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Mechanism of Prostaglandin E_2 Stimulation of Renin Secretion (40325)

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Intrarenal infusion of prostaglandins or the prostaglandin precursor, arachidonic acid, have been shown to stimulate renin secretion in dogs (1), rats (2), and rabbits (3). In addition, inhibition of prostaglandin synthesis decreases endogenous renin secretion (3), renin secretion in response to hemorrhage (4), and furosemide-stimulated renin secretion (5). In dogs in which renin release has been blocked by indomethacin, infusion of prostaglandin E_2 (PGE_2) significantly increased the release of renin beyond the original control values (6).

The mechanism by which PGE_2 increases renin secretion may involve one or a combination of three factors. First, the hormone may have a direct effect upon the juxtaglomerular apparatus. Second, PGE_2 may activate a vascular baroreceptor mechanism by vasodilatation of the renal vasculature (7). Third, PGE_2 may stimulate a tubular macula densa receptor since in addition to decreasing renal resistance, PGE_2 infusion also increases renal sodium excretion (6). In the present experiments, the mechanism by which PGE_2 stimulates renin secretion was evaluated by comparison of the effect of PGE_2 on renin secretion with the vasodilating agents acetylcholine, bradykinin and eledoisin.

Materials and methods. Male mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg iv). Following insertion of a cuffed endotracheal tube, dogs were artificially ventilated (Harvard Apparatus, Inc.). A femoral artery and two femoral veins were cannulated for the recording of arterial blood pressure, infusion of inulin (3% solution at 1 ml/min), and infusion of saline. Blood pressure was recorded with a strain gauge pressure transducer (Statham P23AA) and a direct writing oscillograph (Grass polygraph). The left kidney was exposed via a flank incision and the ureters of both kidneys were cannulated with polyethylene tubing. A noncannulating electromagnetic flowmeter probe (Carolina Medical Electronics) was placed on the renal artery and renal blood flow was recorded on the oscillograph. Renal venous blood samples were collected by placing a curved 20-gauge needle attached to polyethylene tubing into the renal vein. A curved 22-gauge needle attached to polyethylene tubing was inserted into the renal artery distal to the flow probe for the intrarenal infusion of PGE_2, acetylcholine, bradykinin, and eledoisin. Each dog was hydrated prior to the experiment with a solution containing 140 mEq/liter sodium chloride and 3.0 mEq/liter potassium chloride, infused at 5.0 ml/min until the total urine flow rate reached 0.5 to 1.5 ml/min. The infusion rate was then decreased to equal the urine flow rate. Experiments were begun 1 hr following the completion of surgery.

In each experiment, two control clearance periods of 10 min duration each were followed by the infusion of one of the vasodilating agents. The rate of infusion of the drug was adjusted to increase renal blood flow 20 to 40%. Two additional clearance periods were obtained. Systemic arterial and renal venous blood samples were collected at the midpoint of each clearance period. Drug infusion was stopped and a 30-min period ensued during which renal blood flow returned to control levels. Drug metabolism was assumed to be complete when RBF was stable again and the next control period and drug treatment were begun. The order of administration of acetylcholine, bradykinin, and prostaglandin E_2 was randomized throughout the experiments. Eledoisin was always administered last, due to its presumed slower rate of metabolism. The range of doses of each vasodilator used were as follows: acetylcholine, 210 to 420 ng/kg/min; bradykinin, 7 to 21 ng/kg/min; eledoisin, 15 to 32 ng/kg/min; and prostaglandin E_2, 14 to 60 ng/kg/min.

Analytical and statistical procedures. Plasma and urine inulin concentration were

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determined by the diphenylamine method described by Walser *et al.* (8). GFR was estimated by the clearance of inulin. Plasma renin concentration was determined by radioimmunoassay for the generated angiotensin I (9). Hematocrit was measured on all arterial blood samples by the micromethod. Renal plasma flow was calculated from the renal blood flow and hematocrit. Sodium and potassium concentration of both plasma and urine were determined by flame photometry and the electrolyte excretion rates were calculated. Renin secretion was calculated as the product of the renal venous–arterial renin concentration difference and renal plasma flow. Renal blood flow and renin secretion mean differences were tested by a paired *t* analysis. Sodium and potassium excretion was calculated as the percentage increase from control and treatments were compared by one-way analysis of variance. The 0.05 level of probability was used as the criterion of significance.

