Effects of Renal Medullary and Intravenous Norepinephrine on Renal Antihypertensive Function

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Abstract—Increasing renal arterial pressure activates at least 3 antihypertensive mechanisms: reduced renin release, pressure natriuresis, and release of a putative renal medullary depressor hormone. To examine the role of renal medullary perfusion in these mechanisms, we tested the effects of the infusion of norepinephrine, either infusion into the renal medullary interstitium or intravenous infusion, on responses to increased renal arterial pressure in pentobarbital-anesthetized rabbits. We used an extracorporeal circuit, which allows renal arterial pressure to be set to any level above or below systemic arterial pressure. With renal arterial pressure initially set at 65 mm Hg, intravenous and medullary interstitial norepinephrine (300 ng · kg⁻¹ · min⁻¹) similarly increased mean arterial pressure (by 12% to 17% of baseline) and reduced total renal blood flow (by 16% to 17%) and cortical perfusion (by 13% to 19%), but only medullary norepinephrine reduced medullary perfusion (by 28%). When renal arterial pressure was increased to ≈160 mm Hg, in steps of ≈65 mm Hg, urine output and sodium excretion increased exponentially, and plasma renin activity and mean arterial pressure fell. Medullary interstitial but not intravenous norepinephrine attenuated the increased diuresis and natriuresis and the depressor response to increased renal arterial pressure. This suggests that norepinephrine can act within the renal medulla to inhibit these renal antihypertensive mechanisms, perhaps by reducing medullary perfusion. These observations support the concept that medullary perfusion plays a critical role in the long-term control of arterial pressure by its influence on pressure diuresis/natriuresis mechanisms and also by affecting the release of the putative renal medullary depressor hormone. (Hypertension. 2000;35:965-970.)

Key Words: kidney medulla ■ laser-Doppler flowmetry ■ norepinephrine ■ natriuresis ■ renal circulation

It has been hypothesized that the level of medullary blood flow (MBF) is an important determinant of urinary sodium excretion (U\textsubscript{Na}\textsuperscript{+}V) and, indeed, may be the key initiating factor in the pressure natriuresis response.\textsuperscript{1} In turn, the impact of MBF on the pressure natriuretic mechanism provides an explanation for the effects of chronic changes in MBF on the long-term control of arterial pressure.\textsuperscript{1} Thus, in rats, chronic reductions in MBF shift the pressure natriuresis relation toward higher pressures and lead to hypertension in normotensive animals. Conversely, chronic increases in MBF shift the pressure natriuresis relation toward lower pressures and ameliorate hypertension in spontaneously hypertensive rats.\textsuperscript{1}

From studies using an extracorporeal circuit in anesthetized rabbits,\textsuperscript{2} we recently obtained preliminary evidence indicating that influences on the release and/or actions of the putative renal medullary depressor hormone might also contribute to the impact of MBF on the long-term control of arterial pressure. In this model, 3 major renal antihypertensive mechanisms can be studied simultaneously. Thus, when renal arterial pressure (RAP) is acutely increased in this model, plasma renin activity (PRA) is reduced (indicating reduced renal renin release), urine flow (U\textsubscript{Vol}) and U\textsubscript{Na}\textsuperscript{+}V increase exponentially (pressure diuresis/natriuresis), and systemic mean arterial pressure (MAP) is reduced. The depressor response to increased RAP appears to be largely independent of the reduced activity of the renin-angiotensin system, in view of the fact that it is little affected by the blockade of angiotensin-converting enzyme.\textsuperscript{3} It also appears to be largely independent of the associated diuresis and natriuresis, in view of the fact that it is little affected by the release of the putative renal medullary depressor hormone.\textsuperscript{4} We recently found that this depressor response to increased RAP was blunted by medullary interstitial infusion of [Phe\textsuperscript{2},Ile\textsuperscript{3},Orn\textsuperscript{8}]vasopressin (V\textsubscript{1}-agonist), a treatment that selectively reduces MBF,\textsuperscript{2} indicating a possible role of MBF in the release of this putative hormone. However, we were unable to determine whether this effect of medullary interstitial infusion of the V\textsubscript{1}-agonist was specifically due to reduced MBF or to some other action of the agent. For example, this treatment also reduced total renal blood flow (RBF) and cortical blood flow (CBF). We also could not exclude the possibility of non–flow-mediated extravascular actions on V\textsubscript{1}.
The aim of the present study was to more directly test for a role of the medullary microcirculation in modulating the antihypertensive responses to increased RAP. To this end, we made use of our recent observation that medullary interstitial infusion of norepinephrine (NE) reduces MBF (twice as much as CBF, whereas intravascular NE reduces only CBF). Therefore, we compared the effects of medullary interstitial infusion and intravenous infusion of NE on antihypertensive responses to increased RAP. Thus, using this experimental design, we could control for the effects of NE exerted outside the renal medulla in a way that was not possible in our previous experiment with the V₁-agonist. Our results support the concept that MBF plays a key role in the regulation of arterial pressure, not only through its impact on pressure natriuretic/diuretic mechanisms but also via its effects on the release of the putative renal medullary depressor hormone.

