Endothelial Derived Relaxing Factor Controls Renal Hemodynamics in the Normal Rat Kidney

Christine Baylis, Paul Harton, and Kevin Engels

ABSTRACT
These studies were conducted in the conscious, chronically catheterized rat to determine whether the endothelial derived relaxing factor (EDRF) controls renal function in the normal state. Administration of the EDRF synthesis inhibitors N-monomethyl-L-arginine (NMA; 100 mg/kg body weight) or N-nitro-L-arginine methylester (NAME; 10 mg/kg body wt) led to a large, sustained rise in blood pressure, a large rise in renal vascular resistance, a fall in renal plasma flow, a relatively slight reduction in glomerular filtration rate, and a consequent rise in filtration fraction. In addition, a marked natriuresis occurred because of a reduction in the fractional reabsorption of sodium. In separate studies, a continuous infusion of excess L-arginine (300 mg/kg body wt per min) attenuated the NMA- or NAME-induced rise in blood pressure and reversed the renal hemodynamic effects such that a significant rise in renal plasma flow was seen. L-Arginine alone produced a selective renal vasodilation and large increases in sodium excretion.

These observations support earlier suggestions that tonic release of EDRF controls the basal blood pressure and also show that renal function in the normal unstressed rat is markedly influenced by EDRF. These studies suggest that, in addition to controlling renal plasma flow, EDRF may have other, complex actions at the glomerulus. The natriuresis seen after acute inhibition of EDRF with NMA or NAME was probably the result of a pressure natriuretic response to the abrupt rise in blood pressure and also, perhaps, reflects removal of an EDRF influence to directly enhance sodium reabsorption somewhere in the nephron.

Key Words: GFR, renal plasma flow, renal vascular resistance, natriuresis, conscious rat

Vascular endothelial cells produce an endothelial derived relaxing factor (EDRF) which is released in response to a variety of agonists including acetylcholine (ACh) and bradykinin (BK) and which mediates the vasodilation associated with ACh and BK (1). The second messenger for EDRF-induced relaxation of vascular smooth muscle is cGMP (2), and EDRF itself is now known to be nitric oxide (3). EDRF originates from the terminal guanidino nitrogen of arginine by an enzyme-dependent step (nitric oxide synthase), and EDRF generation can be blocked with the specific substrate competitors N-monomethyl-L-arginine (NMA) (4,5) or N-nitro-L-arginine methylester (NAME) (6,7). Thus, the vasodilatory response to agents such as ACh can be blocked by NMA or NAME (6–8).

Of considerable physiologic importance, recent reports have indicated that, in addition to blocking agonist-stimulated effects of EDRF, the drug NMA produces dose-dependent, prolonged increases in arterial blood pressure (BP) when given to anesthetized rabbits, guinea pigs, or rats in the basal state (8–10). In addition, NMA or NAME causes large increases in BP when administered to the conscious rat (11–13). These observations have therefore raised the possibility that tonic release of EDRF plays a major role in the control of normal BP, via control of vascular tone. Many agents that directly influence vascular tone also control kidney function and thus regulate BP by both direct and indirect mechanisms. The studies presented here were therefore conducted in the conscious, chronically catheterized male rat to establish whether EDRF controls normal kidney function.

METHODS

Studies were conducted on 15 male Sprague-Dawley rats (age, 4 to 5 months) obtained from Harlen-Sprague-Dawley Inc. Rats were allowed ad lib access to drinking water and a diet containing approximately 24% protein and 0.5% sodium. In preliminary surgery, conducted under general anesthesia and by a full sterile technique, catheters were placed in the
left femoral artery and vein and in the urinary bladder. The vascular catheters were exteriorized at the back of the neck, primed with a 1:1 solution of dextrose (50%) and heparin (1,000 U/mL), and plugged. The bladder was irrigated with a neomycin solution and plugged so that rats were able to void normally through the urethra. Further details of this preparation are given elsewhere (14,15). At least 7 days were allowed for full recovery after surgery before renal function experiments were conducted, and, before experiments, rats received extensive handling and were trained to sit quietly in a restraining cage for intervals of 3 to 4 h.

