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### Research Article

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# Evidence for an In Vivo Antagonism between Vasopressin and Prostaglandin in the Mammalian Kidney

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**ABSTRACT** These studies were undertaken to examine whether an antagonism between vasopressin and prostaglandin occurs in vivo in the mammalian kidney. All experiments were performed in steroid-replaced hypophysectomized dogs undergoing a water diuresis. In the first group of studies the effect of two consecutive intravenous doses (100 mU) of vasopressin was examined. The second dose of vasopressin was preceded by an injection of the carrier solution for solubilizing indomethacin or meclofenamate. No enhancement of the antidiuretic effect of the second dose of vasopressin was observed as urinary osmolality ( $U_{osm}$ ) increased from  $92 \pm 5$  to  $252 \pm 18$  mosmol/kg  $H_2O$  ( $P < 0.001$ ) after the first dose and from  $109 \pm 8$  to  $209 \pm 10$  mosmol/kg  $H_2O$  ( $P < 0.001$ ) after the second dose of vasopressin. In another group of studies the second dose of vasopressin was preceded by the administration of a potent inhibitor of prostaglandin synthesis, indomethacin (2 mg/kg). The  $U_{osm}$  increased from  $93 \pm 9$  to  $244 \pm 33$  mosmol/kg  $H_2O$  ( $P < 0.001$ ) after the first dose of vasopressin, but after the second dose of vasopressin the  $U_{osm}$  increased to a significantly greater degree from  $106 \pm 14$  to  $702 \pm 69$  mosmol/kg  $H_2O$  ( $P < 0.001$ ). In a third group of studies the antidiuretic effect of the same 100-mU dose of vasopressin was examined before and after the administration of meclofenamate (2 mg/kg), an inhibitor of prostaglandin synthesis which is chemically dissimilar from indomethacin.  $U_{osm}$  increased from  $83 \pm 7$  to  $216 \pm 16$  mosmol/kg  $H_2O$  ( $P < 0.001$ ) after the first dose and from  $101 \pm 8$  to  $734 \pm 86$  mosmol/kg  $H_2O$  ( $P < 0.001$ ) after the second dose of vasopressin. As in the indomethacin studies this en-

hancement in the antidiuretic effect of vasopressin after inhibition of prostaglandin synthesis was highly significant ( $P < 0.001$ ). These results therefore implicate a physiological role of prostaglandin in modulating the hydroosmotic effect of vasopressin in the mammalian kidney.

## INTRODUCTION

The prostaglandins, a group of naturally occurring unsaturated fatty acids, have been implicated in the regulation of hormonal action in various tissues. In the kidney, a role for prostaglandins has been ascribed in the regulation of blood flow (1-4), sodium excretion (5-8), and water excretion (6, 9-11). Because prostaglandins are found in highest concentration and are synthesized in the renal medulla (12-15), a role of the prostaglandins in regulation of renal water movement across the medullary collecting duct epithelium is particularly attractive. In this regard, in vitro studies in the toad bladder (16-18) and rabbit collecting duct (19) have demonstrated that prostaglandin  $E_1$  antagonizes the hydro-osmotic effect of vasopressin. In addition, in the toad bladder inhibitors of prostaglandin synthetase have been shown to enhance the hydro-osmotic effect of vasopressin (20, 21). Furthermore, prostaglandins have been demonstrated to inhibit vasopressin-mediated increases in cyclic AMP production in toad bladder epithelium (22) and rat renal medulla (23), as well as vasopressin-mediated increases in adenylyl cyclase activity in hamster renal medulla (24). These latter findings (22-24) suggest an explanation for the mechanism whereby prostaglandin  $E_1$  may antagonize the effect of vasopressin on osmotic water movement.

An in vivo antagonism between prostaglandins and vasopressin has been difficult to establish. Although the intrarenal infusion of prostaglandin is known to cause

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a diuresis, this effect has not been dissociated from changes in renal hemodynamics or solute excretion (6, 7, 10) and has been shown to occur in the absence of vasopressin (11). The present study therefore was undertaken to further investigate a potential prostaglandin-vasopressin interaction in vivo in the mammalian nephron.

