Gastrointestinal osmoreceptors and renal sodium excretion in humans

LARS JUEL ANDERSEN, THOMAS ULRIK SKRAM JENSEN, MORTEN HEIBERG BESTLE, AND PETER BIE

Department of Medical Physiology, Panum Institute, University of Copenhagen, and Danish Aerospace Medical Centre of Research, Rigshospitalet, DK-2200 Copenhagen; Department of Clinical Physiology, Herlev Hospital, DK-2730 Herlev; and Department of Physiology and Pharmacology, University of Southern Denmark, Odense, DK-5000 Odense, Denmark

Methods

Experiments were performed in eight healthy male volunteers. Subjects were 24–30 yr old and weighed 73.9–84.6 kg. All gave informed consent, and the study was approved by the Ethics Committee of Copenhagen (j.nr. KF 01–011/96).

Approximately 2 wk before the experiments, each subject’s extracellular volume (ECV) was determined as the distribution volume of [51Cr]EDTA according to the method described by Brøchner-Mortensen (6). On the same day, lean body mass (LBM) was determined by counting the naturally present radionuclide 40K in a whole body counter (NE 8114 3pi, 

http://www.ajpregu.org 0363-6119/00 $5.00 Copyright © 2000 the American Physiological Society
Plastic Scintillator System Nuclear Enterprise) according to Hassager et al. (19). Total body water was then calculated from LBM by multiplication by a factor 0.72 kg H₂O/kg LBM. Determinations of total body water and ECV as well as all experiments were performed after the subjects had been on a controlled diet containing 150 mmol NaCl/day for 4 days. Sodium turnover was assessed by measuring 24-h urinary sodium excretion on the day before the experiment.

The night before the experiment the subject slept at the laboratory. At 0700 h, he was awakened and consumed a light standardized low-salt breakfast (3 slices of toast, 15 g marmalade, and 500 ml tap water). The subject was instrumented with two catheters (Venflon, 18 gauge) in superficial cubital veins for blood sampling and injection of saline. After the catheters were inserted, the subject emptied his bladder and was weighed. The subject remained supine throughout the study and was allowed to stand up only for micturition. Initial hydration status was maintained throughout the experiment by drinking water in amounts equal to those voided plus 1 ml/min as replacement for the insensible water loss minus the volume of saline injected intravenously to maintain sodium balance (see below). Room temperature was kept at -24°C.

Each experiment lasted 8 h and was divided into 1-h periods. After 1 h of baseline, a soft nasogastric polyurethane tube (Ch. 8, Meda) was introduced after local anesthesia with lidocaine. The position of the tube in the ventricle was verified by brief aspiration of gastric juice. Saline was infused through the tube over the first 30 min of period 2, after which it was gently removed. After period 2, sampling continued for another six periods. Two series of saline infusion were performed. In the one series (Iso), the salt load was infused as isotonic saline in amounts equal to 10% of measured ECV (1.44 ± 0.01 liters of 0.9% saline). In the other series (Hyper), an identical amount of sodium was infused as a hypertonic solution (0.26 ± 0.01 liters of 5% saline). Infusions were administered by an automatic infusion pump (LifeCare pump, model 4, Abbott). In an additional series (water), infusion of saline was replaced by drinking of tap water in amounts equal to 3.5% of measured total body water (1.46 ± 0.03 liters of water). The protocol of the time control series (control) was identical to the infusion series, but without infusion. All experiments were performed on separate days with at least 2 wk of recovery between experiments.

Urine was collected by voluntary micturition during the last minute of every hour. After each urine collection, urinary concentration of sodium was measured, and the excreted amount of sodium was replaced by intravenous injection of isotonic saline in the beginning of the subsequent period to maintain the sodium load. The volume of water administered orally to maintain hydration status was reduced correspondingly (see above).

