Effects of daily sodium intake and ANG II on cortical and medullary renal blood flow in conscious rats

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Gross, Volkmar, Theresa M. Kurth, Meredith M. Skelton, David L. Mattson, and A. W. Cowley, Jr. Effects of daily sodium intake and ANG II on cortical and medullary renal blood flow in conscious rats. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R1317–R1323, 1998.—Implanted optical fibers and laser-Doppler flow measurement techniques were used for the sequential measurement of regional renal blood flow in conscious rats to determine the effects of an increase of daily NaCl intake on the renal cortical blood flow and blood flow to the outer and inner medulla. Cortical blood flow was increased significantly (32%) by the second day when NaCl intake was increased from 1 to 7 meq/day and was increased further (50%) on the second day after a further elevation of NaCl intake to 13 meq/day. Blood flow to the outer and inner medulla was not changed as NaCl intake was elevated. The increase in renal cortical flow was closely associated with significant reductions in circulating concentrations of ANG II from 31 to 16 pg/ml. Rats given a continuous infusion of nonpressor doses of ANG II (5.0 ng·kg⁻¹·min⁻¹) to maintain constant plasma concentrations of ANG II as sodium intake was increased exhibited no increase of cortical flow. We conclude that reductions of plasma ANG II associated with incremental increases of daily sodium intake result in a rise of renal cortical flow. The elevated blood flow to the renal cortex may enhance sodium excretion and contribute to long-term sodium homeostasis.

THE PRESENT STUDY addressed how changes in sodium intake may influence regional renal blood flows. The potential role that distribution of blood flow within the kidney can play in the normal regulation of sodium excretion became a subject of interest in the early 1950s based on studies of Trueta et al. (27) and Scher (25) who observed that blood flow was not uniform to all regions of the kidney. From these observations arose the idea that changes in blood flow to specific regions of the kidney might affect glomerular filtration or tubular function and contribute to whole kidney excretory function. This concept was reinforced when Morgan and Berliner (22) demonstrated that the long loops and greater size of juxtamedullary nephrons resorb a greater proportion of sodium and water delivered from the proximal tubules. Despite considerable interest and many efforts to test this concept, evidence for this theory of sodium homeostasis has been extrapolated only from short-term anesthetized animal studies and the theory has never been proven. The reason for this is that techniques required for determining sequential changes of cortical and medullary blood flow in the unanesthetized, unstressed state have not been available (1).

In recent years, we have refined and validated the use of laser-Doppler flowmetry techniques to measure changes of microvascular blood flow in various regions of intact kidneys that enable the daily sequential determination of regional blood flow in unanesthetized rats. It has been shown that small optical fibers implanted into the renal cortex and medulla of rats can be used for the simultaneous measurement of changes in blood flows to these respective regions in conscious rats. These fibers have not altered total renal blood flow, glomerular filtration rate (GFR), the ability to concentrate urine, or the ability to excrete a sodium load (12, 13, 17, 18). Using these techniques, we examined the effects of a high-salt (NaCl) diet on renal cortical and medullary blood flow. Based on earlier studies from our research program (7), which demonstrated that acute isotonic volume expansion with isotonic NaCl significantly increased renal papillary blood flow, we hypothesized that under conditions of a chronic high salt intake delivered intravenously as isotonic saline that the same response would be observed. This, as shown by the results of the present study, was not observed in these chronically instrumented rats. Indeed, it was the cortical blood flow that exhibited a significant increase. For this reason and given the well-characterized changes of renin secretion and circulating ANG II to changes of daily sodium intake, the role of the renin-angiotensin system in the observed renal blood flow responses were also evaluated. Circulating ANG II was maintained constant at normal levels by continuous intravenous infusion throughout the experimental protocol to determine the role that this endocrine system may play in the modulation of regional renal blood flow with changes in daily sodium intake.

METHODS
Experiments were performed on adult male Sprague-Dawley rats (weighing 310–340 g) purchased from SASCO (Madison, WI). The animals were housed in individual cages in the Animal Resource Center. The rats were fed a low-sodium rat chow (Dyets AIN 76 20,0000 with 0.4 g/100 g NaCl; Bethlehem, PA) and water ad libitum until the beginning of the experimental period when the rats were fed a concentrated liquid diet containing no sodium (Dyets AIN 713751).

