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Research Article

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Magnesium Absorption in the Human Small Intestine

RESULTS IN NORMAL SUBJECTS, PATIENTS WITH CHRONIC RENAL DISEASE, AND PATIENTS WITH ABSORPTIVE HYPERCALCIURIA

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ABSTRACT Magnesium absorption was studied in the normal human jejunum and ileum by in vivo intestinal perfusion, using test solutions containing from 0 to 20 mM Mg (as $MgCl_2$). As luminal Mg concentration was increased, the rate of absorption in the jejunum rose progessively with a tendency towards saturation at the higher concentrations. The kinetics and rates of Mg absorption in the ileum were comparable to those in the jejunum, with the exception that at higher luminal concentrations the ileal absorptive process was fully saturated. Using test solutions containing various combinations of Ca and Mg, we found that Ca had little or no influence on Mg absorption, even through Mg depressed Ca absorption to a modest extent. Patients with end-stage renal disease, who had a reduced rate of Ca absorption (presumably due to deficiency of 1,25-dihydroxycholecalciferol) were found to have a severe depression of Mg absorption. On the other hand, patients with absorptive hypercalciuria and nephrolithiasis, who had an increased rate of Ca absorption, were found to absorb Mg normally. These results suggest that Mg absorption in the human is mediated by a transport process different from that which facilitates Ca absorption, and that normal Mg absorption may be dependent on vitamin D. Our results do not establish whether or not the normal intestine can absorb Mg against an electrochemical gradient.

INTRODUCTION

Previous experiments in animals have produced several differences of opinion concerning the site and mechanism of Mg absorption by the intestine. For one example, in rat everted gut sacs, Aldor and Moore (1) concluded that Mg absorption decreased progressively from proximal to distal small bowel, whereas Ross (2) found that the ileum was the principal site of Mg absorption. For another example of controversy, some workers have concluded that Mg absorption is passive (1, 3), whereas others have found evidence of active Mg transport (4). Finally, some experimental data suggest a common transport system for Mg and Ca (5–7), while other results do not (8, 9). Regardless of whether Ca and Mg share a common transport system, vitamin D (10, 11) and parathyroid hormone (12) stimulate Mg as well as Ca absorption.

Relatively little is known about Mg absorption in man. Based on the time curve of the appearance in blood of orally ingested isotopes, the proximal small bowel is believed to be the major site of absorption (13). Colonic absorption can also occur as evidenced by hypermagnesemia after rectal enemas (14). Balance studies suggest that vitamin D may increase Mg absorption (15, 16); however, serum Mg concentration is not high in patients with vitamin D intoxication (17).

The purpose of the present series of experiments was to gain a better understanding of Mg absorption in humans by use of in vivo intestinal perfusion. In normal subjects, the kinetics of Mg absorption were determined in 30-cm segments of jejunum and ileum by perfusing test solutions that contained from 0 to 20 mM $MgCl_2$. In additional studies in normals, the effect of Ca on Mg and of Mg on Ca absorption was measured. Patients with end-stage renal disease, who are known to have malabsorption of Ca due to a deficiency of 1,25-dihydroxycholecalciferol, were studied to see if Mg absorption was similarly depressed. Finally, patients with hypercalciuria and renal stone formation due to hyperab-

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sorption of Ca (18) were studied to see if their Mg absorption was also increased.

METHODS

Controls and patients. Normal healthy volunteers were selected who had no history of gastrointestinal or kidney disease. The group consisted of 3 females and 11 males with a mean age of 29 (range 21–42 yr). None were on chronic medication.

One female and four male patients with end-stage renal disease were studied. Their mean age was 35 (range 19–56 yr). Each was undergoing hemodialysis three times a week. Three male patients, ages 60, 45, and 48, with absorptive hypercalciuria (18) were studied.

Informed consent was obtained from each normal subject and patient, and these experiments were approved by a Human Research Review Committee.

Intestinal perfusion. Subjects were intubated with a triple-lumen polyvinyl tube as previously described (19–21). Under fluoroscopic control, the infusion site was placed at the ligament of Treitz for the jejunal studies. In the ileal studies, the infusion site was in the mid-ileum. Intestinal perfusion was begun after an 8-h fast in each subject, and approximately 48 h after hemodialysis in the renal patients. Test solutions were prewarmed to 37°C and infused at a constant rate of 11 ml/min with a peristaltic pump (Desaga multichannel peristaltic pump, Brinkman Instruments, Inc., Westbury, N. Y.). After a 50-min equilibration period, sampling from collection sites located 10 and 40 cm from the infusion site was begun and continued for a 1-h period. The collection rate was 1.5 ml/min at each site and sampling was staggered, i.e., the distal collection was started and stopped 10 min after the proximal collection, based on previous estimates of transit time of fluid through segments of human small intestine (22). Samples were collected anaerobically in 30-ml plastic syringes for three 20-min periods and then pooled. Four test solutions, selected in a randomized fashion, were perfused in each subject unless otherwise specified.

