Hormonal regulation of renal sodium and water excretion during normotensive sodium loading in conscious dogs

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Sandgaard, Niels C. F., Jens Lundbaek Andersen, and Peter Bie. Hormonal regulation of renal sodium and water excretion during normotensive sodium loading in conscious dogs. Am. J. Physiol. Regulatory Integrative Comp. Physiol. 278: R11–R18, 2000.—Saline was infused intravenously for 90 min to normal, sodium-replete conscious dogs at three different rates (6, 20, and 30 µmol·kg−1·min−1) as hypertonic solutions (HyperLoad-6, HyperLoad-20, and HyperLoad-30, respectively) or as isotonic solutions (IsoLoad-6, IsoLoad-20, and IsoLoad-30, respectively). Mean arterial blood pressure did not change with any infusion of 6 or 20 µmol·kg−1·min−1. During HyperLoad-6, plasma vasopressin increased by 30%, although the increase in plasma osmolality (1.0 mosmol/kg) was insignificant. During HyperLoad-20, plasma ANG II decreased from 14 ± 2 to 7 ± 2 pg/ml and sodium excretion increased markedly (2.3 ± 0.8 to 19 ± 8 µmol/min), whereas glomerular filtration rate (GFR) remained constant. IsoLoad-20 decreased plasma ANG II similarly (13 ± 3 to 7 ± 1 pg/ml) comitant with an increase in GFR and a smaller increase in sodium excretion (1.9 ± 1.0 to 11 ± 6 µmol/min). HyperLoad-30 and IsoLoad-30 increased mean arterial blood pressure by 6–7 mmHg and decreased plasma ANG II to ~6 pg/ml, whereas sodium excretion increased to ~60 µmol/min. The data demonstrate that, during slow sodium loading, the rate of excretion of sodium may increase 10-fold without changes in mean arterial blood pressure and GFR and suggest that the increase may be mediated by a decrease in plasma ANG II. Furthermore, the vasopressin system may respond to changes in plasma osmolality undetectable by conventional osmetry.

angiotensin II; volume expansion; vasopressin; blood pressure; natriuresis.

THE RELATIVE IMPORTANCE of the humoral, hemodynamic, and nervous mechanisms in the regulation of renal sodium excretion is still controversial. The relative roles of the arterial blood pressure and the renin-angiotensin-aldosterone system in providing sodium homeostasis are particularly complex. Recently, we demonstrated (4) that a sodium load simulating daily sodium intake induced natriuresis concomitant with a decrease in plasma ANG II level and a small, but significant, increase in arterial blood pressure. Under these circumstances, the natriuresis may be explained by the decrease in plasma ANG II level and by the increase in arterial blood pressure. Sodium loading was also performed during normotensive ANG II clamping, i.e., a constant infusion of ANG II sufficient to normalize arterial blood pressure during control conditions. Under these conditions, >90% of the natriuretic response to sodium loading was blocked, indicating a pivotal role of ANG II in the control of renal sodium excretion. However, the procedure of sodium loading still increased arterial blood pressure. Different methods may be used to isolate the effect of an increase in renal perfusion pressure, including aortic cuffs (22) and pharmacological pressure control (1). In this study we chose to infuse different sodium loads at rates that are too small to change arterial blood pressure and to measure the concomitant endocrine and renal excretory changes. In this way it might be possible to separate the effects of humoral factors from those of changes in arterial blood pressure without interfering with intrarenal hemodynamics or constricting the renal artery. To our knowledge the responses to such small, slow sodium loads in conscious dogs have not previously been reported.

METHODS

Animals

The experiments were performed in conscious female Beagle dogs weighing 11.5–16 kg. The dogs were kept on a fixed diet (Special Diets Services, Witham, UK) and received one meal a day at around 1400. Mean daily sodium intake was 2.2 ± 0.1 mmol/kg body wt (mean ± SE). The dogs had free access to tap water. Before the study, several surgical interventions were performed as described in the preceding paper (4). The dogs were trained for several months before the experiments, which were approved by the Danish Animal Experiments Inspectorate.