The renal function experiments were conducted in the afternoon as follows: Rats were placed in a restraining cage, the bladder pin was removed, and a collection tube with a side arm was attached to the bladder catheter. This allows irrigation of the bladder with sterile, distilled water both before the experiment and 2 min before the end of each urine collection (flush volume = 0.5 mL), thus allowing complete recovery of all urine and preventing any dead-space errors. The indwelling arterial catheter was connected to a pressure transducer and BP recorder via a three-way stopcock to allow continual recording of BP and occasional sampling of arterial blood. A continual i.v. infusion of 0.9% NaCl solution containing tritiated inulin (2 to 5 Ci/mL) and \( p \)-aminohippuric acid (PAH; 1%) was given at the rate of 5 \( \mu L/min/100\) g rat body wt; this is a nonexpanding infusion rate which approximately equals urine output in this preparation. After an 80-min equilibration time, when plasma inulin and PAH concentrations had plateaued, a control observation period was begun in which two- to 30-min urine collections were made and arterial blood samples (150 \( \mu L \)) were taken at the midpoint of each urine. After centrifugation and removal of plasma for later analysis (see below), the red blood cells were reconstituted with an equal volume of sterile, isotonic NaCl and were restored to the rat.

After completion of control measurements, one of the following experiments were conducted. In Group Ia, eight rats received increasing doses of NMA (Calbiochem) given as i.v. boluses and BP was monitored for 5-min intervals between each dose. The first dose was 20 mg/kg body wt (250 mg/mL: 8 \( \mu L/100\) g body wt), the second dose was 30 mg/kg body wt (250 mg/mL: 12 \( \mu L/100\) g body wt), and the final dose was 50 mg/kg body wt (250 mg/mL: 20 \( \mu L/100\) g body wt). Preliminary studies have indicated that the effect of NMA is very prolonged (BP remains at a stable, elevated level for several hours). Five minutes after the final dose of NMA (which produced a cumulative dose of 100 mg NMA/kg body wt) was given, two more 20- to 30-min urine collections with midpoint bloods were taken. In Group Ib, seven rats received a single i.v. bolus of NAME (Bachem; 10 mg/kg body wt) (50 mg/mL: 20 \( \mu L/100\) g body wt) and, 5 min later, two further 20- to 30-min clearances were measured. Pilot studies had indicated that this dose of NAME was supermaximal and evoked increases in BP equivalent to the cumulative 100 mg/kg body wt dose of NMA given to Group Ia rats. In Groups Ia and Ib experiments, rats received a continual infusion of the control infusate solution throughout the experimental period. In Group II experiments \((N = 10)\), rats again received i.v. boluses of the EDRF blockers \((N = 5, NMA, 100\) mg/kg; \( N = 5, NAME, 10\) mg/kg); 5 min later, rats received a bolus (300 mg/kg) of L-arginine (500 mg/mL; 60 \( \mu L/100\) g body wt) and then the infusate was switched to a solution of the same composition as the control except that it also contained L-arginine (1 g/mL; 5 \( \mu L/100\) g body wt/min) delivered at the rate of 50 mg/kg body wt/min. The L-arginine-containing solution was given throughout the next 60 min and two further 20- to 30-min clearance measurements were made. In Group III experiments, nine rats received the bolus and infusion of L-arginine, as in Group II experiments, but were not given EDRF inhibitors.

The volumes of all urine samples were measured gravimetrically, the urine was analyzed for tritiated inulin activity, PAH, and sodium and potassium concentrations, and corrections were made for the distilled water flush. Arterial blood samples were analyzed for hematocrit (Hct), tritiated inulin activity, and PAH, sodium, and potassium concentrations. Tritiated inulin activity was measured in 10-\( \mu L\) samples of urine and plasma in a Packard scintillation counter. PAH concentration was measured colorimetrically (16), and sodium and potassium concentrations were measured with a flame photometer with lithium chloride as internal standard. These measurements allow the calculation of inulin clearance, which equals glomerular filtration rate (GFR); PAH clearance, which when factored for renal PAH extraction (0.85) equals renal plasma (RPF); renal vascular resistance (RVR); urinary excretion of sodium and potassium \((U_{NaV}\) and \(U_{KV}\), respectively), and the fractional excretion of sodium \((FE_{Na})\). These calculations are described elsewhere (14,15). Data are expressed throughout as mean \( \pm SE\), and statistical significance (where \( P < 0.05\)) was determined by paired and unpaired t-test and ANOVA where appropriate.

