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Light-chain-induced renal tubular acidosis: effect of sodium bicarbonate on sodium-proton exchange

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Abstract. We measured sodium-proton (Na^+/H^+) exchange in lymphocytes and platelets of a 46-year-old woman with the adult Fanconi syndrome before, during, and after treatment with $NaHCO_3$. Kappa light chains in her urine and unique but rarely observed crystalline structures confirmed the presence of light-chain nephropathy. Her glomerular filtration rate was only moderately impaired at 72 ml/min. $NaHCO_3$ at 1, 3, and 5 mmol/kg/day for 5 days increased her serum HCO_3 and pH from 17 to 21 mmol/l and 7.28 to 7.39 respectively. Plasma renin and aldosterone values were decreased by $NaHCO_3$. Na^+/H^+ exchange (δH_i/min) was measured with the fluorescent marker BCECF after acidification of lymphocytes and platelets with sodium propionate at five (10–50 mM) doses. Na^+/H^+ exchange was accelerated in this patient compared to normal controls. $NaHCO_3$ treatment significantly decreased Na^+/H^+ exchange in lymphocytes, but not in platelets. These findings suggest that Na^+/H^+ exchange can be influenced by $NaHCO_3$ ingestion at doses that only modestly affect systemic pH. Since Na^+/H^+ exchange is involved in stimulus response coupling, cell growth regulation, cell differentiation, and perhaps the progression of nephrosclerosis, these observations may have clinical relevance.

Key words: renal tubular acidosis; Fanconi syndrome; Bence Jones protein; light chain nephropathy; sodium-proton exchange; sodium bicarbonate; multiple myeloma; electron-microscopy

Introduction

Renal Fanconi syndrome in adults is an uncommon cause of proximal renal tubular acidosis and is generally associated with multiple myeloma, light-chain proteinuria, or amyloidosis [1,2]. We were recently referred an asymptomatic woman in whom glycosuria and proteinuria had been serendipitously identified. Elevated amounts of kappa light chains in her urine and multiple electron-dense, cytoplasmic, crystalline inclusions on renal biopsy secured the diagnosis. Sodium bicarbonate ($NaHCO_3$) loading, up to 5 mmol/kg/day, caused only a modest increase in her plasma pH and plasma HCO_3 concentrations; however, it did decrease the accelerated sodium–proton (Na^+/H^+) exchange in her lymphocytes. This patient allowed us to corroborate our earlier observations, that Na^+/H^+ exchange in lymphocytes is increased in patients with renal acidosis compared to values at a more normal systemic pH [3]. We now present evidence that Na^+/H^+ exchange can be influenced by clinically attainable alkalinization.

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Subjects and methods

Case Report

A 46-year-old woman was referred because of glycosuria and proteinuria on routine urinalysis. She denied any symptoms or lack of wellbeing. There was no family history of hypertension, renal disease, diabetes, or malignancy. She weighed 59 kg, was 161 cm tall, and had a blood pressure of 140/85 mmHg. The rest of her physical examination was entirely normal. The haemoglobin was 14.4 g/dl, haematocrit 44 vol%, white blood cell count 6800, and platelet count 247,000/mm^3. Tests of liver function and thyroid function were completely normal. Serologies for collagenoses and tests for cryoglobulins were negative. Multiple blood sugar values and an oral glucose tolerance test were normal. The sodium was 139 mmol/l, chloride 111 mmol/l, potassium 4.2 mmol/l, calcium 2.26 mmol/l, and phosphate 0.7 mmol/l. The blood urea nitrogen was 32 mg/dl, and uric acid concentration was 1.1 mg/dl. An arterial blood sample disclosed a plasma pH of 7.35, PO_2 100 mmHg, PCO_2 33 mmHg, and plasma HCO_3 18 mmol/l. The serum protein electrophoresis disclosed only a marginal decrease in

gammaglobulins. Plasma vitamin D_3 values, plasma parathyroid hormone, plasma renin activity, and plasma aldosterone were within normal limits.

