

Renal Transport of Urate

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All urate transport occurs across the renal epithelial cells of the proximal tubule. Most of the filtered urate is reabsorbed in the S1 segment of the early proximal tubule. This is followed by tubular secretion in the S2 segment of the proximal tubule and approximately 50% of the filtered urate flows back into the tubular lumen. Most of the secreted urate undergoes postsecretory reabsorption that occurs predominantly in the last S3 segment of the proximal tubule. Recently, four proteins that transport urate have been identified at the molecular level. These proteins are an electrogenic urate uniporter, urate transporter/channel (UAT), two members of the organic anion transporter (OAT) family, OAT1 and OAT3, and a protein with some homology to OAT4, designated URAT1.

Key Words: Uric acid, Urate transporters, Proximal tubule

Introduction

Uric acid stones can be formed under hyperuricemic condition and kidney handles uric acid by complex processes. Recently, new insights have been gained into some of the specific channels/transporters responsible for uric acid handling, and abnormalities of these proteins, which may play a role in the pathogenesis of uric acid nephrolithiasis^{1, 2)}.

Under normal condition, less than 5% of circulating urate is bound to plasma proteins and thus urate is freely filtered in the renal glomerulus, with its concentration in the ultrafiltrate almost equaling that in plasma. As urate excretion approximates 5-10% of its filtered load in adult humans, the filtered urate is almost reabsorbed³⁾.

All urate transport occurs across the renal epithelial cells of the proximal tubule (Fig. 1). Since transport is bi-directional, urate anions must be capable of moving both from lumen to blood and from blood to lumen. Most of the filtered urate is re-

absorbed in the S1 segment of early proximal tubule, which is followed by tubular secretion in the S2 segment of the proximal tubule, and ultimately about 50% of the filtered urate flows back into the tubular lumen. Most of the secreted urate undergoes postsecretory reabsorption that occurs predominantly in the S3 segment of the proximal tubule⁴⁾.

Based on the studies of membrane vesicles derived from the renal cortex, two mechanisms of urate transport have been described; an electroneutral urate/anion exchanger and an electrogenic urate

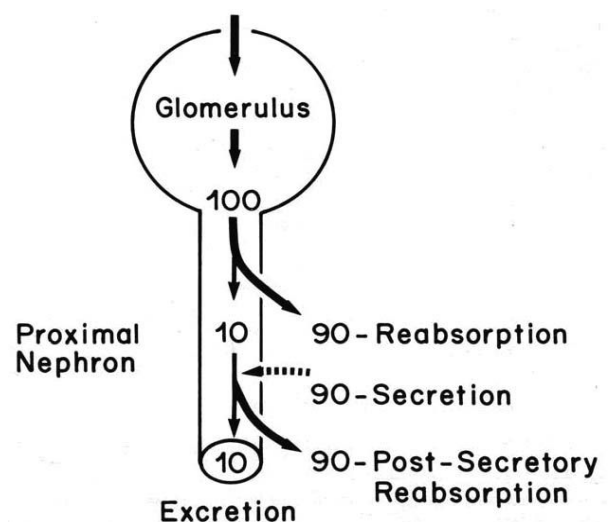


Fig. 1. A model of urate transport in the human kidney. Numbers indicate percentage of total filtered urate.

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uniporter^{5, 6)}. Recently, four proteins that transport urate have been identified at the molecular level. These include an electrogenic urate uniporter, urate transporter/channel (UAT), two members of the organic anion transporter (OAT) family, OAT1 and OAT3, and a protein with some homology to OAT4, designated URAT1.

Urate transporter/channel (UAT)

This channel is highly selective for urate as compared to the inorganic ions potassium, cesium, calcium, chloride and sulfate⁷⁾. Xanthine and adenosine block the activity of UAT channel. Interaction of glucose with UAT may be responsible for the alterations in plasma urate concentration as observed in diabetes mellitus⁸⁾.

The human UAT gene is mapped to the short arm of human chromosome 17 and human UAT has been immunocytochemically detected in apical membranes of mature renal proximal tubule. UAT may play an important role in urate transport and secretion into the tubular lumen⁹⁾.

