Effect of Nephrectomy and of Adrenergic Receptor Blockers on the Cardiorenal Actions of Endothelin (43066)

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Abstract. **The cardiorenal actions of endothelin-1 (ET-1) were evaluated in rats following nephrectomy, in rats during α-adrenergic blockade with phentolamine, and in rats during β-adrenergic blockade with propranolol. Female rats were anesthetized with pentobarbital and, following surgery, were allowed 60 min to stabilize before 3 × 20 min-control clearances were collected. ET-1 was then infused at a rate of 100 ng kg^{-1} min^{-1} for 30 min, the infusion was stopped, and three additional clearances were collected. Four groups of rats were studied: in Group 1 (n = 10), ET-1 was infused; in Group 2 (n = 5), a bilateral nephrectomy was performed 120 min before infusing ET-1; in Group 3 (n = 5), ET-1 was infused into rats treated with phentolamine (0.015 mg kg^{-1} min^{-1}); and in Group 4 (n = 5), ET-1 was infused into rats treated with propranolol (0.015 mg kg^{-1} min^{-1}). At 30 min during infusion of ET-1 into Group 1 rats, mean arterial blood pressure had increased (P < 0.01) by 27 ± 2% (SE) and the glomerular filtration rate had decreased (P < 0.01) by 71 ± 6% of baseline values. Nephrectomy potentiated and prolonged the ET-1-induced systemic vasoconstriction. Phentolamine had no effect on the cardiorenal actions of ET-1 whereas propranolol enhanced ET-1-induced changes in mean arterial blood pressure; mean arterial blood pressure increased 38 ± 2% at 30 min during ET-1 + propranolol infusion (P < 0.01 versus value with ET-1 alone). These data indicate that the kidney affects ET-1-induced systemic vasoconstriction and that β-adrenergic (but not α-adrenergic) receptors are activated during infusion of ET-1 with a resultant attenuation of ET-1-induced changes in systemic blood pressure.**

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Several laboratories have demonstrated that media from endothelial cells in culture release a potent vasoconstrictor peptide (1–3). More recently, endothelin, a 21-residue peptide, has been isolated from vascular endothelial cells in culture (4). The endothelin-induced contraction of vascular smooth muscle *in vitro* is dependent on extracellular Ca^{2+} and is reduced by Ca^{2+} channel antagonists but is not affected by antagonists of α-adrenergic receptors, histamine H_1 receptors, cyclooxygenase, or lipoxygenase (1–4).

A number of studies have demonstrated that endothelin is a potent vasoconstrictor in both the dog and the rat and that the renal circulation is particularly sensitive to the peptide (5–11). Among the *in vivo* responses to endothelin are increases in plasma renin activity, plasma norepinephrine concentrations, and plasma epinephrine concentrations (5, 6). Therefore, in the current study we have evaluated (i) the potential contribution of the kidneys in the systemic response to endothelin by determining the effects of endothelin on mean arterial blood pressure in bilaterally nephrectomized rats and (ii) the potential role of norepinephrine and epinephrine in the endothelin-induced changes in mean arterial blood pressure and renal function by determining the cardiorenal actions of endothelin in rats treated with α- and with β-adrenergic receptor antagonists.

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Materials and Methods

Twenty-five female Sprague-Dawley rats (200–300 g) were maintained on standard rat chow and water *ad libitum* for at least 1 week prior to the initiation of the experiments. Rats were deprived of water at 16:00 hr the day before the experiments; the experiments started at 08:00 hr the following morning. At the time of the renal clearance experiments, all rats were anesthetized

with sodium pentobarbital (60 mg/kg). Rectal temperature was maintained at 37 ± 0.5°C by a radiant heat lamp connected to a temperature controller. A tracheostomy was performed with PE-240 tubing and the left femoral vein and artery were cannulated with PE-50 tubing. Blood pressure was monitored with a pressure transducer and displayed on a chart recorder. Immediately after catheterization of the femoral vein, saline containing 3% creatinine was infused at a rate of 0.024 ml/min and maintained throughout the experiment. Finally, the bladder was cannulated with PE-100 tubing via a small (0.5-cm) abdominal incision. The rats were then administered 1.3 mg of pentobarbital, a procedure repeated at 20 and 40 min after surgery.

