Role of Vasopressin in Rats with Bilateral Ureteral Obstruction (43223)

ALVARO A. REYES,* GARY ROBERTSON,† AND SAULO KLAHR*,[1]

Renal Division, Washington University School of Medicine, Saint Louis, Missouri 63110 and Department of Medicine,† University of Chicago, Chicago, Illinois 60611*

Abstract. **After unilateral release of bilateral ureteral obstruction (BUO), there is a significant increase in renal vasoconstriction that accounts for the marked decrease in glomerular filtration rate and effective renal plasma flow seen in this setting. We examined the potential role of antidiuretic hormone (ADH), a vasoconstrictor of the renal circulation, on renal hemodynamics in female Sprague-Dawley rats with BUO of 24-hr duration. Rats with BUO had significantly higher plasma values of ADH (65.1 ± 12.2 vs 12.1 ± 4.1 pg/ml), sodium (145.4 ± 0.91 vs 138.6 ± 1.06 mEq/liter), and osmolality (375.6 ± 2.0 vs 310.1 ± 3.6 mOsm/kg) than sham-operated rats. Rats with BUO pretreated with enalapril, an angiotensin-converting enzyme inhibitor, before obstruction had somewhat higher, but not significantly different, plasma values for ADH (84.6 ± 20.8 pg/ml) than rats with BUO not given enalapril. Rats with unilateral ureteral obstruction of 24-hr duration had plasma levels of ADH (8.2 ± 1.3) not different from those in sham-operated rats. Rats with BUO pretreated with a specific antagonist of the V_1-type receptor for ADH had significantly greater values for the glomerular filtration rate (2.31 ± 0.24 vs 1.44 ± 0.08 ml/min/kg body wt) and the effective renal plasma flow (8.95 ± 0.71 vs 3.81 ± 0.44 ml/min/kg body wt) and significantly lower values for mean arterial pressure (140.3 ± 2.0 vs 159.1 ± 5.5 mm Hg) than did BUO rats not given the antagonist. The results indicate that high levels of ADH play an important role in the decrease in the glomerular filtration rate and effective renal plasma flow observed in rats with BUO of 24 hr. The significant increase in ADH levels after BUO of 24-hr duration may be due to an increase in osmotic stimulation as a consequence of hypernatremia. Activation of the renin-angiotensin axis, known to occur after BUO or unilateral ureteral obstruction of 24-hr duration, does not appear to have a role in the increased circulating levels of ADH.**

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Remarkable decreases in glomerular filtration rate (GFR) and effective renal plasma flow (ERPF), associated with multiple abnormalities of tubular function and the development of systemic hypertension, are constant features of obstructive nephropathy (1). After unilateral release of bilateral ureteral obstruction (BUO) of 24-hr duration, there is a significant increase in renal vascular resistance resulting in sustained vasoconstriction that is, at least in part, responsible for the decrease in GFR and ERPF (2). The role of two major vasoconstrictors, angiotensin II and thromboxane A_2, in this process has been demonstrated previously (3). Administration of OKY-046, an inhibitor of the thromboxane synthase, to rats before obstruction significantly increased GFR and ERPF after unilateral release of BUO of 24-hr duration when compared with values obtained in untreated rats with BUO (3). Micropuncture studies localized the site of action of thromboxane A_2 to the afferent and efferent glomerular arterioles (4). Pretreatment of rats with enalapril, an angiotensin-converting enzyme inhibitor, before and during obstruction, significantly increased GFR and ERPF (3). Moreover, simultaneous inhibition of both angiotensin II and thromboxane A_2 production markedly raised GFR of the postobstructed kidney, but not to normal levels, indicating that the increased vascular tone of the renal microcirculation, which plays an important role in the pathophysiology of BUO (3), may involve additional vasoconstrictor substances. Among these, the role of antidiuretic hormone (ADH), a known vasoconstrictor, remains to be elucidated in the setting of obstructive nephropathy.

[1] To whom correspondence and requests for reprints should be addressed at Department of Medicine, Jewish Hospital at Washington University Medical Center, 216 S. Kingshighway, St. Louis, MO 63110.