Roentgenograms of the thorax, axial skeleton and hands were unremarkable. An ultrasound examination showed kidneys which were normal in size and consistency. No abnormal calcifications or calculi were found. The plasma creatinine was 1.27 mg/dl, creatinine clearance 76 ml/min, 24-h urine protein excretion ranged between 2.3 and 3.8 g/day. The urinalysis revealed + + proteinuria and + + glycosuria. Granular casts were identified in the urinary sediment. A urine disc protein electrophoresis showed a mixed, tubular pattern. The urinary excretion of amino acids was generally increased with values for individual amino acids 4–10 times above the normal range. A fourfold increase in the normal urinary excretion of β_2 microglobulin was found. Urinary immunoelectrophoresis disclosed the presence of kappa light chains. A percutaneous renal biopsy and bone marrow biopsy were performed. The patient consented to a bicarbonate loading test after the University of Erlangen committee on human subjects had given approval. The protocol consisted of observation for 5 days, ingestion of 1 mmol/kg, 3 mmol/kg, and 5 mmol/kg $NaHCO_3$ daily each for 5 days, and an additional 10-day recovery period. On the last day of each period, 24-h urine samples were collected. Arterialized venous blood was obtained for electrolytes, pH, PCO_2, HCO_3, and Na^+/H^+ exchange in lymphocytes and platelets three times during the baseline phase, at the end of each treatment phase, and twice during the recovery phase.

Histology

Renal tissue was obtained for light- and electron-microscopy. A bone marrow biopsy was also obtained. The tissue preparation was done according to standard techniques. The material for light microscopy was fixed in 4% buffered formalin, embedded in paraplast, cut in 3-µm-thick sections and stained with haematoxylin, PAS, PASM, and trichrome stains. The material for electron-microscopy was fixed in 3% buffered glutaraldehyde, embedded in Epon and ultrathin sections were stained with lead citrate and uranyl acetate, and evaluated with a Phillips EM 200. Snap-frozen tissue was used for immunofluorescence.

Preparation of platelet-rich plasma and isolation of lymphocytes

The blood was anticoagulated by the addition of 20% (vol/vol) of acid citrate dextrose [3]. Platelet-rich plasma was prepared by centrifugation of blood at 200 g for 15 min at room temperature. The upper two-thirds of the supernatant was used for the preparation of 2′-7′-bis(carboxyethyl)5,6-carboxyfluorescein (BCECF)-loaded platelets and the remaining pellet was resuspended 1 : 1 with Hepes-buffered RPMI 1640 medium, pH 7.4. Lymphocytes were prepared after centrifugation of blood on a Ficoll gradient.

Measurement of pH_i

Cytosolic pH was determined using the fluorescent pH indicator BCECF. Pelleted platelets were resuspended in Hepes buffer consisting of 140 mM NaCl, 5 mM KCl, 5 mM KH_2PO_4, 1 mM $MgSO_4$, 10 mM Hepes (free acid), and 5 mM glucose, pH 6.5 (at 37°C). 10 µM BCECF-AM (final concentration; Molecular Probes Inc., Eugene, OR) was added, and the cells were incubated for 30 min at 37°C. Thereafter, 1 µM PGI_2 was added and the cells were washed twice in Hepes buffer, pH 6.5, by repeated centrifugation. The final platelet pellet was resuspended in Hepes buffer, pH 7.4, at a concentration of 5×10^9 cells/ml. 100-µl aliquots of these suspensions were transferred to 2 ml of Hepes buffer in a cuvette and prewarmed at 37°C. All measurements were conducted within 1 h after loading. During this time leakage of BCECF did not exceed 10% as assessed by comparison of fluorescence of platelets and corresponding supernatants and was, therefore neglected.

Lymphocytes and platelets were incubated with 10 µM BCECF-AM for 30 min at 37°C in RPMI 1640 medium and washed twice in this medium by repeated centrifugation. Before prewarming to 37°C, aliquots of lymphocytes were briefly spun down in an Eppendorf centrifuge and then resuspended into Hepes buffer before being used for fluorescence measurements (final concentration 1×10^3 cells/µl). This procedure efficiently removes extraneous dye. Leakage of dye during prewarming was $<10\%$ and was therefore not corrected. The fluorescence of BCECF was recorded under constant stirring using a KONTRON SFM 24 spectrofluorimeter (Kontron, Düsseldorf, FRG) equipped with a thermostatted cuvette holder. Wavelengths for excitation and emission were set to 495 and 530 nm respectively. Calibration of the BCECF signals in terms of pH_i was performed using the K^+/nigericin method [3].

Determination of Na^+/H^+ exchange activity

Na^+/H^+ exchange was activated by addition of various amounts of Na^+-propionate (final concentrations 10–50 mM) from a 1-M stock solution, pH 7.4 [3]. Recovery of pH_i in lymphocytes and platelets was inhibited by $>90\%$ at 10 µM of the specific inhibitor 5-(N-ethyl-N-isopropyl)-amiloride. Both findings suggest that pH_i recovery was almost exclusively mediated by Na^+/H^+ exchange. Osmotic activation of the antiport by 50 mM NaCl failed to affect pH_i (data not shown). Initial rates of EIPA-sensitive pH_i recovery were calculated as described in detail [3] and are expressed as δpH_i/min. The relationship between pH_i and pH_i recovery could best be described by a sigmoidal function as stated earlier [3].

