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Interaction between Calcium and Cadmium in the 1,25-Dihydroxyvitamin D_3 Stimulated Rat Duodenum

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Interaction between Calcium and Cadmium in the 1,25-Dihydroxyvitamin D_3-Stimulated Rat Duodenum. TORAASON, M., AND FOULKES, E. C. (1984). *Toxicol. Appl. Pharmacol.* 75, 98–104. It has been suggested that calcium and cadmium compete for an intestinal transport system that is vitamin D dependent. To further test this hypothesis, the interaction between calcium and cadmium during transport in the duodenum of rat was investigated. Control rats maintained on a diet adequate in vitamin D, calcium, and phosphorus were compared to rats on the same diet administered 500 ng of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) 4 hr before transport measurement with everted sacs. Active transport of calcium was evident in control rats and was further stimulated by exogenous $1,25(OH)_2D_3$. Added to mucosal bathing fluid 10 μM cadmium partially inhibited active calcium transport both in controls and in rats receiving $1,25(OH)_2D_3$; 100 μM cadmium completely blocked active transport in both groups. Water transport was also inhibited by 10 and 100 μM cadmium. Cadmium uptake and transport were not affected by $1,25(OH)_2D_3$. The accumulation of cadmium in mucosal tissue was significantly inhibited by 1 mM calcium, but there was no significant effect on uptake or transmural transport. The findings suggest that cadmium and calcium do not interact specifically at a $1,25(OH)_2D_3$-dependent transport site. The interaction between calcium and cadmium in the duodenal mucosa could be related to the action of cadmium in blocking active transport processes.

Calcium metabolism is impaired by exposure to cadmium. The most pronounced effect is skeletal deformation due to loss of calcium from bone, apparently due in a large part to lowered calcium absorption and increased calcium secretion in the digestive tract (Ando *et al.*, 1977, 1978). Calcium absorption in the intestine depends on the vitamin D steroid-like hormone, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (Frolik and DeLuca, 1971). Cadmium can block conversion of 25-hydroxyvitamin D_3 ($25(OH)D_3$) to the highly active $1,25(OH)_2D_3$ in kidney mitochondria *in vitro* (Feldman and Cousins, 1973), suggesting that cadmium could act at this level to impair calcium absorption in the intestine. However, studies with intact rat and chick indicate it is unlikely that the effects of cadmium on the intestine are mediated indirectly by the inhibition of $1,25(OH)_2D_3$ production (Feldman and Cousins, 1973; Larsson and Lorentzon, 1974; Suda *et al.*, 1974).

At the level of the intestine, cadmium has been repeatedly demonstrated to inhibit calcium transport. Chronic cadmium administration not only reduces calcium absorption, it blocks the stimulation of calcium transport by exogenous $1,25(OH)_2D_3$ (Corradino, 1979; Fullmer *et al.*, 1980; Ando *et al.*, 1981; Chertok *et al.*, 1981). Cadmium also has a direct

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effect on the absorption and transmural transport of calcium. Cadmium introduced into the rat duodenum at the time of measurement of calcium transport inhibits calcium movement in a dose-dependent fashion (Yuhas *et al.*, 1978; Chertok *et al.*, 1981). Tsuruki *et al.* (1978) reported that this inhibition was the result of competition between calcium and cadmium for a vitamin D-dependent transport site, but Hamilton and Smith (1978) demonstrated noncompetitive inhibition of calcium transport by cadmium and supported their conclusion by showing that calcium had no effect on cadmium absorption in the duodenum of the rat. Foulkes (1980), however, did find that calcium inhibited cadmium uptake in the rat jejunum, and Koo *et al.* (1978) reported that calcium inhibited cadmium uptake in the chick duodenum. Furthermore, Koo *et al.* (1978) found that vitamin D enhanced cadmium absorption in the duodenum of vitamin D-deficient chicks. Therefore, despite the contradictory findings of Hamilton and Smith (1978), there is evidence that cadmium may be transported by a vitamin D-dependent transport route, and the inhibition of calcium transport by cadmium may result from competition for this route. To further test this hypothesis, an animal model that clearly demonstrates the action of 1,25-$(OH)_2D_3$ on intestinal calcium transport was used in the present study to examine the effects of cadmium on calcium transport and calcium on cadmium transport.

