Journal of Cellular Biochemistry 57:392–398 (1995)

# Calcium Transport in Epithelial Cells of the Intestine and Kidney

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**Abstract** The central role of 1α,25-dihydroxyvitamin $D_3$ in the regulation of calcium balance is well established. By increasing the absorption of calcium in the intestine and the reabsorption of filtered calcium in the kidney tubule, the hormone maintains an appropriate calcium balance. The cellular mechanisms that underlie the increase in calcium transport in epithelial cells in response to 1α,25-dihydroxyvitamin $D_3$ are beginning to be defined. These events include an increase in the movement of calcium across the apical membrane of the cell, an increase in the movement of calcium across the cell, and an increase in the extrusion of calcium at the basolateral portion of the cell. In this *Prospects* article, I will discuss the nature of the various processes and proteins involved in transcellular calcium movement, and I will attempt to highlight various future areas of research. 

**Key words:** calcium transport, calbindin, calcium pump, vitamin D–receptor, 1α,25-dihydroxyvitamin $D_3$

The central role of the vitamin D endocrine system in calcium homeostasis is now well established [DeLuca and Schnoes, 1983; Kumar, 1984]. Research during the early part of this century demonstrated the critical role of the fat-soluble vitamin, vitamin D, in preventing rickets [Mellanby, 1919; McCollum et al., 1922]. The pioneering experiments of Nicolaysen showed that vitamin D was essential for the maintenance of a positive calcium balance when dietary calcium was reduced [Nicolaysen and Eeg-Larsen, 1953]. DeLuca and colleagues at the University of Wisconsin and Kodicek and colleagues at Cambridge defined the metabolic processes needed for the biotransformation of vitamin D to its biologically active metabolite, 1α,25-dihydroxyvitamin $D_3$ [DeLuca and Schnoes, 1983; Kumar, 1984]. It is now well established that vitamin $D_3$ is metabolized to an essential intermediary metabolite, 25-hydroxyvitamin $D_3$, by hepatic, microsomal, and mitochondrial cytochrome P-450 containing vitamin $D_3$ 25-hydroxylases [DeLuca and Schnoes, 1983; Kumar, 1984, 1990]. 25-hydroxyvitamin $D_3$ itself is metabolized to the bioactive metabolite of 1α,25-dihydroxyvitamin $D_3$, in kidney proximal tubules, by a multicomponent cytochrome P-450 containing enzyme, 25-hydroxyvitamin $D_3$ 1α-hydroxylase [DeLuca and Schnoes, 1983; Kumar, 1984, 1990]. 1α,25-dihydroxyvitamin $D_3$ is transported to the intestine, the distal tubule of the kidney, and bone, where by various mechanisms it increases the movement of calcium from the lumen into the extracellular fluid or from the marrow space into bone matrix [DeLuca and Schnoes, 1983; Kumar, 1984, 1990; Kumar et al., 1994; Wasserman et al., 1992a,b]. It is also clear that 1α,25-dihydroxyvitamin $D_3$ must bind to an intracellular receptor, the 1α,25-dihydroxyvitamin $D_3$ receptor (usually abbreviated as VDR), that is related to a number of other sterol and steroid receptors in order to induce transcription of various genes [Pike, 1991]. How 1α,25-dihydroxyvitamin $D_3$ influences calcium movement in the intestine, the kidney, and bone will be the subject of this Prospect article.

## MECHANISM OF ACTION OF 1α,25-DIHYDROXYVITAMIN $D_3$ IN THE INTESTINE

In considering the movement of calcium across an intestinal absorptive cell such as the duodenal cell, it is important to remember that the absorption of this divalent ion is an energy requiring process [Martin and DeLuca, 1969; Wasserman et al., 1984]. The movement of cal-

Received August 11, 1994; accepted August 15, 1994.

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cium across the apical membrane of an intestinal epithelial cell is favored by the fact that concentrations of calcium within the cell are considerably lower than those in the intestinal lumen and by the fact that the cell is electronegative compared to the intestinal lumen [Wasserman et al., 1984]. Concentrations of calcium in intestinal contents may be as high as $10^{-3}$ M, whereas concentrations of calcium within the cell are approximately $10^{-6}$ M. Therefore, the movement of calcium across the apical membrane does not require the expenditure of energy [Wasserman et al., 1984]. In contrast, the movement of calcium from within the cell into the extracellular fluid space and across the basolateral membrane requires the expenditure of energy [Wasserman, et al., 1984, 1992a,b] because concentrations of calcium within extracellular fluid and blood are considerably higher than those within the cell and because the cell is electronegative relative to the extracellular fluid compartment. ATP is required for the function of an ATP-driven calcium pump and for providing a sodium gradient (via the activity of the sodium/potassium ATPase) for the activity of a sodium-calcium exchanger [Wasserman et al., 1984, 1992a,b].