Test solutions. All solutions contained 0.5% polyethylene glycol (a nonabsorbable volume marker), 50 mM NaCl, 5 mM KCl, and 10 mM D-xylose. $MgCl_2$ and Ca gluconate concentrations were varied between 0 and 20 mM as indicated in the results. Mannitol was added to keep the osmolality of the solutions in the jejunum at 200 mosmol/kg and in the ileum at 290 mosmol/kg. When these solutions are perfused into the jejunum and ileum, net water movement is near zero (19, 23); therefore, there was no significant effect of bulk water flow on Mg movement, and clinically significant plasma volume changes in the patients with chronic renal disease were prevented.

Blood samples. Blood samples were drawn for Ca, Mg, and electrolyte determinations before and at the end of each study.

Analysis. Samples were analyzed for polyethylene glycol, electrolytes, and xylose concentrations according to methods previously described (19, 23, 24). Mg and Ca concentrations were analyzed in triplicate by atomic absorption spectrophotometry (25, 26).

Calculations. Rates of absorption or secretion of Mg, Ca, Na, K, and water in the 30-cm test segment are calculated from the perfusion rate, change in concentration of polyethylene glycol, and concentration of specific ions and solutes. Results are expressed as the mean±SE. The concentrations of ions in the perfusate are expressed as the arithmetic mean of the concentration determined at the proximal and distal ends of the test segment.

RESULTS

Kinetics of Mg absorption in normal subjects

Jejunum. Test solutions containing 0, 0.5, 1, and 5 mM $MgCl_2$ were perfused in the jejunum of six normal subjects. On a separate test day 11 subjects were perfused with solutions containing 5, 10, 15, and 20 mM $MgCl_2$. The composite results of these studies are shown on the left side of Fig. 1. When the perfusion solutions contained no Mg, a small amount of Mg was secreted into the lumen. As luminal Mg concentration rose from near 0 to 5 mM, absorption increased rapidly. Although absorption continued to increase at higher concentrations, it did so more gradually.

Serum Mg concentrations before and at the end of the two perfusion periods are shown in Table I. There was no change in Mg concentration at the end of experiment in subjects perfused with test solutions containing 0–5 mM $MgCl_2$. However, the serum Mg concentration increased slightly in those subjects receiving solutions containing 5–20 mM $MgCl_2$. Since approximately one-third of serum Mg has been shown to be bound by protein (27), serum ionized Mg concentration during jejunal perfusion in our subjects was presumably about 0.6 mM.

Ileum. Test solutions containing the same concentrations of $MgCl_2$ as used in the jejunal studies were perfused into the ileum of five normal subjects. As shown on the right side of Fig. 1, the rate of Mg absorption increased rapidly as the luminal concentration rose from near 0 to 10 mM. Further increases in luminal concentration were not associated with a further rise in Mg absorption rate. Except for the fact that the absorptive process was fully saturated in the ileum above 10 mM luminal concentration, the kinetics and absolute rates of Mg absorption were similar to those noted in the proximal jejunum.

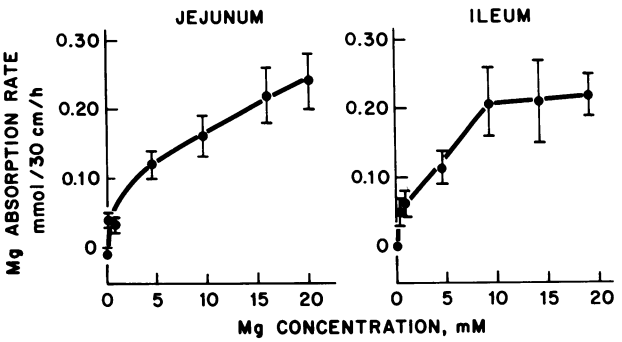

FIGURE 1 Mg absorption rate at different luminal Mg concentrations in the normal jejunum and ileum.