Exact characterization of the antiport's kinetic parameters can only be achieved by the nigericin pH_i clamp method or by the NH_4Cl prepulse method [3]. Determination of true v_{mqax} requires acidification to pH_i 6.0, whereas with propionate acidification beyond pH_i 6.6 (at pH_o 7.4) cannot be achieved. Further, pH_i

recovery rates are dampened and the original baseline pH is not re-established due to the continuous influx of propionic acid. However, we wished to examine antiport activity in two cell specimens from one individual at the same occasion, which requires fast experimental procedures. This renders application of the nigericin pH_i clamp method impossible, since this technique is time consuming. Further, prolonged storage of blood may affect antiport activity. Finally, neither the nigericin pH_i clamp technique nor the NH_4Cl prepulse method can be applied to platelets as these techniques require one or more centrifugation steps. In platelets this is possible only in the presence of agents that raise cAMP, or an acidic extracellular pH, in order to prevent any preactivation or aggregation of these cells. Since these manipulations might have caused unforeseen effects on antiport activity, we preferred to use acidification by propionate, which enabled us to apply the same procedure to both cell types. Finally, all these potential confounders are present to a similar extent in all cell preparations under all conditions. This notion is also supported by the evaluation of the immediate effects of propionate addition on pH_i in platelets and lymphocytes under the various states investigated. Identical amounts of Na^+ propionate produced similar acidification of the cells (buffering capacity), whereas only pH_i recovery rates were different (see results).

Statistical analysis

We conducted a repeated measures analysis of variance on the Na^+/H^+ exchange data. Since each observation was derived from a different set of cells, the data could be analysed as independent observations. We tested for the ∂pH_i/min after each the five doses of propionate under control, under HCO_3 administration, and under recovery conditions. We also compared the slopes of the relationships between ∂pH_i/min and pH_i. A P value <0.05 was accepted as significant.

Results

Renal biopsy

The renal tissue for light-microscopy contained 12 normal glomeruli and two completely sclerosed glomeruli. The latter were surrounded by scattered lymphocytic infiltrates. The tubules were slightly dilated and the lumina did not contain casts. The proximal tubular epithelium exhibited minimal vacuolization (Figure 1). Crystalline structures were present within individual cells. No evidence of light-chain deposit disease, amyloidosis, or cast nephropathy was found. Immunofluorescence for immunoglobulins (IgG, IgM, IgA, complement factors C3 and C4 was negative. By electron-microscopy, the normal architecture of the glomeruli was confirmed. Proximal and distal tubules contained numerous highly osmiophilic protein crystals without suprastructure. These crystalline structures were suggestive of light chains. Identical crystals were found in the bone marrow (Figure 2).

Na^+/H^+ exchange

Plasma Na, Cl, and K barely changed while plasma HCO_3 increased incrementally from 17 to 21 mmol/l and plasma pH increased incrementally from 7.28 to 7.39 with $NaHCO_3$ loading. UNaV increased from 102 to 275 mmol/24 h at the highest dose of $NaHCO_3$, while UCl and K excretion increased modestly. Ca excretion showed no consistent change. Urine pH increased from 6.1 at baseline to 8.3 at the highest dose of $NaHCO_3$ and decreased to 5.7 thereafter. Plasma renin activity decreased from 2.95 to 0.84 ng/Ang I/ml/h, while plasma aldosterone decreased from 589 to 294 ng/ml with $NaHCO_3$ loading.

In Figure 3 are shown pH_i recovery rates in lymphocytes before (panel A), during (panel B), and after (panel C) $NaHCO_3$ therapy. The lymphocytes obtained during $NaHCO_3$ therapy displayed reduced pH_i recovery rates after propionate; the δpH_i/min at each dose of propionate differed across treatments ($P<0.05$) compared to values obtained before or after $NaHCO_3$ therapy. The parameters from the data in Figure 3 yielded an apparent v_{max} of 0.071 δpH_i/min before and 0.067 δpH_i/min afterwards. During $NaHCO_3$ therapy, on the other hand, the rate was reduced to 0.041 δpH_i/min. The apparent half-maximum activation occurred at pH_i 6.9 before, pH_i 6.87 during, and pH_i 6.85 after the treatment. Thus the increase in apparent v_{max} in lymphocytes was not accompanied by an alkaline shift in the Na^+/H^+ exchanger activation curve. Moreover, the slope of the line generated by the relationship between δpH_i/min and pH_i with $NaHCO_3$ therapy differed from that obtained either before or after $NaHCO_3$ treatment ($P<0.05$).

