Urate Excretion by the Isolated Perfused Rat Kidney and Modification by Drugs (42997)

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Abstract. **Urate excretion in the isolated perfused rat kidney was studied over a wide range of perfusate urate concentrations (13.9–376.8 μM). Fractional excretion of urate (FE_{urate}) averaged 57.9 ± 2.0% (range, 58.5–59.6%), showed marked interanimal variability, but was not dependent on the perfusate-free urate concentration. In paired experiments, the effects of five drugs (probenecid, pyrazinoate, furosemide, salicylate, and oxonate) on FE_{urate} were evaluated. A low concentration of pyrazinoate (0.2 mM) decreased FE_{urate} (62.0 ± 1.9 vs 53.8 ± 2.4%, $P < 0.05$), as did 0.8 mM pyrazinoate (59.5 ± 2.4 vs 48.4 ± 2.7%, $P < 0.05$). Probenecid (1 mM) decreased FE_{urate} (59.3 ± 3.1 vs 52.0 ± 2.5%, $P < 0.05$) but 2.5 mM probenecid did not alter FE_{urate} (48.0 ± 6.3 vs 47.8 ± 6.9%). Oxonate (0.1 mM) also decreased FE_{urate} (75.8 ± 4.2 vs 67.1 ± 2.1%, $P < 0.05$) while 0.2 mM oxonate had no effect (66.4 ± 3.5 vs 61.5 ± 4.6%). Neither salicylate nor furosemide affected FE_{urate}, although both drugs caused a saliuresis and diuresis. Thus, urate transport in rat kidneys *in vitro* is not dependent on urate concentration, unlike man. Some drugs known to affect urate excretion in humans and rats did not have similar effects in isolated kidneys. Isolated organ studies provide additional information is understanding renal urate handling.** [P.S.E.B.M. 1989, Vol 192]

Urate is the end product of purine metabolism in man, and elevated serum levels of urate have been associated with hypertension, atherosclerotic disease, and gout. Urate concentrations in serum are determined by the balance of urate production and urate excretion and elevated serum urate levels are usually due to decreased excretion of urate rather than increased production of the anion (1). Since urate is excreted by the kidney through a complex interplay of glomerular filtration, tubular secretion, and tubular reabsorption, knowledge of the various components of urate excretion is important in understanding urate metabolism. Studies of urate transport have been done in intact animals and isolated tubule and vesicle preparations. However, systematic investigation of urate excretion using animal experiments is difficult because urate excretion varies in different species. Urate may be produced or metabolized in the kidney (2–4), and most mammals convert the relatively insoluble urate to the more soluble allantoin (5–7).

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The rat reabsorbs urate avidly from the tubule, similar to the human. Studies in the isolated kidney demonstrated formation of urate when hypoxanthine was added to the perfusate, but metabolism of urate to allantoin was not present (5). Although studies have identified many of the transport processes for urate, controversy still remains concerning concentration-dependent excretion of urate by the rat and drug effects in the intact organ. The isolated perfused rat kidney is a well-described system (8) that permits control of urate levels in the perfusion medium and eliminates naturally occurring substances or systemic effects which may affect urate transport. The isolated rat kidney, therefore, represents a reasonable model to examine the renal excretion of urate over a wide range of perfusate urate concentrations. We also studied the effects of various chemicals reported to alter urate excretion either in the rat or in the human (3, 9–12).

Materials and Methods

Kidneys were isolated without interruption of flow as previously described (13). Standard perfusion medium contained, in mmol/liter: sodium 145, potassium 5.0, calcium 1.25, magnesium 1.18, bicarbonate 25, chloride 123, phosphate 1.20, sulfate 0.77, and glucose 5 with inulin 42 mg/dl and bovine serum albumin (Fraction V) 6.8 g/dl. The volume of the recirculating

perfusate was 130 ml. The solution was oxygenated with a flow-through oxygenator using 5% carbon dioxide-95% oxygen, providing a final pO_2 near 290 mm Hg, and pumped in a pulsatile flow.

Experimental Design. After initiation of perfusion and stabilization time of 20 min, a series of eight 5-min clearance periods were collected, giving a total perfusion time of 60 min. Urine samples were collected for each entire 5-min period and the volume was determined by weight. Arterial samples were taken from the perfusate reservoir at the 3-min point of each clearance period. Two clearance periods were designated as baseline controls prior to the addition of any chemical (20–30 min). Kidneys with a glomerular filtration rate (GFR) < 0.5 ml/min and a fractional excretion of sodium (FE_{Na}) > 10% in these periods were excluded. The control periods (20–30 min) were followed by the experimental periods (30–60 min), divided into two 15-min segments, each containing three clearance periods.