TABLE I

Serum Mg Concentrations

	Prestudy	Poststudy	*P* value*
		mM	
Normal jejunum			
0–5-mM test solutions, $n = 6$	0.83±0.04	0.83±0.04	0.3
5–20-mM test solutions, $n = 11$	0.92±0.02	0.99±0.03	<0.05
Normal ileum			
0–5-mM test solutions, $n = 5$	0.84±0.07	0.89±0.10	0.3
5–20-mM test solutions, $n = 5$	0.89±0.06	0.91±0.02	0.7
Renal disease, jejunum			
0–10-mM test solutions, $n = 5$	1.01±0.08	0.97±0.09	<0.01
Hypercalciuria, jejunum			
1–5-mM test solutions, $n = 3$	0.91±0.06	0.89±0.04	

* Paired *t* test.

As shown in Table I, there was no statistically significant increase in mean serum Mg concentrations after ileal perfusion of either set of four test solutions.

Inhibition studies in the normal jejunum

Effect of calcium on magnesium absorption. Jejunal perfusion studies were performed in seven normal subjects using four test solutions, each containing 2.5 mM $MgCl_2$ and either 0, 5, 10, or 20 mM Ca gluconate. As shown in Table II, the rate of Mg absorption was not altered to a statistically significant extent by the presence of Ca.

Ca absorption rates at the four luminal Ca concentrations are also given in Table II, and can be compared with Mg absorption rates at these same concentrations, as depicted in Fig. 1. Ca absorption at 5 and 10-mM luminal concentrations was about 40% higher than Mg absorption at these concentrations. From 20-mM solutions the rate of Ca absorption was approximately twice that of Mg.

TABLE II

Effect of Ca on Mg Absorption from 2.5-mM $MgCl_2$ Test Solutions, in the Jejunum of Seven Normal Subjects

Ca concentration in test solution	Ca absorption	Mg absorption	
mM	*mmol/30 cm/h*	*mmol/30 cm/h*	*P value**
0	−0.07±0.02	0.06±0.01	—
5.0	0.17±0.02	0.05±0.02	0.8
10.0	0.22±0.03	0.04±0.01	0.6
20.0	0.48±0.09	0.05±0.01	0.6

* Paired *t* test for the difference between Mg absorption with and without Ca.

TABLE III

Effect of Mg on Ca Absorption from 5.0-mM Ca Gluconate Test Solutions, in the Jejunum of Nine Normal Subjects

Mg concentration in test solution	Mg absorption	Ca absorption	
mM	*mmol/30 cm/h*	*mmol/30 cm/h*	*P value**
0	0.00±0.003	0.20±0.03	—
1	0.04±0.01	0.15±0.03	0.2
5	0.09±0.02	0.12±0.02	0.05
10	0.12±0.04	0.15±0.03	0.1

* Paired *t* test for the difference between Ca absorption with and without Mg.

Effect of Mg on Ca absorption. These studies were performed in nine normal subjects. Each test solution contained 5 mM Ca gluconate and either 0, 1, 5, or 10 mM $MgCl_2$. The results are shown in Table III. The rate of Ca absorption was reduced by 25% with 1 and 10 mM $MgCl_2$ and by 40% with 5 mM $MgCl_2$, but the change was statistically significant only with the 5-mM $MgCl_2$ solution.

The rate of Mg absorption from these test solutions is also given in Table III. When Ca and Mg were both present in the perfusion solution at a concentration of 5 mM, the rate of Ca absorption exceeded that for Mg by about 25%.

Mg absorption in the jejunum of patients with chronic renal disease

Test solutions containing 1, 5, and 10 mM $MgCl_2$ were perfused in five patients with chronic renal disease. As shown in Fig. 2, the rate of Mg absorption was markedly depressed compared with normal.

The fourth test solution perfused in these patients contained 5 mM Ca gluconate and no $MgCl_2$. The rates

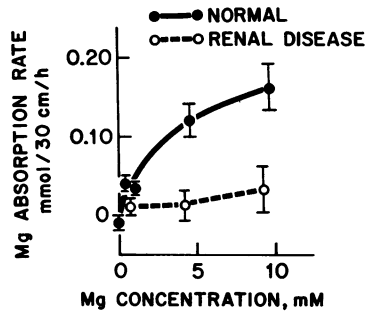

FIGURE 2 Comparison of jejunal Mg absorption in normal subjects and patients with chronic renal failure at different luminal Mg concentrations.

TABLE IV

Jejunal Absorption of Mg and Ca from 5 mM $MgCl_2$ or Ca Gluconate Test Solutions in Normal Subjects and in Patients with Chronic Renal Disease

	Mg absorption	Ca absorption
	mmol/30 cm/h	*mmol/30 cm/h*
Normal, $n = 9$	0.12±0.02	0.20±0.03
Chronic renal disease, $n = 5$	0.01±0.02	0.03±0.03

of Mg and Ca absorption from 5-mM test solutions in normal subjects and in patients with chronic renal disease are compared in Table IV. The results demonstrate that these particular renal disease patients did, in fact, have a severe impairment of Ca absorption, as expected from previous studies in other such patients (28).