In contrast, no significant differences in v_{max} were observed in the platelets (Figure 4). The parameters varied between 0.070 δpH_i/min before (panel A), 0.066 δpH_i/min during (panel B) and 0.068 δpH_i/min after (panel C) $NaHCO_3$ treatment. The pH_i values at which the apparent half-maximum activation of the antiporter occurred, varied only in a narrow range between 6.9 and 6.86.

Finally, neither a change in basal pH_i of the lymphocytes nor of the platelets was seen during the entire study. The values averaged 7.07 ± 0.04, 7.09×0.05, and 7.06 ± 0.03 for lymphocytes and 7.13 ± 0.04, 7.12 ± 0.03, and 7.14 ± 0.01 for platelets on day 0, 15, and 25 respectively. In addition to the constant pH_i values, enhancement of the lymphocyte antiport could not be attributed to changes in the buffering capacity for H^+, since the addition of 50 mM propionate caused the same degree of immediate acidification of the cells on all days (0.043 ± 0.04 on day 0, 0.045 ± 0.09 on day 15 (maximal $NaHCO_3$ therapy) and 0.042 ± 0.03 after 10 days of recovery. Similar values were recorded for the platelets.

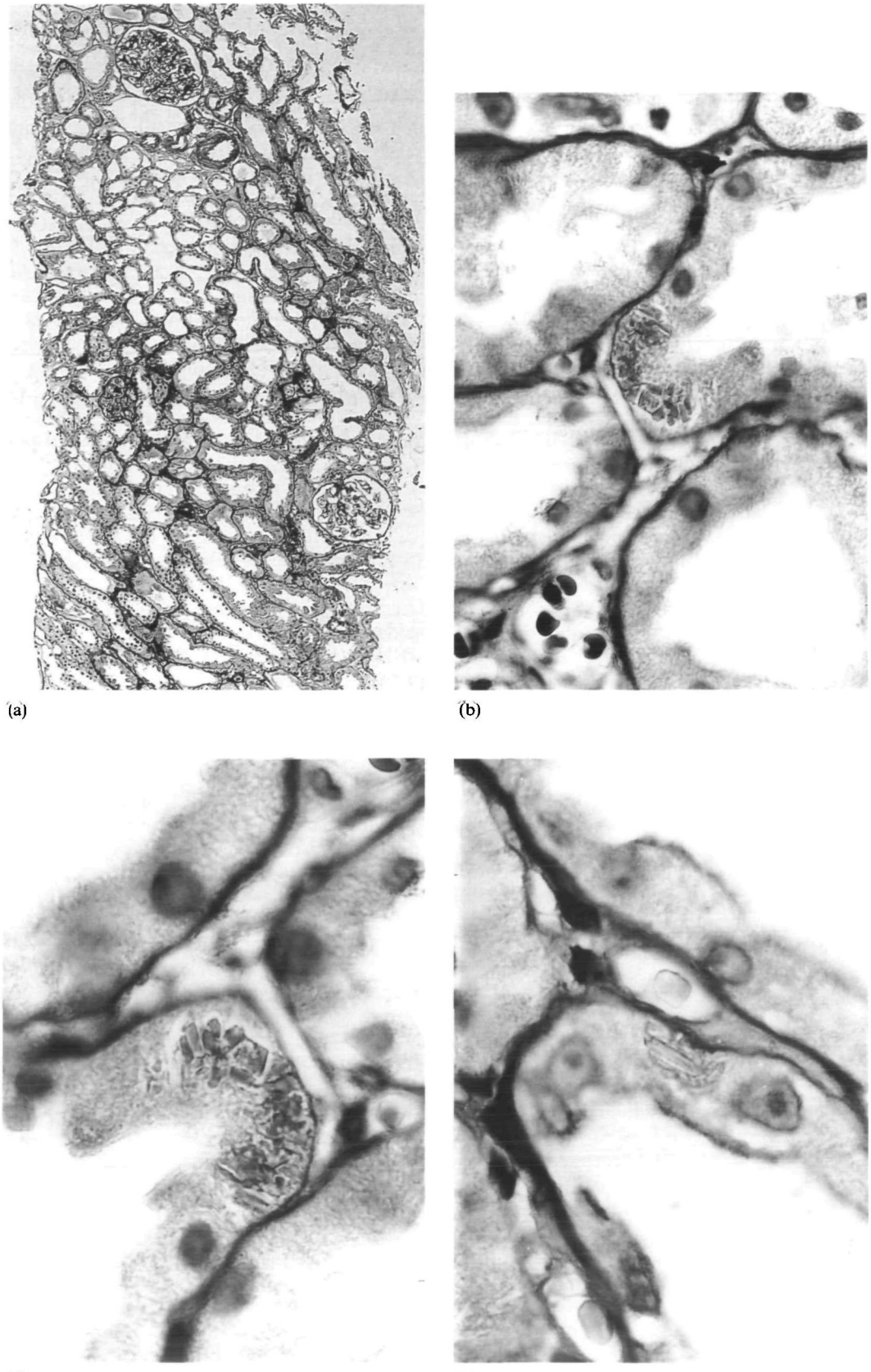

Fig. 1. Panel A shows an overview by lower power (×70, PAS stain). Tubular dilatation is evident. Panels B, C, and D show individual tubules with crystalline structures (×850). These were elucidated further by electron-microscopy.

