The renal urate handling in humans has been explained for many years by a “four-component model.” The purpose of this review is to reevaluate the validity of the theory behind this hypothetical model in the light of the transport mechanisms that were characterized recently in the apical membrane (brush-border membrane; BBM) of human proximal tubule.

In humans, the uricase gene is not expressed, and uric acid is the end product of purine metabolism. It is a trioxypurine of which only the hydroxyl group in position 8 (pKₐ 5.75) is dissociable at physiological pH. The kidney plays a predominant role in its elimination, two-thirds of the daily production of uric acid being excreted by the renal route and the other one-third being eliminated by the gastrointestinal tract. In the plasma, 98% of the uric acid is dissociated and present as sodium urate, which is freely filtered, being bound by <5% to plasma proteins. Thus uric acid enters the proximal tubule in its anionic form, its concentration in the ultrafiltrate being close to that of plasma. Both uric acid and urate, being hydrophilic, hardly permeate the tubular cells in the absence of facilitated mechanisms.

The transport mechanisms for urate, as for organic anions in general, are localized in the proximal tubule (Fig. 1). In humans, urate is extensively reabsorbed, which results in excretion of ~10% of the filtered load of urate (FEurate = renal clearance of urate/glomerular filtration rate = 10%) (1). In the mammalian proximal tubule, micro-puncture and microperfusion studies, as well as earlier stop-flow techniques, demonstrated that urate is bidirectionally transported with a predominance of reabsorption, in species such as rats, dogs, and Cebus monkeys, or secretion, as in pigs and rabbits (13). The distal parts of the nephron and the collecting ducts are hardly permeable to urate. A simplified scheme of urate handling by the nephron of reabsorbing mammals is provided in Fig. 1. In humans, experiments on renal handling of urate hitherto have been limited to the study of the effects of urate loading and of the different drugs interfering with urate excretion in vivo. Such experiments demonstrated a secretory transport for urate in a group of male gout patients with low filtration rates infused with uric acid and a uricosuric drug, when the FEurate rose from values below the filtration load (reabsorption) to values slightly exceeding the filtration load (secretion) (6). Urate secretion is also observed in hereditary hypouricemia, in which an increase in renal urate clearance is caused by a specific inborn error of urate transport (14). These observations suggest that urate is not only reabsorbed but also secreted in humans as in other mammals, reabsorption being predominant. Many attempts have been made to estimate the respective importance of the reabsorptive and secretory fluxes in pharmacological experiments, by measuring the effects of uricosuric and antiuricosuric drugs, in an endeavor to selectively inhibit the reabsorption or the secretion of urate.

Drug effect on urate excretion

Many endogenous compounds and drugs...
interfere with the tubular transport of urate, which results either in uricosuria or in antiuricosuria; some of these are listed in Table 1. The effects of benzbromarone, probenecid, and tienilic acid and of the antiuricosuric drug pyrazinamide, in three groups of normal subjects, are shown in Table 2. Under the acute administration of therapeutic doses of the uricosuric drugs, the FEurate of normal subjects increased from control values between 7 and 10% to values between 30 and 54%, urate reabsorption being partially inhibited (Table 2). The acute administration of large oral doses of pyrazinamide (2–3 g) reduced the FEurate to values as low as 0.64–2.4% (Table 2). Pyrazinamide is a drug used in tuberculosis therapy. Its active metabolite, pyrazinoic acid (pyrazinoate), decreases the renal excretion of urate and thus is responsible for the hyperuricemia induced by pyrazinamide. The decrease in urate excretion by pyrazinamide, which was first interpreted as reflecting an increase in urate reabsorption, is most frequently considered to result from the inhibition of urate secretion. On the basis of the hypothesis that the oral administration of 2–3 g of pyrazinamide causes a selective and complete blockage of urate secretion, pyrazinamide has been used for measuring the importance of urate secretion in humans. The difference in the amount of urate excreted before and after pyrazinamide was thought to give a minimum estimate of urate secretion (9). Using such experimental approaches, secretion was estimated to represent about one-half the filtered amount of urate. For experimental purposes, and to tentatively uncover the defect in urate transport in gouty subjects, pyrazinamide and a uricosuric drug were occasionally given simultaneously, with the aim of inhibiting secretion and reabsorption, respectively. When pyrazinamide and benzbromarone or probenecid were administered together, the FEurate was below controls (Table 2), the uricosuric effect of benzbromarone and probenecid being depressed. The uricosuric effect of tienilic acid was reduced to a lesser extent by the administration of pyrazinamide. Considering that pyrazinamide is an inhibitor of urate secretion, and to interpret the blunting of the uricosuric effect by pyrazinamide, a four-component model of urate excretion in humans was postulated many years ago (2, 9).