Organic anion transporter 1 (OAT1)

Human OAT1 is mapped to chromosome 11q13.1. In the kidneys, it is localized in the basolateral membrane of proximal convoluted tubule cells with expression more predominant in the S2 than in S1 and S3 segments. Insofar as OAT1 transports urate and resides in the basolateral membrane of proximal tubule cells, it has also been proposed to play a role in the peritubular uptake of urate, which is the first step required for urate secretion (Fig. 2). Although human OAT1 is not mutated in individuals with familial juvenile gouty nephropathy, but the mutation in this transporter is considered to be a likely cause of familial juvenile gouty nephropathy.

Organic anion transporter 3 (OAT3)

The human homologue of OAT3 has been cloned and its gene is mapped to chromosome 11q11.7. OAT3 protein is localized in the basolateral membrane in all segments of the renal proximal convoluted tubule cells, but unlike OAT1, it is also expressed in the thick ascending loop of Henle, distal tubule, connecting tubule, and collecting duct cells.

Significance of the expression of OAT3 in areas of the nephron other than the cells of proximal convoluted tubule in regard to urate transport is currently unknown. Although OAT3 has been demonstrated to transport urate, this transport does not operate via electroneutral anion exchange as previously thought (Fig. 2). In fact, the exact mechanism

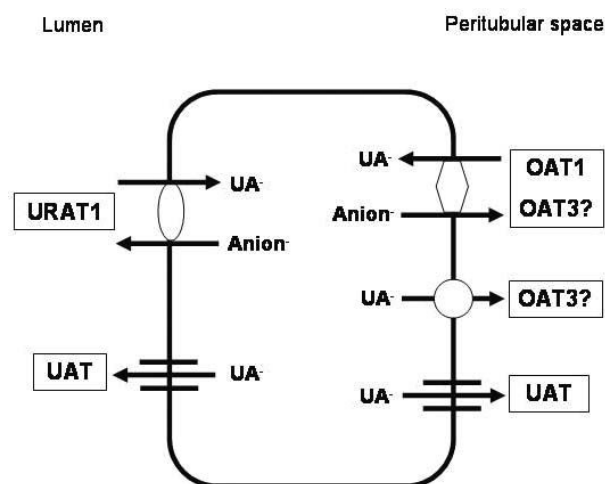


Fig. 2. A model of transcellular urate transport in renal proximal tubule cells. URAT1 represents an apical membrane electroneutral urate-anion exchange protein that is likely to be responsible for cellular urate uptake of filtered urate (reabsorption). UAT represents the urate transporter/channel that is poised to allow efflux of urate from the cells into the lumen (secretion). UAT may also reside in the basolateral membrane and participate in urate reabsorption. Organic anion transporters (OATs) 1 and 3 represent basolateral membrane urate transport proteins. OAT1 is known to be an electroneutral urate/organic anion exchanger while the mechanism of transport on OAT3 has not been defined. One or both of these basolateral proteins are likely to participate in transcellular urate flux, but it is unknown whether they function in a reabsorptive (cell to peritubular space) or secretory (peritubular space to cell) direction. UA-represents urate.

by which OAT3 transports urate remains to be determined.

Urate-anion exchanger (URAT1)

URAT1 is an OAT-related transporter and its gene is mapped to chromosome 11q13. Like OAT1 and OAT3, however, it is not selective for urate but displays affinity for a wide range of organic anion substrates. Importantly, in contrast to the basolateral membrane localization of OAT1 and OAT3, URAT1 has been shown to localize in the apical membranes of renal proximal tubular cells. Consequent to its presence in the apical membrane URAT1 has been considered to be the molecular representation of the protein responsible for transport of urate from the tubular lumen into the cell (Fig. 2). Individuals with mutations of URAT1 gene have hypouricemia and increased urate excretion.

Conclusion

We come to know that there are four distinct proteins that appear to be involved in the renal handling of urate. However, the bi-directional transport of urate within the proximal tubules still remains unknown.

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