Blood (12 ml) was sampled in heparinized tubes at the beginning and the end of the baseline period, just after the end of saline infusion, and in the middle of every remaining 1-h period for measurements of sodium, osmolality, hematocrit, protein, albumin, creatinine, and oncotic pressure. Additional blood samples for hormone analyses (20 ml) were collected in prechilled polyethylene tubes containing aprotinin (300 KIU/ml) and EDTA (3 µmol/ml) in periods 1, 2, 4, 6, and 8. The withdrawn blood was replaced by twice the amount of saline. Blood samples were centrifuged at +4°C, and plasma was stored at -18°C until later analysis for concentrations of ANG II and atrial natriuretic peptide (ANP).

Hematocrit was determined by centrifugation (Microfuge, Christ). Oncotic pressure was determined by a colloid osmometer (4400 Colloid Osmometer, Wescor). Hemoglobin and plasma concentrations of albumin and protein were measured by a SMAC3 instrument (Bayer). Urine and plasma sodium concentrations were measured by an ion-selective electrode system (KNA-2, Radiometer), and osmolality was measured by freezing-point depression (model 3DI, Advanced Instruments). Concentrations of creatinine were measured by conventional spectrophotometry.

Arterial systolic and diastolic pressures were recorded semiautomatically four times during each experimental period (Propaq 102, Dämeca), and the mean of these values was used to calculate mean arterial pressure (MAP) from the following formula: MAP = diastolic pressure + 1/3 × pulse pressure.

Hormone concentrations in plasma and urine samples were quantified by radioimmunoassays after extraction. Thawed samples were acidified with 4% acetic acid, and peptides were extracted by use of C₁₈ Sep-Pak cartridges (Waters), as previously described (14). After elution, the samples were dried and stored at -18°C in tubes topped with N₂ until analysis for hormone immunoreactivity. ANP was determined according to the assay procedure described earlier (35) by use of an antibody (RAS8798) purchased from Peninsula Laboratories. Extraction recovery was 85%. Detection limit was 1.5 pg/ml sample, and intra-assay coefficient of variation was 6%. Immunoreactivity of ANG II was determined by use of an antibody (Ab-5–030682) produced by P. Christensen. The assay procedure has been described by Kappelgaard et al. (22). Extraction recovery was 83%. Detection limit was 1.4 pg/ml sample. Intra-assay and interassay coefficients of variation were 5% and 16%, respectively. The procedure for measuring endothelin-1 concentrations in extracted urine samples has been described previously (13). The detection limit was 0.16 pg/ml urine, and extraction recovery was 91%. Intra-assay and interassay coefficients of variation were 5.2 and 6.5%, respectively. Samples for measurements of plasma arginine vasopressin (AVP) were collected, but the assay failed for technical reasons and the samples were lost. Hormone results have not been corrected for incomplete recovery.

Time control results have recently been presented as part of another study describing the effects of intravenous salt loading (2).

Statistics. Results are presented as means ± SE. Data were subjected to one-way ANOVA for repeated measures (39). In case of significantly large F values, all possible differences were evaluated by Newman-Keuls test. Selected differences between series were evaluated using paired Student’s t-test. Level of significance was in all cases 0.05.

RESULTS

Total body water calculated from ⁴⁰K measurements varied between 38.7 and 45.0 liters with a mean of 41.6 ± 0.8 liters (52.5 ± 1.2% of body wt). ECV varied between 13.9 and 14.8 liters with a mean of 14.4 ± 0.1 liters (18.1 ± 0.2% of body wt). Twenty-four-hour sodium excretion was 142 ± 6 mmol during the last day of controlled sodium intake.

Plasma sodium concentration and osmolality increased immediately after infusion of hypertonic saline and remained elevated throughout the observation period (Fig. 1). During Iso and control, plasma sodium concentration remained unchanged, whereas plasma osmolality decreased slightly but significantly. Plasma
sodium as well as plasma osmolality decreased markedly during water (Fig. 1).

Oncotic pressure and plasma protein decreased very similarly during Isot and Hyper (Fig. 2). The same variables also tended to decrease during water and control, but the decreases were smaller and more gradual than during Isot and Hyper (Fig. 2). Hematocrit and plasma albumin followed a very similar pattern. Hematocrit decreased from 42.8 ± 0.9 to 40.1 ± 0.9% and from 43.1 ± 0.8 to 39.9 ± 1.1% during Isot and Hyper, respectively. Smaller decreases from 43.2 ± 0.8 to 41.8 ± 0.9% and from 43.4 ± 0.9 to 41.7 ± 0.8% were observed during control and water, respectively. Plasma albumin decreased from 631 ± 6 to 582 ± 7 µM during Isot, from 639 ± 10 to 587 ± 9 µM during Hyper, and from 631 ± 6 to 604 ± 10 µM during water but remained unchanged during control.

