TUBULAR HANDLING OF URIC ACID AND FACTORS INFLUENCING ITS RENAL EXCRETION: A SHORT REVIEW

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ABSTRACT

In this review, the authors briefly examine the most recent evidence concerning the role of several proteins involved in tubular urate transport. They also analyse the influence of extracellular volume, electrolyte disorders, acid-base imbalance, and insulin-resistance on renal clearance of uric acid.

Keywords: Uric acid, urate transport, tubular handling, urate clearance.

INTRODUCTION

Uric acid is produced from purine nucleotide metabolism. The formation of uric acid involves purine degradation to inosinic acid and hypoxanthine. The latter is converted by the xanthine oxidase enzyme to xanthine and uric acid. In most mammals, uric acid is then converted to a more soluble allantoin by hepatic uricase.1 In humans it is not further degraded and constitutes a metabolic end-product that is mainly excreted by the kidneys and, to a lesser extent, by the gastrointestinal tract.2 Uric acid is a weak acid with a dissociation constant of pK 5.75. Thus, at a physiological plasma pH of 7.4, uric acid is in its more soluble deprotonated form. Its serum level in normal conditions is 3.5–6.8 mg/dL and is determined by the balance of synthesis and excretion rates. Higher values are associated with gout, nephrolithiasis, progression of chronic kidney disease, diabetes mellitus, hypertension, and cardiovascular damage.3-5 Since the majority of uric acid is excreted by the kidney following the filtration, reabsorption, and secretion processes, the knowledge of uric acid tubular handling helps us to understand the main pathophysiological mechanisms underlying the alterations of its metabolism and to identify new therapeutic targets.

TUBULAR HANDLING OF URIC ACID

The kidney plays a pivotal role in uric acid homeostasis and excretion. Traditionally, uric acid was considered to be freely filtered by the glomerulus and subsequently reabsorbed and secreted along the renal tubule with a fractional excretion of ~10%. Nevertheless, the molecules responsible for bidirectional transcellular urate transport remain partially unknown. In recent years, many studies have demonstrated the role of several proteins belonging to the organic anion transporter (OAT) family, which is involved in urate transport.

Initially, urate transporter (URAT) 1, encoded by the SLC22A12 gene, was identified as a reabsorptive URAT on the apical membrane of the renal proximal tubule.6 In humans, a mutation of this encoding gene has been associated to Type 1 renal idiopathic hypouricaemia, characterised by low serum level and high renal excretion of uric acid.7 Several drugs, such as probenecid and losartan, could decrease the serum urate levels by exercising
inhibitory effects on URAT1, therefore confirming the important role of this molecule in the urate transport.

Besides URAT1, other molecules belonging to the OAT family are expressed on the tubular cell membrane. They form a renal tubular secretory pathway for organic anions including drugs and toxins, however, recent evidence suggests that these proteins also play a role in urate transport.\textsuperscript{6,10} OAT1 and OAT3, encoded by the SLC22A6 and SLC22A8 genes, respectively, are localised to the basolateral membrane of the renal proximal tubules. In experimental murine models, the absence of OAT1 and OAT3 determines a defective renal excretion of urate;\textsuperscript{10} OAT4, encoded by the SLC22A11 gene, is instead expressed in the apical cell membrane.

Glucose transporter (GLUT) 9, encoded by the SLC2A9 gene, was initially reported as a fructose or GLUT but recent evidence suggests that it is involved in voltage-dependent urate transport.\textsuperscript{11-13} Two isoforms have been identified in experimental studies, GLUT9a and GLUT9b, localised on the basal and apical side of the cellular membrane, respectively. Thus, it has been hypothesised that GLUT9b regulates the luminal uptake and GLUT9a regulates the interstitial exit of urate.\textsuperscript{14-16} In humans however, exogenous expression of GLUT9 has been confirmed only at the basolateral side of renal proximal tubules.