How does 1α,25-dihydroxyvitamin $D_3$ influence the movement of calcium across the intestinal absorptive epithelium? Does the process involve the synthesis of new protein and the activation of transcription of specific genes within the nucleus? Does it occur solely as a result of the activation of nongenomic processes? In my view, the field has been hampered by the notion that the movement of calcium in response to 1α,25-dihydroxyvitamin $D_3$ occurs as a result of either a genomic activation process or as a result of a nongenomic mechanism. Based on review of data obtained from various laboratories, the process probably involves both genomic and nongenomic events. It is difficult to ascribe precise quantitative importance to either one of these processes, although experiments concerning genomic control of calcium transport have been far more easy to design and conduct.

Several groups have demonstrated the importance of new protein synthesis in calcium transport in the intestine. Briefly, blocking protein synthesis by actinomycin D or cycloheximide results in a decrease in intestinal calcium transport [Kowarski and Schacter, 1975; Corradino, 1973a,b; Francheschi and DeLuca, 1981]. Experiments of nature, involving mutations of the vitamin D receptor gene, have clearly demonstrated a central role for protein synthesis in intestinal calcium transport [Liberman et al., 1986; Castells et al., 1986; Gamblin et al., 1985]. Humans with vitamin D–dependency rickets, type II, have high circulating 1α,25-dihydroxyvitamin $D_3$ concentrations, do not exhibit 1α,25-dihydroxyvitamin $D_3$–induced protein synthetic events, such as the induction of 24-hydroxylase activity in response to 1α,25-dihydroxyvitamin $D_3$, and manifest rickets and calcium malabsorption [Gamblin et al., 1985]. These data suggest that protein synthesis is crucial to the response of the intestinal cell to 1α,25-dihydroxyvitamin $D_3$. Several proteins that could play a role in calcium movement, such as the vitamin D–dependent calcium binding proteins and the plasma membrane calcium ATPase or calcium pump among others, are induced following the administration of 1α,25-dihydroxyvitamin $D_3$ [Wasserman and Taylor, 1966; Borke et al., 1990; Ghijsen et al., 1982; Wasserman et al., 1992a,b; Cai et al., 1993].

On the other hand, intestinal perfusion experiments performed by Norman and his colleagues have shown that following the infusion of 1α,25-dihydroxyvitamin $D_3$ into perfused intestinal loops maintained ex vivo, there is a rapid increase in calcium movement from the intestinal lumen into the extracellular fluid space independent of the synthesis of new protein [Nemere and Norman, 1990; Zhou et al., 1992a,b; Nemere et al., 1991a,b]. This process, known as transcaltachia, is not blocked by inhibitors of protein synthesis or Golgi or microfilament function and is blocked by 1β,25-dihydroxyvitamin $D_3$ and nifedipine [Nemere and Norman, 1987, 1990; Zhou et al., 1992b; Norman et al., 1992, 1993]. PTH (1-34), PTH-related protein (1-34), and BAY K8644 increase transcaltachia [Zhou et al., 1992a; de Boland et al., 1990]. Lysosomal and endocytic vesicles are thought to play a role in transcaltachia [Nemere and Norman, 1990; Nemere et al., 1991a,b]. The opening of $Ca^{2+}$ channels in the basolateral portion of the cell associated with exocytosis of $Ca^{2+}$ containing vesicles in response to protein kinase C and protein kinase A activation are believed to play a role in this process [de Boland and Norman, 1990a]. The precise quantitative role of transcaltachia in intestinal calcium transport is not certain. It is to be noted that transcaltachia does not play a major role in intestinal calcium

transport in vivo in the vitamin D–deplete state, since transcaltachia is observed only in vitamin D–replete animals. Additionally, as noted earlier in vitamin D–dependency rickets, type II, calcium transport is low, despite extremely high plasma 1α,25-dihydroxyvitamin $D_3$ concentrations.