Following surgery and a 60-min stabilization period, 3 × 20-min clearance periods (C_1, C_2, and C_3) were performed with a 0.2-ml arterial blood sample obtained between C_1 and C_2. An intravenous infusion of porcine/human endothelin (endothelin-1 was purchased from Peninsula Laboratories, dissolved in 0.5 *N* acetic acid, divided into aliquots which were used for each experiment and stored at −80°C) was then initiated for 30 min at a rate of 100 ng kg^{-1} min^{-1}. Urine samples were collected every 15 min during the infusion of endothelin (E_1 and E_2). A second arterial blood sample (0.2 ml) was collected immediately following E_2. The infusion of endothelin was stopped, 3 × 20-min recovery clearances were performed (R_1, R_2, and R_3), and 0.5 ml of arterial blood was collected following R_3. Upon completion of each experiment, all rats were sacrificed with a lethal injection of sodium pentobarbital and the kidneys were removed, cleaned of excess tissue, blotted dry, and weighed.

Four groups of rats were evaluated: Group 1 (n = 10) received an infusion of only endothelin; Group 2 (n = 5) received a bilateral nephrectomy 120 min prior to the infusion of endothelin; Group 3 (n = 5) was infused with endothelin plus an intravenous infusion of phentolamine (the α-adrenergic receptor antagonist was infused at 0.015 mg kg^{-1} min^{-1} during the 1-hr stabilization period, during the experimental period, and during the recovery period); and Group 4 (n = 5) was infused, intravenously, with endothelin plus propranolol (the dose of the β-adrenergic receptor antagonist was 0.015 mg kg^{-1} min^{-1} and was also administered throughout the entire experiment). The dose of phentolamine and of propranolol employed in the present study has been shown to effectively block the α- and β-adrenergic receptors in our previous reports (12, 13).

Chemical Determinations. Urine volume was determined gravimetrically. Urinary and plasma concentrations of sodium, potassium, and calcium were determined with an atomic emission spectrophotometer. Creatinine concentrations in urine and blood were measured according to the method of Folin and Wu (14). The clearance of creatinine and excretion rates of sodium ($U_{Na}V$) and potassium (U_KV) were calculated by standard formulas (U = urine concentration and V = urine flow rate). The clearance of creatinine was equated with the glomerular filtration rate (GFR) (15).

Statistical Analysis. Differences within each group were determined by one-way analysis of variance for repeated measurements and Duncan's new multiple range test. Differences between groups were evaluated using Student's t test for pooled data. Values were accepted as significantly different when the probability of no difference was less than 5%. Mean ± SE are reported.

Results

Figure 1 illustrates the effects of endothelin (100 pg kg^{-1} min^{-1}) on mean arterial blood pressure (MAP) and GFR. At 30 min during the infusion of endothelin, relative to the baseline values, MAP had increased (P < 0.01) by 27 ± 2% (28 ± 2 mm Hg) and the GFR had decreased (P < 0.0 1) by 71 ± 6%. As summarized in Table I, other variables of renal function were also significantly reduced. At 30 min during endothelin infusion, U_KV, $U_{Na}V$, and V had decreased by 71 ± 5%, 65 ± 10% and 71 ± 3% (P < 0.01, P < 0.01, and P < 0.01, relative to corresponding baseline values, respectively).

The effects of nephrectomy on endothelin-induced increases in mean arterial blood pressure are summarized in Figure 2. Nephrectomy significantly enhanced both the absolute increase in MAP (ΔMAP 52 ± 8 mm Hg, P < 0.01 compared with Group 1) and the fractional increase in MAP (78 ± 16%, P < 0.05 compared with Group 1) at 30 min during infusion of endothelin. In addition, MAP remained significantly elevated above the baseline value in Group 2 during the 60-min postinfusion period. By contrast, as illustrated in Figure 1, MAP decreased to values that were significantly lower than baseline in control rats during the 60 min following endothelin infusion.