RESULTS

Body weight for the group of eight male rats in Group Ia was 333 ± 9 g and in Group Ib was 349 ± 14 g. As shown in Table 1, for both Groups Ia and Ib in the control state, the mean BP was normal and GFR and RPF were as reported previously for this
Increased tubular rejection of sodium, as indicated slightly with NMA, the natniuresis was the result of concentration (UNa). To increases in urine flow (V) and urinary sodium significantly elevated by blockade of EDRF, due both RPF; thus, filtration fraction (FF) rose. UNaV was GFR also fell, but by a lesser percentage than did a large rise (almost a doubling) in RVR, which natu-
tonic, endogenous EDRF production with NMA led to changed by NMA; both values were in the normal and plasma potassium concentration (PK) was un-
preparation (14,15). Urine flow rate, UNaV, and the fractional excretion of sodium were low, indicative of a nonexpanded preparation.

In Group ia, after completion of the control measurements, the first dose of NMA (20 mg/kg body wt) raised mean BP by 24 ± 3 mm Hg; the second dose (an additional 30 mg/kg body wt, given 5 min later) raised BP by a further 12 mm Hg to 36 ± 2 mm Hg above the mean control value; addition of the final dose of 50 mg/kg body wt 5 min later (to give a cumulative dose of 100 mg/kg body wt) led to little further increase in BP, with BP remaining at 40 ± 3 mm Hg above the control value at 5 min after the final bolus. During the renal function studies (conducted over the 60-min period after the last dose of NMA), the large rise in BP due to NMA was sustained (Table 1). Hct rose slightly but significantly with NMA. Plasma sodium concentration (PNa) fell slightly and plasma potassium concentration (PK) was unchanged by NMA; both values were in the normal range throughout the study (Table 1). Blockade of tonic, endogenous EDRF production with NMA led to a large rise (almost a doubling) in RVR, which naturally resulted in a marked fall in RPF. As expected, GFR also fell, but by a lesser percentage than did RPF; thus, filtration fraction (FF) rose. UNaV was significantly elevated by blockade of EDRF, due both to increases in urine flow (V) and in urinary sodium concentration (UNa). Since both GFR and PNa fell slightly with NMA, the natniuresis was the result of increased tubular rejection of sodium, as indicated by the sixfold rise in FENa. Potassium excretion (UnK) changed only slightly with NMA (20% fall) with reciprocal changes occurring in V and urinary potassium concentration (UnK). Group Ib received the alternate EDRF blocker NAME, and most of the responses were similar to NMA. A marked and sustained hypertensive response was observed and RVR approximately doubled, leading to substantial falls in RPF and a less-well-marked decline in GFR. The only variable which responded differently to NAME versus NMA was UnK, which failed to change with NAME, whereas a significant increase was seen with NMA (Table 1); however, the increase in V, UNaV, and FENa and the tendency of UnK to decline were all similar between Groups ia and Ib.

Because of the overwhelming similarity in responses to NMA and NAME, the data from Groups ia and Ib; P < 0.02 by unpaired t test. NS, not significant.
TABLE 2. Summary of systemic and renal variables in conscious, male rats studied in control and then during EDRF blockade with either NMA or NAME (Group I; \(N = 15\)) during EDRF blockade and concomitant l-arginine administration (bolus, 300 mg/kg; infusion, 50 mg/kg body wt/min) (Group II; \(N = 10\)), or during infusion of l-arginine alone (Group III; \(N = 9\)).