### The four components of urate excretion

This model includes 1) glomerular filtration, 2) a nearly complete reabsorption of filtered urate, and 3) secretion followed by 4) postsecretory reabsorption. This model postulates that most excreted urate derives from secretion, because after pyrazinamide administration in vivo ("inhibition of secretion") only 1–2% of the filtered load is excreted (Table 2). Because of the low amount of urate left in tubular...

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**TABLE 1.** Selection of substances that alter the renal tubular handling of urate

<table>
<thead>
<tr>
<th>Substances That Decrease Urate Secretion</th>
<th>Substances That Increase Urate Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate</td>
<td>Orotate</td>
</tr>
<tr>
<td>Acetoacetate</td>
<td>Probenecid*</td>
</tr>
<tr>
<td>β-Hydroxybutyrate</td>
<td>Sulfinpyrazone*</td>
</tr>
<tr>
<td>Nicotinate</td>
<td>Benzbromarone*</td>
</tr>
<tr>
<td>Pyrazinamide/pyrazinoate (tuberculostatic)</td>
<td>Losartan (antihypertensive drug)</td>
</tr>
<tr>
<td></td>
<td>Tienilic acid (diuretic)*</td>
</tr>
</tbody>
</table>

*Drugs used clinically to treat hyperuricemia.
Transport mechanisms in membranes of the human proximal tubule

In urate-reabsorbing nonprimate mammals, e.g., rats and dogs, a urate/anion exchanger has been identified in the BBM of the proximal tubule, which accepts multiple monovalent organic anions, aliphatic or aromatic, including p-aminohippurate, as well as chloride and hydroxyl ions. The physiological role of the anion exchanger was demonstrated in situ in tubular and peritubular capillary perfusion experiments. Such a urate/anion exchanger is absent in rabbits and species differences strongly suggest that the urate/anion exchanger is absent in rabbits and species differences strongly suggest that the uricosuric drugs, is about one order of magnitude lower than the affinities of the anion exchanger, and in particular for pyrazinoate, beside being substrates for the exchanger, are also transported by sodium cotransport and can stimulate urate uptake by BBM vesicles, when added to the uptake medium, in the presence of an inward directed sodium gradient (cis stimulation) (10). The uricosuric drugs probenecid, benz bromarone, sulfinpyrazone, tienilic acid, salicylate, and losartan cis inhibit urate uptake when added to the uptake medium (11).

In addition to the urate/anion exchanger, a voltage-sensitive pathway for urate transport has been identified in human BBM (Fig. 2, left, mechanism 2). The affinity of this pathway for the substrates of the anion exchanger, and in particular for pyrazinoate and the uricosuric drugs, is about one order of magnitude lower than the affinities of the anion exchanger (10). Because of the cell electronegativity, the voltage-sensitive pathway should favor cell-to-lumen efflux in vivo. The urate transport mechanisms in the basolateral membrane are still undefined. A voltage-sensitive transport (Fig. 2, left, mechanism 3) might be the mechanism facilitating urate efflux to the interstitium (second membrane step in reabsorption). The mechanisms involved in urate transport from peritubular space to the proximal cell, the first membrane step in secretion, have not been elucidated, although we looked for a urate/anion exchanger. In the pig, a secreting mammal, urate is transported across the basolateral membrane by a mechanism similar to that of p-aminohippurate, a urate/α-ketoglutarate exchanger; however, in humans urate is transported by mechanisms other than that of p-aminohippurate (10).