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After secretion by the supraoptic and paraventricular nuclei of the hypothalamus, ADH binds to specific receptors to produce either peripheral vasoconstriction (V_1 receptors) or antidiuresis (V_2 receptors). The presence of V_1 receptors at the level of the postglomerular circulation has been suspected since administration of ADH, in the nanomolar range, caused a dose-dependent reduction in the diameter of the efferent arteriole without inducing changes in the diameter of the afferent arteriole (5). The vasoconstriction of the efferent arteriole was inhibited by pretreatment with a V_1-selective receptor antagonist. Videomicroscopy studies by Zimmerhackl *et al.* (6) demonstrated an ADH-related decrease in blood flow at the level of the vasa recta of the kidney medulla that was antagonized by the V_1 receptor antagonist $d(CH_2)_5Tyr(Me)AVP$.

The present studies were designed to explore the potential role of ADH in renal hemodynamics in rats with BUO of 24-hr duration. We measured plasma levels of ADH in normal rats, rats with BUO of 24-hr duration, rats with BUO pretreated with an angiotensin II-converting enzyme inhibitor prior to obstruction, and rats with unilateral ureteral obstruction. A potential functional role of ADH in obstructive nephropathy was explored by measuring GFR and renal plasma flow in rats that had unilateral release of BUO of 24-hr duration and that had or had not been given a specific V_1 receptor antagonist before obstruction.

Methods

Animals and Chemicals. We utilized 45 female Sprague-Dawley rats obtained from Sasco Inc. (Omaha, NE) weighing 170–233 g (mean weight, 195 ± 2.2 g). After arrival, the animals were housed five or six to a cage, were fed a standard rat chow containing 22.8% protein (Ralston Purina, St. Louis, MO), and had water *ad libitum*. Experiments were performed at least 7 days after arrival of the animals.

The V_1 receptor antagonist [1-(β-Mercapto-β,β-cyclopentamethylene propionic acid)-2-(*O*-methyl) tyrosine]-Arg^8-vasopressin was purchased from Bachem Inc. (Torrance, CA) and stored at −20°C until use. One week before the studies it was dissolved in distilled water to a final concentration of 840 μg/ml and administered intraperitoneally (2.5 μg/hr) through a miniosmotic pump (model 2002; Alza Corp., Palo Alto, CA) designed to deliver 0.61 μl/hr. The pump was inserted through a small suprapubic incision under ether anesthesia, after which the rats were returned to their cages without food or water restriction. Inulin was purchased from Sigma Chemical Co. (St. Louis, MO) and *p*-aminohippurate acid (PAH) was purchased from Merck, Sharp & Dohme (West Point, PA).

Ureteral Obstruction. BUO was performed in 26 rats 1 week after insertion of the miniosmotic pump by ligating both ureters at the junction of the lower one third and upper two thirds through a small suprapubic incision under ether anesthesia. These rats were returned to their cages and were not allowed food or water. They were studied 24 hr later. In the six rats in which unilateral ureteral obstruction (UUO) was performed, only the left ureter was ligated, and the rats were returned to their cages and were not allowed food or water. A sham operation was performed on six rats in which the abdominal cavity was opened and both ureters manipulated but not obstructed. These rats were returned to their cages and used in experiments for determination of vasopressin levels. These rats were also deprived of water and food for 24 hr.

Clearance Studies and Blood Pressure Determinations. This procedure was performed in 14 rats that had BUO and in 7 sham-operated rats. Standard clearance techniques were performed as described previously (3). Briefly, under light ether anesthesia, a left femoral artery catheter (PE 50), a left femoral vein catheter (PE 10), and a left ureteral catheter (PE 10) were inserted. The rats were secured in plastic holders and, 2 hr after recovery from anesthesia, were studied in the awake state. A priming dose of chemical inulin designed to produce plasma levels of 70–150 mg/dl and a dose of chemical PAH calculated to produce plasma levels of 1–2 mg/dl were infused in 0.6 ml of normal saline administered over a 3-min period. This was followed by a sustained infusion delivered at 40 μl/min which contained sufficient inulin and PAH to maintain constant plasma levels of these compounds. After an equilibration period of at least 60 min after unilateral release of BUO, three consecutive 20-min collections of urine and blood were obtained for estimation of GFR by inulin clearance (C_{in}), and ERPF by PAH clearance (C_{PAH}), and for sodium excretion. Blood pressure was recorded throughout the studies using the femoral artery catheter connected to a Harvard Apparatus (model VT-1; Winston Electronics Co., Millbrae, CA).

