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Chronic activation of plasma renin is log-linearly related to dietary sodium and eliminates natriuresis in response to a pulse change in total body sodium

Mads Kjolby and Peter Bie
Department of Physiology and Pharmacology, Institute of Medical Biology, University of Southern Denmark, Odense, Denmark

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Kjolby M, Bie P. Chronic activation of plasma renin is log-linearly related to dietary sodium and eliminates natriuresis in response to a pulse change in total body sodium. Am J Physiol Regul Integr Comp Physiol 294: R17–R25, 2008. First published November 7, 2007; doi:10.1152/ajpregu.00435.2007.—Responses to acute sodium loading depend on the load and on the level of chronic sodium intake. To test the hypothesis that an acute step increase in total body sodium (TBS) elicits a natriuretic response, which is dependent on the chronic level of TBS, we measured the effects of a bolus of NaCl during different low-sodium diets spanning a 25-fold change in sodium intake on elements of the renin-angiotensin-aldosterone system (RAAS) and on natriuresis. To custom-made, low-sodium chow (0.003%), NaCl was added to provide four levels of intake, 0.03–0.75 mmol·kg⁻¹·day⁻¹ for 7 days. Acute NaCl administration increased PV (+6.3–8.9%) and plasma sodium concentration (~2%) and decreased plasma protein concentration (~6.4–8.1%). Plasma ANG II and aldosterone concentrations decreased transiently. Potassium excretion increased substantially. Sodium excretion, arterial blood pressure, glomerular filtration rate, urine flow, plasma potassium, and plasma renin activity did not change. The results indicate that sodium excretion is controlled by neurohumoral mechanisms that are quite resistant to acute changes in plasma volume and colloid osmotic pressure and are not down-regulated within 2 h. With previous data, we demonstrate that RAAS variables are log-linearly related to sodium intake over a >250-fold range in sodium intake, defining dietary sodium function lines that are simple measures of the sodium sensitivity of the RAAS. The dietary function line for plasma ANG II concentration increases from theoretical zero at a daily sodium intake of 17 mmol Na/kg (intercept) with a slope of 16 pM increase per decade of decrease in dietary sodium intake.

renin-angiotensin-aldosterone system; sodium intake; potassium; renin function line; dietary function line

The precise relationship between sodium metabolism, body fluid volumes, and arterial blood pressure remains unclear. Years ago, Guyton et al. (11) established the important role of the kidney in blood pressure regulation. Subsequently, a large body of evidence has been interpreted to indicate that the only manner by which the renal excretory process can respond to sustained changes in arterial pressure is by the direct actions of arterial pressure on renal excretion, the so-called pressure-natriuresis mechanism (5). This concept remains the basis for numerous studies of blood pressure regulation (e.g., 21), often using the model of the anesthetized rats infused with vasopressin, aldosterone, norepinephrine, and hydrocortisone (29). The importance of blood pressure changes to renal function, including electrolyte excretion, is beyond any reasonable doubt. However, the mechanism of the pressure-natriuresis is unknown (for a review, see Refs. 8 and 10), although it is possibly associated in one way or another with changes in renal medullary blood flow (for a review, see Ref. 6). Other data are not easily compatible with the notion of a dominating role of the pressure natriuresis mechanism. Solid results seem to indicate that under normal physiological conditions, total body sodium is an essential variable coupled to renal sodium excretion by mechanisms other than arterial pressure [(32); for a review, see also (28)]. Traditional procedures of sodium loading, i.e., at rates of 20 μmol·min⁻¹·kg⁻¹ body wt⁻¹ or more, are most often associated with substantial increases in blood pressure concomitant with a natriuretic response (e.g., Ref. 4) congruent with the concept of a pressure natriuresis. However, under normal conditions, acute sodium loading may cause natriuresis without any change in blood pressure (27, 30), and occasionally a significant natriuretic response to slow sodium loading may develop concomitant with a significant, albeit minute, decrease in arterial pressure (2). In addition, it has been shown in freely moving dogs that the natriuretic response to more robust sodium loading remains intact when changes in renal arterial pressure are prevented by a servocontrol mechanism (31). A substantial number of experimental results, therefore, seem to demonstrate that mechanisms serving to maintain sodium balance can be activated without any increase in (renal) arterial blood pressure.

