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The Effects of Metabolic Acidosis on Jejunal Phosphate and Glucose Transport in Weanling Rats

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ABSTRACT. To investigate the effects of metabolic acidosis on jejunal phosphate and glucose absorption, *in vivo* and *in vitro* transport studies were performed on weanling rats fed 1.5% NH_4Cl for three days and on group pair-fed controls. Both *in vivo* and *in vitro*, acidosis significantly depressed phosphate transport without effecting glucose transport. *In vitro*, the decrease of phosphate transport was due to a depression of sodium-phosphate cotransport, but not of sodium independent phosphate transport. This corresponded to a significant increase of the Km of sodium–phosphate cotransport with no change of the Vmax. Treatment of the acidotic animals with intraperitoneal 1,25 dihydroxycholecalciferol did not restore phosphate transport to control levels. These studies indicate that in weanling rats, metabolic acidosis selectively suppresses jejunal phosphate transport independent of circulating levels of 1,25 dihydroxycholecalciferol. (*Pediatr Res* 20: 763–767, 1986)

Abbreviations

BBMV, brush border membrane vesicles
$1,25(OH)_2D_3$, 1,25 dihydroxycholecalciferol

Phosphate transport across both the renal proximal tubule and the jejunum is an active process taking place against an electrochemical gradient, and inhibitable by arsenate (1, 2). Transport consists of a saturable, electroneutral sodium–dependent component, and a nonsaturable, sodium–independent component (1, 2). Both renal and jejunal phosphate transport decline during maturation (3, 4).

The normal skeleton is an important participant in the buffering of acid (5). During metabolic acidosis, skeletal hydrogen ion retention results in significant loss of trabecular bone (6, 7). Metabolic acidosis is also associated with phosphaturia independent of parathyroid hormone and dietary phosphate intake (8, 9). This phosphaturia appears to represent a direct inhibition of renal brush border membrane sodium-phosphate cotransport by metabolic acidosis (10).

The present studies were undertaken in an effort to determine whether metabolic acidosis affects jejunal phosphate transport in a manner similar to renal phosphate transport. Metabolic acidosis was acutely induced in weanling animals and jejunal phosphate and glucose transport were assessed both *in vivo* and *in vitro*.

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MATERIALS AND METHODS

Study design. Newborn litters of Sprague Dawley rats were obtained from Sasco Industries (Omaha, NE). Mothers were allowed free access to food and water, and the pups were allowed to suckle freely. At 17 days of age, litters were separated from the mothers and randomly divided into two groups. Group 1 (acidotic) was offered pulverized standard food to eat and 1.5% NH_4Cl to drink. The animals were allowed free access to water and food. Group 2 (control) was pair fed as a group with the first group and offered water to drink *ad libitum*. After 3 days, arterial blood gases were obtained, and jejunal glucose and phosphate transport were measured *in vivo* and *in vitro*.

In vivo transport studies. In vivo transport was measured using a recirculating perfusion technique (11). Briefly, the proximal 20 cm of jejunum were cannulated with polyethylene inflow and outflow catheters and flushed with ice cold saline buffer and air. The intestinal segment was perfused at 0.1 ml/min with a solution consisting of 145 mM NaCl, 20 mM Hepes/Tris (pH 6.5), and 0.1 mM glucose labelled with ^{3}H-glucose (specific activity 50 Ci/mmol, New England Nuclear, Boston, MA), or 0.3 mM KH_2PO_4 labeled with $KH_2{}^{32}PO_4$ (specific activity 1 Ci/mmol, New England Nuclear). After a 20-min equilibration period, duplicate 100-μl aliquots were sampled every 10 min for 40 min. The rate of glucose or phosphate absorption was calculated by determining the rate of disappearance of the solute from the perfusate. Fluid shifts were assessed using ^{3}H or ^{14}C labeled inulin as a nonabsorable marker (specific activity 0.5 and 50 Ci/mol, respectively, New England Nuclear) and absorption was corrected for fluid shifts. ^{3}H, ^{14}C, and ^{32}P-labeled radioactivities were determined by double isotope counting and calculating techniques (12). Absorption results were expressed in terms of dry intestinal length since dry length correlates best with intestinal surface area (13).