Breast cancer resistance protein, ATP-binding cassette sub-family G member 2 (ABCG2), is a protein expressed on the epithelial cells of several organs, especially the placenta, liver, and intestine, and mediates the transport of various chemical compounds including anti-cancer drugs. In the kidney, it is expressed at the apical side of proximal tubules. It has recently been reported to excrete urate, however given its higher expression in the liver and intestine, it likely contributes to the regulation of intestinal urate rather than renal excretion.\textsuperscript{17,18} Paradoxically, in ABCG2 knockout mice an increased renal excretion of urate has been reported, likely due to a compensatory effect or decreased intestinal excretion.\textsuperscript{19} NPT (sodium-phosphate cotransporter) 1 and NPT4 proteins belong to the SLC17 family and they are expressed in the apical cellular membrane of proximal tubules. They were initially identified as sodium-dependent phosphate transporters\textsuperscript{20} but subsequent studies revealed that they can contribute to in vivo excretion of several organic anions, including urate.\textsuperscript{21}

In summary, URAT1, GLUT9, and OAT4 ensure the reabsorption of uric acid on the apical and basolateral sides of the tubular cell membrane, respectively. ABCG2, NPT1, and NPT4, provide exit from the cells in the tubular lumen (Figure 1). Other molecular mechanisms contributing to the renal uptake of uric acid at proximal tubular cells have been identified but their specific role and importance in human pathophysiology is still under investigation. Table 1 reports the various URATs, their localisation, and their pathogenetic role in human and animal disease states.

**Figure 1:** Schematic representation of the location and function of urate transporters on the cell membrane.

FACTORS INFLUENCING RENAL EXCRETION OF URIC ACID

The renal clearance of uric acid can be affected by several factors. Genome-wide association studies have demonstrated that single nucleotide polymorphisms of genes encoding for URATs can determine impaired or increased excretion of urate with consequent alteration of serum uric acid values. Electrolyte alterations, especially sodium and chloride, may influence serum urate levels. It has been reported that a higher long-term sodium intake is associated with an increase of serum uric acid. It has been established that each 1 g increase of sodium intake is associated with a 1.2 μmol/L increase in serum uric acid. Elevated serum uric acid could reflect the endothelial dysfunction of these subjects in response to high sodium intake, but it could also be consequent to altered function of NPTs in response to elevated sodium load into the proximal tubule. NPT activity can also be influenced by tubular chloride concentration as a result of its chloride dependence and inhibitor sensitivity. In addition, electrolyte concentration can affect peritubular oncotic pressure and peritubular hydrostatic pressure or transtubular electrochemical gradient, thereby facilitating or slowing uric acid reabsorption. On the other hand, the state of hydration of the extracellular fluid compartment exerts an important influence on the tubular reabsorption of sodium and other filtered ions, including urate. Contraction of extracellular fluid volume determines an activation of the renin-angiotensin-aldosterone system, leading to increased sodium ion (Na⁺) reabsorption. This enhanced tubular uptake of sodium is associated with an up to 47% decrease in the clearance of uric acid and hyperuricaemia. Conversely, volume expansion results in a decrease in the net tubular reabsorption of uric acid. As renal sodium reabsorption is the main method of regulating the extracellular volume, these findings suggest a close relation between reabsorption of sodium and urate in the proximal tubule. Other studies have suggested a similar relation between phosphate and uric acid reabsorption. However, it has been reported that the enhanced urate clearance observed in patients with syndrome of inappropriate antidiuretic hormone secretion is not only due to an increase of effective vascular volume but also by an undetermined mechanism of vasopressin-1 receptor stimulation. The well-known diuretic-induced hyperuricaemia may be attributed to reduced vascular volume but it has also been proposed that URAT1 could mediate urate-furosemide exchanges because furosemide is secreted into the lumen while enhancing urate uptake. Acid-base status can also influence uric acid clearance. We must first consider that OATs are not urate-specific; organic anions such as sulfate, phosphate, lactate, and ketones; as well as drugs,
consequently impairing renal uric acid excretion.

In response to an acid load, the kidney increases reabsorption of filtered bicarbonate ions and excretion of hydrogen ions (H\(^+\)). H\(^+\) is secreted in the lumen by Na\(^+\)/H\(^+\) exchanger 3 (NHE3) and to a lesser extent by a proton pump. The Na\(^+\)/H\(^+\) exchange by NHE3 plays a pivotal role for reabsorption of filtered bicarbonate ions and ammoniagenesis.\(^\text{30}\) Within the tubular lumen, the secreted H\(^+\) combines with filtered bicarbonate ions leading to carbonic acid formation. The latter is then split into H\(_2\)O and CO\(_2\), which diffuses into the cell where it is rehydrated to carbonic acid. Ammonium (NH\(_3\)) is formed in the kidney by deamination of glutamine to glutamic acid. Once NH\(_3\) has been protonated to ammonia (NH\(_4\)\(^+\)), this is secreted into the tubular lumen and subsequently excreted into the urine as ammonium chloride (NH\(_4\)Cl). Ammoniagenesis is the main renal system for the buffering and removal of H\(^+\) from the body.