Methods

Animals

Twenty-nine male New Zealand White rabbits, weighing 2.50 to 2.94 (mean 2.62) kg, were studied. Before experimentation, all rabbits were allowed food and water ad libitum. At the conclusion of the experiment, they were killed with an intravenous overdose of pentobarbital sodium. All experiments were approved in advance by the Monash University Standing Committee on Ethics in Animal Experimentation.

Extracorporeal Circuit

To control and alter RAP, an extracorporeal circuit was established in anesthetized (pentobarbital at 90 to 150 mg plus 30 to 50 mg/h [Nembutal], Boehringer-Ingelheim) artificially respired rabbits as previously described. Blood was withdrawn from the aorta at a rate of 90 mL/min by a roller pump (Masterflex model 7521-45, Barnant Co) and returned to the rabbit via 2 limbs, one to the renal artery and the other to the vena cava. RAP was controlled by adjusting a Starling resistor incorporated into the vena caval limb, while total flow through the circuit remained constant. For example, increasing the mechanical resistance in the vena caval limb by use of the Starling resistor diverts blood flow toward the renal limb, thus increasing RAP. The circuit dead space (24 mL) was filled with 10% dextran 40 in 154 mmol/L NaCl (Gentran 40, Baxter Healthcare) containing 2 IU/mL heparin (Monoparin, Fisons Pharmaceuticals). Therefore, there was some initial hemodilution when the circuit was established; thus, hematocrit was relatively low (see Results).

To remove the confounding influence of the right kidney, which would otherwise be perfused at systemic arterial pressure, a right nephrectomy was performed in preparation for establishment of the extracorporeal circuit. The left ureter was then cannulated, and the kidney was denervated and placed in a stable cup for positioning of laser-Doppler flow probes. For measurement of MBF, a 26-gauge needle-type probe (DP4s, Moor Instruments Ltd) was advanced 10 mm below the mid region of the lateral surface of the kidney with use of a micromanipulator (Narashige). A standard plastic straight probe (DP2b, Moor Instruments Ltd) was placed on the dorsal surface of the kidney for measurement of CBF. In 14 rabbits, medullary infusion catheters were acutely positioned laterally, 10 mm either side of the laser-Doppler flow probe, and advanced so that their tips lay 8.5 mm below the cortical surface (at the junction of the outer and inner stripes of the outer medulla).

The extracorporeal circuit was then established, and RAP was set at ~65 mm Hg for a 60-minute equilibration period. A bolus dose of [³H]inulin (4 μCi, NEN Research Products) was administered in 1.0 mL of 154 mmol/L NaCl. An infusion of 10% (vol/vol) polyethylene (Hemaccel, Hoechst) containing 200 IU/mL sodium heparin and 0.3 μCi/mL [³H]inulin was then initiated (0.18 mL · kg⁻¹ · min⁻¹), which continued for the duration of the experiment. Body temperature was maintained between 36°C and 38°C.