In vitro transport studies. In vitro transport was measured using jejunal brush border membrane vesicles (14). Briefly, animals were anesthetized with ether and 0.4 ml of blood was withdrawn from the abdominal aorta for arterial blood gas measurements. The entire jejunum was removed and washed with ice cold 0.9 N saline and everted over a glass rod. Brush border membrane vesicles were prepared by sequential precipitation with 0.01 M $MgCl_2$ and differential centrifugation (15). The purity of the vesicle preparation for rats of varying ages has been previously demonstrated in our laboratory using morphologic criteria, enzymatic enrichment studies, and functional transport studies (15).

Glucose and phosphate uptakes were measured by a rapid filtration technique (16) using Sartorius cellulose nitrate filters of 0.45 μm pore size (Sartorius Filters Inc., Hayward, CA) that had been presoaked in stop solution containing 100 mM mannitol, 100 mM choline chloride, 20 mM hepes/tris, and 50 mM magnesium chloride (pH 7.4). Glucose stop solution also con-

tained 0.2 mM phlorizin. Incubations were carried out at room temperature using $KH_2{}^{32}PO_4$ (specific activity 1 Ci/mmol) or ^{3}H-glucose (specific activity 50 Ci/mmol) as a label (New England Nuclear). The composition of the incubation media for each individual experiment is described in the figure legends.

The protein content of the vesicle solution was determined by the method of Lowry *et al.* (17) using bovine serum albumin 1 mg/ml as a standard.

Statistical methods. For the *in vivo* perfusion studies, all results presented are the mean ± SEM of at least six observations in at least three animals. For the *in vitro* vesicle studies, all results presented are the mean ± SEM of at least six observations from at least two separate vesicle preparations. Each vesicle preparation involved 10 to 12 suckling animals. Km and Vmax were determined according to a computer model for estimation of kinetic parameters (18). Data were analyzed using the Student's *t* test and regression analysis.

RESULTS

After the 3-day feeding period, the animals drinking NH_4Cl developed a significant metabolic acidosis as compared to the group drinking water (Table 1). The animals drinking NH_4Cl had a mean arterial pH of 7.22 as compared to 7.46 in the control group ($p < 0.05$). Weights at the outset of the 3-day feeding period were identical in the two groups (Table 1). Despite being group pair fed, weight gain in the acidotic group was significantly less than in the control group ($p < 0.05$). Jejunal segments were examined in several of the acidotic animals and were found to be histologically normal.

In vivo perfusions. Table 2 depicts the absorption of 0.3 mM phosphate in the acidotic and control animals. In both the control and acidotic animals, absorption of phosphate was linear throughout the 60-min perfusions ($p < 0.05$). At each time point, phosphate uptake in the acidotic animals was significantly less than uptake in the control group ($p < 0.05$).

To determine whether the observed difference in phosphate transport between the two groups represented a general effect of metabolic acidosis on intestinal transport processes, or a specific effect on phosphate transport, the intestinal absorption of 0.1 mM glucose was examined in the acidotic and control rats in a similar fashion (Table 2). In both the control and acidotic animals, absorption of glucose was linear throughout the 60-min perfusions ($p < 0.05$). In contrast to phosphate absorption, glucose uptake in the control and acidotic animals was comparable at each time point.

In vitro transport. Effects of Acidosis upon Glucose and Phosphate Uptake by BBMV. To further define the effects of metabolic acidosis on jejunal phosphate and glucose transport, transport of glucose and phosphate was investigated using jejunal brush border membrane vesicles. Previous studies in our laboratory have demonstrated that both glucose and phosphate enter the intravesicular space with minimal binding to the vesicle membrane (4, 15).

To define the effects of sodium on phosphate uptake, jejunal brush border membrane vesicles from acidotic and control animals were prepared in a Na+–free buffer and incubated in either a Na+–containing buffer or a choline-containing buffer (Fig. 1). In vesicles from both groups of animals, phosphate uptake at 5, 10, 20, 90, and 300 s was significantly greater in the presence of Na+ than in the presence of choline ($p < 0.05$). At 180 min, phosphate uptake in the presence and absence of Na+ was the same, indicating equilibrium had been reached. At all time points, phosphate uptake in the absence of Na+ was comparable between the acidotic and control vesicles ($p > 0.2$). In contrast, at 5, 10, 20, 90, and 300 s, phosphate uptake in the presence of Na+ was significantly less in the vesicles prepared from acidotic animals as compared to vesicles prepared from controls ($p < 0.05$).

