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Unanticipated stimulatory action of glucocorticoids on epithelial calcium absorption. Effect of dexamethasone on rat distal colon.

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Research Article

We studied the action of a glucocorticoid (GC, dexamethasone) and 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] on transepithelial calcium (Ca) transport in rat distal colon. GC 1.2 mg or 1,25(OH)2D3 270 ng were given daily for 4 d and Ca fluxes were measured in vitro in the absence of electrochemical gradients (Ussing technique). Results: (a) Both 1,25(OH)2D3 and GC increased Ca absorptive flux from 24 +/- 3 (SEM) to 50 +/- 1 and from 23 +/- 1 to 38 +/- 4 nmol/cm2 per h, respectively (in each case n = 9, P less than 0.01); both steroid hormones had no effect on Ca secretory flux. (b) GC, but not 1,25(OH)2D3 increased the short-circuit current Isc) from 30 +/- 5; to 111 +/- 13 microA/cm2 (P less than 0.01), reflecting stimulation of electrogenic sodium (Na) transport. Choline replacement of Na in the bathing buffer abolished both the Isc and the active Ca transport induced by GC, but has no effect on the 1,25(OH)2D3-stimulated active Ca absorption. (c) When the buffer Ca concentration ([Ca]) on both sides of the epithelium was reduced from 1.25 to 1.25 X 10(-2) mM, the GC-induced, but not the 1,25(OH)2D3-induced, stimulation in Ca absorption was abolished. This suggests that the GC-stimulated Ca absorption may require a "threshold" Ca gradient across the luminal membrane through which Ca influx occurs. Thus, contrary […]

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Unanticipated Stimulatory Action of Glucocorticoids on Epithelial Calcium Absorption

EFFECT OF DEXAMETHASONE ON RAT DISTAL COLON

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ABSTRACT We studied the action of a glucocorticoid (GC, dexamethasone) and 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] on transepithelial calcium (Ca) transport in rat distal colon. GC 1.2 mg or 1,25$(OH)_2D_3$ 270 ng were given daily for 4 d and Ca fluxes were measured in vitro in the absence of electrochemical gradients (Ussing technique). Results: (*a*) Both 1,25$(OH)_2D_3$ and GC increased Ca absorptive flux from 24±3 (SEM) to 50±1 and from 23±1 to 38±4 nmol/cm^2 per h, respectively (in each case $n = 9$, $P < 0.01$); both steroid hormones had no effect on Ca secretory flux. (*b*) GC, but not 1,25$(OH)_2D_3$ increased the short-circuit current (Isc) from 30±5; to 111±13 μA/cm^2 ($P < 0.01$), reflecting stimulation of electrogenic sodium (Na) transport. Choline replacement of Na in the bathing buffer abolished both the Isc and the active Ca transport induced by GC, but has no effect on the 1,25$(OH)_2D_3$-stimulated active Ca absorption. (*c*) When the buffer Ca concentration ([Ca]) on both sides of the epithelium was reduced from 1.25 to 1.25 × 10^{-2} mM, the GC-induced, but not the 1,25$(OH)_2D_3$-induced, stimulation in Ca absorption was abolished. This suggests that the GC-stimulated Ca absorption may require a "threshold" Ca gradient across the luminal membrane through which Ca influx occurs. Thus, contrary to the current consensus, this study demonstrates that GC stimulates active Ca transport and that this action is mediated through a mechanism dependent on the presence of Na and a critical [Ca] in the ambient medium.

INTRODUCTION

Previous studies have demonstrated that calcium (Ca) transport in various segments of intestine responds to 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$][1] stimulation differently (1–4). Thus, while the duodenum and proximal colon respond to physiological or near-physiological quantities of 1,25$(OH)_2D_3$, the Ca absorptive mechanism in jejunum and ileum is only stimulated by supraphysiological doses of this hormone (2). Furthermore, while 1,25$(OH)_2D_3$ causes parallel stimulation of both Ca and inorganic phosphate (P) in all small intestinal segments (1), in proximal colon the stimulation of Ca transport is not associated with simultaneous stimulation in P transport (3).