Even a small step-up change in total body sodium has consequences for all body fluid compartments, that is, increases in plasma and interstitial sodium concentrations, as well as plasma and interstitial volumes, the latter occurring at the expense of a decrease in intracellular volume. The increase in plasma volume will decrease plasma protein concentration and thereby plasma colloid-osmotic pressure. It was hypothesized that the magnitude of the changes in renal function associated with these primary changes in body fluid volumes and composition, and, in particular, the natriuretic response,

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depends on the chronic level of sodium intake. Therefore, we designed experiments to investigate the effects of a nonpressor, acute sodium-loading procedure on body fluids and renal function in trained, conscious dogs chronically exposed to a low-salt diet without or with modest salt supplements. Acute sodium loading was performed over a few minutes to allow a detailed analysis of the dynamics of the acute endocrine and renal responses. The hypothesis was rejected in the sense that the combined increase in plasma osmolality, sodium concentration, and volume together with the decrease in colloid osmotic pressure were insufficient to generate a statistically significant increase in sodium excretion at any level of chronic sodium intake investigated.

METHODS

Animals

Experiments were performed in six conscious female Beagle dogs, weighing 13.4–16.2 kg. The dogs had free access to tap water and were fed a custom-made, low-sodium diet composed of oatmeal, boiled rice, and peanut butter (sodium ion content 0.003%), to which various amounts of sodium was added (see below). The dogs received one meal a day at 2:00 PM.

Before the study, all animals had undergone two-stage surgery during general anesthesia, as previously described (36). Briefly, stage 1 included a procedure in which both common carotid arteries were displaced into skin loops to facilitate arterial puncture during experiments, and an episiotomy was performed to ease catheterization of the urinary bladder. At least 3 wk later, the dogs underwent stage 2, consisting of bilateral ovariectomy and hysterectomy (to prevent spontaneous changes in sex hormone concentrations to affect the stage 2, consisting of bilateral ovariectomy and hysterectomy (to prevent spontaneous changes in sex hormone concentrations to affect the schedule and the results). Recovery was uneventful. On the night before experiments, the water supply was interrupted at midnight by a timer-controlled electric valve. The experimental protocol was approved by the Danish Animal Experiments Inspectorate.

Experimental Protocols

The dogs were fed the low-salt diet without or with addition of individually calculated amounts of NaCl. All dogs participated in four experiments. Sodium supplementation depended on the body weight of the dog and the amount of daily food intake (mean = 252 ± 3 g). The final sodium intakes were 0.03, 0.15, 0.35, and 0.75 mmol·kg⁻¹·day⁻¹. The dogs were fed individually to keep their body weight constant. NaCl-adjusted food was fed for exactly 7 days before experimentation. Potassium intake was constant (2.79 mmol·kg⁻¹·day⁻¹). Previous data from our lab (17) and from Reinhardt and Seeliger (for a review, see Ref. 28) indicate that a new steady state is reached within 2 or 3 days after a sudden change in dietary sodium intake.

Over many sessions, the dogs were trained to rest in a canvas sling for up to 6 h. Each dog participated in all experiments with intervals of at least 14 days. Each experiment included a control period of 1 h, a sodium bolus (1.2 mmol/kg), followed by a 2-h recovery period. The sodium bolus was administered to the dog as a hypertonic 1 M solution (1.2 ml/kg body wt), given intravenously within 2 min. The measurements consisted of 20-min urine-sampling periods; blood sampling occurred at t = −5, 30, 55, 75, 95, 115, and 175 min.

Baseline conditions were thus characterized by 9 h of water deprivation. In the morning, the dog was brought to the laboratory and 45 min later placed in a canvas sling where a sterile catheter (Intracath, Becton-Dickinson, Sandy, UT) was introduced into the inferior vena cava via the femoral vein and used for infusions. Another catheter (Insyte-W, Becton Dickinson, Sandy, UT) was placed in a common carotid artery, allowing continuous measurements of arterial blood pressure interrupted only by periodic sampling of arterial blood. After application of a lidocaine-containing gel (2%), a modified silicone Foley catheter (Norta, Beiersdorf, Hamburg, Germany) was inserted into the bladder.

