JCI The Journal of Clinical Investigation

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J Clin Invest. 1973;52(2):463-471. https://doi.org/10.1172/JCI107203.

Research Article

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Mechanism of Effect of Prostaglandin E_1 on Renal Water Excretion

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ABSTRACT The present study examined the effect of prostaglandin E_1 (PGE_1) on renal water excretion in the anesthetized dog. Renal perfusion pressure was kept constant by adjustment of a suprarenal aortic clamp. In seven experiments the intravenous administration of PGE_1 (7 μg/min) significantly increased urinary osmolality from 76 to 381 mosmol ($P < 0.001$) and decreased free water clearance from 2.2 to -0.02 ml/min ($P < 0.001$). These effects promptly were reversed with cessation of the infusion. This antidiuretic effect occurred both in innervated and denervated kidneys and was not associated with changes in glomerular filtration rate, renal vascular resistance, or solute excretion rate. In 10 experiments in hypophysectomized dogs no effect of intravenous PGE_1 on free water clearance and urinary osmolality was observed. The intrarenal administration of PGE_1 (1 μg/min) to six water-loaded and two hypophysectomized dogs caused no systemic vascular changes and increased rather than decreased free water clearance (2.83 to 4.08 ml/min, $P < 0.001$). No significant change in urinary osmolality occurred. Glomerular filtration rate was not altered by the intrarenal infusion, but reversible changes in solute excretion rate and renal vascular resistance occurred. These results thus indicate that the antidiuresis associated with intravenous PGE_1 is mediated primarily by the release of vasopressin rather than alterations in renal hemodynamics or solute excretion. The diuretic effect of intrarenal PGE_1 occurs in the absence of vasopressin and is most likely mediated primarily by increased distal delivery of tubular fluid to the diluting segment of the nephron rather than changes in water permeability of the renal tubular epithelium.

A preliminary report of this work was presented at the Fifth International Congress of Nephrology in Mexico City on 12 October 1972.

Dr. Berl is a postdoctoral fellow supported by the National Kidney Foundation. Dr. Schrier is an Established Investigator of the American Heart Association. Dr. Schrier's present address is the University of Colorado School of Medicine, Denver, Colo., 80220. (Reprint requests should be addressed to Dr. Schrier.)

Received for publication 1 August 1972 and in revised form 28 September 1972.

INTRODUCTION

The prostaglandins, a group of naturally occurring fatty acids, have been implicated in the regulation of hormonal action in various tissues. The results of in vitro studies in the toad bladder (1, 2) and the rabbit collecting duct (3) indicate that prostaglandin E_1 (PGE_1)[1] may antagonize the hydro-osmotic effects of vasopressin. PGE_1 has also been found to inhibit the vasopressin-mediated changes in adenyl cyclase activity and 3',5'-adenosine monophosphate (cyclic AMP), thereby providing an explanation for the mechanism whereby PGE_1 may antagonize the in vitro effect of vasopressin on osmotic water movement (4). In the absence of vasopressin, an in vitro effect of PGE_1 has not been observed on water movement in the toad bladder (1) but PGE_1 has been reported to enhance water movement in the rabbit collecting duct (3).

The in vivo effects of PGE_1 on renal water excretion in the mammalian nephron have been less intensely investigated. Infusion of PGE_1 into the renal artery of the dog has been reported to increase free water clearance (5–7), but whether the presence of vasopressin is necessary for such an effect to occur has not been defined. In contrast to this diuretic effect of intrarenal PGE_1, the infusion of PGE_1 intravenously may be associated with an antidiuresis (8). Whether such an antidiuretic effect occurs as a result of the endogenous release of vasopressin (ADH), alterations in systemic

[1] *Abbreviations used in this paper:* ADH, antidiuretic hormone; C_{H_2O}, free water clearance; FF, filtration fraction; GFR, glomerular filtration rate; PGE_1, prostaglandin E_1; RVR, renal vascular resistance; U_{osm}, urinary osmolality.

TABLE I

The Effects of Intravenous PGE_1 on Systemic and Renal

	Cardiac output			Systemic arterial pressure			Renal perfusion pressure			Arterial hematocrit volume			GFR		
	Pre-control	PGE_1	Post-control‡	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control
	liters/min			*mm Hg*			*mm Hg*			%			*ml/min*		
Mean	3.1	3.8	3.1	148	130	142	119	118	118	43.0	43.2	41.0	42.3	41.8	46.0
± SE	±0.3	±0.2	±0.2	±2.4	±0.9	±2.5	±3.6	±2.9	±2.5	±1.3	±1.6	±1.1	±3.1	±2.4	±3.7
P value	<0.02	<0.05		<0.001	<0.001		NS	NS		NS	<0.02		NS	NS	

* The results are the mean values from seven experiments; the values for renal hemodynamic and electrolyte excretion are expressed per kidney.
‡ Precontrol, PGE_1, and Postcontrol represent periods before, during, and after prostaglandin infusion, respectively.
NS = not significant, (*P* value >0.5).

and renal hemodynamics or a primary effect of the agent on the water permeability of the collecting duct is not known.