Physiological role of the apical urate/anion exchanger

We postulate that from the lumen, urate enters the proximal tubular cell in exchange for intracellular fluid during the “inhibition of urate secretion,” reabsorption is negligible, and inhibition of reabsorption by uricosuric drugs can only induce a minor increase in urate excretion. Consequently, a postsecretory site of urate reabsorption was postulated, which would be the site of action of uricosuric drugs. This ingenious model, which fits with the observed effects of drugs, is valid only if pyrazinamide inhibits urate secretion, which was never demonstrated. Indeed, there are a few observations that suggest that pyrazinamide is not an inhibitor of urate secretion. First, animals that eliminate urate by net secretion, chicken, rabbits and pigs, do not respond to pyrazinamide, the active metabolite of pyrazinamide (1). Second, experiments by Guggino and Aronson (4) on urate transport in BBM vesicles of dogs strongly suggest that pyrazinamide could stimulate urate reabsorption. Similar experiments in human BBM vesicles, reported below, also support pyrazinamide stimulation of reabsorption.

### Table 2. Fractional excretion of uric acid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control (no drug)</th>
<th>Uricosuric Drug</th>
<th>Pyrazinamide 2–3 g po</th>
<th>Pyrazinamide + Uricosuric Drug</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benz bromarone (200 mg po)</td>
<td>7 ± 0.03</td>
<td>39 ± 0.06</td>
<td>0.64 ± 0.002</td>
<td>3 ± 0.02</td>
<td>7</td>
</tr>
<tr>
<td>Probenecid (500 mg iv)</td>
<td>8 ± 0.9</td>
<td>27 ± 2.1</td>
<td>1.8 ± 0.5</td>
<td>5.9 ± 0.7</td>
<td>15</td>
</tr>
<tr>
<td>Tienilic acid (500 mg po)</td>
<td>10 ± 1.1</td>
<td>54 ± 8</td>
<td>2.4 ± 0.03</td>
<td>25 ± 3.5</td>
<td>8</td>
</tr>
</tbody>
</table>

Fractional excretion (%) of uric acid by 3 groups of healthy subjects with normal plasma concentration of urate (~300µM).
Urate leaves the cell through the urate/anion exchanger. Both anions are taken into the cell by sodium cotransport; from the cell it is again available for urate exchange. Bottom: administration of nicotinate and pyrazinoate (PZA-) provides additional substrates for the urate/anion exchanger. Both anions are taken into the cell by sodium cotransport, from where they stimulate urate uptake. From the lumen they are recycled again to the cell by sodium cotransport (4). In contrast, orotate, which is not transported with sodium, competes with urate for transport through the urate/anion exchanger (1) and thus decreases the reabsorption of urate. Uricosuric drugs such as benz bromaron and probenecid act in a similar way at the luminal surface of the tubular cells, reducing access of the urate to the urate/anion exchanger. Modified from Ref. 10 with permission.

**FIGURE 2.** Scheme of membrane mechanisms involved in urate reabsorption. Top: urate transport mechanisms of human proximal tubules are shown on left. Mechanism 1, urate/anion exchanger; mechanism 2, apical voltage-sensitive pathway; mechanism 3, basolateral voltage-sensitive pathway. Physiological substrates for the exchanger (X) are lactate, β-hydroxybutyrate, acetoacetate, etc. Many of these substrates are compounds reabsorbed from the proximal tubule by sodium cotransport. On right, cooperation of a sodium-anion co-transport (4) with the urate/anion exchanger (1) is shown. From the lumen, urate enters the cells in exchange for X, which enters the lumen. Urate leaves the cell through the basolateral voltage-sensitive pathway (3), and X is recycled to the cell by sodium cotransport; from the cell it is again available for urate exchange. Bottom: administration of nicotinate and pyrazinoate (PZA-) provides additional substrates for the urate/anion exchanger. Both anions are taken into the cell by sodium cotransport, from where they stimulate urate uptake. From the lumen they are recycled again to the cell by sodium cotransport (4). In contrast, orotate, which is not transported with sodium, competes with urate for transport through the urate/anion exchanger (1) and thus decreases the reabsorption of urate. Uricosuric drugs such as benz bromaron and probenecid act in a similar way at the luminal surface of the tubular cells, reducing access of the urate to the urate/anion exchanger. Modified from Ref. 10 with permission.

