Kidney International, Vol. 21 (1981), pp. 365–370

Role of renal prostaglandins during antidiuresis and water diuresis in man

REBECCA M. WALKER, ROBERT S. BROWN, and JEFFERY S. STOFF

Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory, Department of Medicine, Beth Israel Hospital, Boston, Massachusetts

Role of renal prostaglandins during antidiuresis and water diuresis in man. The relationship of renal prostaglandins to antidiuretic hormone action and water diuresis was examined in 13 normal subjects and 2 subjects with diabetes insipidus. Following overnight water deprivation, an oral water load caused a prompt and sustained rise in the rate of urinary PGE_2 excretion from 7.7 ± 1.2 to 81.6 ± 26.4 ng/hr ($P < 0.0001$) in 7 normal subjects. Because the simultaneous increase in urinary excretion of urea was only 17% of the rise in urinary PGE_2, passive wash-out of renal PGE_2 probably accounts for only a small fraction of the increment in PGE_2 excretion. Administration of the antidiuretic hormone analogue DDAVP to 6 normal subjects during sustained water diuresis resulted in a decrease in PGE_2 excretion and urine flow rate comparable to that of dehydrated subjects. Thus, PGE_2 excretion varied directly with urine flow rate over a wide range of states of hydration in all 13 normal subjects. One patient with central diabetes insipidus and one with nephrogenic diabetes insipidus demonstrated a similar positive correlation of PGE_2 excretion rate and urinary flow rate in states of hydration, dehydration, and after administration of DDAVP. In the patient with nephrogenic diabetes insipidus, this relationship of PGE_2 excretion rate to urine flow rate was unaffected by DDAVP over a broad range of urine flow rates. Inhibition of prostaglandin synthesis with indomethacin in 6 normal subjects resulted in a significant decline in free water clearance (7.7 ± 1.0 to 4.7 ± 0.9 ml/min, $P < 0.001$) and an increase in the minimal U_{Osm} (61 ± 4 to 93 ± 19 mOsm/kg, $P < 0.01$) achieved during water diuresis without a change in creatinine or osmolar clearances. Furthermore, the tightly linked relationship of PGE_2 excretion rate to urine flow rate was reduced in 5 of 6 subjects during indomethacin treatment. We conclude that urinary PGE_2 excretion varies directly with urine flow rate and is not directly dependent on ADH activity or state of hydration in man. The rise in PGE_2 excretion during water diuresis may enhance the excretion of free water since indomethacin treatment blunted free water clearance while suppressing the rise in PGE_2 excretion.

Rôle des prostaglandines rénales au cours de l'antidiurèse et de la diurèse aqueuse chez l'homme. La relation entre les prostaglandines rénales et l'action de l'hormone antidiurétique et la diurèse aqueuse a été étudiée chez 13 sujets normaux et 2 sujets atteints de diabète insipide. A la suite d'une restriction d'eau pendant la nuit précédant l'étude, une charge d'eau par voie orale a déterminé une augmentation rapide et prolongée du débit urinaire de PGE_2 de 7,7 ± 1,2 à 81,6 ± 26,4 ng/hr ($P < 0,001$) chez 7 sujets normaux. Puisque l'augmentation simultanée de l'excrétion urinaire d'urée était seulement de 17% de l'augmentation de la PGE_2 urinaire, un lavage passif de la PGE_2 rénale explique probablement une partie seulement de l'augmentation de l'excrétion de PGE_2. L'administration d'un analogue de l'hormone antidiurétique, DDAVP, à 6 sujets normaux au cours d'une diurèse aqueuse prolongée a eu pour conséquence une diminution de l'excrétion de PGE_2 et du débit urinaire comparable à celle des sujets déshydratés. Ainsi l'excrétion de PGE_2 varie directement avec le débit urinaire sur un large éventail d'états d'hydratation chez tous les 13 sujets normaux. Un malade atteint de diabète insipide central et un malade atteint de diabète insipide néphrogénique ont eu une corrélation positive semblable du débit d'excrétion de PGE et du débit urinaire dans les états d'hydratation, de déshydratation, et après l'administration de DDAVP. Chez le malade atteint de diabète insipide néphrogénique, cette relation de l'excrétion de PGE_2 au débit urinaire n'a pas été affectée par DDAVP sur un large éventail de valeurs du débit urinaire. L'inhibition de la synthèse de prostaglandine par l'indométhacine chez 6 sujets normaux a eu pour conséquence une diminution significative de la clairance de l'eau libre (7,7 ± 1,0 à 4,7 ± 0,9 ml/mn, $P < 0,001$) et une augmentation de la valeur minimale de U_{osm} (61 ± 4 à 93 ± 19 mOsm/kg, $P < 0,01$) obtenues au cours d'une diurèse aqueuse sans modification de la clairance de la créatinine ou de la clairance osmolaire. De plus, la relation étroite entre l'excrétion de PGE_2 et le débit urinaire a été réduite chez 5 des 6 sujets au cours du traitement par l'indométhacine. Nous concluons que l'excrétion urinaire de PGE_2 varie directement avec le débit urinaire et n'est pas directement dépendante de l'activité de l'ADH ou de l'état d'hydratation chez l'homme. L'augmentation de l'excrétion de PGE_2 au cours de la diurèse aqueuse peut accroître l'excrétion d'eau libre puisque le traitement par l'indométhacine atténue la clairance de l'eau libre en même temps qu'il supprime l'augmentation de l'excrétion de PGE_2.