The present investigation was therefore undertaken to investigate the mechanisms whereby PGE_1 may alter renal water excretion in the mammalian nephron. Intravenous infusion of PGE_1 was found to produce an antidiuresis which could be dissociated from a diminution in renal perfusion pressure, renal hemodynamics, or solute excretion rate and could be abolished by acute hypophysectomy. The intrarenal infusion of prostaglandin, in an amount comparable to that reaching the kidney during the intravenous infusion, was never associated with such an antidiuresis, but rather increased free water excretion even in the absence of endogenous vasopressin. This increase in free water excretion occurred without significant alterations in urinary osmolality and appeared to be primarily related to increased delivery of tubular fluid to the diluting segment of the nephron. These results thus demonstrate that prostaglandin E_1 may alter renal water excretion by both extrarenal and intrarenal mechanisms.

METHODS

25 experiments were performed on 15 mongrel dogs of either sex weighing 20–30 kg. Food was withheld for 18 h and water was allowed ad lib. The animals were anesthetized with intravenous (i.v.) pentobarbital (30 mg/kg), intubated, and ventilated with a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). Light anesthesia was maintained throughout the experiment by administration of supplemental doses of pentobarbital. Six animals underwent transbuccal hypophysectomy via a 2 cm hole in the hard palate on the morning of the experiment and were then treated in the same manner as the remainder of the animals. All animals received 5 mg of deoxycorticosterone intramuscularly (i.m.) and the hypophysectomized animals also received dexamethasone (0.8 mg i.m. and 0.8 mg i.v.). Each animal received an i.v. infusion of 2.5 g/100 ml dextrose at 20 ml/min for 50 min while the following surgery was performed through bilateral retroperitoneal flank incisions. Catheters were placed in both ureters; kidneys were denervated by stripping the nerves from the renal pedicle and then applying 95% ethanol. In eight animals, including two hypophysectomized, a 23 gauge needle was placed in the left renal artery for infusion of PGE_1. An adjustable Blalock clamp was placed around the aorta above both renal arteries for use in controlling renal perfusion pressure. Catheters were also inserted into the femoral and brachial arteries to allow continuous monitoring of arterial pressures with Statham transducers (Statham Instruments, Inc., Oxnard, Calif.). A jugular vein catheter was placed in the right atrium for injection of indocyanine green to measure cardiac output by the dye dilution method as previously described (9). After completion of the above surgery an intravenous infusion of a 0.9% sodium chloride solution (0.5 ml/min) was started containing sufficient inulin and *p*-aminohippuric acid to maintain levels between 15–20 mg/100 ml and 1–3 mg/100 ml, respectively. If 30 min after the infusion of the liter of 2.5% g/100 ml glucose, the urinary osmolality of any animal was above 150 mosmol/kg, an additional 600 ml of 2.5 g/100 ml glucose was administered over 20 min. Thereafter, the infusion rate was decreased to 4 ml/min above urine flow. Experiments were only performed in those animals in which urine osmolality was below 150 mosmol/kg. In these animals the experiments were started after the urine flow rate had stabilized for 30 min. Throughout the experiment the periods of urine collection were 5–10 min in duration and arterial and renal venous blood samples were obtained at the midpoint of alternate urine collections. Cardiac outputs were measured every third period. The effect of intravenous and intrarenal PGE_1 on renal water excretion was examined by the following protocols:

Intravenous studies. Seven experiments in six animals with intact hypothalamohypophyseal tracts and 10 experiments in six acutely hypophysectomized animals were performed according to the following protocol. After three stable control periods an i.v. infusion of PGE_1 was started. A 20–30 min equilibration period was allowed, then three to five experimental urine collections were made. The i.v. infusion of PGE_1 was then discontinued and after another 20–30 min equilibration period, three to five postcontrol urine collections were made. In all but four of these studies the renal perfusion pressure was maintained constant throughout the study by adjustment of a suprarenal aortic clamp.

Intrarenal studies. Eight experiments in eight animals (including two hypophysectomized and three intact animals which were also used in the i.v. studies) were performed with the same protocol as in the i.v. studies except that the PGE_1 was infused into one renal artery. The dose used (1 μg/min) was chosen to avoid systemic hemodynamic

RVR			FF			Urinary sodium excretion			Urinary potassium excretion			Osmolar clearance		
Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control
mm Hg/ml per min						*μeq/min*			*μeq/min*			*ml/min*		
0.584	0.609	0.584	0.333	0.343	0.346	11	22	17	27	36	36	0.86	0.83	0.98
±0.1	±0.1	±0.1	±0.02	±0.03	±0.02	±3.2	±8.2	±7.3	±2.2	±4.5	±2.8	±0.04	±0.1	±0.1
	NS NS			NS NS			NS NS			<0.05 NS			NS <0.01	

changes but to equal or exceed the amount of PGE_1 estimated to reach the kidney during the i.v. studies.

