Chronic Metabolic Acidosis Decreases Albumin Synthesis and Induces Negative Nitrogen Balance in Humans

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Abstract

Chronic metabolic acidosis has been previously shown to stimulate protein degradation. To evaluate the effects of chronic metabolic acidosis on nitrogen balance and protein synthesis we measured albumin synthesis rates and urinary nitrogen excretion in eight male subjects on a constant metabolic diet before and during two different degrees of chronic metabolic acidosis (NH_4Cl 2.1 mmol/kg body weight, low dose group, and 4.2 mmol/kg body weight, high dose group, orally for 7 d). Albumin synthesis rates were measured by intravenous injection of [$^2H_5$ring]phenylalanine (43 mg/kg body weight, 7.5 atom percent and 15 atom percent, respectively) after an overnight fast. In the low dose group, fractional synthesis rates of albumin decreased from $9.9\pm1.0\%$ per day in the control period to 8.4 ± 0.7 (n.s.) in the acidosis period, and from $8.3\pm1.3\%$ per day to 6.3 ± 1.1 ($P < 0.001$) in the high dose group. Urinary nitrogen excretion increased significantly in the acidosis period ($\Sigma\Delta$ 634 mmol in the low dose group, 2,554 mmol in the high dose group). Plasma concentrations of insulin-like growth factor-I, free thyroxine and tri-iodothyronine were significantly lower during acidosis. In conclusion, chronic metabolic acidosis causes negative nitrogen balance and decreases albumin synthesis in humans. The effect on albumin synthesis may be mediated, at least in part, by a suppression of insulin-like growth factor-I, free thyroxine and tri-iodothyronine. (*J. Clin. Invest.* 1995. 95:39–45.) Key words: albumin • metabolic acidosis • protein synthesis • nitrogen balance • insulin-like growth factor-I

Introduction

Chronic metabolic acidosis is associated with severe growth retardation in humans and rats (1–4), and an increase in muscle protein degradation in rats (5–7). A putative causal role of metabolic acidosis in the development of whole body protein catabolism is supported by the fact that alkali-induced correction of metabolic acidosis normalized growth in children with

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renal tubular acidosis (4) and improved nitrogen balance significantly in acidotic patients with moderate to severe chronic renal insufficiency (8).

In dogs, HCl-induced acute metabolic acidosis increased leucine oxidation and plasma concentrations of essential and non-essential amino acids, whereas alkalosis, induced by $NaHCO_3$ infusion, had the opposite effect (9). Chronic mineral acidosis accelerated both whole body protein degradation and oxidation in rats (7). Moreover, chronic metabolic acidosis in rats has also been suggested to result in negative nitrogen balance based on isolated 24 or 48 h urinary nitrogen excretion values (10, 11).

In humans, the influence of sustained metabolic acidosis per se on protein or nitrogen metabolism has not been reported. However, prolonged fasting associated with ketoacidosis was shown to induce protein wasting resulting in increased nitrogen excretion in obese subjects (12). Moreover, wasting of lean body mass is a common feature in patients with chronic uremic acidosis (13). The increase in whole body protein degradation reported in acute (14) and chronic (15) mineral acidosis in normal subjects might be an important pathogenic factor responsible for the loss of lean body mass in human uremia. In addition, the subjects with chronic mineral acidosis were also reported to exhibit a simultaneous increase in whole body protein synthesis and leucine oxidation in the post-absorptive state (15). However, the effects of pure sustained metabolic acidosis, in the absence of other metabolic abnormalities, on 24 h nitrogen balance have not previously been reported in humans.

Skeletal muscle protein degradation has been reported to play a quantitatively important role in whole body protein catabolism in metabolic acidosis and can be normalized by systemic alkali administration in rats with uremic acidosis (6, 11). In cultured myocytes in vitro, where protein degradation was enhanced in acidified media, protein synthesis decreased by nearly 30% when pH was lowered from 7.4 to 7.2, and increased to nearly 130% at pH 7.6 (16). In addition, acute respiratory acidosis has been reported to decrease muscle protein synthesis in rats (17), whereas increasing extracellular pH over the range 7.4 to 8.9 stimulated protein synthesis by nearly 60% in the working TRIS or Hepes-buffered perfused rat heart (18). Even the effect of severe chronic renal insufficiency (acidosis presumed) on muscle protein synthesis remains controversial as both decreased (5, 19) and normal rates have been reported (20).

