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Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate

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Site and mechanism of enhanced gastrointestinal absorption of aluminum by citrate. Clinical and experimental studies have shown that citrate markedly enhances the intestinal absorption of aluminum (Al), but the site and mechanism of enhanced absorption are unknown. To determine where in the gastrointestinal tract aluminum citrate (Alcitr) was absorbed, Alcitr was gavaged with D-[1-^{3}H] glucose in male Sprague-Dawley rats. Plasma Al levels increased rapidly and simultaneously peaked with D-[1-^{3}G] glucose, suggesting early proximal bowel absorption. In in vitro duodenal and jejunal everted gut preparations, Alcitr incubation resulted in increased tissue Al levels and markedly enhanced transmural transport of Al and citr. Unlike citr, the transmural movement of Al was independent of temperature (37°C vs. 4°C). On the other hand, Al lactate (al Lac) increased tissue associated Al levels but had no effect on transmural Al movement. To determine if this large flux of Al following Alcitr administration was due to paracellular movement, ruthenium red and Ussing chamber studies were used to evaluate the morphologic and functional integrity of cellular tight junctions. Alcitr, as opposed to $AlCl_3$, markedly increased ruthenium red deposits in intercellular spaces, especially around goblet cells, and induced a prolonged significant reduction in transmural resistance. Alcitr also resulted in rapid and nearly complete (99.7%) chelation of free calcium, an event known to disrupt cellular tight junction integrity. Taken together, these data suggest that enhanced Al absorption following administration of Alcitr occurs in the proximal bowel via the paracellular pathway due to the opening of cellular tight junctions.

There is little information available regarding the factors that control and modulate the absorption of non-essential and potentially toxic trace elements from the gastrointestinal tract. One element of recent interest is aluminum, since orally administered aluminum compounds have been shown to exert toxicity, at least in individuals with compromised renal functions [1–5]. Attempts to characterize aluminum absorption have been met with difficulties because a suitable isotope is not available, and aluminum compounds previously employed formed insoluble hydroxides at a physiological pH [6], which makes the interpretation of in vitro studies difficult, if not impossible. Therefore, indirect means of evaluating aluminum absorption, like change in urinary aluminum or serum or tissue burden of aluminum following an oral load, have been largely utilized [7–11]. Using these techniques, it would seem that at least four factors influence aluminum absorption: the dose of aluminum administered, the solubility of the aluminum compound, the uremic state and the concomitant administration of aluminum compounds with citrate [2, 3, 9, 11, 12–14]. Although other factors such as parathyroid hormone and vitamin D have been suggested to affect aluminum absorption, the data available are largely conflicting and difficult to resolve [9, 15–17].

Citrate may be the most important clinical modulator of aluminum absorption. It has previously been shown that aluminum absorption is increased when a variety of different aluminum compounds are administered with several forms of citrate [18–21]. In patients with renal failure, the concomitant administration of aluminum compounds with citrate has resulted in extremely high plasma aluminum levels with associated toxicity [2]. In fact, it would seem that virtually every case of aluminum toxicity described in nondialyzed uremic children, as well as adults, has resulted from the combined administration of aluminum-containing phosphate binding gels and Shohl's solution (sodium citrate) [16, 17].

The present studies, therefore, were carried out to characterize the gastrointestinal site of citrate-enhanced aluminum absorption and to determine the cellular mechanism responsible for citrate's marked enhancement of aluminum absorption.

Methods

All studies were carried out using male Sprague-Dawley rats weighing 250 to 350 g (Simonsen-Mill Rendering Plant, Quimby, Iowa, USA). For the in vivo studies, animals were housed in metabolic cages (Nalgene) and standard rat chow was withdrawn 16 hours prior to gastric lavage.

In an attempt to determine if the maximum aluminum absorption occurred in the proximal part of the small intestine serial bloods were obtained at timed intervals (0 to 420 min) following the gavage of 0.89 mmol/kg of aluminum citrate with 2 μCi D-[1-^{3}H] glucose (Amersham) and 3.3 mmol D-glucose.