Similar experiments were performed using 0.1 mM glucose as a substrate (Fig. 2). In vesicles from both groups of animals, glucose uptake at 20 s and 1 and 2 min was significantly greater in the presence of Na+ than in the presence of choline ($p < 0.05$). Both groups of vesicles demonstrated a transient "overshoot" at 20 s. At 60 min, glucose uptake in the presence and absence of Na+ was the same, indicating equilibrium had been reached. In contrast to phosphate, glucose uptake both in the presence and absence of Na+ was the same in vesicles prepared from acidotic and control animals ($p > 0.2$).

Effect of Acidosis on Kinetics of Phosphate Uptake by BBMV. In an effort to determine the kinetics of sodium–dependent phosphate transport, vesicles from acidotic and control animals were incubated in a Na+ containing buffer with phosphate concentration varying from 0.01 to 1.0 mM (Fig. 3). Uptake was measured at 10 s, during the linear phase of uptake (1, 19). Both in the presence and absence of Na+, phosphate uptake increased as the concentration of phosphate in the media was increased. The active component of phosphate uptake can be considered the difference of sodium–dependent uptake and sodium–independent uptake. In both groups, the active component of phosphate uptake was described by a rectangular hyperbola. Table 3 depicts kinetic data for active phosphate uptake in acidotic and

Table 1. *Weights and blood gas data in control and acidotic animals*

	Control	Acidotic
Initial wt (g)	29.3 ± 1.7	30.2 ± 1.0
Final wt (g)	38.6 ± 1.1	33.2 ± 1.0*
Arterial pH	7.46 ± 0.04	7.22 ± 0.12*
Serum CO_2 (mmol/liter)	22.8 ± 2.0	10.6 ± 3.5*
pCO_2 (mm Hg)	31.0 ± 6.5	25.5 ± 5.9

* $p < 0.05$.

Table 2. *Effect of metabolic acidosis on in vivo jejunal phosphate and glucose absorption**

Phosphate absorption (nmol/100 cm dry length) after perfusion for:	10 min	20 min	30 min	40 min
Control	1.35 ± 0.2	1.97 ± 0.3	2.83 ± 0.5	3.47 ± 0.2
Acidotic	0.63 ± 0.2†	1.17 ± 0.2†	1.95 ± 0.1†	2.88 ± 0.2†
Glucose absorption (nmol/100 cm dry length) after perfusion for:	**10 min**	**20 min**	**30 min**	**40 min**
Control	19.0 ± 0.5	43.4 ± 3.9	66.4 ± 8.8	88.4 ± 10.1
Acidotic	18.9 ± 2.8	38.5 ± 5.1	62.7 ± 4.7	84.8 ± 5.9

* Twenty cm of jejunum were perfused for 40 min with buffer pH (6.5) containing 0.3 mM KH_2PO_4 or 0.1 mM *d*-glucose.
† $p < 0.05$.