The effects of metabolic acidosis on nonmuscle proteins, such as albumin, may contribute substantially to nitrogen imbalance in chronic metabolic acidosis. The synthesis of albumin, the most abundant hepatic secretory protein, is decreased in various clinically important conditions, e.g., septicemia or trauma (21). Metabolic acidosis accompanies many of these

conditions, but its contribution to the decrease in protein/albumin synthesis has not been reported in any species.

Therefore, the aims of the present study were to investigate the independent effects of chronic extrarenal (NH_4Cl-induced) metabolic acidosis on nitrogen metabolism and albumin synthesis in normal human subjects.

Methods

Albumin synthesis rates and urinary nitrogen excretion were measured in eight healthy male subjects in a dedicated metabolic room with controlled regular intake of meals, that were part of another metabolic study (22), before and during NH_4Cl-induced metabolic acidosis. All subjects ingested a constant metabolic diet for at least 5 d before the base-line measurements and throughout the experiment. The diet contained 2,800 kcal, 17.7 g (1263 mmol) nitrogen and 3.448 L of water per kg body weight per day. Diet nitrogen was verified by direct analysis. Nitrogen intake by direct assay was found to be higher than the value of 14.2 g estimated previously from nutrition tables (22).

Experimental design. After the baseline measurements of albumin synthesis and urinary nitrogen excretion at the end of the control period, two different levels of metabolic acidosis were induced by oral NH_4Cl administration. Four subjects (30±6.4 yr, mean±SD) were fed 2.1 mmol NH_4Cl per kg body weight in gelatine capsules divided in six doses (low dose group), whereas the other four subjects (27.3±7.3 yr) received 4.2 mmol NH_4Cl/kg daily in six divided doses (high dose group). Albumin synthesis rates were again measured after 7 d of NH_4Cl ingestion, when a new acid-base steady-state was obtained in all subjects. Nitrogen excretion rates were measured daily during acidosis.

Measurement of albumin synthesis rates. Albumin synthesis rates were measured after an overnight fast by flooding with [$^2H_5$ring]-phenylalanine, as described previously (23, 24). In brief, 43 mg of [$^2H_5$ring]phenylalanine (Tracer Technologies, Sommerville, MA) per kg body weight with an isotopic enrichment of 7.5 atom percent in the first measurement, and 15 atom percent in the second measurement were intravenously injected over 10 min. The [$^2H_5$ring]phenylalanine was mixed with unlabeled L-phenylalanine (Merck, Darmstadt, Germany) in 0.45% NaCl and the solution sterile filtered by the hospital pharmacy. Blood samples were drawn from the opposite cubital vein at 10-min intervals up to 90 min. Plasma samples were stored at −20°C. After thawing, albumin was isolated by ethanol extraction from trichloroacetic acid precipitated plasma proteins as described previously (23, 25, 26). In every subject the purity of the albumin isolates was checked by SDS-gel electrophoresis indicating a single band corresponding to human albumin. After repeat washes with 0.2 mol/liter perchloric acid, the albumin was hydrolyzed in 6 mol/liter HCl for 24 h at 105–110°C. The hydrolysates were purified by washing with distilled water and then dried down in a stream of N_2. Phenylalanine was converted to β-phenethylamine by enzymatic conversion with tyrosine decarboxylase (Sigma, Poole, Dorset, UK) and the enrichment of the heptafluorobutyryl derivative of β-phenethylamine was measured on a VG 12-250 quadrupole mass spectrometer under electron impact ionisation (VG Masslab, Manchester, UK) as described previously (24, 27). The plasma free phenylalanine enrichment, reflecting the precursor pool for albumin synthesis, was determined by gas chromatography mass spectrometry on the VG 12-250 mass spectrometer, using the tertiary butyldimethylsilyl derivative and electron impact ionisation (28).