In the apical membrane, 1α,25-dihydroxyvitamin $D_3$ causes a change in the lipid composition [O'Doherty, 1979; Matsumoto et al., 1981; Adams et al., 1970]. Phosphatidyl choline synthesis is increased both by the de novo synthesis of phosphatidyl choline and an increase in the methylation of phosphatidyl ethanolamine [Matsumoto et al., 1981]. It has been suggested that a change in the phosphatidyl choline/phosphatidyl ethanolamine ratio results in an increase in the fluidity of the apical membrane and an increase in the numbers of surface calcium channels that allow the flux of calcium into the intestinal cell [Adams et al., 1970]. The increase in the rate of calcium movement across the apical membrane in response to 1α,25-dihydroxyvitamin $D_3$ is not dependent upon protein synthesis, as it is not blocked by various inhibitors of protein synthesis. This process, while important for the initial movement of calcium into the cell, is only one of several processes necessary for the transcellular movement of calcium. For example, glucocorticoids inhibit 1α,25-dihydroxyvitamin $D_3$–mediated calcium flux in the intestine; following the administration of glucocorticoids to 1α,25-dihydroxyvitamin $D_3$–treated animals, one observes normal uptake of calcium in apical brush-border membranes, but transcellular movement of calcium is diminished [Schultz et al., 1982]. This suggests that events other than apical brush-border membrane events are also important to the movement of calcium across an intestinal epithelial cell.

Within the duodenal absorptive cell, 1α,25-dihydroxyvitamin $D_3$ increases the synthesis of the vitamin D–dependent calcium binding protein [Wasserman and Taylor, 1966]. There are two classes of the vitamin D–dependent calcium binding proteins: one with an $M_r$ of approximately 9,000 and another with an $M_r$ of approximately 28,000 [Wasserman and Taylor, 1966; Gross and Kumar, 1990]. The two classes of protein bind either two or four moles of calcium per mole of protein [Gross and Kumar, 1990]. These proteins are induced following the administration of 1α,25-dihydroxyvitamin $D_3$ but not calcium to D-deficient animals [Gross and Kumar, 1990]. Although the proteins are vitamin D–dependent and increase in amount in parallel with intestinal calcium transport, it has, been more difficult to elucidate their precise mechanism of action [Gross and Kumar, 1990]. Experiments by Feher et al. [1990] have shown in vitro at least that diffusion of calcium across an artificial compartment is enhanced by the addition of calcium binding proteins to the compartment. Calcium binding proteins are redistributed in the cell following the administration of 1α,25-dihydroxyvitamin $D_3$, and this process could in some manner increase calcium transport across the cell [Nemere et al., 1991b]. Additionally, others have suggested that calcium binding proteins, bound to calcium, increase the activity of the calmodulin-dependent plasma membrane calcium pump present in the basolateral portion of the cell [Walters, 1989].

In the basolateral portion of the intestinal absorptive cell, 1α,25-dihydroxyvitamin $D_3$ increases the bioactivity and the quantity of the plasma membrane calcium pump [Wasserman et al., 1992a,b; Cai et al., 1993]. The time course of induction of the plasma membrane calcium pump amount and activity following the administration of 1α,25-dihydroxyvitamin $D_3$ suggests that the protein plays a critical role in the movement of calcium out of the cell into the extracellular fluid space [Wasserman et al., 1992a,b; Cai et al., 1993]. An increase in the amount of the plasma membrane calcium pump in response to 1α,25-dihydroxyvitamin $D_3$ is mediated by an increase in the transcription of the plasma membrane calcium pump isoform-1 gene and a subsequent increase in the synthesis of this protein [Cai et al., 1993].

A model for the movement of calcium across the intestinal epithelial cell in the D-deficient state as well as the D-replete state is shown in Figure 1.