Everted gut preparations

Fasting Sprague-Dawley rats were anesthetized with methoxyflurane, and everted gut sacs of 5 cm were prepared according to a modified technique of Parson, and Wilson and Wiseman [22, 23]. Duodenum (1 cm distal to the pylorus) and proximal jejunum (8 cm distal to the pylorus) segments were filled with 0.7 ml of Kreb's bicarbonate solution (Na 135.0, K 0.5, Ca 2.5, Mg 1.2, phosphate 1.0, Cl 121.4, bicarbonate 24,

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glucose 11.5 mM with Al less than 0.1 μmol). A bicarbonate buffer was used to resemble the environment of the small intestine fluid and because aluminum does not form significant complexes with bicarbonate [24]. The modifications in the serosal fluid volume were corrected with ^{3}H-polyethylene glycol (molecular wt 4,000, New England Nuclear Corporation, Boston, Massachusetts, USA) [6]. The gut sacs were weighed, suspended in 50 ml of Kreb's bicarbonate solution containing 370 micromolar of aluminum citrate or 370 μM of aluminum lactate and incubated for one hour at 37°C or 4°C. A mixture of 95% O_2 and 5% CO_2 was bubbled through the solution to maintain oxygenation and a pH of 7.40. Following the incubation, the gut sacs were removed and gently rinsed in four dishes of cold Kreb's bicarbonate solution for two minutes. The fluid contents were then drained with a needle and syringe and the gut opened, rinsed and processed for tissue aluminum determination. Aluminum transmural (mucosal-serosal) transport (change in the total serosal fluid aluminum divided by the wet weight) and tissue aluminum content were determined. The everted gut preparation was not done with aluminum chloride because of its poor solubility due to hydroxide formation at the pH used [25]. Only preparations with an intact metabolism, as assessed by a glucose serosal/mucosal ratio greater than 1, were accepted (more than 95% of our preparations). The basal aluminum contamination of the serosal fluid due to the aluminum mucosal bath (concentration of 370 μM) did not exceed 0.6 μM and was subtracted from all serosal fluid aluminum determinations. Basal aluminum tissue content was 5 ± 4 pmol/mg wet weight. In some aluminum citrate experiments, the transport of citrate was also measured with the use of aluminum ^{14}C-citrate. This compound was formed by incubating an excess of aluminum chloride with ^{14}C-citric acid for one hour (New England Nuclear Corporation) [26].

Isolated loop with ruthenium red

For the ruthenium red studies, fasting rats under methoxyflurane anesthesia had their duodenums exposed by an abdominal incision. A polyethylene catheter was inserted through a stomach incision and duodenal content flushed with warm saline. After expelling the residual fluid with air, the distal end was tied with silk and filled with either 1 ml of aluminum chloride (18.5 μmol per ml) or aluminum citrate (18.5 μmol per ml) in normal saline. Control rats had the instillation of only 1 ml of normal saline. The proximal end was then closed with silk without comprising the blood circulation and the abdominal incision was closed. Following a one-hour recovery period, the rat was anesthetized and its duodenum fluid replaced with 1 ml of ruthenium red solution (ruthenium red 0.1%, sodium cocodylate 0.1 M, glutaraldehyde 2%, pH 7.2). The isolated loop, with both ends tied, was then excised from the rat and fixed in 2% glutaraldehyde for three hours. The bowel content was then replaced with sodium cocodylate 0.1 M and ruthenium red 0.1% and the gut sac was kept overnight at 5°C in a bath of sodium cocodylate 0.1 M. The following morning the sac content was replaced with a mixture of 2% osmium tetraoxide, ruthenium red 0.1% and sodium cocodylate 0.1 M, and the whole preparation was put in a solution of osmium tetraoxide 2% and sodium cocodylate 0.1 M for three hours while sheltered from light. After osmium fixation, the duodenum was rinsed with distilled water, opened and cut in pieces of 2 mm^2.

Following dehydration in graded ethanol solution, specimens were incubated first for 30 minutes in propylene oxide: ethanol 1:1, then propylene oxide for one hour, and finally they were stored at 4°C overnight in propylene oxide: ethanol (1:1). The following day the sections were put in a fresh 100% plastic solution for three periods of one hour and dried at 60°C overnight in 100% fresh plastic solution. Ultrathin sections were then cut and viewed with a Philips CM-12 electron microscope.