Calculation of albumin synthesis rates. Albumin synthesis was calculated as a fractional synthesis rate (FSR)[1] (percent/day), i.e., the percentage of the intravascular albumin mass synthesized per day (23). The FSR was calculated by dividing the increase in [$^2H_5$ring]-

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1. *Abbreviations used in this paper:* FSR, fractional synthesis rate; HDG, high-dose group; LDG, low-dose group; fT_4, free plasma thyroxin; T_3, tri-iodthyronine; TSH, thyroid-stimulating hormone.

Table I. Characteristics of Subjects

	Control		Acidosis	
	Weight	Plasma albumin	Weight	Plasma albumin
Low dose group				
1	65.1	43	64.1	41
2	53.8	45	53.4	47
3	61.2	43	60.5	42
4	62.0	46	60.9	43
Mean±SD	60.5±4.8	44.3±1.5	59.7±4.5‡	43.3±2.6
High dose group				
5	66.4	42	65.2	42
6	76.2	43	73.7	42
7	56.5	47	53.5	45
8	58.3	47	57.4	46
Mean±SD	64.4±9.0	44.8±2.6	62.5±8.9*	43.8±2.1
Total	62.4±7.0	44.5±2.0	61.1±6.7	43.5±2.2

Body weight (in kg) and plasma albumin concentrations (in g/liter) of the subjects in the control period and during metabolic acidosis. *P = 0.033; $^\ddagger P$ = 0.015 versus control period.

phenylalanine enrichment in albumin by the area under the curve of the precursor enrichment, from the equation (23, 29, 30):

$$FSR = (P_2 - P_1) \times 100/A$$

where P_2 is the isotopic enrichment of phenylalanine in albumin at 90 min, and P_1 at 50 min. The area under the curve for the precursor enrichment was calculated by summation of the areas between successive measurement points on the curve of the plasma free phenylalanine enrichment. The appropriate section of the curve was determined by subtracting one secretion time, i.e., the time between start of injecting the label and the appearance of the first enriched albumin molecules, because the albumin molecules appearing at the time corresponding to P_1 were synthesized one secretion time earlier.

Urinary nitrogen excretion. In all subjects 24-h urine was collected for 4 d in the control period and for 7 d during NH_4Cl administration. 24-h nitrogen excretion was determined photometrically after wet incineration followed by formation of indophenol with salicylate and hypochlorite in triplicate (31). The reported changes in urinary nitrogen excretion are corrected for the change in nitrogen intake (as NH_4Cl) by subtraction.

Other measurements. Plasma albumin concentrations were determined with bromcresol purple. Plasma acid-base composition was determined in arterialized venous blood samples as described previously (22, 32, 33).

Plasma concentrations of insulin-like growth factor-I (IGF-I), free thyroxin (fT_4), tri-iodothyronine (T_3) and of thyroid-stimulating hormone (TSH) were measured by standard radio-immuno-assay methods.

Statistics. The results are given as means±SD. Statistical comparisons were performed using the paired Student's t test (two-tailed) with a significance level of $P < 0.05$.

The study protocol was approved by the ethics committee of the University of Berne School of Medicine.

Results

All subjects tolerated the study well. In Table I body weights and plasma albumin concentrations are summarized. All subjects in both groups lost weight in response to NH_4Cl administration. Plasma albumin concentration decreased significantly

Table II. Blood Acid–Base Composition

	Control			Acidosis		
	pH	pCO₂	HCO₃⁻	pH	pCO₂	HCO₃⁻
Low dose group						
1	7.425	37.6	24.3	7.357	29.9	16.2
2	7.439	35.6	24.0	7.361	34.1	19.5
3	7.416	35.0	23.6	7.329	32.5	19.7
4	7.445	37.7	25.9	7.390	35.0	21.1
Mean±SD	7.431±0.013	36.5±1.4	24.5±1.0	7.375±0.019*	32.9±2.2	19.1±2.1*
High dose group						
5	7.430	40.3	26.7	7.349	30.0	16.5
6	7.419	38.3	24.7	7.268	30.2	13.8
7	7.444	35.7	24.4	7.246	31.2	13.5
8	7.451	37.9	26.4	7.347	30.0	16.4
Mean±SD	7.436±0.014	38.1±1.9	25.6±1.2	7.303±0.053*	30.4±0.6*	15.1±1.6‡
Total	7.434±0.013	37.3±1.8	25.0±1.2	7.339±0.054*	31.6±2.0*	17.1±2.8‡

