Effects of Uricosuric and Antiuricosuric Agents on Urate Transport in Human Brush-Border Membrane Vesicles1

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ABSTRACT

Inhibition of [14C]-urate uptake by uricosuric and antiuricosuric agents was investigated in human brush-border membrane vesicles, urate being transported either by anion exchange mechanisms or by voltage sensitive pathway. The IC50 for drugs on [14C]-urate uptake in vesicles loaded with 1 mM cold urate or with 5 mM lactate was, respectively: 0.7 and 0.3 μM for benzbromarone; 6 and 4 μM for salicylate; 133 and 13 μM for losartan; 520 and 190 μM for sulfinpyrazone and 807 and 150 μM for probenecid. The IC50 ratio for [14C]-urate uptake in exchange for cold urate or for lactate varied from about 1 for salicylate to 10 for losartan, supporting the hypothesis that two distinct anion exchangers are involved in urate transport. Application of Hill equation revealed that urate/anion exchangers have more than one binding site, possibly two binding sites with high cooperativity, for benzbromarone and sulfinpyrazone, but only one for probenecid, salicylate and losartan. The uricosuric diuretic, tienilic acid was 10 to 50 times more potent than hydrochlorothiazide, chlorothiazide and furosemide, for inhibiting [14C]-urate uptake in exchange for cold urate. This higher potency is the reason of its uricosuric properties. All uricosuric agents, as well as the antiuricosuric agents, pyrazinoate and ethambutol, had much lower potency for inhibiting [14C]-urate uptake through the voltage sensitive pathway (apical secretory step) than through the urate/anion exchangers. This suggests that antiuricosuria, induced by pyrazinoate and ethambutol, as well as by low concentrations of uricosuric agents, does not result from an inhibition of the apical voltage sensitive pathway.

Under physiological conditions FEurate in human is about 10% (Gutman, 1966). When uricosuric drugs, such as benzbromarone, sulfinpyrazone or probenecid are administered to reduce hyperuricemia, FEurate increases up to values of about 20 to 40% (Gutman, 1966; Sinclair and Fox, 1975). It is generally accepted that these drugs act from the lumenal side of proximal tubules and inhibit urate reabsorption (Diamond, 1978). Other drugs, such as the tuberculostatics pyrazinamide and ethambutol, and most diuretics, reduce FEurate (Emmerson, 1978). Thus, administration of a single dose of 2 to 3 g of pyrazinamide to human can lead to FEurate values of less than 1% (Steele and Rieselbach, 1975). It is generally considered that antiuricosuric drugs act by inhibiting the tubular secretion of urate. However, there is some evidence that they might stimulate urate reabsorption (Guggino and Aronson, 1985).

The membrane mechanisms involved in urate reabsorption by the human kidney have been partly elucidated (Roch-Ramel and Diezi, 1997). To be reabsorbed, urate crosses the apical membrane of proximal tubules through anion exchangers that exchange luminal urate for intracellular organic anions. Two urate/anion exchangers have been described in human brush-border membranes, one for which urate has more affinity than lactate (that we will call the “high urate affinity exchanger”), and the other one for which lactate has more affinity than urate (the “low urate affinity exchanger”) (Roch-Ramel et al., 1996, a and b). These anion exchangers appear essential for urate reabsorption because only urate reabsorbing species possess anion exchangers with affinity for urate (Guggino et al., 1983; Roch-Ramel and Diezi, 1997). The transport mechanisms allowing transfer of urate from cell to peritubular interstitium, the second step in reabsorption, have still not been fully characterized. Preliminary data suggest that in humans as in rats (Polkowski and Grassl, 1993), the efflux of urate from proximal cell to peritubular space occurs through a voltage sensitive pathway. The membrane mechanisms involved in urate secretion have been only partly elucidated. The mechanism allowing urate uptake from peritubular interstitium to cell remains unknown, whereas the efflux of urate from cell to lumen occurs through a voltage-sensitive pathway (Roch-Ramel and Diezi, 1997; Roch-Ramel et al., 1994).