Surgical Preparation
All surgical procedures were performed using aseptic techniques. Rats were anesthetized with a mixture of acepromazine (2.7 mg/kg intramuscularly) and ketamine (123 mg/kg...
intramuscularly) and placed on a heated surgical table to maintain body temperature at 37°C. Catheters were placed in the femoral artery for the measurement of arterial blood pressure and in the femoral vein for the delivery of intravenous solutions; both catheters were advanced to 2–2.5 cm below the branching of the renal vessels. The catheters were then tunneled subcutaneously, exteriorized at the back of the neck, and passed through a flexible spring to the top of the cage where they were attached to a swivel that allowed the animal to move freely about the cage while being continuously infused. During the same surgery, the left kidney was exposed via a flank incision and two flexible optical fibers (0.5 mm diameter) shaped to conform to the size and contour of the kidney were implanted in two of three locations, outer cortex, outer medulla (red medulla), and/or the inner medulla (white medulla), for flow measurements as described previously from our laboratory (13, 17). Each fiber was inserted through a hole made in the renal capsule with a 25-gauge needle, and the tips of the superficial cortical and medullary fibers were implanted to a depth of 1.5 mm for outer cortical blood flow, 3 mm for outer medullary flow, and 5 mm for inner medullary flow. Optical fibers were secured by placing a drop of cyanoacrylate gel around the edge of a latex washer, which was attached to and encircled the fibers at a predetermined distance from the tip of the fibers. The fibers were protected in a polyethylene sheath, tunneled under the skin and exteriorized at the back of the neck. The fibers were brought up through the flexible spring with the catheters. Animals were kept warm until they had recovered from anesthesia. Penicillin (40,000 U intramuscularly) was administered postoperatively to avoid infection, and Buprenex (0.3 mg/0.3 ml sc), a narcotic analgesic, was given for management of any pain associated with the recovery from surgery.

Experimental Design

Protocol 1: Increasing NaCl intake in normal Sprague-Dawley rats. GROUP 1: CORTICAL AND MEDULLARY RENAL BLOOD FLOW. Twelve rats were instrumented for measurement of arterial blood pressure and cortical and medullary blood flow. Three to four days after surgery, a concentrated liquid diet containing no sodium (Dyets AIN 713751) was given to the rats ad libitum along with water. During this experimental control period, a continuous intravenous infusion of isotonic saline was administered at 6–7 ml/day, which provided ~1 meq/day of NaCl.

After 2 days of control measurements, the daily NaCl intake was increased by intravenous infusion to 7 meq/day (45 ml saline/day). After 2 days at this level of NaCl, daily intake was increased to 13 meq/day (85 ml saline/day). An NaCl intake of 13 meq/day is comparable to that ingested by rats maintained on a 4% NaCl diet. The infusion rate was then returned to that used in the control period (6–7 ml/day or 1 meq/day). Two days for each level of NaCl intake was chosen because it has been shown that sodium balance is achieved in normal rats within this period (9). MAP, renal blood flows, and hematocrit were measured on the last 2 control days, on each of the days of increased NaCl intake, and for 3 days after returning to the control intake (1 meq/day).

GROUP 2: PLASMA ELECTROLYTES, OSMOLALITY, PROTEIN CONCENTRATION, AND COLLOID ONCOTIC PRESSURE. Seven rats were prepared with arterial and venous catheters. On the last control day of 1 meq/day, the second day of 13 meq/day, and the third postcontrol day (1 meq/day), 2 ml blood was drawn in lithium-heparin tubes (Becton-Dickinson, Rutherford, NJ) for determination of plasma sodium, potassium, protein, plasma osmolality, and plasma colloid oncotic pressure (COP). Washed cells from a donor rat prepared as previously described (8) were diluted to the recipient rat hematocrit and were infused into the venous line over a 2-min period after the arterial withdrawal. Arterial blood pressure was determined daily as in group 1.

GROUP 3: PLASMA ANG II CONCENTRATIONS. Sprague-Dawley rats (n = 9) were prepared with an arterial and venous catheter. Arterial blood (1 ml) was withdrawn in chilled tubes for ANG II determination on the last control day and the second day of high NaCl intake (13 meq/day). In these rats, the daily food and water intake were also measured. The total water intake was calculated to include drinking, the amount in the food, and the amount of water in the intravenous NaCl infusion.