The analytical procedures and calculations used in the present experiments have been referred to elsewhere (10). The Student paired *t* test was used for statistical analysis of results obtained in the same animal and the unpaired *t* test was used for analysis of results in different groups of animals. A P value < 0.05 was considered significant.

RESULTS

The results of the effect of intravenous or intrarenal prostaglandin on any of the parameters measured were not statistically different in the innervated and denervated kidneys; therefore the results of all the kidneys have been analyzed together.

Intravenous prostaglandin E_1 studies (Figs. 1–3, Tables I and II). The effects of PGE_1 on systemic and renal hemodynamics, and electrolyte excretion in the group of intact animals are shown in Table I. The i.v. PGE_1 was associated with a significant increase in cardiac output from 3.1±0.3 to 3.8±0.2 liters/min ($P < 0.02$) which decreased to 3.1±0.2 liters/min ($P < 0.05$) after cessation of the infusion. A simultaneous fall in mean arterial blood pressure from 148±2.4 to 130±0.9 mm Hg ($P < 0.001$) also occurred which increased to 142±2.5 mm Hg ($P < 0.001$) after discontinuance of the infusion. The i.v. infusion of PGE_1 was therefore associated with a substantial decline in total peripheral resistance. With the exception of exp. 4, renal perfusion pressure was kept constant throughout all of the experiments by the adjustment of a suprarenal aortic clamp. When i.v. PGE_1 was given, the hematocrit did not change from the control value but a mean decrease from 43.2±1.6 to 41.0±1.1 vol percent ($P < 0.02$) occurred after cessation of the infusion. GFR, RVR, and FF were not significantly changed during the i.v. infusion of PGE_1. The changes in sodium and potassium excretion, and osmolar clearance were variable; of these parameters only the potassium excretion increased significantly during the i.v. infusion of PGE_1. In the absence of a change in renal arterial pressure and renal hemodynamics or a decrease in solute excretion rate, the infusion of PGE_1 was associated with a significant decrease in free water clearance (CH_2O) and an increase in urinary osmolality (U_{osm}). The mean CH_2O decreased from 2.27±0.2 ml/min before to − 0.02 ±0.2 ml/min during i.v. PGE_1 ($P < 0.001$) and increased to 2.02±0.3 ml/min ($P < 0.001$) after cessation

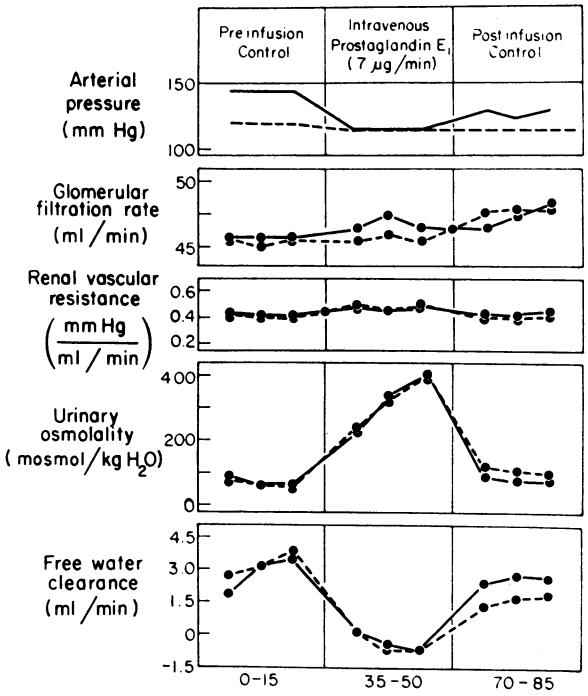

FIGURE 1 Antidiuretic effect of i.v. prostaglandin in an intact dog. The solid line represents results from the right kidney and the dotted line represents results from the left kidney, except in the arterial pressure panel where the solid line and dotted lines denote systemic and renal perfusion pressure, respectively. The increase in urinary osmolality and the decrease in free water clearance was associated with a decrease in systemic arterial pressure. Renal perfusion pressure, GFR, and RVR were not significantly changed.