Measurements

Systemic arterial pressure was measured by connecting an ear artery catheter to a pressure transducer (Cobe). Heart rate (HR) was measured by a tachometer activated by the pressure pulse. RAP was measured in a side-arm catheter, 3 mm proximal to the tip of the cannula inserted into the renal artery. Blood flow through the renal limb was measured with an in-line ultrasonic flow probe (type 4N, Transonic Systems Inc). The laser-Doppler flow probes were connected to a laser-Doppler flowmeter (DRT4, Moor Instruments Ltd). These signals were amplified, recorded, and digitized, as previously described, to provide 60-second means expressed as follows: systemic MAP, mm Hg; HR, bpm; RAP, mm Hg; RBF, mL/min; and CBF and MBF, perfusion units (equivalent to the instrument output in mV×10).

PRA and plasma and urinary concentrations of [³H]inulin and sodium were made as previously described. [³H]Inulin clearance was used to estimate glomerular filtration rate (GFR). At the completion of each experiment, the left kidney was removed and desiccated, and its dry weight was determined. All values of RBF, GFR, U₁₀₀₀, and U₂₀₀₀/V are therefore expressed per gram of dry kidney weight (expressed as g [mean 1.77±0.03 g]).

Experimental Protocols

General

Each experimental protocol consisted of 2 phases. Phase 1, which followed the 60-minute equilibration period, tested the effects of either outer medullary interstitial (protocol 1) or intravenous (protocol 2) infusion of NE on systemic and renal hemodynamics. The second phase of each protocol involved testing the effect of these treatments on the responses to increased RAP. For technical reasons, we were unable to reliably monitor MBF during step increases in RAP, so laser-Doppler measurements are reported only for phase 1 of the experiment.

Protocol 1: Effects of Outer Medullary Interstitial NE

After 10 minutes of stable baseline readings, outer medullary interstitial infusion of either NE (300 ng · kg⁻¹ · min⁻¹, n=6) or its vehicle (154 mmol/L NaCl, 20 μL · kg⁻¹ · min⁻¹, n=8) was started and was continued for the rest of the experiment. Twenty minutes later, RAP was set at ~65, 85, 110, 130, and 160 mm Hg for consecutive 20-minute periods and, once set, was not readjusted. Urine produced by the left kidney was collected during the final 15 minutes of each period. Arterial blood (1 mL) for clearance measurements was collected from an ear artery catheter at the midpoint of each 15-minute clearance period, and samples (1 mL) for determination of PRA were collected at the midpoint of the first, third, and fifth clearance periods. Blood volume was replaced by an equivalent volume of 10% polygeline solution (Hemaccel). At the end of the fifth clearance period, RAP was set to ~65 mm Hg for a further 20 minutes.

Protocol 2: Effects of Intravenous NE

This protocol was identical to protocol 1, except NE (300 ng · kg⁻¹ · min⁻¹, n=7) or its vehicle (20 μL · kg⁻¹ · min⁻¹, n=8) was administered intravenously via an ear vein catheter.

Statistical Analysis

Phase 1

To test whether each of the NE or vehicle treatments altered baseline systemic and renal hemodynamics, average levels of each variable during the period 10 to 20 minutes after the initiation of the infusion were compared with the levels during the 10-minute control period by paired t test.
Phase II
These data were analyzed by ANOVA adapted for repeated measures with the use of SYSTAT software (version 5.05). To protect against the increased risk of comparison-wise type I error resulting from compound asymmetry, probability values were adjusted by use of the Greenhouse-Geisser correction. To test whether increasing RAP altered each variable, a 1-way analysis was first performed on all vehicle-treated rabbits to provide the main effect of increasing RAP (P_RAP). The interaction term between RAP and treatment (vehicle or NE) was then determined from 2-way analyses for each route (intravenous and medullary interstitial). This tested for effects of NE infusion on the responses to increased RAP.

Results
Effects of Renal Medullary Interstitial NE on Systemic and Renal Hemodynamics
Renal medullary interstitial infusion of NE (300 ng · kg⁻¹ · min⁻¹) was accompanied by progressive hemodynamic changes that reached steady state by 10 minutes after the infusion began. The changes involved increases in RAP (by 19 ± 4% of its baseline level during the period 10 to 20 minutes after beginning the infusion) and MAP (by 17 ± 4%) and reductions in RBF (16 ± 3%), CBF (13 ± 2%), and MBF (28 ± 9%) but no significant change in HR (1 ± 2% change). Medullary interstitial infusion of the vehicle had no significant effect on any of these variables.