METHODS

Animals. Male, Sprague–Dawley rats obtained from Charles River Breeding Laboratories (Portage, Mich.) were allowed several days to become accustomed to their new housing where photoperiod (12-hr light/12-hr dark), temperature (24 ± 2°C), and humidity (50 ± 10%) were controlled. Rats received Purina rat chow (Ca, 2%; P, 1%; vitamin D_3, 300 IU/g) and tap water *ad libitum*. When rats weighed between 210 and 250 g they were killed for intestinal transport measurements. All transport experiments were performed in the early afternoon.

Vitamin D. The vitamin D metabolite, 1,25$(OH)_2D_3$ (compliments of Dr. Uskokovic, Hoffman–LaRoche, Nutley, N.J.) was administered to rats 4 hr prior to intestinal transport measurements. Rats received 0.5 μg of 1,25$(OH)_2D_3$ in 50 μl of 95% ethanol by ip injection. Control rats received 50 μl of 95% ethanol.

Intestinal transport. The intestinal transport of calcium and cadmium was measured with everted duodenal sacs. Preparation of the sacs is described elsewhere (Toraason and Wright, 1981). Each sac was filled with 0.5 ml of the medium described below and incubated in 10 ml of medium for 60 min with continuous gassing with 5% CO_2 in O_2. After completion of incubation, each sac was rinsed in a large volume of iced saline for 30 sec and blotted on absorbant paper; the contents were drained into a test tube. The ends including ties were trimmed from the sac, and each sac was again rinsed in a large volume of iced saline for 30 sec. After blotting it on absorbant paper, the duodenal segment was weighed to the nearest milligram. With a stainless-steel spatula, the mucosa was scraped from the serosa, and the mucosal tissue was then gently spread across a piece of Whatman filter paper. This technique resulted in the separation of a soft homogenous portion of the mucosa from fibrous tissue. Between 50 and 100 mg of the soft tissue was placed in a tared scintillation vial and weighed to the nearest milligram. In some experiments, the serosa was scraped clean of all adhering tissue, and a 50- to 100-mg piece was placed in a tared scintillation vial and weighed to the nearest milligram.

Biological solutions. The incubation media used in transport experiments contained 125 mM NaCl, 25 mM glucose, and 30 mM Tris buffer (Tham, Fisher Scientific, Springfield, N.J.). The pH was adjusted to 7.4 with NaOH or HCl. To all solutions, 0.1 μCi/ml of [^{3}H]polyethylene glycol (PEG) (molecular weight 4000) was added to serve as a nonabsorbable volume marker. Solute concentration in tissues was corrected for solute present in the extracellular space as defined by [^{3}H]PEG; in most cases, washing and blotting of mucosal scrapings and serosal segments removed all detectable [^{3}H]PEG. In experiments concerned with calcium transport, 0.25 mM $CaCl_2$ and 0.08 μCi/ml of ^{45}Ca were added to both mucosal and serosal bathing fluids, giving an initial serosal-to-mucosal (S/M) calcium concentration ratio of 1. An increase in this ratio constitutes movement of calcium against an electrochemical gradient and is, therefore, an indication of active transport (Wasserman and Taylor, 1969). Cadmium has not been demonstrated to be actively transported; therefore, the ^{109}Cd S/M ratio would not increase during incubation if cadmium were included at equivalent concentrations on both sides of the membrane. Where cadmium transport was to be measured, 1 μM $CdCl_2$ and 0.1 μCi/ml of ^{109}Cd were included only in the mucosal bathing fluid, so that the small amount of cadmium transported to the serosal compartment could be readily detected. Calcium or cadmium was included only in the mucosal bathing solution when used to inhibit the transport of the other.

