Normotensive sodium loading in conscious dogs: regulation of renin secretion during β-receptor blockade

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Bie P, Mølstrøm S, Wamberg S. Normotensive sodium loading in conscious dogs: regulation of renin secretion during β-receptor blockade. Am J Physiol Regul Integr Comp Physiol 296: R428–R435, 2009. First published December 10, 2008; doi:10.1152/ajpregu.90753.2008.—Renin secretion is regulated in part by renal nerves operating through β1-receptors of the renal juxtaglomerular cells. Slow sodium loading may decrease plasma renin concentration (PRC) and cause natriuresis at constant mean arterial blood pressure (MAP) and glomerular filtration rate (GFR). We hypothesized that in this setting, renin secretion and renin-dependent sodium excretion are controlled by via sympathetic nerve terminals as a result of renal nerve activity

THE HOMEOSTATIC REGULATION of renal sodium excretion remains enigmatic. It is generally accepted that the antinatriuretic actions of the renin-angiotensin-aldosterone system (RAAS) under most conditions dominate the regulation of total body sodium (8, 11, 26), whereas the antidiuretic action of vasopressin is crucial for the maintenance of osmolality (5). Together, these mechanisms provide the relatively independent control of renal sodium and water excretion rates indispensable for body fluid control.

Adjustment of renin secretion to changes in sodium balance is mediated by at least three mechanisms: renal baroreceptor activity, renal nerve activity, and the macula densa (MD) pathway (32, 41). The renal baroreceptor mechanism modulates renin secretion in response to the changes in renal arterial pressure (33, 35, 36). Renal nerves are mainly effenter renal sympathetic fibers providing sympathetic tone to multiple renal structures, including the renin-secreting juxtaglomerular cells (9, 10, 16); renin secretion from these cells is mediated by the action on β1-receptors of norepinephrine released from renal sympathetic nerve terminals as a result of renal nerve activity (hereafter called β1-mediated renal nerve activity). The MD signaling adjusts renin secretion (34) and afferent arteriolar resistance (29) to tubular ion concentrations. In the intact animal, renal arterial pressure and sympathetic nerve activity are easily related to body fluid volume. The relationship between fluid balance and the concentrations of sodium and chloride at the MD is less clear. In any case, uncertainty prevails with regard to the relative importance of the three pathways in the daily changes in renin secretion.

Studies of the effects of slow sodium loading of dogs and humans have indicated that robust natriuresis may be initiated without any increase in arterial blood pressure (1–4, 25, 27, 28). Actually, in one of these studies, the natriuretic response to acute sodium loading developed concomitantly with a small fall in mean arterial pressure (MAP) (2), clearly illustrating that an increase in blood pressure is not a prerequisite for natriuresis. In these studies, natriuresis during sodium loading occurred concomitant with decreases in renin system activity, and deactivation of the RAAS seems to be a necessary condition of the development of a natriuretic response. This is supported by the results of another study in which plasma ANG II levels were clamped (by converting enzyme inhibition and infusion of ANG II) at physiological levels during sodium loading; the natriuresis was virtually absent as long as ANG II was administered despite the use of larger amounts of saline, which elevated the arterial blood pressure (7). Therefore, these results show that the natriuretic effect of small increases in blood pressure is easily overridden by the antinatriuretic effect of normal levels of activity of the RAAS.

Although it is possible that sodium excretion will be affected by undetectable changes in blood pressure and glomerular filtration rate (GFR), it remains remarkable that multifold changes in sodium excretion occur without any trend toward increases in either variable. Under such conditions renal nerve activity seemed to be the most likely mechanism controlling renin secretion and RAAS-dependent sodium excretion, i.e., slow sodium loading was assumed to decrease renal nerve traffic followed by a fall in the rate of secretion of renin and increase in the rate of RAAS-dependent excretion of sodium.
Consequently, it was hypothesized that blockade of the adrenergic receptors mediating the secretion of renin would eliminate, or at least blunt, the deactivation of renin secretion as well as the RAAS-dependent increase in sodium excretion occurring during slow sodium loading.