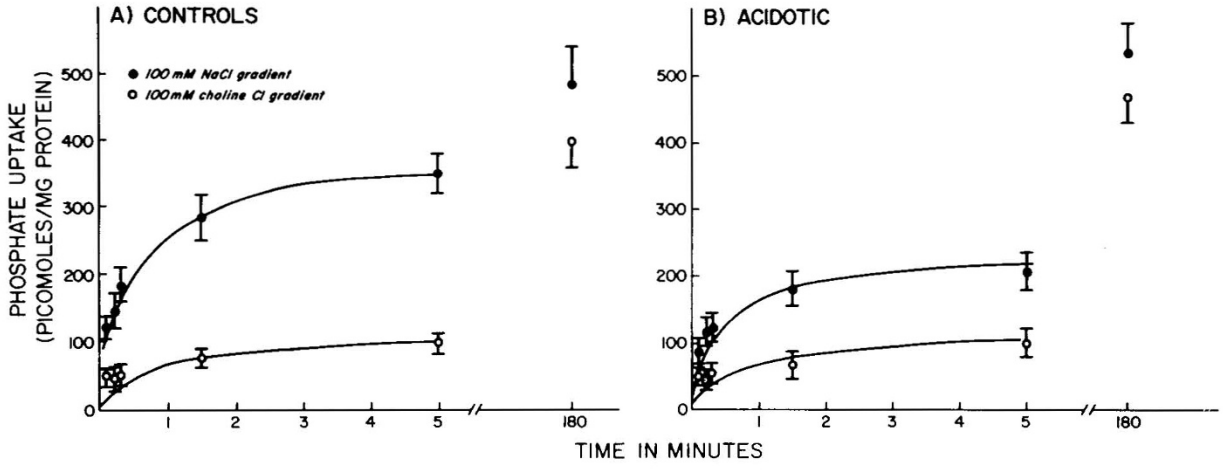

Fig. 1. Phosphate uptake into jejunal brush border membrane vesicles: effects of a sodium gradient. Jejunal brush border membrane vesicles from 21-day-old control rats (*A*) and acidotic rats (*B*) were loaded with a buffer containing 0.1 M mannitol, 0.1 M choline chloride, and 20 mM Hepes/Tris (pH 7.4). The vesicles were incubated at room temperature in a medium containing 0.1 mM phosphate, 0.1 M mannitol, 20 mM Hepes/Tris (pH 7.4), 0.1 M NaCl (●) or 0.1 M choline Cl (○). Phosphate uptake is expressed as pmol/mg of vesicle protein.

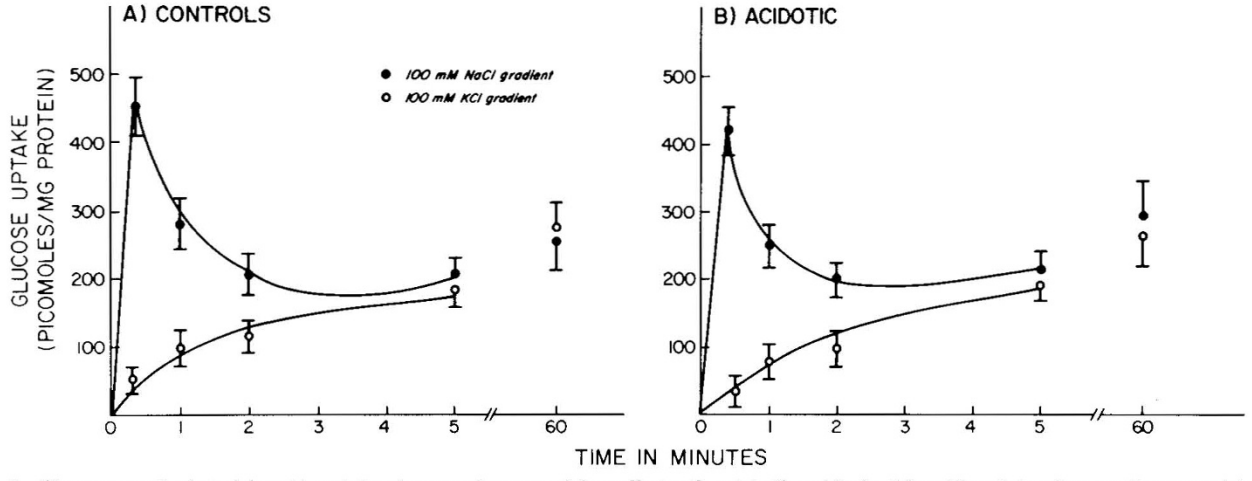

Fig. 2. Glucose uptake into jejunal brush border membrane vesicles: effects of metabolic acidosis. Jejunal brush border membrane vesicles from 21-day-old control rats (*A*) and acidotic rats (*B*) were loaded with a buffer containing 0.1 M mannitol, 0.1 M choline chloride, and 20 mM Hepes/Tris (pH 7.4). The vesicles were incubated at 37° C in a medium containing 0.1 mM d-glucose 0.1 M mannitol, 20 mM Hepes/Tris (pH 7.4), 0.1 M NaCl (●), or 0.1 M KCl (○). Glucose uptake is expressed as pmol/mg of vesicle protein.

