Effect of growth hormone on renal and systemic acid-base homeostasis in humans

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Sicuro, Anita, Katia Mahlbacher, Henry N. Hultner, and Reto Krapf. Effect of growth hormone on renal and systemic acid-base homeostasis in humans. Am. J. Physiol. 274 (Renal Physiol. 43): F650–F657, 1998.—The effects of recombinant human growth hormone (GH, 0.1 U·kg body wt−1·12 h−1) on systemic and renal acid-base homeostasis were investigated in six normal subjects with preexisting sustained chronic metabolic acidosis, induced by NH₄Cl administration (4.2 mmol·kg body wt−1·day−1). GH administration increased and maintained plasma bicarbonate concentration from 14.1 ± 1.4 to 18.6 ± 1.1 mmol/l (P < 0.001). The GH-induced increase in plasma bicarbonate concentration was the consequence of a significant increase in net acid excretion that was accounted for largely by an increase in renal NH₄⁺ excretion sufficient in magnitude to override a decrease in urinary titratable acid excretion. During GH administration, urinary pH increased and correlated directly and significantly with urinary NH₄⁺ concentration. Urinary net acid excretion rates were not different during the steady-state periods of acidosis and acidosis with GH administration. Glucocorticoid and mineralocorticoid activities increased significantly in response to acidosis and were suppressed (glucocorticoid) or decreased to control levels (mineralocorticoid) by GH. The partial correction of metabolic acidosis occurred despite GH-induced renal sodium retention (180 mmol; gain 0.2 kg, P < 0.005) and decreased glucocorticoid and mineralocorticoid activities. Thus GH (and/or insulin-like growth factor I) increased plasma bicarbonate concentration and partially corrected metabolic acidosis. This effect was generated in large part by and maintained fully by a renal mechanism (i.e., increased renal NH₄⁺ production and NH₄⁺/net acid excretion).

metabolic acidosis; renal acidification; glucocorticoid; ammoniagenesis

CHRONIC METABOLIC ACIDOSIS (CMA) has profound effects on the growth hormone (GH)/insulin-like growth factor I (IGF-I) endocrine axis in humans. We have reported recently that NH₄Cl-induced CMA results in decreased IGF-I serum concentrations and an apparent insensitivity to the peripheral action of GH (9). Both reduced IGF-I concentration and GH insensitivity could mediate some of the sequelae of CMA such as the induction of negative nitrogen balance (3). Since GH/IGF-I is a potent stimulus to renal sodium reabsorption (5, 19) and since augmented renal sodium reabsorption can stimulate net acid excretion and reduces the severity of (or even abrogates) CMA (14), it is conceivable that the CMA-induced derangements of the GH/IGF-I endocrine axis might modulate the systemic and renal acid-base response to CMA itself.

Several hormones have been shown to cause a sustained increase in plasma bicarbonate concentration by a renal mechanism: mineralocorticoid (30), glucocorticoid (21), and parathyroid hormone (PTH) (22), as well as 1,25-dihydroxycholecalciferol (23), have all been shown to stimulate renal acid excretion and increase plasma bicarbonate concentration if hypersecreted or administered in large doses. However, such an effect has not been reported for GH/IGF-I.

GH administration might affect acid-base equilibrium by several renal mechanisms. First, GH might increase acid excretion by augmenting ammonia production, as suggested by studies in isolated canine proximal tubules (11). Second, based on preliminary data from cell culture models, proximal tubule hydrogen ion secretion might be increased by GH and/or IGF-I–induced stimulation of the luminal Na/H antiporter (NHE3; Refs. 2 and 24). Third, GH administration is known to result in sodium retention (5, 19; for review see Ref. 15) and could, thereby, secondarily stimulate distal proton secretion. Although no effect of GH/IGF-I on overall proximal tubule sodium transport was found (29), IGF-I has been shown to activate sodium channels in A-6 cells, a distal tubule-derived cell line (17) and to stimulate transepithelial sodium transport in the toad bladder (6), a model of the mammalian collecting duct. Thus both proximal and distal effects might be expected to stimulate sodium-dependent renal net acid excretion.