## METHODS

Studies were performed on 20 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 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. All animals underwent transubcual hypophysectomy through the hard palate on the morning of the experiment (25). Only animals exhibiting urine osmolalities less than 100 mosmol/kg H<sub>2</sub>O without exogenous fluid administration were used in the study to insure completeness of hypophysectomy. All animals received 5 mg deoxycorticosterone intramuscularly and 1.6 mg dexamethasone (0.8 mg intravenously and 0.8 mg intramuscularly). Each animal received an intravenous infusion of 2.5 g/100 ml dextrose at 10 ml/min for 60 min. Catheters were placed in both ureters and in both renal veins through bilateral flank incisions and a catheter was placed in the aorta via the branchial artery for continuous measurement of arterial pressure with Statham transducers (Statham Instruments, Inc., Oxnard, Calif.). After completion of the above surgery, an intravenous infusion of 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. Throughout the remainder of the experiment, 2.5 g/100 ml dextrose was infused at a rate of 2–4 ml/min above urine flow rate. The periods of urine collection during the experiments were 5–10 min in duration and arterial and renal venous blood samples were obtained at the midpoint of alternate urine collections.

The experimental protocol for the experiments is demonstrated in Fig. 1. After an equilibration period to allow for recovery from surgery and stabilization of urine flow, urine samples for precontrol clearance measurements were collected. Immediately after these collections, an intravenous bolus of 100 mU vasopressin (aqueous Pitressin, Parke, Davis & Company, Detroit, Mich.) was administered. After a 10-min equilibration period, experimental clearance periods were obtained. After the effect of vasopressin on urine flow had disappeared, approximately 45 min after its administration, postcontrol urine collections were made. After these collections, the animals randomly received an intravenous bolus of one of three solutions: six dogs were given indomethacin, 2 mg/kg; seven dogs received meclofenamate, 2 mg/kg; and seven dogs were given a control solution consisting only of the carrier solutions used for solubilizing indomethacin or meclofenamate. In two of the indomethacin studies, one of the kidneys was not used because of surgical mishap. 10 min after the injection of one of the three solutions, precontrol periods were obtained again and were followed immediately by a second intravenous bolus of 100 mU vasopressin. As before, clearance measurements were started within 10 min and postcontrol clearance measurements were obtained later after the effects of vasopressin

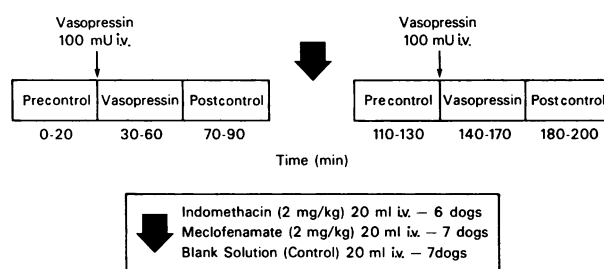


FIGURE 1 Protocol for three groups of experiments with blank solution, indomethacin, or meclofenamate administration before second bolus of vasopressin.

had dissipated. This protocol allowed the study of the response to two separate injections of vasopressin in dogs with intact prostaglandin synthesis (dogs receiving the carrier solutions) and in dogs in which prostaglandin synthesis had been inhibited by either indomethacin or meclofenamate before the second vasopressin injection (26).

The analytical procedures and calculations used in these experiments have been referred to elsewhere (27). Student's *t* test and analysis of variance were used for statistical analysis. A *P* value < 0.05 was considered significant.

