Effects of growth hormone on renal tubular handling of sodium in healthy humans

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Am J Physiol Endocrinol Metab 281: E1326–E1332, 2001.—To investigate the mechanisms behind the water- and sodium-retaining effects of growth hormone (GH), we studied the effect of GH on 1) water and sodium homeostasis, 2) the renin-angiotensin-aldosterone system (RAAS), and 3) lithium clearance (CLi) with and without concomitant prostaglandin (PG) synthesis inhibition with ibuprofen. GH administration for 6 days induced a significant increase in plasma renin, which was abolished by coadministration of ibuprofen (mU·l⁻¹·h⁻¹; control: 22.4 ± 4.3; GH: 37.7 ± 8.8; ibuprofen: 15.2 ± 3.0; GH + ibuprofen: 19.7 ± 2.5; ANOVA: P < 0.01). Comparable increments in extracellular volume were seen after 6-day treatment with GH alone and in combination with ibuprofen [liters: control, 21.63 ± 0.90; GH, 20.80 ± 1.00 (ANOVA; P < 0.0005); ibuprofen, 19.38 ± 0.90; GH + ibuprofen, 21.63 ± 1.37 (ANOVA; P < 0.0005)]. Treatment with GH increased CLi and changed the tubular handling of sodium and water. The absolute distal sodium reabsorption was increased, and this was only partially counterbalanced by decreased reabsorption in the proximal tubules. The data demonstrate that GH-induced activation of the RAAS can be blocked by concomitant PG synthesis inhibition and that the tubular effects of GH include increased distal nephron sodium and water reabsorption.

The mechanisms behind the antinatriuretic and water-retaining effects of growth hormone (GH) are complex and not yet fully clarified. There is evidence of a direct sodium-retaining effect of GH on the tubules (1, 17), which is present even in the absence of the adrenals (19, 29). In addition, several studies have demonstrated an effect of GH on sodium and water homeostasis via stimulation of the renin-angiotensin-aldosterone system (RAAS) (7, 13, 16, 24). The extracellular volume (ECV) is increased by GH, and in one study, blockade of the RAAS with either captopril or spironolactone prevented this effect (24).

GH administration causes increased glomerular filtration rate (GFR) and renal plasma flow (RPF) (6), an effect probably mediated via insulin-like growth factor I (IGF-I) (11, 15). Prostaglandin (PG) synthesis inhibition can block these effects (14, 33), suggesting that GH increases GFR and RPF via vasodilating PGs. It is not clarified whether the effects of GH on sodium homeostasis involve PGs. However, intrarenal PGs also stimulate renin secretion (25); therefore, the effects of GH on tubular sodium handling may be mediated via PG stimulation of RAAS.

To further elucidate the mechanisms behind the water- and sodium-retaining effects of GH, we studied the effect of GH on water and sodium homeostasis and on the RAAS with and without concomitant PG synthesis inhibition in healthy humans. Measurements of lithium clearance (CLi), a method for determining proximal and distal tubular reabsorption of sodium and water (32), were included to obtain information about GH-mediated effects on segmental tubular sodium handling and on the relation of this to RAAS activation.

SUBJECTS AND METHODS

Subjects. Eight healthy males volunteered, all with body mass index <25 and a mean age of 26.1 yr (23–31 yr). The study was approved by the local ethics committee and the Danish National Board of Health, and informed consent was obtained from each subject.

Design. The subjects were examined during four different periods of 6 days each in random order with 4-wk intervals. During each period, the subjects received an individually prepared sodium-fixed diet containing 200 mmol of sodium. The diet was otherwise identical to the subjects’ prestudy diets based on a careful nutritional interview by a clinical dietician. One period served as a control, whereas the participants during the other periods received either GH (6 IU/m² Norditropin, Novo Nordisk, Novo Nordisk, Copenhagen, Denmark), ibuprofen (400 mg × 3 Ibuprofen “DAK”, Nycomed Denmark, 3 Ibuprofen “DAK”, Nycomed Denmark, Nordic), or spironolactone. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Copenhagen, Denmark), or GH (6 IU/m²) plus ibuprofen (400 mg × 3). GH was administered once daily by subcutaneous injections into an abdominal skinfold at 2000. Ibuprofen was given orally each day at 0800, 1600, and 2400.