As shown in Table I, mean serum Mg concentration was slightly higher in the patients with chronic renal disease than in normals. Serum Mg concentration fell slightly during the perfusion experiments, presumably due to dilution secondary to water absorption (see last section of Results).

Mg and Ca absorption in the jejunum of patients with absorptive hypercalciuria

Jejunal absorption of Mg was measured in three patients with idiopathic absorptive hypercalciuria using test solutions containing 1 and 5 mM $MgCl_2$. As shown in Table V, the rate of Mg absorption with the 1 mM $MgCl_2$ test solution was similar to that in normal subjects, whereas with the 5-mM $MgCl_2$ solution Mg absorption in the patients was less than the average normal result. A third test solution containing 5 mM Ca gluconate and no $MgCl_2$ demonstrated about a 50% increase in average Ca absorption in patients with idiopathic hypercalciuria when compared to normals.

As shown in Table I, the serum Mg concentrations in the patients were essentially the same as in normal subjects.

Water, electrolyte, and xylose movement in normal subjects and patients

As shown in Table VI, there was slight water secretion in the jejunal test segment of both normal subjects and patients. The water absorption which we postulate caused the slight fall in serum Mg concentration in the renal disease patients (Table I) must have occurred in lower segments of the small bowel and (or) in the colon. Water movement in the ileum of normal subjects was near zero. The mean Na concentration in the test segment was 88 meq/liter in the jejunum of normal subjects, as compared to 55 meq/liter in the ileum. The difference is due to higher permeability of the proximal small bowel to NaCl (23).

Potential difference (PD) across the mucosa can be estimated from the concentration of potassium at the distal end of the test segment (29). Estimated jejunal PD in these studies was near zero in the normal and patient groups. Thus, differences in PD could have had no effect on the different rates of Mg absorption observed in the jejunum of normal and renal disease patients. Estimated PD in the ileal studies was about 6 mV (lumen positive), and this probably caused a slight enhancement of Mg absorption in the ileum when luminal Mg concentration was lower than that required to saturate the Mg absorption process.

Xylose absorption was the same in the jejunum of the normal subjects as in the two disease groups. Xylose absorption is less in the ileum than in the jejunum because of different permeability characteristics (23, 30). In data that are not shown, changing Mg concentration from 0 to 20 mM in the test solutions had no effect on the potassium concentration of fluid collected from the distal end of the test segment. This suggests that Mg concentration, within this range, has no effect on PD across the intestine.

DISCUSSION

These experiments demonstrate that the Mg absorptive process in the human small bowel in vivo tends to become saturated as the luminal concentration of Mg is increased above about 10 mM. Whether or not the small bowel can absorb Mg against an electrochemical gradi-

TABLE V

Jejunal Absorption of Mg and Ca in Normals and in Patients with Absorptive Hypercalciuria

	Mg absorption*	Ca absorption‡
	mmol/30 cm/h	*mmol/30 cm/h*
5-mM test solutions		
Normal subjects	0.12±0.02	0.20±0.03
Absorptive hypercalciuria		
H. O.	0.10	0.34
C. J.	0.03	0.28
M. J.	0.02	0.41
1-mM test solutions		
Normal subjects	0.03±0.01	
Absorptive hypercalciuria		
H. O.	0.05	
C. J.	0.04	
M. J.	0.01	

* From solutions containing Mg Cl_2.

‡ From solutions containing Ca gluconate.

TABLE VI

Water, Electrolyte, and Xylose Movement in Normal Subjects and Patients

	Δ H_2O	Mean Na	Δ Na	Distal K	PD	Δ Xylose
	ml/30 cm/h	*meq/liter*	*meq/30 cm/h*	*meq/liter*	*mV*	*mmol/30 cm/h*
Jejunum						
Normal	+27±5	87.9±0.8	+12.3±0.6	4.28±0.10	0.7±0.5 (Lumen $^+$)	−1.13±0.09
Renal	+31±6	85.5±1.7	+12.9±1.0	4.77±0.10	0.4±0.8 (Lumen $^-$)	−1.15±0.07
Hypercalciuria	+13±8	86.4±1.8	+11.4±0.8	4.62±0.11	0.4±1.4 (Lumen $^+$)	−1.24±0.23
Ileum						
Normal	−4±7	55.4±0.9	+1.3±1.2	3.43±0.08	6.1±0.7 (Lumen $^+$)	−0.50±0.04

(+) denotes secretion; (−) denotes absorption.