An intravenous bolus of creatinine (6.8 ml ≈ 1.6 mmol creatinine) was given 1 h before the beginning of the experiment followed by a continuous infusion of creatinine (6 ml/h ≈ 24 μmol/min) throughout the experiment. The solution containing creatinine also contained glucose and urea (creatinine 240 mM, urea 25 mM, glucose 40 mM). In the dog, creatinine clearance is a valid measure of GFR (20). An intravenous bolus of Evans blue dye dissolved in sterile H2O (7.6 ± 0.1 ml) (Sigma E-2129, Sigma Chemicals, St. Louis, MO; 0.5 mg/kg body wt) was given (tEB = 0 min) to estimate the plasma volume (PV) (37). Arterial blood samples (2 ml) were drawn at tEB = 30 min, tEB = 60 min, tEB = 85 min to estimate the plasma volume before the sodium bolus and after the sodium bolus at tEB = 105 min, tEB = 125 min, tEB = 145 min, and tEB = 205 min. Evans blue dye concentrations were measured by two wavelength (627 nm and 740 nm) spectrophotometry within 12 h. The two-wavelength spectrophotometry was used to eliminate the contribution from plasma lipids to the measured absorption.

Arterial blood samples of 8 ml were obtained at t = −5 min, t = 55 min, t = 115, and t = 175 min for determination of hormone concentrations. Arterial BP was measured continuously by a pressure transducer (BLPR, World Precision Instruments, Stevenage, Hertfordshire, UK) connected to a blood pressure monitor (BP1-C, World Precision Instruments). The blood pressure monitor was connected to a computer and provided values of mean arterial pressure from the analog pressure signal on the basis of a 100 Hz analog-to-digital sampling frequency and custom-designed software (LabVIEW, National Instruments, Austin, TX). Heart rate (HR) was calculated continuously on the basis of the blood pressure curve analyzed by custom-designed software (LabVIEW). The data were subsequently averaged over the 20-min period.

Analyses

The concentration of sodium and potassium ions in plasma and urine was measured by flame photometry (Model 943, Instrumentation Laboratory, Lexington, MA). Plasma and urine osmolalities were determined by freezing point depression (Advanced Osmometer, model 3D3, Advanced Instruments, Needham Heights, MA). Plasma protein concentration was measured by refractometry (Clinical refractometer T2-NE, Atago, Tokyo, Japan). Concentrations of creatinine in urine and plasma were measured by a creatinine autoanalyzer (Beckman Creatinine Analyzer, Beckman Instruments, Fullerton, CA).

Plasma Hormones

Arterial blood samples for determination of angiotensinogen (AGT), ANG II, plasma renin activity (PRA), and aldosterone (Aldo) were obtained in precooled 10-ml polyethylene tubes (Minisorb, Nunc, Roskilde, Denmark) containing EDTA (25 μmol) and aprotonine (Novo Nordisk, Soeborg, Denmark) [2700 Kallikrein inhibitor units (KIU)]. The samples were centrifuged immediately at 4°C, and plasma was stored at −18°C until extraction performed by use of Sep-Pak C18 columns (Waters, Milford, MA). For extraction, the plasma sample was acidified by the addition of three volumes of acetic acid (4%) containing 0.1% trifluoroacetic acid. Measurements of hormone concentrations in plasma extracts were performed by radioimmunoassays.

AGT. AGT was measured by quantitative conversion to ANG I by exposure to excess renin, followed by measurement of the formed ANG I by radioimmunoassay using the antibody-trapping method of Poulsen and Jørgensen (26), as was described recently (17). The intra-assay and interassay coefficients of variation were 2.8% and 11.1%, respectively.
ANG II. ANG II in plasma was determined using a specific antibody (Ab-5-030682), as described previously (4). The detection limit was 1.4 pg/ml, and the extraction recovery of unlabeled ANG II added to plasma was 114%. The intra-assay and interassay coefficients of variation were 4.9% and 8.7%, respectively.