Ussing chamber

The effect of aluminum citrate on the transmural resistance of jejunal preparations was studied with a modified Ussing apparatus [27, 28]. Proximal jejunal segments were opened on the mesenteric border and mounted unstripped on the Ussing chamber with a tissue aperture of 0.5 square cm. Each hemichamber contained 10 ml of the same Kreb's bicarbonate solution described in the everted gut protocol, and was bubbled with 95% O_2 and 5% CO_2 at 37°C. Both mucosal and serosal solutions were connected with agar bridges to calomel electrodes for the direct measurement of the potential difference (PD) and to Ag-AgCl electrodes for the passage of a direct current through the tissue. An automatic dual voltage clamp (616-C3, Bioengineering, University of Iowa, Iowa, USA) was used to deliver the current (20 μ A^2 cm) and to record the PD and the short circuit current (Isc). Resistance (R) was calculated from the PD and the Isc and corrected to a surface area of 1 square cm. After an equilibration period of 10 minutes of stability aluminum citrate (N = 5; 18.5 mM) was added to the mucosal bath (final concentration). Controls (N = 3) consisted of the same Kreb's bicarbonate solution without the addition of aluminum. The small increase in osmolality did not affect the resistance as shown by the absence of significant modifications with the addition of sodium acetate (55.5 mM). Additional controls consisted of sodium citrate (N = 3; 55.5 mM) and EDTA (N = 2; 0.6 mM), two compounds known to open tight junctions. The volume was kept constant and all solutions were buffered at a pH of 7.4 at a temperature of 37°C.

Calcium chelation

Aluminum citrate, chloride and lactate, respectively, were added to a Kreb's bicarbonate solution (pH 7.4 with 95% O_2 and 5% CO_2, 2.25 mM of calcium) for a final aluminum concentration of 18.5 mM. Free calcium activity was determined before and after aluminum load with a calcium electrode [29] (Model 932-00, Orion Research Inc., Boston, Massachusetts, USA) and a dose-response curve was determined for aluminum citrate.

Analytical determinations

All samples were carefully manipulated to avoid aluminum contamination. Only plastic containers or Pyrex glass washed with EDTA were used. Bloods were drawn with EDTA. Determinations of aluminum in plasma, urine, tissue and solutions were performed on a flameless atomic absorption spectrometer (Perkin-Elmer 5000, Norwalk, Connecticut, USA) according to a previously described method [30]. Standard double isotope techniques were used to quantitate the ^{3}H-polyethylene glycol and ^{14}C-citrate using a Beckman LS 5801 liquid scintillation spectrometer (Beckman Instruments, Fullerton, California, USA). Statistical analysis was performed using a computer

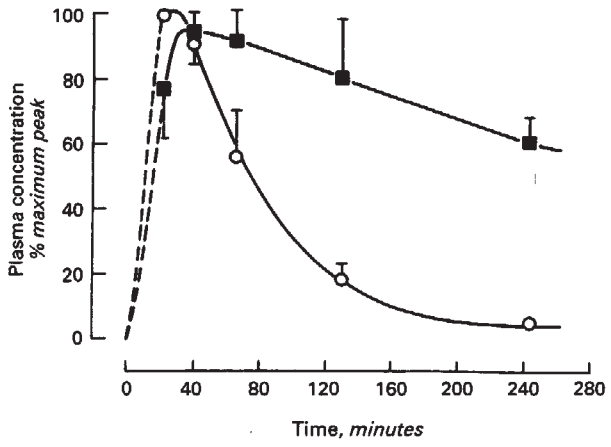

Fig. 1. *Plasma aluminum (○) and D(1-^{3}H) glucose (■) as a percent of maximum value after gavage of 1 ml of a solution containing 0.89 mmol kg^{-1} body wt of aluminum citrate and 2 nCi of D(1^{-3}H) glucose in a carrier solution of 3.30 mM glucose.* Both plasma aluminum and D(1-^{3}H) glucose peaked before 45 min after gavage. Values represent the mean SD, $N = 3$.

statistical pack (Human System Dynamics, Northridge, California, USA). The Mann-Whitney test was used for comparison of two groups, and Kruskal-Wallis was carried out for comparison of more than two groups. Results are expressed as mean ± 1 SD unless otherwise stated.