Regulation of renal water excretion is required for the maintenance of a constant concentration of the body fluids. Although antidiuretic hormone (ADH) plays a crucial role in the renal handling of water, a number of other hormones are also of substantial importance. In recent years, it has been recognized that renal prostaglandins have potent effects on water metabolism during antidiuretic conditions. These effects are exerted principally by antagonism of the hydroosomotic effect of antidiuretic hormone. In this regard, it has been demonstrated that exogenously added prostaglandin E_1 inhibits vasopressin-stimulated water transport in the toad bladder model [1], as well as the isolated perfused collecting tubule of the rat [2]. A similar role for endogenous prostaglandins is inferred from the observation that pharmacologic inhibition of renal prostaglandin synthesis is associated with an enhanced responsiveness to antidiuretic hormone in rat and man [3, 4].

Recently, studies performed in our laboratory have shown that prostaglandins have effects on water metabolism independent of their interaction with ADH. In rats undergoing water diuresis or with hereditary diabetes insipidus, free water excre-

Received for publication February 27, 1981
and in revised form July 14, 1981

0085–2538/82/0021-0365 $01.20

Table 1. Effect of dehydration and water loading on the excretion of water, urea, and PGE_2[a]

	Water deprivation	Maximal water diuresis
U_{Osm}, *mOsm/kg* H_2O	906 ± 85	58 ± 5
C_{H_2O}, *ml/min*	− 0.8 ± 0.2	7.2 ± 0.8
Urea excretion, *mg/hr*	480 ± 44	882 ± 225
PGE_2 excretion, *ng/hr*	7.7 ± 1.2	81.6 ± 26.4

[a] Determinations under water deprivation were made after 10 hours of dehydration. Water diuresis values were obtained in the second hour after water loading. All results found during water diuresis were significantly different from those after water deprivation ($P < 0.001$).

tion is markedly suppressed by inhibitors of prostaglandin synthesis [5]. In addition, enhanced urinary excretion of prostaglandin E_2 (PGE_2) has been reported in dogs after an acute intravenous water load [6] and in man, when chronic polyuria is induced by progressive increments in daily water intake [7]. In this regard, Craven, Briggs, and Derubertis [8] have demonstrated a threefold increase in PGE_2 synthesis by slices of medullary tissue of the rat kidney incubated in isotonic media, a condition that mimics the low medullary osmolality generated during water diuresis. These studies are consistent with the view that PGE_2 synthesis is enhanced during water diuresis and suggest an important regulatory role for prostaglandins in modifying water excretion in the absence of ADH. Recent studies using the Brattleboro rat strain have suggested, however, a conflicting view [9, 13]. In these studies, there was a lower than normal PGE_2 excretion in rats with hereditary diabetes insipidus undergoing diuresis and an increase in PGE_2 excretion during antidiuresis following arginine vasopressin or DDAVP administration. The present investigation was designed to study the importance of prostaglandins in the water metabolism of man, pursuing the following questions: (*1*) Is prostaglandin excretion enhanced with acute induction of water diuresis and with the polyuria of diabetes insipidus? (*2*) Does ADH alter PGE_2 excretion? (*3*) Is there a role for renal prostaglandins in the excretion of water?

Methods

Clinical Studies: (a) Normal Subjects. Group 1 ($N = 7$) of normal subjects (4 male, 3 female; ages 24 to 43 years) was studied after water deprivation for 10 hours. Following two baseline hourly urine collections, a standard oral water load (20 ml/kg) was given over 30 min, and urine was collected for 4 hours while replacing hourly urine volumes with an equivalent volume of water by mouth.

Group 2 ($N = 6$) of normal subjects (4 male, 2 female; ages 20 to 33 years) was given an identical water load. Following the 4 hours of sustained water diuresis, water intake was discontinued and 40 μg of 1-desamino-8-D-arginine vasopressin (DDAVP) (Ferring Pharmaceuticals, Ltd.) was administered intranasally. Urine was collected hourly during 4 hours of water loading and the 3 hours following DDAVP and analyzed for osmolality, creatinine, urea nitrogen, and PGE_2. This entire study was repeated after the oral administration of indomethacin, 150 mg daily for 3 days.