## 1α,25-DIHYDROXYVITAMIN $D_3$–MEDIATED CALCIUM TRANSPORT IN THE KIDNEY

The kidney reabsorbs approximately 98% of filtered calcium [Kumar et al., 1988]. It has been suggested that since virtually all filtered calcium is reabsorbed by the kidney [Costanzo and Windhager, 1978, 1980; Friedman and Gesek, 1993], this organ is not important in the maintenance of calcium balance. This is an error, as even small changes in the calcium absorption in the kidney result in quantitatively large losses of calcium from the body. Normally, in humans,

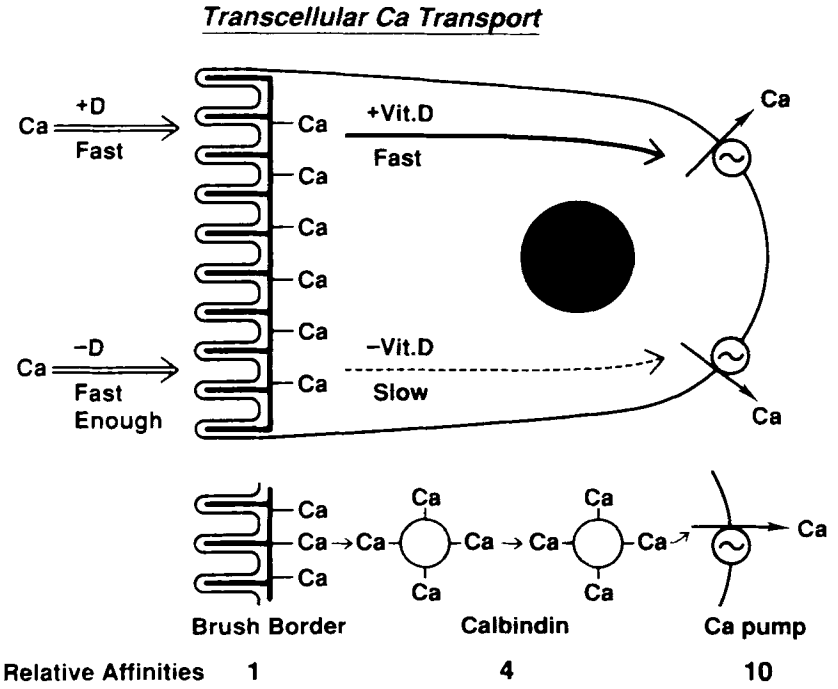


Fig. 1. The transcellular diffusional–active transport model of $Ca^{2+}$ absorption. (Reproduced from Wasserman et al., 1992a, with permission of the American Institute of Nutrition.)

the kidneys filter approximately 10,000 mg of calcium via the glomeruli per 24 h. Only 200 mg of filtered calcium appears in the urine in a 24 h period. Hence, even a small change in the amount of calcium absorption by the kidney will result in a quantitatively large change in the amount of calcium appearing in the urine. Approximately 60% of filtered calcium is absorbed in the proximal tubule, another 10–15% is absorbed in the Loop of Henle, and the remaining 15–25% is reabsorbed in the distal tubule and collecting duct. Proximal tubular calcium reabsorption is sodium-dependent, and alterations in the efficiency of sodium reabsorption in the proximal tubule determine how much calcium is reabsorbed in this nephron segment. For example, the administration of sodium chloride in the form of isotonic saline is associated with a diuresis and rejection of sodium and calcium in the proximal tubule. On the other hand, in volume depletion where there is avid sodium reabsorption, an associated increase in calcium reabsorption is observed. Generally, sodium and calcium reabsorption in the proximal tubule occur in parallel with one another. On the other hand, in the distal tubule calcium reabsorption can, and often is, dissociated from sodium reabsorption [Kumar et al., 1988]. Hormone-regulated calcium reabsorption, including 1α,25-dihydroxyvitamin $D_3$–mediated calcium absorption in the kidney, occurs in the distal nephron [Kumar et al., 1988, 1994; Bouhtiauy et al., 1993; Friedman and Gesek, 1993].

In vivo studies have shown that 1α,25-dihydroxyvitamin $D_3$ increases calcium reabsorption in the kidney, and it is likely that 1α,25-dihydroxyvitamin $D_3$ exerts its effect in the distal nephron [Bouhtiauy et al., 1993]. Immunohistochemical studies have clearly shown that many of the proteins involved in calcium flux in the intestine are present exclusively in the distal convoluted tubule [Kumar et al., 1994; Borke et al., 1987]. For example, the vitamin D–dependent calcium binding protein is present exclusively in distal tubular segments; additionally, the basolateral plasma membrane calcium pump is also present, at least by immunohistological criteria, predominantly in the distal tubule of the kidney [Borke et al., 1987]. Finally, the sodium-calcium exchanger is also present exclusively in the distal segment of the nephron [Ramachandran and Brunette, 1989]. Significant amounts of the vitamin D receptor also occur in distal segments of the nephron [Kumar et al., 1994]. Hence the entire machinery for the genomic effects of 1α,25-dihydroxyvitamin $D_3$ ap-

pears to be present in the distal segments of the kidney.