Protocol 2: Increasing NaCl intake with fixed plasma ANG II in normal Sprague-Dawley rats. GROUP 1: CORTICAL AND MEDULLARY RENAL BLOOD FLOW. Eleven rats were prepared for these studies to determine the extent to which the renal hemodynamic changes were the result of suppression of ANG II. The rats were fed in the same manner described in protocol 1, except that during the control period (1 meq NaCl/day) and throughout the entire experimental protocol rats received a continuous low-dose intravenous infusion of ANG II (5.0 ng·kg⁻¹·min⁻¹). As determined during the first week of this study, this dose of ANG II did not result in a significant elevation of MAP during 3 days of infusion at a sodium chloride intake of 1 meq/day. After 3 additional days of NaCl infusion together with ANG II, NaCl intake was increased to 7 meq/day for 2 days and then to 13 meq/day for 2 days, after which it was returned to 1 meq/day for 3 additional days.
Measurements of cortical and inner medullary blood flow and MAP were made daily. Sprague-Dawley rats (n = 10) were prepared with arterial and venous catheters. The sodium loading and ANG II infusion protocol was identical to that described above in group 1. In these rats, arterial blood samples (1 ml) were drawn for measurement of ANG II on the final control day (1 meq/day) and the last day of 13 meq/day salt + 5 ng·kg⁻¹·min⁻¹·ANG II.

Analytic and Biochemical Analyses

Sodium and potassium concentrations were determined using a flame photometer (model 143, Instrumentation Laboratories, Lexington, MA). Plasma protein concentrations were measured by refractometry (model TS, American Optical, Buffalo, NY). COP was determined using a model 4400 colloid osmometer (Wescor, Logan, UT). Plasma osmolality was measured by vapor pressure osmometry (model 5C, Wescor, Logan, UT). Samples were routinely run in duplicate.

Plasma levels of ANG II were measured using techniques previously described (23). Blood was collected in chilled tubes containing 12.5 mM EDTA and 2.6 mM phenanthroline, and plasma was removed and frozen at −80°C until analysis. ANG II was extracted from the plasma using a Sep-Pak (Waters C₁₈) column and eluted with methanol. The extract was evaporated under nitrogen and redissolved in 150 µl of 0.1 M CH₃COOH and passed through a Millipore LCR3 filter unit. The filtrate (100 µl) was injected onto a Waters Bondapak C₁₈ 10-µm (300 × 2.1 mm) column and run under isocratic conditions with a mobile phase of 0.85% H₃PO₃ in methanol. For each sample, two preinjection blanks were collected. The 2-min window was verified by injection of ANG II plasma extract containing [³H]ANG II before and after the series of unknowns was injected. A 20-min stripping (to 75% methanol) and reequilibration cycle was allowed between injections of sample. The entire eluent volume from the 2-min window was collected, dried, and stored at −35°C until assayed. ANG II concentrations in the collected fraction were determined by radioimmunoassay (delayed trace addition; charcoal separation). Calculations of plasma ANG II levels were made without adjustment for loss during extraction or separation. Preliminary assessment of recovery of added ANG II or added [³H]ANG II to plasma indicated a consistently high recovery of ≥85%. Results are reported as ANG II pg/ml.

Statistical Analysis

Values are given as means ± SE. One-way repeated-measures ANOVA was performed on each group followed by a Duncan’s multiple-range test for significance. Values of P < 0.05 were considered significant.

RESULTS

Protocol 1: Effects of Increasing NaCl Intake in Normal Sprague-Dawley Rats

Figure 1 summarizes the responses of cortical blood flow, outer and inner medullary blood flow, and MAP to increasing levels of daily NaCl intake. During the control period, the voltage signals of fibers implanted in the renal cortex averaged 1.2 ± 0.1 V (n = 9). For the same time period, outer medullary blood flow signals averaged 1.5 ± 0.3 V (n = 5) and the inner medullary flow signals averaged 0.8 ± 0.06 V (n = 6). Increasing the NaCl intake from 1 to 7 meq/day resulted in a significant increase of 32% in cortical blood flow by day 2. As NaCl intake was increased to 13 meq/day, cortical blood flow reached its highest level of 1.8 ± 0.2 V, or nearly 50% above control values. After return of the NaCl intake to 1 meq/day, the cortical flow signals returned to levels not significantly different from control. Neither outer medullary nor inner medullary blood flow signals were changed with elevations of daily NaCl intake. MAP did not change significantly with any level of NaCl intake.