Blood acid-base composition of the subject in the control period and during metabolic acidosis (pH in U; pCO_2 in mmHg; HCO_3^- in mmol/liter). * $P < 0.05$; ‡ $P < 0.001$ versus control period.

in the high dose group, whereas a nonsignificant fall occurred in the low dose group.

In Table II, the plasma acid base composition of all subjects on the study days (i.e., when albumin synthesis rates were measured) are summarized. NH_4Cl administration induced a significant decrease in plasma HCO_3^- concentrations in both the low (meanΔ = 5.4 mmol/liter, $P < 0.05$) and the high dose group (meanΔ = 10.5 mmol/liter, $P < 0.001$).

Fig. 1 demonstrates the enrichment in plasma free phenylalanine, reflecting the precursor pool for albumin synthesis. Shortly after the intravenous injection of the large dose of
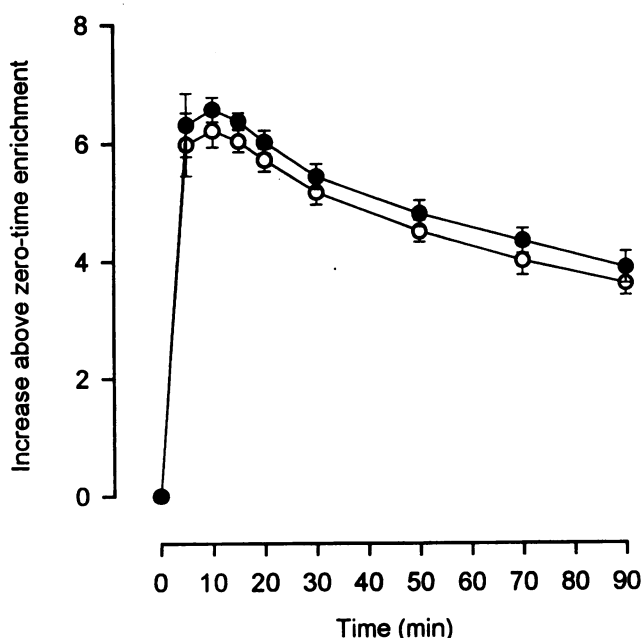
Figure 1. Plasma free phenylalanine enrichment after injecting 43 mg [²H₅ring]phenylalanine per kg body weight at zero time. Open symbols in the control and filled symbols in the acidosis period.
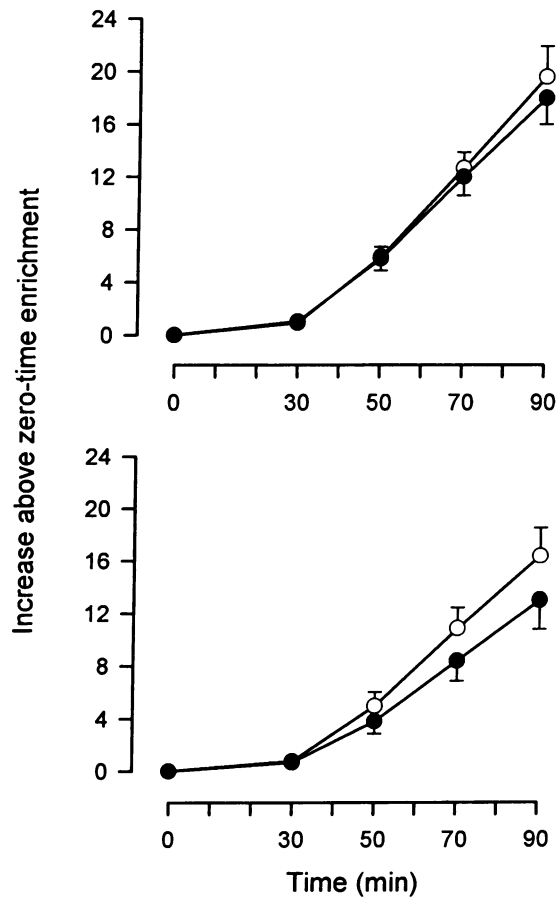
[²H₅ring]phenylalanine the enrichment in plasma free phenylalanine reached a peak value, succeeded by a plateau for approximately 20 min. Thereafter, a progressive slow decline in plasma free phenylalanine enrichment occurred up to 90 min. Metabolic acidosis had no influence on plasma free phenylalanine enrichments.