Results

Initial studies were conducted to determine if citrate caused an enhancement of aluminum absorption in the proximal small bowel. Results of in vivo gavage studies are shown in Figure 1. That aluminum absorption from aluminum citrate did occur in the proximal small bowel is suggested in Figure 1. ^{3}H-glucose was used as a marker of early proximal bowel absorption. The absorption of aluminum mirrored that of glucose indicating that it, too, was absorbed in the proximal gastrointestinal tract.

Since plasma aluminum levels returned to baseline values within 240 minutes while 98% of the aluminum remained in the gastrointestinal tract [3], this suggests that little aluminum was absorbed more distally. Because the above studies were consistent with the aluminum citrate being absorbed in the proximal region of the intestine, everted gut studies were carried out in the duodenal and jejunal segments. Following incubation with a luminal medium containing 370 μM aluminum citrate at 37°C, tissue-associated aluminum content increased from a baseline of 5 to 91 ± 27 and 115 ± 60 pmol per mg of wet weight in the duodenum and jejunum, respectively. In contrast, when the incubation was performed at 4°C, tissue-associated aluminum was not different from control baseline value (P = NS; Table 1). However, aluminum transmural movement, as determined by the delta in the serosal fluid aluminum, was 60 times over baseline ($P < 0.001$) and was temperature independent (37°C vs. 4°C, P = NS, Table 1). In contrast to aluminum, both tissue-associated uptake and transmural transfer of citrate were markedly decreased at 4°C (Table 1). Although tissue-associated aluminum from aluminum lactate was greatly increased over that found with aluminum citrate and similarly affected by cold, there was no transmural transfer into serosal fluid (Table 2). This was in spite of similar solubility of aluminum lactate and citrate in the incubating medium as determined by the aluminum content post-incubation. There was no difference in the final serosal fluid volume between aluminum citrate and lactate.

The markedly enhanced temperature-independent transmural movement of aluminum in response to aluminum citrate suggested that citrate, a compound known to open epithelial tight junctions [31], might have enhanced paracellular aluminum movement by transiently opening cellular tight junctions. Ruthenium red, a low molecular weight, impermeable cell coat marker [32], was used to evaluate tight junctions structural integrity. Ruthenium red was applied in the presence of 2% glutaraldehyde to the mucosal surface. Its presence in the intercellular spaces was then used to evaluate the structural integrity of tight junctions. In control, early intestinal segments previously exposed to normal saline only, minimal or no ruthenium red deposits could be visualized between adjacent epithelial cells (Fig. 2A). The mucosal epithelium was intact and did not appear to have undergone cellular injury. Incubation prior to fixation and ruthenium red application with aluminum citrate resulted in an intense infiltration of ruthenium red deposits into the paracellular spaces, especially around goblet cells (Fig. 2B) and was consistent with an opening of the tight junctions. In fact, entire goblet cells were outlined with ruthenium red (Fig. 2C). Minimal ruthenium red deposits could be visualized between epithelial cells. Aluminum chloride pre-incubation resulted in minimal or no ruthenium red localized to intercellular spaces, but it did cause patchy apical membrane sloughing (Fig. 2D) which was not seen either with normal saline or aluminum citrate pre-incubation.

To further characterize the effect of aluminum citrate on tight junctions functional integrity, the effect of aluminum citrate (18.5 mM) on transmural resistances of proximal jejunum segments was studied using modified Ussing chamber techniques. As is shown in Figure 3, transcellular resistance in control studies remained stable with a means value of 26 ± 4 ohm · cm^2. Transcellular resistance decreased rapidly following the addition of aluminum citrate (18.5 μM) and stabilized after 15 minutes of exposure at 19 ± 2 ohm · cm^2 ($P < 0.01$). Sodium citrate (55.5 mM) was used as a positive control and had a similar effect on the rate of decrease in transcellular resistance (−9 ± 1, $P < 0.01$). Neither 55.5 mM Na acetate (−2 ± 2 ohm · cm^2) nor 18.5 mM aluminum chloride (−2 ± 2 ohm · cm^2) had any significant prolonged effect on transcellular resistance.