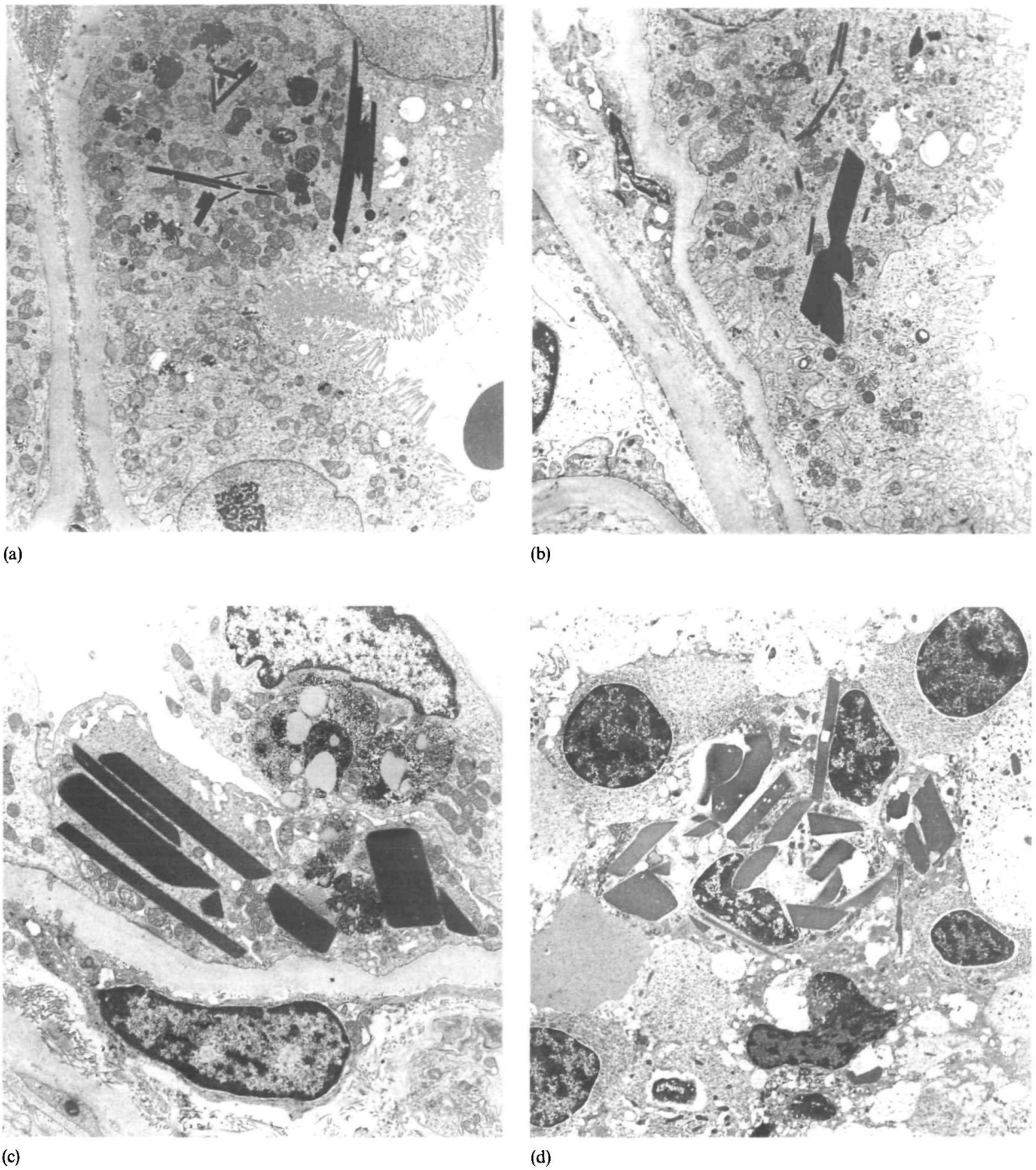

Fig. 2. Panels A, B, and C show the presence of protein crystals in tubular epithelial cells by transmission electron-microscopy. Panel D shows the presence of protein crystals in a specimen of bone marrow. The magnifications are 5×957, 5×1305, 5×1972, and 5×957 respectively.

Discussion

This patient presented with an unusual, but well-described proximal renal tubular acidosis resulting from the effects of deposited light chains [1,2]. She had all the clinical features of the adult Fanconi syndrome, as well as kappa light chains in her urine. The renal biopsy showed none of the typical renal complications of multiple myeloma, i.e. amyloidosis, cast nephropathy or light-chain deposit disease [9]. Rather, slight vacuolization of proximal tubular cells and intracellular