The question whether glucocorticoids have similar action on Ca transport in both small and large intestine has not been answered. Because a number of studies have reported a suppressive effect of glucocorticoids on duodenal Ca absorption (5–9), in this study we examined the effect of a glucocorticoid (dexamethasone) on colonic Ca transport. Rather unexpectedly, we found that this hormone stimulated Ca absorption in rat distal colon, further stressing the segmental differences in intestinal Ca transport processes.

METHODS

Male Holtzman rats weighing 250–300 g were housed in individual cages and weighed daily. They were fed Purina rat chow (Ca = 1.2%, P = 0.8%, Ralston Purina Co., St. Louis,

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[1] *Abbreviations used in this paper*: [Ca], calcium concentration; 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; Gt, tissue conductance; Isc, short-circuit current; Jms, mucosal-to-serosal fluxes; Jnet, net flux; Jsm, serosal-to-mucosal fluxes; PD, transmural potential difference; PEG, polyethylene glycol.

MO) and given water ad lib. Two series of experiments were performed. In the first series rats were randomized into control and dexamethasone (Decadron, Merck Sharp & Dohme, West Point, PA) treatment groups. Dexamethasone (1.2 mg/d) was given subcutaneously each morning (7a.m.–9a.m.) for 4 d. Control rats were given equal volume of the solvent, normal saline. In the second series rats were given $1,25(OH)_2D_3$, 270 ng/d, in propanediol, following an identical injection schedule. The control rats were injected with vehicle only. Chemically synthesized $1,25(OH)_2D_3$ was generously provided by Dr. M. Uskokovic of Hoffman-LaRoche Inc., Nutley, NJ, courtesy of Dr. A. W. Norman. On the morning of the last injection the rats were killed by guillotine and a 5–7-cm segment of distal colon was taken just proximal to a lymph node found regularly at the distal end of the colon. The segment was cut open along the mesenteric border into a flat sheet, rinsed with buffer (see below) and mounted across Lucite chambers that exposed a circular area of epithelium of 0.67 cm^2. The rats were not fasted before the study.

Transmural Ca and P fluxes were studied in vitro using the modified Ussing technique described in detail in previous publications (1, 3). An additional study was carried out to examine the effect of dexamethasone on unidirectional, paracellular fluid fluxes using [^{3}H]polyethylene glycol (PEG, molecular weight 900) as a marker. The rats were prepared exactly as those used for Ca and P fluxes. A modified Krebs-Ringer-HCO_3 buffer containing, in millimoles per liter, 143 Na, 1.25 Ca, 1.18 P, 1.20 Mg, and 11 D-glucose, was used unless stated otherwise. Sodium-free buffer was prepared by substituting sodium chloride and sodium bicarbonate with choline chloride (Fisher Scientific Co., Pittsburgh, PA) and choline bicarbonate (Sigma Chemical Co., St. Louis, MO), respectively. Amiloride was supplied through courtesy of Merck, Sharpe & Dohme, and theophylline was purchased through Sigma Chemical Co. ^{45}Ca as $CaCl_2$ and [^{3}H]PEG