Because of the critical importance of extracellular calcium for the maintenance of tight junctions and because citrate is known to chelate calcium, calcium binding ability of different preparations of aluminum was studied. Aluminum citrate, chloride and lactate were put in a Kreb's bicarbonate solution gassed with 95% O_2 and 5% CO_2 with a final concentration of 18.5 mM. Aluminum lactate did not complex any calcium, and aluminum chloride complexed only 19.9% of the available calcium (Table 3). Aluminum citrate, on the other hand, complexed almost all the calcium present (99.7 ± 0.1%) with a ratio of 1.99 ± 0.16 aluminum per calcium (calculated at 50% complex capacity, Fig. 4). Of interest is that aluminum chloride formed a whitish compound when put in a pH greater than 3, a phenomenon that represents the formation of a large, high molecular weight colloid in association with phosphates and hydroxides [25].

Table 1. Transmural transport and tissue-associated aluminum in everted gut preparation

		Aluminum			Citrate		
		N	Tissue	Transport	*N*	Tissue	Transport
Duodenum	37°C	12	91 ± 27	6.63 ± 3.64	6	432 ± 128	493 ± 120
	4°C	10	16 ± 10[a]	6.01 ± 2.15	6	112 ± 33[a]	38 ± 11[a]
Jejunum	37°C	12	115 ± 60	9.38 ± 5.43	6	394 ± 66	587 ± 189
	4°C	10	14 ± 9[a]	6.38 ± 2.15	6	106 ± 19[a]	35 ± 10[a]

Results are expressed in picomoles mg^{-1} weight. Everted gut segments were incubated in a bath containing 370 μM of aluminum citrate for one hour. Segments were washed and their content aspirated with a syringe for aluminum determination.
[a] $P < 0.001$ between 37°C and 4°C; P = NS between jejunum and duodenum (ANOVA).

Table 2. Transmural transport and tissue-associated aluminum in everted gut preparations in response to aluminum lactate

		N	Aluminum tissue content	Transmural transport
Duodenum	37°C	6	2118 ± 788	ND
	4°C	6	486 ± 234[a]	ND
Jejunum	37°C	6	2342 ± 396	ND
	4°C	6	788 ± 423[a]	ND

Results are expressed in picomoles mg^{-1} wet weight. ND: non-detectable. Aluminum lactate concentration was 370 μM (See Table 1 for details).
[a] $P < 0.001$ between 37°C and 4°C; P = NS between jejunum and duodenum (ANOVA)

Discussion

The present investigations confirm previous studies in animals and man showing that citrate markedly enhances the absorption of aluminum from the gastrointestinal tract [18–21]. They also outline the gastrointestinal site and mechanism by which citrate increases the absorption of aluminum. As determined by urinary aluminum excretion following gavage, approximately 40 to 50 times more aluminum was absorbed following aluminum citrate ingestion than from other aluminum compounds [3]. Furthermore, absorption occurs early in the intestine with the plasma aluminum peak coinciding with the glucose peak. This early enhancement of aluminum absorption by citrate would be expected since citrate would be rapidly and completely absorbed early in the small intestine and not available to enhance aluminum absorption more distally. The early proximal absorption of citrate has also been used to explain why calcium when given with citrate is much more effective phosphate binder in vivo than in vitro [33].