osmiophilic crystals compatible with light chain crystals were found. Thus our patient is unusual. The overall incidence of crystals in kidneys of patients with plasma cell dyscrasia accounts for about 6%; crystals in large amounts are found in only

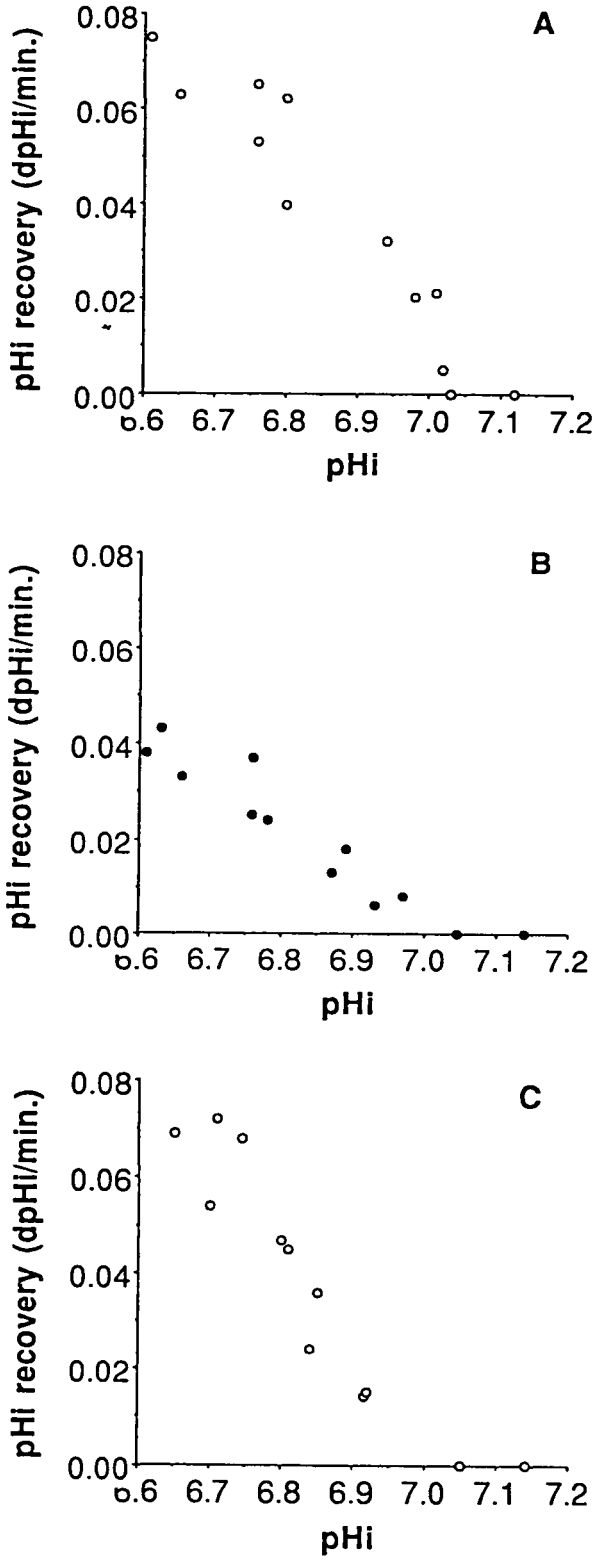

Fig. 3. The effect of $NaHCO_3$ on Na^+/H^+ exchange rates in lymphocytes. On the ordinate are shown the pooled pH_i recovery rates (∂pH_i/min) during control (panel A), day 15 of $NaHCO_3$ ingestion (panel B), and 10 days after $NaHCO_3$ treatment (panel C). On the abscissa is shown then pHi values obtained by acidifying the cells with sodium propionate. The slopes of the regression relationships are different ($P<0.05$); that in panel B after $NaHCO_3$ treatment is flatter than before (A) or after (C) the treatment.