Scintillation spectroscopy. Radionuclides were counted

on a programmed Packard Model 460 liquid scintillation spectrometer. Duplicate 100-μl samples of all incubation solutions were counted in 10 ml of Biofluor (New England Nuclear Corp., Boston, Mass.). Tissues were digested in 100 μl of Protosal (New England Nuclear) overnight at 55°C. Following digestion, 100 μl of 30% hydrogen peroxide was added to vials. After 30 min, samples were cooled to room temperature, and 100 μl of glacial acetic acid and 10 ml of Biofluor were added. Separate quench curves were used for tissues and solutions in the calculation of counting efficiency.

Statistical analysis. Analysis of variance (ANOVA) was used to test for statistically significant differences. Duncan's multiple range test was used to identify experimental groups that were significantly different from controls or other experimental groups. Data are presented as means ± SE.

RESULTS

Figure 1 shows ^{45}Ca S/M ratios achieved across everted duodenal sacs during 60 min of incubation. The S/M ratio of 3.35 in control rats indicates active transport of calcium, and $1,25(OH)_2D_3$ significantly enhanced active transport. The 10 μM cadmium present during incubation inhibited active transport of calcium in the presence or absence of $1,25(OH)_2D_3$, but it did not abolish the effect of $1,25(OH)_2D_3$. When the cadmium concentration in the incubation medium was 100 μM, the ^{45}Ca S/M ratio was reduced to nearly 1 in control and $1,25(OH)_2D_3$-dosed rats. Anaerobic incubation also reduced the ^{45}Ca S/M ratio to 1.

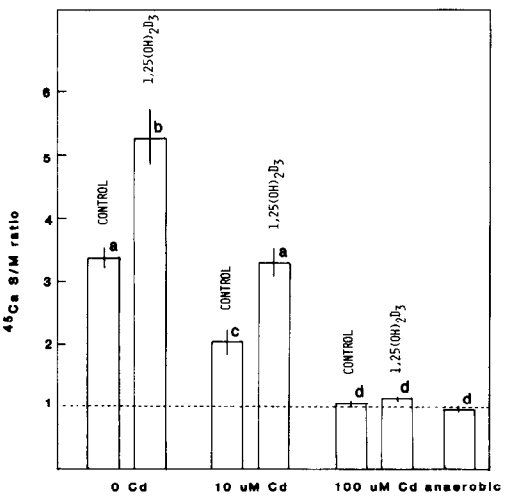

FIG. 1. ^{45}Ca S/M ratios obtained across everted duodenal sacs after 60 min of incubation in the presence or absence of cadmium. Dotted line represents initial S/M ratio. Rats were administered 0.5 μg of $1,25(OH)_2D_3$ in 0.05 ml ethanol 4 hr before transport measurement. Controls received 0.05 ml ethanol. Bars are means ± SE of four rats. Bars with different letters are significantly different ($p < 0.05$).

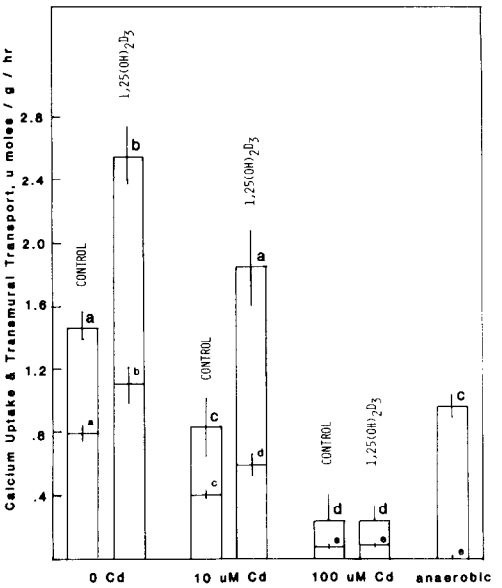

FIG. 2. Calcium uptake from mucosal bathing fluid and calcium transport to serosal compartment in everted duodenal sacs. The top of the bar represents uptake and the lower horizontal line through the bar represents transmural transport. Bars are means ± SE of four rats. Bars with different letters are significantly different ($p < 0.05$).