Tissue-associated aluminum, as well as transmural movement of aluminum into the serosal fluid, was studied. With aluminum citrate, there was a prompt increase in tissue-associated aluminum and citrate in the mucosal cells. This seemed to be an energy-requiring process and not just non-specific binding, since tissue levels of both citrate and aluminum could be markedly decreased by incubation at 4°C. However, we did not show conclusively that this represented cellular uptake by the tissue. In association with the fall in tissue levels of citrate at 4°C, there was a corresponding decrease in transmural transfer of citrate. These findings would be consistent with citrate's being taken up by mucosal cells by an energy-dependent mechanism and transported into the serosal fluid. Since C^{14} citrate was measured, it is possible that rather than citrate being directly transported into the serosal fluid, it is metabolized in the intestinal cell and its metabolites are transported into the serosal fluid. Although tissue levels of aluminum were reduced at 4°C, the transmural movement of aluminum was unaffected by cold. This suggests that the majority of the transmural movement of aluminum did not occur through cellular transport processes but rather via a paracellular pathway. This was further supported by the fact that tissue levels of aluminum in response to aluminum lactate were approximately 25 times as great as from aluminum citrate, and yet there was no transmural movement of aluminum when aluminum lactate was used. The lack of correlation between tissue aluminum content and transcellular aluminum movement is consistent with aluminum moving passively into serosal fluid through paracellular pathways. Although some investigators have suggested that aluminum is actively transported [34, 35], they failed to account for the insolubility of the aluminum compounds at the pH employed. This property of aluminum chloride with the resulting precipitation of aluminum may overestimate the aluminum movement.

To determine if citrate enhanced aluminum absorption through the paracellular pathway by opening cellular tight junctions, studies with ruthenium red and the Ussing chamber were carried out. Ruthenium red is an electron dense substance that does not permeate cells and can therefore be used as a marker of tight junction structural integrity [32]. While normal saline and aluminum chloride resulted in minimal paracellular ruthenium red deposits, aluminum citrate was associated with abundant ruthenium red paracellular deposits. This was especially apparent around goblet cells which are known to have tight junctions that are more permeable than adjacent columnar absorptive cells [36, 37]. Additional evidence supporting the opening of the tight junctions by aluminum citrate was obtained by using the Ussing chamber to quantitate the effect of aluminum citrate on transmural electrical resistance. In proximal bowel, transmural resistance is determined by the number of tight junction strands [36]. A reduction in resistance is synonymous with a reduction in the tight junction's functional and structural integrity [36]. In our studies, EDTA and sodium citrate, compounds known to open tight junctions and reduce transepithelial resistances [31], were used as positive controls and, as expected, resulted in a prolonged reduction in electral resistance consistent with the opening of tight junctions. Likewise aluminum citrate, but not aluminum chloride nor aluminum lactate, produced a prolonged reduction in transcellular resistance, consistent with the opening of tight junctions.