## RESULTS

The effect of vasopressin on urinary osmolality in seven control animals receiving a carrier solution before the second dose of vasopressin is shown in Fig. 2. Urine osmolality (Uosm)<sup>1</sup> rose from 92±5 to 252±18 mosmol/kg H<sub>2</sub>O (*P* < 0.001) and fell to 114±7 mosmol/kg H<sub>2</sub>O (*P* < 0.001) after the first injection of vasopressin. With the second dose of vasopressin Uosm increased from 109±8 to 209±10 mosmol/kg H<sub>2</sub>O (*P* < 0.001) and fell to 112±9 mosmol/kg H<sub>2</sub>O (*P* < 0.001) in the postcontrol period. The magnitude of the antidiuresis was slightly but significantly less after the second dose of vasopressin (*P* < 0.005). Free water clearance (C<sub>H<sub>2</sub>O</sub>) demonstrated parallel changes in these control animals. With the first injection of vasopressin C<sub>H<sub>2</sub>O</sub> declined from 1.54±0.32 to 0.23±0.13 ml/min (*P* < 0.001) and returned to 1.39±0.21 ml/min in the post control period (*P* < 0.001). C<sub>H<sub>2</sub>O</sub> declined from 1.65±0.19 to 0.43±0.11 ml/min (*P* < 0.001) with the second injection of vasopressin and rose to 1.73±0.27 ml/min in the postcontrol period (*P* < 0.001). Although the decrease in C<sub>H<sub>2</sub>O</sub> was less after the second injection of vasopressin, this difference was not statistically significant.

The effect of vasopressin on Uosm in six animals treated before the second dose of vasopressin with indomethacin (2 mg/kg) is shown in Fig. 3. The response to the first dose of vasopressin was similar to that observed in the control animals. With the first injection

<sup>1</sup> Abbreviations used in this paper: C<sub>H<sub>2</sub>O</sub>, free water clearance; Uosm, urinary osmolality.

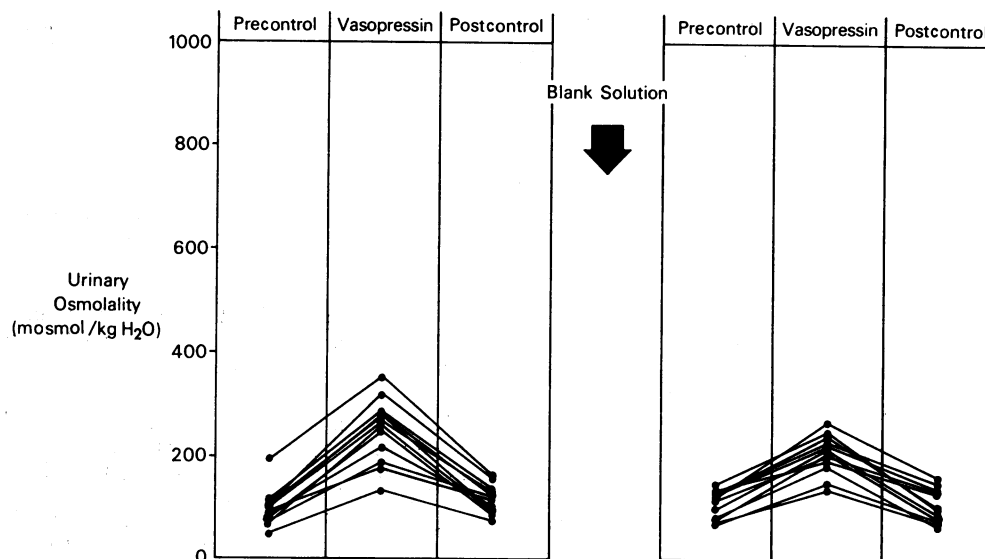


FIGURE 2 Failure of blank solution to enhance antidiuretic effect of second bolus of vasopressin. Each point represents the mean of three clearance periods for each kidney.

of vasopressin Uosm increased from  $93 \pm 9$  to  $244 \pm 33$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) and fell to  $100 \pm 13$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) in the postcontrol period. However, in contrast to the control animals, indomethacin administration markedly enhanced the response to vasopressin as Uosm rose from  $106 \pm 14$  to  $702 \pm 69$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) and fell to  $133 \pm 29$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) in the postcontrol period. The increase in Uosm after vasopressin in indomethacin-treated animals was significantly ( $P < 0.001$ ) greater

than that observed in control periods. Changes in  $C_{H_2O}$  with the first injection of vasopressin were similar to those observed in the control animals as  $C_{H_2O}$  declined from  $1.76 \pm 0.26$  to  $0.31 \pm 0.18$  ml/min ( $P < 0.001$ ) and rose to  $1.44 \pm 0.20$  ml/min ( $P < 0.001$ ) in the postcontrol period. As with Uosm the second injection of vasopressin after indomethacin resulted in a significantly greater fall in  $C_{H_2O}$  ( $1.26 \pm 0.25$  to  $-0.65 \pm 0.12$ ,  $P < 0.001$ ) than before indomethacin. With the second bolus of vasopressin, the increase in Uosm and the decrease