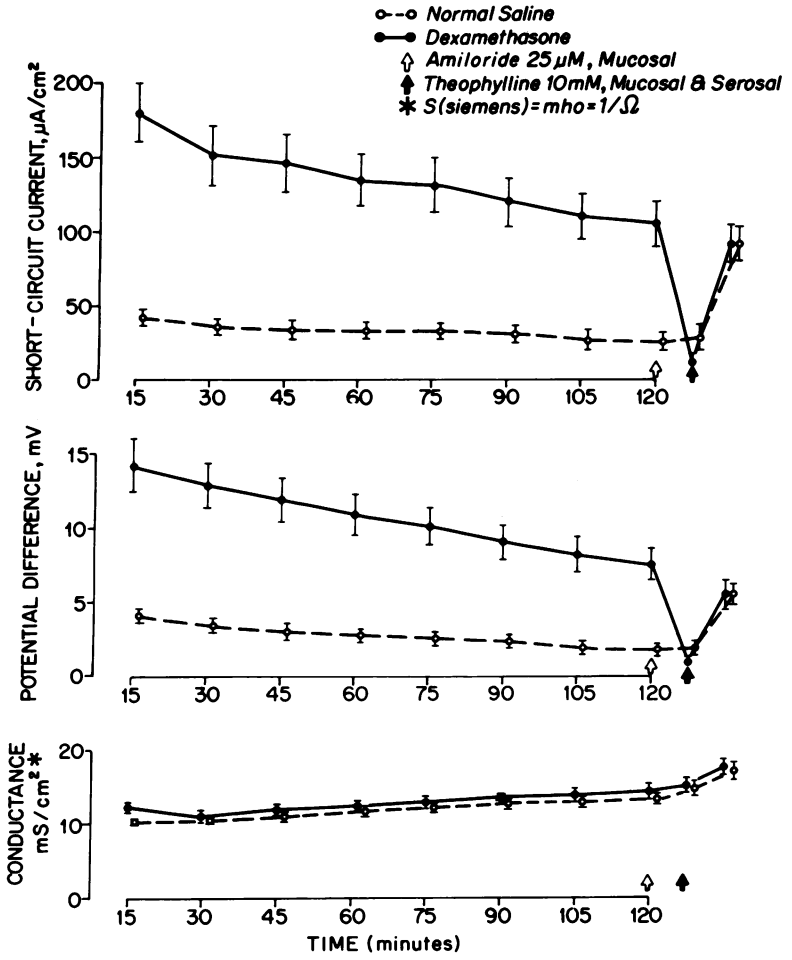

FIGURE 1 Isc, PD, and Gt of distal colon from dexamethasone-treated (continuous line) and control, normal saline-treated (discontinuous line) rats. Measurements were made at 15-min intervals from the time of mounting in Lucite chambers. At the end of each study amiloride was added to the mucosal compartment. This was followed by the addition of theophylline to both the mucosal and the serosal compartments (n = 18). Data represent mean±SEM.

were obtained from New England Nuclear, Boston, MA. The radioisotopes were counted in a Beckman LS 250 dual-window liquid scintillation spectrometer (Beckman Instruments, Inc., Fullerton, CA) and ion fluxes were calculated as described (10). The transmural, potential difference (PD) was abolished using automatic voltage clamps (Netronics, Inc., Hudson, MA) that passed a short-circuit current (Isc) across the epithelium after a correction for the resistance of buffer between the agar bridge tips (10). Tissue conductance (Gt) was monitored at 15-min intervals by recording the current required for the voltage clamp to produce an increase in PD of 10 mV. Net flux (Jnet) is calculated as the difference between unidirectional mucosal-to-serosal flux (Jms) and serosal-to-mucosal flux (Jsm) across pieces of adjacent colon with conductances that matched within 70%. Statistical comparisons of independent variables within treatment groups was made using one-way analysis of variance. When the analysis of variance indicated a difference between means, Dunnett's format for multiple t test comparisons was used to obtain probability estimates (11).

RESULTS

The electrical parameters of the colonic epithelium from dexamethasone- or $1,25(OH)_2D_3$-treated rats and their respective controls are summarized in Figs. 1 and 2. Treatment with dexamethasone caused a clear increase in Isc and PD when compared with controls.