The specific aim of this study was to investigate the response to a modest amount of sodium chloride without unnecessary volume signals. Therefore, the protocol included a very slow infusion of hypertonic sodium chloride simulating the intake of excess NaCl. However, this procedure stimulates the secretion of vasopressin, and it could be anticipated that changes in urine flow would render the measurements of renal clearances inaccurate. Therefore, the antidiuretic action of vasopressin was blocked by pretreatment with a vasopressin V2 receptor antagonist. Administration of vasopressin V2 antagonists to conscious dogs is associated with a robust positive clearance of free water (15), which unopposed would lead to dehydration. Therefore, body fluid volume was accurately sustained by means of a computerized servosystem controlling an infusion of sodium-free solution at a rate continuously adjusted to the urine flow. In this manner, deviations in total body fluid volume were kept within narrow limits (~0.1%) throughout the experiments.

METHODS

Animals. The experiments were performed in seven trained, conscious, beagle bitches weighing 13–16 kg. The dogs were kept in a group and fed either a commercial maintenance diet (daily intake of \(Na^+\)/K\(^+\): 2.3/2.9 mmol·kg\(^{-1}\)·day\(^{-1}\)) or a custom-made very low-sodium diet composed of organic, salt-free peanut butter, organic oat flakes, and boiled rice. The sodium ion content of this diet was 0.003% and provided dietary intakes of sodium and potassium of 0.03 and 2.9 mmol·kg\(^{-1}\)·day\(^{-1}\), respectively. The custom-made diet was provided for 7 days before each experiment. Prior to the study, the dogs underwent two-stage surgery during general anesthesia under antiseptic conditions as previously described (42). First, both common carotid arteries were displaced to skin loops to facilitate arterial puncture and a chronic episiotomy was established to ease the catheterization of the bladder. Second, bilateral ovariectomy and a hysterectomy were carried out to prevent spontaneous changes in sex hormone concentrations to affect the experiments. After full recovery, the dogs were investigated 18–20 h after the latest meal and 8 h after water withdrawal. The experimental protocol was approved by the Danish Animal Experiments Expectorate.

Experimental protocols. On the night before the experiments, the supply of drinking water was interrupted at midnight by a timer-controlled electric valve to ensure a uniform degree of hydration in the morning. Baseline conditions, therefore, are characterized by some 9 h of water deprivation. In the laboratory, the dogs were placed in a sling and instrumented by sterile intra-arterial, intravenous, and bladder catheters allowing blood pressure measurements, intravenous infusions, and urine sampling, respectively. Arterial blood pressure and heart rate were measured continuously by computer based on 100-Hz sampling as described previously (19). Blood samples were obtained via the arterial catheter.

GFR was determined by the clearance of exogenous creatinine using bolus injection and continuous infusion as previously described (19); in the dog, values of creatinine and inulin clearances are indistinguishable.

In all experiments, vasopressin V2 receptors were blocked by bolus injection following by continuous infusion throughout the experiments of the V2 antagonist OPC 31260 [1 mg/(kg body wt) plus 1 mg·(kg body wt\(^{-1}\)·h\(^{-1}\))]. Regardless of urine flow, body fluid volume was maintained by servocontrolled fluid infusion based on continuous measurement of the body weight of the dog; a computer-controlled infusion pump kept body weight within ~0.1% of the control value measured at the time of instrumentation.

After appropriate control measurements over 40 min, slow sodium loading was performed by intravenous infusion of 2 M NaCl solution at 10 µl·(kg body wt\(^{-1}\)·min\(^{-1}\)) for 180 min providing a total of 3.6 mmol·kg body wt\(^{-1}\)·experiment\(^{-1}\).

For any one dog, experiments were conducted with intervals of no less than 2 wk. The sequence of experiments was varied between the dogs. In part of the experiments, metoprolol was used for blockade of \(\beta_1\)-adrenergic receptors [bolus 2 mg/kg body wt, infusion rate 0.9 mg·(kg body wt\(^{-1}\)·h\(^{-1}\))]. Metoprolol administration was started 60 min before the start of the control period and continued throughout the experiments (Fig. 1). It has been shown in dogs that similar regimens of metoprolol administration (0.5–2.0 mg/kg iv or 0.5–2.0 µg·kg\(^{-1}\)·min\(^{-1}\) into the renal artery) abolishes the increase in renin secretion associated with low level renal nerve stimulation (17, 20), administration of the \(\beta_1\)-adrenoceptor agonist prenalterol (21), and exercise (43).

Analyses. Arterial blood samples were obtained and centrifuged immediately at 4°C. Analyses of sodium, potassium, osmolality, and creatinine in plasma and urine, as well as plasma concentrations of ANG II, renin (PRC), aldosterone, vasopressin, and atrial natriuretic peptide (ANP) were performed as previously described (19).