Experimental Groups. Seven groups of rats were studied (Table I). Group 1 ($n = 7$) consisted of sham-operated rats. Group 2 ($n = 7$) consisted of rats in which BUO of 24-hr duration was performed after 1 week of having a miniosmotic pump implanted for the intraperitoneal infusion of distilled water (0.61 μl/hr). Group 3 ($n = 7$) consisted of rats in which BUO of 24-hr duration was performed after 1 week of having a miniosmotic pump implanted for the intraperitoneal infusion of the V_1 receptor antagonist dissolved in distilled water at 2.5 μg/hr. Groups 4–7 (six rats in each group) were used for determination of circulating levels of vasopressin: (i) Six normal rats deprived of water for 24 hr (Group 4); (ii) six rats with BUO of 24-hr duration (Group 5); (iii) six rats with BUO of 24-hr duration that were pretreated with enalapril, an angiotensin-converting enzyme inhibitor (5 mg/kg body wt by

Table I. Different Groups of Rats Studied

Renal function studies
- Group 1 ($n = 7$): Sham-operated rats given distilled water intraperitoneally via a miniosmotic pump for 1 week
- Group 2 ($n = 7$): Rats with BUO of 24-hr duration given distilled water intraperitoneally via a miniosmotic pump for 1 week before and during the period of obstruction
- Group 3 ($n = 7$): Rats with BUO of 24-hr duration given a V_1 receptor antagonist (5 μg/hr) intraperitoneally via a miniosmotic pump for 1 week before and during the period of obstruction

Determination of plasma levels of vasopressin
- Group 4 ($n = 6$): Sham-operated rats
- Group 5 ($n = 6$): Rats with BUO of 24-hr duration
- Group 6 ($n = 6$): Rats with BUO of 24-hr duration that were given enalapril (5 mg/kg body wt by gastric lavage) twice a day for 2 days before and at the time of BUO
- Group 7 ($n = 6$): Rats with UUO of 24-hr duration

gastric lavage twice a day 48 hr before and at the time of obstruction) (Group 6); and (iv) six rats that had UUO of 24-hr duration (Group 7). These rats were sacrificed by decapitation, and the blood was immediately collected from the trunk in centrifuge tubes containing 50 μl of heparin. Samples were centrifuged immediately and the plasma was separated and kept at −20°C until determinations were performed as described below. Additional samples were obtained in heparinized capillary tubes to assess hematocrit values and for determination of sodium, potassium, blood urea nitrogen (BUN), glucose, and osmolality.

Analytic. Sodium and potassium were measured by standard flame photometry (Instrumentation Laboratory Inc., Lexington, MA). Plasma osmolality was measured in a vapor pressure osmometer (Wescor Inc., Logan, UT). ADH in plasma was determined as described previously (7). Inulin was determined using the anthrone method (8) and PAH was measured by a modification of the method of Smith *et al.* (9).

Calculations. Clearance values for inulin and PAH were calculated using standard formulas. For each rat, the values of three consecutive clearance periods were averaged. Values for plasma osmolality were measured in triplicate and values did not differ from each other by more than 4 mOsm/kg. These values were averaged for each rat. Intergroup comparisons were performed by means of analysis of variance. Differences were considered significant when $P < 0.05$.