Experimental Protocol

The same six dogs were used for all experiments, and in the last two infusion series (see below) one more dog was included. In each dog, experiments were performed at intervals of >1 wk. At midnight before the experiment, an electric valve controlled by a timer interrupted the water supply. On the experimental day, the dog was transferred to the laboratory and prepared for study as previously described (4). Briefly, catheters were placed in a central vein, in a carotid artery, and in the bladder. After a 30-min control period, isotonic or hypertonic salt loading was initiated and continued for 90 min (t = 120 min) followed by a 30-min recovery period.
The first sample of arterial blood was obtained at \( t = -5 \) min; subsequent samples were obtained 25 min into each sampling period. Samples of 1 ml drawn at \( t = -5 \) min, \( t = 55 \) min, and \( t = 85 \) min were used to measure the plasma creatinine, whereas electrolyte, ANG II, vasopressin, and creatinine levels were measured from 15-ml samples obtained at \( t = 25 \) min, \( t = 115 \) min, and \( t = 145 \) min.

The renal, hemodynamic, and humoral responses to intravenous sodium loads of different magnitude were investigated in seven experimental series of six or seven experiments.

IsoLoad-6. An intravenous infusion of isotonic NaCl solution (154 mmol/l) was initiated at \( t = 30 \) min and continued for 90 min at a rate of 6 \( \mu \)mol·kg\(^{-1}\)·min\(^{-1}\), i.e., at a flow rate of 0.039 ml·kg\(^{-1}\)·min\(^{-1}\). Saline loading was followed by a 30-min recovery period (\( n = 6 \)).

HyperLoad-6. This experimental series was identical to the IsoLoad-6 series, except that the same sodium load (6 \( \mu \)mol·kg\(^{-1}\)·min\(^{-1}\) NaCl) was administered as a hypertonic (2 mol/l NaCl) solution. Thus the infusion rate was 0.003 ml·kg\(^{-1}\)·min\(^{-1}\) (\( n = 6 \)).

IsoLoad-20. The IsoLoad-20 series was identical to the IsoLoad-6 series, except that isotonic NaCl solution (154 mmol/l) was administered and a hypertonic (2 mol/l NaCl) solution from \( t = 30 \) to 120 min. The rate of infusion was 0.01 ml·kg\(^{-1}\)·min\(^{-1}\) (\( n = 6 \)).

IsoLoad-30. IsoLoad-30 involved infusion of isotonic NaCl solution (154 mmol/l) for 90 min at a rate of 30 \( \mu \)mol·kg\(^{-1}\)·min\(^{-1}\), i.e., at a rate of 0.195 ml·kg\(^{-1}\)·min\(^{-1}\) (\( n = 7 \)).

HyperLoad-30. A sodium load of 30 \( \mu \)mol·kg\(^{-1}\)·min\(^{-1}\) NaCl was administered as a hypertonic (2 mol/l NaCl) solution from \( t = 30 \) to 120 min. Thus the rate of infusion was 0.015 ml·kg\(^{-1}\)·min\(^{-1}\) (\( n = 7 \)).

Arterial blood pressure was measured continuously by a pressure transducer (Statham P50, Gould) connected to a patient monitor (Dialogue 2000, Danica Elektronik, Rødovre, Denmark). This provided analog-to-digital conversion at a rate of 300 Hz on the basis of a 7-s time window and calculation of mean arterial blood pressure. Heart rate was calculated from the electrocardiogram signal. Data were sampled from the monitor every 10 s by computer and subsequently averaged over 30-min periods.

Analyses

The concentrations of sodium and potassium ions in plasma and urine were measured by flame photometry (model 243, Instrumentation Laboratory). Plasma and urine osmolality was determined by freezing-point depression (model 3D3, Advanced Instruments, Needham Heights, MA). Plasma protein concentration was measured by a refractometer (model T2-NE, Atago, Tokyo, Japan). Concentrations of creatinine in urine and plasma were measured by the Jaffe reaction, as described by Bonsnes and Taussky (5).

The analyses of hormone levels in plasma were performed by radioimmunoassay after extraction as previously described (10).

Immunoreactivity of vasopressin in extracts of plasma was measured using an antibody (AB3096) produced in this laboratory. The antibody and the method have been described earlier (4, 11). The detection limit was 0.2 pg/ml, and the mean recovery of unlabeled vasopressin was 68%. Intra- and interassay coefficients of variation were <8%.

To determine ANG II immunoreactivity in plasma, a specific antibody (Ab-5–03682) was used as described earlier (4). Detection limit was 1.4 pg/ml, and the mean recovery of unlabeled ANG II was 88%. Intraassay coefficient of variation was 5%, and interassay coefficient of variation was 7%.