The present studies were therefore designed to evaluate the effects of sustained recombinant human GH administration on the renal and systemic regulation of acid-base homeostasis. To this end, the effects of prolonged GH administration were examined in human subjects with preexisting NH₄Cl-induced CMA.

METHODS

To assess the effects of recombinant human GH on the renal and systemic regulation of acid-base homeostasis in preexisting NH₄Cl-induced metabolic acidosis, six normal male subjects were examined under metabolic balance conditions. None were smokers, nor were they taking any drugs before or during the study. They ingested a constant metabolic diet during the three study periods (control, acidosis, and acidosis with GH administration). The diet was calculated to provide, per kilogram of body weight per day (in mmol): 1.8 sodium, 1.1 potassium, 44.4 ml water, and 36 kcal.

To characterize the acid-base and electrolyte status, 24 h urines were collected, and fasting arterial blood samples (16) were obtained in a heparin-coated syringe from a heated hand or forearm vein at 7 AM. Blood samples were accepted if the partial pressure of oxygen was >70 mmHg (9.3 kPa). For hormonal analysis, daily blood samples were obtained in the fasting state at 7 AM, and samples were kept on ice until centrifuged at 4°C. The serum samples were stored at −20°C until analyzed.

All subjects volunteered for the study, were paid for their participation, and gave written informed consent. The study
Table 1. Steady-state plasma acid-base and electrolyte composition during control and experiment

<table>
<thead>
<tr>
<th>Period</th>
<th>H⁺ (nmol/l)</th>
<th>Pco₂ (mmHg)</th>
<th>HCO₃⁻ (mmol/l)</th>
<th>Unmeasured Anions (mmol/l)</th>
<th>Na⁺ (mmol/l)</th>
<th>K⁺ (mmol/l)</th>
<th>Cl⁻ (mmol/l)</th>
<th>CO₃²⁻ (mmol/l)</th>
<th>Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>39.4±0.8</td>
<td>39.7±0.6</td>
<td>24.2±0.7</td>
<td>14.5±0.5</td>
<td>131.4±0.7</td>
<td>1134±1.3†</td>
<td>36.6±0.1†</td>
<td>109.5±1.4</td>
<td>69.2±1.5†</td>
</tr>
<tr>
<td>Acidosis</td>
<td>50.9±0.8*</td>
<td>30.8±0.9*</td>
<td>14.1±1.4*</td>
<td>13.1±0.7</td>
<td>144.2±0.8</td>
<td>1134±1.3†</td>
<td>3.6±0.1†</td>
<td>109.5±1.4</td>
<td>67.6±1.6†</td>
</tr>
<tr>
<td>Acidosis + GH</td>
<td>44.5±0.5*</td>
<td>33.7±0.8†</td>
<td>18.6±1.1*</td>
<td>12.4±0.7</td>
<td>144.0±1.0</td>
<td>109.5±1.4</td>
<td>3.5±0.1</td>
<td>24.6±0.20†</td>
<td>69.4±1.7†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pco₂, arterial carbon dioxide tension. To convert values for Pco₂ to kilopascals, multiply by 0.1333.

Unmeasured anions were calculated as $(Na^+ + K^+ + NH_4^+ - [Cl^- + HCO_3^-])$ mmol per liter. GH, growth hormone. *P < 0.001 compared with previous steady-state period. †P < 0.005 compared with previous steady-state period.

Protocol was approved by the ethics committee of the Kantonsspital, St. Gallen, Switzerland.

Experimental design. After establishment of the control period metabolic steady-state [variation of plasma bicarbonate concentration by no more than 1.5 mmol/l and by 3 mmHg (0.4 kPa) for Pco₂ during at least 4 days], CMA was induced by oral administration of NH₄Cl (4.2 mmol·kg body wt⁻¹·day⁻¹) in gelatin capsules in six divided doses. On day 8, recombinant human GH (Genotropin, 0.1 U/kg body wt every 12 h; Kabi Pharmacia) was administered subcutaneously with continued acid feeding, and observations were carried out for eight additional days.