Results. Infusion of PGE_2 significantly increased renal blood flow (Fig. 1). The increase in renal blood flow was associated with an increase in renin secretion from a control value of 925±327 to 1710±486 ng/min (Fig. 1). Eledoisin also increased renal blood flow but did not change renin secretion (Fig. 1). Both acetylcholine and bradykinin increased renal blood flow but neither drug affected renin secretion (Fig. 2).

Renal vasodilation with acetylcholine, bradykinin, PGE_2, or eledoisin increased both sodium and potassium excretion of the treated kidney (Table I). The percentage increases following each drug were not significantly different from each other. The sodium and potassium excretion of the contralateral kidney was not affected by drug infusion. The glomerular filtration rate of the treated and untreated kidneys did not change during drug infusion. Unilateral renal vasodilation did not alter the mean systemic blood pressure.

Discussion. The secretion of renin may be altered by a vascular mechanism located in the afferent glomerular arteriole (7) since decreases in renal resistance stimulate the release of renin (10). The present experiments demonstrate that PGE_2 increased both ipsilateral renal blood flow and renin secretion (Fig. 1) while not affecting mean systemic blood pressure or contralateral renal function. Renal vasodilation due to acetylcholine, bradykinin, or eledoisin, however, did not affect renin secretion (Figs. 1 and 2). Since the increase in renal blood flow was similar following infusion of all drugs, a vascular

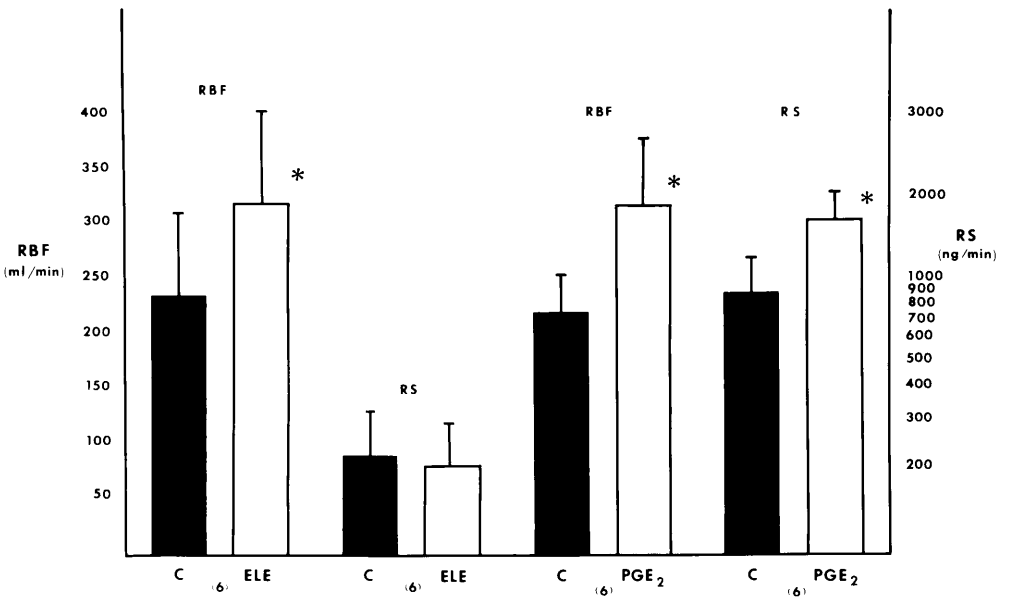

FIG. 1. Effect of prostaglandin E_2 (PGE_2) and eledoisin (Ele) on renal blood flow (RBF) and renin secretion (RS). C = control. Values are expressed as means ± SEM. $n = ( )$. $^*p < 0.05$.

mechanism does not appear to be primarily responsible for the increase in renin secretion following PGE_2.

Intrarenal infusion of bradykinin has been shown to increase renal PGE secretion (11). Therefore, bradykinin may affect renin secretion in a manner similar to that of PGE_2. In the present experiments, the dose of bradykinin which increased renal blood flow approximately 20 to 40% of control was less than the dose of bradykinin previously reported to increase PGE release (11). Thus, the plasma or tissue PGE_2 concentration achieved in response to bradykinin in these experiments may not have been sufficient to elicit a response similar to that produced by the infusion of PGE_2.