Statistics

Data are presented as means ± SE. The results were evaluated by one-way ANOVA for repeated measurements within and between groups. Possible inhomogeneity of variance was assessed by use of Levene's test. When inhomogeneity was present, the data were logarithmically transformed before analysis. If the results of the ANOVA were significant (\( P < 0.05 \)), all differences between means were investigated systematically by Newman-Keuls test. P values smaller than 0.05 were considered to indicate significance.

RESULTS

Systemic Hemodynamics

In all series, low and constant control levels of mean arterial blood pressure and heart rate were observed. During and after administration of isotonic and hypertonic saline at rates of 6 and 20 \( \mu \)mol·kg\(^{-1}\)·min\(^{-1}\), mean arterial blood pressure and heart rate remained unchanged (Table 1). HyperLoad-30 increased mean arterial blood pressure but did not change heart rate. IsoLoad-30 increased mean arterial blood pressure to similar values while heart rate was elevated, indicating activity of the Bainbridge reflex (Table 1).

Plasma Electrolytes, Osmolarity, and Protein Concentration

During HyperLoad-6 and IsoLoad-6, no significant changes occurred in plasma sodium and potassium concentrations or in plasma osmolality (Table 2 and Fig. 1). In both series, plasma protein concentration exhibited small, but significant, decreases (Table 2). HyperLoad-20 increased plasma sodium concentration by 1% and plasma osmolality by 6 mosmol/kg, whereas HyperLoad-30 increased plasma sodium by 4 mmol/l and plasma osmolality by 7 mosmol/kg (Table 2 and Fig. 1). IsoLoad-20 and IsoLoad-30 decreased plasma protein concentration without changes in plasma sodium, plasma potassium, and plasma osmolality.

Hormones

During HyperLoad-6 experiments, plasma vasopres- sin was increased by 30% (from 0.84 ± 0.05 to 1.11 ± 0.09 pg/ml) despite the absence of measurable changes in plasma osmolality (Fig. 1). The larger, and measurable, osmotic stimuli occurring during the HyperLoad-20 and HyperLoad-30 series further augmented plasma vasopressin to 3.21 ± 0.22 and 4.01 ± 0.46 pg/ml, respectively. In all hypertonic series, plasma vasopressin remained elevated in the recovery period. In IsoLoad-6, -20, and -30 series, plasma vasopressin levels were unchanged throughout the experiment (Fig. 1).

During HyperLoad-6 and IsoLoad-6 experiments, no changes were observed in the plasma levels of ANG II (Fig. 2). In HyperLoad-20 and IsoLoad-20 series, plasma...
Table 1. Hemodynamic variables

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Control</th>
<th>HyperLoad-6</th>
<th>IsoLoad-6</th>
<th>HyperLoad-20</th>
<th>IsoLoad-20</th>
<th>HyperLoad-30</th>
<th>IsoLoad-30</th>
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Mean arterial blood pressure, mmHg

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<td>146.0 ± 0.4</td>
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<td>115</td>
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<td>143.8 ± 0.4</td>
<td>147.5 ± 0.4*†</td>
<td>144.3 ± 0.9</td>
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<td>145</td>
<td>145.3 ± 0.6</td>
<td>145.7 ± 0.3</td>
<td>144.0 ± 0.4</td>
<td>147.7 ± 0.2*†</td>
<td>144.7 ± 0.6</td>
<td>148.0 ± 1.0*†</td>
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Plasma potassium, mmol/l

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<th>Time, min</th>
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<th>IsoLoad-6</th>
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<th>IsoLoad-20</th>
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<td>115</td>
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<td>4.0 ± 0.1</td>
<td>3.9 ± 0.0</td>
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<tr>
<td>145</td>
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<td>4.0 ± 0.1</td>
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Plasma protein, g/100 ml

Table 2. Plasma electrolytes and protein concentration

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<th>IsoLoad-6</th>
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<td>5.3 ± 0.1</td>
<td>5.2 ± 0.1</td>
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<td>5.7 ± 0.1</td>
<td>5.6 ± 0.1</td>
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<tr>
<td>115</td>
<td>5.5 ± 0.1</td>
<td>5.2 ± 0.1*</td>
<td>5.0 ± 0.1*</td>
<td>5.2 ± 0.1*</td>
<td>5.0 ± 0.2*</td>
<td>5.2 ± 0.1*</td>
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<tr>
<td>145</td>
<td>5.4 ± 0.1</td>
<td>5.1 ± 0.1*</td>
<td>5.0 ± 0.1*</td>
<td>5.1 ± 0.1*</td>
<td>5.1 ± 0.1*</td>
<td>5.2 ± 0.1*</td>
<td>5.2 ± 0.1*</td>
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</table>