Figure 2 shows calcium uptake and transmural transport in everted duodenal sacs. $1,25(OH)_2D_3$ significantly enhanced both uptake and transport, although the effect on uptake was greater. Calcium uptake and transport were significantly inhibited by 10 μM cadmium. Inclusion of 100 μM cadmium in the incubation medium further reduced uptake and transport to similar low levels in both control and $1,25(OH)_2D_3$-administered rats. Under anaerobic conditions, transmural transport of calcium fell to 0, but calcium uptake was at approximately the same level as when 10 μM cadmium was included in the incubation medium.

Figure 3 shows that $1,25(OH)_2D_3$ significantly enhanced mucosal tissue accumulation of calcium. The 10 μM cadmium significantly inhibited mucosal accumulation in control and $1,25(OH)_2D_3$-administered rats, but uptake was still greater in rats receiving $1,25(OH)_2D_3$. Calcium accumulation into mucosal tissue was further inhibited by the presence of 100 μM cadmium, and there was no difference between control and $1,25(OH)_2D_3$-administered rats. Under anaerobic conditions, mucosal tissue calcium was the same as that in the 100 μM cadmium-exposed group.

Figure 4 shows cadmium uptake and transmural transport in everted duodenal sacs. Administration of $1,25(OH)_2D_3$ or incubation in 1 mM calcium had no effect on uptake or transport of cadmium. Under anaerobic conditions, cadmium absorption was significantly decreased, whereas transmural transport of cadmium was significantly enhanced.

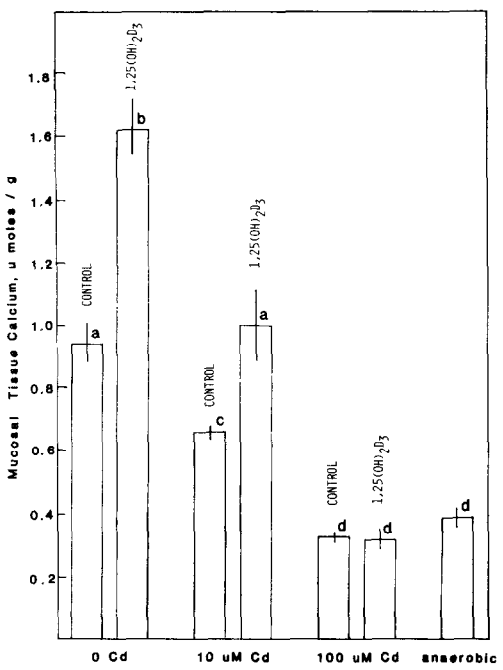

FIG. 3. Calcium accumulation in mucosal tissue scrapings after 90 min of incubation. Bars are means ± SE of four rats. Bars with different letters are significantly different ($p < 0.05$).