Phentolamine did not affect either the endothelin-induced increase in MAP (Fig. 3) or the decrease in renal function (Fig. 4 and Table I). Specifically, MAP increased 30 ± 6% and the GFR decreased 83 ± 5% during infusion of endothelin into phentolamine-treated rats. By contrast, the endothelin-induced increase in MAP was enhanced by propranolol (Fig. 3). Specifically, at 30 min during the infusion of endothelin into propranolol-treated rats, MAP increased 38 ± 2% (P < 0.01 versus the baseline value and P < 0.01 versus corresponding value with endothelin alone). The absolute change in MAP at 30 min during infusion of endothelin was also significantly (P < 0.02) greater in propranolol-treated rats compared with Group 1 (Δmm Hg = 38 ± 2 vs 28 ± 2, respectively). It is also of interest to note that the postinfusion

Table I. Effects of ET-1-Induced Changes in Cardiorenal Function in Control Rats (Group 1) and in Rats Treated with Phentolamine (Group 2), or with Propranolol (Group 3)[a]

	Control	E_1	E_2	R_1	R_2	R_3
Group 1 (n = 10, ET-1 alone)						
U_KV (μEq/min)	1.01 ± 0.12	0.95 ± 0.09	0.30 ± 0.10[b]	0.21 ± 0.04[b]	0.52 ± 0.13[b]	0.58 ± 0.10[b]
$U_{Na}V$ (μEq/min)	0.51 ± 0.09	0.49 ± 0.11	0.17 ± 0.06[b]	0.12 ± 0.02[b]	0.29 ± 0.04[b]	0.32 ± 0.05[b]
V (μl/min)	14 ± 1	11 ± 1	4 ± 1[b]	5 ± 1[b]	11 ± 2	14 ± 1
GFR (ml/min)	2.7 ± 0.1	1.5 ± 0.1[b]	0.7 ± 0.1[b]	0.6 ± 0.1[b]	1.2 ± 0.2[b]	1.3 ± 0.1[b]
MAP (mm Hg)	106 ± 1	133 ± 3[b]	135 ± 2[b]	107 ± 8	84 ± 3[b]	86 ± 3[b]
Group 2 (n = 5, ET-1 + phentolamine)						
U_KV (μEq/min)	0.69 ± 0.12	0.58 ± 0.14	0.09 ± 0.03[b]	0.08 ± 0.02[b]	0.17 ± 0.08[b]	0.38 ± 0.14[c]
$U_{Na}V$ (μEq/min)	0.37 ± 0.13	0.34 ± 0.15	0.08 ± 0.03[c]	0.13 ± 0.02	0.24 ± 0.09	0.26 ± 0.12
V (μl/min)	8 ± 1	7 ± 1	2 ± 1[b]	5 ± 1[c]	12 ± 2	14 ± 1
GFR (ml/min)	2.3 ± 0.2	1.2 ± 0.1[b]	0.3 ± 0.1[b]	0.5 ± 0.1[b]	1.3 ± 0.2[b]	1.7 ± 0.1[b]
MAP (mm Hg)	100 ± 4	124 ± 3[b]	131 ± 1[b]	102 ± 10	89 ± 5	96 ± 6
Group 3 (n = 5, ET-1 + propranolol)						
U_KV (μEq/min)	1.67 ± 0.14	1.36 ± 0.16[c]	0.18 ± 0.04[b]	0.18 ± 0.06[b]	0.58 ± 0.16[b]	0.64 ± 0.31[b]
$U_{Na}V$ (μEq/min)	0.99 ± 0.20	1.43 ± 0.28	0.25 ± 0.07[b]	0.31 ± 0.09[b]	0.37 ± 0.07[b]	0.36 ± 0.17[c]
V (μl/min)	17 ± 1	7 ± 2	3 ± 1[b]	6 ± 1[b]	16 ± 2	17 ± 1
GFR (ml/min)	2.5 ± 0.1	1.4 ± 0.2[b]	0.3 ± 0.1[b]	0.5 ± 0.2[b]	1.3 ± 0.3[b]	1.4 ± 0.2[b]
MAP (mm Hg)	100 ± 1	133 ± 2[b]	139 ± 2[b]	112 ± 5	92 ± 11	93 ± 7