TABLE II

The Effects of Intravenous PGE_1 on Systemic and Renal

	Cardiac output			Systemic arterial pressure			Renal perfusion pressure			Arterial hematocrit volume			GFR		
	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control
	liters/min			*mm Hg*			*mm Hg*			%			*ml/min*		
Mean	3.2	3.6	3.0	116	93	113	97	87	89	42.7	43.3	42.0	41.8	42.6	42.6
± SE	±0.2	±0.4	±0.3	±3.3	±5.2	±5.0	±1.6	±4.2	±3.7	±1.1	±1.1	±1.3	±1.2	±1.2	±1.2
P value	NS	<0.02		<0.001	<0.005		<0.02	NS		NS	<0.01		NS	NS	

* The results are the mean values from 10 experiments; the values for renal hemodynamic and electrolyte excretion are expressed per kidney. See Table I for abbreviations.

of the i.v. PGE_1 infusion. At the same time the U_{osm} was 76±3 mosmol/kg before and 381±26 mosmol/kg ($P < 0.001$) during the i.v. PGE_1 infusion and decreased to 91±9 mosmol/kg ($P < 0.001$) after cessation of the i.v. infusion of PGE_1. The results of a representative experiment are shown in Fig. 1.

The effects of i.v. PGE_1 on systemic and renal hemodynamics, and electrolyte excretion in the acutely hypophysectomized dog are shown in Table II and were quite similar to the results observed in the intact animals (Table I). Although the control arterial pressures were lower in the group of hypophysectomized animals the glomerular filtration rates and renal blood flows were comparable to those in intact animals. Acutely hypophysectomized animals prepared in this manner have been previously shown to respond to the exogenous administration of vasopressin (11). As in the intact animals, i.v. PGE_1 was associated with a fall in arterial pressure as cardiac output increased and total peripheral resistance decreased. The cardiac output increased in five of the six experiments in which it was measured. This increase in cardiac output did not, however, reach a level of statistical significance, but the diminution in cardiac output after cessation of the infusion did. In 7 of the 10 experiments the renal perfusion pressure was within 6 mm Hg of the control perfusion pressure during the i.v. infusion of PGE_1. The GFR, RVR, and FF were not altered significantly from the control values to the PGE_1 period of infusion, but the RVR and FF increased significantly during the postinfusion control period. Arterial hematocrit decreased significantly after cessation of the i.v. infusion of PGE_1. The urinary sodium and potassium excretion, and osmolar clearance were unaltered during these i.v. PGE_1 experiments in acutely hypophysectomized animals. Although the effects of i.v. PGE_1 on systemic and renal hemodynamics and electrolyte excretion were comparable in the intact and hypophysectomized animals, no alteration in U_{osm} or C_{H_2O} occurred during the i.v. PGE_1 infusion in the hypophysectomized animals as exemplified by the dog in Fig. 2. The mean C_{H_2O} was 2.02±0.3 ml/min before, 1.93±0.3 ml/min during, and 1.86±0.3 ml/min after the i.v. PGE_1 infusion. At the same time the respective U_{osm} was 86±10 mosmol/kg before, 94±8 mosmol/kg during, and 94±9 mosmol/kg after the i.v. PGE_1 infusion. None of these values for C_{H_2O} and U_{osm} were statistically different during the infusion period as compared to either the pre- or postinfusion control periods. The different effects of i.v. PGE_1 on U_{osm} and C_{H_2O} in all of the intact animals versus the hypophysectomized animals are shown in Fig. 3.

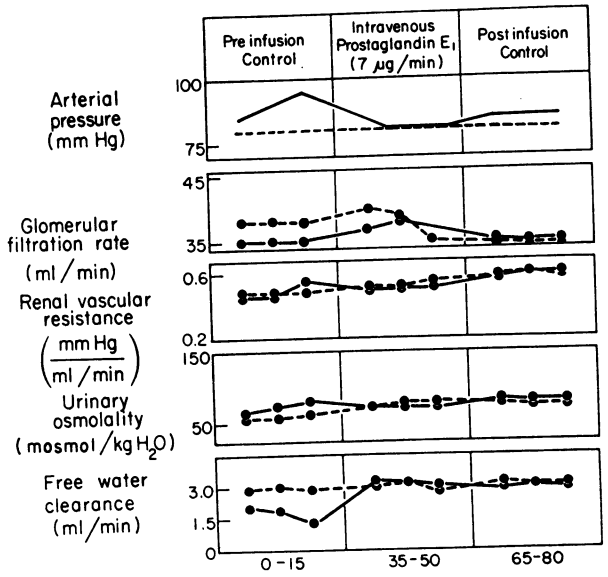

FIGURE 2 Absence of antidiuretic effect to i.v. prostaglandin E_1 in a hypophysectomized dog. Solid lines represent the left kidney and dotted lines the right kidney except for arterial pressure where the solid and dotted lines denote systemic and perfusion pressure, respectively.

