oocytes expressing variable amounts of the UT-B protein, which showed that, with expression levels comparable to those estimated for the human erythrocyte membrane, the UT-B protein does not confer water permeability (Sidoux-Walter et al., 1999). The major pathway for transport of water in erythrocytes is through the water channel Aquaporin-1 (AQP1), and the red blood cells of individuals lacking the Colton blood antigen that carries AQP1 shrink at a slower rate in hypertonic solution, when compared to erythrocytes from control and Jk_{null} individuals, which have normal expression of AQP1 (Sidoux-Walter et al., 1999). In addition to defective urea transport in red blood cells, relatively mild impairment of urinary concentrating ability was found in patients with a JK(a-b-) blood type with otherwise normal renal function determined by 24 hour creatinine clearance

(Sands et al., 1992), indicating that absence of the erythrocyte urea transporter results in limited renal urea recycling and decrease in maximal concentrating ability.

The cloning of the Slc14A1 gene, which encodes the UT-B urea transporter/Kidd blood group protein, allowed Lucien et al. to clarify the molecular basis for the Jk_{null} phenotype (Lucien et al., 1998). The Kidd/UT-B gene includes 11 exons, spanning about 30 kb of genomic DNA on chromosome 18 (Olives et al., 1995; Lucien et al., 1998), where it is found adjacent to the larger Slc14A2 gene, which encodes multiple UT-A transporter isoforms (Bagnasco et al., 2001; Bagnasco, 2003). The translated DNA sequence from exon 4 to exon 11 was found to be mutated in two Jk_{null} individuals, one lacking exon 6 and the other lacking exon 7, both resulting in a truncated protein, incapable of mediating urea transport when expressed in oocytes (Lucien et al., 1998).

Table 1. UT-B urea transporter/Kidd blood group expression in mammalian extra-renal tissues

Tissue	Species	Reference
Brain	Rat	Couriaud, Ripoche & Rousselet, 1996
		Tsukaguchi et al., 1997
		Berger, Tsukaguchi & Hediger, 1998
		Hu et al., 2000
		Timmer et al., 2001
		Trinh-Trang-Tan et al., 2003
		Lucien et al., 2005
Testis	Rat	Tsukaguchi et al., 1997
		Timmer et al., 2001
		Fenton et al., 2002
Spleen	Rat	Promeneur et al., 1996
		Tsukaguchi et al., 1997
Intestine	Rat	Timmer et al., 2001
	Human	Inoue et al., 2004
	Ovine	Marini et al., 2004
	Rat	Inoue et al., 2005
	Rat	Lucien et al., 2005
	Bovine	Stewart et al., 2005
Ureter and bladder	Rat	Spector et al., 2004
	Rat	Lucien et al., 2005

Regulation of the UT-B/Kidd Urea Transporter Expression

The long-term regulation of urea transporter expression has been mostly studied in the kidney. UT-B is expressed in the non-fenestrated endothelial cells of the descending vasa recta (Timmer et al., 2001), with a subcellular distribution in both apical and basolateral membranes (Lim et al., 2005). Kim et al. identified expression of the UT-B protein in rat glomeruli, which we have also noticed in human kidney (Bagnasco, unpublished observation). In mouse kidney, Jung et al. reported immunolocalization of the UT-B protein in the proximal tubule (Jung et al., 2003). The UT-B protein is detected in the endothelial cells of descending vasa recta of rat fetuses, before appearance of any other urea transporter, and increases after birth (Kim et al., 2001). While increased tonicity in the medulla, driven by activity of the NKCC2 transporter, is likely to stimulate the tonicity-responsive transcription of the UT-A transporter gene in the post-natal kidney (Nakayama et al., 2000), the factors involved in the developmental regulation of UT-B expression have not been elucidated.

Presence of the UT-B/Kidd mRNA and protein has also been documented in other tissues beside the kidney, listed in Table 1. Although several studies have examined changes in the abundance of UT-B in the kidney and in some extra-renal sites in different conditions, the involvement of transcriptional and post-transcriptional regulatory mechanisms of UT-B expression have not been investigated to the same extent as for the UT-A transporter, and remains undefined.

The effect of changes in hydration on the expression of UT-B has not been clearly established. Water deprivation for two days did not affect UT-B protein abundance in rat renal medulla, and in rat brain (Trinh-Trang-Tan et al., 2003), and UT-B was unchanged in rat bladder after two days of water deprivation, and water load (Spector et al., 2004). However, in a recent study, increased intensity of UT-B endothelial staining of rat descending vasa recta was observed after three days of water deprivation, and was associated with increased expression of UT-A3 and decreased expression of UT-A1 in the IMCD tubules of water-deprived rats, whereas less intense UT-B staining was noted in water-loaded rats (Lim et al., 2005). Rats treated with furosemide for 6 days exhibited decreased abundance of UT-B in inner medulla (Trinh-Trang-Tan et al., 2002). In the same study, a six-day infusion of the V2 vasopressin receptor agonist [Deamino-Cys1,D-Arg8] vasopressin (dDAVP) resulted in significant decrease in the abundance of UT-B protein in rat inner medulla (Trinh-Trang-Tan et al., 2002). It is not clear if shorter-term administration of furosemide and dDAVP would produce similar effects.