Sodium excretion increased in all experimental series (Fig. 3). At no time did the natriuresis during Hyper exceed that during Isot. In periods 6 and 7, hypertonic saline actually induced a significantly smaller natriuresis than isotonic saline (253 ± 26 and 261 ± 25 vs. 390 ± 39 and 383 ± 47 µmol/min). Measured as cumulated sodium excretion, isotonic saline also induced the greatest natriuresis, and the response to hypertonic saline was not significantly greater than that observed during water or control (Fig. 3).

Urine flow and free water clearance increased in all experimental series except during Hyper in which urine flow remained low and free water clearance decreased (Fig. 4).

MAP increased slightly but consistently during water and Isot. This was due to increases in diastolic pressure since systolic arterial pressure remained unchanged (Table 1). During Hyper, diastolic and MAP increased only transiently. During control, there was only an inconsistent increase in diastolic arterial pressure. Heart rate tended to decrease in all series in a very similar way, but the decrease was only statistically

**Fig. 1. Plasma concentration of sodium (A) and plasma osmolality (B). Values are means ± SE. Control; water loading; Isotonic saline loading; hypertonic saline loading. *Significantly different from preinfusion value by ANOVA (P < 0.05) and Newman-Keuls test.**

**Fig. 2. Plasma oncotic pressure (A) and plasma protein concentration (B). Values are means ± SE. Control; water loading; Isotonic saline loading; hypertonic saline loading. *Significantly different from preinfusion value by ANOVA (P < 0.05) and Newman-Keuls test.**
significant during control. There were no significant changes in creatinine clearance (Table 1).

Plasma concentrations of ANG II decreased immediately after both salt-loading procedures but also decreased somewhat during control and water (Fig. 5). From period 4 to 8, plasma ANG II remained suppressed to 22 ± 6, 35 ± 6, 47 ± 5, and 61 ± 6% of preinfusion levels during Isot, Hyper, water, and control, respectively. Basal plasma concentrations of ANG II varied between series (Fig. 5). Samples were not measured in the same assay, which may explain at least some of this variation. Basal plasma concentrations of ANP varied between 31 ± 6 and 41 ± 6 pg/ml and were not affected by any of the loading procedures (Fig. 5). Urinary excretion rates of endothelin-1 varied between 14 ± 5 and 19 ± 3 pg/min and also remained statistically unchanged in all series.

**DISCUSSION**

The purpose of this study was to test the hypothesis that intragastric infusion of hypertonic saline induces a greater natriuresis than infusion of the same amount of salt as an isotonic solution because of stimulation of gastrointestinal osmoreceptors involved in the control of renal sodium excretion. However, the results were unable to support the hypothesis, since the natriuresis during Hyper was actually smaller than that observed during Isot.

The implicit assumption of the present experimental design is that intragastric infusion of hypertonic saline induces an increase in sodium concentration of the portal blood that is not obtained with infusion of isotonic saline. This increase in sodium concentration is hypothesized to stimulate osmoreceptors located in the intestines or the liver. If the hypothetical gastrointestinal osmoreceptors play an important role in sodium homeostasis compared with the well-known effect of volume expansion, the hypertonic load should induce a greater natriuresis than the isotonic load. Similarly, the decrease in portal sodium concentration after water...
loading should be expected to decrease renal sodium excretion. The stimulus used in the present investigation (−220 mmol) is physiological relevant and close to the average daily dietary sodium intake in Western Europe and North America. To minimize the variation in response between subjects, the degree of salt and water loading was determined by the respective spaces of distribution, i.e., by the individually measured ECV and total body water.