(b) Nephrogenic diabetes insipidus. A white male patient, age 40, with lithium-induced nephrogenic diabetes insipidus (daily urine volume of 7 to 11 liters), whose polyuria persisted for more than a year after lithium was withdrawn, was studied. Maximal urine osmolality after 7 hours of dehydration and 5% weight loss was 130 mOsm/kg H_2O (despite a high plasma ADH of 14.6 μU/ml) and 181 mOsm/kg H_2O 3 hours after DDAVP (40 μg) was given. Several series of hourly urine collections were obtained in the patient. Urine was collected in hours 8 to 10 of dehydration and the subsequent 3 hours after intranasal DDAVP (40 μg) was given. Collections were also obtained during two periods of sustained water diuresis (induced as described above for normal subjects): one following maintenance of normal hydration, and the other following overnight dehydration. Urine obtained in each hourly period was analyzed as in the normal subjects.

(c) Central diabetes insipidus. A white female patient, age 62, with central diabetes insipidus of 3 months' duration, secondary to metastatic breast carcinoma, had 24-hour urine collections before and during DDAVP treatment. Urine volume ranged from 10 to 12 liters/day and 2 to 4 liters/day with DDAVP treatment (10 to 20 μg/day). The patient was studied after dehydration to a level of 5% below normal body weight and maintenance of that level of dehydration by oral intake of water each hour equivalent to urinary losses, and then following administration of DDAVP.

All subjects and patients were studied at the Clinical Research Center of Beth Israel Hospital and gave informed consent to the studies. All protocols for the studies were approved by the Committee on Clinical Investigations, New Procedures and New Forms of Therapy of Beth Israel Hospital.

Laboratory studies. Urine was refrigerated immediately after collection, and aliquots were stored at −20° C until assayed. Five to six milliliters of each sample were lyophilized after addition of 5000 to 6000 cpm of ^3H-PGE_2 to monitor recovery (65 to 75%). Samples were resuspended in 2 ml of double distilled water and extracted in organic solvents followed by elution on silicic acid columns as previously described [10]. Urinary immunoreactive PGE_2 was measured by radioimmunoassay using highly specific antibody prepared as previously described [10]. The assay had been validated by the addition of known amounts of authentic, highly purified PGE_2 (courtesy of J. Pike, Upjohn Co.) within the anticipated experimental range and by the use of conditions which are known to inhibit and stimulate prostaglandin synthesis.

Urine urea was measured as urea nitrogen and expressed as milligrams of urea. Urine osmolality was measured by freezing-point depression (Advanced Instruments, Newton Highlands, Massachusetts). Plasma antidiuretic hormone was measured by Nichols Institute (San Pedro, California).

All values are expressed as mean ± SEM unless otherwise indicated. The relationship between urine volume and PGE_2 excretion was examined by correlation analysis. Slopes and intercepts were calculated using model II linear regression because both variables come from underlying normal distributions [11].

Results

(1) Effect of dehydration and water loading on PGE_2 excretion rate in normal subjects. The maximal urine osmolality of 7 normal subjects (group 1) after 10 hours of dehydration was 906 ± 85 mOsm/kg H_2O and fell to a minimum of 58 ± 5 mOsm/kg H_2O after oral water loading (Table 1). The rate of urea excretion doubled from 480 ± 44 to 882 ± 225 mg/hr during maximal diuresis, whereas PGE_2 excretion increased tenfold,

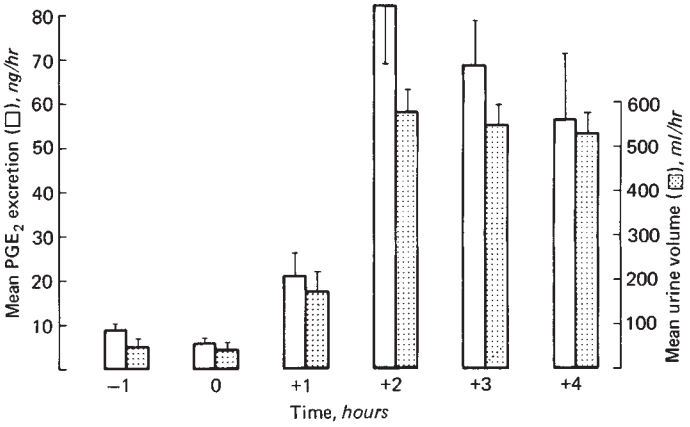

Fig. 1. *Effect of water deprivation and water loading on PGE_2 excretion rate and urine flow rate in 7 normal subjects (group 1) after 10 hours of dehydration (hour 0) followed by oral water loading (see text).* All data are mean ± SEM. Increases in urine volume and PGE_2 excretion from hours 1 to 4 are highly significant ($P < 0.01$).