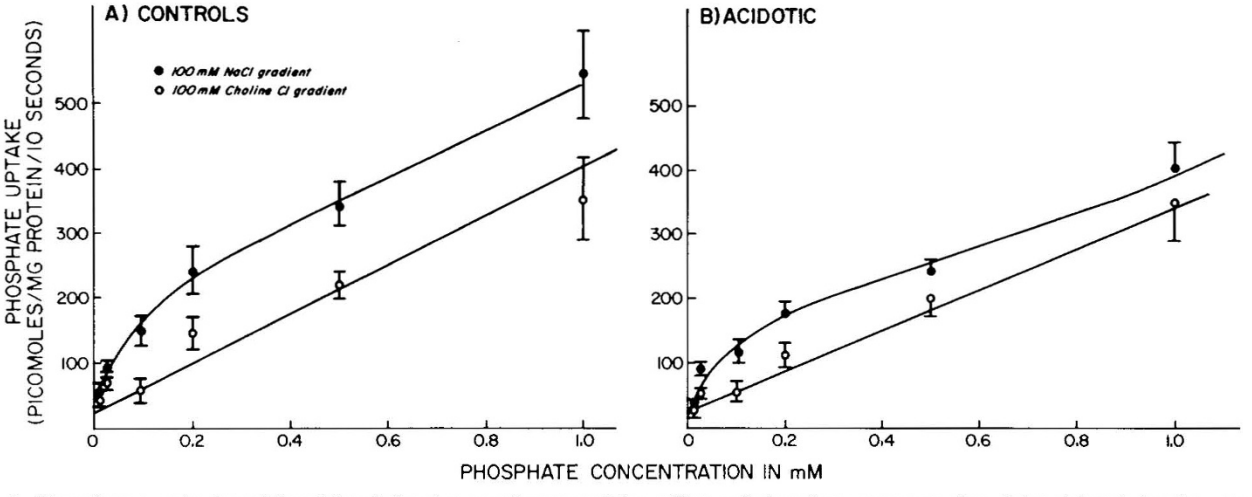

Fig. 3. Phosphate uptake into jejunal brush border membrane vesicles: effects of phosphate concentration. Jejunal brush border membrane vesicles from 21-day-old control rats (*A*) and acidotic rats (*B*) were loaded with a buffer containing 0.1 M mannitol, 0.1 M choline chloride, and 20 mM Hepes/Tris (pH 7.4). The vesicles were incubated with increasing phosphate concentrations in 0.1 M mannitol, 20 mM Hepes/Tris (pH 7.4), and 0.1 M NaCl (●) or 0.1 M Choline Cl (○). Uptake was measured at 10 s.

control animals. As seen, Vmax values were similar in both the acidotic and control animals, however, Km for the acidotic group was significantly greater than the corresponding value for the controls ($p < 0.05$).

Effect of 1,25(OH)$_2$D$_3$ on Phosphate Uptake into BBMV from Acidotic Animals. To determine whether the observed differences in phosphate uptake between the vesicles from the acidotic and control animals were due to inadequate circulating levels of 1,25(OH)$_2$D$_3$, acidotic animals were injected intraperitoneally with 1 μg of 1,25(OH)$_2$D$_3$ (Hoffman-LaRoche, Nuxley, NJ) 48 and 24 h prior to sacrifice. Phosphate uptake was measured as before in the presence and absence of Na+ (Fig. 4). Both Na+–independent and Na+-dependent phosphate uptake tended to be lower in the injected group than in the uninjected group, however, the differences were not statistically different ($p > 0.1$).

DISCUSSION

The results of these studies indicate that metabolic acidosis induced by the feeding of NH_4Cl impairs jejunal phosphate absorption in weanling rats both *in vivo* and *in vitro*. Glucose absorption is unaffected by metabolic acidosis suggesting that observed changes in phosphate transport do not represent generalized effects on intestinal transport processes. The depression of phosphate transport is due to inhibition of sodium coupled phosphate cotransport. Passive phosphate uptake is unaffected by acidosis. Kinetic analysis indicates the suppression of phosphate transport is due to a change in the Km but not the Vmax of sodium phosphate contransport. This reflects a change in the affinity of the sodium-phosphate cotransporter for phosphate without effecting the number or activity of the transporters.