A lack of calcium in the diet is associated with an increase in the release of parathyroid hormone and an increase in the synthesis of 1α,25-dihydroxyvitamin $D_3$ in proximal tubular segments. 1α,25-dihydroxyvitamin $D_3$ exerts its effects together with parathyroid hormone in distal nephron segments [Bouhtiauy et al., 1991, 1993; Friedman and Gesek, 1993]. The stimulatory effects of parathyroid hormone alone on apical membrane calcium absorption in distal tubule cells have been delineated by several investigators [Friedman and Gesek, 1993; Bouhtiauy et al., 1991]. 1α,25-dihydroxyvitamin $D_3$ increases the synthesis of vitamin D–dependent calcium binding protein in the distal nephron and, perhaps in a manner analogous to that seen in the intestine, increases the synthesis and activity of the plasma membrane calcium pump. These factors serve to increase absorption of calcium in the distal nephron.

PCR analysis of different nephron segments has shown that the plasma membrane calcium pump is present both in the distal as well as in the proximal nephron [Magosci et al., 1992]. On the other hand, immunohistochemical studies suggest that the plasma membrane calcium pump is present predominantly in the distal tubule of the rat and human kidney [Borke et al., 1987, 1988]. It is possible that the plasma membrane calcium pump present in the proximal tubule of the kidney plays a role in the maintenance of intracellular calcium homeostasis but does not play an important role in the movement of calcium across proximal tubular cells. In the proximal tubule, the movement of calcium is predominantly paracellular. In the distal tubule, however, the plasma membrane calcium pump probably does play an important role in the movement of calcium across the distal tubule epithelial cell in response to 1α,25-dihydroxyvitamin $D_3$.

## FUTURE DIRECTIONS FOR RESEARCH

There are several unanswered questions with respect to how calcium moves across epithelia in the intestine and the kidney. In the intestine, a substantial amount of paracellular calcium movement occurs, especially when luminal calcium concentrations are high. The mechanism by which this occurs is uncertain and requires clarification. Similarly, in the proximal tubule the manner in which paracellular movement of calcium occurs and is regulated needs to be clearly defined.

The role of a sodium-calcium exchanger in the absorption of calcium in the intestinal cell, as well as in the distal tubular cell of the kidney tubule, needs to be investigated. The structure of the sodium-calcium exchanger in the intestine and the structure of the sodium-calcium exchanger in the distal tubular cell need to be ascertained. Are these two proteins similar to one another, and are they similar to the sodium-calcium exchanger of the canine heart? Are they regulated by 1α,25-dihydroxyvitamin $D_3$ or other calciotropic proteins? How important a role do they play in vitamin $D_3$–regulated calcium transport?

Another important area of research involves the role of the plasma membrane calcium pump in renal tubular calcium absorption. There is an apparent discrepancy between the amount of the plasma membrane calcium pump determined by immunohistochemical methods vs. the amount of the plasma membrane calcium pump as determined by PCR methods. Does the proximal tubular plasma membrane calcium pump play an important role in transcellular calcium flux, and, if so, how important is its role in this tubular segment?

With respect to transcaltachia, it will be important to define how important a role this process plays in calcium absorption in the intestine under physiologic circumstances. The precise role of calcium binding protein in the movement of calcium across the cell still remains to be clearly elucidated. While the time course of induction of calcium binding protein suggests that it plays a role in the movement of calcium across epithelia, other approaches, such as gene deletion "knock-out" experiments, need to clearly define the role of the vitamin D–dependent calcium binding protein in the movement of calcium across the intestine and the distal tubular epithelium.

## ACKNOWLEDGMENTS

This work was supported by NIH grants DK 25409 and DK 42971.

## REFERENCES

Adams TH, Wong RG, Norman AW (1970): Studies on the mechanism of action of calciferol. 2. Effects of the polyene antibiotic, filipin, on vitamin D–mediated calcium transport. J Biol Chem 245:4432–4442.

Borke JL, Minami J, Berma A, Penniston JT, Kumar (1987): Monoclonal antibodies to human erythrocyte membrane $Ca^{++}$-$Mg^{++}$ adenosine triphosphatase pump recognize an epitope in the basolateral membrane of human kidney distal tubule cells. J Clin Invest 80:1225–1231.