Results

The general characteristics of the three groups of rats that had measurements of renal function are summarized in Table II. All three groups had comparable body weights and hematocrit values. Rats with BUO (Groups 2 and 3) had significantly higher values for urine flow and for fractional water excretion than sham-operated rats (Group 1). Total and fractional sodium excretion and total and fractional potassium excretion were also greater after unilateral release of BUO than in sham-operated rats. Values for plasma sodium in rats with BUO did not differ significantly from those obtained for normal rats. Rats with BUO of 24-hr duration had significantly higher values for filtration fraction than sham-operated rats. The administration of the V_1 receptor antagonist in rats with BUO (Group 3) significantly decreased values for filtration fraction when compared with values obtained in the group of rats with BUO that received vehicle (Group 2). This was due to a greater increase in ERPF than in GFR in the former group of rats. Rats with BUO pretreated with a V_1 receptor antagonist (Group 3) had significantly lower values for fractional water excretion and lower, but not significantly different, values for fractional sodium excretion than rats with BUO given vehicle (Group 2). Plasma potassium was significantly higher in rats with BUO than in sham-operated rats. Rats pretreated with the V_1 receptor antagonist (Group 3) had significantly higher values for plasma potassium than rats with BUO given vehicle (Group 2).

The values for mean arterial pressure for sham-operated rats (Group 1) and for rats with BUO that were or were not pretreated (Groups 3 and 2, respectively) with a V_1 receptor antagonist are depicted in Figure 1. Sham-operated rats had significantly lower values for mean arterial pressure (130.4 ± 2.0 mm Hg) than rats with BUO given vehicle (159.1 ± 5.5 mm Hg). The rats that received the V_1 receptor antagonist for 1 week before and during BUO (Group 3) had significantly lower values for mean arterial pressure (140.3 ± 4.2 mm Hg) than rats that received vehicle alone before and during BUO (Group 2).

Values for GFR as measured by C_{in}, and for ERPF as measured by C_{PAH}, for the three groups of rats are shown in Figure 2. Normal rats (Group 1) had significantly higher values for GFR and ERPF (6.46 ± 0.36 and 24.7 ± 2.1 ml/min/kg body wt, respectively) than rats with BUO (both Groups 2 and 3). Rats with BUO that received the V_1 receptor antagonist (Group 3) had significantly higher values for GFR (2.31 ± 0.24 ml/min/kg body wt) and for ERPF (8.95 ± 0.71 ml/min/kg body wt) than rats with BUO that received vehicle (Group 2) (1.44 ± 0.08 ml/min/kg body wt and 3.81 ± 0.44 ml/min/kg body wt, respectively).

Values for plasma ADH in rats of Groups 4–7 are shown in Figure 3. Rats with BUO of 24-hr duration (Group 5) had plasma levels of ADH that were 5-fold greater than those of sham-operated rats (Group 4). Rats with BUO pretreated with enalapril (Group 6) before obstruction had a higher, but not significantly different, value for plasma ADH than rats with BUO not given enalapril (Group 5). Rats with UUO (Group

Table II. General Characteristics of Three Groups of Rats in which Physiologic Studies were Performed

Group	n	Weight (g)	Hematocrit (%)	Filtration fraction	Urine flow (μl/min)	Sodium (μEq/liter)	FE_{Na}[a] (%)	Potassium (μEq/liter)	FE_K (%)	FE_{H_2O} (%)
Sham	7	212.0 ± 5.3[b]	44.9 ± 0.9	0.26 ± 0.01	25.6 ± 3.5	146.1 ± 0.8	1.8 ± 0.2	3.8 ± 0.1	22.4 ± 2.0	2.5 ± 3.9
BUO	7	197.7 ± 7.9	42.9 ± 0.5	0.39 ± 0.03	40.8 ± 1.7	146.4 ± 1.0	10.6 ± 1.3	4.2 ± 0.1	95.9 ± 8.8	15.0 ± 1.5
BUO + V_1 antagonist	7	197.7 ± 7.9	42.1 ± 0.6	0.28 ± 0.02	42.6 ± 5.1	143.5 ± 1.7	6.3 ± 0.7	4.5 ± 0.1	73.6 ± 7.4	9.4 ± 0.6
Analysis of variance		NS	NS	a,c[c]	a,b	NS	a,b,c	a,b	a,b,c	a,b,c

[a] FE_{Na}, fractional sodium excretion; FE_K, fractional potassium excretion; FE_{H_2O}, fractional water excretion; NS, not significant.
[b] Results are expressed as mean ± SE. Differences are considered significant when $P < 0.05$.
[c] a, $P < 0.05$ for comparisons between sham and BUO; b, $P < 0.05$ for comparisons between sham and BUO + V_1 antagonist; and c, $P < 0.05$ for comparisons between BUO and BUO + V_1 antagonist.