During each study period, blood samples were drawn on days 0, 2, 4, and 6 at 0800 after an overnight fast. All blood samples were drawn after ≥50 min of rest in the supine position. The blood samples were analyzed for concentrations of IGF-I, insulin, renin, aldosterone, and NH₂-terminal proatrial natriuretic factor (proANF). Bioimpedance measurements were done at the same time (Animeter, HTS Engineering, Odense, Denmark). On days 0 and 6, 24-h ambulatory blood pressure and heart rate were measured every 20 min during the daytime (0600–2400) and every hour during the night with a portable automatic monitor (SpaceLabs, model 90202, Redmond, WA). Twenty-four-hour urinary collections were made on days 0, 2, 4, and 6 for determination of sodium and potassium excretions.

On day 5, the subjects were admitted to the clinical research unit at 2200. The following day, intravenous catheters were inserted into a cubital vein for blood sampling and into an antebrachial vein on the contralateral arm for infusion of isotopes.

**ECV, plasma volume, and GFR.** ECV was determined using ⁸₂Br as previously described (2). ⁸₂Br was injected at 0900, and blood samples were drawn 4 h later. Determination of plasma volume (PV) was done between 1300 and 1400 by intravenous injection of ¹²⁵I followed by blood sampling every 10 min for 50 min (8). GFR was measured using a single injection of ⁵¹Cr-EDTA (4).

**Lithium and sodium clearance.** On day 5, the subjects received 300 mg of lithium carbonate (Lithiumkarbonat “Dak”, Nycomed Danmark) by mouth at 2200. On day 6, blood samples for analysis of lithium and sodium were collected at 0900 and 1300, and urine was collected between 0900 and 1300.

**Assays.** Sodium and potassium concentrations in serum and urine were measured by routine methods at the Department of Clinical Chemistry, Aarhus University Hospital. Serum GH was determined by a time-resolved immuno-fluorometric assay (TR-IFMA; Delfia, Wallac, Finland). Serum IGF-I was measured with an in-house TR-IFMA (10), and insulin analyses were performed by radioimmunoassay (RIA) as previously described (26). Plasma and urinary concentrations of lithium were determined by emission photometry and atomic absorption spectrophotometry, respectively. Plasma renin concentrations were determined with an antiserum from Penninsula Laboratories, Belmont, CA (22).

**Calculations and statistical methods.** On the basis of the assumptions that lithium is reabsorbed only in the proximal tubules in the same proportion as sodium and water and that lithium is not reabsorbed in the distal nephron, Cₗᵢ represents the delivery of isotonic fluid at the end of the proximal tubules. The following estimates of segmental tubular handling of sodium and water can be calculated using Cₗᵢ, GFR, sodium clearance (C₅₉₈), plasma concentrations of sodium (P₅₉₈) and lithium (Pₗᵢ), urinary concentrations of lithium (Uₗᵢ), sodium (U₅₈), and potassium (Uₖ), and urine flow rate (V).

\[
Cₗᵢ = V × Uₗᵢ / Pₗᵢ
\]

proximal absolute reabsorption of sodium (PAR₅₉₈)

\[
PAR₅₈ = (GFR - C₅₉₈) × P₅₉₈
\]

proximal fractional reabsorption of sodium (PFR₅₉₈)

\[
PFR₅₈ = (1 - C₅₉₈ / GFR) × 100%
\]

distal absolute reabsorption of sodium (DARₕ₆₀)

\[
DAR₅₈ = (C₅₉₈ - C₅₉₈) × P₅₉₈
\]

distal fractional reabsorption of sodium (DFRₕ₆₀)

\[
DFR₅₈ = (1 - C₅₉₈ / C₅₉₈) × 100%
\]

distal absolute reabsorption of water (DARₖ₆₀)

\[
DAR₉₅₈ = C₉₅₈ - V
\]

distal fractional reabsorption of water (DFR₉₅₈)

\[
DFR₉₅₈ = (1 - V / C₅₉₈) × 100%
\]

urinary sodium excretion rate (U₅₈)

\[
U₅₈V = U₅₈ × V
\]

urinary potassium excretion rate (U₅₆₀)

\[
U₅₆₀V = U₅₆₀ × V
\]