Analytical procedures. Analysis of plasma and urine electrolyte and acid-base composition was performed as described previously (26). IGF-I was determined radiimmunometrically after acid-ethanol extraction of serum (7). Serum and urinary aldosterone (aldosterone-18-glucuronide in urine) and cortisol were measured by gas chromatography. Urinary unmeasured anion excretion was calculated as $((Na^+ + K^+ + NH_4^+) - ([Cl^- + HCO_3^-]), P, valence was calculated by the method of Bank and Schwartz (4).

All steady-state values (acid-base, electrolyte and endocrine) represent the means of the last 3 days of the corresponding study periods.

RESULTS

All subjects tolerated the protocol well. In agreement with our previous observations (9), serum IGF-I concentration decreased from 36.4 ± 2.2 during control to 22.1 ± 1.4 mmol/l (P < 0.005) during acidosis. GH administration during continued acidosis increased serum IGF-I concentration significantly to 87.0 ± 8.4 mmol/l (P < 0.001 compared with acidosis). Table 2 depicts the characteristic natriuresis and kaliuresis of extrarenal CMA (5, 25). As shown and illustrated in Fig. 1 and Table 1, mean body weights decreased significantly by 1.6 ± 0.2 kg during acidosis (P < 0.005). As described previously by others and us (27, 35), this weight loss was accounted for by acidosis-induced negative sodium balance of 315 mmol for the 7-day acidosis period. Despite continued NH₄Cl feeding, GH administration induced a significant gain in weight of 1.8 ± 0.2 kg (P < 0.005), accounted for in part by a large GH-induced sodium retention (3, 4) of 180 mmol (P < 0.025) for the 8 days of GH treatment (Table 2; Fig. 1).

In comparison with the control period, neither acidosis nor GH administration during acidosis affected blood pressure significantly. None of the subjects developed edema during GH administration.

Table 1 and Fig. 2 depict the changes in plasma acid-base composition during control, acidosis, and acidosis with GH administration periods. GH decreased blood hydrogen ion concentration significantly from 50.9 ± 0.8 to 44.5 ± 0.5 mmol/l (P < 0.001) and induced a large and significant increase in plasma
bicarbonate concentration from 14.1 ± 1.4 to 18.6 ± 1.1 mmol/l (P < 0.001). Plasma unmeasured anion concentration did not change significantly in response to GH.

The effects of GH administration during acidosis on urinary acid-base composition are shown in Table 2 and illustrated in Fig. 3. GH raised urinary pH significantly from 5.37 ± 0.04 to 5.58 ± 0.05 U (P < 0.005). NH₄⁺ excretion increased significantly during the first 3 days of GH administration, resulting in a significant increase in the cumulative change in NH₄⁺ excretion of +194 mmol for the 8-day GH period (P < 0.025). Titratable acid excretion decreased cumulatively by 82 mmol, which was significantly elevated during the GH period [not significant (NS)]. Net acid excretion increased significantly during the first 3 days of GH administration, resulting in a significant increase in net acid excretion of 112 mmol for the 8-day GH period (P < 0.001). Despite the large magnitude of potassium excretion in response to GH administration, the first days during which plasma bicarbonate concentration increased significantly, whereas net acid excretion during the steady state (days 6–8) of GH administration was not significantly different from the steady-state values during acidosis prior to GH administration (Table 2). Thus the GH-induced increase in plasma bicarbonate concentration was accounted for largely by a renal mechanism, and its maintenance was fully accounted for by a renal mechanism. Steady-state urinary unmeasured anion excretion, an index of organic anion excretion (21), was not different during acidosis and acidosis with GH administration.