Statistics. Data are reported as means ± SE. The results were assessed by one-way ANOVA adjusted for repeated measurements. In case of significance, all differences were evaluated by the Newman-Keuls test. Differences between series were tested by one-way ANOVA at the time of control or the time of peak deviation followed by the Newman-Keuls test when appropriate. Level of significance was \(P = 0.05\). In cases of obvious inhomogeneity of variances, e.g., the results of sodium excretion, analyses were performed after logarithmic transformation.

RESULTS

On regular diet and no pretreatment, MAP averaged 112 ± 3 mmHg and heart rate was 60 ± 4 beats/min (Fig. 2). Both low-salt diet per se and acute metoprolol treatment during regular salt intake tended to decrease MAP (to 105 ± 4 and

Fig. 1. Timeline of the experiments. Instrum., instrumentation.
prolol administration (ANOVA and Newman-Keuls test. Values are means ± SE, n = 7.

107 ± 4 mmHg, respectively), but not to statistically significant degrees. Heart rate did not change with low-salt diet (62 ± 3 beats/min) or with metoprolol during regular salt diet (64 ± 3 beats/min). During low-salt diet, metoprolol treatment was associated with similar nonsignificant trends (MAP: 105 ± 4 to 101 ± 2 mmHg, heart rate: 62 ± 3 to 58 ± 2 beats/min). Values of plasma osmolality were 1–1.5% lower during low-salt diet compared with regular diet (Table 1). PRC, ANG II, and aldosterone increased significantly during low-salt diet (16 ± 2 to 25 ± 4 mIU/l, 16 ± 2 to 31 ± 4 pg/ml, and 230 ± 26 to 1,750 ± 210 pg/ml, respectively, Fig. 3). Metoprolol treatment decreased PRC both on regular diet (−35%, P < 0.005) and on low-salt diet (−43%, P < 0.001), see Fig. 3. These differences in hormone concentrations were not associated with differences between the control rates of excretion of sodium, which across the series of experiments showed statistically indistinguishable mean values ranging from 0.7 to 1.9 μmol/min. Metoprolol pretreatment increased the basal rate of potassium excretion by threefold compared with nontreated conditions.

These data indicate that in the control condition prior to the acute salt loading, metoprolol-sensitive components of sympathetic tone, regardless of diet, controlled one-third to one-half of the renin system activity and was markedly antikaliuretic, but had little, if any, effect on blood pressure or heart rate.

Sodium loading, regular diet. The sodium loading elevated plasma Na⁺ and osmolality by 4.5% over 3 h (Table 1) without change in MAP (Fig. 2) or plasma ANP (Table 2). The renin system variables (PRC, ANG II, and aldosterone) did not change during the first hour of infusion (providing 1.2 mmol NaCl/kg body wt); thereafter, progressive declines were evident (Fig. 3), and PRC, plasma ANG II, and aldosterone ultimately decreased by 30%, 39%, and 51%, respectively, compared with control levels. GFR was stable for the first hour of infusion, tended to become elevated during the second hour of infusion, and ultimately increased by some 12% (Fig. 2). Urine flow doubled and urine osmolality fell by 30%. In the individual dogs, control urinary sodium and potassium concentration ranges were 0.3–1.6 mol/l and 0.2–3.0 mmol/l, respectively. Urine osmolality varied between 86 and 127 mOsm/kg. Therefore, sodium and potassium salts together constituted <10% of the urinary osmoles. Sodium excretion increased markedly (8-fold, P < 0.0001, Fig. 2), albeit with large individual variations. In all but one dog, sodium excretion was clearly augmented, and in three of the seven dogs, the increase exceeded one order of magnitude. Potassium excretion increased more consistently, on average to about fourfold that of control (Fig. 2).

Sodium loading, low-salt diet. As the result of the low-salt diet, control values of PRC, ANG II, and aldosterone increased by 53%, 93%, and 660%, respectively. In this setting, the salt-loading procedure increased plasma sodium, osmolality, and vasopressin concentration to levels very similar to those measured under normal dietary conditions. As expected, the renin system, activated by the low-salt diet, was inhibited by the sodium loading procedure, but remarkably, the relative decreases of the elevated PRC, ANG II, and aldosterone of −33%, −39%, and −55%, respectively, were virtually identical to the corresponding changes during the regular diet of −30%, −39%, and −51%, respectively (Fig. 4). The responses of plasma aldosterone are particularly illustrative; the 51% fall under normal diet (239 to 116 pg/ml) is in relative terms almost identical to the 55% decrease during low-salt diet (1,806 to 819 pg/ml), despite the seven- to eightfold difference between the starting points. GFR did not change significantly (Fig. 2). Urine flow increased by 86%, and mean urine osmolality decreased from 101 to 72 mOsm/kg; both changes are very similar to the corresponding changes during normal diet (87% and 105 to 78 mOsm/kg). Sodium excretion did not change significantly within the 3 h of observation (4 dogs showed very stable or slightly decreasing values, in 2 dogs...
modest increases were found, and 1 dog reacted with a steep 18-fold rise). However, potassium excretion increased sevenfold (Fig. 2).