Borke JL, Minami J, Berma AK, Penniston JT, Kumar R (1988): Co-localization of erythrocyte $Ca^{++}$-$Mg^{++}$ ATPase and vitamin D–dependent 28-kilodalton-calcium binding protein. Kidney Int 34:262–267.

Borke JL, Caride A, Verma AK, Penniston JT, Kumar R (1990): Cellular and segmental distribution of $Ca^{2+}$-pump epitopes in rat intestine. Pflugers Arch 417:120–122.

Bouhtiauy I, Lajeunesse D, Bronette MG (1991): The mechanism of parathyroid hormone action on calcium reabsorption by the distal tubule. Endocrinology 128:251–258.

Bouhtiauy I, Lajeunesse D, Bronette MG (1993): Effect of vitamin D depletion on calcium transport by the luminal and basolateral membranes of the proximal and distal nephrons. Endocrinology 132:115–120.

Cai Q, Chandler JS, Wasserman RH, Kumar R, Penniston JT (1993): Vitamin D and adaptation to dietary calcium and phosphate deficiences increase intestinal plasma membrane calcium pump gene expression. Proc Natl Acad Sci USA 90:1345–1349.

Castells S, Greig F, Fusi MA, Finberg L, Yasmura S, Liberman UA, Eil C, Marx SJ (1986): Severely deficient binding of 1,25-dihydroxyvitamin D to its receptors in a patient responsive to high doses of this hormone. J Clin Endocrinol Metab 63:252–256.

Corradino RA (1973a): 1,25-Dihydroxycholecalciferol: Inhibition of action in organ-cultured intestine by actinomycin D and alpha-amanactin. Nature 243:41–43.

Corradino RA (1973b): Embryonic chick-intestine in organ culture: Response to vitamin $D_3$ and its metabolites. Science 179:402–405.

Costanzo L, Windhager E (1978): Calcium and sodium transport by the distal convoluted tubule of the rat. Am J Physiol 235:F492–F506.

Costanzo L, Windhager E (1980): Effects of PTH, ADH, and cyclic AMP on distal tubular Ca and Na reabsorption. Am J Physiol 239:F478–F485.

de Boland AR, Norman AW (1990): Evidence for involvement of protein kinase C and cyclic adenosine, 3′,5′-monophosphate-dependent protein kinase in the 1,25-dihydroxy-vitamin $D_3$–mediated rapid stimulation of intestinal calcium transport (transcaltachia). Endocrinology 127:39–45.

de Boland AR, Nemere I, Norman AW (1990): $Ca^{2+}$-channel agonist bay K8644 mimics $(1,25(OH)_2$-vitamin $D_3$ rapid enhancement of $Ca^{2+}$ transport in chick perfused duodenum. Biochem Biophys Res Commun 166:217–222.

DeLuca HF, Schnoes HK (1983): Vitamin D: Recent advances. Annu Rev Biochem 52:411–439.

Feher JJ, Fullmer CS, Fritzsch GK (1990): Comparison of the enhanced-steady state diffusion of calcium by calbindin-$D_{9k}$ and calmodulin. Possible importance in intestinal calcium absorption. Cell Calcium 10:189–203.

Francheschi RT, DeLuca HF (1981): The effect of inhibitors of protein and RNAse synthesis on $1\alpha,1,25$-dihydroxyvitamin $D_3$–dependent calcium uptake in cultured embryonic duodenum. J Biol Chem 256:3848–3852.

Friedman PA, Gesek FA (1993): Calcium transport in renal epithelial cells. Am J Physiol 264:F181–F198.

Gamblin GT, Liberman UA, Eil C, Downs RW Jr, DeGrange DA, Marx SJ (1985): Vitamin D–dependency rickets type II. Defective induction of 25-hydroxyvitamin $D_3$–24-hydroxyvitamin $D_3$ in cultured skin fibroblasts. J Clin Invest 75:954–960.

Ghijsen WEJM, DeJong MD, Van Os CH (1982): ATP-dependent calcium transport and its correlation with $Ca^{2+}$-ATPase activity in basolateral membranes of rat duodenum. Biochem Biophys Acta 689:327–336.