The changes in plasma protein, COP, plasma sodium and potassium concentrations, plasma osmolality, and hematocrit measured at 1 and 13 meq/day are summarized in Table 1. Plasma protein concentrations averaged 5.6 ± 0.1 g/dl and COP averaged 16.5 ± 0.3 mmHg.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (1 meq/day)</th>
<th>13 meq/day</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PNa, meq/l</td>
<td>140.3 ± 0.16</td>
<td>142.2 ± 0.52*</td>
<td>0.16</td>
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<tr>
<td>PK, meq/l</td>
<td>4.93 ± 0.23</td>
<td>4.25 ± 0.07*</td>
<td>0.21</td>
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<tr>
<td>Posmol, mmol/kg</td>
<td>286.1 ± 2.4</td>
<td>285.7 ± 3.1*</td>
<td>0.12</td>
</tr>
<tr>
<td>PProt, g/dl</td>
<td>5.6 ± 0.1</td>
<td>5.7 ± 0.1*</td>
<td>0.1*</td>
</tr>
<tr>
<td>COP, mmHg</td>
<td>16.5 ± 0.3</td>
<td>17.3 ± 0.4*</td>
<td>0.4*</td>
</tr>
<tr>
<td>Hct, %</td>
<td>36 ± 1</td>
<td>34 ± 1*</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. PNa, plasma sodium; PK, plasma potassium; Posmol, plasma osmolality; PProt, plasma protein; COP, oncotic pressure; Hct, hematocrit. *P < 0.05 compared with initial 1 meq/day value.

Fig. 1. Summary of effect of changing intake of NaCl by intravenous infusion of isotonic saline on cortical blood flow (n = 9), medullary blood flow, and mean arterial pressure (MAP; n = 11) in conscious rats. Medullary blood flow was measured in the outer medullary region (n = 5) and the inner medullary region (n = 6). *Significant difference from both control days (1 meq).
during the control period of 1 meq/day NaCl intake and remained constant even at an NaCl intake of 13 meq/day. Plasma protein and COP both exhibited a small but significant rise above the initial control in the postcontrol period when NaCl intake was returned to 1 meq/day NaCl diet (Table 1). Plasma sodium concentration increased 2 meq/day with the NaCl intake of 13 meq/day (P < 0.05), and plasma potassium tended to decrease. The plasma osmolality remained unchanged throughout the experiment.

Figure 2 (solid bars) summarizes the plasma ANG II concentrations observed during an NaCl intake of 1 meq/day and 13 meq/day NaCl intake. Plasma ANG II levels decreased significantly to 16.5 ± 4.2 pg/ml on the final day of 13 meq/day NaCl intake from average control concentrations of 31.7 ± 6.5 pg/ml on 1 meq/day.

The daily food intake was not significantly influenced by the change of NaCl intake. On the final day of the control period, rats averaged 18 g of the liquid food compared with 15 g consumed on the final day of the 13 meq/day NaCl intake. The total water intake (drinking water plus water intake in the form of liquid food) averaged between 28 and 31 ml in the control period when rats were receiving 6–7 ml of isotonic saline and decreased to 18 ml during the 2 days when the rats were receiving 45 ml of isotonic saline.

Protocol 2: Effects of Increasing NaCl Intake With Fixed Plasma ANG II

Intravenous ANG II infusion prevented the decrease in plasma ANG II concentrations in rats with high NaCl intake as shown in Fig. 2 (open bars). Plasma ANG II concentrations on 1 meq/day averaged 32.3 ± 9.2 pg/ml. When NaCl intake was increased to 13 meq/day in the presence during infusion of continuous ANG II (5.0 ng·kg⁻¹·min⁻¹), plasma ANG II concentrations averaged 29.4 ± 9.8 pg/ml when the NaCl level was increased to 13 meq/day, levels not significantly different from control. These concentrations contrast significantly with reductions that were seen when ANG II was not infused, where concentrations decreased significantly to 16.5 ± 4.2 pg/ml on the final day of 13 meq/day NaCl intake.

In contrast to the rats that could normally suppress ANG II with high NaCl intake, renal cortical blood flow did not change with increased NaCl intake in the rats with fixed plasma ANG II. As shown in Fig. 3, during the final 2 control days with an NaCl intake of 1 meq/day and in the absence of ANG II infusion, cortical blood flow averaged 1.15 ± 0.2 V and inner medullary flow averaged 0.7 ± 0.07 V. Administration of ANG II at 5 ng·kg⁻¹·min⁻¹ did not significantly influence these control blood flow levels during the low NaCl control period. Importantly, increased levels of NaCl intake resulted in no change of either cortical or medullary blood flow, indicating that the rise of cortical blood flow with increases of NaCl intake could be attributed to the reduction of circulating levels of ANG II.