Table 2. Urinary acid-base and electrolyte composition during control and experiment

<table>
<thead>
<tr>
<th>Study Period</th>
<th>pH</th>
<th>NH₄⁺ mmol/24 h</th>
<th>Titratable Acidity mmol/24 h</th>
<th>HCO₃⁻</th>
<th>Net Acid mmol/24 h</th>
<th>Na⁺ mmol/24 h</th>
<th>K⁺ mmol/24 h</th>
<th>Cl⁻ mmol/24 h</th>
<th>Unmeasured Anions mmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.21 ± 0.16</td>
<td>49 ± 4</td>
<td>13 ± 1</td>
<td>0.3 ± 0.4</td>
<td>62 ± 5</td>
<td>129 ± 3</td>
<td>70 ± 3</td>
<td>126 ± 4</td>
<td>91 ± 9</td>
</tr>
<tr>
<td>Acidosis</td>
<td>5.37 ± 0.04*</td>
<td>328 ± 12*</td>
<td>38 ± 3†</td>
<td>0.2 ± 0.4</td>
<td>365 ± 12*</td>
<td>128 ± 7</td>
<td>86 ± 5†</td>
<td>417 ± 8°</td>
<td>84 ± 14</td>
</tr>
<tr>
<td>Δ (day 7)</td>
<td>+194†</td>
<td>-82§</td>
<td>0</td>
<td>+315‡</td>
<td>+307‡</td>
<td>-180§</td>
<td>-385$</td>
<td>-148§</td>
<td>-98</td>
</tr>
<tr>
<td>Acidosis + GH</td>
<td>5.58 ± 0.05†</td>
<td>332 ± 14</td>
<td>29 ± 2†</td>
<td>0.2 ± 0.5</td>
<td>364 ± 14</td>
<td>130 ± 7</td>
<td>39 ± 3†</td>
<td>412 ± 11</td>
<td>75 ± 15</td>
</tr>
</tbody>
</table>

Values are means ± SE; Δ denotes the cumulative change in excretion, calculated as the accumulated sum of the daily differences (or deltas) from the previous steady-state period. *P < 0.001 compared with previous steady-state period; †P < 0.025 compared with previous steady-state period; ‡Significantly different from zero (P < 0.001). §Significantly different from zero (P < 0.025).

Renal H⁺ secretion per 24 h was calculated as the sum of net acid excretion per 24 h plus bicarbonate reabsorbed per 24 h, utilizing creatinine clearance (Table 1) as an estimate of glomerular filtration rate (GFR). Renal H⁺ secretion averaged 2,570 ± 115 mmol/day during acidosis and increased significantly to 3,953 ± 109 mmol/day (P < 0.001) during acidosis with GH treatment.

Figure 4 illustrates a strong direct correlation of urine pH with urinary NH₄⁺ concentration during acidosis, both without and with GH administration (r = 0.736, P < 0.001), suggesting that increased NH₃ production rather than increased trapping of NH₃ into a more acidic (distal) tubular lumen accounted, at least in part, for the increase in NH₄⁺ excretion in response to GH (25).

Figure 5 and Tables 1 and 2 illustrate and confirm our previous findings that CMA induces renal hypokalemia in humans (26). However, as depicted by Fig. 5 and Table 2, GH administration resulted in a large and significant sustained decrease in urinary potassium excretion. The cumulative decrease in potassium excretion during GH administration averaged 385 mmol (P < 0.001). Despite the large magnitude of potassium retention, plasma potassium concentration was not altered significantly by GH and hypokalemia persisted (Table 1; Fig. 5). Thus potassium might have undergone cellular accumulation as a result of the effect of GH to induce a positive nitrogen balance.
Figure 6 depicts the effect of acidosis and of acidosis with GH administration on mineralocorticoid and glucocorticoid activities. In response to acidosis, plasma aldosterone concentration increased significantly from 20.0 ± 1.6 to 54.4 ± 3.8 ng/dl (P < 0.005). GH with continued acidosis significantly decreased plasma aldosterone concentration to control levels (18.9 ± 2.5 ng/dl, P < 0.005 compared with acidosis without GH). Similarly, urinary aldosterone excretion increased significantly from 14 ± 3 to 58 ± 15 µg/day during acidosis and decreased to 15 ± 4 µg/day during acidosis and GH (for both comparisons, P < 0.005).