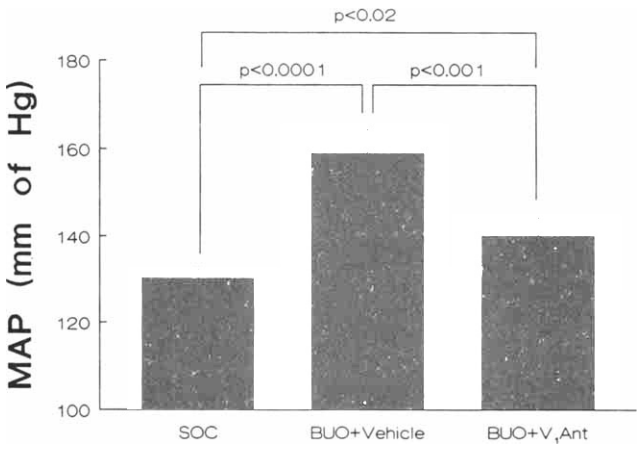

Figure 1. Mean arterial pressure (MAP) measurements in the three groups of rats in which renal function studies were performed. Each group consisted of seven rats. Sham-operated rats (SOC) received vehicle (distilled water) for 8 days and rats with BUO received either vehicle or V_1 receptor antagonist (V_1-Ant) (5 μg/hr) via a miniosmotic pump for 1 week before and during obstruction. Direct measurements were obtained at the time of clearance studies via a femoral artery catheter. Differences were considered significant when $P < 0.05$.

7) had plasma ADH levels not different from sham-operated control rats.

Values for plasma osmolality obtained in rats of Groups 4–7 are shown in Figure 4. Rats with BUO (Group 5) had significantly greater plasma osmolality values than sham-operated rats (Group 4) (375.6 ± 2.0 vs 310.1 ± 3.6 mOsm/kg). Pretreatment of rats with BUO with enalapril (Group 6) significantly decreased values for plasma osmolality (361.1 ± 1.6 mOsm/kg) compared with rats that had BUO (Group 5). Rats with UUO (Group 7) had significantly lower values for plasma osmolality (321.2 ± 0.6) than rats that had BUO and were pretreated with enalapril, and osmolality values in rats with UUO were also significantly greater than values obtained in sham-operated control rats.

Values for plasma glucose, BUN, sodium, and potassium obtained in rats from Groups 4–7 are summarized in Table III. There were no statistically significant differences in plasma glucose values among the groups. Rats with BUO (Group 5), rats with BUO pretreated with enalapril (Group 6), and rats with UUO (Group 7) had significantly higher plasma sodium values than sham-operated rats (Group 4). Rats with BUO (Group 5) and those with BUO given enalapril (Group 6) had significantly higher values for plasma potassium than sham-operated rats (Group 4) and rats with UUO (Group 7). Rats with BUO pretreated with enalapril (Group 6) had significantly lower values for plasma potassium than rats with BUO not given enalapril (Group 5). Rats with UUO had lower, but not significantly different, values for plasma potassium than sham-operated rats. Rats with BUO (Groups 5 and 6) had significantly higher values for BUN than sham-operated rats (Group 4) or rats with UUO (Group 7).

Discussion

Renal function is significantly decreased after unilateral release of BUO of 24-hr duration. GFR is reduced by 65–70% and ERPF is reduced by 60–65%. The decreased renal blood flow is due to increased resistance of the renal microcirculation. Both thromboxane A_2 and angiotensin, two potent vasoconstrictors, play a role in the increased resistance of the renal circulation seen in obstructive nephropathy (3, 10). Inhibition of angiotensin and thromboxane A_2 synthesis, alone or in combination, before obstruction markedly increased GFR and ERPF after unilateral release of BUO of 24-hr duration (3). This indicates that vasoconstriction due to these vasoactive substances has a role in the pathogenesis of BUO (3). However, the values for GFR and ERPF did not return to the values seen in normal rats, suggesting that other mechanisms may have a role in the vasoconstriction of the renal circulation.