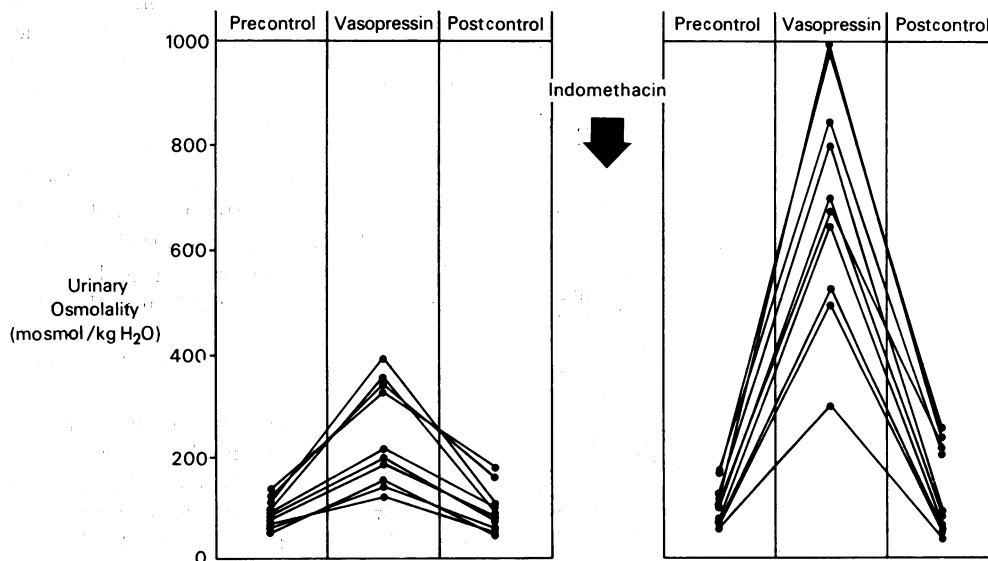


FIGURE 3 Effect of indomethacin to enhance the antidiuretic effect of vasopressin. Each point represents the mean of three clearance periods for each kidney.