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ABSTRACT

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In our study we investigated the effects of uricosuric and antiuricosuric drugs on the apical transport mechanisms. As the urate/anion exchangers play a major role in urate reabsorption, uricosuric drugs should interact with these transport mechanisms. However, anion exchangers allowing bidirectional transport, urate could as well use the exchangers to leave tubular lumen and enter the cell (reabsorptive direction), or to leave the cell and enter into the tubular lumen (secretory direction). Consequently, antiuricosuric as well as uricosuric drugs might exert their effect by interacting with the urate/anion exchangers. Drugs acting on the voltage-sensitive pathway, in contrast, are expected to be antiuricosuric, because the cell electronegativity favors urate transfer from cell to lumen. An inhibition of this pathway would result in a decrease of urate secretion.

Our data demonstrate that uricosuric and antiuricosuric compounds inhibited urate transport through the urate/anion exchangers. All compounds, including pyrazinoate, had at least 10 times more affinity for the exchangers than for the voltage sensitive pathway. Thus, the effect of drugs on urate transport at the apical membrane appear to be principally on the urate/anion exchangers, the effect on the voltage sensitive pathway being of secondary importance.

Methods

Membrane vesicle preparation. BBMV were isolated as already described (Roch-Ramel et al., 1994) from renal tissue of tumor patients (50–72 yr old), immediately after nephrectomy. Briefly, after removal of the capsid, macroscopically tumor free renal cortex was isolated by dissection. The cortex was maintained 12 to 72 hr in ice-cold sterile culture medium until the membrane purification procedure. BBMV were prepared according to the EGTA/Mg2⁺ precipitation method (Biber et al., 1981). Briefly, portions of total cortex (0.8 g) were homogenized in 16 ml of isotonic buffer containing 300 mM mannitol, 5 mM EGTA and 12 mM Tris-HCl, pH 7.4. BBM purification was achieved by two precipitations with MgCl₂ and a series of differential centrifugations. The purified membranes were suspended in a buffer containing 300 mM mannitol and 20 mM HEPES-Tris, pH 7.4. The final volume of the BBMV suspension was adjusted to yield a protein content of 25 to 30 mg/ml. The vesicles were frozen and stored in liquid nitrogen until use.

As demonstrated earlier (Roch-Ramel et al., 1994), BBM were enriched by a factor of 17, compared to basolateral membranes, leading to only a 6% contamination of BBMV by basolateral membranes vesicles.

Protein determination. Protein content was determined by the Bio-Rad protein assay kit (Bio-Rad Laboratories GmbH, München, Germany) using bovine plasma γ-globulin as the standard.

Transport experiments. BBMV were thawed on ice and diluted in the appropriate volume of intravesicular buffer (to have 50–65 μg protein/filter) (Roch-Ramel et al., 1994). Intravesicular buffer contained 300 mM mannitol, 20 mM HEPES-Tris, pH 7.4. In trans-stimulation experiments with 1 mM urate or 5 mM lactate loaded BBMV, nine volumes of BBMV were incubated for 90 min in one volume of media containing either 10 mM urate or 50 mM lactate. In chloride trans-stimulation experiments, BBMV were prepared and loaded as described earlier (Roch-Ramel et al., 1994). In experiments in which [1⁴C]-urate uptake was stimulated through the voltage-sensitive pathway, BBMV were preincubated with 4 to 7 μM protein of valinomycin dissolved in ethanol or for control conditions with ethanol alone (Roch-Ramel et al., 1994).

The uptake of [1⁴C]-urate was studied at 25°C by the rapid-filtration technique, the vesicle suspension being warmed for 15 min at 25°C before initiation of transport. In trans-stimulation experi-
As shown in figures 1, A and B, the four drugs inhibited [14C]-urate uptake in exchange for cold urate or 5 mM lactate. The inhibitory effect of probenecid was also investigated in BBMV preloaded with 40 mM chloride. The data of figure 2 show that benzbromarone inhibited urate uptake through both urate/anion exchangers. The probenecid IC50 was about 2. Data for each sigmoid originated from at least three different membrane preparations. IC50 and napp are given in table 1.