All statistical calculations were done with SPSS for Windows, version 10.0 (SPSS, Chicago, IL). Twenty-four-hour urinary output (U₅₈), sodium excretion (U₅₈V), and potassium excretion (U₅₆₀V) were calculated as areas under the curves (AUC) of the measurements at days 0, 2, 4, and 6 according to the linear trapezoidal rule (20). PVs of renin (AUCₐₚ₉₈), aldosterone (AUCₐₚ₉₈), and NH₂-terminal proANF (AUCₐₚ₉₈) were calculated in the same way. Differences between treatment regimens were tested by analysis of variance with repeated measurements (ANOVA, general linear model). P values refer to overall effect of treatment (ECV, PV, Cₗᵢ, AUC₉₅₈, AUC₅₈, AUC₉₅₈) or to the overall effect of time and treatment (IGF-I, insulin, bioimpedance, weight, renin, aldosterone, and NH₂-terminal proANF). P values <0.05 were considered significant. When significant changes occurred, paired t-tests were used for post hoc comparisons. These results are indicated as follows: P < 0.05 compared with the control situation. When necessary, logarithmic transformations were performed to obtain normality. All results are expressed as mean ± SE.

**RESULTS**

**IGF-I and insulin.** Treatment with GH as well as GH in combination with ibuprofen caused a significant increase in serum IGF-I levels [day 6 (in µg/l): control, 279 ± 27; GH, 636 ± 52 (P < 0.05 vs. control); ibuprofen, 269 ± 13; GH + ibuprofen, 653 ± 64 (P < 0.0001); Fig. 1] as well as in insulin levels [day 6 (in pmol/l): control, 29.1 ± 3.3; GH, 94.6 ± 29.0 (P < 0.0001); ibuprofen, 28.1 ± 3.0; GH plus ibuprofen, 74.4 ± 18.6 (P < 0.005)].

**Renin, aldosterone, and ANF.** GH administration induced a significant increase in plasma renin with a peak after 2 days, which was completely abolished by coadministration of ibuprofen. Ibuprofen administra-
tion alone reduced the renin concentrations compared with the control period (Table 1 and Fig. 2A). Similar changes were observed in plasma aldosterone (Table 1 and Fig. 2B), whereas plasma NH₂-terminal proANF remained unchanged during all study conditions (Table 1).

**Blood pressure and heart rate.** No differences in 24-h mean systolic and diastolic blood pressure were detected between the different study situations. Heart rate (s⁻¹) on day 6 was increased after administration of GH, but not significantly so after treatment with ibuprofen or GH plus ibuprofen (control, 72.0 ± 2.9; GH, 85.0 ± 3.5 (P < 0.01); ibuprofen, 70.8 ± 2.5; GH plus ibuprofen, 79.8 ± 3.5 (P < 0.01)).

**Fluid and electrolyte excretions.** The mean 24-h urinary output (AUCU, ml/24 h) decreased significantly during GH and GH plus ibuprofen treatment (Table 1 and Fig. 3A). The mean 24-h urinary sodium excretion (AUCU-Na, mmol/24 h) was reduced during GH treatment (Table 1 and Fig. 3B), and the mean 24-h urinary potassium excretion (AUCU-K, mmol/24 h) decreased during both GH and GH plus ibuprofen treatment (Table 1 and Fig. 3C). Serum sodium and potassium concentrations did not change significantly during the treatment periods (data not shown).