Values are means ± SE (n = 6), except in HyperLoad-30 and IsoLoad-30 (n = 7). Saline was infused for 90 min from t = 30 min to t = 120 min. *Significantly different from control series (P < 0.05).
IsoLoad-6, but sodium excretion was elevated above control level in the recovery period of HyperLoad-6 series. During the HyperLoad-20 and IsoLoad-20 series, renal sodium excretion increased to 19 ± 6 and 11 ± 6 µmol/min, respectively, and was further augmented in the recovery period (26 ± 9 and 14 ± 6 µmol/min, respectively). Sodium excretion during the HyperLoad-30 and IsoLoad-30 series exhibited large, but similar, increases during the infusion periods (61 ± 13 and 65 ± 17 µmol/min, respectively). In contrast, during the recovery period, sodium excretion rate continued to increase in the HyperLoad-30 series (to 83 ± 19 µmol/min), whereas it leveled off in the IsoLoad-30 series (63 ± 16 µmol/min). Comparing the results of hypertonic infusions with those of isotonic infusions, there was a trend toward higher levels of sodium excretion in the recovery period in the hypertonic series. In most series, GFR did not increase persistently. In other series, the relative changes in GFR were much smaller than the corresponding changes in the rates of excretion of sodium. Therefore, the pattern of changes in fractional sodium excretion was very similar to that of absolute sodium excretion (Table 3).

DISCUSSION

The purpose of this study was to identify the relative importance of changes in arterial blood pressure and other natriuretic factors by measuring the response to sodium loads, which were too small to change arterial blood pressure. These circumstances were achieved by administration over 90 min of sodium loads increasing from 25% of daily sodium intake. With the use of this approach, under highly standardized conditions it was possible to increase renal sodium excretion by ~10-fold without any change in mean arterial blood pressure, heart rate, or GFR.

In the control situations, mean arterial blood pressure was stable, averaging 108 mmHg (Table 1). A threshold for blood pressure elevation by saline infusion was apparent as administration of 6 and 20 µmol·kg⁻¹·min⁻¹ did not change mean arterial blood pressure, and infusion of 30 µmol·kg⁻¹·min⁻¹ in
increased mean arterial blood pressure by 6–7 mmHg. Over 90 min, the two highest rates correspond to sodium loads of 80 and 125% of daily sodium intake. The effects on mean arterial blood pressure appear to depend on the infusion rate of sodium rather than the total amount of sodium infused. This follows from the finding that mean arterial blood pressure did not change at all during the full 90 min of HyperLoad-20 or IsoLoad-20 but increased significantly well within the first 60 min of infusion in the HyperLoad-30 and IsoLoad-30 series. The amounts of sodium infused within these time frames are identical. So the blood pressure of these conscious dogs was increased by infusion of NaCl at rates larger than a threshold, somewhere between 20 and 30 mmol·kg\(^{-1}\)·min\(^{-1}\). Other reports of the effects of acute sodium loading on mean arterial blood pressure in dogs have not provided comparable results. Cowley et al. (7) showed that a 10-min volume expansion with 400 ml isotonic saline in conscious dogs, corresponding to \(\sim 410 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\), increased mean arterial blood pressure by 6 mmHg, whereas the same load for 30 min (\(\sim 140 \text{ mmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\)) did not change mean arterial blood pressure (8). Kaczmarczyk et al. (15) reported an increase of 10 mmHg in mean arterial pressure after infusion of 150 μmol·kg\(^{-1}\)·min\(^{-1}\) of sodium chloride to conscious dogs for 60 min, whereas Pinilla et al. (21) infused \(\sim 170 \text{ μmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}\) for 45 min in anesthetized dogs without measuring any change in mean arterial blood pressure. Recently, Krieger and Romero (16) increased mean arterial blood pressure by 14 mmHg in anesthetized dogs with a load of 130 mmol·kg\(^{-1}\)·min\(^{-1}\) sodium for 60 min. There is no obvious explanation for the difference between these results; however, it might well be due to differences between the experimental conditions, particularly with regard to sodium intake and volume status. Nevertheless, our data clearly demonstrate that infusion of NaCl at rates from 30 mmol·kg\(^{-1}\)·min\(^{-1}\) may cause immediate blood pressure increases and, in the case of isotonic loading, also tachycardia.