Intrarenal prostaglandin E_1 studies (Fig. 4, Table III). In the intrarenal studies one-seventh of the i.v. dose of PGE_1 was infused directly into the renal artery. This amount (1 µg/min) was calculated from cardiac output and renal blood flow measurements to at least

RVR			FF			Urinary sodium excretion			Urinary potassium excretion			Osmolar clearance		
Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control
mm Hg/ml per min						*μeq/min*			*μeq/min*			*ml/min*		
0.454	0.420	0.457	0.337	0.351	0.368	3	3	4	24	26	27	0.78	0.85	0.88
±0.03	±0.02	±0.02	±0.02	±0.01	±0.01	±0.3	±0.4	±0.6	±2.2	±2.1	±2.9	±0.03	±0.06	±0.07
NS	<0.005		NS	<0.025		NS	NS		NS	NS		NS	NS	

equal the amount of the drug reaching the renal circulation during the i.v. studies. The intrarenal infusion of this dose of PGE_1 was not associated with any of the systemic hemodynamic effects which occurred during the i.v. studies (Table III). The arterial pressure, cardiac output, and total peripheral resistance were not significantly different before, during, or after intrarenal PGE_1. The deficiency of endogenous vasopressin in these studies seemed documented by the control level of U_{osm} of 67±7 mosmol/kg. In addition, exps. 7 and 8 were performed in acutely hypophysectomized animals undergoing a water diuresis. The intrarenal infusion of PGE_1 was associated with an increase in C_{H_2O} from 2.83±0.4 to 4.08±0.5 ml/min ($P < 0.001$) in the infused kidney, which decreased to 2.24±0.5 ml/min ($P < 0.001$) after cessation of the PGE_1 infusion. At the same time the mean C_{H_2O} in the contralateral kidneys was 1.83±0.3 ml/min before, 1.56±0.3 ml/min during, and 1.44±0.3 ml/min after the infusion of PGE_1. The U_{osm} in the infused kidneys was 67±7, 67±7, 87±14 mosmol/kg before, during, and after the infusion of PGE_1 and at the same time was 83±11, 94±13, 98±13 mosmol/kg in the contralateral kidney. None of the values for U_{osm} and C_{H_2O} were significantly different in the contralateral kidney. The changes in C_{H_2O} in the infused kidney were significantly different as was the increase in U_{osm} which occurred after cessation of the infusion ($P < 0.05$). The individual values for U_{osm} and C_{H_2O} in the infused and noninfused kidney are shown in Fig. 4.

The increase in C_{H_2O} in the infused kidney was associated with a significant decrease in RVR and FF, and an increase in GFR. While the RVR and FF increased significantly after cessation of the PGE_1 infusion the GFR was unchanged. The intrarenal PGE_1 was also associated with a significant increase in urinary sodium and potassium excretion and osmolar clearance in the infused kidney. There was no change in renal hemodynamics or electrolyte excretion in the contralateral kidney except for an increase in GFR during the PGE_1 infusion which was not reversible after cessation of the infusion.

DISCUSSION

The present investigation was undertaken to examine the mechanisms whereby PGE_1 may affect renal water excretion in the mammalian nephron. The results demonstrate that PGE_1 may exert divergent effects on renal water excretion depending on the dose and route of administration. The i.v. administration of PGE_1 was consistently associated with an antidiuresis which occurred independent of changes in renal perfusion pressure, renal hemodynamics, renal innervation, and changes in solute excretion rate (Fig. 1, Table I). These findings suggested that i.v. PGE_1 either stimulated the release of endogenous vasopressin or directly

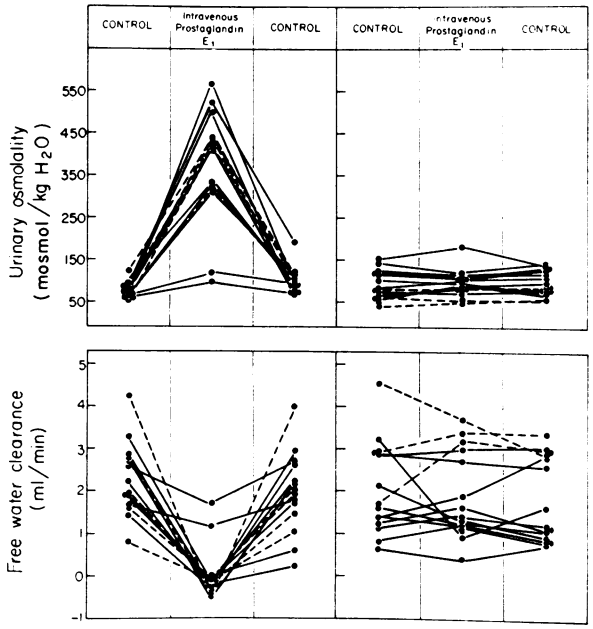

FIGURE 3 Effect of i.v. prostaglandin E_1 on urinary osmolality (above) and free water clearance (below) in the intact (left) and the hypophysectomized dogs (right). Each point represents the mean of three to five collections. Dotted lines indicate results of denervated kidneys, and solid lines indicate results from innervated kidneys.