Figure 6 also depicts the significant increments in urinary excretion rates of cortisol and its metabolite, tetrahydrocortisol (THF), during acidosis and subsequent decreases in response to GH administration. Cortisol excretion increased from 29 ± 6 to 46 ± 10 µg/24 h during acidosis (P < 0.025) and decreased to 23 ± 5 µg/24 h during acidosis and GH (P < 0.025 in comparison to acidosis without GH; NS in comparison to control). THF excretion averaged 1,695 ± 185 µg/day during control, increased significantly to 2,131 ± 211 µg/day during acidosis (P < 0.025), and decreased to 1,243 ± 124 µg/day in response to GH (P < 0.005). The excretion value during acidosis with GH treatment was significantly lower than during the control period (P < 0.05). Plasma cortisol concentration averaged 18.9 ± 1.7 and 19.3 ± 1.6 µg/dl during control and acidosis, respectively (NS). During acidosis with GH, plasma cortisol concentration decreased significantly to 14.5 ± 1.3 (P < 0.05 in comparison to both control and acidosis without GH).

Figure 6 also illustrates that the ratio of the sum of THF and allo-THF to tetrahydrocortisone (THE) excretion was not affected significantly by either acidosis or acidosis with GH administration, suggesting that neither circumstance resulted in an altered intrarenal conversion of cortisol to cortisone and thus altered mineralocorticoid receptor occupancy by cortisol.

**DISCUSSION**

These studies report the effects of GH administration on the renal and systemic regulation of acid-base homeostasis. They also report the effects of metabolic acidosis on mineralocorticoid and glucocorticoid activities in humans. The novel and key findings are 1)
chronic GH administration results in an increase in plasma bicarbonate concentration, generated in large part by a significant increase in renal acid excretion and maintained by a large increase in renal hydrogen ion secretion; 2) the increase in renal acid excretion is the result of augmented NH₃ production and excretion of sufficient magnitude to override the concomitant decrease in titratable acid excretion; and 3) glucocorticoid (and mineralocorticoid) activity are enhanced in human CMA, and GH suppresses glucocorticoid and normalizes mineralocorticoid activities in preexisting CMA in humans.

Is the GH/IGF-I effect direct or mediated by other endocrine systems? GH/IGF-I is thus the fifth class of hormones beside mineralocorticoid, glucocorticoid, and PTH, as well as 1,25-dihydroxycholecalciferol, that, when administered in large doses or hypersecreted, results in a sustained increase in the plasma bicarbonate concentration by a renal mechanism (21–23, 30). The finding that GH administration resulted in large increases in the rates of renal hydrogen secretion and sodium chloride reabsorption, sufficient to cause 1) an increase in net acid excretion despite reclamation of an increased filtered load of bicarbonate and 2) an expanded extracellular fluid volume, as evidenced by weight gain and sodium retention despite an increased filtered sodium load, cannot be explained by the effects of enhanced mineralo- or glucocorticoid activities which decreased in response to GH (Fig. 6). In addition, there was no evidence for inhibition of the renal conversion of cortisol to cortisone inasmuch as the ratio of THF/TE was not affected by GH administration (Fig. 6). PTH and/or 1,25-dihydroxycholecalciferol are also unlikely mediators of the response to GH. Serum intact PTH concentrations show little variation, and 1,25-dihydroxycholecalciferol concentrations increase only slightly and transiently in response to GH (8, 10, 31). The present studies thus reveal that GH or hormones for which it acts as secretagogue have substantial and novel potency to stimulate renal acidification and, thereby, result in a sustained increase in plasma bicarbonate concentration.