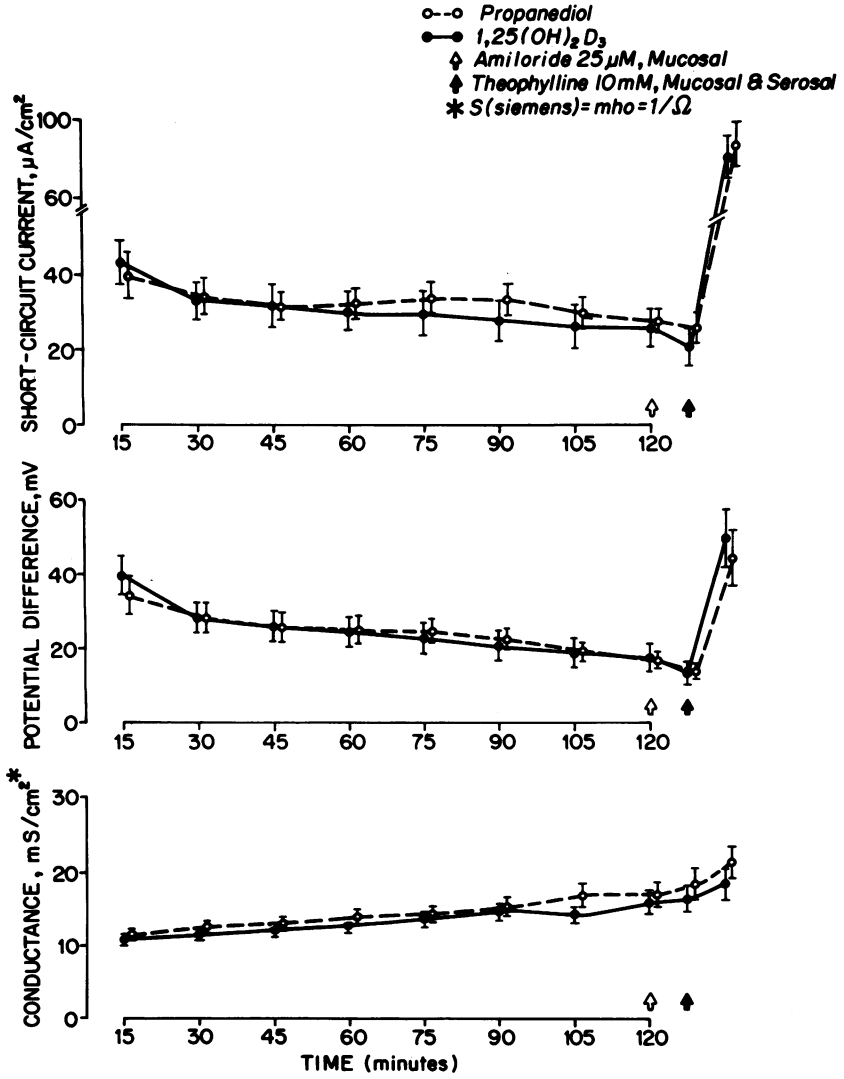

FIGURE 2 Electrical parameters of distal colon from $1,25(OH)_2D_3$-treated (continuous line) and control, propanediol-treated (discontinuous line) rats. See also Fig. 1 legend (n = 14). Data represent mean±SEM.

The augmented Isc and PD were completely suppressible by the addition of amiloride to the mucosal compartment. At the end of each study, theophylline was added to both the serosal and mucosal compartments. An increase in both Isc and PD was used as an index for tissue viability. $1,25(OH)_2D_3$ treatment caused no discernible changes in Isc, PD, or Gt when compared with vehicle-injected rats. In these colonic segments, the addition of amiloride to the mucosal compartment caused no observable changes and the addition of theophylline led to an anticipated increase in Isc and PD without significant changes in Gt.

The unidirectional Ca fluxes, measured at 15-min intervals over a period of 2 h, attained steady rates at ~60 min and remained stable for the subsequent 60 min. This is in conformity with our previous experience (3). The results presented for unidirectional fluxes represent the average of at least three to four steady-state measurements for each flux experiment. Unidirectional Ca fluxes across colonic segments from $1,25(OH)_2D_3$-treated and control rats are depicted in Fig. 3. In control studies Jms was not different from Jsm indicating the absence of a net flux for Ca. Treatment with $1,25(OH)_2D_3$ caused a marked stimulation in Jms, with Jsm remaining unchanged, resulting in a net flux for Ca in the absorptive direction. Fig. 4 summarizes the results of dexamethasone treatment on unidirectional Ca fluxes in distal colon. In colonic segments from control, normal saline-injected rats Jms was again not different from Jsm. Dexamethasone treatment resulted in changes in Ca transport similar to those seen with $1,25(OH)_2D_3$ i.e., a stimulation in Jms but no change in Jsm. To ascertain if either the glucocorticoid or $1,25(OH)_2D_3$ stimulatory action on Ca transport is sodium dependent, further studies were carried out in sodium-free buffer. Table I depicts the Gt and Isc in colonic segments from either dexamethasone- or $1,25(OH)_2D_3$-treated rats measured in buffer