PRA. PRA was determined by the antibody-trapping method of Poulsen and Jørgensen (26) using excess angiotensinogen, as described recently (17). Results are reported in mIU/l based on the WHO International Standard (ref. no. 68-356), National Institute for Biological Standards and Control, Hertfordshire, UK) determined along with the plasma samples in each assay. The detection limit was 0.3 mIU/l. The intra-assay and interassay coefficients of variation were 6.2% and 8.9%, respectively.

Aldo. Plasma Aldo was measured using a commercial kit (COAT-A-COUNT, Diagnostic Products, Los Angeles, CA). The detection limit was 11 pg/ml. The intra-assay and interassay coefficients of variation were 4.1% and 7.8%, respectively.

cAMP and cGMP. Cyclic AMP and/or GMP concentrations in plasma have been shown to change in association with specific neurohumoral interventions in cardiorenal function (16, 18, 24, 34, 35). cAMP and guanosine cGMP were measured using commercially available assays (Cayman Chemical, Ann Arbor, MI), which were based on a competitive enzyme immunoassay. The detection limit for nonacetylated cAMP and cGMP was 9 pmol/ml and 1 pmol/ml, respectively. The IC50 was ~60 pmol/ml and 4 pmol/ml, respectively. The interassay coefficients of variation for cAMP and cGMP were 9.8% and 10.3%, respectively.

Statistics

Data are presented as means ± SE. The results were evaluated by one-way ANOVA for repeated measurements. If the results of the ANOVA were significant (P < 0.05), all differences between means were investigated systematically with Newman-Keuls’ test. Differences between series were investigated using one-way ANOVA, and all differences were tested using a post hoc test, Newman-Keuls’ test. Deviations were considered significant when P values were smaller than 0.05 (1). Statistical tests were performed by use of GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA).

RESULTS

In all series, low and constant control levels of mean arterial blood pressure and HR were observed (Table 1). Mean arterial blood pressure (MABP), systolic-, or diastolic blood pressure did not change significantly after the bolus, and there was no significant difference between series. HR increased transiently after administration of the bolus in two out of the four series (0.15 and 0.75 mmol·kg⁻¹·day⁻¹). Plasma volume increased (Fig. 1) in the four different series by 8.9% ± 0.6%, 7.1% ± 0.6%, 6.3% ± 1.0%, and 7.5% ± 1.5%, respectively (overall average 7.4%).

Plasma Electrolytes, Osmolality, and Protein Concentration

Plasma sodium concentration increased in all four series after the bolus injection (Fig. 2) 2.4% ± 1.1%, 1.6% ± 0.3%, 1.3% ± 0.3%, and 1.5% ± 0.4%, respectively (P < 0.05). Plasma osmolality increased by 1.5% ± 0.5%, 1.4% ± 0.4%, 1.5% ± 0.3%, and 1.1% ± 0.2%, respectively (P < 0.05). Plasma protein decreased 8.1% ± 1.7%, 6.4% ± 1.1%, 6.9% ± 1.2%, and 7.4% ± 1.2%, respectively (P < 0.05). There was no difference between series. Plasma potassium did not increase after the bolus except for the last sample in one series (0.03 mmol·kg⁻¹·day⁻¹). The hematocrit did not change.

Hormones

PRA decreased transiently by 19% immediately after the bolus in one series (sodium intake 0.03 mmol·kg⁻¹·day⁻¹, P < 0.05). In the other experimental series, nonsignificant trends toward a fall in PRA were seen immediately after the bolus (Fig. 3). Plasma ANG II decreased transiently by 30% in all but one series. In the 0.03 mmol·kg⁻¹·day⁻¹ series, ANG II did not decrease significantly. There was no difference between series. Plasma aldosterone did not increase after the bolus except for the last sample in one series (0.03 mmol·kg⁻¹·day⁻¹). The hematocrit did not change.

Table 1. Hemodynamic variables

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<th>0.03 mmol·kg⁻¹·day⁻¹</th>
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Mean values are presented ± SE, n = 5. MABP, mean arterial blood pressure, and pulse. *Significant difference from values at control period; n = 5.
bolus. The plasma concentrations of cAMP and cGMP, therefore, do not provide hints with regard to the specific mechanisms involved in the present responses.