TABLE III

The Effect of Renal Arterial Infusion of PGE_1 on Systemic and Renal

Exp. no.	Cardiac output			Systemic arterial pressure			Renal perfusion pressure			Arterial hematocrit volume			GFR			
	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control		Pre-control	PGE_1	Post-control
	liters/min			*mm Hg*			*mm Hg*			%				*ml/min*		
1	3.9	4.3	3.8	156	152	145	120	120	120	45.0	44.5	44.8	I	34.2	36.4	38.1
													C	31.2	35.2	36.8
2	5.2	4.2	3.5	175	173	175	135	137	135	45.5	45.0	45.0	I	45.8	48.2	52.0
													C	43.6	44.8	47.8
3	2.0	1.8	1.7	150	150	147	125	125	125	44.0	45.0	45.0	I	42.7	49.0	47.8
													C	42.5	43.6	48.5
4	4.3	3.0	2.6	153	155	155	118	120	120	49.0	50.0	49.0	I	45.0	51.0	51.0
													C	47.0	52.0	52.0
5	4.0	3.8	2.8	135	140	145	115	115	115	43.0	43.0	43.0	I	65.9	72.3	63.4
													C	58.3	63.9	56.4
6	4.3	3.6	3.6	130	130	135	115	115	115	42.3	42.0	41.0	I‡	42.2	51.7	46.4
													C	36.9	44.4	43.9
7	3.4	3.4	3.4	135	140	135	100	100	100	49.0	49.0	49.0	I	48.3	46.0	46.0
													C‡	39.3	40.7	38.6
8				120	108	107	120	108	107	37.3	36.5	35.3	I	47.6	52.2	51.0
													C‡	43.9	46.9	48.5
Ipsilateral (I)																
Mean	3.9	3.4	3.1	144	144	143	119	118	117	44.4	44.4	44.0		46.5	50.9	49.5
SE	±0.3	±0.4	±0.2	±7.0	±5.1	±6.8	±2.2	±3.9	±4.3	±1.3	±1.4	±1.6		±3.1	±3.4	±2.4
P value		NS	NS		NS	NS		NS	NS		NS	NS			<0.01	NS
Contralateral (C)																
Mean														42.8	46.4	46.6
SE														±3.0	±3.2	±2.5
P value															<0.005	NS

Dogs 7 and 8 were hypophysectomized.

I—indicates values in ipsilateral kidney receiving renal arterial infusion; C—indicates values in the noninfused contralateral kidney.

‡ Denervated kidneys.

increased the water permeability of the collecting duct epithelium. The latter possibility was considered tenable because of the in vitro findings which demonstrated that in the absence of vasopressin PGE_1 increased osmotic water movement across the rabbit collecting duct (3). The alternative possibility was that the antidiuresis associated with i.v. PGE_1 administration was primarily mediated by increased release of vasopressin. In this regard, the increase in cardiac output, diminution in total peripheral resistance and decrease in systemic arterial pressure observed during the i.v. PGE_1 administration were quite similar to those changes in systemic hemodynamics which occurred in association with the antidiuresis induced by beta adrenergic stimulation with i.v. isoproterenol (12). Even though both isoproterenol (13) and vasopressin (14) have been found to increase the level of 3′,5′-adenosine monophosphate (cyclic AMP) in the renal medulla, the antidiuretic effect of i.v. isoproterenol has been recently demonstrated to be primarily mediated by increased release of vasopressin rather than a direct effect on the water permeability of the collecting duct epithelium (12).

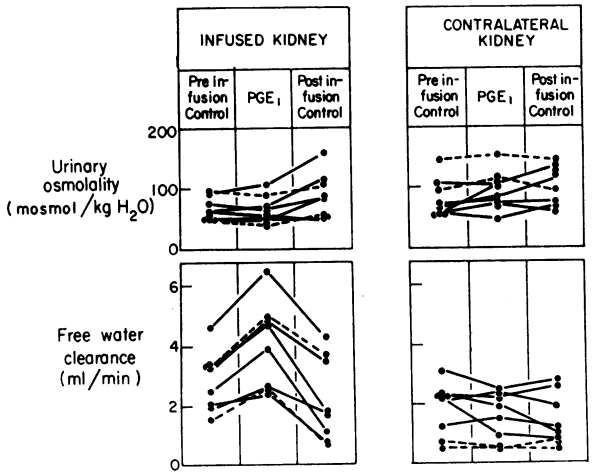

FIGURE 4 Effect of intrarenal prostaglandin E_1 on urinary osmolality (above) and free water clearance (below) in the infused (left) and contralateral (right) kidney. Each point is a mean of three to five periods. The solid lines denote results from intact dogs and the dotted lines denote results in the hypophysectomized dogs.