<table>
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<th>BP (mm Hg)</th>
<th>Hct (vol %)</th>
<th>(P_{\text{no}}) (mEq/liter)</th>
<th>(P_{\text{x}}) (mEq/liter)</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>FF</th>
<th>RVR (mm Hg/ml/min)</th>
<th>(U_{\text{no}}) (mEq/liter)</th>
<th>(U_{\text{x}}) (mEq/liter)</th>
<th>(V) (µl/min)</th>
<th>(U_{\text{no}})V (µEq/min)</th>
<th>(U_{\text{v}})V (µEq/min)</th>
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<td>0.13</td>
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<td>1</td>
<td>0.1</td>
<td>0.13</td>
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<td>45.0*</td>
<td>140</td>
<td>3.9</td>
<td>3.30*</td>
<td>16.1*</td>
<td>0.235*</td>
<td>5.2*</td>
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<td>38</td>
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\* Significant difference in the change between Groups I and II; † significant difference in the change between Groups II and III. Statistical significance is determined where \(P < 0.05\) by ANOVA on change (difference between control and experimental period) between the respective groups. \(P\) values given are by paired \(t\) test, control versus experimental, within each group. NS, not significant.

completely prevented by l-arginine, and, in fact, a statistically significant rise in RPF and fall in FF were seen in Group II. Large increases were seen in \(V\), \(U_{\text{no}}\)V, \(F_{\text{Na}}\), and \(U_{\text{x}}\)V, which probably were the result of an osmotic diuresis in response to l-arginine.

The response to l-arginine alone is shown in Group III rats (Table 2). Here, l-arginine showed the expected, specific renal vasodilatory response associated with various amino acids (17-19). There was no change in BP, and RVR declined significantly, causing a large rise in RPF and a nonsignificant increase in GFR with a resultant decline in FF. As in Group II, large rises in \(V\), \(U_{\text{no}}\)V, \(U_{\text{x}}\)V, and \(F_{\text{Na}}\) were seen during l-arginine infusion; the only differences in the response to l-arginine in Groups II versus III were that the magnitude of the natriuresis and increase in \(F_{\text{Na}}\) were significantly smaller in rats receiving l-arginine alone (Group III) versus rats receiving concomitant EDRF blockers plus l-arginine (Group II).

DISCUSSION

These studies confirm previous reports that tonic release of EDRF plays an important role in the regulation of BP in the normal animal (6-13). The magnitude of the NMA-induced rise in BP seen here is particularly remarkable because these are normal, conscious, chronically catheterized rats with all of the BP buffer mechanisms intact; thus, the impact of removal of any one BP control system should be minimized. The observations presented here suggest that, in the basal state, BP is lowered by tonic release of EDRF, and, although systemic hemodynamics were not measured in this study, it seems most likely that EDRF is controlling BP by reducing total peripheral resistance (1). In recent reports, Gardiner and colleagues (12,13) observed large, prolonged, and dose-dependent increases in resistance of renal, mesenteric, and hindquarters vascular beds in the conscious rat after acute, i.v. administration of NMA or...
NAME. In this study, we also observed large rises in RVR with NMA/NAME administration, suggesting that tonic release of EDRF normally lowers RVR. Because NMA/NAME also produced large, acute rises in BP in this study, some of the increase in RVR must be attributed to an autoregulatory response (20) although direct renal vasoconstriction due to inhibition of locally formed EDRF is also most likely occurring. In recent reports on the isolated perfused rat kidney, EDRF inhibitors gossypol and hemoglobin (which inhibit distal to EDRF synthesis) have been reported to reduce the basal rate of cGMP production (21) and others report that NMA (as well as gossypol or methylene blue) leads to significant increases in basal RVR (22).

A crucial question in the interpretation of the present studies relates to the specificity of the EDRF synthesis inhibitors used here. EDRF (nitric oxide) is formed from the substrate L-arginine by the enzymatic cleavage of the terminal guanidino nitrogen(s) (4,5,23). The original EDRF synthesis blocker NMA acts by competing with L-arginine for the nitric oxide synthase enzyme, and, in vitro, the effects of NMA can be acutely reversed by excess L-arginine but not by d-arginine (4,5). More recently, alternative NO-substituted arginine analogs have been demonstrated to inhibit EDRF synthesis and nitro arginine has been reported to possess increased potency (24). In the study reported here, we have shown that in the normal, intact, awake rat, two structurally dissimilar EDRF blockers exert similar systemic and renal actions, with NAME being more potent than NMA. Furthermore, we demonstrate that the actions of both blockers are acutely reversible by administration of excess L-arginine. Thus, our present in vivo observations agree with earlier in vitro work. Although we investigated basal release of EDRF in this study, others have investigated agonist-stimulated EDRF actions on the kidney. The ACh-induced renal vasodilation observed in cyclooxygenase-blocked dogs is blunted by concomitant NMA administration (25), and, because ACh-induced falls in RVR are mediated by EDRF, this provides further evidence for the specificity of NMA.