[a] Values are mean ± SE.
[b] $P < 0.01$ compared with corresponding control value.
[c] $P < 0.05$ compared with corresponding control value.

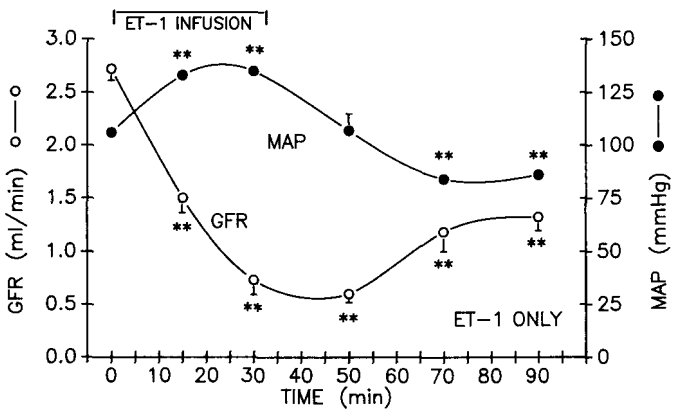

Figure 1. GFR (open circles) and MAP (solid circles) are plotted before (C), during (E_1 and E_2), and after (R_1, R_2, and R_3) an intravenous infusion of endothelin (100 ng kg^{-1} min^{-1}) into Group 1 rats (n = 10). * and ** = $P < 0.05$ and $P < 0.01$ compared with corresponding baseline value, respectively.

hypotension observed in Group 1 rats during clearance periods R_2 and R_3 was not present in either the phentolamine or propranolol group. On the other hand, the absolute values for MAP were not significantly different among the three groups during the recovery periods.

The percentage of decrease in the GFR in propranolol-treated rats was 89 ± 3% ($P < 0.01$ versus the corresponding baseline value) but, relative to Group 1 rats, the fractional change was of borderline significance ($P < 0.1$ but >0.05).

Finally, the endothelin-induced decreases in excretion rates of potassium, sodium, and urine flow rate are summarized in Table I. In rats treated with phentolamine, U_KV, $U_{Na}V$, and V decreased 84 ± 8% ($P <$ 0.01), 67 ± 11% ($P < 0.05$), and 71 ± 8% ($P < 0.0$ 1), respectively, at 30 min during infusion of endothelin but these changes were not significantly different from the corresponding decreases in rats infused with endothelin alone. Similarly, in rats treated with propranolol, U_KV, $U_{Na}V$, and V decreased 89 ± 2% ($P < 0.01$), 74 ± 7% ($P < 0.01$), and 75 ± 10% ($P < 0.01$) of the baseline values, respectively, at 30 min during infusion of endothelin. Again, the decreases were not significantly different from corresponding changes in Group 1 rats.