Further studies were therefore undertaken to distinguish between a direct effect of i.v. PGE_1 to increase water permeability of the distal nephron in the absence of vasopressin and an antidiuretic effect mediated by

RVR			FF			Urinary sodium excretion			Urinary potassium excretion			Osmolar clearance		
Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control	Pre-control	PGE_1	Post-control
ml/min per mm Hg						*μeq/min*			*μeq/min*			*ml/min*		
0.492	0.346	0.508	0.255	0.189	0.290	25	93	34	30	38	31	1.10	1.70	1.16
0.695	0.727	0.657	0.329	0.384	0.362	14	22	46	29	30	34	1.04	1.08	1.26
0.330	0.324	0.392	0.205	0.215	0.275	21	71	34	30	36	32	0.78	1.18	0.87
0.427	0.461	0.483	0.255	0.266	0.312	1	1	3	25	26	25	0.61	0.58	0.56
0.492	0.395	0.523	0.303	0.282	0.357	8	78	21	24	35	31	0.83	1.52	0.97
0.516	0.554	0.582	0.316	0.352	0.551	7	17	23	25	31	32	0.90	0.92	0.95
0.409	0.345	0.512	0.309	0.294	0.426	10	12	9	27	41	39	0.76	0.83	0.77
0.377	0.365	0.378	0.265	0.318	0.324	13	14	15	32	41	49	0.82	0.83	1.00
0.215	0.141	0.305	0.220	0.156	0.290	18	100	4	45	53	28	1.43	1.85	0.99
0.392	0.509	0.582	0.357	0.497	0.496	9	7	1	33	35	21	1.08	1.10	0.82
0.446	0.292	0.566	0.283	0.226	0.385	2	10	2	25	57	35	0.79	1.10	0.85
0.485	0.511	0.580	0.266	0.340	0.373	2	1	1	18	23	25	0.63	0.62	0.70
0.419	0.262	0.423	0.399	0.233	0.464	2	17	3	23	45	35	0.74	0.96	0.91
0.490	0.405	0.526	0.350	0.280	0.363	2	2	2	13	12	16	0.37	0.35	0.41
0.428	0.191	0.366	0.268	0.140	0.280	13	71	10	28	35	24	0.89	1.45	0.76
0.456	0.335	0.370	0.266	0.229	0.259	6	5	8	21	20	20	0.69	0.69	0.69
0.404	0.287	0.449	0.280	0.217	0.346	12	57	14	29	43	32	0.91	1.32	0.91
±0.03	±0.03	±0.03	±0.02	±0.02	±0.03	±3.0	±13.2	±4.7	±2.5	±1.7	±1.2	±0.34	±0.12	±0.05
	<0.005	<0.001		<0.02	<0.001		<0.005	<0.01		<0.005	<0.005		<0.001	<0.005
0.474	0.483	0.519	0.300	0.332	0.380	6	9	12	25	27	28	0.77	0.77	0.81
±0.04	±0.05	±0.04	±0.02	±0.03	±0.03	±1.8	±2.8	±5.5	±2.4	±3.1	±3.6	±0.1	±0.1	±0.1
	NS	NS		NS	NS		NS	NS		NS	NS		NS	NS

increased release of endogenous vasopressin. In acutely hypophysectomized animals receiving glucocorticoid replacement, i.v. PGE_1 was found to cause qualitatively similar alterations in systemic hemodynamics as in the intact animals; and yet, in this circumstance, i.v. PGE_1 was not associated with an alteration in renal water excretion (Figs. 2 and 3). These present findings were therefore interpreted to indicate that the antidiuretic effect of i.v. PGE_1 is mediated primarily by increased release of endogenous vasopressin.[2]

Additional studies were performed to investigate whether the intrarenal infusion of PGE_1 is associated with an antidiuresis, thus suggesting an additional effect of PGE_1 to increase the water permeability of the collecting duct. Although results of previous studies have demonstrated that the infusion of PGE_1 into the renal artery is associated with a diuresis rather than an antidiuresis (5–7), these studies have been performed in hydropenic animals. Thus, the diuretic effect of PGE_1 found in these previous studies could have been related to a direct antagonistic effect of PGE_1 with the action of vasopressin. Such an antagonism between PGE_1 and vasopressin has been observed in in vitro studies in the toad bladder (1) and the rabbit collecting duct (3). The present intrarenal studies were therefore performed in animals undergoing a water diuresis so as to examine the effect of PGE_1 on renal water excretion in the absence of vasopressin. In order to avoid the initiation of any extrarenal effect leading to increased release of ADH, a dose of PGE_1 was infused into the renal artery which did not produce changes in systemic hemodynamics but which delivered an amount of the drug to the renal circulation equal to or greater than that amount which reached the kidney during the i.v. infusion of PGE_1. In all of these studies the infusion of PGE_1 into the renal artery was associated with an increase rather than a decrease in free water clearance