In Fig. 2, the curves for the phenylalanine enrichment in albumin of both measurements are shown. With a delay of ~ 30 min (i.e., the secretion time; 23) after injecting the large dose of phenylalanine the enrichment in albumin started to increase and followed an approximately linear time-course thereafter (see 23). In 3 out of 4 subjects in the low dose NH_4Cl group the enrichments were slightly lower in the acidotic period, whereas one subject showed a clear decrease in enrichment while he was acidotic. In contrast, in the high dose group all four subjects had substantially lower enrichments in albumin under acidotic conditions. As an indication of the accuracy of the mass spectrometry analyses all curves were smooth and the rise in enrichment of albumin occurred at the same time, i.e., at about 30 min. This was also reflected by the secretion times, which were not different between the two measurements. In the first measurement the secretion time was 32.5±1.6 min versus 32.3±2.1 min ($P = 0.7$; $n = 8$) in the second measurement. In Table III the FSRs are summarized separately for the low and the high dose group. Control values were well within the expected range of albumin synthesis (23, 25, 26, 34, 35). All subjects showed a decrease of FSR. However, this difference reached statistical significance only in the high dose group and when the two groups were combined.

Urinary nitrogen excretion in the low dose group averaged 997±116 mmol/24 h (i.e., 14.0±1.6 g/24 h) in the control period and 1088±116 mmol/24 h (i.e., 15.2±1.6 g/24 h; P = 0.156) during acidosis (after correction for NH_4Cl ingestion), while in the high dose group nitrogen excretion averaged 1012±180 mmol/24 h (i.e., 14.2±2.5 g/24 h) and 1377±236 mmol/24 h (i.e., 19.3±3.3 g/24 h; $P < 0.001$), respectively. Ingestion of high dose NH_4Cl induced an increased nitrogen excretion rate (1377±236 mmol/24 h) in comparison with the

Figure 2. Phenylalanine enrichment of plasma albumin after injecting 43 mg [^{2}H$_5$ring]phenylalanine per kg body weight at zero time. Open symbols in the control and filled symbols in the acidosis period; (*upper panel*) low dose NH$_4$Cl group; (*lower panel*) high dose NH$_4$Cl group.

low dose group (1088±116 mmol/24 h, $P < 0.001$). Fig. 3 depicts the daily changes in urinary nitrogen excretion during acidosis compared with control and the sum of the daily changes during acidosis. The daily nitrogen excretion is expressed as the difference from the average daily excretion during the control period. As the dietary intake was identical throughout, this method of presentation is equivalent to a nitrogen balance, if stool losses are assumed to be constant. The cumulative increase in nitrogen excretion averaged 634 mmol on day 7 of low dose NH$_4$Cl and 2554 mmol in the high dose NH$_4$Cl group (Fig. 3). The plasma concentrations of IGF-I, f T$_4$, T$_3$, and TSH are shown in Table IV. IGF-I, f T$_4$, and T$_3$ all showed small, but statistically significant declines during the acidosis period, when the low and high dose groups were combined, with no change in TSH. There were no significant correlations by linear regression analysis between the plasma hormone concentrations and the other measured metabolic variables.