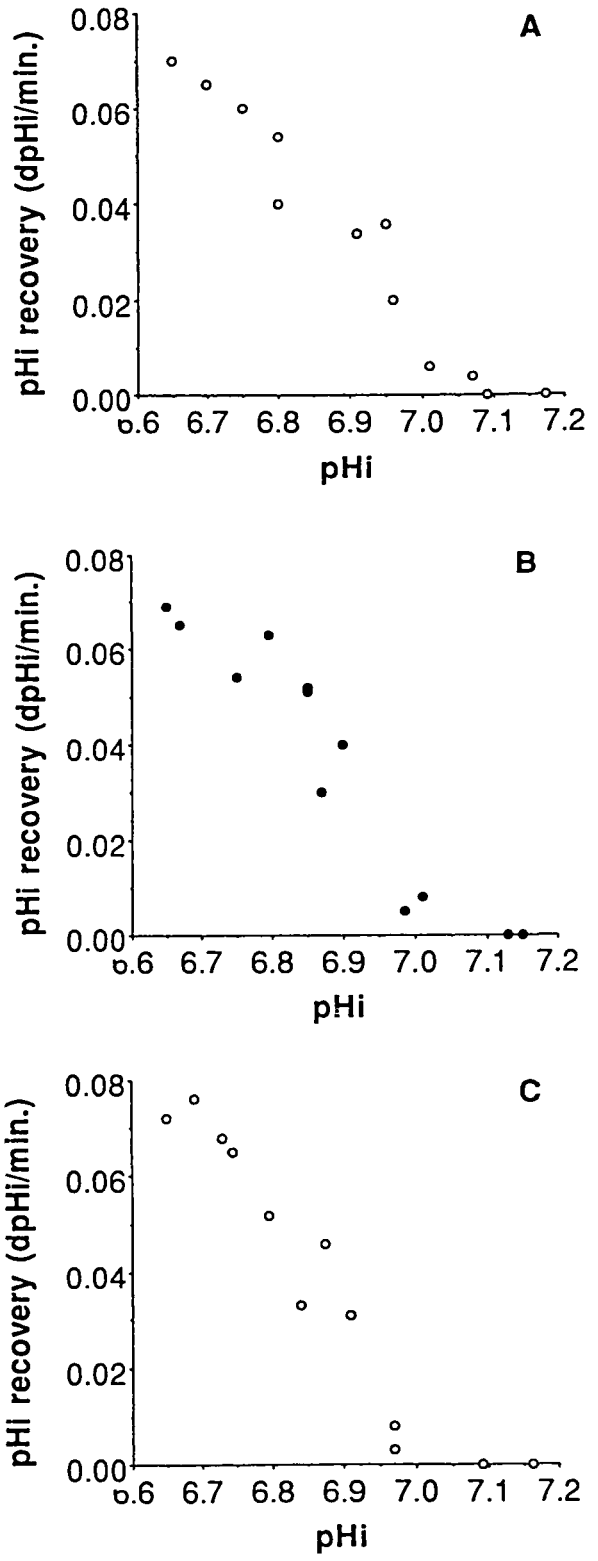

Fig. 4. The effect of $NaHCO_3$ on Na^+/H^+ exchange rates in platelets (see Figure 3). The slopes of the regression relationships are not different, indicating no effect of $NaHCO_3$ treatment on Na^+/H^+ exchange rates in platelets.

1% of cases. In cases of cast nephropathy, crystals in tubular casts and/or tubular epithelium were reported in 18 of 24 patients [10], and in eight of 12 patients with concomitant Fanconi's syndrome [1]. Cases of tubular vacuolization with intracytoplasmic crystals associated with Fanconi's syndrome without cast nephropathy are highly uncommon. To our knowledge only three cases were reported in the literature [1,11,12]. Two were associated with kappa chain [1,11], one with lambda light-chain excretion [12]. We believe our light- and electron-photomicrographs of both bone marrow and renal tissue are an excellent example of this rare condition.