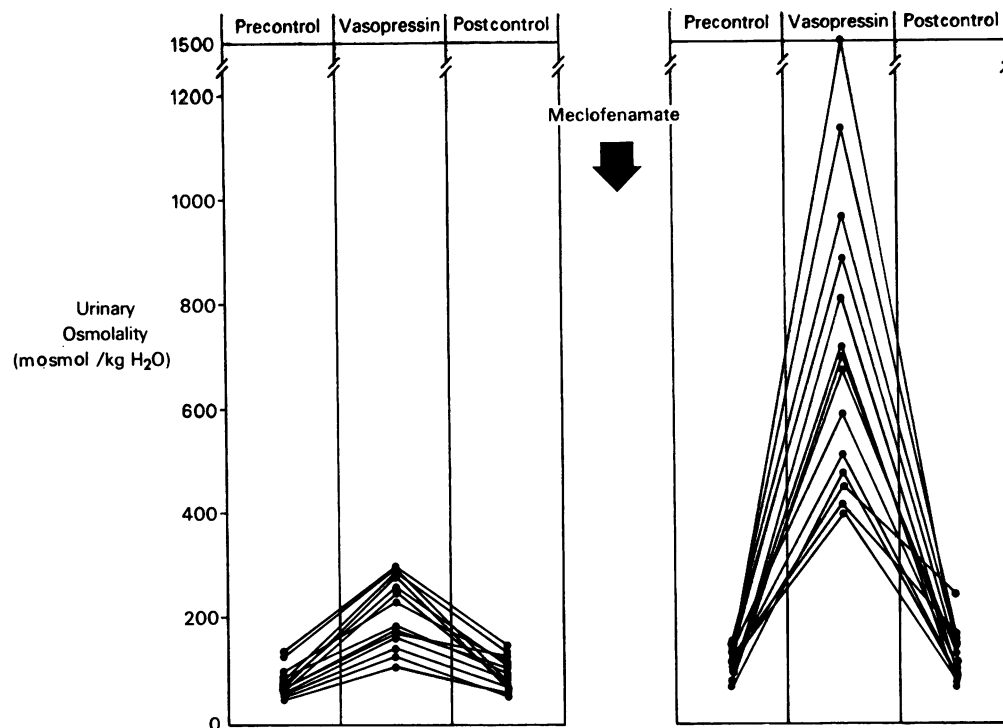


FIGURE 4 Effect of meclofenamate to enhance the antidiuretic effect of vasopressin. Each point represents the mean of three clearance periods for each kidney.

in  $C_{H_2O}$  after indomethacin were significantly greater ( $P < 0.05$ ) than that observed in the control animals after an injection of carrier solution.

Further studies were undertaken with meclofenamate, a chemically dissimilar inhibitor of prostaglandin synthetase (26, 28). The results of sequential doses of vasopressin on Uosm in seven animals treated with meclofenamate (2 mg/kg) before the second dose of vasopressin are shown in Fig. 4. The response to the first dose of vasopressin was similar to that observed in the control and indomethacin-treated animals as Uosm increased from  $83 \pm 7$  to  $216 \pm 16$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) and fell to  $102 \pm 7$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ). In contrast to the control animals, but similar to the animals that received indomethacin, the response to vasopressin was enhanced after meclofenamate as Uosm rose from  $101 \pm 8$  to  $734 \pm 86$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ) and fell to  $118 \pm 12$  mosmol/kg H<sub>2</sub>O ( $P < 0.001$ ). This increase in Uosm after vasopressin in these meclofenamate-treated dogs was significantly greater than that observed in control animals ( $P < 0.001$ ). Changes in  $C_{H_2O}$  with the first injection of vasopressin in these animals were similar to those observed in both the control and indomethacin groups, as  $C_{H_2O}$  decreased from  $1.82 \pm 0.28$  to  $0.26 \pm 0.09$  ml/min ( $P < 0.001$ ) and rose to  $1.36 \pm 0.20$  ( $P < 0.001$ ) in the postcontrol period. In contrast to the control animals and similar to the in-

domethacin-treated animals, the second injection of vasopressin resulted in a greater fall in  $C_{H_2O}$  from  $1.47 \pm 0.05$  to  $-0.58 \pm 0.06$  ml/min ( $P < 0.001$ ), which rose to  $1.46 \pm 0.23$  ml/min ( $P < 0.001$ ) in the postcontrol period. This effect on  $C_{H_2O}$  was also significantly greater than in the control animals ( $P < 0.05$ ). The glomerular filtration rate, renal blood flow, and solute excretion for all of the studies are shown in Fig. 5. No significant differences in these parameters for any experimental group was observed.

## DISCUSSION

Several lines of evidence derived from in vitro experiments suggest that the prostaglandins inhibit the hydro-osmotic action of vasopressin (16-19). Attempts to evaluate the physiologic significance of these findings in vivo have been based on experiments in which exogenous prostaglandins were infused systemically (11) or into a renal artery (6, 7). Many difficulties have arisen in interpreting such experiments. First, when prostaglandins of the E or A series are given systemically they cause vasodilatation, a decrease in arterial pressure, and an increase in release of vasopressin (11). These effects are likely to obscure any influence the prostaglandins might have on the renal hydro-osmotic action of vasopressin. Similarly, when the pros-