Discussion

The present data demonstrate for the first time in any species that chronic metabolic acidosis decreases albumin synthesis, and induces a state of sustained negative nitrogen balance. Thus, the present study provides strong evidence that chronic meta-

Table III. Albumin Synthesis Rates

	FSR	
	Control	Acidosis
Low dose group		
1	10.1	9.3
2	8.7	7.9
3	11.0	7.9
4	9.8	8.5
Mean±SD	9.9±1.0	8.4±0.7
High dose group		
5	9.4	7.5
6	7.0	5.8
7	9.4	6.9
8	7.4	5.1
Mean±SD	8.3±1.3	6.3±1.1*
Total	9.1±1.4	7.4±1.4‡

Albumin synthesis of the subjects in the control period and during metabolic acidosis, expressed as FSR in percent per day (%/d). * $P < 0.01$; ‡ $P < 0.001$ versus control period.

bolic acidosis not only increases whole body protein degradation and amino acid oxidation (15), but has profound effects on protein synthesis.

Different degrees of metabolic acidosis were induced with two different levels of NH$_4$Cl as reflected by the significant difference in steady-state plasma concentrations of bicarbonate between the low and the high dose group (Table II). Ingestion of 2.1 mmol NH$_4$Cl per kg body weight (low dose group) induced a non-significant increase of nitrogen excretion, whereas 4.2 mmol (high dose group) induced a significant and sustained increase in urinary nitrogen excretion, suggestive of a graded effect of metabolic acidosis. Therefore, metabolic acidosis may be an important mediator of negative nitrogen balance, increased protein breakdown, and decreased protein synthesis in acidotic patients with chronic renal failure, sepsis or trauma.

The cumulative increases in urinary nitrogen excretion over the 7-d acidosis period are equivalent to a daily loss of ~ 8 grams of protein in the low dose group and of ~ 31 grams in the high dose group. Thus, mild to moderate chronic metabolic acidosis induces a quantitatively impressive protein degradation in a dose- or severity-dependent way. Albumin synthesis rate decreased significantly in the subjects with the more severe metabolic acidosis, whereas in the low dose group a smaller, but nonsignificant decline in FSR of albumin occurred. However, as with nitrogen excretion the data on albumin synthesis are also suggestive of a graded response. The observed decrease in albumin synthesis (15) is not inconsistent with the reported increase in whole body protein synthesis, which is an aggregate change in all the protein of the body, each of which is regulated separately. Albumin synthesis accounts for ~ 10% of liver protein synthesis (36), i.e., ~ 10–15 g protein per day in a healthy subject (23). In conditions with severe protein/albumin losses, such as the nephrotic syndrome, synthesis rates of albumin can be augmented approximately by a factor of 1.5 (25), thus contributing substantially to the net whole body protein synthesis rate of ~ 200 g protein per day in an adult (37). Assuming an
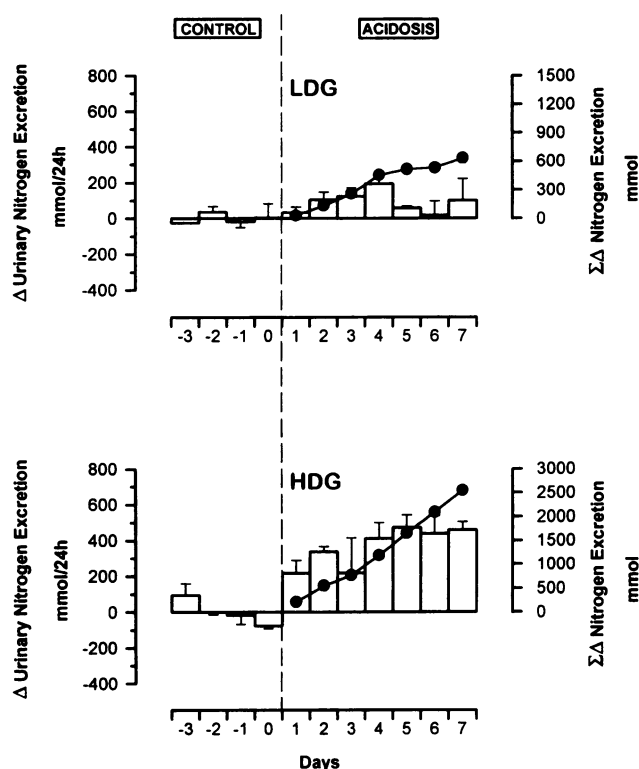
Figure 3. Effects of metabolic acidosis on urinary nitrogen (N) excretion. *LDG*, low dose NH$_4$Cl group; *HDG*, high dose NH$_4$Cl group. Δ urinary N excretion denotes the daily changes in urinary N excretion, as compared with the average urinary N excretion in the control period. $\Sigma\Delta$ N excretion denotes the cumulative changes in urinary N excretion from the average N excretion in the control period.