Effect of GH/IGF-I on renal sodium and potassium handling. Although natriuresis and chloruresis were
observed during triamcinolone-, PTH-, and 1,25-
dihydroxycholecalciferol-induced increases in plasma
bicarbonate concentration (21–23), the present studies
confirm the substantial antinatriuresis of GH (5, 19),
raising the possibility that, as in chronic mineralocorti-
coid-stimulated renal acidification (18), augmented re-
nal sodium reabsorption (Fig. 1; Table 2) is prerequisite
to the enhanced hydrogen ion excretion in response
to GH.

GH-induced stimulation of renal acidification ap-
ppears unique for its concomitant effect to induce potas-
sium retention (Fig. 5). The most likely mechanism for
this phenomenon is that potassium might have under-
gone cellular accumulation as a result of the anabolic
effect of GH. However, we are not able to discern addi-
tional small effects of GH on renal regulation of
cell potassium homeostasis, because of the imperfections
of the metabolic balance technique and because stool
content was not analyzed.

Possible mechanisms of GH/IGF-I-stimulated renal
acidification. Although the mechanism(s) and nephron
group(s) responsible for the observed stimulation of
renal acidification remain to be elucidated, our results
provide substantial insights. The observed increase in
renal net acid excretion was due almost exclusively to
a large and significant increase in urinary NH4+
excretion, sufficient in magnitude to offset a reduction in
urinary titratable acid excretion (Fig. 3; Table 2),
which, in turn, occurred despite both a significant
increase in urine pH and a significant decrease in
urinary phosphate available for titration by renal hydro-
gen ion secretion. Preliminary evidence has been re-
ported from several cell culture models consistent with
a possible role for either GH or IGF-I to increase both
proximal and distal sodium-dependent acidification by
cellular mechanisms (2, 6, 17, 24; see introduction).
Utilizing a model of proximal tubule acidification, the
ex vivo isolated perfused rat kidney, addition of GH but
not IGF-I to perfusate stimulated net hydrogen ion
secretion and NH4+ excretion, even when corrected for
increased filtered bicarbonate load (33). This finding
consistent with the results reported herein that renal
hydrogen ion secretion is increased by GH. Our find-
ings do not exclude the possibility that GH-associated,
GFR-induced increments in luminal flow or increased
luminal bicarbonate concentration might account for
our observations in the absence of enhancement of
specific cellular proton transporter number or activity.
Interestingly, the above cellular transport mechanisms
do not account for the present observation of a signifi-
cant increase in urine pH, in the absence of a simulta-
nous GH-induced increase in renal ammonia produc-
tion. Even if GH enhanced proximal luminal entry of
NH4+ (i.e., substitution of NH4+ for H+ on the apical
Na/H antiporter NHE3), luminal entry of NH2 at that
site would not be expected to result in an increased
urine pH, unless such a process also increased peritubu-
lar or cellular NH3 concentration (i.e., increased renal
NH3 production), providing for a greater supply of NH3
for diffusion into the lumen, raising distal luminal pH
by virtue of the property of NH3 as a base.

During both combined periods of CMA, urine pH
correlated directly and significantly with urinary ammo-
nium concentration (Fig. 4). Thus, over the range of
ammonium values reported, a GH-induced stimulation
of NH3 production can be inferred, since increments in
urinary pH are accounted for by NH3 buffer variation
direct pH-NH3 relation) rather than by increased
trapping of NH3 in an increasingly acidic lumen (in-
verse relation, see Ref. 25). Nevertheless, the results of
in vitro studies reveal divergent results regarding the
ability of GH to augment renal ammonia production.
Studies in suspensions of isolated canine proximal
tubules have shown significant GH-induced increments
in ammonia production and Na-K-ATPase activity (11).
On the other hand, studies in ex vivo isolated perfused
kidneys from hypophysectomized rats using high perfus-
ate concentrations of glutamate and glutamine have
shown significant GH-induced decrements in ammonia
production (33). Utilizing cultured LLC-PK1 cells (de-
pired from porcine proximal tubule), GH addition re-
sulted in an increase in ammonia production in cells
grown on plastic, but not when grown on semiperme-
able supports (34). Reconciliation of in vitro results
with the present in vivo demonstration of increased
NH3 production will require further investigation.

