PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 156, 514-517 (1977)

Alterations in Urine Flow Rate and Urate Excretion in the Rat (39969)

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Introduction. The current studies were designed to examine the effect of variations in urine flow rate, urine osmolality, and antidiuretic hormone (ADH) on urate excretion in the rat. Alterations in the extracellular fluid volume and the rate of solute excretion have been demonstrated to affect the urinary excretion of urate (1, 2). The influence of changes in urine flow rate, however, has not been clearly defined, and species variations may exist (3-5). Urine flow rate and urine osmolality are a function of the collecting tubule and duct cells, given a constant glomerular filtration rate (GFR) and rate of solute excretion. The results of the present investigations advance evidence that these nephron sites are not important determinants of the rates of urate excretion.

Materials and methods. Male Sprague-Dawley rats were used in all studies. Catheters were placed in both femoral veins, femoral artery, and the urinary bladder, under light ether anesthesia. The animals were placed in restraining cages and allowed to awaken. Through one venous catheter, [*methoxy*-^{3}H]inulin in isotonic saline (25 μCi/ml) was infused at a rate of 1.2 ml/hr for the duration of the study. Through the other venous catheter, in five animals, a solution of 0.21% saline was infused at a rate of 12 ml/hr. After 90 min of equilibration and after the urine flow rate and osmolality had stabilized, a timed urine collection of 10 to 20 min was obtained. A blood sample (1 ml) was obtained from the femoral artery and replaced with the same volume of blood from a donor rat. The infusion was then sequentially changed to 0.425% and 0.85% saline at infusion rates of 6 and 3 ml/hr, respectively. At each infusion rate, an equilibration period was permitted to elapse until urine flow rate and osmolality stabilized. In five animals, the order of infusions was reversed. In these animals, following the infusion of 0.21% saline at a rate of 12 ml/hr, the infusion solution was changed to 0.85% saline at 3 ml/hr, and vasopressin tannate in oil (Parke Davis, Detroit, Mich.), 200 mU, was administered subcutaneously. After stabilization, blood and urine samples were collected.

Mean arterial blood pressure was measured during the course of the study. Radioactivity of blood and urine samples was determined in Biofluor (New England Nuclear Corp., Boston, Mass.). Sodium and potassium concentrations were measured by flame photometry, uric acid concentrations by a uricase method utilizing the Beckman glucose analyzer (Beckman Instruments, Inc., Fullerton, Calif.), and osmolality by freezing point depression in an Advanced Instruments (Newton Highlands, Mass.) osmometer. Hematocrits were determined in microhematocrit tubes. The GFR was calculated from the clearance of inulin and is expressed as microliters per minute per gram kidney weight. All results are expressed as means ± SEM.

Results. At a constant GFR and rate of solute excretion, changes in the urine flow rate are a function of the collecting tubule and collecting duct. In all animals studied, the blood pressure, arterial hematocrit, and plasma urate concentrations remained constant throughout the period of study. As seen in Table I, the GFR, the urinary excretion of sodium, and urinary osmole excretion were constant in all periods of study. The results obtained were similar regardless of the order of infusion of solutions of saline of varying concentrations and the results are pooled for statistical purposes. The data points for individual animals are shown graphically in Fig. 1.

The administration of hypotonic (0.21%) saline at a rate of 12 ml/hr resulted in a urine flow rate of 100 μl/min/g kidney weight and a urine osmolality of 140 mOsm/kg of H_2O. The urinary excretion of urate

ISSN 0037-9727

TABLE I. ALTERATIONS IN URINE FLOW RATE AND URATE EXCRETION IN THE RAT.[a]

	Perfusion solution and delivery rate							
	0.85% NaCl, 3 ml/hr		0.425% NaCl, 6 ml/hr		0.21% NaCl, 12 ml/hr		ADH (0.85% NaCl), 3 ml/hr
GFR (μl/min/g kidney wt)	1108.5 ±85.0		1154.7 ±73.4		1089.8 ±80.2		1102.2 ±115.7
$U_{Na}V$ (μequiv/min/g kidney wt)	3.12 ±0.50		3.97 ±0.95		3.64 ±0.94		4.23 ±0.94
U_{osm} (mOsm/kg of H_2O)	551.5 ±94.7		282.2 ±13.3		140.3 ±13.9		709.2 ±93.5
		$P < 0.05$		$P < 0.01$		$P < 0.001$	
V (μl/min/g kidney wt)	30.8 ±4.43		55.3 ±6.44		100.4 ±9.27		18.6 ±2.25
		$P < 0.01$		$P < 0.01$		$P < 0.001$	
UV_{osm} (μOsm/min/g kidney wt)	13.28 ±1.10		15.0 ±1.9		13.8 ±2.0		12.64 ±2.16
UV_{urate} (μg/min/g kidney wt)	2.48 ±0.19		2.83 ±0.35		2.81 ±0.36		2.82 ±0.23

[a] Values are means ± SEM.