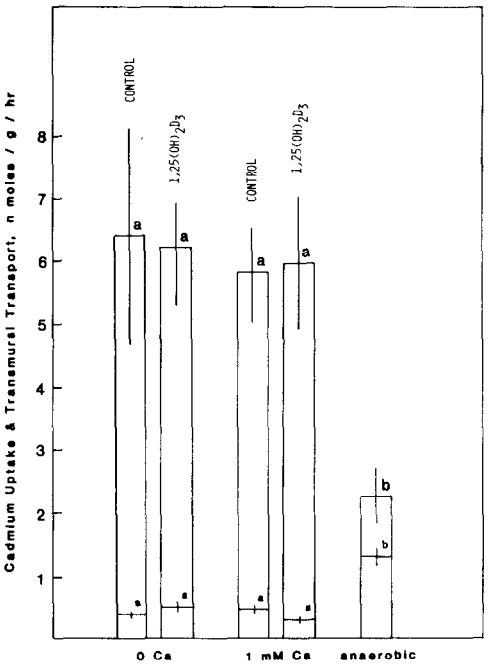

FIG. 4. Cadmium uptake from mucosal bathing fluid and cadmium transport to serosal compartment in everted duodenal sacs. The top of the bar represents uptake and the lower horizontal line through the bar represents transmural transport. Bars are means ± SE of four to six rats. Bars with different letters are significantly different ($p < 0.05$).

Figure 5 shows the mucosal and serosal tissue accumulation of cadmium during a 60-min incubation. Administration of $1,25(OH)_2D_3$ had no significant effect on tissue cadmium. The 1 mM calcium decreased only mucosal, not serosal, accumulation of cadmium. The small amount of cadmium in serosal tissue relative to mucosal tissue, indicates that there was retention of cadmium by mucosal tissue that prevented movement of cadmium into the serosal compartment. Anaerobic incubation decreased mucosal cadmium, but increased serosal cadmium.

Water movement was estimated by the change in concentration of the nonabsorbable marker, [^{3}H]PEG, in those sacs used to measure calcium transport (Figs. 1–3). During incubation, water moved into the serosal compartment. $1,25(OH)_2D_3$ did not significantly affect the transport of water into the duodenal

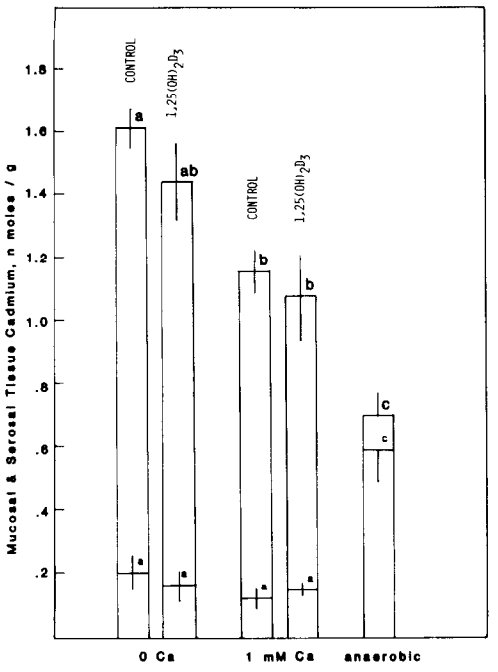

FIG. 5. Cadmium accumulation in mucosal tissue scrapings and serosal tissue after 60 min of incubation. The top of the bar represents mucosal tissue, and the lower horizontal line through the bar represents serosal tissue. Bars are means ± SE of four to six rats. Bars with different letters are significantly different ($p < 0.05$).

sac. Cadmium significantly inhibited water transport: 10 μM cadmium reduced water transport by 33%, and 100 μM cadmium reduced it by 50%. Under anaerobic conditions, water transport was reduced by 63%.

DISCUSSION

The vitamin D metabolite $1,25(OH)_2D_3$ plays a vital role in maintaining calcium homeostasis. An increase or decrease in circulating $1,25(OH)_2D_3$ has a corresponding effect on calcium absorption in the small intestine. Serum concentrations of $1,25(OH)_2D_3$ are normally maximum in weanling rats undergoing rapid growth (Halloran and DeLuca, 1980). As rats age, body weight stabilizes and the need for calcium declines; circulating $1,25(OH)_2D_3$ also declines and there is a decrease in intestinal calcium transport (Armbrecht *et al.*, 1980; Gishan *et al.*, 1980). The present study confirms earlier observations (Lee *et al.*, 1981; Toraason and Wright, 1981) that administration of $1,25(OH)_2D_3$ stimulates duodenal calcium transport in adult male rats maintained on a diet adequate in vitamin D, calcium, and phosphorus. $1,25(OH)_2D_3$ increased calcium uptake from mucosal bathing fluid, accumulation in mucosal tissue, and transport to the serosal compartment. In this same model, $1,25(OH)_2D_3$ did not affect mucosal uptake, transmural transport, or tissue accumulation of cadmium. This suggests that the major uptake and transport route for cadmium is not that of $1,25(OH)_2D_3$-dependent calcium transport.