Discussion

The results of the present study demonstrate that intravenous infusions of endothelin at a dose of 100 ng

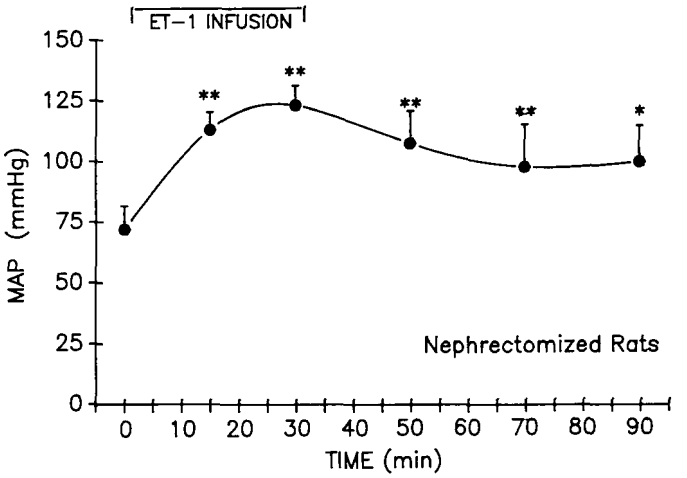

Figure 2. MAP values are shown before, during, and after an intravenous infusion of endothelin (100 ng kg^{-1} min^{-1}) in rats (n = 5) with total nephrectomy. * and ** = $P < 0.05$ and $P < 0.01$ compared with corresponding baseline value, respectively.

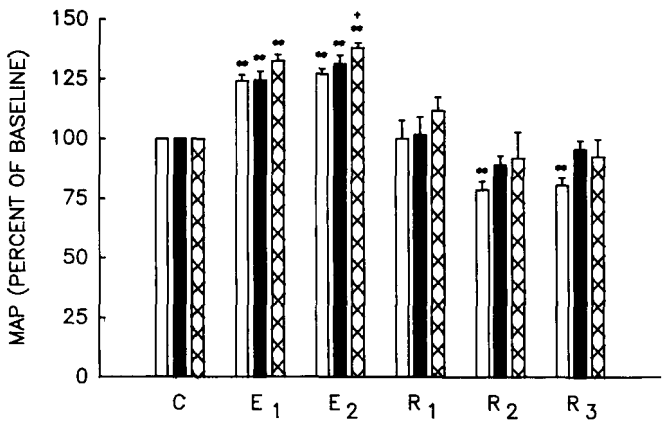

Figure 3. MAP values (% of baseline) are shown before, during, and after an infusion of endothelin (100 ng kg^{-1} min^{-1}) intravenously. Open bars are from Group 1 infused with endothelin alone (n = 10), solid bars are from Group 2 (n = 5) infused with endothelin plus phentolamine (0.015 mg kg^{-1} min^{-1}), and hatched bars are from Group 3 (n = 5) infused with endothelin plus propranolol (0.015 mg kg^{-1} min^{-1}). ** = $P < 0.01$ compared with corresponding pre-endothelin infusion value; + = $P < 0.01$ compared with corresponding value in rats treated with endothelin alone.

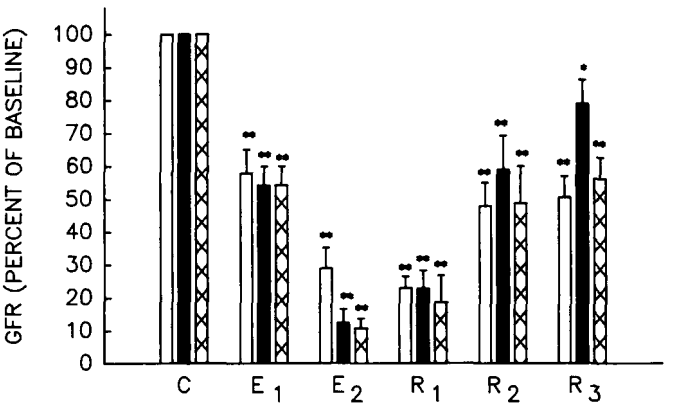

Figure 4. GFR values (% of baseline) are plotted before, during, and after infusion of endothelin (100 ng kg^{-1} min^{-1}) intravenously. Open bars are from Group 1 infused with endothelin alone (n = 10), solid bars are from Group 2 (n = 5) infused with endothelin plus phentolamine (0.015 mg kg^{-1} min^{-1}), and hatched bars are from Group 3 (n = 5) infused with endothelin plus propranolol (0.015 mg kg^{-1} min^{-1}). * = $P < 0.01$ compared with the corresponding pre-endothelin infusion value.

kg^{-1} min^{-1} induce significant increases in MAP and marked decreases in the GFR and that the systemic response to the peptide is potentiated by either nephrectomy or by the β-adrenergic receptor antagonist, propranolol.