A significant increase in both ECV and PV was seen after GH administration. Coadministration of ibupro-

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**Table 1. Effect of treatment with GH, ibuprofen, or both on ECV, PV, the renin-angiotensin-aldosterone system, and urinary electrolyte excretion**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GH</th>
<th>GH + Ibuprofen</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECV, l</td>
<td>19.57 ± 0.92</td>
<td>20.80 ± 1.00*</td>
<td>21.38 ± 1.37*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PV, l</td>
<td>3.60 ± 0.16</td>
<td>4.00 ± 0.19*</td>
<td>3.52 ± 0.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUCRenin, mU·l⁻¹·24 h</td>
<td>224 ± 4.3</td>
<td>37.7 ± 8.8**</td>
<td>15.2 ± 3.0**</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AUCAldosterone, pmol·l⁻¹·24 h</td>
<td>255 ± 30</td>
<td>339 ± 47**†</td>
<td>227 ± 42</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AUCAFP, pg·l⁻¹·24 h</td>
<td>528 ± 106</td>
<td>801 ± 90</td>
<td>635 ± 85</td>
<td>NS</td>
</tr>
<tr>
<td>AUCU, ml/24 h</td>
<td>2.315 ± 300</td>
<td>1.823 ± 193*</td>
<td>2.423 ± 240</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>AUCU-Na, mmol/24 h</td>
<td>179 ± 11</td>
<td>132 ± 16*</td>
<td>181 ± 13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>AUCU-K, mmol/24 h</td>
<td>85 ± 10</td>
<td>57 ± 5*</td>
<td>82 ± 5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means ± SE. GH, growth hormone; ECV, extracellular volume; PV, plasma volume; AUC, area under the curve; ANF, atrial natriuretic factor; U, urinary concentration. P values obtained by overall analysis of variance with repeated measurements (general linear model). *Paired t-test for experimental group vs. control, P < 0.05; †paired t-test for GH vs. GH + ibuprofen, P < 0.05.
fen did not influence these changes (Table 1 and Fig. 4, A and B). During GH and GH plus ibuprofen treatment, the increments in ECV and PV were reflected in a significant decrease in bioimpedance and an increase in weight on day 6 (Table 2).

GFR, CLi, and renal tubular sodium handling. In Table 3, values of GFR, CLi, PARNa, PFRNa, DARNa, DFRNa, DH2O, DFH2O, UNaV, UKV, and V are listed. GFR did not change significantly after any of the treatment periods. GH administration induced a significant increase in CLi. Treatment with ibuprofen caused a minor, nonsignificant decrease in CLi, and compatible with this, treatment with GH plus ibuprofen caused a smaller increase in CLi than did GH alone. In the proximal tubules, PARNa was unaffected by the different treatments. In contrast, a significant overall effect of the different treatments on PFRNa was observed, and after treatment with either GH alone or in combination with ibuprofen, PFRNa was reduced, although not significantly compared with the control period. In the distal tubules, DARNa and DARH2O were signifi-
cantly increased by treatment with GH, whereas non-significant increments were seen after treatment with both GH and ibuprofen. Treatment with GH alone or in combination with ibuprofen tended to increase DFR$_{Na}$, but these increments were not significant. There was an overall effect of the different treatments on DFR$_{H_{2}O}$, but no significant differences between the control situation and the treatment periods were disclosed. The proportions of the filtered load of sodium (GFR $\times$ P$_{Na}$) reabsorbed in the proximal and distal tubules, respectively, were clearly affected by GH. The expected increased reabsorption of sodium was observed only in the distal tubules and was almost completely compensated for by decreased reabsorption in the proximal tubules (Fig. 5). $U_{NaV}$, $U_{Kv}$, and $V$ did not change significantly after any of the treatment periods.

**DISCUSSION**

In the present study, we investigated the effects of GH administration with and without concomitant PG synthesis inhibition on sodium and water metabolism in healthy humans. This is the first study to document distinct alterations in renal tubular handling of sodium and water after GH treatment using measurements of $C_{Li}$.

GH administration for 6 days caused a significant increase in plasma renin. Concomitant treatment with ibuprofen completely neutralized these changes, and although measurements of PG synthesis were not performed, these data indicate that the stimulatory effect of GH on renin secretion involves synthesis of PGs. This confirms the findings of previous studies (33); furthermore, parallel changes in plasma aldosterone were observed in the present study. Our data demonstrate that the changes in renin and aldosterone concentrations were more pronounced within the first 2–4 days of GH treatment. This supports earlier observations that the initial change in RAAS tends to subside during prolonged GH treatment (16, 21).