MAP values ranged between 102 and 108 mmHg during low NaCl intake. The addition of 5 ng·kg⁻¹·min⁻¹ ANG II to low intravenous NaCl intake did not affect MAP. It was only on the second day with 13 meq/day NaCl intake that an increase of MAP was observed, at which time pressure rose to 118 ± 2 mmHg. MAP decreased rapidly when the NaCl intake level was returned to 1 meq/day to the levels observed in the initial control period (Fig. 3, bottom).

DISCUSSION

In the present study, a 50% elevation of renal cortical blood flow was observed as daily NaCl intake was increased from 1 to 13 meq/day. Our data, however, indicate that the increase of cortical blood flow did not result from a redistribution of total renal blood flow.
because medullary blood flow remained unchanged. The present observations are also consistent with micro-puncture studies by Steiner et al. (26) who reported that chronic NaCl depletion increases both afferent and efferent arteriolar resistances in the superficial cortex of normal rats. They also are consistent with observations of Horster and Thurau (10) who found that, in rats receiving a low-sodium diet, 41% of the total glomerular was formed in juxtamedullary nephrons compared with 11% in rats on a high-sodium diet (10).

The mechanism(s) whereby an increase of cortical blood flow would enhance the excretion of sodium is not completely understood, and the present studies were not designed to determine these detailed mechanisms. Nevertheless, it is interesting to speculate on these events. Arterial pressure remains virtually unchanged in normal rats and in humans in response to daily changes of sodium intake (4) as was seen in the present study. Elevated GFR and total renal blood flow have been observed in rats fed a high-sodium diet (11), which would be expected with a reduction of cortical vascular resistance unless a parallel reduction of efferent arteriolar resistance simultaneously occurred. It appears that the tubular glomerular feedback mechanism does not have a net feedback gain sufficient to overcome excess delivery of sodium to the distal tubule. It also appears that the thick ascending limb of Henle cannot completely compensate for excess load of sodium delivered under chronic conditions of high salt intake. This may be because a rise of glomerular pressure related to a reduction of preglomerular vascular resistance would be expected to result in an elevation of postglomerular blood flow and peritubular capillary pressure. These events could contribute to enhanced sodium excretion due to shifts of the Starling forces and fluid flux across peritubular capillaries of the cortex, which in turn would increase the renal interstitial fluid pressure and depress tubular sodium reabsorption (3, 11, 24).

Acute studies comparing responses to intravenous infusions of whole blood, albumin, or saline solutions indicated that it is the reduction of plasma oncotic pressure with isotonic volume expansion that results in a reduction of renal tubular reabsorption and the enhancement of sodium excretion (5, 7, 11). The results of our present chronic studies, however, would suggest that the changes in COP, which appear to prevail in the natriuresis observed after acute isotonic volume expansion, cannot account for the changes of cortical blood flow that were observed in rats maintained chronically on a high sodium intake. Specifically, the plasma COP did not change significantly in the present study, indicating that this mechanism was not involved in changes of blood flow observed with chronic elevations of NaCl intake.

Role of ANG II in Cortical Blood Flow Response to a Chronic High NaCl Intake

The present studies demonstrated an important role for the renin-angiotensin system in the renal blood flow responses to a high salt intake. When circulating levels of ANG II were maintained at a constant concentration throughout the periods of high salt intake, renal cortical blood flow did not increase during the period of high NaCl intake. These data indicate that the 50% rise of cortical flow that was observed in normally responding rats was a result of reductions of plasma ANG II and an associated reduction of renal cortical vascular resistance to blood flow.