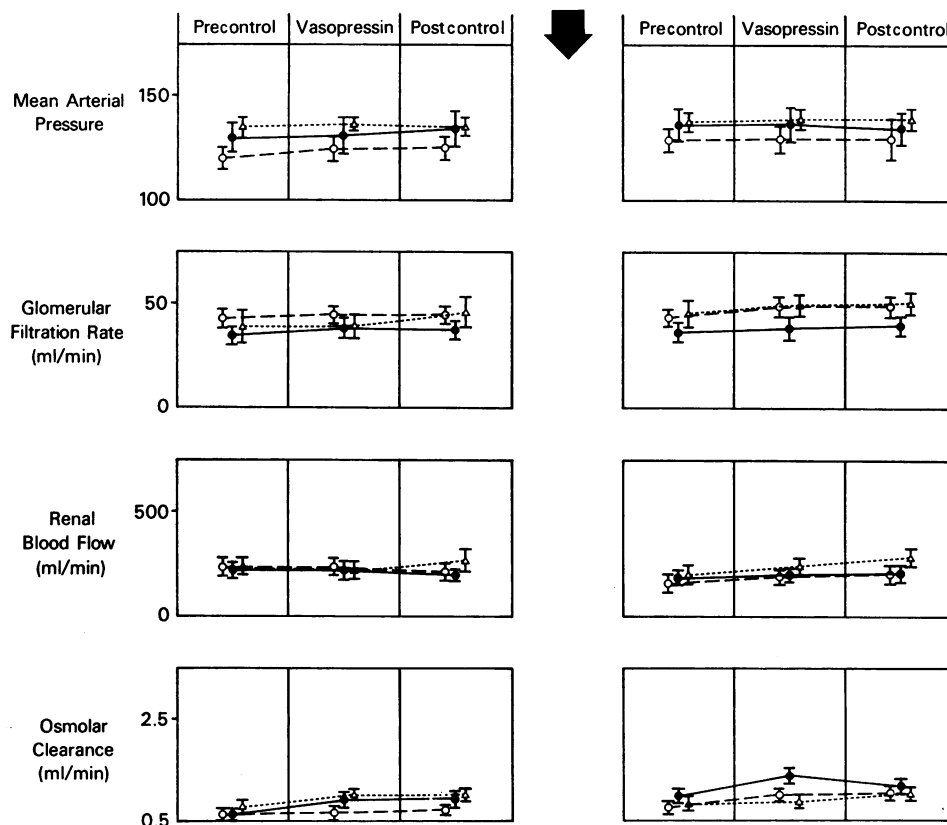


FIGURE 5 Mean arterial pressure, glomerular filtration rate, renal blood flow, and osmolar clearance in all three groups of experiments. Solid circles, open triangles, and open circles denote control, indomethacin, and meclofenamate experiments, respectively.

taglandins are infused intrarenally they cause increased solute excretion and renal vasodilatation (6). Both of these effects might interfere with the ability of vasopressin to enhance urine concentration without necessarily altering its cellular action on collecting ducts (29, 30). Furthermore, exogenously infused prostaglandins are likely to be distributed within the kidney quite differently from endogenous renal prostaglandins. Endogenous prostaglandins occur in greater concentration in the medulla (14, 15), while prostaglandins infused into the renal artery may be distributed primarily to the cortex, which receives approximately 90% of renal blood flow. Since the medullary collecting ducts are the major site of action of vasopressin, renal prostaglandins in the medulla are well situated to play a modulating role on the tubular response to vasopressin.

In the present study another approach was used in an effort to document an *in vivo* effect of endogenous prostaglandins on vasopressin activity. The renal responsiveness to exogenous vasopressin was evaluated before and after the administration of indomethacin, a drug known to inhibit the synthesis of endogenous prostaglandins (1, 26, 28, 31). The main finding in our

study was that the response of urinary osmolality to vasopressin was enhanced threefold by pretreatment with indomethacin. The enhancement occurred despite solute excretion rates, total renal blood flow, and estimated distal tubular fluid delivery rates which were no different to those existing before treatment with indomethacin.

Several controls were integrated into the present study to insure that indomethacin was primarily responsible for the observed enhancement of vasopressin activity. First, the studies were performed in dogs that had been acutely hypophysectomized. Previous studies have shown that in such hypophysectomized animals vasopressin release in response to a wide variety of acute stimuli is virtually abolished (11, 25, 32-34). Thus, any effects on urinary osmolality due to alterations in endogenous vasopressin were minimized. Moreover, both pre- and post-control periods were obtained after each bolus of exogenous vasopressin to exclude any residual effect of endogenous vasopressin.