In the distal tubule, urine acidification is primarily achieved by a H\(^+\)-ATPase proton pump. In this instance, Na\(^+\) reabsorption indirectly influences H\(^+\) or potassium ion (K\(^+\)) excretion because the removal of cationic Na\(^+\) from the tubular fluid makes the lumen more electronegative, thereby promoting the secretion of H\(^+\) or K\(^+\) into the lumen.\(^\text{31}\) A low K\(^+\) availability secondary to hypokalaemia as well as an acidic state determines an increased H\(^+\) excretion in this site that contributes to urine acidification and maintenance of acid-base balance. For the same reason, anion chloride ions (Cl\(^-\)) can modify the negative charge into the tubular lumen, contributing to H\(^+\) excretion and low urinary pH. Interestingly, urinary pH is simply a measure of free H\(^+\) ions in urine but does not reflect renal net acid excretion because NH\(_4\)\(^+\) and titratable acidity determine the majority of renal acid excretion. A reduced generation of NH\(_4\)\(^+\) can determine an increase of urinary free H\(^+\) and low urinary pH, consequently impairing renal uric acid excretion.\(^\text{32,33}\)

Furthermore, as uric acid is a weak acid with a pK value of 5.35 in urine, a low urine pH can determine uric acid crystallisation and subsequent stone formation even if its excretion rate is normal. Observational studies as well as clinical experience suggests that the majority of pure uric acid stone formers exhibit lower urinary pH and fractional urate excretion when compared to healthy controls.\(^\text{33,34}\) It has been postulated that the reason for a lower urinary pH in these subjects is a defective urinary ammonia excretion, likely associated to an insulin-resistant state.\(^\text{33}\)

Diabetes mellitus and insulin resistance have been associated to low renal clearance of uric acid. The impact of insulin resistance, evaluated by a homeostasis model assessment, showed an inverse correlation between homeostasis model assessment and clearance of uric acid in patients with normal renal function.\(^\text{35}\) Unfortunately in this study the relationship between insulin resistance and urinary pH was not investigated. Moreover, in healthy subjects, uric acid excretion was investigated after insulin infusion using the euglycaemic clamp technique. Insulin caused a statistically significant decline in fractional renal urate excretion.\(^\text{36}\) Furthermore, uric acid stone formers showed a higher prevalence of metabolic syndrome, which is characterised by insulin resistance.\(^\text{37}\)

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of drug for the treatment of Type 2 diabetes mellitus, that act by blocking the tubular SGLT2-mediated glucose uptake. Patients treated with SGLT2 inhibitors showed that besides decreased glycosuria, lower serum uric acid levels and increased urate excretion were present.\(^\text{38,39}\) These findings support the hypothesis that hyperinsulinaemia, glucose levels, and tubular glucose uptake influence uric acid excretion. This influence can occur by regulation of GLUT9 activity which is also involved in glucose transport. Alternatively, we can hypothesise that insulin resistance determines low NH\(_4\)\(^+\) production and that low urinary pH conditioning creates reduced uric acid excretion. Both these hypotheses could explain the epidemiological link between diabetes mellitus, hyperuricaemia, gout, and stone formation. In Table 2 the main factors influencing renal handling of uric acid in human diseases are summarised.
CONCLUSIONS

Hyperuricaemia is associated with gout, hypertension, diabetes mellitus, and renal and cardiovascular damage. Serum uric acid levels mainly depend on uric acid synthesis and its renal excretion. Several proteins identified in recent years are involved in tubular urate transport and influence its renal clearance. In addition, clinical and experimental studies have shown that several haemodynamic and metabolic derangements can affect uric acid renal excretion. Therefore, genetic mutations, drugs, electrolyte disorders, acid-base imbalance, variation of effective vascular volume such as renin-angiotensin system alteration, reduced ammonia generation, and insulin resistance can influence urate renal clearance. These are all contributing factors to the occurrence of hyperuricaemia, gout, renal stone formation, and renal failure. The knowledge of the intrinsic homeostatic systems regulating uric acid excretion has a great impact in clinical practice because it provides us with a better understanding of pathophysiological alterations as well as aiding the development of further therapeutic strategies and novel drugs.

REFERENCES

19. Ichida K et al. Decreased extra-renal urate excretion is a common cause of

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SIADH: syndrome of inappropriate antidiuretic hormone secretion.