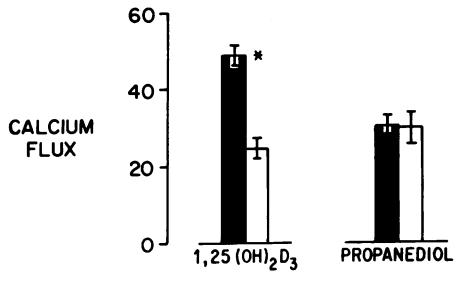

FIGURE 3 Unidirectional calcium fluxes, in nanomoles per square centimeter per hour, across distal colon from $1,25(OH)_2D_3$-treated and control, propanediol-treated rats. Jms are represented by dark columns and Jsm are represented by light columns. $^*P < 0.01$; ($n = 9$).

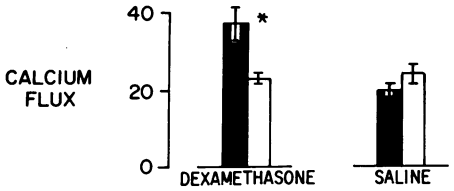

FIGURE 4 Unidirectional calcium fluxes, in nanomoles per square centimeter per hour, across distal colon from dexamethasone-treated and control, normal saline-treated rats. Jms are represented by dark columns and Jsm are represented by light columns. $^*P < 0.05$; ($n = 9$).

with or without sodium. It is clear that the substitution of sodium by choline resulted in a dramatic reduction in Gt and Isc in both treatment groups. Table I further demonstrates that while the absence of Na in the ambient medium completely abolished the dexamethasone-stimulated Ca absorption, it had no effect on the $1,25(OH)_2D_3$-stimulated Ca absorption. Fig. 5 illustrates the effect of dexamethasone and $1,25(OH)_2D_3$ on Ca Jnet measured in buffers with decreasing Ca concentration [Ca]. Two observations will be emphasized. First, the magnitude of the stimulation in Jnet was lower in dexamethasone-treated rats at all [Ca] tested. Second, when the buffer [Ca] was decreased to 1.25×10^{-2} mM, the Ca stimulatory action of dexamethasone was no longer observed, while the stimulatory action of $1,25(OH)_2D_3$ remained intact. Finally, the measurement of unidirectional [^{3}H]PEG fluxes (Table II) indicated that dexamethasone treatment did not alter either Jms or Jsm of this extracellular marker across the distal colonic epithelium. Although Jsm appeared to exceed Jms in both dexamethasone- and vehicle-treated groups, the difference was not significant in either group and Jnet was not significantly different from zero in both instances.

DISCUSSION

Our observation that glucocorticoid stimulates active transmural Ca absorptive flux appears at variance with the general consensus that this steroid hormone depresses intestinal Ca absorption (5–8, 12–14). Careful review of the published data, however, failed to marshal a consistent argument for a negative effect of glucocorticoid on intestinal Ca absorption.

Balance studies in man with hyperadrenocortical function revealed increased fecal Ca loss, although true Ca absorption was not depressed in face of adequate dietary Ca intake (15). The majority of the studies on the interrelationship between glucocorticoid and intestinal Ca absorption in man were carried out using radioisotopic tracers. Based on data collected using a

TABLE I

Effects of Buffer Na on Ca Fluxes, Gt, and Isc Across Distal Colon of Rats Treated with either Dexamethasone or 1,25(OH)$_2$D$_3$