The rise in RVR led to a fall in RPF, as would be anticipated (26). The GFR was relatively protected, however, and did not fall in proportion to the fall in RPF, as evidenced by an increase in FF. An NMA-induced rise in FF was also reported by others in the anesthetized rat (10) and suggests that EDRF has complex actions on glomerular hemodynamics. A recent in vitro study has shown that EDRF increases both basal and BK-stimulated cGMP production in cultured rat glomerular mesangial cells and also attenuates angiotensin II-induced mesangial cell contraction (27). In another study, EDRF derived from calf glomerular endothelial cells augmented basal mesangial cell cGMP production and mediated BK-induced rises in calf mesangial cell cGMP (28). These observations suggest that tonic EDRF relaxes the mesangial cells, thereby increasing filtration surface area, and thus maintains a high value of the glomerular capillary ultrafiltration coefficient (Kf). Blockade of EDRF production with NMA should therefore lower Kf, an effect anticipated to accentuate, rather than diminish, an NMA-induced fall in GFR (26). In order for FF to be elevated and GFR protected in the face of declines in both Kf and RPF and little change in systemic oncotic pressure, NMA must elevate glomerular BP, implying that EDRF is tonically active to preferentially vasodilate the efferent arteriole (26).

We have some preliminary micropuncture data which confirm this hypothesis, and, in a recent preliminary study, Zatz and de Nucci (29) also report large rises in glomerular BP (due to a preferential efferent arteriolar constriction) and declines in Kf after i.v. NMA in the anesthetized rat.

In this conscious, chronically catheterized rat preparation, UNaV remains low and does not increase with time alone, i.e., in the absence of any intervention (14). The marked natriuretic response seen with NMA is therefore the result of inhibition of basal EDRF release. This natriuresis must result from reductions in tubular reabsorption of sodium somewhere in the nephron (as indicated by the large rise in FE Na, because both filtered sodium and RPF fell. With an acute rise in BP of the magnitude seen here, a "pressure natriuresis" component probably contributes to the NMA-induced rise in UNaV (30). In view of the magnitude of the NMA-induced rise in UNaV and the fact that the renal hemodynamic alterations would oppose a natriuresis, it seems likely that removal of a tonic EDRF-induced increase in tubular sodium reabsorption might also contribute to the natriuretic actions of NMA. Unfortunately, little insight into EDRF actions to control UNaV can be derived from the L-arginine studies because the massive solute diuresis provoked by L-arginine administration overwhelmed the effects of EDRF inhibition alone. Since EDRF is produced in the renal medulla (31), however, it is certainly a viable candidate for control of regulation of UNaV.

One final point arising from the studies reported here relates to the ability of various amino acids to produce a specific renal vasodilation. We and others (17–19) have shown that glycerine or mixed amino acids produce renal vasodilation in both awake and anesthetized preparations. In the present study, Group III rats demonstrated a significant renal vasodilation to L-arginine alone and, even in the presence of the EDRF synthesis inhibitors, L-arginine increased RPF (Group II) although the reduction in RVR was blunted versus Group III. In a recent preliminary report, King et al. (10) have suggested that
mediates the renal vasodilation seen in response to a mixed amino acid infusion. Since EDRF is ubiquitous, the renal-specific response to amino acids is puzzling. From our studies, it is unclear whether the EDRF blockers blunt the l-arginine-induced fall in RVR by directly inhibiting the l-arginine-induced, EDRF-dependent reduction in RVR or whether the prior renal vasoconstriction (due to inhibition of endogenous EDRF release) blunts the response to amino acid by altering the starting point from which the reduction in renal vascular tone occurs.

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