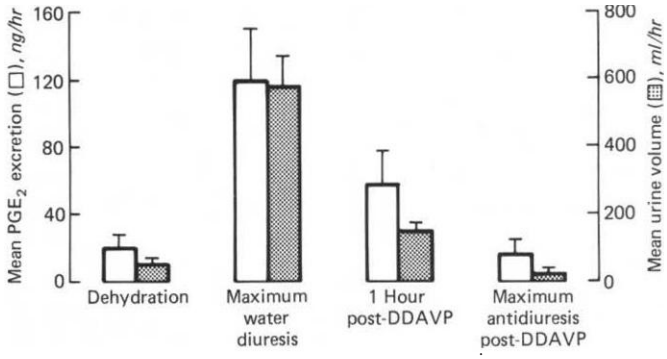

Fig. 2. *Influence of exogenous ADH (DDAVP) on PGE_2 excretion rate and urine flow rate in 6 normal subjects (group 2).* Values after dehydration and DDAVP are significantly different from those during maximal diuresis ($P < 0.001$) by paired t test).

Table 2. Statistical analysis of relationship between rates of urine flow and PGE_2 excretion in 7 subjects

Subject[a]	*Y*-intercept	Slope	*P*[b]
A	−27.4	0.32	<.02
B	− 9.9	0.29	<.002
C	− 4.2	0.08	NS
D	9.2	0.07	<.001
E	− 3.6	0.06	<.01
F	3.4	0.10	<.001
G	4.6	0.12	<.01

[a] For each subject, the relationship between urine volume (x) and PGE_2 excretion (y) is best fit by a line derived by regression analysis (model II).

[b] P indicates statistical difference between an individual slope and a slope of zero.

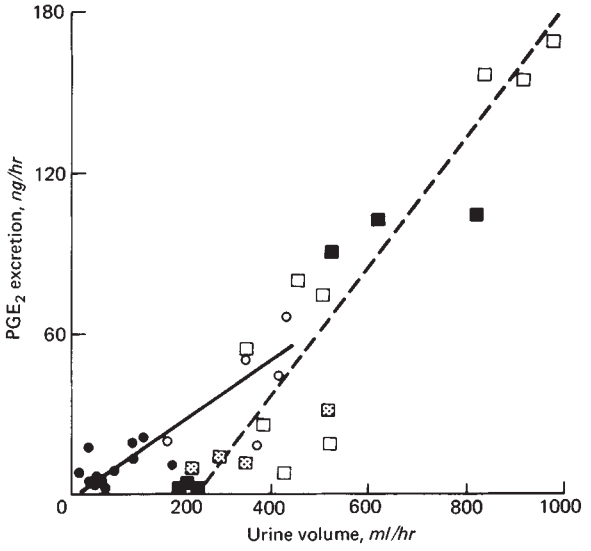

Fig. 3. *Relationship of PGE_2 excretion rate and urine flow rate in central diabetes insipidus* (solid line) *and nephrogenic diabetes insipidus* (dashed line). The patient with central diabetes insipidus was studied after cessation of ad lib water intake, before DDAVP (*open circles*) and following DDAVP (*closed circles*). The patient with nephrogenic diabetes insipidus was studied after water loading (*open squares*), after dehydration (*stippled squares*), and after DDAVP (*closed squares*). The values with DDAVP in which urine volume was greater than 400 ml/hr were obtained during water loading.

from a baseline of 7.7 ± 1.2 to 81.6 ± 26.4 ng/hr ($P < 0.001$). The increase in PGE_2 excretion was present during the first hour of water diuresis, increased to a maximal rate by 2 hours, and remained constant during the period of sustained water diuresis (Fig. 1). Analysis of the relationship in each subject reveals that 6 of the 7 subjects showed strong positive correlation between the rate of urine flow and the excretion of PGE_2, with statistical significance ranging between $P < 0.001$ and $P < 0.02$ (Table 2). Thus, when subjects were studied during dehydration (high ADH levels) and during water loading (low ADH levels), PGE_2 excretion and urine flow rate were tightly linked.

(2) Effect of ADH on PGE_2 excretion rate. To determine whether the ADH level or the state of hydration was primarily influencing the relationship of PGE_2 excretion and urine flow, we performed additional experiments. To eliminate the usual association of increased ADH with a low state of hydration, we administered DDAVP to water-loaded normal subjects. DDAVP resulted in a marked fall in urine volume and a corresponding decline in PGE_2 excretion rate to levels indistinguishable from those after water deprivation (Fig. 2). Because these subjects were water-loaded, this observation tends to exclude the state of hydration as a factor in PGE_2 excretion rate.