This is the first step of urate reabsorption. From the tubular lumen anions such as lactate, β-hydroxybutyrate, and acetoacetate are reabsorbed by sodium cotransport (mechanism 4), thereby providing a constant gradient of intracellular anions, which drives urate into the cells. However, these anions are also produced by intracellular metabolism. When the amount of intracellular anions available for exchange with urate is increased, reabsorption might be stimulated, which results in a decrease in urate excretion and in hyperuricemia. This is what happens in humans during fasting or starvation because of the accumulation of ketone bodies or also during experimental infusion of β-hydroxybutyrate or acetoacetate to normal subjects (3). We suggest that the hyperuricemia induced by lactate and ketone bodies results from a stimulation of urate reabsorption and not, as postulated earlier, by an inhibition of urate secretion.

**Mechanism of action of uricosuric and antiuricosuric agents**

The urate/anion exchanger might be the site of action of uricosuric as well as antiuricosuric agents, depending on their presence either in the lumen or in the proximal tubular cells. This is illustrated by the comparison of the in vivo effect of orotate and nicotinate, two substrates that have a similar affinity for the urate/anion exchanger (12). In humans orotate is uricosuric, whereas nicotinate is antiuricosuric (3). The main difference between the two substrates is that nicotinate is reabsorbed from the proximal tubule by sodium cotransport, whereas orotate is not. Both nicotinate and orotate can stimulate urate transport through the urate/anion exchanger (Fig. 2, bottom), but only nicotinate is recycled into the cell by sodium cotransport. In contrast to nicotinate, orotate remains in the lumen, where it competes with urate cellular uptake, which explains its uricosuric effect. It has long been recognized that uricosuric drugs act from the tubular lumen. All uricosuric compounds investigated in the human BBM vesicle model inhibited urate uptake through the urate/anion exchanger. In vivo, they compete with urate in the lumen for the exchanger, either for binding or for transport, the net result being uricosuria.

Pyrazinoate, the active metabolite of pyrazinamide, is a pyrazine analog of nicotinate. Like nicotinate it is reabsorbed by a sodium cotransport mechanism, and most probably it stimulates urate uptake by the proximal cells in a way similar to nicotinate. When pyrazinamide is administered and metabolized to pyrazinamide, the cooperation of the urate/pyrazinoate exchange and of the sodium-pyrazinoate cotransport (Fig. 2, bottom) provides a constant increase in the anion gradient that stimulates urate reabsorption.

**Why is the uricosuric effect of drugs blunted by pyrazinamide?**

Two points need to be considered. First, the reabsorptive capacity of the human kidney is large. When the filtered load of urate of normal subjects is doubled, following several days’ ingestion of yeast RNA and pyrazinamide administration, the reabsorption of urate is also doubled, the reabsorptive transport still not being saturated (9). Second, when therapeutic doses of uricosuric drugs are administered to normal subjects, the reabsorption of urate is only partially inhibited...
Urate secretion

Urate secretion was suggested to be important because of the strong decrease of urate excretion by pyrazinamide. It is now evident from the human BBM vesicle studies that pyrazinamide has a major effect on reabsorption and that urate secretion in humans has been largely overestimated. At present the role of secretion is undefined; we suggest that it contributes only in a minor way to urate excretion in normal individuals.

Conclusions

The urate handling by the human kidney does not seem to proceed according to the four-component model proposed earlier. Secretion appears to be minor, and reabsorption and secretion might coexist along the whole proximal tubule. In humans urate reabsorption in the kidney is mediated mainly by the urate/anion exchanger of the apical membrane of the proximal tubule. Intracellular substrates for the exchanger stimulate the reabsorption of urate, whereas uricosuric agents inhibit urate reabsorption from the lumen. Urate leaves the cell through the basolateral voltage-sensitive pathway, along its electrochemical gradient.

The authors thank Dr. H. A. Simmonds and Prof. J. Diezi for their critical reading of the manuscript.

The authors’ work was supported by grants from the Swiss National Fund for Scientific Research.

References


Science may be described as the art of systematic over-simplification.

Karl Popper, to a reporter from the London Observer, 1982.