Three groups of experiments were done. We evaluated the effect of time on GFR and FE_{Na} in isolated perfused kidneys in the absence of urate or other chemicals (Group 1, $n = 15$). In these experiments, vehicle (1 ml of 0.45 M Na_2CO_3) was added to the perfusate reservoir at the start of each experimental segment. The initial clearance period in each segment was discarded to allow for distribution of the added vehicle. In urate experiments (Group 2), various concentrations of urate were added to the perfusate at the start of the first experimental segment only while vehicle was added at the beginning of the second segment. Again, the initial clearance period in each segment was discarded to allow for distribution of the added vehicle or chemical. Finally, (Group 3), urate was added to the perfusate at the start of the first experimental segment and various drugs were added to the perfusate at the start of the second segment.

The amount of each chemical added was based on an average perfusion volume of 130 ml. We evaluated he effects of pyrazinoate (200 and 800 μM), probenecid (1000 and 2500 μM), oxonate (100 and 200 μM) salicylate (1500 and 6000 μM), and furosemide (350 and 750 μM) on the excretion of urate in this system. These drug concentrations were extrapolated from approximate plasma concentrations from previous whole animal studies which had shown effects on urate excretion (3). All chemicals except furosemide were dissolved in 0.45 M Na_2CO_3 prior to addition to the perfusate reservoir in a bolus injection in volumes not exceeding 1.6 ml. The commercially available furosemide solution for intravenous use provided the concentrated form of this chemical. Urate was used as sodium urate (Sigma, St. Louis, MO). The sequence of all experiments and the addition of drugs was randomized.

Urate Binding Determination. Binding of urate to albumin was determined by equilibrium dialysis. Two-milliliter aliquots of Krebs-Henseleit buffer containing 6.8 g/dl bovine serum albumin and various concentrations of urate were placed in cellulose acetate dialysis tubing (Spectrapor 4) and sealed. Duplicate samples were dialyzed for 3 hr in a water bath shaker at 37°C against 20 ml of albumin-free Krebs-Henseleit buffer containing the same concentration of urate. Urate binding was determined for urate alone and after addition of pyrazinoate (200 or 800 μM) probenecid (1000 or 2500 μM), oxonate (100 or 200 μM), furosemide (350 or 750 μM), or salicylate (1500 or 6000 μM). Total urate was plotted against the ratio of free to total urate to obtain the urate binding curves which were used to determine free urate perfusate concentrations from total urate concentrations.

Analytical Methods. Urine and perfusate samples were analyzed for inulin, sodium, potassium, and urate. Inulin was determined using a standard autoanalyzer colorimetric method (Technicon AutoAnalyzer I) (14). The presence of urate or other drugs used in the experiments did not interfere with inulin measurements. Concentrations of urate less than 30 μM were determined using reverse phase high-performance liquid chromatography with amperometric detection (15). Concentrations of urate greater than 30 μM were determined by a standard autoanalyzer technique (Technicon AutoAnalyzer II) (16). Inulin did not interfere with urate determinations. Sodium and potassium were determined by flame photometry. GFR was estimated from inulin clearance and fractional excretion of urate and sodium were calculated in relation to inulin clearance.

Data Collection and Statistics. Individual clearance data were averaged from duplicate sample measurements. Data from individual kidneys in Group 2 were combined into groups based on the perfusate urate concentration. Data from individual kidneys in Group 3 were combined into groups based on the concentration of the drug added. Results (mean ± SE) were compared by paired t-test and analysis of variance. A probability value of less than 0.05 was accepted as significant.

Results

A small, but predictable degree of protein-urate binding was found *in vitro*. Equilibrium dialysis binding studies showed 3–10% binding of urate to bovine serum albumin with urate concentrations ranging from 10 to 550 μM. Addition of drugs to the medium decreased urate binding by less than 10% at low urate concentrations (<50 μM) but did not alter urate binding at higher urate concentrations.

The effect of perfusion time on GFR and FE_{Na} was evaluated in control experiments (Group 1). There was no significant change in GFR over the standard hour of perfusion (Table I). Sodium excretion increased steadily. These changes occurred in a predictable manner in all control experiments. Similar qualitative

changes of a lesser magnitude would have been expected had amino acids been added to the perfusate (17). These results are standard and are considered adequate for this preparation (8).