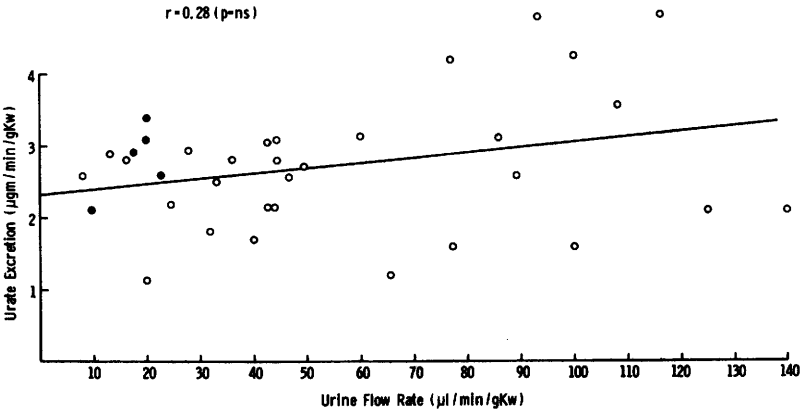

FIG. 1. The relationship between urine flow rate and the urinary excretion of urate. Each point is the average of two collection periods. Closed circles indicate animals receiving vasopressin.

averaged 2.81 μg/min/g kidney weight. The infusion of a solution of 0.425% saline at a rate of 6 ml/hr resulted in a significant decrease in urine flow rate to 55.3 μl/min/g kidney weight, and a significant increase in osmolality to 282.2 mOsm/kg of H_2O (both values $P < 0.05$ compared to values obtained with the infusion of 0.21% saline). Urate excretion, however, was not significantly different and averaged 2.83 μg/min/g kidney weight.

The infusion of 0.85% saline at a rate of 3 ml/hr resulted in a further decrease in urine flow rate (30.8 μl/min/g kidney weight) and an increase in urine osmolality (551.5 mOsm/kg of H_2O), but no change in urate excretion (2.48 μg/min/g kidney weight). The administration of ADH decreased urine flow rate and increased urine osmolality, but was without effect on urate excretion.

Discussion. The current studies were designed to alter the rate of water reabsorption in the collecting tubule and duct cells by varying the rate of infusion of water. Given a constant GFR, solute administration, and solute excretion, changes in urine flow become the exclusive function of distal nephron segments. The results of the present investigations indicate that, despite a threefold change in the urine flow rate and urine osmolality, urinary urate excretion remains constant. The additional administration of ADH, while further altering urine

flow rate and urine osmolality, was without effect on urate excretion.

The nephron site of urate reabsorption in the rat and other species has been under intensive investigation in several laboratories (5-9). Evidence from many, but not all, laboratories indicates that most of the urate filtered at the glomerulus is reabsorbed in the proximal convoluted tubule (6-8). The renal handling of urate at other nephron sites, however, has not been fully elucidated. Evidence has been presented both for and against significant urate reabsorption in the loop of Henle in the rat (7, 8, 10). Direct microperfusion studies of the rat distal convoluted tubule suggest that this nephron segment is impermeable to urate (11). Indirect assessment of urate reabsorption in the collecting ducts by comparison of the fractional rates of urate reabsorption measured in the distal convoluted tubule and in the final urine has not presented consistent evidence for urate reabsorption (7-9). The effect of urine flow rate has not been examined by these techniques, however, and it is generally difficult to alter independently urine flow rates in the anesthetized animal in the absence of volume expansion or drug administration. Steele and co-workers induced large changes in urine flow rate in the rat by the administration of lithium and observed no change in urate excretion (4). Since lithium may alter the tubular reabsorption of sodium and the secretion of hydrogen ion, these findings, although consistent with those of the present study, cannot be considered definitive (12, 13). Kramp and co-workers performed direct intratubular microinjections into the distal convoluted tubule of the rat and observed that the recovery rate of injected urate was 96%, suggesting that the collecting duct is slightly permeable to urate and may account for as much as 10% of net reabsorption (14). Prior studies from this laboratory, using identical techniques to those of Kramp et al., failed to provide evidence for collecting duct urate reabsorption (1). The specific effect of alterations in urine flow rate, however, was not evaluated in either study. Whether a small amount of urate is reabsorbed by the collecting duct or not, the urinary excretion of urate does not appear to be significantly changed by large alterations in collecting duct function in the rat.

The results of the present study in the rat contrast with studies in man, in which urate excretion does demonstrate some flow rate dependence (3, 15). Furthermore, evidence has been advanced that, in man, vasopressin administration, in the absence of change in urine flow rate, enhances urate reabsorption (15). Vasopressin has also been demonstrated to increase the rate of urate transport by the toad bladder, a tissue which is believed to respond like the collecting duct of the mammalian kidney (16). The discrepancy between these findings and those of the current investigations in the rat may be due to species differences.

Summary. The effect of alterations in urine flow rate and osmolality in urate excretion in the rat was examined by clearance techniques. The results of these studies indicate that large variations in water reabsorption in the terminal segments of the nephron do not affect the rate of urate excretion. Vasopressin administration, while decreasing urinary flow rate and increasing the osmolality of the urine, was also without effect on urate excretion.

The authors gratefully acknowledge the technical assistance of D. Steplock, S. Sansom, and E. Pace, and the secretarial assistance of P. Dunham.

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Received June 8, 1977. P.S.E.B.M. 1977, Vol. 156.