Effects of Intravenous NE on Systemic and Renal Hemodynamics
Intravenous NE (300 ng · kg⁻¹ · min⁻¹) was also accompanied by reductions in RBF (by 17 ± 9% of its baseline value) and CBF (by 19 ± 3%) and by increases in MAP (12 ± 4%) and RAP (4 ± 1%). However, unlike renal medullary NE, intravenous NE had no significant effect on MBF (1 ± 8% change). Intravenous infusion of the vehicle was accompanied by small variations in MAP (4 ± 1%), HR (1 ± 1%), and RBF (4 ± 2%) but no significant changes in RAP, CBF, or MBF.

Effects of Increasing RAP in Vehicle-Treated Rabbits
Renal Hemodynamic Variables
As shown in Figure 1, as RAP was increased from 66 ± 1 to 158 ± 3 mm Hg, there were progressive increases in RBF (from 13 ± 1 to 29 ± 2 mL · min⁻¹ · g⁻¹) and GFR (from 0.8 ± 0.1 to 3.0 ± 0.4 mL · min⁻¹ · g⁻¹) (P_RAP < 0.001). Renal vascular resistance and filtration fraction responded biphasically. As RAP was increased from ~65 to ~110 mm Hg, renal vascular resistance increased from 5.9 ± 0.8 to 7.7 ± 2.3 mm Hg · mL⁻¹ · min · g⁻¹ when RAP was increased to ~160 mm Hg (P_RAP = 0.05). Filtration fraction also responded in a similar manner, increasing from 3.5 ± 1.1% to 9.3 ± 1.9% as RAP was increased from ~65 to ~110 mm Hg before decreasing to 8.0 ± 1.4% when RAP was increased to ~160 mm Hg (P_RAP < 0.001).

Renal Excretory Variables
As shown in Figure 2, as RAP was increased from ~65 to ~160 mm Hg, there were progressive increases in U_VOL (from 0.09 ± 0.02 to 1.24 ± 0.09 mL · min⁻¹ · g⁻¹) and U_K⁺ V (from 12 ± 2 to 161 ± 13 μmol · min⁻¹ · g⁻¹) and in the fractional excretions of urine (from 12 ± 1% to 43 ± 3%) and sodium (from 11 ± 2% to 40 ± 3%) (P_RAP < 0.001).

Systemic Hemodynamic Variables
As shown in Figure 3, as RAP was increased from ~65 to ~160 mm Hg, MAP fell progressively from 78 ± 3 to 50 ± 5 mm Hg and at an increasing rate of 0.04 ± 0.06 to 0.96 ± 0.15 mm Hg/min (P_RAP < 0.001). Hematocrit decreased gradually from 22.1 ± 0.9% to 21.6 ± 0.9% as RAP was increased from ~65 to ~110 mm Hg and increased thereafter to 22.5 ± 0.9% when RAP was increased to ~160 mm Hg (P_RAP = 0.04). HR tended to decrease (from 266 ± 5 to 253 ± 8 bpm) as RAP increased toward ~160 mm Hg (P_RAP = 0.05).

Plasma Renin Activity
PRA progressively fell as RAP was increased, averaging 14 ± 3, 12 ± 2, and 7 ± 3 ng angiotensin I · mL⁻¹ · h⁻¹ when RAP was ~65, 110, and 160 mm Hg, respectively (P_RAP = 0.04).

Effects of Medullary Interstitial and Intravenous NE on Responses to Increased RAP
The RAP-dependent increases in RBF were significantly attenuated by medullary interstitial NE (Figure 1). RAP-
dependent increases in \( U_{\text{V}} \) and \( U_{\text{Na}} \) (Figure 2) and decreases in MAP (Figure 3) were significantly attenuated, but no significant effect on PRA was observed. Medullary interstitial NE also significantly altered the response of hematocrit to increased RAP, attenuating the increase in hematocrit as RAP was increased above \( \approx 110 \) mm Hg.

Intravenous infusion of NE did not significantly influence any of the responses to increased RAP (Figures 1 to 3).