We administered $NaHCO_3$ to our patient in order to document that the threshold for HCO_3 was drastically reduced [13]. Our patient had difficulty tolerating the 5 mmol/kg/day dose because of gastrointestinal side-effects. We encountered urine pH values above 5.5. Thus it is quite possible that our patient also had some degree of distal tubular dysfunction. We failed to determine the pCO_2 of her urine, which would admittedly have clarified matters.

Na^+/H^+ exchange or *antiport* is important in regulation of pH_i, cell volume, stimulus response coupling, and cell proliferation [14]. The finding that Na^+/H^+ exchange is increased in hypertension and diabetes raises the possibility that Na^+/H^+ exchange may be relevant to the pathogenesis of these conditions or their complications [15,16]. Since Nath *et al.* [17] showed that $NaHCO_3$ treatment ameliorated the course of chronic renal failure in rats with 5/6 nephrectomy, particularly in terms of reducing interstitial proliferative changes which may be related to ammonia production [18], it occurred to us that perhaps the acidosis of chronic renal disease is associated with accelerated Na^+/H^+ exchange. In an earlier study [3], we observed such an increase in Na^+/H^+ exchange in lymphocytes of patients with chronic renal disease compared to normal subjects as well as in normal subjects given NH_4Cl for 5 days. Patients with chronic renal disease had a mean pH_i recovery (δpH/min) of 0.08 (range 0.07–0.11), compared to a mean 0.05 observed in normal subjects [3]. Our patient's δpHi/min value was 0.08. We were also able to show by means of quantitative, reverse transcription polymerase chain reaction [19] that NHE-1 mRNA was increased under the condition of metabolic acidosis, suggesting that additional antiporter protein was produced. A recent study of erythrocytes from patients with renal insufficiency supports this view [20].

The Na^+/H^+ exchanger in lymphocytes and platelets is not identical with the Na^+/H^+ exchanger present on renal tubular brush border epithelium. Krapf *et al.* studied the effects of metabolic acidosis induces on Na^+/H^+ exchange in renal tissue and were able to show an increase in antiport mRNA in renal tubular cells [21,22]. Moe *et al.* [8,23] were able to confirm that mouse renal cortical tubule cells and an opossum kidney cell line responded to a 24-h *in vitro* metabolic acidosis with an almost twofold increase in Na^+/H^+ exchange activity. This increase in antiport activity was accompanied by a threefold increase in antiport mRNA. These results could be confirmed by feeding rats with a diet that induced metabolic acidosis. The increase in antiport activity could also be inhibited by the addition of cycloheximide to the culture medium. These findings could apply to Na^+/H^+ exchange in lymphocytes and platelets.

If one accepts the hypothesis of an as yet unidentified pH_i-sensor in these cells, an effect on antiport mRNA and *de-novo* regulation of the corresponding protein synthesis in lymphocytes appears conceivable. Platelets, on the other hand, are non-nucleated 'cells' which have only a minor capability of protein synthesis, if any. It is possible that the relatively short-term $NaHCO_3$ treatment was insufficient to assure adequate numbers of new circulating platelets with decreased antiport activity. Since we could only measure the overall platelet Na^+/H^+ exchange activity, minor differences were most likely under the detection limits of our assay.

It is also possible that circulating agonists influenced Na^+/H^+ exchange in the lymphocytes of our patient. Although her renin and aldosterone values were normal prior to the intervention, the administration of $NaHCO_3$ had a suppressing effect on renin and aldosterone not dissimilar from that reported after sodium citrate by Sharma *et al.* [24]. Aldosterone enhances Na^+/H^+ exchange activity in human lymphocytes *in vitro* [25–27]. Angiotensin is also able to stimulate Na^+/H^+ exchange [28]. Thus we cannot rule out the possibility that the decrease in Na^+/H^+ exchange we observed after $NaHCO_3$ in lymphocytes was mediated by hormones instead of a direct pH effect.

It is possible that acidosis *per se* may be important in the progression of chronic renal disease. Protein degradation is enhanced and growth is impaired by acidosis in uraemia [29]. Na^+/H^+ exchange may be involved in these effects. In contrast to our findings and those of Corry *et al.* [20], Greiber and Mitch found that the antiport was decreased in thymocytes of uraemic rats [30]. Additional studies will be necessary to elucidate these issues. Finally, the above-mentioned findings by Nath *et al.* [17] have not received the attention they deserve. Although reduced protein intake is an accepted preventative strategy in chronic renal failure management, control of acidosis when applied at all is primarily conducted to prevent bone disease. We suggest that control of renal acidosis may be directly relevant to the progression of chronic renal disease, perhaps by influencing Na^+/H^+ exchange.

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