intravascular albumin pool of 150 g (23), the decrease in the albumin FSR by $\sim$ 25% in the high dose group relates to a decrease of protein synthesis of $\sim$ 3 g/24 h. The difference in the corrected urinary nitrogen excretion of 5 g/24 h between the control and the acidosis period equals $\sim$ 31 g of protein. Thus, assuming no change in albumin catabolism, the observed decrement of 3 g/24 h albumin synthesis rate accounts for 10% of the protein equivalent of the corrected urinary nitrogen losses. In many catabolic conditions suppression of albumin synthesis might be more severe, since other factors, such as low energy/protein intake and inflammatory stimuli (e.g., cytokines) are known to inhibit albumin synthesis (21, 36). Nutrient intake was controlled in the present study by a constant metabolic diet, which provided an identical amount of energy and protein in the control and acidosis periods. An effect of nutrition on albumin synthesis rates is therefore excluded. However, the remaining

90% protein equivalent to the urinary nitrogen losses probably occurred mainly through changes in total body protein breakdown (15).

A potential error in measuring albumin synthesis in the acidosis period may have occurred through an increased catabolism of proteins within the liver associated with changes in the endogenous supply of unlabeled amino acids. Whereas the equilibration of the hepatic precursor pool enrichment for albumin synthesis with the plasma free amino acid enrichment, which was used as the precursor for calculating the albumin synthesis rate, was previously demonstrated after a flooding dose of labeled amino acid in normal healthy subjects (23), no data are available in acidotic subjects. However, as compared to other methods, i.e., the constant infusion technique (30), the large amount of labeled amino acid injected in the present study is more likely to achieve an isotopic equilibration between the hepatic precursor pool and the plasma phenylalanine, which would minimize any error in albumin synthesis rates.

The possibility might be considered that the observed increment in urinary nitrogen excretion during chronic NH$_4$Cl loading is associated with an offsetting reduction in stool nitrogen excretion, thereby preventing negative balance. This possibility is unlikely for at least two reasons. First, stool nitrogen excretion has been reported as unchanged during a 3-d NH$_4$Cl load (3.1–4.2 mmol/kg per 24 h) in normal human subjects ingesting a constant whole food diet (38). Second, the increment in urinary nitrogen excretion (corrected for changes in nitrogen intake) during the steady-state of acidosis in the present studies (high dose group) averaged 365 mmol or 5.11 g/24 h. This increment exceeds the measured values for total stool nitrogen excretion (0.9–1.4 g/24 h) as assessed during a wide variety of whole-food dietary intakes (38–40). Thus, due to the magnitude of the observed changes, a reduction in stool nitrogen output is extremely unlikely to account for the increased urinary nitrogen excretion.

We have also investigated potential hormonal mechanisms mediating the acidosis-induced negative nitrogen balance and down-regulation of albumin synthesis. Growth hormone, IGF-I, thyroid hormones and cortisol are among the most important hormones regulating protein synthesis/degradation. Growth hormone administration was shown to stimulate amino acid transport and protein synthesis (41), an effect which is probably mediated by IGF-I (42). Thyroid hormones enhance hepatic albumin mRNA expression, and hypothyroidism has opposite effects (36), while cortisol is known to directly increase albumin synthesis and degradation in humans (43). In rats, chronic metabolic acidosis has been demonstrated to stimulate muscle proteolysis in the presence of an increase in urinary corticosterone excretion, but to have no effect on protein synthesis (11).