Further support that the state of hydration does not independently affect PGE_2 excretion rate is found in a patient with central diabetes insipidus. During water deprivation with dehydration to 5% below normal body weight, both urine volume and PGE_2 excretion remained high (Fig. 3). Only after administration of DDAVP did urine volume and PGE_2 excretion fall in a manner similar to normals. Thus, PGE_2 excretion correlates directly with urine flow and is independent of the state of hydration.

Because ADH could affect urinary PGE_2 excretion independent of its associated effect on urine flow rate, a patient with nephrogenic diabetes insipidus was studied under dehydrated and water-loaded conditions. Figure 3 demonstrates that urinary PGE_2 excretion varied directly with changes in urine

Table 3. Effect of indomethacin on the excretion of an oral water load in normal subjects[a]

	Control	Indomethacin	*P*
C_{Cr}, *ml/min*	82.3 ± 9.1	76.6 ± 15.8	NS
C_{H_2O}, *ml/min*	7.7 ± 1.0	4.7 ± 0.9	<0.0001
C_{Osm}, *ml/min*	2.0 ± 0.3	1.9 ± 0.2	NS
Minimal U_{osm}, *mOsm/kg* H_2O	61 ± 3.6	93 ± 19.1	<0.01

[a] Six normal subjects were studied before and after treatment with indomethacin (150 mg/day for 3 days). Creatinine clearance was measured on a 24-hr urine collection while the subjects were on ad lib diet and activity. Maximal free water clearance (C_{H_2O}), C_{Osm}, and minimal U_{osm} were determined in hours 2 or 3 after an oral water load with continuing replacement. Values expressed are mean ± SEM for all the subjects, while statistical difference was determined by paired *t* test in each subject.

volume induced by dehydration and water loading in the presence or absence of DDAVP. Because ADH activity was high during dehydration (endogenous ADH) when PGE_2 excretion was low and high during hydration (exogenous ADH) when PGE_2 excretion was high, it seems likely that the relationship of PGE_2 excretion to urine flow rate is independent of ADH.

(3) Effect of prostaglandin synthesis inhibition on water and PGE_2 excretion. If the increase in PGE_2 excretion exerts an important influence on water metabolism, inhibition of prostaglandin synthesis should impair water excretion. To test this possibility, we administered water loads with continuing hourly replacement of urine volume before and following indomethacin treatment (150 mg/day for 3 days) in 6 normal subjects (group 2, $N = 6$). Endogenous creatinine clearance, collected during ad lib water and solute intake, was not altered by indomethacin treatment (Table 3). During indomethacin treatment, free water clearance was markedly decreased from 7.7 ± 1.0 to 4.7 ± 0.9 ml/min ($P < 0.0001$ by paired *t* test), whereas osmolar clearance remained constant. The minimal urine osmolality achieved during water loading was substantially higher following indomethacin treatment (93 ± 19.1 vs. 61 ± 3.6 mOsm/kg H_2O $P < 0.01$), indicating a failure to maximally dilute the urine (Table 3).

The administration of indomethacin caused a decrease in both urine PGE_2 excretion and urine flow rate following water loading (Fig. 4). In a similar fashion to the first group of normal subjects (Table 2), four of six subjects during control conditions showed a positive correlation between urine flow rate and PGE_2 excretion rate with statistical significance ranging between $P < 0.01$ to $P < 0.05$ (Table 4). The decrease in the slopes following indomethacin treatment was significant in 5 subjects ($P < 0.02$, by paired *t* test). The slope of subject 6 after indomethacin treatment was excluded from the data analysis because it was greater than 2 SD from the mean of all slopes in both groups 1 and 2. The indomethacin treatment, therefore, diminished both the functional response to free water loading and the diuresis-associated increase in prostaglandin E_2 excretion.

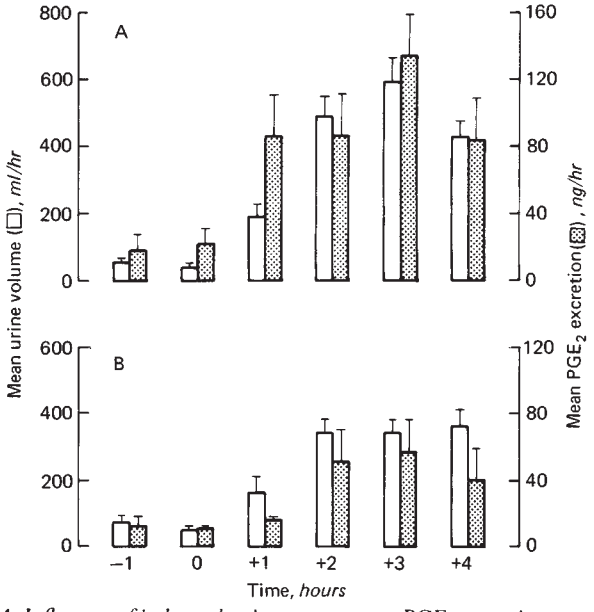

Fig. 4. *Influence of indomethacin treatment on PGE_2 excretion rate and urine flow rate in 6 normal subjects (group 2) during water deprivation and water loading.* **A** is before indomethacin; **B** during indomethacin. The rise of both urine volume and PGE_2 excretion was suppressed by indomethacin treatment.