Renal Variables

Diuresis did not change significantly (Fig. 4). Over the duration of time following the acute intravenous sodium load, there was no significant sustained natriuretic response. The total amount of excreted sodium in the 2 h following its administration corresponds to 1% of the sodium bolus (<100 μmol). For comparison, extracellular sodium in a 14-kg dog is of the order of 4 × 10^5 μmol. Potassium excretion increased about threefold transiently in three out of four series (0.15 to 0.75 mmol·kg⁻¹·day⁻¹) after the bolus. GFR only transiently increased in two series (0.35 and 0.75 mmol·kg⁻¹·day⁻¹).

In summary, the natriuretic responses were totally absent (one series), transient (two series), or minute and delayed (one series), providing a pattern of sodium retention, irrespective of the present sodium loading.
DISCUSSION

Our overall aim was to study renin-angiotensin-aldosterone (RAAS) activity at low sodium intakes at steady state and during acute perturbation. The results demonstrate 1) that chronic changes in sodium intake may change steady-state renin system activity over the range of 10 to 50 mmol/1 for ANG II and 50 to 2,400 pg/ml for aldosterone, 2) that most of this variation occurs at sodium intakes of less than 0.5 mmol·kg⁻¹·day⁻¹, 3) that the present, acute sodium load (1.2 mmol/kg) equivalent to ~50 days of intake on a low-sodium diet (<0.03 mmol·kg⁻¹·day⁻¹) results in relatively little suppression of the RAAS during the subsequent 2-h observation period, and 4) that, at chronic low sodium intake, an acute increase in total body sodium results in a negligible natriuresis during the subsequent 2-h observation period.

Steady State

The range of sodium intake studied was 0.03 to 0.75 mmol·kg⁻¹·day⁻¹. A “normal” sodium intake does not exist. For dogs in an experimental setting fed with conventional commercial chow, the intake of sodium usually is of the order of 2–3 mmol·kg⁻¹·day⁻¹, which is considered regular sodium intake. Ingestion of 0.3–0.5 mmol·kg⁻¹·day⁻¹ is traditionally considered as low-sodium intake (9, 14, 15, 22). However, we have found that in Beagle dogs, a sodium intake of 0.5 mmol·kg⁻¹·day⁻¹ is fully adequate for normal growth and development (unpublished observations). The present results extend by more than one order of magnitude the observations of the undisturbed response to low-sodium diet (0.3–0.5 mmol·kg⁻¹·day⁻¹) in the dog.

The result was a steady increase in renin system activity, demonstrating that, in terms of plasma variables, the operating range of the renin system is larger below the conventional low-salt intake of 0.5 mmol·kg⁻¹·day⁻¹ than above; that is, most of the operating range of the renin system is outside the change studied when going from regular sodium intake to a conventional low-salt diet. The minimum daily requirement for sodium ions in these dogs is not known, except that it is very low. It is likely that the lowest rate of sodium intake used in the present study, 0.03 mmol·kg⁻¹·day⁻¹, was providing sodium at a rate lower than that of minimum sodium loss; refer to the basal rate of sodium excretion in this series (~1 μmol/min = ~1.5 mmol/day = ~0.1 mmol·kg⁻¹·day⁻¹). The minimum daily requirement of sodium ions is the lowest rate of intake, which is compatible with long-term steady state. From the present (fasting) control levels of sodium excretion, it may be estimated that the minimal daily requirement is of the order of 0.1–0.2 mmol·kg⁻¹·day⁻¹. However, at higher, once-a-day intakes of sodium, the rate of sodium excretion shows a marked diurnal variation with a postprandial peak (see below). Additional investigations, including sodium balance studies over more than 7 days, are required to determine this parameter.
Previous studies have shown increases in plasma volume during large increments in sodium intake (7, 17). The relatively small changes in dietary sodium intake investigated in this study did not yield statistically significant changes in the control values of plasma volume.

