Renal Transport of Urate in Humans
Françoise Roch-Ramel and Barbara Guisan

The theory of the “four-component model” of urate excretion in humans is reevaluated, considering that a decrease in urate excretion induced by drugs like pyrazinamide or by endogenous compounds like lactate and ketone bodies might be a result of stimulation of urate reabsorption and not, as previously considered, of inhibition of urate secretion.

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 $FE_{urate}$ 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 $FE_{urate}$ 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 $FE_{urate}$ 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 excretion, the four components of urate excretion was thought to give a minimum estimate of urate secretion (9).

FIGURE 1. Schematic representation of urate handling by the human nephron. Urate is secreted and reabsorbed along the proximal tubule (shown in gray). Reabsorption is predominant, and fractional excretion in the final urine approximates 10%. In some mammalian species secretion predominates (see text).

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>
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<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.
identified. 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 (5). The physiological role of the anion exchanger was demonstrated in situ in tubular and peritubular capillary perfusion experiments. Such a urate/anion exchanger is an essential mechanism for urate reabsorption. The presence of a similar urate/anion exchanger was demonstrated in human BBM vesicles prepared from normal sections of human kidneys excised because of carcinoma (Fig. 2, left, mechanism 1) (10). The substrate affinities for the human anion exchanger are largely identical to those of dogs, with the exception that p-aminohippurate and hydroxyl ions are not substrates. The aromatic substrates pyrazinamide, nicotinate, and orotate have about the same affinity as urate for the anion exchanger. The affinity of the aliphatic compounds lactate, β-hydroxybutyrate, and acetoacetate is about one order of magnitude lower. These substrates, 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 intra-

<table>
<thead>
<tr>
<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>Benzibromarone (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>
</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>
</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>
</tr>
</tbody>
</table>

Fractional excretion (%) of uric acid by 3 groups of healthy subjects with normal plasma concentration of urate (~300µM).
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.

Pyrazinamide, 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 pyrazinoate, the cooperation of the urate/pyrazininate exchange and of the sodium-pyrazininate 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.
(Table 2); an amount at least equal to 40–50% of the filtrated load is still reabsorbed. We postulate that the reabsorptive capacity of the human proximal tubule is such that even if part of the reabsorptive mechanism is inhibited by uricosuric drugs, the cellular recycling of pyrazinamide is efficient enough to stimulate the reabsorption of urate through the urate/anion exchanger.

**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.

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**References**


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

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