Discussion

Renal excretion of water is influenced by several factors including glomerular filtration rate, antidiuretic hormone, and tubular function. Recent studies suggest that prostaglandins play a crucial role in modifying water excretion in animals. In both the rat made polyuric by the induction of hypercalcemia [12] and the dog given intravenous water loads [6], a linear relationship between PGE_2 excretion rate and urine flow rate has been demonstrated.

The present study was directed toward an exploration of the relationship of PGE_2 excretion and urine flow in man. Our findings in normal man show that PGE_2 excretion rate is directly related to urine volume during both antidiuresis and acute induction of water diuresis. In two pathologic states of polyuria, nephrogenic and central diabetes insipidus, a similar correlation of PGE_2 excretion rate with urine flow rate was demonstrated. This observation is consistent with the report of a stepwise increase of daily PGE_2 excretion with chronic water loading in man [7].

Considerable controversy has emerged in regard to the effect of antidiuretic hormone on renal prostaglandin synthesis. Studies of toad bladder [14] and renal medullary interstitial cells in culture [15] have demonstrated that vasopressin directly stimulates prostaglandin biosynthesis. These observations are supported by studies in intact animals in which DDAVP administration in the Brattleboro rat, with central diabetes insipidus, resulted in an increase in PGE_2 excretion [9, 13]. Because previous studies have provided substantial evidence that exogenous PGE_1 and PGE_2 inhibit ADH action [1, 2, 16–18] whereas inhibition of endogenous prostaglandin synthesis enhances the response to ADH [4, 17, 19], it has been proposed that ADH-stimulated PGE_2 synthesis provides a negative feedback loop to limit ADH action. Recent studies, however, have challenged this proposal. During water diuresis when ADH is suppressed, a rise in PGE_2 excretion has been demonstrated in the dog [6] and man [7]. Furthermore, a recent report of the effect of vasopressin or DDAVP on the toad bladder failed to detect stimulation of prostaglandin biosynthesis [20]. Our results present additional evidence in man that ADH does not enhance

Table 4. Statistical comparison of relationship of urine flow and PGE_2 excretion in control and indomethacin conditions

	Control			Indomethacin		
Subject	*Y* intercept	Slope	*P*[a]	*Y* intercept	Slope	*P*[a]
1	40.1	.11	<.02	1.3	.07	NS
2	−6.1	.19	<.05	3.8	.03	NS
3	2.8	.13	NS	30.6	−.04	NS
4	−32.4	.35	NS	−29.4	.26	NS
5	−3.2	.50	<.01	−30.0	.23	NS
6	22.6	.24	<.05	−8.5	.60	<.01

[a] *P* indicates statistical difference of the slope in control or indomethacin conditions from a slope of zero. See footnote Table 2 for additional detail.

renal prostaglandin production, as reflected by urinary PGE_2 excretion. During antidiuresis, induced by either overnight dehydration when endogenous ADH is abundant or after administration of the vasopressin analogue (DDAVP) to water loaded subjects, the prostaglandin excretion rate decreased in parallel with the decrease in urine flow rate. Thus, ADH action in man is associated with a decrease in urinary PGE_2 excretion and presumably a decrease in renal PGE_2 biosynthesis. In fact, a suppressive effect of vasopressin cannot be entirely ruled out as PGE_2 excretion consistently decreased when DDAVP was given. Such a suppression in normal man lacks sufficient proof because of the inevitable association of vasopressin action with low urine flow rates. In these studies in man we cannot exclude a direct stimulatory effect of ADH on PGE_2 biosynthesis in a compartment not in equilibrium with the final urine. This seems unlikely however, since infusion of either arachidonic acid or angiotensin II, known to increase renal PGE_2 biosynthesis, produces a concomitant rise in urinary PGE_2 excretion [21]. These studies strongly support the view that urinary PGE_2 excretion is a valid marker for intrarenal biosynthesis of prostaglandins [21].