Protein intake and urea load appear to affect abundance of the UT-B protein, suggesting that expression of urea transporters might be regulated to save urea and recycle nitrogen with low-protein diet or malnutrition, or to eliminate excess urea generated by protein catabolism. The presence of urea transporters in the intestine could play a role in modulating the transfer of urea from the blood to the intestinal lumen and its degradation by intestinal bacterial flora into CO_2 and NH_3, which could re-enter the systemic circulation and salvage urea

nitrogen. We showed that a low-protein diet regimen for 12 days is associated with significant increase of the UT-B protein in the outer medulla of rat kidneys, whereas a high-protein diet produces the opposite effect (Inoue et al., 2005). In rat colon, we noticed a decrease in UT-B expression with low-protein diet (Inoue et al., 2005). With reduced protein intake, up-regulated expression of UT-B in the outer medulla would likely increase urea recycling and conserve urea, and, if we assume that urea is transferred from the blood into the intestinal tract, down-regulation of intestinal UT-B would limit loss of urea and also contribute to urea and nitrogen conservation. In the ureter and in the bladder, no significant changes in UT-B expression were found with low and high protein regimen (Spector et al., 2004). In rat fed 20% urea, the urea concentration is increased in outer and inner medulla, and two studies have shown up-regulation of UT-B expression in the outer medulla (Inoue et al., 2005; Kim et al., 2005). Kim et al. speculated that increase in UT-B and UT-A2 protein abundance observed in urea-fed rats may be induced with high medullary interstitial concentration of urea, and promote increased urea recycling. However, such possibility does not fit with the observation of reduced UT-B expression in the medulla of rats fed high-protein diet (Inoue et al., 2005), a condition also associated with high medullary concentration of urea (Fenton et al., 2005). Thus, the regulatory mechanisms involved in such conditions are still unclear and may include possible tissue-specific factors.

Significant reduction in brain UT-B expression has been reported in rats after sub-total nephrectomy to induce uremia (Hu et al., 2000), associated with increased expression of AQP4 and AQP9 (Trinh-Trang-Tan, Cartron & Bankir, 2005), which might be a factor in the development of neurological symptoms attributed to brain swelling during dialysis disequilibrium syndrome, a complication of acute hemodialytic treatment. The presence of UT-B in human brain has not been demonstrated.

Potassium depletion has been recently found to result in significant decrease in the expression of the UT-A and UT-B transporters in mice, and in changes of the intracellular distribution of UT-B, which shifts from the predominant membrane localization seen in controls, to the cytoplasm in potassium-depleted animals (Jung et al., 2003). Such variation in the intracellular localization of UT-B has not been reported previously, and it is not known if it occurs in other conditions.

Other animal studies have shown decrease in the expression of UT-B and UT-A transporters with aging (Combet et al., 2003; Trinh-Trang-Tan et al., 2003), after long-term treatment with the calcineurin inhibitor cyclosporine (Lim et al., 2004), with lithium administration (Klein et al., 2002), and during ureteral obstruction (Li et al., 2004). Recently, mice with selective deletion of individual UT-A and UT-B urea transporters have been generated, all showing a variable degree of decreased urea excretion and impairment in their ability to concentrate urine, supporting an important physiological role for these transporters for normal renal function (Yang et al., 2002; Fenton et al., 2004; Uchida et al., 2005). Studies in mice lacking UT-B suggest that its major contribution is to promote urea recycling into the vascular compartment of the inner medulla (Yang & Bankir, 2005). The UT-B -/- mice have elevated plasma urea and decreased urea excretion, and are markedly unable to adapt to high urea loads such as during high protein intake (Bankir, Chen & Yang, 2004). Interestingly, the UT-B -/- mice show upregulation of the UT-A2 urea transporter (Klein et al., 2004), which may be an adaptive mechanism to sustain urea recycling in the outer medulla. It is not known if JK_{null} individuals, who display reduced ability to concentrate urine (Sands et al., 1992), are less able to tolerate high urea/protein loads or pharmacological treatments that may depress urea transporter expression, and it is not clear if lack of the UT-B/Kidd protein is associated with upregulation of the UT-A transporter in humans. Similar to UT-B knock-out mice, mice with combined deficit of UT-A1 and UT-A3 transporters in the IMCD renal tubule are also unable to adapt to increased protein and urea loads (Fenton et al., 2005). Recently, mice lacking the UT-A2 transporter have also been described, which maintain their ability to concentrate urine in normal conditions and after dehydration; their urine osmolality is lower than in wild-type mice only when dehydration is combined with low-protein diet and limited supply of urea (Uchida et al., 2005). The UT-A2-/- mice show a mild increase in UT-B expression compared to wild-type mice, probably representing an adaptive response. Overall, the UT-A2-/- mice show the mildest alteration in renal function among UT knock-out mouse models characterized so far, which suggests that the UT-B transporter may contribute more significantly than UT-A2 to recycling of urea in the outer medulla, and to the whole urine concentration process.

Further investigations of mice with selective deficits of the UT-B urea transporter may help clarify its regulation and its significance in the kidney and in extra-renal tissues under pathologic conditions.

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