[2] It has been suggested that glucocorticoid administration may suppress the release of vasopressin (15). Such an explanation for the present results, however, seems unlikely, since these hypophysectomized animals are known to have a severe deficiency, if not complete absence of endogenous vasopressin (16). After hypophysectomy and before fluid administration, the U_{osm} in animals prepared in such a manner averaged 67 mosmol/kg (16). Moreover, recent evidence in adrenalectomized dogs suggests that glucocorticoid hormone may not be involved in the suppression of vasopressin release (17).

as the level of urinary osmolality remained in a range compatible with maximal suppression of vasopressin release and impermeability of the collecting duct. The increase in free water clearance therefore seemed to be related to an increased delivery of tubular fluid to the diluting segment of the nephron. Since the alterations in GFR were comparable in the infused and noninfused kidneys, a depression in proximal tubular fluid reabsorption may have been primarily responsible for the increased distal delivery of tubular fluid in the infused kidney.

In qualitative terms, the effect of intrarenal PGE_1 to increase free water clearance in the present animals undergoing a water diuresis was similar to previous observations in hydropenic animals (5–7). On the basis of the present results it therefore seems reasonable to conclude that at least part of the effect of PGE_1 to increase water excretion in hydropenic animals must be related to increased delivery of tubular fluid to the diluting segment of the nephron rather than any direct antagonism of the action of vasopressin. The present results should not, however, be taken to exclude an additional inhibitory effect of PGE_1 on the action of vasopressin. The results during i.v. PGE_1 do, however, suggest that if such an inhibitory effect occurs it can be overcome by the effect of i.v. PGE_1 to increase the endogenous release of vasopressin. Studies designed to demonstrate such an inhibitory effect of PGE_1 on the action of vasopressin in vivo must therefore avoid the extrarenal effects of the drug to release vasopressin, as well as the intrarenal effects of the PGE_1 to increase the delivery of tubular fluid to the distal diluting segment. In the present study the dose of PGE_1 infused into the renal artery caused no systemic vascular effects, but intrarenal hemodynamic alterations were consistently observed. In the presence of such renal vascular effects of PGE_1 any in vivo effect on renal water excretion cannot be attributed to an antagonism of the action of vasopressin (5–7). We have found that prior renal vasodilatation with acetylcholine does not abolish the effect of intrarenal PGE_1 to either enhance renal hemodynamics or renal water excretion.[3] Moreover, a dissociation of the effects of intrarenal PGE_1 on renal hemodynamics and renal water excretion in the hydropenic dogs has not been observed with different doses of PGE_1 (5–6). Thus if, as suggested by in vitro results (1–3), an antagonism between PGE_1 and vasopressin occurs, it may not be possible to dissociate this effect from the renal hemodynamic effects of PGE_1 in in vivo experiments.

In summary, in the present investigation i.v. PGE_1 was associated with an antidiuresis which occurred in the absence of changes in renal hemodynamics, renal nerves, and renal solute excretion but was abolished by removal of the source of vasopressin release. The alterations in systemic hemodynamics during i.v. PGE_1 may initiate this increased release of vasopressin by diminishing parasympathetic afferent tone (11), a pathway which may also mediate the effect of changes in volume status and adrenergic tone on vasopressin release (12). While in hypophysectomized dogs i.v. PGE_1 altered neither renal hemodynamics nor renal water excretion, the infusion of PGE_1 directly into the renal artery of normal and hypophysectomized animals undergoing a water diuresis was associated with alterations in renal hemodynamics and an increase in free water clearance. This effect of intrarenal PGE_1 to increase renal water excretion in the absence of vasopressin was related primarily to increased delivery of tubular fluid to the distal diluting segment of the nephron.

[3] Berl, T., and R. W. Schrier. Unpublished observation.

ACKNOWLEDGMENTS

We are indebted to Mr. John Pike, The Upjohn Company, Kalamazoo, Mich. for supplying us with prostaglandin E_1. The authors are also indebted to Miss Lisbeth Streiff and Vicki Neel for invaluable technical assistance and to Mrs. Vicki Wagner and Loretta Durkin for secretarial assistance.

This work was supported by grants HE 13319-01 and AM 12753 from the National Institutes of Health, and by NGR 05-025-007 from the National Aeronautics and Space Administration and the Bay Area Heart Association.

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