Substantial dehydration or the administration of DDAVP to patients with central and nephrogenic diabetes insipidus also resulted in a decrease in urinary PGE_2 with the decrease in urine volume. It is of interest that the patient with nephrogenic diabetes insipidus had much higher PGE_2 excretion rates when urine volumes were maintained with hydration (despite maximal ADH effect following DDAVP) than when urine volumes were low after overnight dehydration (despite similar high levels of ADH, endogenous or exogenous). This finding would suggest in this subject that it is the urine flow rate to which PGE_2 excretion rate is related and not the plasma level of ADH. The observation that the patient with nephrogenic diabetes insipidus had a correlation of urine flow rate to PGE_2 excretion comparable to normal subjects argues against a possible suppressive effect of vasopressin on PGE_2 excretion. Such a patient, however, may not be representative of normal physiology since inability to alter water permeability in response to DDAVP might not be the only abnormality in nephrogenic diabetes insipidus (that is, ADH-mediated alterations in prostaglandin synthesis may also be abnormal). The same relationship pertains in normal subjects, in which the effect of varying the state of hydration was eliminated by the administration of DDAVP after water loading. In this case, ADH primarily caused a decrease in urine volume with a resultant decrease in PGE_2 excretion.

A central question raised by the tightly linked relationship of prostaglandin excretion rate and urine flow rate is whether the presence of enhanced urinary prostaglandin excretion implies a functional role for prostaglandins or rather represents the passive wash-out effect of an increase in urine flow rate. Kirschenbaum [6] suggests that this abundant appearance of prostaglandins in dilute urine may be attributed to a diffusion-limited, flow dependent process. In the present study, the excretion of urea, known to be freely diffusible across cell membranes, also was related to urine flow rate but exhibited only a two-fold increase in excretion rate in contrast to the ten-fold rise in PGE_2 excretion rate seen during water diuresis. This suggests that simple diffusion alone does not account for the large increment in PGE_2 excretion and that the synthesis of PGE_2 may be stimulated during excretion of a water load. Moreover, when prostaglandin synthesis was inhibited with indomethacin, the positive relationship of prostaglandin excretion rate and urine flow rate was markedly attenuated (Fig. 4, Table 4). Associated with this disruption in the linkage between prostaglandin excretion and urine flow rate was a marked alteration in tubular function, as free water excretion was depressed and maximal urinary dilution was substantially impaired without concomitant changes in creatinine or osmolar clearances.

If the increase in urinary prostaglandin excretion represents an increase in renal prostaglandin biosynthesis during the induction of a water diuresis, several potential signals for this response may be involved. Craven et al [8] reported that prostaglandin synthesis is enhanced in medullary slices of the rat kidney incubated in isosmotic media, rather than in media made hypertonic by the addition of urea. This suggests that a decrease in medullary osmolality induced by water loading may stimulate prostaglandin formation. Alternatively mechanical dilatation of tubules induced by increased urinary flow rate might alter plasma membrane surface sufficiently to activate phospholipase activity resulting in an increase in prostaglandin synthetic rate. The increase in urinary prostaglandin excretion found in the postobstructive state may be an example of this effect [22]. It is of interest that a defect in concentrating ability also characterizes the state of postobstructive diuresis.

Regardless of the signal for enhanced prostaglandin synthesis, the increase in PGE_2 could contribute to the maintenance of conditions favoring diuresis by antagonism of the effects of any residual ADH, and by increasing vasa recta blood flow leading to further dilution of the medulla. In addition, inhibition of active chloride transport by PGE_2 at the thick ascending limb of

the loop of Henle [23] would decrease the accumulation of medullary solute contributing further to the formation of a dilute urine.

This study does not explore the mechanism by which prostaglandins enhance water excretion but documents the closely linked, linear relationship of prostaglandin excretion rate and urine flow rate in normal man and in diabetes insipidus. This relationship is shown to be primarily dependent on urine flow rate and not the state of hydration or the presence or absence of ADH. In addition, the functional importance of this relationship is reflected by the decrease in free water clearance and impairment of urinary dilution under conditions of prostaglandin synthesis inhibition. These results are consistent with the view that PGE_2 modulates the renal excretion of water in man.

Acknowledgments

This work was supported by Grant 1 RO1 AM 26155 from the U.S. Public Health Service to Dr. Stoff and by a grant (RR-01032) from the General Clinical Research Center Branch, Division of Research Resources. It was presented in part at the National Meeting of the American Federation of Clinical Research, Washington, D.C., 1980. Dr. Walker is a fellow of the Kidney Foundation of Canada. Diane Leone and Jonathan Ellis gave technical assistance, Dr. Franklin H. Epstein gave support and encouragement, Dr. Bernard Ransil gave assistance in data analysis, and the nursing and dietary staff of the Clinical Research Center of Beth Israel Hospital gave clinical help.