Stimulation of gastrointestinal osmoreceptors. It was not possible to measure sodium concentration in the portal blood. However, measurements from the systemic circulation may be used as an index of changes in the blood supplying the gastrointestinal osmoreceptors. It is assumed that, during intragastric hypertonic saline infusion, the sodium concentration of portal blood is at least as high as that of the systemic circulation. In fact, sodium concentration in the portal circulation should markedly exceed that of the systemic circulation, since by the time of peripheral blood sampling, the portal blood has been diluted by mixing of blood from extra-abdominal vascular beds. As expected, plasma sodium concentration and plasma osmolality increased immediately after administration of the hypertonic load as an indication of absorption of the salt load from the gut (Fig. 1). It could be argued that different fractions of the load were absorbed from the intestines during different protocols. However, the two salt-loading procedures induced similar decreases in hematocrit, plasma protein, plasma albumin, and oncotic pressure, indicating that the increases in ECV were identical in the two situations. It is therefore highly unlikely that the absorption of salt from the intestines was less complete during Hyper than during Isot. Finally, systemic plasma tonicity was markedly reduced after water loading, and it appears perfectly reasonable to assume that gastrointestinal osmoreceptors were activated during Hyper, deactivated during water, and unaffected during Isot and control.

<table>
<thead>
<tr>
<th>Sampling Period</th>
<th>1 (30 min)</th>
<th>2 (90 min)</th>
<th>3 (150 min)</th>
<th>4 (210 min)</th>
<th>5 (270 min)</th>
<th>6 (330 min)</th>
<th>7 (390 min)</th>
<th>8 (450 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>80 ± 2</td>
<td>81 ± 2</td>
<td>82 ± 2</td>
<td>82 ± 3</td>
<td>81 ± 2</td>
<td>80 ± 2</td>
<td>82 ± 2</td>
<td>83 ± 2</td>
</tr>
<tr>
<td>Isotonic</td>
<td>82 ± 2</td>
<td>87 ± 2*</td>
<td>87 ± 2*</td>
<td>86 ± 2*</td>
<td>84 ± 2</td>
<td>86 ± 3*</td>
<td>88 ± 3*</td>
<td>87 ± 2*</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>82 ± 2</td>
<td>86 ± 1*</td>
<td>85 ± 2</td>
<td>82 ± 1</td>
<td>81 ± 1</td>
<td>82 ± 2</td>
<td>83 ± 2</td>
<td>84 ± 1</td>
</tr>
<tr>
<td>Water</td>
<td>82 ± 2</td>
<td>88 ± 2*</td>
<td>89 ± 2*</td>
<td>88 ± 3*</td>
<td>87 ± 2*</td>
<td>87 ± 2*</td>
<td>87 ± 2*</td>
<td>88 ± 2*</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>116 ± 4</td>
<td>117 ± 4</td>
<td>117 ± 4</td>
<td>118 ± 3</td>
<td>114 ± 4</td>
<td>115 ± 4</td>
<td>117 ± 4</td>
<td>118 ± 4</td>
</tr>
<tr>