Effects of Resetting RAP to \( \approx 65 \) mm Hg
When RAP was reset to \( \approx 65 \) mm Hg, RBF returned to levels similar to those observed during the initial period (most leftward point in Figure 1) in vehicle-treated rabbits (\(-3\pm4\%\) different from its previous level during the period 15 to 20 minutes after RAP was reset to \( \approx 65 \) mm Hg) and in rabbits treated with medullary interstitial NE (\(-13\pm4\%) and intravenous NE (\(39\pm27\%)\). MAP rose when RAP was reset to \( \approx 65 \) mm Hg but did not completely recover to its previous level in vehicle-treated rabbits (\(-28\pm5\%)\) and in rabbits treated with outer medullary NE (\(-14\pm6\%)\) and intravenous NE (\(-30\pm10\%)\).

Discussion
We have recently shown in anesthetized rabbits that medullary interstitial infusion of NE (300 ng \cdot kg\(^{-1}\) \cdot min\(^{-1}\)) reduces MBF more than CBF and that intravenous infusion of the same dose reduces CBF only.\(^5\) In the present study, we used these findings as a tool to examine the role of MBF in modulating the renal antihypertensive responses to increased RAP. Our major finding was that medullary interstitial NE, but not intravenous NE, attenuated both the pressure diuresis/natriuresis response and the depressor response to increased RAP. These observations provide further support for the hypothesis that MBF plays an important role in the control of arterial pressure, both through its involvement in the mechanisms mediating pressure diuresis/natriuresis and in the mechanisms mediating the release of the putative renal medullary depressor hormone.

Consistent with our previous observations in a conventional anesthetized rabbit preparation,\(^5\) in the extracorporeal circuit model, infusion of NE increased MAP and reduced RBF and CBF similarly by the 2 routes. This indicates significant systemic spillover of NE infused into the renal medulla and, probably also, spillover into the renal cortex, consistent with our previous extensive characterization of this method.\(^5\) However, our results also indicate that these renal cortical and extrarenal effects of NE can be effectively controlled for by intravenous infusion. The striking difference between the effects of NE infused by the 2 routes was that medullary interstitial infusion of NE reduced MBF by \(\approx 30\%)\, whereas intravenous NE had little or no effect on MBF. Thus, our present experimental design provided a good paradigm for examining the effects of reduced MBF on the renal antihypertensive responses to increased RAP. We can also be fairly confident that these infusions provided relatively constant renal hemodynamic effects, inasmuch as in all experimental groups, RBF levels were similar at the end of the
experiment, when RAP was reset to \( \approx 65 \text{ mm Hg} \), compared with RBF levels during the initial period at this level of RAP.

Thus, our finding (ie, medullary interstitial, but not intravenous, infusion of NE attenuates both the pressure diuresis/natriuresis response and the depressor response to increased RAP) provides evidence for a role of the renal medulla in both these renal antihypertensive mechanisms. Because intravenous infusion of NE did not significantly affect these responses, we can confidently exclude roles for NE mediated outside the kidney that are related, for example, to its systemic pressor effect, modulation of hormone release from extrarenal sites, or inhibition of the peripheral response to the putative renal medullary depressor hormone. We can also probably exclude contributions mediated solely in the cortical microvasculature, inasmuch as RBF and CBF were similarly reduced by medullary interstitial and intravenous infusions of NE. Roles for the renin-angiotensin system also appear unlikely in view of the fact that levels of PRA in rabbits receiving medullary interstitial infusions of NE were indistinguishable from those in vehicle-treated control rabbits.

### Pressure Natriuresis

Medullary interstitial, but not intravenous, NE attenuated the diuretic and natriuretic responses to increased RAP. This effect likely also accounts for the statistically significant influence of medullary interstitial NE on hematocrit responses to increased RAP, because the reduced diuresis/natriuresis would attenuate hemoconcentration at high levels of RAP. Tubular elements probably play a key role in mediating the attenuated diuresis/natriuresis, because medullary interstitial NE did not significantly affect the relation between GFR and RAP. Our results indicate a role of the renal medulla in mediating the effects of medullary interstitial infusion of NE on the pressure diuresis/natriuresis response, but our present experiment does not definitively demonstrate that these effects were mediated by the effect of NE on MBF. In particular, a direct effect of NE on tubular function in the medulla cannot be discounted, because tubular adrenoceptors are certainly known to directly influence fluid and sodium reabsorption in the kidney.\(^{7,8}\)