The effect of perfusate urate concentration on urate excretion was evaluated with urate concentrations from 13.9 to 376.8 μM. The number of animals in each group varied because not all experiments met the inclusion criteria of GFR and FE_{Na}. No concentration of urate tested had any specific effect on GFR or FE_{Na}. With each perfusate urate concentration, we found a similar FE_{urate}, and the FE_{urate} was constant throughout the experimental segments with a mean of 57.9 ± 2.0% (Table II).

The effect of various drugs on urate excretion was then evaluated. Pyrazinoate (200 and 800 μM), probenecid (1000 and 2500 μM), oxonate (100 and 200 μM), furosemide (350 and 750 μM), and salicylate (1500 and 6000 μM) were added to the perfusate in separate experiments. FE_{urate} was measured before and after the addition of each concentration of each drug (Table III). Perfusate urate concentrations were the same as those tested in Group 2, but, in these comparisons, we combined all experiments irrespective of urate concentration because separate analysis by urate concentration showed no concentration-dependent effects. The most striking decrease in FE_{urate} occurred with pyrazinoate. A concentration-dependent effect of this drug was not noted and FE_{urate} was decreased similarly at both concentrations of drug tested. Probenecid and oxonate had a significant effect on FE_{urate} at low doses, with FE_{urate} decreased in these experiments, whereas higher doses had no effect. Salicylate and furosemide had no effect on FE_{urate}. Finally, salicylate and furosemide initiated a significant natriuresis without altering FE_{urate}.

Table I. Effect of Time on Isolated Kidney Perfusion

Perfusion time interval (min)	GFR (ml/min)	FE_{Na} (%)	Urine flow (ml/min)
35–45	0.67 ± 0.05	9.7 ± 1.1	0.09 ± 0.01
50–60	0.57 ± 0.04	12.7 ± 1.5	0.09 ± 0.01

Note. n = 15 kidneys. Values are mean ± SE. P, not significant.

Table II. Fractional Excretion of Urate in Isolated Kidneys

n	Urate free (μmol/liter)	FE_{urate} (%)	FE_{Na} (%)	Urine flow (ml/min)
10	16.1 ± 1.9	59.1 ± 7.1	16.0 ± 0.8	0.13 ± 0.01
11	34.2 ± 4.3	53.1 ± 6.8	14.7 ± 1.3	0.13 ± 0.01
14	83.0 ± 9.8	59.9 ± 3.6	17.5 ± 1.2	0.15 ± 0.04
14	164.9 ± 20.0	58.5 ± 2.6	16.6 ± 1.2	0.15 ± 0.01
14	364.1 ± 17.1	58.7 ± 3.0	16.6 ± 1.2	0.15 ± 0.01
Mean		57.9 ± 2.0		

Note. Values are mean ± S.E.
[a] n = number of kidneys studied.

Table III. Effects of Drugs on the Fractional Excretion of Urate in the Isolated Rat Kidney

Drug	n	GFR (ml/min)	FE_{Na} (%)	Urine flow (ml/min)	FE_{urate} (%)
Pyrazinoate	16	0.78 ± 0.05	13.8 ± 0.6	0.14 ± 0.01	62.0 ± 1.9
(0.2 mM)		0.59 ± 0.04	18.3 ± 1.0	0.15 ± 0.01	53.8 ± 2.4*
Pyrazinoate	16	0.90 ± 0.04	13.0 ± 0.9	0.15 ± 0.01	59.4 ± 2.4
(0.8 mM)		0.67 ± 0.04	18.0 ± 1.4	0.17 ± 0.01	48.4 ± 2.7*
Probenecid	15	0.68 ± 0.04	17.3 ± 1.3	0.16 ± 0.01	59.3 ± 3.1
(1 mM)		0.58 ± 0.03	20.7 ± 1.3	0.16 ± 0.01	52.0 ± 2.5*
Probenecid	10	0.71 ± 0.08	14.9 ± 1.2	0.13 ± 0.01	48.0 ± 6.3
(2.5 mM)		0.60 ± 0.20	18.0 ± 1.0	0.15 ± 0.01	47.8 ± 6.9
Oxonate	6	0.68 ± 0.04	18.6 ± 1.9	0.12 ± 0.02	75.8 ± 4.2
(0.1 mM)		0.56 ± 0.08	26.7 ± 1.6*	0.15 ± 0.02	67.1 ± 2.1*
Oxonate	4	0.65 ± 0.07	17.4 ± 1.4	0.13 ± 0.02	66.4 ± 3.5
(0.2 mM)		0.45 ± 0.04	29.6 ± 2.0*	0.16 ± 0.02*	61.5 ± 4.6
Furosemide	14	0.83 ± 0.05	16.4 ± 1.6	0.15 ± 0.01	65.6 ± 2.1
(0.35 mM)		0.72 ± 0.06	33.4 ± 1.1*	0.28 ± 0.02*	67.3 ± 2.7
Furosemide	14	0.77 ± 0.07	17.5 ± 2.2	0.15 ± 0.02	62.3 ± 2.9
(0.75 mM)		0.66 ± 0.06	36.5 ± 1.7*	0.29 ± 0.02*	65.1 ± 2.7
Salicylate	6	0.95 ± 0.07	15.4 ± 1.3	0.14 ± 0.01	66.7 ± 2.7
(1.5 mM)		0.64 ± 0.04	27.3 ± 3.1*	0.19 ± 0.02*	62.2 ± 2.1
Salicylate	6	0.97 ± 0.07	15.4 ± 1.4	0.16 ± 0.02	69.6 ± 4.9
(6 mM)		0.69 ± 0.05	32.1 ± 2.9*	0.26 ± 0.02*	66.0 ± 4.3