<td>Isotonic</td>
<td>119 ± 3</td>
<td>119 ± 3</td>
<td>122 ± 3</td>
<td>118 ± 3</td>
<td>119 ± 3</td>
<td>119 ± 3</td>
<td>122 ± 3</td>
<td>121 ± 2</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>117 ± 2</td>
<td>120 ± 2</td>
<td>119 ± 3</td>
<td>117 ± 2</td>
<td>114 ± 2</td>
<td>115 ± 2</td>
<td>115 ± 2</td>
<td>118 ± 1</td>
</tr>
<tr>
<td>Water</td>
<td>119 ± 3</td>
<td>120 ± 3</td>
<td>123 ± 3</td>
<td>123 ± 4</td>
<td>121 ± 3</td>
<td>119 ± 3</td>
<td>120 ± 3</td>
<td>120 ± 3</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>61 ± 2</td>
<td>62 ± 2</td>
<td>65 ± 2*</td>
<td>65 ± 2*</td>
<td>65 ± 1*</td>
<td>63 ± 1</td>
<td>64 ± 2*</td>
<td>65 ± 2*</td>
</tr>
<tr>
<td>Isotonic</td>
<td>63 ± 2</td>
<td>71 ± 2*</td>
<td>69 ± 2*</td>
<td>69 ± 2*</td>
<td>67 ± 2</td>
<td>69 ± 3*</td>
<td>70 ± 3*</td>
<td>70 ± 2*</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>64 ± 2</td>
<td>70 ± 1*</td>
<td>68 ± 2</td>
<td>65 ± 1</td>
<td>64 ± 2</td>
<td>66 ± 2</td>
<td>67 ± 2</td>
<td>67 ± 2</td>
</tr>
<tr>
<td>Water</td>
<td>63 ± 2</td>
<td>72 ± 2*</td>
<td>71 ± 2*</td>
<td>71 ± 2*</td>
<td>70 ± 2*</td>
<td>71 ± 2*</td>
<td>71 ± 2*</td>
<td>71 ± 2*</td>
</tr>
<tr>
<td><strong>Heart rate, beats/ min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>58 ± 3</td>
<td>58 ± 4</td>
<td>56 ± 3</td>
<td>56 ± 3</td>
<td>54 ± 2*</td>
<td>53 ± 3*</td>
<td>54 ± 3*</td>
<td>52 ± 2*</td>
</tr>
<tr>
<td>Isotonic</td>
<td>57 ± 2</td>
<td>60 ± 4</td>
<td>59 ± 3</td>
<td>57 ± 2</td>
<td>54 ± 2</td>
<td>54 ± 3</td>
<td>56 ± 3</td>
<td>53 ± 2</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>56 ± 2</td>
<td>56 ± 3</td>
<td>58 ± 4</td>
<td>55 ± 2</td>
<td>52 ± 2</td>
<td>53 ± 2</td>
<td>52 ± 2</td>
<td>51 ± 2</td>
</tr>
<tr>
<td>Water</td>
<td>58 ± 3</td>
<td>56 ± 3</td>
<td>56 ± 2</td>
<td>55 ± 2</td>
<td>53 ± 2*</td>
<td>54 ± 2</td>
<td>55 ± 2</td>
<td>55 ± 3</td>
</tr>
<tr>
<td><strong>Creatinine clearance, ml/ min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>152 ± 9</td>
<td>145 ± 7</td>
<td>145 ± 15</td>
<td>137 ± 5</td>
<td>132 ± 2</td>
<td>142 ± 6</td>
<td>128 ± 9</td>
<td>138 ± 9</td>
</tr>
<tr>
<td>Isotonic</td>
<td>159 ± 7</td>
<td>150 ± 9</td>
<td>153 ± 12</td>
<td>143 ± 17</td>
<td>142 ± 21</td>
<td>166 ± 13</td>
<td>161 ± 19</td>
<td>147 ± 13</td>
</tr>
<tr>
<td>Hypertonic</td>
<td>132 ± 5</td>
<td>138 ± 13</td>
<td>125 ± 11</td>
<td>149 ± 11</td>
<td>132 ± 10</td>
<td>131 ± 10</td>
<td>119 ± 15</td>
<td>141 ± 13</td>
</tr>
<tr>
<td>Water</td>
<td>144 ± 12</td>
<td>153 ± 9</td>
<td>155 ± 9</td>
<td>147 ± 8</td>
<td>139 ± 8</td>
<td>145 ± 7</td>
<td>151 ± 10</td>
<td>157 ± 12</td>
</tr>
</tbody>
</table>