Effects of losartan and its metabolite (exp 3174) on [14C]-urate uptake through urate/anion exchangers. Losartan, an antagonist of angiotensin II with uricosuric properties (Burnier et al., 1995; Nakashima et al., 1992), is a member of a new class of antihypertensive drugs (Carr and Prisant, 1996). We investigated the ability of losartan and its metabolite, exp 3174, to interfere with [14C]-urate transport. The data of figure 3 and table 1 show that losartan...
TABLE 1
IC_{50} and Hill n_{app} coefficients for uricosuric agents

<table>
<thead>
<tr>
<th></th>
<th>Human BBMV</th>
<th></th>
<th>Rat BBMV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[14C]-urate/urate</td>
<td>IC_{50} (μM)</td>
<td>n_{app}</td>
<td>[14C]-urate/lactate</td>
</tr>
<tr>
<td>Benzbrozamone</td>
<td>0.7 ± 0.2</td>
<td>2.3 ± 0.3</td>
<td></td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>Probenecid</td>
<td>807 ± 420</td>
<td>1 ± 0.1</td>
<td></td>
<td>150 ± 60</td>
</tr>
<tr>
<td>Salicylate</td>
<td>5.5 ± 1.4</td>
<td>1 ± 0.1</td>
<td></td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>520 ± 140</td>
<td>2.1 ± 0.3</td>
<td></td>
<td>190 ± 20</td>
</tr>
<tr>
<td>Tienilic acid</td>
<td>−20 μM</td>
<td></td>
<td></td>
<td>20 ± 5</td>
</tr>
<tr>
<td>Losartan</td>
<td>133 ± 22</td>
<td>0.9 ± 0.2</td>
<td></td>
<td>13.2 ± 2</td>
</tr>
<tr>
<td>EXP 3174</td>
<td>2.2 ± 0.2</td>
<td>0.9 ± 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>3 ± 0.55</td>
<td>0.8 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>203 ± 28</td>
<td>1 ± 0.2</td>
<td></td>
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</tr>
</tbody>
</table>

IC_{50} and Hill n_{app} coefficients were calculated from curves of figures 1 to 3. Tienilic acid IC_{50} was estimated from data of figure 6. [14C]-urate uptake was stimulated either in exchange for lactate, or urate, or chloride. For comparison, IC_{50} obtained in rat BBMV, in which [14C]-urate uptake was stimulated in exchange for hydroxyl ions, are shown in the last column (Dan and Koga, 1990; Edwards et al., 1990). IC_{50} measured when [14C]-urate uptake was stimulated in exchange for lactate were significantly lower than IC_{50} measured when [14C]-urate uptake was stimulated in exchange for urate (P < .05).

^a Data by Dan and Koga, 1990.

^b Data by Edwards et al., 1996.

Fig. 2. Inhibitory effect of benzbromarone metabolites on [14C]-urate uptake in exchange for cold urate. The log-concentration inhibitory effect of benzbromarone shown in Fig. 1A was reproduced (●) for direct comparison with data obtained for benzane (○), M1 (1-hydroxybenzbrozamone) (▲) and M2 (6-hydroxybenzbrozamone) (○). Sigmoids were calculated by applying Hill equation (see "Methods"). Data for each sigmoid came from at least three different membrane preparations. IC_{50} and n_{app} are given in table 1.

IC_{50} were 13.2 ± 2, 133 ± 22, and 20 ± 5 μM, respectively, for [14C]-urate uptake stimulated in exchange for lactate, cold urate and chloride respectively. Exp 3174, the metabolite of losartan, was about 20 times less potent than losartan to inhibit [14C]-urate uptake in exchange for chloride, IC_{50} for Exp 3174 was 593 ± 87 μM compared to 20 ± 5 μM for losartan. Losartan and Exp 3174 n_{app} were close to one, suggesting that the urate/anion-exchangers had only one binding site for these uricosuric agents (table 1).

Fig. 3. Inhibitory effect of losartan and EXP 3174 on urate uptake through urate/anion exchange mechanisms. Inhibitory effect of losartan was investigated on [14C]-urate uptake stimulated either in exchange for cold urate (○), lactate (△) or chloride (▲). EXP 3174 was tested only on [14C]-urate uptake stimulated in exchange for chloride (○). Sigmoids were calculated by applying Hill equation (see "Methods"). Data for each sigmoid originate from at least three different membrane preparations. IC_{50} and n_{app} are given in table 1.