The present study was designed to investigate the potential role of ADH, as a vasoconstrictor of the renal circulation, in obstructive nephropathy. Two findings described in this study strongly suggest that ADH plays a role in the vasoconstriction of the renal circulation seen in rats with BUO. First, significantly higher circulating levels of ADH were present in rats with BUO than in sham-operated control rats or rats with UUO.

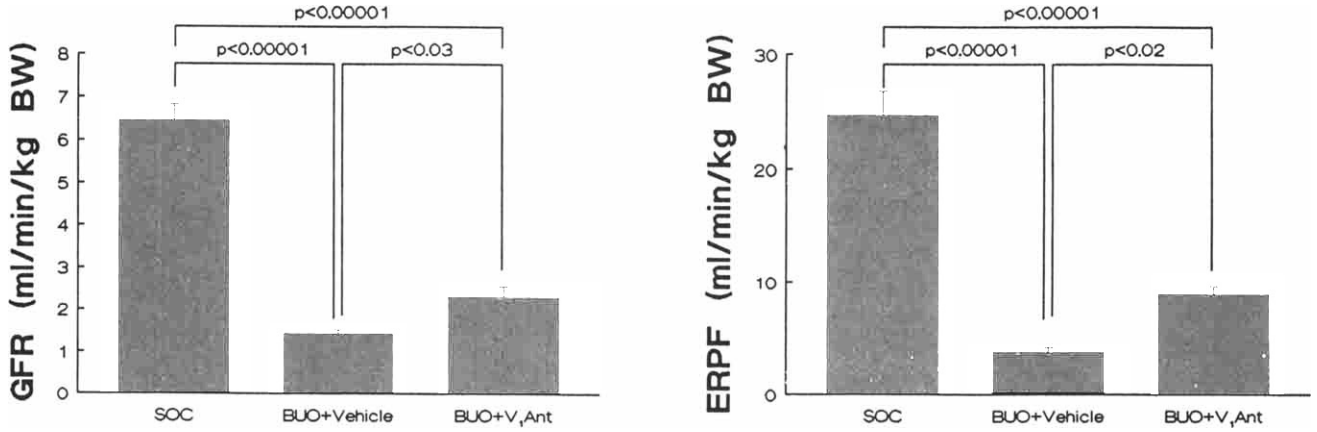

Figure 2. GFR and ERPF in the three groups of rats. Each group consisted of seven rats. Sham-operated rats (SOC) received vehicle (distilled water) for 8 days and rats with BUO received either vehicle or V_1 receptor antagonist (V_1-Ant) via a miniosmotic pump for 1 week before and during obstruction. Results are expressed as mean ± SE. Values from sham-operated rats are for one kidney. Studies in rats with BUO were performed after unilateral release of obstruction of 24-hr duration. Differences are considered significant when $P < 0.05$.

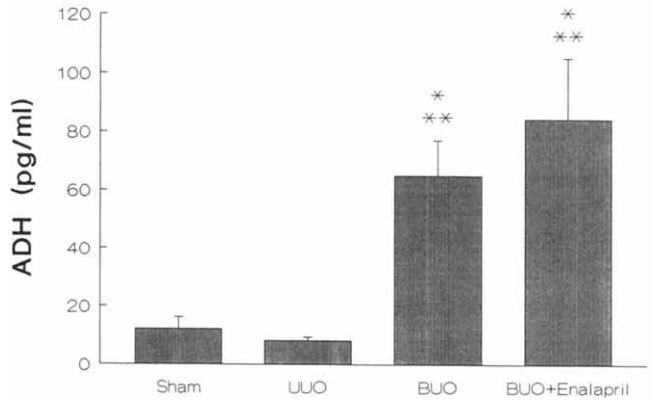

Figure 3. Plasma levels of ADH in four groups of rats. Each group of rats consisted of six rats that were deprived of water and food 24 hr before sample collection. Rats were sacrificed by decapitation. * Values significantly different from those obtained in sham-operated rats. ** Values significantly different from those obtained in rats with UUO.