During and after the infusion period in IsoLoad-20 and HyperLoad-20 series, we observed a natriuretic response without any change in mean arterial blood pressure. In the latter experiment, the natriuresis occurred without increases in GFR, possibly because the effects of the sodium loading were counterbalanced by the decrease in the activity of the renin-angiotensin system. Other natriuretic factors must, therefore, be responsible for this natriuresis. An obvious candidate is

<table>
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<th>Time, min</th>
<th>Control</th>
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<th>IsoLoad-6</th>
<th>HyperLoad-20</th>
<th>IsoLoad-20</th>
<th>HyperLoad-30</th>
<th>IsoLoad-30</th>
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<td>0–30</td>
<td>1019 ± 160</td>
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<td>1301 ± 106</td>
<td>1443 ± 181</td>
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<td>1571 ± 412</td>
<td>632 ± 99*</td>
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<td>1408 ± 113†</td>
<td>1183 ± 96</td>
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<td>713 ± 88*</td>
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<td>GFR, ml/min</td>
<td>0–30</td>
<td>41.8 ± 1.9</td>
<td>40.0 ± 1.9</td>
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<td>Osomolar clearance, ml/min</td>
<td>0–30</td>
<td>0.44 ± 0.05</td>
<td>0.49 ± 0.03</td>
<td>0.43 ± 0.04</td>
<td>0.45 ± 0.04</td>
<td>0.45 ± 0.04</td>
<td>0.46 ± 0.05</td>
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<td>Fractional sodium excretion, %</td>
<td>0–30</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
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<tr>
<td>Potassium excretion, mmol/l</td>
<td>0–30</td>
<td>15.8 ± 2.3</td>
<td>19.8 ± 2.5</td>
<td>17.4 ± 1.9</td>
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<td>30–60</td>
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<td>120–150</td>
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<td>23.2 ± 1.5†</td>
<td>30.0 ± 3.0</td>
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Values are means ± SE (n = 6), except in HyperLoad-30 and IsoLoad-30 (n = 7). Saline was infused for 90 min from t = 30 min to t = 120 min. *Significantly different from preinfusion level (P < 0.05); † significantly different from control series (P < 0.05).
ANG II, because plasma levels were inversely correlated with renal sodium excretion. Figure 3 shows the relationship between mean arterial blood pressure, plasma ANG II, and renal sodium excretion, with three points from each experiment: preinfusion, end-infusion, and recovery values. Sodium excretion was increased only when the plasma levels of ANG II were <10 pg/ml, and this relationship does not appear to be affected by mean arterial blood pressure changes in the range of 95–125 mmHg. These results support a number of previous conclusions from both animal and human investigations (2, 4, 21, 23) that the decrease in plasma levels of ANG II is a major factor determining sodium excretion during salt loading. The present study was not designed to evaluate in detail the immediate effects of a decrease in plasma ANG II on renal sodium handling; however, the intrarenal effects of ANG II have been studied intensively in micropuncture experiments. The overall effect of ANG II on proximal tubular function in vivo is still unclear, but recently it was reported that ANG II may directly stimulate sodium reabsorption in the distal tubule of the rat (26).

This may explain at least part of the natriuretic effect of a decrease in plasma ANG II under conditions of constant arterial blood pressure and GFR. Another possible intrarenal mechanism is that the decrease in ANG II allows intrarenal hydrostatic pressure to rise, thereby inhibiting tubular sodium reabsorption (6).

The explanation for the fall in the activity of the renin-angiotensin system in our experiments is not straightforward, at least not when it occurs without changes in GFR or blood pressure. Plasma ANG II is generated by renin and converting enzyme. Renin secretion is regulated by 1) changes in renal perfusion pressure (14), 2) changes in sodium chloride concentration at the macula densa (24), and 3) changes in renal nerve activity (19). During HyperLoad-20 and IsoLoad-20 experiments, an increase in renal perfusion pressure cannot directly explain the decrease in renin activity, because mean arterial blood pressure did not change. However, regulation of renin secretion by changes in renal perfusion pressure is a complex relationship involving transmural pressure, tangential wall tension, and the arteriolar diameter at the level of the renin-secreting juxtaglomerular cells. Thus it is very difficult to completely dismiss the intrarenal vascular baroreceptor mechanism in the suppression of renin secretion in this study. Increases in sodium delivery to macula densa may have occurred both in HyperLoad-20 and IsoLoad-20 series and elicited decreases in renin secretion and ANG II production. In both series, the filtered load of Na⁺ was increased: in HyperLoad-20 experiments, plasma sodium increased by 1% and GFR was unchanged; in the IsoLoad-20 series, GFR increased by ~8%, whereas plasma sodium was unchanged. If the macula densa-mediated mechanism was responsible in the former case, then it must be very sensitive and capable of reacting to a 1% increase in filtered load. However, different and very specific experimental approaches are required to evaluate possible relations between filtered load, macula densa electrolyte concentrations, and renin secretion operating at such small deviations.