Effects of uricosuric drugs on [14C]-urate uptake through the voltage sensitive pathway. The data of figure 4 show that all investigated uricosuric agents inhibited to some extent [14C]-urate uptake through the voltage sensitive pathway. The inhibitory potencies of all agents were lower for the voltage sensitive pathway than for the exchangers. At the concentration of 1 mM, salicylate, losartan and probenecid inhibited [14C]-urate uptake by less than 50%, whereas 1 mM sulfinpyrazine inhibited uptake by 72 ± 6%. Benzbromarone was more potent, 10 and 100 μM inhibiting [14C]-urate uptake by 52 ± 9% and 90 ± 3%, respectively.

Fig. 4. Inhibitory effect of uricosuric agents on urate uptake through the voltage sensitive pathway. Data are mean ± S.E. of five experiments performed on different membrane preparations.

Effects of ethambutol and pyrazinoate, two antiuricosuric compounds, on [14C]-urate transport mechanisms. Ethambutol and pyrazinamide are anturicosuric drugs (Emmerson, 1978). The decrease in urate excretion observed during pyrazinamide administration is due to...
pyrazinoate, a metabolite of pyrazinamide (Weiner and Tinker, 1972). Data shown in figure 5 compare the effects of ethambutol (fig. 5A) and pyrazinoate (fig. 5B) on urate transport through the voltage sensitive pathway and the urate/anion exchangers. Ethambutol had a low inhibitory potency on [14C]-urate uptake through the "high urate affinity exchanger" and the voltage sensitive pathway, 5 mM ethambutol inhibiting [14C]-urate uptake by 43 ± 4 and 16 ± 6%, respectively (fig. 5A). It was slightly more potent for inhibiting [14C]-urate uptake through the "low urate affinity exchanger," as 1 mM inhibited [14C]-urate uptake by 51 ± 4%. The potency of pyrazinoate to inhibit [14C]-urate uptake through the voltage dependent pathway was also low, 1 mM inhibiting uptake by only 36 ± 4%. At this concentration, pyrazinoate inhibited totally [14C]-urate uptake through both urate/anion exchangers (fig. 5B). At the concentration of 0.1 mM, pyrazinoate inhibited [14C]-urate uptake through the "high urate affinity exchanger" by 63 ± 2%, and in contrast, cis-stimulated [14C]-urate uptake through the "low urate affinity exchanger."

**Effects of diuretics on [14C]-urate uptake.** Furosemide and thiazide diuretics reduce the FEurate and consequently induce hyperuricemia. Part of the effect is secondary to the contraction of extracellular volume, but a direct effect on urate tubular transport has also been postulated (Kahn, 1988; Steele and Oppenheimer, 1969). To avoid diuretic-induced hyperuricemia, diuretics with uricosuric properties, such as tienilic acid, were developed (Diamond, 1978). The data of figure 6 compare the effects of furosemide, hydrochlo-

![Fig. 5](image1.png)

**Fig. 5.** Effect of antituricosuric compounds on urate-stimulated uptake through anion exchange mechanisms and voltage sensitive pathway. A, Ethambutol inhibitory effect on [14C]-urate uptake. B, Pyrazinoate effect on [14C]-urate uptake. Positive values represent inhibition of uptake, whereas negative values represent stimulation of [14C]-urate uptake. Data are mean ± S.E. of four to five experiments performed on different membrane preparations.

![Fig. 6](image2.png)

**Fig. 6.** Effect of diuretics on urate uptake through anion exchange mechanisms, and voltage sensitive pathway. A, Inhibitory effect on [14C]-urate stimulated uptake in exchange for cold urate. B, Inhibitory effect on [14C]-urate stimulated uptake through the voltage sensitive pathway. Data are mean ± S.E. of four experiments performed on different membrane preparations.

![Urate Transport in Human BBMV](image3.png)

**Discussion**

Our data demonstrate that antiuricosuric as well as uricosuric drugs have a higher affinity for the urate/anion exchangers than for the voltage sensitive pathway. Thus, at the apical membrane, the effect of these drugs is most probably the result of an interaction with urate transport through the urate/anion exchangers. The effect on the vectorial transport of urate will depend on the relative concentrations of the
drug in the lumen and in proximal cells. Drugs with affinity for the urate/anion exchangers will be uricosuric when acting from the lumen, whereas they will be antiuricosuric when acting from the intracellular space. The exchange of urate for chloride appears to proceed through the same exchanger as the exchange of urate for lactate, the “low urate affinity exchanger,” because the IC₅₀ of probenecid and losartan, drugs investigated in both experimental conditions, were not statistically different when [¹⁴C]-urate uptake was stimulated either through exchange for lactate or through exchange for chloride. In contrast, probenecid and losartan IC₅₀ measured when [¹⁴C]-urate uptake was stimulated in exchange for cold urate, differed statistically from those measured when urate uptake was stimulated in exchange for chloride or for lactate.