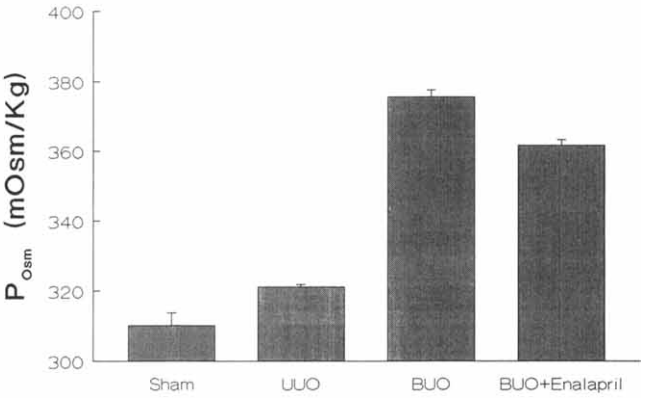

Figure 4. Values for plasma osmolality in four groups of rats that had measurements of ADH. Each group consisted of six rats. Rats were deprived of food and water before sample collection and were sacrificed by decapitation. P_{Osm}, plasma osmolality. For clarity, P values were not included in the figure. The values were: sham versus UUO rats, $P < 0.005$; sham versus BUO rats, $P < 0.0001$; sham versus BUO rats given enalapril, $P < 0.0001$; UUO rats versus BUO rats, $P < 0.0001$; UUO rats versus BUO rats given enalapril, $P < 0.0001$; and BUO rats versus BUO rats given enalapril, $P < 0.0005$.

Second, blockade of the V_1 receptor for ADH, by using a receptor antagonist, resulted in significantly greater values for GFR and ERPF after unilateral release of BUO in rats (Fig. 2). Furthermore, rats with BUO pretreated with the V_1 receptor antagonist had significantly lower values for systemic blood pressure than those observed in rats with BUO not given the V_1 receptor antagonist.

The 5-fold increase in the plasma levels of ADH in rats with BUO of 24-hr duration, when compared with sham-operated controls (Fig. 3), is probably related to the 20–25% increase (approximately 65 mOsm/kg) in plasma osmolality in rats with BUO of 24-hr duration. This increase in plasma osmolality was due in part to significant changes in the level of plasma sodium, which is, by far, the major determinant of plasma osmolality and vasopressin release. By contrast, there were no differences in plasma sodium concentrations between sham-operated rats and rats with BUO that underwent functional studies (Table II). The reason for the differences in plasma sodium concentration between rats with BUO and sham-operated control rats in one group of animals (Table III) but not in the other (Table II) is not immediately apparent. Elevated levels of BUN contributed to the higher levels of plasma osmolality observed in rats with BUO. However, the higher values of BUN of rats with BUO may not account for the increased release of ADH observed in these rats. It is known that urea does not stimulate ADH release due to the fact that this substance is highly permeable across cell membranes and is usually in chemical equilibrium in the intracellular and extracellular space. Thus, cell volume alterations necessary to stimulate the release of ADH by neurons of the supraoptic and paraventricular

Table III. Plasma Chemistries in Rats that had Measurements of ADH

	Glucose (mg/dl)	BUN (mg/dl)	Sodium (mEq/liter)	Potassium (mEq/liter)
Sham-operated control rats	104.5 ± 4.5[a]	18.1 ± 2.15	138.6 ± 1.06	6.12 ± 0.22
BUO	114.6 ± 8.9	119.6 ± 9.0	145.4 ± 0.91	7.79 ± 0.34
BUO + enalapril	113.6 ± 3.2	113.8 ± 13.5	145.1 ± 1.23	7.03 ± 0.16
UUO	102.5 ± 2.3	28.2 ± 1.26	142.6 ± 1.2	5.66 ± 0.21
Analysis of variance	Not significant	a,b,e,f[b]	a,b,c	a,b,d,e,f

[a] Results are expressed as mean ± SE. Each group consisted of six rats. Differences were considered significant when $P < 0.05$. Rats were deprived of water and food for 24 hr before sample collection. Rats were sacrificed by decapitation in the awake state without stress.
[b] Statistical comparisons among the groups ($P < 0.05$). a, Sham-operated rats versus rats with BUO; b, sham-operated rats versus rats with BUO given enalapril; c, sham-operated rats versus rats with UUO; d, rats with BUO versus rats with BUO given enalapril; e, rats with BUO versus rats with UUO; and f, rats with UUO versus rats with BUO given enalapril.