Changes in renal sympathetic nerve activity may also have been involved in the natriuresis seen during the present experiments. A decrease in renal sympathetic nerve activity is a contributory factor to the natriuresis observed after volume expansion (for review, see Ref. 9) also in conscious dogs (18). Changes in renal sympathetic nerve activity may affect sodium excretion either via changes in renin secretion or by directly affecting tubular transport. The latter was clearly demonstrated in conscious dogs by Persson et al. (20). In our study, sympathetic nerve activity is assumed to be low, because control heart rates were ~55 beats/min. Therefore, withdrawal of renal sympathetic nerve activity under the present circumstances most likely was a mechanism left with only a narrow range of operation. However, we cannot rule out the possibility that a decrease in renal sympathetic nerve activity, small as it might have been, nevertheless played a significant role in the natriuresis during salt loading in this study.

Other factors may have been involved but appear even more unlikely. Changes in atrial natriuretic peptide (ANP) may have affected sodium excretion during nonhypertensive salt loading. Plasma ANP was not measured in the present experiments, because in a previous study (4) it was found that plasma ANP was not elevated during hypertonic infusion and made only a small (14%) increase during isotonic infusion of 60 μmol·kg⁻¹·min⁻¹, i.e., 2–10 times the stimulus inten-
osity used in the present work. A primary role of ANP thus seems highly improbable.

Colloid osmotic pressure has been found to play a substantial role in renal excretion of salt after volume expansion (8). In the present study, reductions in colloid osmotic pressure are likely to have occurred in all infusion series, because plasma protein concentration changed and it could be argued that this may have contributed to the natriuretic response to salt loading. However, in our experiments it seems to be secondary to ANG II, because some 90% of the much larger natriuretic response to 60 µmol·kg\(^{-1}\)·min\(^{-1}\) can be blocked by normotensive ANG II clamping (4). Therefore, if colloid osmotic pressure changes did contribute to the present natriuresis, the effect was probably minor.

Sodium status is normally sensed by volume/baroreceptors (17). However, there are data supporting the notion that osmoreceptors, possibly of central location, also may play a role in the afferent pathway of sodium homeostasis (2, 11–13). In the present study, we found that renal sodium excretion tended to increase to higher levels in HyperLoad-20 and -30 series compared with the corresponding isotonic series, especially during the recovery period, although it did not reach statistical significance. Considering the fact that the degree of extracellular volume expansion elicited by hypertonic saline is smaller than the expansion generated by the same amount of sodium as an isotonic solution, these results indicate that osmoreceptors may play a role in mediating the natriuretic response to a hypertonic sodium load, but further investigation is necessary to illustrate the importance and the effector mechanisms in osmoregulation of normal body fluid regulation and of different pathophysiological conditions in sodium and water homeostasis, particularly the main sensory mechanism behind and the specific actions of ANG II withdrawal capable of regulating renal sodium excretion by at least one order of magnitude without changes in filtration rate. Such information is crucially important to the understanding of normal body fluid regulation and of different pathophysiological conditions in sodium and water handling, i.e., arterial hypertension and congestive heart failure.

The expert technical assistance of Sigurd K. Hansen in the dog laboratory and Birthe Lynderup Christensen, Trine Eidsvold, Inge H. Pedersen, and Barbara Sørensen with the analyses is gratefully appreciated. Aprotinine was kindly provided by Novo Nordisk. Drs. Niels-Henrik Holstein-Rathlou and Paul Peter Leyssac provided valuable insight with regard to the interpretation of the results.

The work was supported by grants from The Danish Medical Research Council, the Novo Nordisk Foundation, and the Vélux Foundation.

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Received 15 March 1999; accepted in final form 26 July 1999.

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