Values are means ± SE. Isotonic or hypertonic saline was infused intragastrically between 60 and 90 min, or water was administered orally between 60 and 90 min. *Significantly different from period 1 (P < 0.05) by ANOVA and Newman-Keuls test.
However, others have compared the renal effects of oral vs. intravenous salt loading (7, 8, 18, 24, 29, 36). Lennane et al. (24) and Carey (7) found that normal subjects excreted a hypertonic sodium load more rapidly when it was administered orally than intravenously, supporting the existence of a splanchnic sodium input monitor regulating renal sodium excretion. Their investigations were performed on sodium-depleted subjects, and some of the discrepancies between these and the present results may be due to the differences between the protocols. Possibly, osmoregulatory control of sodium excretion may only be measurable within certain limits of sodium status. However, very recently, Singer et al. (36) were unable to show an excess natriuresis after oral administration of a sodium load in subjects on very low sodium intake (10 mmol/day) as well as in subjects on high sodium (350 mmol/day). In subjects on normal sodium intake (~150 mmol/day), sodium excretion was initially lower after oral compared with intravenous salt loading, but 3 h after administration, oral loading induced an excess natriuresis. However, cumulated excretions were statistically identical (36). In separate experiments, we have infused isotonic and hypertonic salt loads intravenously into the same subjects in doses identical to those of the present study (2). Because the experimental setup was identical to the present apart from the route of administration and the time of infusion (90 min), the results are directly compatible. Intravenous infusion of isotonic and hypertonic saline increased renal sodium excretion from 99 ± 19 to 414 ± 29 µmol/min and from 84 ± 10 to 349 ± 33 µmol/min, respectively (2). In this study, intragastric isotonic and hypertonic saline increased sodium excretion from 104 ± 15 to 406 ± 39 µmol/min and from 85 ± 15 to 325 ± 39 µmol/min, respectively. Accordingly, intragastric administration of neither isotonic nor hypertonic saline induced a natriuresis that exceeded the response to the corresponding intravenous loading procedure. Taken together, these findings are not in favor of the hypothesis that increased portal sodium concentration acts as an important stimulus to renal sodium excretion in humans. Similarly, others have also been unable to detect the function of gastrointestinal or hepatic osmoreceptors under physiological conditions (4, 16, 18, 23, 32, 34).

**Natriuretic mechanisms.** As pointed out previously (2), data from control show that the supine position does not provide a stable baseline with regard to renal excretory function. In contrast, the seated position provides stable time control conditions (3). Therefore, the position of the subjects must be carefully considered in future human studies of water and electrolyte homeostasis.

Plasma ANG II is probably the main controller of the natriuretic response to intravenous saline loading (2, 3, 37). Plasma ANG II also decreased in all experimental series in the present study. Relatively, the most pronounced decrease was observed during Isot, which was associated with the greatest natriuresis. We find it likely that ANG II plays a pivotal role in the natriuresis of salt loading irrespective of the route of administration, a notion that is supported by the findings of Singer and co-workers (36, 37).

In contrast, plasma ANP was unaffected by intragastric infusion of hypertonic and isotonic saline infusion, and it seems unlikely that ANP contributed to the natriuresis during any of the loading procedures. Singer et al. (36) also observed that plasma ANP was unaffected by oral sodium loading, whereas secretion was stimulated after intravenous loading in subjects on normal and high sodium intake. Previously, we have observed marked natriureses following intravenous administration of isotonic as well as hypertonic saline without measurable increases in plasma ANP levels (2, 3, 15). Although long-term changes in sodium intake may be reflected in plasma ANP levels (3, 36), the role of ANP in the response to acute sodium loading seems less clear. Possibly, short-term regulation of ANP secretion is rate sensitive and plasma ANP is only increased after relatively rapid intravenous salt loading, whereas procedures involving smaller rates of increases, e.g., intestinal absorption or slow infusion, fail to stimulate ANP secretion (3, 36).
Urinary excretion of endothelin-1 was also unaffected by the salt loading, and the observed changes in sodium excretion cannot be attributed to changes in this parameter.

Plasma AVP concentration most likely increased during Hyper and decreased in all the other series. This notion is supported by the observed changes in urine flow and free water clearance. Because there is indication that a physiological increase in plasma AVP concentration may promote antinatriuresis in humans (1), it is possible that part of the increase in sodium excretion during Isot, control, and especially during water was induced by a fall in plasma AVP. Similarly, the natriuresis during Hyper may have been inhibited by an increase in plasma AVP concentration. Accordingly, the surprisingly small differences between sodium excretions during Hyper and water may be accounted for by opposite changes in plasma AVP.

It is generally accepted that an increase in arterial blood pressure may induce pressure natriuresis. Previously we have not observed any increases in arterial pressure in response to intravenous administration of similar doses of sodium (3), but during Isot, MAP increased slightly but significantly. During Hyper, only a transient increase was observed. It is possible that the rises in arterial pressure contributed to the natriuresis in the present study. However, it is noteworthy that the most consistent increase in MAP was observed during water, indicating the increase in arterial pressure may not necessarily be related to the degree of extracellular volume expansion.