A tubular mechanism located at the macula densa region of the distal nephron also affects renin secretion by sensing changes in tubular sodium or chloride transport (12). Acetylcholine and PGE_2 have been shown to decrease proximal tubular sodium reabsorption (13). Similarly, bradykinin decreased proximal tubular sodium reabsorption by a mechanism related to vasodilation of the renal vasculature (14). The present data demonstrate that intrarenal infusion of acetylcholine, bradykinin, PGE_2, or eledoisin increased sodium and potassium excretion (Table I) to a similar degree in all experiments without affecting GFR. Since changes in tubular sodium reabsorption or changes in potassium excretion following infusion of acetylcholine, bradykinin, eledoisin, or PGE_2 are similar, the changes in electrolyte excretion do not account for the PGE_2-induced increase in renin secretion. PGE_2 has been shown to increase renin release *in vitro* (15). Although Weber *et al.* did not report PGE_2 to increase renin release, arachidonic acid, PGE_2, and endoperoxide I and II all increased renin release *in vitro* (16). In the present experiments, both the hemodynamic and tubular responses produced by PGE_2 appear to be similar to those elicited by bradykinin, eledoisin, and acetylcholine *in vivo*. Thus, PGE_2 may increase renin secretion by a direct ac-

TABLE I. EFFECT OF ACETYLCHOLINE, BRADYKININ, PGE_2 AND ELEDOISIN ON SODIUM AND POTASSIUM EXCRETION.

Treatment	Na excretion[a]	K excretion[a]
Acetylcholine	301.2 ± 135.2	26.2 ± 12.3
Bradykinin	385.7 ± 212.1	75.9 ± 30.6
PGE_2	121.4 ± 36.6	22.5 ± 12.3
Eledoisin	478.0 ± 231.3	118.8 ± 51.6

[a] Values expressed as percent increase.

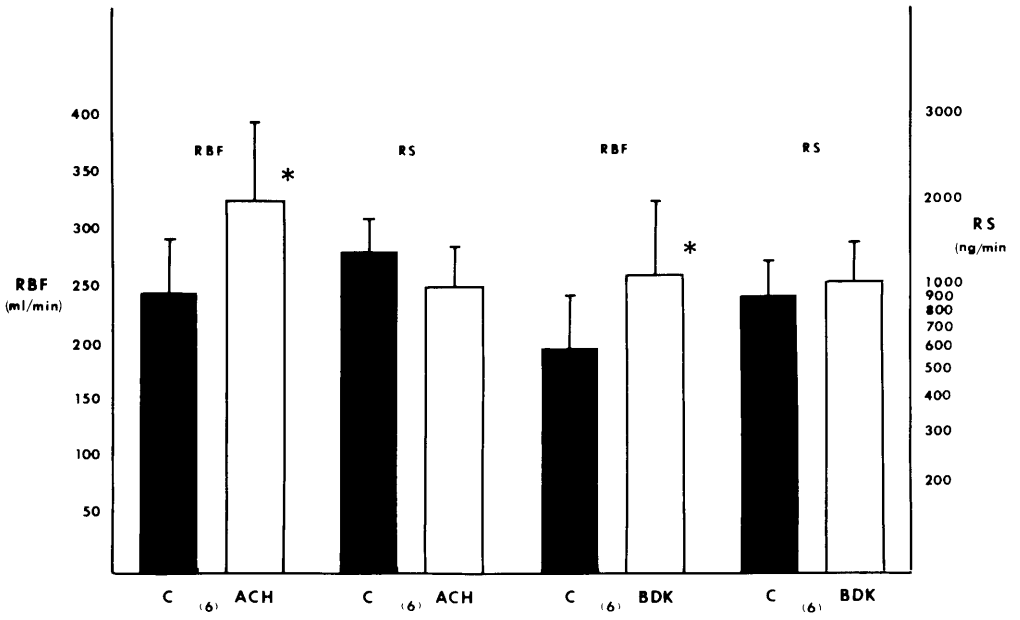

FIG. 2. Effect of bradykinin (Bdk) and acetylcholine (Ach) on renal blood flow (RBF) and renin secretion (RS). C = control. Values are expressed as means ± SEM. n = ( ). *$p < 0.05$.

tion on the vascular juxtaglomerular cells or a component of the juxtaglomerular apparatus.

Summary. Intrarenal infusion of acetylcholine, bradykinin, eledoisin, and PGE_2 increased renal blood flow to a similar degree. Sodium and potassium excretion were similarly affected by each vasodilator. Renin secretion increased following PGE_2 but was unaffected by acetylcholine, bradykinin, or eledoisin. It is suggested that PGE_2 increases renin secretion by a direct effect on the juxtaglomerular apparatus.

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