Medullary Blood Flow Response

The constancy of the medullary flow and rise of cortical flow was not anticipated, but may be explained by observations made after acute isotonic and isoncotic loading studies in anesthetized rats. Fenoy and Roman (7) used laser-Doppler flowmetry techniques combined with videomicroscopy to examine whether changes in plasma oncotic pressure or hematocrit played a role in the redistribution of renal blood flow and the natriuretic response to extracellular fluid expansion with saline. It was found that acute isotonic sodium loading produced a 46% increase in the flow of red blood cells in the papilla of anesthetized Munich-Wistar rats, primarily because of an increase in the number of functional capillaries perfused with moving red blood cells. An equivalent expansion of plasma volume delivered as an isoncotic load using an albumin solution (1.25% body wt) produced only a 17% increase in flow of red blood cells to the papilla. It was also observed in this study that total renal blood flow was unchanged with acute isotonic saline loading but increased nearly 50% with isoncotic loading with the albumin solution. The greatly attenuated increase of papillary blood flow with isoncotic plasma volume expansion indicated that the changes in plasma oncotic pressure in some way signaled the rise in papillary flow after isoncotic saline volume expansion. The blood flow responses observed in the acute studies could not be attributed to elevations of renal perfusion pressure, changes in renal nerve activity, or known endocrine responses, because the perfusion pressure to the kidneys was controlled at normal levels by use of aortic clamps, kidneys were denervated, and circulating antinatriuretic hormones were “fixed” at normal to high physiological plasma levels by continuous intravenous infusion. These observations may be directly relevant to the present study, because responses of chronically instrumented rats receiving a high sodium intake resembled the responses seen with acute isoncotic volume expansion. That is, medullary blood flow remained unchanged and cortical blood flow increased. This could perhaps have been predicted from the acute studies, because the COP was not reduced during chronic administration of excess sodium and even rose slightly by the end of the high NaCl-intake period.

Nevertheless, there are a number of mechanisms that we supposed might lead to an increase of medullary blood flow in rats maintained chronically on a high sodium intake. Many of the neural, endocrine, and paracrine responses to a high sodium intake would have predicted an increase of blood flow to the kidney.
Suppression of the renin-angiotensin system with a high sodium intake may be expected to reduce medullary blood flow. However, Mattson et al. (19) found that the renal medullary circulation of normal rats was very insensitive to the vasoconstrictor actions of ANG II, which would conform to our chronic observations in the present study. Renal kinins increase with an increased salt intake (2), and we have shown that infusion of bradykinin into the renal medulla selectively increases renal papillary blood flow, which is associated with increased sodium and water excretion (15). The same can be said of renal prostaglandin and renal 20-hydroxyeicosatetraenoic acid responses to a high salt intake (6, 14, 20, 28). Recent studies would also suggest that a high sodium intake might lead to an increase of medullary blood flow via stimulation of nitric oxide (NO) production. We have shown that selective inhibition of medullary nitric oxide synthase (NOS) activity with renal medullary interstitial infusion of NG-nitro-L-arginine methyl ester reduced papillary blood flow and was associated with decreased sodium and water excretion, indicating that NO exerts a tonic influence on the renal medullary blood flow and sodium homeostasis (21). Furthermore, a high-salt diet selectively increased medullary NOS activity and expression of NOS protein levels as determined by Western blot analysis (16). Given the responses of renal, endocrine, and paracrine systems to increases of sodium intake and given the responses of the medullary circulation to acute isotonic volume expansion, the responses of the medullary circulation to an increased sodium intake were not anticipated.

In summary, the present study demonstrated that increasing daily sodium intake caused substantial increases in renal cortical blood flow in conscious rats. The increases in renal cortical flow were closely associated with significant reductions in circulating ANG II concentrations. Continuous infusion of nonpressor doses of ANG II, which fixed the circulating levels of ANG II at the low salt intake control level, prevented the increase in renal cortical blood flow as salt intake was increased. We conclude that suppression of ANG II is the major factor responsible for increasing renal cortical blood flow after chronic high sodium intake. The results of the present study also show that, despite the endocrine and paracrine responses that might predict a rise of medullary flow with a high sodium intake, the net interaction of these various systems appears to yield a constancy of blood flow to both the outer and inner medulla in the face of large changes in daily sodium intake. Changes in renal cortical blood flow appear to play an important role in the chronic regulation of sodium excretion. If renal cortical blood flow is not able to increase with NaCl loading, an increase in blood pressure ensues. This observation bears an important relevance to NaCl-induced increases in arterial blood pressure, as observed in salt-sensitive forms of hypertension.

The authors thank the Biochemical Core Lab staff, Lisa Henderson, Camille Torres, and Kelly Frigerio, for the measurement of ANG II; Rosalie Zamiatowski for the measurements of electrolytes, protein and oncopressor effects; and Nicole Gruber for secretarial assistance. This study was supported by National Heart, Lung, and Blood Institute Grant HL-29587. V. Gross was supported by Deutsche Forschungsgemeinschaft Gr 1112/3–1.

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Received 10 October 1997; accepted in final form 22 January 1998.

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