If cadmium were transported by a $1,25(OH)_2D_3$-dependent route, then calcium and cadmium would inhibit the uptake or accumulation of each other because of competition for the transport route. Although calcium concentrations of 10 mM and above have been demonstrated to inhibit cadmium absorption (Foulkes, 1980; Koo *et al.*, 1978), 1 mM calcium, which is a thousandfold greater than the 1 μM cadmium concentration used, does not block the uptake or transmural transport of cadmium. Cadmium accumulation in mucosal tissue, however, was reduced by 1 mM calcium. Perhaps inside or on the surface of mucosal cells there is a binding site for which cadmium and calcium compete. A likely candidate in the cytosol would be intestinal calcium-binding protein (CaBP), which depends on $1,25(OH)_2D_3$ (Armbrecht *et al.*, 1980). Cadmium's affinity for CaBP is comparable to that of calcium (Ingersoll and Wasserman, 1971). If cadmium binds to CaBP inside the cell, then an increased cadmium accumulation in mucosal tissue should be evident in $1,25(OH)_2D_3$-dosed rats, unless this is masked by excess nonspecific binding of cadmium to mucosal tissue. Since stimulation of CaBP lags several hours behind elevated calcium transport following $1,25(OH)_2D_3$ administration (Armbrecht *et al.*, 1980; Bronner *et al.*, 1982b), it is possible that CaBP was not significantly increased in the duodenal sacs examined.

Perhaps allowance of enough time for $1,25(OH)_2D_3$ to significantly increase CaBP would have led to an increase in cadmium uptake or accumulation in mucosal tissue.

Calcium is transported across the rat duodenum by both active and passive processes; the active process appears to be dependent on $1,25(OH)_2D_3$ (Frolik and DeLuca, 1971; Bronner *et al.*, 1982a; Pansu *et al.*, 1981, 1983). The ^{45}Ca S/M ratios greater than 1 attained across everted sacs from control rats in the present study demonstrate some degree of active transport. This active transport is apparently due to endogenous circulating $1,25(OH)_2D_3$ (Lee *et al.*, 1981). The administration of $1,25(OH)_2D_3$ to adult rats further stimulated active transport, which was evident by the increased S/M ratios (Fig. 1). The 10 μM cadmium decreased the S/M ratio approximately 40% in both control and $1,25(OH)_2D_3$ groups, and the 100 μM cadmium abolished net active transport of calcium. This blockage resulted not only in decreased uptake and transmural transport but in decreased accumulation as well. Which of these effects are due solely to inhibition of an active transport mechanism is not clear.

Several additional observations suggest that inhibition of calcium transport by cadmium is part of a more generalized effect of cadmium on the intestine. Water transport is inhibited by cadmium and appears to be almost as sensitive to cadmium as is calcium transport. Since water movement depends on solute movement (Curran, 1965), it is likely that the transport of other solutes, in addition to calcium, is also inhibited. In support of this, we have found that active transport of 3-*O*-methylglucose is as sensitive to cadmium as is active transport of calcium (unpublished data). Furthermore, Sugawara and Sugawara (1975) found that 10 μM cadmium inhibited *in vitro* brush border alkaline phosphatase and ATPase, both of which are associated with active transport processes in the intestine. Therefore, the effect of cadmium on calcium transport may be one of several effects of acute exposure to low levels of cadmium. Exactly how this low concentration of cadmium produces the variety of effects in the duodenum is not evident from data presented here.

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