On the other hand, our present results are consistent with the large body of work by Cowley\(^1\) showing that treatments that alter MBF, but not those that influence CBF alone, profoundly influence the pressure diuresis/natriuresis response. Cowley has argued that the chief initiating factor in the pressure natriuresis response is increased MBF and that this leads to a rise in renal interstitial hydrostatic pressure, which in turn inhibits tubular sodium reabsorption.\(^1\) However, there is still considerable controversy regarding this hypothesis,\(^9\) so its further critical evaluation is important. In this respect, the present study is significant because it has used an experimental model, with an extracorporeal circuit, that differs from conventional models for studying pressure natriuresis, in which RAP is altered by adjustable clamps on the aorta or renal artery.\(^{9,10}\) Using this experimental model, we have previously shown that another treatment that reduces MBF, blockade of nitric oxide synthesis with \(N^2\)-nitro-L-arginine, also attenuates the pressure natriuresis response.\(^5,11\) Importantly, our experimental model allows RAP to be set at levels considerably greater than MAP, so that the pressure natriuresis relation can be investigated over a wide range of RAP. The renal vascular responses to increased RAP in the extracorporeal circuit model differ from those in conventional preparations,\(^10\) in that RBF increases considerably as RAP is increased. However, as has been argued previously, autoregulation in this model is seen as an increase in renal vascular resistance in response to increased RAP, but its effect on RBF is limited by the fixed rate of the pump and high resistance of the vena caval limb.\(^3\)

### Putative Renal Medullary Depressor Hormone

As we have observed previously,\(^2\) increased RAP was accompanied by pressure-dependent reductions in MAP. This response has been extensively characterized previously and appears to be unrelated to the accompanying inhibition of the renin-angiotensin system\(^1\) or increase in \(U_{\text{VOL}}\) and \(U_{\text{Na}}^-\).\(^2,4\) On the basis of the finding that the depressor response is abolished by chemical medullectomy,\(^4\) we have proposed that this response to increased RAP is mediated chiefly by release of an as-yet-to-be-characterized depressor hormone from the renal medulla.\(^12\) It may be that this putative hormone is identical, or similar, to “medullipin,” which has been isolated but not yet fully chemically characterized.\(^13\)

Previous studies have shown that some,\(^2,14,15\) but not all, stimuli that reduce MBF\(^11,16\) attenuate the depressor response to increased RAP. In the present study, we found that the depressor response to increased RAP was greatly blunted by medullary interstitial, but not intravenous, infusion of NE. Thus, our results provide the most direct evidence yet obtained, suggesting that the level of MBF influences the release of the putative renal medullary depressor hormone.

Nevertheless, we cannot as yet completely exclude the possibility that some other action of NE in the renal medulla, such as a direct action on renal medullary interstitial cells, the proposed site of storage and release of medullipin,\(^12\) inhibits the release of the putative renal medullary depressor hormone. However, given our previous finding that medullary interstitial infusion of \([\text{Phe}^1,\text{ILE}^2,\text{OMe}^3]\text{vasopressin}\) reduces MBF and attenuates the depressor response to increased RAP,\(^2\) a role for the medullary microvasculature seems worthy of further investigation. To this end, future studies should replicate this experimental paradigm with other pharmacological agents that might selectively decrease and increase MBF.

### Conclusions

Our findings indicate that NE can act within the renal medulla to attenuate the pressure natriuresis response and the release of the putative renal medullary depressor hormone. At present, we cannot be certain that this effect of NE is mediated by the accompanying reduced MBF, but we have strong circumstantial evidence that this is so. Any vasoactive agent is likely to have extravascular effects that might influence the antihypertensive responses to increased RAP. Therefore, the only way we can dissect out the relative roles of effects on MBF from other actions mediated within the renal medulla is to examine the effects of a range of agents that alter MBF. Our experience so far with extracorporeal circuit models such as that used in the
The present study is that only treatments that alter MBF influence these renal medullary antihypertensive mechanisms. Therefore, it seems likely that the medullary microvasculature plays a key role in the mechanisms controlling blood pressure in the long term, not only via actions on the renal handling of salt and water but also by influencing the release of the putative renal medullary depressor hormone.

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References

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