It is unlikely that differences in the brush border membrane vesicle preparations from acidotic and control animals account for the observed differences in phosphate transport in the two groups in that glucose uptake was identical in both groups. Moreover, at equilibrium, glucose and phosphate uptakes were the same in vesicles from control and acidotic animals, indicating similar intravesicular size in the two groups. It appears that the depression of phosphate transport observed in the acidotic animals represents a selective depression of sodium-phosphate cotransport by acidosis.

Table 3. *Kinetics of phosphate uptake in BBMV from control and acidotic rats*

	Control	Acidotic
Km (mM phosphate)	0.059 ± 0.06	0.37 ± 0.02*
Vmax (pmol phosphate/ mg protein/10 s)	96.9 ± 1.02	98.9 ± 1.81

* $p < 0.05$.

In adult animals, 1,25(OH)$_2$D$_3$ is the most biologically active metabolite of vitamin D. The literature describing the effects of metabolic acidosis on vitamin D homeostasis is conflicting. Acidosis inhibits the production of 1,25(OH)$_2$D$_3$ by suppressing renal 1-α-hydroxylase activity in chicks and rats raised on vitamin D–deficient diets and supplied with exogenous vitamin D$_3$ (20–25), however, this suppression of hydroxylase activity is attenuated with prolonged acidosis (26). In vitamin D-replete rats, serum 1,25(OH)$_2$D$_3$ levels are either normal or elevated and rise in response to calcium and phosphate restriction (27, 28). 1,25(OH)$_2$D$_3$ exerts its effects on jejunal phosphate absorption by enhancing the Na+–dependent component of phosphate transport. This is reflected in a change of the Vmax of the sodium–phosphate cotransport system with no effect on the Km (29–31). This is in contrast to the effects of acidosis observed in this study which demonstrated a change in the Km of sodium-phosphate cotransport with no change of the Vmax. While serum levels of the vitamin D metabolites were not measured in this study, intraperitoneal injection of the acidotic animals with pharmacologic doses of 1,25(OH)$_2$D$_3$ did not restore phosphate transport to control levels, providing indirect evidence that the suppression of intestinal phosphate transport by metabolic acidosis is not mediated by changes in vitamin D homeostasis.

Phosphate transport across the renal proximal tubule is very similar to transport of phosphate across the jejunal brush border. Both systems consist of sodium–dependent and sodium–independent components (1, 2). In vitamin D–replete adult rats, fasting depresses brush border sodium–phosphate cotransport and increases urinary phosphate excretion. This is associated with an increase in the Km of the brush border phosphate transport system but no change in the Vmax (32). While the acidotic animals in the current study weighed less than the controls, food intake was equivalent, indicating protein calorie