**Mechanism responsible for uricosuria.** There are a few observations suggesting that uricosuric agents act from the lumen. One study reported that probenecid-induced uricosuria is markedly reduced when probenecid tubular secretion is inhibited by p-aminohippurate (Meisel and Diamond, 1977). Another study observed that the uricosuric effects of probenecid and salicylate were strongly reduced by an acidification of urine. In acidic urine the proportion of nonionized molecules of probenecid and salicylic acid is increased, and because these molecules are hydrophobic they diffuse out of the tubular lumen. This decrease in luminal drug concentration resulted in a concomitant decrease in uricosuria (Gutman, 1966). Uricosuric drugs may either bind to the urate/anion exchangers without being transported, limiting urate access to the transporter or they may compete with urate for transport. In both cases, more urate remains in the tubular lumen. Our data do not allow to distinguish between these two possibilities. All uricosuric compounds investigated here were more potent for inhibiting urate uptake through the “low urate affinity exchanger” than through the “high urate affinity exchanger.” The ratio of IC₅₀ for urate transport through the “high urate affinity exchanger” and through the “low urate affinity exchanger” were about 1 for salicylate, 2 to 3 for benzbromarone and sulfinpyrazone, 5 for probenecid and 10 for losartan. These differences in IC₅₀ ratios give weight to the hypothesis that two anion exchangers might play a role in urate reabsorption (Roch-Ramel et al., 1996, a and b).

Benzbromarone is metabolized by the liver, and two metabolites have been identified, M1 and M2, both of which had affinity for the “high urate affinity exchanger.” The therapeuetic blood concentrations of benzbromarone and its active metabolites are low, about 2 to 4 μM for benzbromarone and about 1 μM for M1 and M2 (De Vries et al., 1993; Walter-Sack et al., 1995). These compounds are strongly protein bound, and consequently only small amounts reach the lumen by glomerular filtration. Nevertheless, benzbrinmarone administration induces a long lasting uricosuria. The high affinity of benzbrinmarone and its metabolites for the urate/anion exchangers explain such important uricosuria. Little is known on the renal excretion of benzbrinmarone, and in particular, it is unknown whether benzbrinmarone is secreted by the kidney. Benzaron, the debrornized benzbrinmarone, had a much lower potency than benzbrinmarone and its metabolites. This demonstrates that, as proposed by Walter-Sack et al. (1988), M1 and M2, but not benzaron, are benzbrinmarone metabolites responsible for its long lasting uricosuric effect.

The log concentration inhibition relationship for benzbromarone and sulfinpyrazone was much steeper than that for salicylate, probenecid and losartan. The application of Hill equation gives a nᵦₑₚ larger than one for benzbromarone and sulfinpyrazone, which indicates that the carrier has more than one binding site for benzbromarone and sulfinpyrazone, possibly two binding sites with high cooperativity (Segel, 1968). The benzbromarone metabolites, M1 and M2, had a nᵦₑₚ of about 1, which suggests that the hydroxylation of benzbrinmarone hindered the binding to a second site.