The above findings are consistent and offer a possible expla-

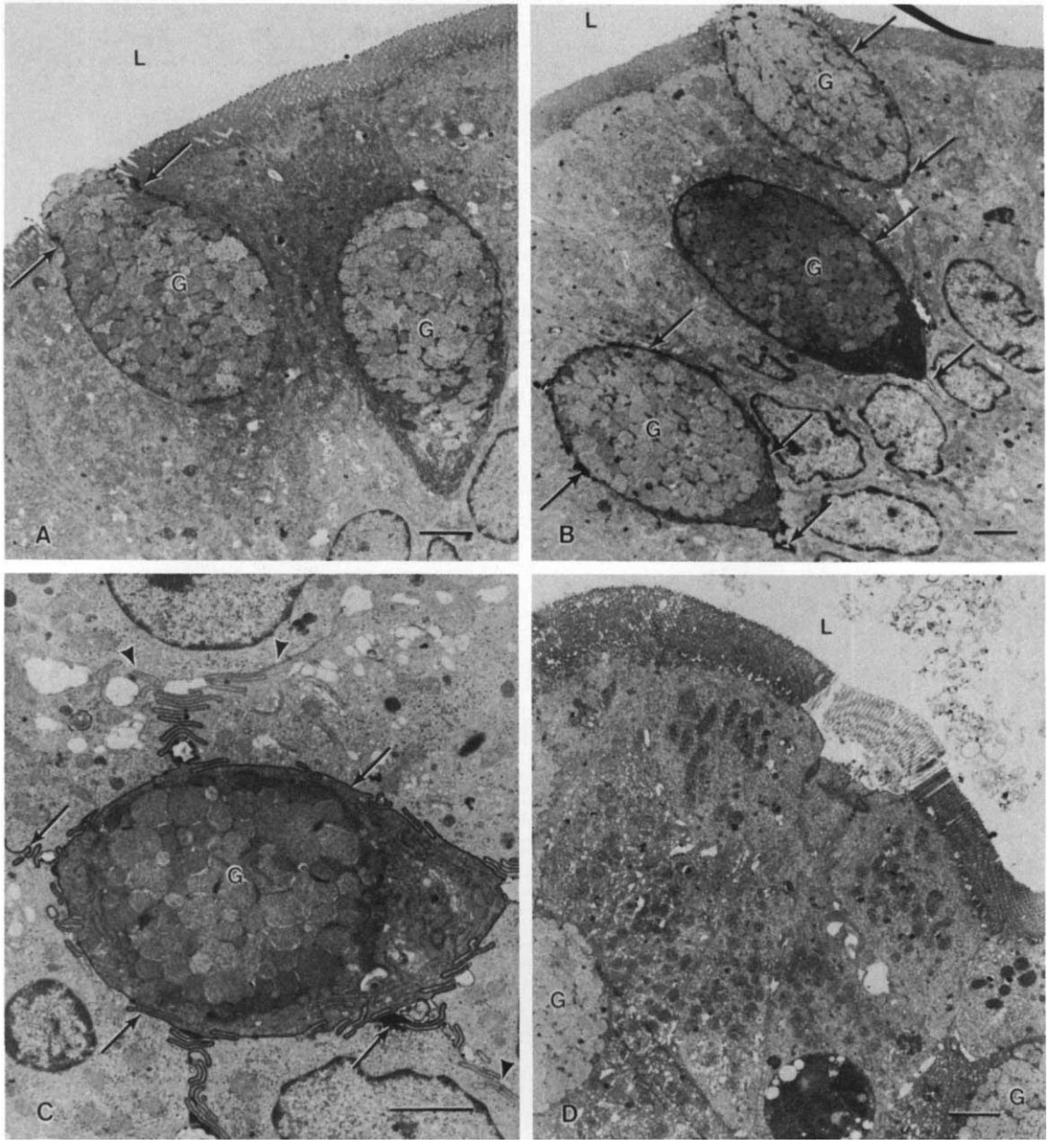

Fig. 2. *Electron micrograph of isolated duodenal loops.* **A.** Following exposure to normal saline, rare ruthenium red deposits could be seen around goblet cells (arrows). No deposits were visible between adjacent columnar epithelial cells (magnification of ×4600). **B.** Following aluminum citrate exposure, dense infiltration of ruthenium red deposits could be visualized around goblet cells (arrows). The mucosal epithelium following both normal saline and aluminum citrate was intact (magnification ×3700). **C.** A goblet cell, at higher magnification, following aluminum citrate treatment. Note the intense, ribbon-like outlining of the entire goblet cell's intercellular space by ruthenium red which fades away at the junction of the columnar epithelial intercellular space (arrows) (magnification of ×7600). **D.** Aluminum chloride pre-incubation resulted in minimal or no ruthenium red in intercellular spaces but caused some patchy sloughings of mucosa (magnification of ×4400; G, goblet cell; L, lumen; bar represents 2 microns).

nation for the increased absorption of aluminum following aluminum citrate therapy. We propose that at least two factors are crucial if enhanced gastrointestinal absorption of aluminum is to occur. First, the aluminum compound must be soluble at the pH of the intestinal fluid, and, second, the compound under question must result in the opening of cellular tight junctions. These conditions are best shown by considering the three compounds studied. Aluminum chloride is poorly absorbed because it is insoluble at intestinal pH and does not alter the permeability of the paracellular pathway. Aluminum lactate, although soluble at physiological pH [3], is poorly absorbed via the paracellular pathway because it has no effect on the functional integrity of the tight junctions. The aluminum in aluminum citrate, however, is soluble at physiologic pH, and by