So far, reports on the effects of GH on ANF have been conflicting. In this study, we measured plasma NH$_{2}$-terminal proANF, which could provide a more robust index of ANF secretion (12). In a previous study, decreased levels of ANF after 14 days of GH administration was reported (23), a finding which was later attributed to IGF-I (22). In the present study, NH$_{2}$-terminal proANF remained unchanged during all study conditions. However, the strength of this finding is limited by the relatively small study population size, thus leaving unanswered the question whether ANF is suppressed during GH administration.

Significant increments were seen in ECV and PV after GH administration both with and without concomitant administration of ibuprofen. Because the RAAS was completely blocked through PG synthesis inhibition, this indicates that the sodium and fluid retention was induced independently of RAAS. These findings are in contrast to those of an earlier study, in which blockade of the RAAS with either spironolactone or captopril prevented GH-induced fluid retention (24). In the present study, the RAAS was blocked to the same extent through PG synthesis inhibition; nevertheless, the GH-induced fluid retention was not obliterated. One could speculate as to whether the RAAS blockade is counterbalanced by a synergistic effect of ibuprofen on the direct renal actions of GH. It is well known that inhibition of PG synthesis induces a temporary retention of sodium and water (9), and many

### Table 2. Bioimpedance and body weight measured on day 6

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GH</th>
<th>Ibuprofen</th>
<th>GH + Ibuprofen</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioimpedance, $\Omega$</td>
<td>$441 \pm 28$</td>
<td>$401 \pm 15^*$</td>
<td>$449 \pm 26$</td>
<td>$388 \pm 17^*$</td>
<td>$&lt;0.005$</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>$79.9 \pm 4.0$</td>
<td>$81.2 \pm 3.8^*$</td>
<td>$80.2 \pm 4.0$</td>
<td>$82.9 \pm 4.2^*$</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE. $P$ values obtained by overall analysis of variance with repeated measurements (general linear model). $^*$Paired $t$-test for experimental group vs. control, $P < 0.05$.

### Table 3. Overall clearance values measured on day 6

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>GH</th>
<th>Ibuprofen</th>
<th>GH + Ibuprofen</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, ml-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$92.9 \pm 3.2$</td>
<td>$98.6 \pm 2.2$</td>
<td>$99.0 \pm 3.9$</td>
<td>$98.4 \pm 3.4$</td>
<td>$0.26$</td>
</tr>
<tr>
<td>$C_{Li}$, ml-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$27.7 \pm 2.4$</td>
<td>$35.2 \pm 1.8^*$</td>
<td>$24.8 \pm 3.7$</td>
<td>$32.1 \pm 2.8$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>PAR$_{Na}$, mmol-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$9.1 \pm 0.3$</td>
<td>$9.0 \pm 0.5$</td>
<td>$10.6 \pm 0.6$</td>
<td>$9.4 \pm 0.5$</td>
<td>$0.06$</td>
</tr>
<tr>
<td>PFR$_{Na}$, %</td>
<td>$70.4 \pm 1.9$</td>
<td>$64.0 \pm 2.3$</td>
<td>$75.3 \pm 3.4$</td>
<td>$67.2 \pm 2.9$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>DARR$_{Na}$, mmol-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$3.7 \pm 0.4$</td>
<td>$4.9 \pm 0.3^*$</td>
<td>$3.4 \pm 0.5$</td>
<td>$4.5 \pm 0.4$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>DARR$_{K}$, %</td>
<td>$96.3 \pm 0.6$</td>
<td>$97.2 \pm 0.9$</td>
<td>$95.1 \pm 0.9$</td>
<td>$97.4 \pm 0.8$</td>
<td>$0.15$</td>
</tr>
<tr>
<td>DARR$_{H_2O}$, ml-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$25.6 \pm 2.2$</td>
<td>$33.6 \pm 1.9^*$</td>
<td>$22.4 \pm 3.5$</td>
<td>$30.9 \pm 2.8$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>DFR$_{H_2O}$, %</td>
<td>$92.7 \pm 1.3$</td>
<td>$95.0 \pm 1.1$</td>
<td>$90.5 \pm 1.8$</td>
<td>$96.0 \pm 0.9$</td>
<td>$&lt;0.05$</td>
</tr>
<tr>
<td>$U_{NaV}$, mmol-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$0.14 \pm 0.04$</td>
<td>$0.12 \pm 0.03$</td>
<td>$0.16 \pm 0.03$</td>
<td>$0.09 \pm 0.02$</td>
<td>$0.27$</td>
</tr>
<tr>
<td>$U_{Kv}$, mmol-min$^{-1}$·1.73 m$^{-2}$</td>
<td>$0.06 \pm 0.02$</td>
<td>$0.06 \pm 0.02$</td>
<td>$0.07 \pm 0.02$</td>
<td>$0.06 \pm 0.01$</td>
<td>$0.39$</td>
</tr>
<tr>
<td>$V$, ml/min$^{-1}$·1.73 m$^{-2}$</td>
<td>$2.1 \pm 0.4$</td>
<td>$1.7 \pm 0.1$</td>
<td>$2.4 \pm 0.5$</td>
<td>$1.3 \pm 0.3$</td>
<td>$0.14$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE. GFR, glomerular filtration rate; $C_{Li}$, lithium clearance. See equations in text (Calculations and statistical methods) for other definitions. $P$ values obtained by overall analysis of variance with repeated measurements (general linear model). $^*$Paired $t$-test for experimental group vs. control, $P < 0.05$. 