During the low-salt diet, the renin system was deactivated by the standard sodium load to an extent, which in relative terms was very similar to the deactivation under normal conditions, but this was not sufficient to elicit a consistent natriuretic response.

**Salt loading, β1-adrenergic blockade.** The metoprolol pre-treatment altered control conditions as well as the response to sodium loading. The effects of metoprolol on the control conditions are described above. The standard sodium loading generated the same changes in plasma sodium, osmolality, and no changes in MAP or heart rate. The mean values of MAP at the end of the infusion was numerically, albeit not statistically, lower than the control values before the infusion, so not even a trend toward an increase in MAP was present. Under the acute metoprolol treatment, the renin system activity was decreased by sodium loading under both dietary conditions (Fig. 3). It is quite remarkable that 1) the sodium loading during metoprolol blockade markedly decreased PRC (−26% and −33%, regular and low-salt diet, respectively) and plasma aldosterone (−69% and −65%), and 2) that these decreases were very similar to those seen without metoprolol in PRC (−30% and −33%) as well as in aldosterone (−51% and −54%). GFR did not change at all during the sodium loading procedure; under normal diet the control GFR was 28.5 ± 2.9 ml/min and in the last 20-min period, GFR was 30.0 ± 2.4 ml/min (Fig. 2). As plasma sodium concentrations increased, the filtered load of sodium increased during salt loading (data not shown).

Under normal diet, the natriuretic response to sodium loading during metoprolol administration was robust (Fig. 2); one dog doubled the rate of excretion of sodium, the other six showed increases by more than one order of magnitude, on average showing a 24-fold increase (1.7 to a maximum of 41 μmol/min, Fig. 2). Under low-salt diet, the absolute values were lower (0.7 to a maximum of 15.9 μmol/min), and the individual responses were less consistent, but the average relative increase (22-fold) was very similar. Therefore, during β1-adrenergic blockade, sodium loading caused natriuresis independent of dietary conditions.

Table 1. Effects of salt loading on plasma parameters with and without metoprolol

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Preinfusion</th>
<th>Salt Loading</th>
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<tbody>
<tr>
<td></td>
<td>15</td>
<td>35</td>
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<tr>
<td>RegCon</td>
<td>300.9 ± 1.0</td>
<td>300.0 ± 1.1</td>
</tr>
<tr>
<td>RegMet</td>
<td>301.6 ± 1.0</td>
<td>300.1 ± 1.2</td>
</tr>
<tr>
<td>LowCon</td>
<td>296.1 ± 1.1</td>
<td>295.4 ± 1.2</td>
</tr>
<tr>
<td>LowMet</td>
<td>296.7 ± 1.0</td>
<td>296.6 ± 1.3</td>
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</tbody>
</table>

Values are means ± SE; n = 7. RegCon, regular diet control; RegMet, regular diet during metoprolol; LowCon, low-salt diet control; LowMet, low-salt diet during metoprolol. *Significant difference from preinfusion value by ANOVA and Newman-Keuls test.
primary homeostatic control of the renin secretion, and thus the 
duress. Together, the results unexpectedly demonstrate that the 
in GFR were absent during three of the four loading proce-
the corrective natriuresis associated with salt loading. Increases 
is also unnecessary for the deactivation of the renin system and 
excretory response. Clearly, a change in arterial blood pressure 
does not prevent acute regulatory downregulation of renin 
secretion, at least not in relative terms, and augments the renal 
response to salt loading. The results are incompatible with the hypoth-
thesis that the renal nerves play a key role in the 
regulation of total body sodium under physiological condi-
tions in mice deficient in β1- and β2-adrenergic receptors (18). They showed that chronic absence of these receptors 
caused marked reductions in PRC but also that the responses to a 
number of acute and chronic inputs to renin secretion persisted 
even at reduced magnitude. In particular, the PRC responses to high- 
and low-sodium diets were well maintained in these 
double knockout mice. However, the study did not address the 
mechanisms involved in the changes in PRC caused by alterations 
in sodium intake in the absence of the β-adrenergic receptors. 