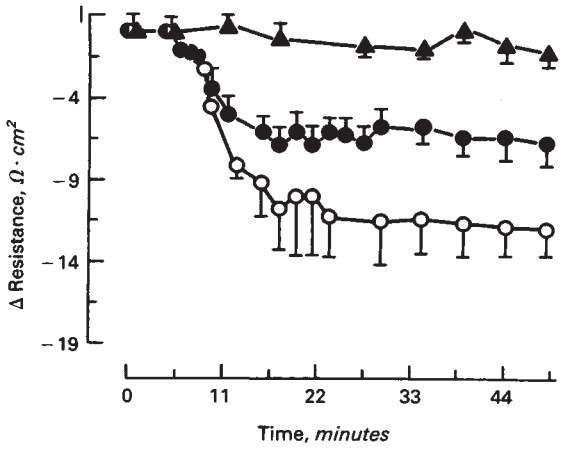

Fig. 3. *Effect of aluminum citrate on proximal jejunal transcellular resistance.* Following an equilibration period of 10 minutes either aluminum citrate ($N = 5$) or sodium citrate ($N = 3$) was added to the mucosal bath to achieve final concentration of 18.5 mM and 55.5 mM, respectively. Symbols are: (▲) control; (●) Al citrate; (○) Na citrate.

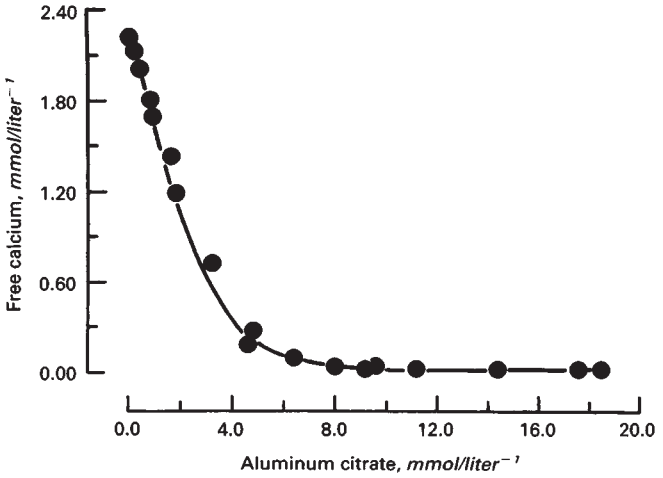

Fig. 4. *The effect of different concentrations of aluminum citrate (0 to 18.5 mM) on free calcium in Kreb's bicarbonate solutions.* Free Ca^{2+} was quantitated using a calcium electrode. Aluminum citrate ($N = 2$) effectively chelated the calcium with a ratio of 1.99:0.16 aluminum per calcium determined when 50% of the calcium was chelated.

Table 3. Determination of free calcium in the presence of aluminum citrate, chloride or lactate

	% Calcium decrease	Free calcium *mM*
Control	0%	2.25
Aluminum citrate	99.7 ± 0.1	0.007 ± 0.002
Aluminum chloride	19.9 ± 0.4	1.80 ± 0.009
Aluminum lactate	No decrease	2.25

Each final aluminum concentration was 18.5 mM. Kreb's bicarbonate solution had a calcium concentration of 2.25 mM. The decrease in free calcium occurred almost instantaneously in all cases.

complexing calcium citrate leads to the opening of cellular tight junctions. This results in a markedly enhanced paracellular movement of the soluble aluminum. Therefore, aluminum citrate's high formation constant, which precludes the formation of insoluble aluminum hydroxide or phosphate [26, 37] in association with its ability to open tight junctions, probably accounts for its high degree of gastrointestinal absorption. Recently Provan and Yokel [38], using different and more indirect methods, have also shown that aluminum absorption is energy-independent and most likely occurs through the paracellular pathway.

Our data have important clinical implications. Since aluminum has a strong formation constant with citrate [26, 39], aluminum compounds should probably not be given concomitantly with citrate in any form, especially to patients with chronic renal failure. It should also be recognized that citrate enhances the gastrointestinal absorption of lead [40, 41] and probably would have a similar effect for a number of other trace elements. Because of the potential that citrate-containing compounds have to enhance the gastrointestinal absorption of a variety of environmental inorganic toxins, the long-term use of calcium citrate [42] and potassium citrate [43] even in patients with normal renal function needs to be re-evaluated.

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