The controlled increments in chronic dietary sodium intake were associated with decreases in plasma ANG II and Aldo in contrast to blood pressure and plasma volume. There was no difference in steady-state sodium excretions at the four different sodium intakes, neither in the control period nor in the recovery period. The dogs were fed in the afternoon and ate all their food very quickly, which means that the control period was 16 h after the latest ingestion. The diet used was finely ground and low in fiber content, and intestinal absorption was presumably fast. It has been shown by Palm et al. (25) that the majority (>90%) of sodium ingested (normal chow) was excreted in the urine within 12 h postprandially. It is plausible, therefore, that differences in the daily pattern of sodium excretion arising from the present, rather small differences in sodium intake, would have been measurable only at some time prior to the start of the present experiments.

In accordance with previous studies of the natriuretic response to acute sodium loading (4, 13, 17, 22, 30), there was no change in MABP associated with the changes in sodium intake. Steady-state RAAS data from this study combined with data (Fig. 5) from Kjolby et al. (17) clearly show a log-linear relationship between RAAS variables and sodium intake during steady-state conditions. A log-linear relationship between PRA and sodium intake was not evident in the previous study (17), as the range of the RAAS studied under these conditions was limited. Pooling the present data with previous results (17) provides data on four circulating parameters of the renin system (plasma AGT, renin, ANG II, and aldosterone) over a >250-fold change in sodium intake. These pooled data show that all the active components of the renin system vary linearly with the logarithm of the intake of sodium. This relationship has several potentially important implications.

First, the log-linear function curves for the renin, angiotensin, and aldosterone provide numerically simple measures of the salt sensitivity of the renin system. These dietary function lines are characterized by two parameters: intercept and slope. Therefore, the concept of log-linear function curves provides simple quantitative tools for analysis of physiological perturbations. For renin in dogs, the present results indicate a theoretical zero of renin secretion (PRC = 0) at a sodium intake of 29 mmol·kg⁻¹·day⁻¹, and an increase in plasma renin concentration of 9 mIU/l for each decade of decrease in sodium intake. For ANG II, the intercept corresponds to a daily sodium intake of 17 mmol·kg⁻¹·body wt⁻¹, and the plasma concentration increases by 16 pM per decade of decrease in sodium intake. At present, it is not known to what extent the log-linear function curves are specific to dogs; neither is it known whether intervention with antinatriuretic or natriuretic systems, for example, NO synthesis, affects the intercept or slope of the function curves.
Second, the log-linear relationship is compatible with the notion that renin system activity over a wide range of sodium intakes is governed by a single dominating process. If so, this mechanism may be studied at low and very low sodium intakes in which differences in renin system activity are easily measurable, and the results, therefore, are more reliable. The dominant role of dietary sodium intake in regulating RAAS activity is additionally supported by the $R^2$ data, which suggest that between 70% (AGT) and 86% (Aldo) of the variance in the levels of the various components of the RAAS can be accounted for by variance in dietary sodium intake.

Interestingly, this type of result relating renin system activity to sodium balance is far from new. It has been known for decades that, in steady states (using equidistant axes), there is some kind of hyperbolic relationship between these variables, for example, renal sodium excretion and plasma aldosterone (19). However, it has been difficult to quantify this relationship, particularly in a way that was suitable as a tool for comparing different functional states. The concept of log-linear relationships, if generally applicable, seems to be able to provide a technique suitable for quantification of the effects of chronic physiological perturbations.