Results of our previous studies (11) indicate that the renin-angiotensin system does not contribute to the endothelin-induced changes in cardiorenal function. Specifically, we reported (11) that the competitive angiotensin II receptor antagonist, Sar^1-Thr^8 angiotensin II, does not affect endothelin-induced changes in either renal function or mean arterial blood pressure. In addition, we also reported (11) that the angiotensin-converting enzyme inhibitor, captopril, significantly attenuates the endothelin-induced changes in renal function but does not alter the peptide-induced increase in mean arterial blood pressure. Thus, intrarenally generated agents such as the kinins may affect the renal actions of endothelin. The results of the current study clearly demonstrate that renal events do affect the increase in mean arterial blood pressure prompted by endothelin since nephrectomy enhances endothelin-induced systemic vasoconstriction. One interpretation of the current results is that the kidney significantly contributes to the clearance of the peptide, either via metabolism or via excretion. Alternatively, or, perhaps in addition to the latter, the kidney may release vasodilator substances that attenuate the endothelin-induced systemic vasoconstriction. Along these lines, it has been shown that endothelin does stimulate the release of prostaglandins from several organs, including the kidney (16–21). We have recently reported, however, that under the

conditions employed in the current experiments, inhibitors of cyclooxygenase do not potentiate the systemic or renal actions of endothelin (22). Thus, further experiments will be required to elucidate the mechanism by which nephrectomy potentiates the endothelin-induced systemic vasoconstriction.

A number of investigators have demonstrated that catecholamines play a key role in the regulation of renal function and renal hemodynamics (23–26). Infusions of norepinephrine into renal artery elicit a decrease in renal blood flow and a release of histamine from the kidney (23). On the other hand, intrarenal artery infusions of the β-receptor agonist, isoproterenol, result in increases in the GFR and a natriuresis (27, 28). With regard to endothelin, *in vivo* studies of Yanagisawa *et al.* (4) demonstrated that the endothelin-induced vasoconstriction could be completely reversed by the β-adrenergic receptor agonist, isoproterenol. The results of the current study demonstrate that α-adrenergic receptor blocker, phentolamine, has no effect on the biologic actions of endothelin; however, the β-adrenergic receptor blocker, propranolol, significantly enhanced the endothelin-induced change in MAP at 30 min during infusion of the peptide. These data indicate that the biologic actions of endothelin are neither mediated nor affected by α-adrenergic receptors, whereas β-adrenergic receptors do modulate a portion of the endothelin-induced changes in arterial blood pressure. Along these lines, Goetz *et al.* (5) have reported that intravenous infusions of endothelin into dogs are associated with increases in the plasma concentration of epinephrine. Thus, the catecholamine may counteract a portion of the vasoconstrictive actions of the peptide *in vivo*.

Results of the present study demonstrate that endothelin is a potent vasoconstrictor and that the renal circulation is particularly sensitive to the peptide. The kidney modulates the systemic action of the peptide, perhaps through metabolic and/or clearance actions or via a secondary release of a vasodilator substance(s). The endothelin-induced increase in mean arterial blood pressure and decrease in renal function are not affected by the α-adrenergic receptor blocker, phentolamine, whereas the endothelin-induced increase in mean arterial blood pressure is potentiated by the β-adrenergic receptor blocker, propranolol.

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Addendum

During the review of this manuscript, Kohno *et al.* (29) also reported that nephrectomy potentiates the endothelin-induced increase in systemic blood pressure and, in addition, that the increase in the plasma concentration of endothelin following a bolus injection of the peptide is greater in nephrectomized rats.

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