Even if the homeostatic regulation of renin secretion may take place without changes in arterial blood pressure, GFR, and 
β1-mediated effects of norepinephrine, several mechanisms 
may be responsible for the change in renin secretion. A direct 
effect on osmolality on juxtaglomerular cells is a possibility; 
other mechanisms include 1) concentration signals operating 
via MD, 2) a component of renal sympathetic nerve activity not 
mediated by β1-adrenoreceptors conveying signals form the 
central nervous system, or 3) an extrarenal humoral substance 
provided to the kidneys by the blood. 

It is well known that the secretion of renin from juxtaglo-
merular cells in vitro is sensitive to extracellular osmolality (12, 37); it was shown that small elevations in osmolality 
clearly decreased renin secretion and vice versa, and it was 
hypothesized that this mechanism could be operative in vivo 
(12). Recently, it has been reported that in single mouse 
perfusion studies, lowering of bath osmolality by some 3% 
increases cell capacitance (by whole cell patch clamp), indic-
ativeness of exocytosis, and augments renin release by 20-fold (38). 
However, the specific role of osmolality in the homeostatic 
regulation of renin secretion in the intact animal has been 
difficult to ascertain (6). Recent data from isolated, perfused 
kidneys seem at odds with the mentioned in vitro results even 
with regard to the direction of change. In the perfused kidney 
model, renin secretion consistently was found to be stimulated 
by an increase in plasma osmolality (22). The present results in 
the conscious dog do not necessarily express a direct, causal 
relationship between plasma osmolality and renin secretion;

**DISCUSSION**

Our results show that although the administration of meto-
prolol reduced the circulating levels of renin substantially, it 
did not impede the deactivation of the renin secretion or the 
natriuretic responses to salt loading. The present study was 
designed to show that the renal nerves play a key role in the 
regulation of total body sodium under physiological condi-
tions. We hypothesized that blockade of the adrenergic recep-
tors mediating the secretion of renin would eliminate, or at 
least blunt the deactivation of the renin system occurring in 
response to modest salt load and that this reduced reactivity of 
the renin system would impede the acute natriuretic response to the 
salt loading. The results are incompatible with the hypothe-
sis. Adrenergic β1-blockade (preventing the transmitter as 
well as the circulating hormone function of norepinephrine) 
does not prevent acute regulatory downregulation of renin 
secretion, at least not in relative terms, and augments the renal 
excretory response. Clearly, a change in arterial blood pressure 
is also unnecessary for the deactivation of the renin system and 
the corrective natriuresis associated with salt loading. Increases 
in GFR were absent during three of the four loading procedures. Together, the results unexpectedly demonstrate that 
the primary homeostatic control of the renin secretion, and thus the 

**Table 2. Effects of salt loading on plasma hormones with 
and without metoprolol**

<table>
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<tr>
<th>Time, min</th>
<th>Preinfusion</th>
<th>Salt Loading</th>
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<tbody>
<tr>
<td></td>
<td>Plasm AVP, pg/ml</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>RegCon: 1.6±0.2</td>
<td>3.5±0.4</td>
</tr>
<tr>
<td></td>
<td>RegMet: 1.7±0.1</td>
<td>4.1±0.6*</td>
</tr>
<tr>
<td></td>
<td>LowCon: 1.7±0.1</td>
<td>4.3±0.3*</td>
</tr>
<tr>
<td></td>
<td>LowMet: 2.1±0.6</td>
<td>4.7±0.5*</td>
</tr>
<tr>
<td>125</td>
<td>RegCon: 129.0±11.8</td>
<td>128.0±12.7</td>
</tr>
<tr>
<td></td>
<td>RegMet: 176.2±24.7</td>
<td>168.1±21.7</td>
</tr>
<tr>
<td></td>
<td>LowCon: 90.8±9.3</td>
<td>96.2±8.9</td>
</tr>
<tr>
<td></td>
<td>LowMet: 131.9±12.4</td>
<td>163.3±18.5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7. ANP, atrial natriuretic peptide. *Significant difference from preinfusion value by ANOVA and Newman-Keuls test.
but if this were the case, they support the notion of an inverse relationship (12) between plasma osmolality and PRC.