Note. n = number of kidneys studied. Studies are paired, without drug and with drug. Line 1 of each set is the control without drug for line 2 with drug. Line 3 is the control without drug for line 4 with drug. Values are mean ± SE.
* $P < 0.05$, paired t test.

Discussion

These experiments in the isolated perfused rat kidney showed a constant net reabsorption of urate over a wide range of perfusate urate concentrations (13.9–376.8 μM). The experiments failed to demonstrate any concentration-dependent change in the fractional excretion of urate, despite bracketing the rat's normal serum urate concentration nearly 10-fold in both directions. *In vivo* urate concentrations were not measured but were assumed to be that reported previously (average 50 μM) (6). Thus, the fractional excretion of urate in these studies was independent of perfusate-free urate concentration. The FE_{urate} found in these experiments corresponded closely with that found by others (9, 18). We specifically chose a simple perfusate composition, despite evidence that the addition of amino acids to the perfusate would increase the GFR, decrease the fractional sodium excretion, and permit perfusions of up to 4 hr (17). We reasoned that added amino acids might alter urate excretion, particularly secretion, as suggested from isolated rabbit tubule studies (19). Although distal tubule function is known to be altered with this simple perfusate, there is no evidence for altered proximal tubule function during short perfusions (≤60 min).

We have previously demonstrated intact proximal tubular organic acid secretion and the effects of secretory inhibition in this simple isolated kidney preparation (13). Attempts were then made to alter urate excretion with five different drugs. These attempts were also not uniformly successful, although other physiologic effects of several of these drugs were readily apparent. The isolated rat kidney thus demonstrated some clear effects of the drugs given. Pyrazinoate consistently decreased FE_{urate}, similar to previous reports in isolated systems (10, 11, 20) and in whole animals (11, 18). The effect on FE_{urate} occurred independent of pyrazinoate concentration in the perfusate. The pyrazinoate-induced net decrease derives either from decreased urate secretion or increased urate absorption, which cannot be differentiated in this model. Previous studies in intact rats and in micropuncture studies have demonstrated decreased urate secretion with possible decreased urate reabsorption as well (9, 11).

Probenecid and oxonate both had a similar concentration-dependent effect on FE_{urate}, with a decrease in FE_{urate} at the low concentration but no effect at the high concentration studied. This finding was different from previous reports in which low concentrations of probenecid actually increased and high concentrations decreased urate excretion (11). Previous studies on para-aminohippuric acid secretion did not show inhibition at similar low concentrations of probenecid. Oxonate was expected to affect FE_{urate} at both concentrations (10, 20, 21). The biphasic effects of probenecid and oxonate on FE_{urate} in our study could be explained by concentration-dependent selective inhibition of urate secretion and reabsorption. In this case, only secretion would be affected at low drug concentrations leading to decreased FE_{urate}. Both secretion and reabsorption would be affected equally at higher drug concentrations without a net change in FE_{urate}. Such separate effects have been suggested by previous *in vivo* and isolated vesicle studies (10, 20, 22–23).