Since GH administration in the present studies did
not alter steady-state net acid excretion (equivalent to
effective endogenous acid production), the increased
plasma bicarbonate concentration and increased fil-
tered bicarbonate load were maintained by a renal
mechanism(s). A renal mechanism also accounted,
that part, for the generation of the increment in
plasma bicarbonate concentration, because the cumula-
tive increase in GH-induced net acid excretion ac-
counted for about two-thirds of the observed incre-
ment in plasma bicarbonate concentration, based on a
50% of body weight effective space of distribution for bicar-
bonate. Moreover, this effect occurred despite ongoing
expansion of the extracellular fluid volume resulting
from the effect of GH to cause greatly positive sodium
and chloride balances.

Effect of acidosis and GH/IGF on gluco- and miner-
alocorticoid activities. The results of the present stud-
ies provide the first evidence in humans that CMA, per
se, results in hypersecretion of cortisol. These results
are consistent with the finding in rats that CMA results
in augmented urinary excretion of cortisol, the
major glucocorticoid steroid in that species (28). Our
results demonstrate hypercortisolism, as manifested
by significant increases in the urinary excretion rates
of both cortisol and its tetrahydro metabolite (THF).
Since THF is neither secreted nor reabsorbed in the
renal tubule (13), altered tubular handling such as
could occur in the case of cortisol cannot account for
increments in THF excretion. We have reported previ-
ously a nonsignificant, 77% increase in urinary cortisol
excretion in acid-fed compared with non-acid-fed hu-
man subjects (26). However, the unpaired design in
that study made detection of significant differences
more difficult than in the present study, where each
subject served as his own control. The finding that fasting
morning plasma cortisol concentration was not altered significantly by CMA suggests that hypersecretion of cortisol occurred during other time points within the 24-h diurnal secretory cycle. The finding of hyperaldosteronism, presumably secondary to CMA-induced renal sodium chloride losses, is consistent with our and other previous reports (26, 32).

GH administration during acidosis resulted in large and significant reductions in 7 AM plasma cortisol concentration and urinary cortisol and THF excretion rates (Fig. 6), significantly below those found prior to induction of acidosis-induced hypercortisolism. Thus GH administration resulted in a state of glucocorticoid deficiency. Since the present studies establish in humans that CMA results in a hyperglucocorticoid state and since glucocorticoid excess results in protein catabolism and negative nitrogen balance, the recent report that protein catabolism produced by glucocorticoid excess in humans can be reversed by GH administration (20) is germane to our results. The potential role of hyperglucocorticoidism in the nitrogen wasting of CMA and the role of GH-induced glucocorticoid deficiency in the reversal of the nitrogen wasting will await further investigation.

Summary and conclusions. GH (and/or IGF-I) increases renal net acid excretion and thereby increases plasma bicarbonate concentration with resultant partial correction of preexisting CMA in humans. The increased bicarbonate concentration is accounted for, in large part, by a renal mechanism. The maintenance phase of the sustained elevation in plasma bicarbonate concentration was also accounted for by a renal mechanism since effective endogenous acid production was unchanged (reflected by steady-state net acid excretion) and the filtered bicarbonate load was increased. Thus increased renal proton secretion maintains plasma bicarbonate at an increased level and filtered load during the steady state. The increase in renal acid excretion is accounted for by increased \(\text{NH}_4^+\) excretion. Increased GH-induced ammonia production appears to contribute to the acid excretory response. CMA induces hyperglucocorticoidism (and hypermineralocorticidism) in humans. Correction of CMA in response to GH occurred despite frankly suppressed glucocorticoid and decreased mineralocorticoid activities and in the absence of evidence for enhanced mineralocorticoid receptor occupancy by cortisol. The previously described derangements of the GH/IGF-I endocrine axis in CMA (decreased IGF-I concentration, GH insensitivity) might thus codetermine the renal response to acidosis and, thereby, the severity of acidosis itself.

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REFERENCES