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and sodium from the proximal tubules (32). From CLi, of lithium provides an estimate of the delivery of water part of the nephron. Consequently, the renal clearance proximal tubules in the same proportions as sodium treatments.

An original observation from this study is the increase in CLi caused by GH administration. Treatment with ibuprofen alone caused a minor decrease in CLi, and treatment with both GH and ibuprofen caused a smaller increase in CLi than treatment with GH alone. The decrease of CLi after ibuprofen may well be due to interference with the measurements of CLi, as PG synthesis inhibition has been reported to cause reabsorption of lithium distal to the proximal tubules (32). Consistent with this, the differences in CLi between the control and GH treatment periods are of the same order of magnitude as they are between the ibuprofen and ibuprofen plus GH periods. This implies that the GH-induced change in CLi is, in fact, unaffected by concomitant ibuprofen treatment.

The increase in CLi and the decrease in PFRNa after GH administration are most likely due to an increase of ECV, which is known to be a major determinant of proximal tubular fluid output (CLi) through its influence on the vascular filling pressures (31). Insulin has well-known antinatriuretic effects (27), and because insulin concentrations were significantly increased during both GH and GH plus ibuprofen treatment, one could speculate as to whether the observed changes in CLi could be mediated through insulin. In a study of insulin action on kidney function with the use of the euglycemic clamp technique, however, CLi remained unchanged with increased insulin levels (28). During GH treatment, DARNa was increased, which could account for the decrease of the mean 24-h sodium excretion, the observed increase in ECV and PV, and the increase of CLi.

The exact mechanisms behind the observed topographic alterations in sodium handling during GH administration remain unclarified in the current setup. In rat kidneys, the GH receptor (GHR) and IGF-I receptor gene expressions are topographically segregated (5). GHR mRNA is primarily expressed in the proximal straight tubule, whereas IGF-I receptor mRNA is predominantly expressed in the glomerulus, distal nephron, and collecting system. Despite the limited number of subjects in the present study, the data suggest that the sodium- and water-retaining effects of GH are exerted primarily at the level of the distal renal tubules. Consequently, these actions of GH could be mediated via IGF-I.

In summary, we have shown that the GH-induced activation of the RAAS, at least as judged by measurements of circulating renin and aldosterone, is transient and can be blocked by concomitant inhibition of PG synthesis. Furthermore, we conclude that GH administration stimulates reabsorption of sodium and fluid in the distal nephron, which may explain the increased proximal tubular fluid output (CLi) and the observed sodium and water retention.

We are indebted to Joan Hansen for skillful technical assistance, and to Jørgen Marquersen, Department of Nuclear Medicine, Aarhus KommuneHospital, for providing isotopes. Novo Nordisk A/S, Copenhagen, Denmark, generously supplied the growth hormone.
REFERENCES