In the present study, we report for the first time a decrease in IGF-I plasma concentration in response to chronic metabolic

Table IV. Hormone Plasma Concentrations

	Control				Acidosis			
	IGF-I	fT$_4$	T$_3$	TSH	IGF-I	fT$_4$	T$_3$	TSH
Mean±SD	42.5±15.4	17.6±1.6	2.3±0.5	2.2±1.0	31.6±14.7*	15.9±1.7*	2.0±0.5*	2.1±1.1

Plasma concentrations of insulin-like growth factor-I (IGF-I in nmol/liter), free thyroxine (fT$_4$ in pmol/liter), tri-jodthyronine (T$_3$ in nmol/liter), and thyroid-stimulating hormone (TSH in mU/liter) in the control period and during metabolic acidosis. * $P < 0.05$ versus control period.

acidosis in normal human subjects. This finding is consistent with recent preliminary data in children with renal tubular acidosis, where both growth hormone and IGF-I levels were decreased (44). Our findings are also consistent with the reported observation that metabolic acidosis depressed the plasma concentration and hepatic gene expression of IGF-I in rats (45). Although IGF-I has not been directly shown to stimulate albumin synthesis, its action is generally anabolic, stimulating protein synthesis in the whole body (42). Thus, it is tempting to speculate that the observed suppression of albumin synthesis may not be directly mediated by metabolic acidosis per se, but may be mediated via the fall in IGF-I. This mechanism may have important implications for protein metabolism in chronic renal failure, since the kidney itself is a site of IGF-I production (46). Whether the binding of IGF-I to IGF-binding proteins is altered in patients with chronic renal failure has not been reported. However, the potential depression of IGF-I in chronic renal failure (47) might be mediated by both metabolic acidosis and a renal mass-mediated decrease of renal IGF-I production.

The fall in $f T_4$ and T_3 plasma concentrations resulting from chronic metabolic acidosis has also not been reported previously in humans, and indicates that metabolic acidosis has inhibitory actions on the peripheral thyroid hormones. In newborn lambs, it was recently reported that HCl-induced acidosis lowered plasma concentrations of thyroid hormones (48). Since thyroid hormones are known to have anabolic effects (36), the decrease of $f T_4/T_3$ may be another pathogenic factor which contributes to the decreased synthesis rates of albumin or other proteins in the present study. However, while it is possible that the changes in plasma levels of both IGF-I and the thyroid hormones are linked to the decrease in albumin synthesis, a causative role for these hormones has not been proved by the present study.

In contrast to observations in rats (11), cortisol excess has no known pathogenic role in altered protein synthesis and negative nitrogen balance in humans with acidosis. We and others have shown that chronic metabolic acidosis does not affect cortisol homeostasis in humans (33, 49).

Two clinically important consequences arise from our observations. First, the magnitude of both increased nitrogen excretion, resulting from an increase in whole body protein degradation (15), and decreased albumin synthesis, indicates that metabolic acidosis may be among the most important factors in protein wasting seen in disease states such as chronic renal failure, sepsis, and trauma. Second, our data suggest that correction of metabolic acidosis in such patients may be important to prevent protein (e.g., muscle protein) wasting. Correction of acidosis may be particularly important in patients with acute or chronic renal failure because it could be predicited to reduce the accumulation of urea, ameliorate uremic symptoms, and therefore, to reduce the need for dialytic treatment.

In conclusion, chronic extrarenal metabolic acidosis induces a dose-dependent and substantial decrease of albumin synthesis in normal human subjects, which may contribute in part to the sustained negative nitrogen balance. The decline in the plasma concentrations of IGF-I and thyroid hormones suggests that metabolic acidosis may act, at least in part, by suppressing regulatory hormones of albumin synthesis and protein anabolism, although the causative role of the changes in plasma hormone levels has to be demonstrated in the future.

Acknowledgments

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