Furosemide and salicylate are also known to alter urate excretion in the human (24) and have been reported to change urate excretion in rats (12, 23). Both failed to change FE_{urate} in the present experiments. Physiologic effects of the two drugs were readily apparent with significant increases in FE_{Na} and urine flow rate. Thus, salicylate and furosemide enhanced sodium excretion without a concurrent effect on urate excretion. These physiologic effects attest the viability of the isolated kidney preparation. These drugs, as well as oxonate, demonstrated a dissociation between FE_{urate} and sodium and water transport (9, 25–27). These findings underscore previous work indicating that the effects of furosemide and salicylate *in vivo* are most likely related to changes in total body fluid balance, glomerular blood flow, and the intratubular presence of an unreabsorbed anion rather than changes in intrinsic renal urate handling.

Investigation of urate excretion *in vivo* in intact mammals other than the great apes and human requires both infusion of urate and inhibition of uricase to maintain elevated serum urate concentrations. Such studies may not accurately reflect intrinsic urate excretion by the kidney. In addition, the kidney may produce (2, 3) or metabolize urate, while uricase is postulated to participate in the carrier-mediated absorption from the tubule (10, 21). Fractional excretion of urate has remained widely variable (12.5–92%) (5, 9, 26, 25, 29) and concentration-dependent excretion in the rat has been demonstrated inconsistently (5, 9, 11, 25, 29, 30). Many studies concerning urate transport have been performed in isolated tubule, microperfusion or micropuncture studies (9, 18, 23, 30, 31), brush border, and basolateral vesicles (10, 20–22), all in order to obviate problems inherent in whole animal preparations. Thus far, these studies have determined that urate is excreted through carrier-mediated saturable transport systems on each side of the tubular cell, as well as passive reabsorption from the tubular lumen (9, 10, 18, 23, 31, 32). However, it is not known to what extent these data from isolated organ elements may reflect urate transport at the intact organ level.

The isolated perfused rat kidney provided a model in which we were able to study urate excretion at the organ level under controlled conditions while urate concentrations were varied over a wide range. The rat has been shown to be a net reabsorber of urate, similar to man. Previous studies in isolated rat kidneys using

radiolabeled hypoxanthine or urate demonstrated renal production of urate from hypoxanthine (2, 3) without metabolism of urate to allantoin (2, 3), despite additional evidence demonstrating the presence of uricase in the proximal tubule (20, 21). Our studies show conclusively that urate transport in the rat is not concentration dependent, unlike that in the human (24). We have also shown that drug effects on urate excretion in the isolated rat kidney do not parallel their reported effects in isolated organelles or other intact animals or man. The difference between studies of the intact organism, man and animal, and the isolated organ may be related to the presence of important regulatory factors operating *in vivo*, including sodium and water balance, hemodynamic factors, and extrarenal handling of urate. Thus, we were able to dissociate clearly the effects of a known "uricosuric" diuretic on sodium and water excretion. These findings indicate a need for isolated organ studies to complement experiments in isolated organelles and intact animals.