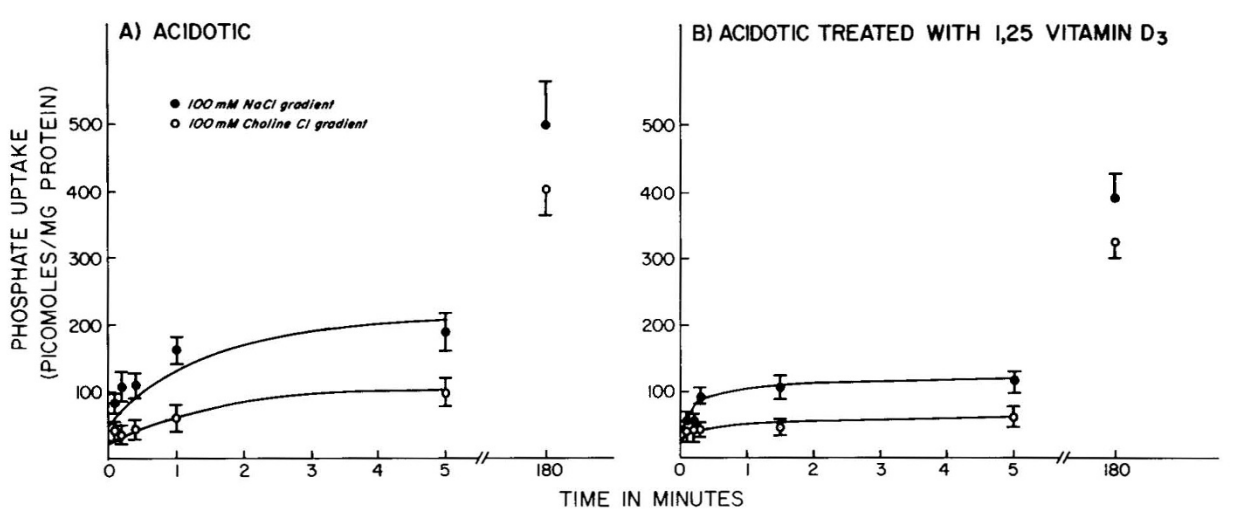

Fig. 4. Phosphate uptake into jejunal brush border membrane vesicles from acidotic rats: effects of 1,25(OH)$_2$ vitamin D$_3$. Jejunal brush border membrane vesicles from 21-day-old acidotic rats were loaded with a buffer containing 0.1 M mannitol, 0.1 M choline chloride, and 20 mM Hepes/Tris (pH 7.4). The vesicles were incubated at room temperature in a medium containing 0.1 mM phosphate, 0.1 M mannitol, 20 mM hepes/tris (pH 7.4), and 0.1 M NaCl (●) or 0.1 M Choline Cl (○). Vesicles depicted in *A* on the *left* were prepared from animals receiving no supplemental vitamin D. Vesicles depicted in *B* on the *right* were prepared from animals receiving 1 μg of intraperitoneal 1,25(OH)$_2$ vitamin D$_3$ 48 and 24 h prior to sacrifice.

restriction does not account for the observed differences in the two groups. Moreover, while effects of fasting on jejunal phosphate transport in weanling animals are unknown, glucose transport increases during protein calorie restriction in young animals (33). The failure of glucose transport to increase significantly in the acidotic animals provides additional evidence that protein–calorie malnutrition did not cause the observed suppression of phosphate transport.

Administration of glucocorticoids depresses renal phosphate reabsorption independent of parathormone release or serum phosphate concentration (34, 35). This phosphaturia appears due to the selective depression of sodium–dependent phosphate transport; sodium–independent phosphate uptake is not altered (36). Glucocorticoid therapy does not alter sodium–dependent or sodium–independent glucose uptake (37) suggesting glucocorticoid therapy does not depress all forms of sodium coupled transport in the kidney.

The effects of glucocorticoids on the intestinal absorption of phosphate are not well established. In experimental animals and in man, glucocorticoid therapy has been reported to depress phosphate absorption (38, 39). The premature weaning of rats is associated with a surge of glucocorticoid release (40), and we have observed that the premature weaning of rats is associated with a decline in jejunal phosphate transport by brush border membrane vesicles (Borowitz SM, Ghishan FK, unpublished observation). Metabolic acidosis constitutes a significant stress and is likely associated with glucocorticoid release, which may mediate the observed depression of phosphate transport observed in the acidotic animals. The failure of acidosis to induce changes in jejunal glucose transport may be explained by the fact that glucocorticoids do not alter jejunal glucose absorption in suckling animals (41).

In conclusion, in weanling rats, metabolic acidosis induced by drinking NH_4Cl for 3 days depresses sodium–coupled jejunal phosphate transport by affecting the Km but not the Vmax of sodium–phosphate cotransport. The observed changes in phosphate transport do not reflect a generalized effect of acidosis on intestinal transport in that glucose transport is unaffected and do not appear to be related to changes in the circulating level of $1,25(OH)_2D_3$ in that injection of pharmacologic doses of the vitamin do not restore phosphate transport to control levels. The etiology of the depression of sodium–phosphate cotransport by metabolic acidosis is unclear. We speculate that the stress of acidosis may cause a surge of glucocorticoid release which depresses sodium–coupled phosphate transport.

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