Perturbation

The acute load administered in the present study was about 50% of the regular daily sodium intake (1.2 mmol·kg$^{-1}$·day$^{-1}$) and, as expected, was associated with a clear increase in plasma volume. It acutely increased plasma sodium and osmolality by 2% concomitant with a 7.4% increase in PV, and 7.3% decrease in plasma protein. According to the planned ANOVA, RAAS activity did not change significantly after the sodium bolus; however, the immediate inhibiting effect of the sodium load on PRA, ANG II, and Aldo is statistically significant for all three variables (paired $t$-test). Data inspection showed that the bolus always elicited a decrease, albeit mostly transient. On a before-and-after basis, this decrease is significant (Student’s $t$-test), although the ANOVA, including the comprehensive data set did not reach significance. PRA decreased by 4.9 ± 3.0 mIU/ml, ANG II by 10.6 ± 6.3 pg/ml, and Aldo by 503 ± 229 pg/ml. Nevertheless, the decline in RAAS activity was not associated with a consistent change in sodium excretion. After transition from normal to low sodium intake, remodeling of the afferent arteriole takes place, that is, the renin-producing cells become more abundant (12). We speculate that sodium excretion is minimized due to hyperactivity of the RAAS, including robust increases in aldosterone concentration and that the small, transient fall in RAAS activity is not sufficient to produce natriuresis. This may be a question of time as well as of magnitude. It is well known that the acute functional transition of the principal cells by aldosterone has a time constant, which is long compared with the present dip in RAAS activity. With regard to magnitude, the lowest value of ANG II and Aldo after the bolus administration was 19 pg/ml and 370 pg/ml, respectively (Fig. 2). It has been shown earlier that the apparent concentrations of ANG II and Aldo permitting natriuresis are substantially smaller than the present nadir concentrations (17). The events leading to a rebound of the RAAS variables after the acute load

![Graphs showing log-linear relationships between various RAAS parameters and sodium intake](image-url)

Fig. 5. RAAS parameters during steady-state vs. low sodium intake. Data are from this study combined with data from a previous study (17). Values are expressed as means ± SE; $n = 6$ at 0.16, 0.5, 1.0, . . . , 8.0, and remaining data points $n = 5$. 

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of NaCl remain to be elucidated. The sodium load was not excreted (i.e., >99% retained, calculated from Fig. 4 and sodium bolus), and the effects on plasma volume and protein concentration were not reversed; consequently, it is difficult to provide a plausible explanation for this rebound.

Potassium excretion increased substantially (2- to 3-fold) after the bolus. This is probably due to chronic high levels of circulating Aldo tuning the principal cells of the collecting duct to sodium reabsorption (production and insertion of K⁺-channels, ENaC, and Na⁺-K⁺-ATPase) and enhancing sodium reabsorption and potassium excretion (33).

MABP, GFR, diuresis, free-water clearance, plasma potassium, PRA, cGMP, and cAMP did not change. It is of particular interest that mean arterial pressure did not increase at all; in several series of experiments, there was not even a trend toward an increase. This is in accordance with previous results in humans (2, 3, 23, 27) and in dogs (30). Actually, in one of these studies in man (2), sodium loading was accompanied by a small, but significant, decrease in arterial blood pressure emphasizing the fact that arterial blood pressure and natriuresis were unrelated under these conditions.

**Perspectives**

Taken together with other results, the present results demonstrate that over almost 3 orders of magnitude, the daily sodium intake determines the activity of renin system in a log-linear fashion. This allows simple quantification of the relationship between sodium metabolism and circulating concentrations of renin, angiotensin, and aldosterone and thus provides specific tools for the analysis of the complex relations between sodium intake, renin system activity, plasma volume and blood pressure control.

The procedure of acute sodium loading elicited kaliuresis, but not natriuresis, at constant blood pressure and elevated plasma volume. It may be functionally important that acute sodium loading, elevating plasma volume and sodium concentration, and decreasing plasma protein concentration, was able to suppress RAAS activity only transiently by the equivalent of the effect of half a decade of sodium intake. This points toward the importance of chronic adjustments of RAAS activity over acute responses and emphasizes that all data on the acute regulation of RAAS activity must be viewed in the light of the prevailing chronic steady-state sodium intake. Consequently, studies of the RAAS should be performed only under controlled dietary conditions, particularly with regard to chronic sodium (and potassium?) intake.

The present data seem to favor a model according to which 1) the absolute level of RAAS activity is set by the chronic intake of sodium (over several days) and 2) the acute regulation of RAAS activity (over hours) is relatively modest, that is, comparable to the effect of a change in chronic dietary sodium intake of half a decade. It is likely that this interaction between the acute dietary intake and an acute load of sodium is a function of the magnitude of the acute load; a larger load may generate a different response. However, the magnitude of the present acute load was chosen to be similar to a regular chronic daily intake of sodium to investigate the mechanisms operative under normal physiological conditions.

**GRANTS**

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**REFERENCES**