Treatment	Buffer	n	Fluxes			Gt	Isc
			Jms	Jsm	Jnet		
			nmol/cm^2/h			mS/cm^2	μA/cm^2
Dexamethasone	−Na	14	27.8±2.2	28.0±2.1	−0.2±1.9	7.3±0.3	4.0±1.0
Dexamethasone	+Na	14	35.0±3.6*	26.4±2.0	8.5±2.8‡	16.8±1.0‡	229.8±15.0‡
1,25(OH)$_2$D$_3$	−Na	14	34.0±2.4*	22.6±1.5	11.5±3.1	9.5±0.7	4.3±2.1
1,25(OH)$_2$D$_3$	+Na	13	35.6±3.8*	21.6±1.3	13.9±3.8	23.6±2.7‡	37.5±6.7‡

Values are mean±1 SEM for (*n*) animals. Gt is expressed in siemens (S = mho 1/Ω).

* Jms vs. Jsm, $P < 0.05$.

‡ +Na vs −Na, $P < 0.01$.

variety of techniques in subjects given different preparations, dosages, and durations of glucocorticoids, intestinal Ca absorption has been shown to increase (16), decrease (12–14), or remain unchanged (17). Studies in intact animals have also revealed that glucocorticoids could cause a spectrum of effects on intestinal Ca absorption ranging from stimulation (6, 18) through no effect (19) to inhibition (20). Ferretti et al. (21) demonstrated that in rat, Ca absorption increased with increasing glucocorticoid (cortisol hemisuccinate) administration up to 16 mg/kg per d and remained high as the dose was increased to 128 mg/kg per d. Intestinal Ca secretion, however, increased exponentially as a function of the dose from 16 mg/kg per d upwards. Thus, at high dose the net Ca absorption was reduced (secondary to a marked increase in Ca secretion) but the true Ca absorption remained stimulated. Glucocorticoid-induced endogenous Ca secretion has also been demonstrated in man (21), rats (20), and dogs (22), although in our study dexamethasone did not alter colonic Ca secretion. The data of Ferretti et al. (21) may explain, at least in part, the divergent findings on the effect of glucocorticoids on intestinal Ca absorption.

Another possible explanation for the differences in the reported effect of glucocorticoids on Ca absorption is that this group of hormones may influence different intestinal segments differently. Favus et al. (8), using

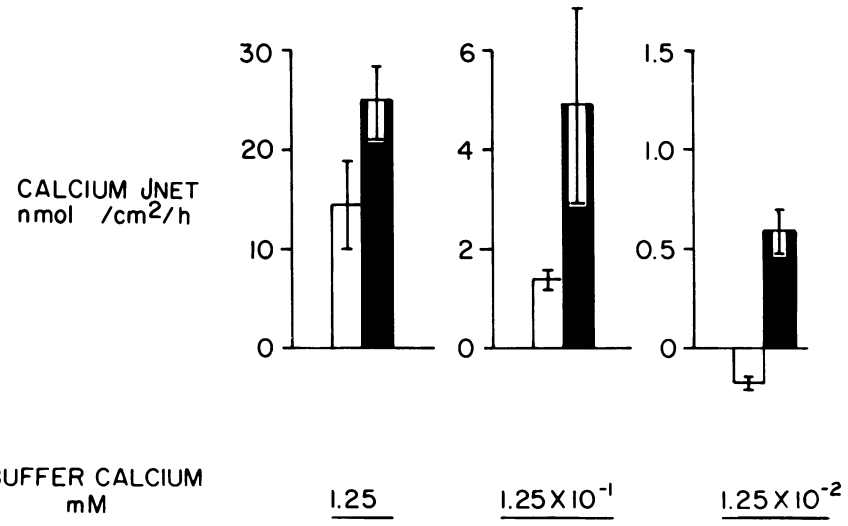

FIGURE 5 Jnet of calcium across distal colon from dexamethasone-treated (light columns) and 1,25(OH)$_2$D$_3$-treated (dark columns) rats. Measurements were made in buffers with three different calcium concentrations.