For Na the result is the average concentration from the proximal and distal ends of the test segment. For K the concentration from the distal end of the segment is reported. PD was estimated from distal K using the Nernst equation, as previously described (29).

ent cannot be determined from our studies, since the serum ionized Mg concentration was not measured.[1]

In the present experiments water movement was near zero. Contraction or expansion of luminal volume would tend to increase or decrease luminal Mg concentration. Since Mg absorption rate is highly dependent on luminal Mg concentration (up to 10 mM), Mg absorption under normal physiologic conditions (i.e., after a meal) would probably be influenced to an important degree by water movement.

Unlike the absorption of other divalent cations such as calcium and iron, which are supposedly absorbed preferentially in the proximal small bowel, Mg is absorbed as well in the ileum as in the proximal jejunum. We found no evidence that one end of the small bowel was different from the other in regard to the rate of Mg absorption, in contrast to what has been reported by previous workers in the rat intestine in vitro (1, 2).

One interesting result of our experiments is that Mg absorption is reduced in the jejunum of patients with chronic renal disease. It is known that these patients have a deficiency of the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (31, 32) and that vitamin D stimulates Mg absorption in vitamin D-deficient animals (10, 11). Most likely, the malabsorption of Mg in patients with renal disease is due to vitamin D deficiency. The fact that Mg absorption in renal disease patients is so markedly depressed suggests that Mg absorption is exquisitely dependent on vitamin D. Of course, renal insufficiency per se might also depress Mg absorption, but if so, the defect would have to be quite specific since most ions and solutes (divalent cations excluded) are absorbed normally in the jejunum and ileum of patients with chronic renal disease (33). Whatever its cause, it seems likely that Mg malabsorption helps protect renal disease patients from the hazards of magnesium overload (34).

If Mg as well as Ca absorption depends on vitamin D, the question arises whether these two divalent cations are absorbed by the same transport mechanism. If so, they might compete for the common diffusion site or transport carrier in the membrane. Our results reveal that Ca has no effect on Mg absorption in the jejunum, even when the Ca concentration in the lumen is eightfold higher than the luminal Mg concentration. This strongly suggests that the Ca and Mg transport systems are separate. On the other hand, the presence of 5 mM Mg in the lumen resulted in a 40% inhibition of Ca absorption. (However, increasing the Mg concentration to 10 mM did not cause a further depression of Ca absorption.) Assuming that the Ca and Mg transport mechanisms are separate, the reason why Mg depresses Ca absorption is not clear. Since Mg has been shown to reduce passive cation movement via shunt pathways in gallbladder mucosa (35, 36), one possibility is that Mg may depress Ca absorption by reducing the passive component (25) of jejunal Ca absorption.

Idiopathic hyperabsorption of calcium is believed to be the cause of hypercalciuria and renal stone formation in some patients. We studied three such patients to see if they also hyperabsorbed Mg, and found that they did not. This is further evidence that the Mg and Ca transport mechanisms are separate.

According to the data shown in Fig. 1, the half-maximal absorption rate of Mg by the human small bowel occurs when the luminal Mg concentration is about 5 mM.

[1] If we assume that two-thirds of serum Mg is in the ionized form (27), the ionized serum Mg concentration in our normal subjects was about 0.6 mM. Since Mg was absorbed from test solutions containing 0.5 mM Mg, and since the PD in these jejunal studies was estimated to be near zero, our data suggest that the intestine can absorb Mg against an electrochemical gradient. However, it is emphasized that our data do not permit a firm conclusion on this point.

This may be compared to a luminal Ca concentration of about 4 mM for half-maximal Ca absorption in the jejunum of normal subjects as measured with a similar technique (25). Therefore, the apparent affinities of the Mg and Ca transport mechanisms for their respective ions are similar according to this criterion. On the other hand, the jejunum absorbs Ca from one and one-half to two times more rapidly than Mg at any given luminal concentration, and the maximum transport velocity for Ca is at least twice as high as that for Mg.

Assuming a maximum transport capacity for Mg of 0.2 mmol/30 cm per h (Fig. 1), and a 300-cm length of small intestine (37), the absorptive capacity of the human small bowel is 2 mmol/h or 48 mmol/day (about 1,100 mg/day). This compares with an average dietary intake of 500 mg/day, of which about 170 mg is absorbed according to balance techniques (38) (which may underestimate absorption somewhat due to secretion of Mg in the digestive juices).

Of course, it must be kept in mind that the test solutions used in our experiments did not contain glucose or other nutrients and that they were designed to result in near zero movement of water. Therefore, our results may not be directly applicable to normal physiological conditions within the gastrointestinal tract.

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