Reprint requests to Dr. Jeffrey Stoff, Renal Unit, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215, USA

References

1. Orloff J, Handler JS, Bergstrom S: Effect of prostaglandin (PGE) on the permeability response of the toad bladder to vasopressin, theophylline and adenosine 3′, 5′-monophosphate. *Nature (Lond)* 205:397–398, 1965
2. Grantham JJ, Orloff J: Effect of prostaglandin E_1 on the permeability response of the isolated collecting tubule to vasopressin, adenosine 3′, 5′-monophosphate and theophylline. *J Clin Invest* 47:1154–1161, 1968
3. Gullner H, Gill JR, Bartter FC, Dusing R: The role of the prostaglandin system in the regulation of renal function in normal women. *Am J Med* 69:718–724, 1980
4. Berl T, Raz A, Wald H, Horowitz J, Czaczkes W: Prostaglandin synthesis inhibition and the action of vasopressin: Studies in man and rat. *Am J Physiol* 232:F529–F537, 1977
5. Stoff JS, Rosa RM, Silva P, Epstein FH: Indomethacin impairs water diuresis in the DI rat: Role of prostaglandins independent of ADH. *Am J Physiol* 241:F231–F237, 1981
6. Kirschenbaum MA, Serros ER: Effects of alterations in urine flow rate on prostaglandin E excretion in conscious dogs. *Am J Physiol* 238:F107–F111, 1980
7. Kaye Z, Zipser R, Hahn J, Zia P, Horton R: The effect of urine volume on renal prostaglandin (PGE) excretion in man (abst). *Clin Res* 27:62A, 1979
8. Craven PA, Briggs R, Derubertis FR: Calcium-dependent action of osmolality on adenosine 3′, 5′-monophosphate accumulation in rat renal inner medulla: Evidence for a relationship to calcium-responsive arachidonate release and prostaglandin synthesis. *J Clin Invest* 65:529–542, 1980
9. Dunn MJ, Greely HP, Valtin H, Kinter LB, Beeuwkes R: Renal excretion of prostaglandins E_2 and F_2 in diabetes insipidus rats. *Am J Physiol* 235:E624–E627, 1978
10. Stoff JS, Stemerman M, Steer M, Salzman E, Brown RS: A defect in platelet aggregation in Bartter's syndrome. *Am J Med* 68:171–180, 1980
11. Cornbleet PJ, Gochman N: Incorrect least-squares regression coefficients in method-comparison analysis. *Clin Chem* 25(3):432–438, 1979
12. Serros ER, Lowe A, Kirschenbaum MA: Prostaglandin-dependent polyuria in conscious hypercalcemic rats (abst). *Clin Res* 27:430A, 1979
13. Walker LA, Whorton AR, Smigel M, France R, Frolich JC: Antidiuretic hormone increases renal prostaglandin synthesis in vivo. *Am J Physiol* 235:F180–F185, 1978
14. Zusman RM, Keiser HR, Handler JS: Vasopressin-stimulated prostaglandin E biosynthesis in the toad urinary bladder. *J Clin Invest* 60:1339–1347, 1977
15. Zusman RM, Keiser HR: Prostaglandin biosynthesis by rabbit renomedullary interstitial cells in tissue culture. Stimulation by angiotensin II, bradykinin and arginine vasopressin. *J Clin Invest* 60:215–223, 1977
16. Lipson LC, Sharp GW: Effect of prostaglandin E_1 on sodium transport and osmotic water flow in toad bladder. *Am J Physiol* 220:1046–1052, 1971
17. Albert WC, Handler JS: Effect of PGE_1, indomethacin, polyphloretin phosphate on toad bladder response to ADH. *Am J Physiol* 226:1382–1386, 1974
18. Urakabe S, Takamitsu Y, Shirai D, Yuasa S, Kimura G, Orita Y, Abe H: Effect of different prostaglandins on the permeability of the toad urinary bladder. *Comp Biochem Physiol* 52C:1–4, 1975
19. Anderson RJ, Berl T, McDonald KM, Schrier RW: Evidence for an in vivo antagonism between vasopressin and prostaglandin in the mammalian kidney. *J Clin Invest* 56:420–426, 1975
20. Bisordi JE, Schlondorff D, Hays RM: Interaction of vasopressin and prostaglandins in the toad urinary bladder. *J Clin Invest* 66:1200–1210, 1980
21. Frolich JC, Wilson TW, Sweetman BJ, Smigel M, Nies AS, Carr K, Watson JT, Oates JO: Urinary prostaglandins, identification and origin. *J Clin Invest* 55:763–770, 1975
22. Fradet Y, Simard J, Grose JH, Lebel M: Enhanced urinary prostaglandin E_2 in postobstructive diuresis in humans. *Prostaglandins Med* 5:29–30, 1980
23. Stokes JB: Effect of prostaglandin E_2 on chloride transport across the rabbit thick ascending limb of Henle. Selective inhibition of the medullary portion. *J Clin Invest* 64:495–502, 1979