TABLE II
Unidirectional Fluxes of [^3H]PEG Across Distal Colon of Rats Treated with Dexamethasone or Vehicle

Treatment	n	Jms	Jsm	Jnet
			nmol/cm²/h	
Dexamethasone	6	6.06±0.67	10.64±1.75	−4.57±2.14
Vehicle	5	6.93±0.66	9.29±1.07	−2.36±1.36

a modified Ussing technique, observed that cortisone acetate caused a marked reduction in Ca absorptive flux in duodenum from vitamin D-deficient rats. This is in clear contrast to our findings in rat distal colon indicating a fundamental difference between the proximal and the distal gut in their response to glucocorticoids. There is, however, a major difference between the two studies: we used vitamin D-replete rats while Favus et al. used vitamin D-deficient rats. It is possible that the presence or absence of vitamin D and its metabolites may alter the action of glucocorticoids on Ca transport. Thus, Spanos et al. (23) reported that cortisol caused a marked stimulation in 25(OH)D_3-1α-hydroxylase activity measured in chick kidney homogenate. The effect was more marked in the vitamin D-replete animal than the vitamin D-deficient animal. Manolagas et al. (24) reported that glucocorticoids caused a dose-dependent increase in cytosolic 1,25$(OH)_2D_3$ receptors in osteoblastlike cells from an osteogenic sarcoma cell line. The possibility thus exists that glucocorticoids may bring about an enhanced target organ response to a given level of 1,25$(OH)_2D_3$.

The postulate that glucocorticoids may induce a suppressive effect on Ca absorption in proximal gut and a stimulatory effect in distal gut finds credence in a number of studies. Thus, in in vitro studies the steroid hormone has been shown to decrease active Ca transport in duodenum (5–9) while in the more distal small bowel Ca transport was either not altered (6, 9) or stimulated (7). In glucocorticoid-treated man the absorption of orally administered radioactive Ca was slower than in untreated subjects in the first hour, similar at around the second hour, and thereafter the absorption was better in the treated than the untreated subjects (16, 25). These findings are consistent with the interpretation that glucocorticoid may cause a proximal inhibitory effect and a distal stimulatory effect on Ca absorption.

The basic mechanism through which glucocorticoids may stimulate Ca absorption is unknown. The observations of Spanos et al. (23) and Manolagas et al. (24) on the stimulatory action of glucocorticoids on 25(OH)D_3-1α-hydroxylase and 1,25$(OH)_2D_3$ cytoreceptor formation have been mentioned. Corradino (26) using organ-cultured, embryonic chick duodenum demonstrated that hydrocortisone caused a clear increase in the same specific Ca-binding protein that was inducible by vitamin D.

Glucocorticoids are known stimulators of active Na absorption, probably through increasing the luminal (brush border) membrane permeability to Na (27, 28). This induced electrogenic Na transport is reflected by an increase in transepithelial Isc, which is characteristically inhibited by amiloride (Fig. 1). It is possible that in addition to Na, glucocorticoids may also increase the apical border permeability to Ca, and thus mimic the action of 1,25$(OH)_2D_3$ (29). The observation that the dexamethasone-stimulated transmural Ca transport required a finite Ca gradient across the cell membrane (Fig. 5) is compatible with such a hypothesis. The mechanism of Ca transport stimulation by glucocorticoids and 1,25$(OH)_2D_3$ is probably different quantitatively and/or qualitatively since the Ca stimulatory action of the latter was not as critically dependent on the transcellular Ca gradient. A further difference between these two hormones on Ca transport is that the glucocorticoid action on Ca is only expressed in the presence of extracellular Na while the 1,25$(OH)_2D_3$ action on Ca is manifested even in the absence of extracellular Na (Table I). The absence of any observable effect of dexamethasone on unidirectional [^3H]PEG fluxes suggests (but does not completely exclude the possibility) that the effect of this hormone on Ca fluxes is not mediated through changes in fluid fluxes across the paracellular pathway. Parenthetically, these data also suggest that the glucocorticoid-induced augmentation in Na, as reflected by the increase in Isc, and water fluxes probably occur through the transcellular route. Finally, it should be stressed that these findings are based on in vitro studies in rat distal colon. Whether dexamethasone has similar effects in man is not known.

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