Losartan is a representative compound of a new class of antihypertensive drugs, the antagonists of angiotensin II at the receptor level (Carr and Prisant, 1996). Losartan was more potent than probenecid and sulfinpyrazone for cis-inhibiting [¹⁴C]-urate uptake through the urate/anion exchangers. EXP 3174, the losartan metabolite, was less potent than the parent compound by 30 times. The lower potency of EXP 3174 fits with the observation that uricosuria is better correlated with losartan plasma concentration than with the metabolite concentration (Burnier et al., 1996; Burnier et al., 1995). Our data in human BBMV are close to those published recently by Edwards et al. in rat BBMV, data shown in the last column of table 1 (Edwards et al., 1996). Thus, in rat as in human BBMV, losartan was about six to seven times more potent than probenecid and sulfinpyrazone for cis-inhibiting [¹⁴C]-urate uptake through the urate/anion exchangers and in BBMV of both species, EXP 3174 was less potent than losartan. However, EXP 3174 was only six to eight times less potent than losartan in rat BBMV. Such differences in drug potencies in rat and human BBMV are not surprising, if one considers that the substrate affinities for rat and human urate/anion exchangers differ. In human, hydroxyl ion is not a substrate of the urate/anion exchangers, whereas it is a good substrate in rats (Roch-Ramel et al., 1994). Another substrate affinity difference is illustrated by the lack of p-aminohippurate affinity for human urate exchangers, while it shows a high affinity for the rat urate/anion exchanger (Kahn et al., 1983; Roch-Ramel et al., 1994). Nevertheless, it appears that rat BBMV can be used as a tool to screen uricosuric compounds, keeping in mind that affinities of drugs for rat and human urate/anion exchangers might differ. Thus, Dan et al. observed in rat BBMV (data shown in last column of table 1) that the rank order of potency of uricosuric drugs for inhibiting urate uptake, was benzbromarone > tienilic acid > sulfinpyrazone > probenecid (Dan and Koga, 1990). We observed a similar rank order of potency in human BBMV.

**Mechanisms responsible for antiuricosuria.** Most uricosuric drugs (probenecid, sulfinpyrazone, salicylate, but not benzbromarone) have been reported to have a biphasic effect on urate transport, antiuricosuria being observed at lower concentrations than uricosuria (Diamond, 1978; Gutman, 1966). Such biphasic effect is particularly evident for salicylic acid (Gutman, 1966). It was suggested that, at low dosage, uricosuric agents could inhibit urate secretion. Our data demonstrate that antiuricosuria does not result from an inhibition of the apical step of secretion, because of the low affinities of uricosuric drugs for the apical voltage-sensitive pathway. It remains that the antiuricosuric effect could be the result of an inhibition of urate uptake at the basolateral membrane, first step of secretion. At present the basolateral
transport mechanisms of urate have not been identified, thus this possibility remains open. However, as discussed earlier by Diamond (Diamond, 1978), an inhibition of urate secretion at low doses, at least in the case of sulfinpyrazone, is not compatible with the net secretion of urate observed when sulfinpyrazone is administered to patients undergoing osmotic diuresis and urate loading (Gutman et al., 1959). An alternative is that antiuricosuria results from a stimulation of urate reabsorption. Sulfinpyrazone, probenecid and salicylate are bound to plasma proteins and reach tubular lumen by secretion. It might be that at low doses, the basolateral uptake allows a cellular concentration relatively high compared to the luminal concentration, and thus the drug could stimulate urate uptake from lumen through the exchanger. Part of the antiuricosuria observed by repetitive p.o. administration of thiazide diuretics or of furosemide (Emmerson, 1978) might result from a similar mechanism, whereas uricosuria observed by i.v. infusion of chlorothiazide or furosemide (Diamond, 1978), might be through the inhibition of the exchanger from the luminal side.

Antiuricosuria induced by stimulation of urate reabsorption is obviously the mode of action of pyrazinamide, as was suggested earlier (Guggino and Aronson, 1985). At the luminal side, PZA enters proximal cells by sodium-cotransport as well as through the “low urate affinity exchanger” for which it has a much higher affinity than urate (Roch-Ramel et al., 1996b). Lactate itself enters proximal cells through a sodium-cotransport mechanism (Roch-Ramel et al., 1996b). From cells, PZA exchanges for urate and stimulates its transfer from lumen to cell, first step in urate reabsorption, which results in antiuricosuria. Because PZA affinity for the voltage-sensitive pathway is about 10 times lower than that for the urate/anion exchangers at the apical membrane, the antiuricosuric effect of PZA is primarily by stimulating cellular uptake of luminal urate. Also, the antiuricosuric effect of ethambutol (Postlethwaite et al., 1972) cannot be explained by the inhibition of urate transport through the voltage-sensitive pathway, for which it has a very low affinity.

In summary, our data demonstrate that uricosuria as well as antiuricosuric agents have more potency for inhibiting urate uptake through the anion exchange mechanisms, which allow transfer of urate from lumen to cell (first step of reabsorption) as well as from cell to lumen (second step in tubular secretion), than for the voltage-sensitive pathway, which is involved only in urate secretion. Drug-induced antiuricosuria could generally result from a stimulation of urate efflux out of the lumen, as is the case for pyrazinamide.

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References