nuclei in the hypothalamus may not occur when urea accumulates (11). Rats with BUO also had significantly higher values for plasma potassium than sham-operated rats. Hyperkalemia is a constant finding after unilateral release of BUO of 24-hr duration (12) but does not occur with UUO of 24-hr duration (2). Because potassium is the prevalent intracellular cation, it is unlikely that it would create a significant osmotic gradient across the membrane to result in the marked changes in plasma ADH observed in these studies.

It is possible that in the BUO model of obstructive nephropathy nonosmotic stimuli play a role in ADH release. These stimuli may include: changes in neurotransmitters, hypoxia, and volume depletion. All animals were studied under the same experimental conditions. Blood samples for ADH determinations were obtained by decapitation in previously resting, awake animals to avoid the effect of nonosmotic stimuli (i.e., anesthetics or neurotransmitter release) known to increase plasma levels of ADH.

Because central nervous system angiotensin II is a potent stimulus for ADH release, we evaluated its role in the increased plasma values of ADH observed after BUO of 24-hr duration. Prior inhibition of angiotensin II production by administration of an angiotensin I-converting enzyme inhibitor did not significantly modify the circulating levels of ADH in rats with BUO. Furthermore, measurements of plasma ADH in rats with UUO, a condition characterized by an increase in the activity of the renin-angiotensin axis (13), revealed no increase in the plasma levels of ADH when compared with sham-operated rats. This occurred despite significantly higher values of plasma osmolality in rats with UUO as compared with sham-operated rats. These data suggest that angiotensin II does not play an important role in the increase in circulating levels of ADH observed in rats with BUO or UUO.

Whatever the mechanism underlying the increase in the circulating levels of ADH after BUO, the data indicate that ADH plays a significant role in obstructive nephropathy. We found that pretreatment with a specific V_1 receptor antagonist significantly decreased systemic blood pressure and increased GFR and ERPF. Peripheral vasodilation appears to be one of the beneficial effects of inhibiting the V_1 receptor. Inasmuch as it is known that the renal vascular bed is more sensitive to the vasoconstrictor action of ADH than the aorta or the carotid arteries (5), it would be expected that the effect of V_1 receptor inhibition would be more marked on kidney function than on blood pressure. However, both were affected by inhibition of the V_1 receptor.

The mechanism by which the V_1 receptor antagonist increased GFR in the present study is not completely clear. Treatment with the antagonist certainly increased effective renal blood flow which may in turn increase GFR. However, the presence of V_1 receptors at the level of the postglomerular circulation may result in greater vasodilation of the efferent arteriole than of the afferent arteriole of the renal glomerulus when the V_1 antagonist is administered. Because vasodilation of the efferent arteriole results in decreased hydrostatic pressure within the glomerulus, the higher values for GFR and ERPF obtained in rats that had BUO of 24-hr duration after inhibition of the V_1 receptors for ADH indicate that there must be a concomitant increase in the capillary surface available for filtration (ultrafiltration coefficient, K_f). In fact, Ausiello *et al.* (14) demonstrated contraction of rat mesangial cells in culture after stimulation with ADH. Furthermore, Jard *et al.* (15) demonstrated the presence of V_1 receptors in mesangial cells. Consequently, the V_1 receptor antagonist may increase GFR through an increase in surface area available for filtration by decreasing the contraction of mesangial cells resulting from increased circulating levels of ADH.

The results of this study demonstrate a significant increase in plasma levels of ADH after BUO of 24-hr duration, which may be explained in part by an increase in osmotic stimulation as a consequence of hypernatremia. This study presents evidence that inhibition of the systemic vasoconstrictor receptor for ADH prior to BUO results in preservation of GFR and ERPF and

decreased systemic blood pressure. The results suggest that high plasma levels of ADH play a role in the decrease in GFR and ERPF observed in obstructive nephropathy.

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