Another control designed for the present study was the injection of two identical doses of vasopressin into the same dog before and after infusion of indomethacin.

Thus, each dog served as its own control. In a series of control animals, which received no indomethacin, the variability of the response to two separate doses of vasopressin was also assessed. In the absence of indomethacin the response to the second dose of vasopressin was not statistically greater than the first. Therefore, the present results clearly demonstrate that indomethacin potentiates the action of vasopressin on the kidney.

The logical inference to be drawn from our results is that indomethacin enhances the action of vasopressin by blocking endogenous prostaglandin production. However, other hypotheses must also be considered. It is recognized that indomethacin exerts other effects in addition to the inhibition of prostaglandin synthetase. For example, the drug is capable of inhibiting cyclic nucleotide phosphodiesterase (18, 35). However, this action only occurs at concentrations approximately 100-fold greater than those required to inhibit prostaglandin synthetase (35). In our *in vivo* experiments the concentration of indomethacin was much less than would be expected to induce significant inhibition of phosphodiesterase. Moreover, the *in vitro* effect of indomethacin to enhance the hydro-osmotic effect of vasopressin occurs when phosphodiesterase activity is inhibited by theophylline (18).

Even so, it was apparent that an attempt to duplicate the enhancement of vasopressin activity with a chemically dissimilar inhibitor of prostaglandin synthetase was necessary. Studies, therefore, were performed with the same experimental protocol, except that meclofenamate rather than indomethacin was used as the inhibitor of prostaglandin synthesis. The results showed that meclofenamate was almost identical to indomethacin in its ability to enhance vasopressin activity. Since the only known action shared by indomethacin and meclofenamate is inhibition of prostaglandin synthesis (36), the inference can logically be drawn that it is through this common action that these agents potentiate the action of vasopressin.

Taken together, therefore, the present results indicate that endogenous prostaglandins are important *in vivo* modulators of the kidney's response to vasopressin. This conclusion is in agreement with *in vitro* studies in the toad bladder (16-18) and rabbit collecting duct (19) which have demonstrated that prostaglandin  $E_1$  antagonizes the hydro-osmotic effect of vasopressin. Further evidence is the finding in the toad bladder that indomethacin enhances the hydro-osmotic effect of vasopressin (20, 21). Vasopressin-mediated increases in cyclic AMP also have been found to be inhibited by prostaglandin in toad bladder epithelium (22) and rat renal medulla (23), and prostaglandin also inhibits vasopressin-stimulated increases in adenyl cyclase activity in the hamster renal medulla (24).

It should be noted, however, that inhibition of prostaglandin synthesis *in vivo* with either meclofenamate or indomethacin has been shown to diminish inner cortical and medullary renal blood flow (3). This hemodynamic consequence of inhibition of prostaglandin synthesis conceivably could lead to enhanced preservation of the hypertonicity in the interstitium of the medulla. As a consequence, osmotic water movement could be increased independent of any increase in the vasopressin-mediated water permeability of the medullary collecting duct. In this regard, however, we have been unable to enhance the effect of vasopressin by the intrarenal administration of norepinephrine and angiotensin (unpublished observation: P. Cadnapaphornchai, J. Boykin, and R. W. Schrier), which decrease total blood flow including outer cortical and medullary blood flow (37). This finding, as well as the considerable *in vitro* data (16-24), thus favors a cellular rather than a vascular mechanism whereby *in vivo* inhibition of prostaglandin synthesis enhances the effect of vasopressin to increase water permeability in the medullary collecting duct. In this regard, it should be noted that the epithelial cells in the medullary collecting duct contain an even higher concentration of prostaglandin than the medullary interstitial cells (14). Thus, medullary prostaglandin is well situated to modulate the cellular action of vasopressin. Although further *in vivo* studies will be needed to determine the relative importance of vascular and cellular mechanisms, the present results would seem to clearly establish that prostaglandin synthesis is an important *in vivo* mediator of the effect of vasopressin in the mammalian nephron.

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