In addition to a direct effect, it is also possible that under the present conditions, the acute sodium loading caused subtle changes in GFR as well as in proximal and loop-of-Henle reabsorption rates so that tubular fluid composition at the MD reflected the level of total body sodium. Although GFR did not change, the filtered load of sodium increased because of the increase in plasma sodium concentration. The concentration of NaCl at the MD is a complex function of GFR, filtered load of sodium, glomerulotubular balance, tubuloglomerulur feedback, and the regulatory control of proximal reabsorption (39); the authors estimated that roughly one-half of a 10% increase in the filtered load of sodium would arrive at the MD. Extrapolating the estimates of Thomson and Blantz (39), the author assumed that the increase in solute concentration at the MD could be substantial (up to 75 mmol/l) depending on the degree of increase in tubular flow rate, and that the increase would be minimal only at unrealistically high increases in tubular flow. It is, therefore, a definite possibility that augmented sodium reabsorption by glomerulotubular balance and/or MD mechanisms lead to deactivation of the RAAS. Several hypotheses seem justified with regard to the coupling to juxtaglomerular cell function. It could be speculated that increases in interstitial concentrations of adenosine, elevated by increases in tubular transport and operating via A1-receptors, reduce renin secretion, ANG II concentration, and aldosterone production, leading to increased sodium excretion, (cf. 40). Small or immeasurable changes in GFR and minor deviations in tubular function could play a major role in the present deactivation of the renin system in response to salt loading. If so, the regulation of total body sodium relies heavily on the complex interaction between renal vascular and proximal tubular functions including glomerulotubular balance and tubuloglomerular feedback.

Up to a few years ago, it was widely believed that the renal nerves were the crucial link between baroreceptor activity to alterations in the renal excretory functions serving blood pressure control (24). Recent evidence seems to have questioned this concept because it was demonstrated that the presence of the renal nerves is not a necessary requirement for achieving long-term changes in arterial pressure during prolonged barore-
renal adrenoreceptors, i.e., receptors other than
the effects of systemic \( \beta_1 \)-adrenergic blockade in the intact animal may be complex. Results of renal nerve recording in anesthetized rabbits before and after administration of the \( \beta_1 \)-blockers atenolol and propranolol have been interpreted to indicate that these cause a reduction in renal efferent nerve traffic (13, 14) concomitant with the expected decrease in arterial blood pressure. The effect on renal nerve activity was believed to be associated with an (unexplained) increase in arterial baroreceptor activity (14). If these results, despite some internal inconsistency, represent a general phenomenon, it can be assumed that in the present experiments metoprolol administration decreased efferent renal nerve activity. We administered metoprolol well in advance of the salt-loading procedure, and the \( \beta_1 \)-adrenergic blockade caused no significant change in any of the measured values except potassium excretion, which was significantly elevated by metoprolol. Any direct inhibitory effect of metoprolol on efferent renal nerve activity seems to be a mediator, i.e., a plausible working hypothesis linking renin secretion to sodium intake or total body sodium does not exist.

In summary, the relative decrease in renin secretion in response to acute salt loading is unaffected by metoprolol; therefore, \( \beta_1 \)-mediated adrenergic control does not mediate the acute, regulatory inhibition of renin secretion, although it does codetermine the level of PRC. The present increase in plasma osmolality of 4–5% may have mediated a decrease in renin secretion; however, the specific nature of this powerful controller of renin secretion remains to be identified.

**Perspectives**

The present model of highly trained conscious dogs represents the sedate conditions of resting mammals. In contrast to renin secretion, heart rate and blood pressure were low and insensitive to metoprolol, indicating a very low sympathetic drive to the circulation and homeostatically relevant sympathetic tone to the juxtaglomerular cells. In this setting, renin secretion was dependent on factors other than arterial blood pressure, GFR, and \( \beta_1 \)-mediated effects of norepinephrine. This finding opens the possibility that the primary mechanism of sodium homeostasis is either an intrarenal mechanism or an extrarenal blood-borne “natriuretic” agent. There is no shortage of intrarenal modulators of renin secretion (e.g., adenosine), nor of potential natriuretic agents (e.g., cardiac glycosides), but it is difficult to see which candidate could qualify as the homeostatic mediator of sodium metabolism.

The interaction between the central nervous system and the kidney is crucial for understanding the mechanisms behind major pathologies such as hypertension. However, without a clear picture of the normal homeostasis, the foundation for clinical hypotheses remains unreliable.

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**GRANT**

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