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1. Hitchings GH. Uric acid: Chemistry and synthesis. In: Kelley WN, Weiner IM, Eds. Uric Acid. New York: Springer-Verlag, p1, 1978.
2. Chin TY, Cacini W, Zmuda MJ, Quebbemann AJ. Quantification of renal uric acid synthesis in the rat. Am J Physiol **238**:F481–F487, 1980.
3. Quebbemann AJ, Harvey RB, Cacini W, Zmuda MJ. Renal formation and excretion of uric acid (UA) in the isolated perfused rat kidney. Pharmacologist **15**:186, 1973.
4. Roch-Ramel F, Tellier M, Peters G. Synthesis and degradation of uric acid in rat renal cortical tissue. Experientia **29**:765–766, 1973.
5. Cook MA, Atkinson JT, Lassiter WE, Gottschalk CW. Uric acid excretion by the rat kidney. Am J Physiol **229**:586–591, 1975.
6. Roch-Ramal F, Peters G. Urinary excretion of uric acid in nonhuman mammalian species. In: Kelley WN, Weiner IM, Eds. Uric Acid. New York: Springer-Verlag, p211, 1978.
7. Weiner IM, Fanell GM. Renal urate excretion in animal models. Nephron **14**:33–47, 1975.
8. Maack T. Physiological evaluation of the isolated perfused rat kidney. Am J Physiol **238**:F71–F78, 1980.
9. Abramson RG, Levitt MF. Use of pyrazinamide to assess renal uric acid transport in the rat: A micropuncture study. Am J Physiol **230**:1276–1283, 1976.
10. Abramson RG, Lipkowitz MS. Carrier-mediated concentrative urate transport in rat renal membrane vesicles. Am J Physiol **248**:F574–F584, 1985.
11. Boudry JF. Effet d'inhibiteurs des transports transtubulaires sur l'excretion renale d'acide urique chez le rat. Pflugers Arch **328**:279–291, 1971.
12. Friedman M. Observations concerning the effects of (1) sodium salicylate and (2) sodium salicylate and glycine upon the production and excretion of uric acid and allantoin in the rat. Am J Physiol **152**:302–308, 1948.
13. MacDougall ML, Wiegmann TB. Excretion of para-aminohippurate in the isolated perfused rat kidney: net secretion and net reabsorption. J Physiol (Lond) **397**:459–469, 1988.
14. Wright WK, Gann DS. An automated anthrone method for the determination of inulin in plasma and urine. J Lab Clin Med **67**:689–693, 1967.
15. Weinman EJ, Steplock D, Sansom SC, Knight TF, Senekjian HO. Use of high-performance liquid chromatography for determination of urate concentrations in nanoliter quantities of fluid. Kidney Int **19**:83–85, 1981.
16. Musser AW, Ortigoza C. Automated determination of uric acid by the hydroxylamine method. Tech Bull Reg Med Tech **36**:21–25, 1966.
17. Epstein FH, Brosnan JT, Tange JD, Ross BD. Improved function with amino acids in the isolated perfused kidney. Am J Physiol **243**:F284–F292, 1982.
18. Abramson RG, Levitt MF. Micropuncture study of uric acid transport in rat kidney. Am J Physiol **228**:1597–1605, 1975.
19. Tanner RJ, Chonko Am, Edwards RM, Grantham JJ. Evidence for an inhibitor of renal urate and PAH secretion in rabbit blood. Am J Physiol **244**:F590–F598, 1983.
20. Abramson RG, King VF, Reif MC, Leal-Pinto E, Baruch SB. Urate uptake in membrane vesicles of rat renal cortex: Effect of copper. Am J Physiol **242**:F158–F170, 1982.
21. Abramson RG, Lipkowitz MS, Rivero D, Masur SK. Cytochemical demonstration of uricase in isolated membrane vesicles of rat renal cortex. Kidney Int **29**:411, 1986.
22. Kahn AM, Shelat H, Weinman EJ: Urate and p-aminohippurate transport in rat renal basolateral vesicles. Am J Physiol **249**:F654–F661, 1985.
23. Kramp RA, Lenoir RH: Characteristics of urate influx in the rat nephron. Am J Physiol **229**:1654–1661, 1975.
24. Steele TH: Urate excretion in man, normal and gouty. In: Kelley WN, Weiner IM, Eds. Uric Acid. New York: Springer-Verlag, p257, 1987.
25. Weinman EJ, Steplock D, Suki WN, Eknoyan G. Urate reabsorption in proximal convoluted tubule of the rat kidney. Am J Physiol **231**:509–515, 1976.
26. Weinman EJ, Knight TF, McKenzie R, Eknoyan G. Dissociation of urate from sodium transport in the rat proximal tubule. Kidney Int **10**:295–300, 1976.
27. Weinman EJ, Eknoyan G, Suki WN. The influence of the extracellular fluid volume on the tubular reabsorption of uric acid. J Clin Invest **55**:283–291, 1975.
28. Boudry JF. Mecanismes de l'excretion d'acide urique chez le rat. Pflugers Arch **328**:265–278, 1971.
29. de Rougemont D, Henchoz M, Roch-Ramel F. Renal urate excretion at various plasma concentrations in the rat: A free-flow micropuncture study. Am J Physiol **231**:387–392, 1976.
30. Lang F, Greger R, Deetjen P. Handling of uric acid by the rat kidney. II. Microperfusion studies on bidirectional transport of uric acid in the proximal tubule. Pflugers Arch **335**:257–265, 1972.
31. Sansom SC, Senekjian HO, Knight TF, Babino H, Steplock D, Weinman EJ: Determination of the apparent transport constants for urate absorption in the rat proximal tubule. Am J Physiol **240**:F406–F410, 1981.
32. Roch-Ramel F, Granges F, Roth L, Widmer J, Weiner IM. Renal handling of urate by nondiuretic and diuretic rats. HPLC-amperometric determination of urate concentrations. Renal Physiol **2**:122–129, 1980.