A decrease in oncotic pressure has been found to be a strong natriuretic stimulus in dogs (9) and humans (21). Because oncotic pressure decreased in all series in parallel with the observed changes in sodium excretion, it is very likely that dilution of plasma was responsible for part of the natriuretic responses. The effect on sodium excretion may be mediated by the direct changes in the physical forces working on the formation of the tubules, but it may also be mediated by a decrease in the activity of the renin-angiotensin system (21). Creatinine clearance did not change measurably, but it must be considered that this parameter is not a very precise estimate of glomerular filtration rate in humans.

Limitations of the study. The present study is performed under strictly controlled and well-defined conditions with regard to sodium status, individual adjustment of dosage, replacement of water, and salt losses throughout the study. Salt loads were administered through a gastric tube, eliminating possible sensory inputs (e.g., salt taste) associated with oral salt loading. The fact that the results were unable to support our hypothesis may be explained by the absence of an important role of gastrointestinal osmoreceptors in sodium homeostasis in normal, sodium-replete subjects. However, there are certain limitations to the design of the study. First of all, the precise location of the gastrointestinal osmoreceptors is unknown, and the exact stimulus cannot be determined because of lack of portal blood samples. Although there is indication that the degree of absorption of sodium was similar during Hyper and Isot, it is possible that the intestinal salt absorption rates were dissimilar in the two series, thus creating dissimilar rates of changes in the ECV. Finally, a possible contribution of osmoreceptors in the regulation of sodium excretion may be overridden by the natriuretic effect of the concomitant volume expansion-induced isotonic as well as hypertonic salt loading.

Summary and conclusion. Intragastric infusion of hypertonic saline did not induce a natriuresis that exceeded that induced by isotonic saline. Furthermore, the cumulated sodium excretion after hypertonic saline did not significantly exceed that after oral water loading. Therefore, we conclude that stimulation of gastrointestinal osmoreceptors was not responsible for the natriuresis of intragastric salt loading in these supine subjects. The natriuretic responses to all the loading procedures were preceded by decreases in plasma ANG II concentration, but no changes were observed in plasma ANP or urinary excretion rate of endothelin-1.

Perspectives

The results were unable to support the notion that renal sodium handling following intragastric salt loading is influenced by gastrointestinal or hepatic osmoreceptors. Instead, the data emphasize the importance of well-known systemic factors in control of sodium excretion, i.e., the renin-angiotensin-aldosterone system. Most experiments dealing with the role of gastrointestinal osmoreceptors have been performed in animals, but the present data indicate a need for implementation of human investigations to clarify the physiological role of gastrointestinal osmoreceptors in sodium homeostasis. Such investigations should be performed in the sitting position to ensure stable baseline conditions and include detailed analysis of the classical control systems.

We thank Bodil Svensson, Birthe Lynderup Christensen, Sigurd Kramer Hansen, Inge Pedersen, Barbara Sørensen, and Trine Eidsvold for expert technical assistance. We also acknowledge the expert assistance of Dr. Steen Levin Nielsen in calculations of the subjects’ extracellular volume and the expert assistance of Dr. Sven Sølvsten Sørensen in measurements of the subjects’ total body potassium.

Preliminary results were presented at Experimental Biology 98 in San Francisco, California, in April 1998.

The experiments were supported by the Danish Medical Research Council, the Danish Foundation for the Advancement of Medical Science, the Kong Christian den Tyndes Foundation, the Engineer August Frederik Wedell Erichsens Foundation, the Direktør Jacob Madensens and Hustru Olga Madensens Foundation, and the Danish Heart Foundation.

Address for reprint requests and other correspondence: P. Bie, Dept. of Physiology and Pharmacology, University of Southern Denmark, 21 Winsløwparken, DK-5000 Odense, Denmark (E-mail: bie@imbmed.sdu.dk).

Received 20 October 1998; accepted in final form 3 August 1999.

REFERENCES