Gross MD, Kumar R (1990): The physiology and biochemistry of vitamin D–dependent calcium binding proteins. Am J Physiol 259:F195–F209.

Kowarski S, Schacter D (1975): Vitamin D–dependent, particulate calcium-binding activity and intestinal calcium transport. Am J Physiol 229:1198–1204.

Kumar R (1984): The metabolism of 1,25-dihydroxyvitamin $D_3$. Physiol Rev 64:478–504.

Kumar R (1990): Vitamin D metabolism and mechanisms of calcium transport. J Am Soc Nephrol 1:30–42.

Kumar R, Penniston JT, Borke JL (1988): $Ca^{++}$-$Mg^{++}$ ATPase calcium pumps in the kidney. News Physiol Sci 3:219–222.

Kumar R, Schaefer J, Grande JP, Roche PC (1994): Immunolocalization of calcitriol receptor 24-hydroxylase cytochrome P-450, and calbindin $D_{28k}$ in the human kidney. Am J Physiol 266:F477–F485.

Liberman UA, Eil C, Marx SJ (1986): Clinical features of hereditary resistance to 1,25-dihydroxyvitamin D (hereditary hypocalcemic vitamin D resistant rickets type II). Adv Exp Med Biol 196:391–406.

Magosci M, Yamaki M, Penniston JT, Dousa TP (1992): Localization of mRNAse coding for isozymes of plasma membrane $Ca^{2+}$-ATPase pump in rat kidney. Am J Physiol 263:F7–F14.

Martin DL, DeLuca HF (1969): Influence of sodium on calcium transport by the rat small intestine. Am J Physiol 216:1351–1359.

Matsumoto T, Fontaine O, Rasmussen H (1981): Effects of $1,25(OH)_2D_3$ on phospholipid metabolism in chick duodenal mucosal cell. J Biol Chem 256:3354–3360.

McCollum EV, Simmonds N, Becker JE, Shipley PG (1922): Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biol Chem 53:293–312.

Mellanby E (1919): An experimental investigation on rickets. Lancet 1:407–412.

Nemere I, Norman AW (1987): Rapid action of 1,25-dihydroxyvitamin $D_3$ on calcium transport in perfused chick duodenum: Effect of inhibitors. J Bone Miner Res 2:99–107.

Nemere I, Norman AW (1990): Transcaltachia, vesicular calcium transport, and microtubule-associated calbindin-$D_{28k}$: Emerging views of 1,25-dihydroxyvitamin $D_3$–mediated intestinal calcium absorption. Miner Electrolyte Metab 16:109–114.

Nemere I, Feld C, Norman AW (1991a): 1,25-Dihydroxyvitamin $D_3$–mediated alterations in microtubule proteins isolated from chick intestinal epithelium: Analyses by isoelectric focusing. J Cell Biochem 47:369–379.

Nemere I, Leathers VL, Thompson BS, Luben RA, Norman AW (1991b): Redistribution of calbindin-$D_{28k}$ in chick intestine in response to calcium transport. Endocrinology 129:2972–2984.

Nicolaysen R, Eeg-Larsen N (1953): The biochemistry and physiology of vitamin D. Vitam Horm 11:29–60.

Norman AW, Nemere I, Muralidharan KR, Okamura WH (1992): 1β,25(OH)$_2$-vitamin $D_3$ is an antagonist of 1α,25(OH)$_2$-vitamin $D_3$ stimulated transcaltachia (the rapid normal stimulation of intestinal calcium transport). Biochem Biophys Res Commun 189:1450–1456.

Norman AW, Bouillon R, Farach-Carson MC, Bishop JE, Zhou L-X, Nemere I, Zhao J, Muralidharan KR, Okamura WH (1993): Demonstration that 1β-25-dihydroxyvitamin $D_3$ is an antagonist of the nongenomic but not genomic biological responses and biological profile of the three A-ring diastereomers of 1α,25-dihydroxyvitamin $D_3$. J Biol Chem 268:20022–20030.

O'Doherty PJA (1979): 1,25(OH)$_2$$D_3$ increases the activity of the intestinal phosphatydal choline deacylation-reacylation cycle. Lipids 14:75–77.

Pike JW (1991): Vitamin $D_3$ receptors: Structure and function in transcription. Annu Rev Nutr 11:189–216.

Ramachandran C, Brunette MG (1989): The renal $Na^+$/$Ca^{2+}$ exchange system is located exclusively in the distal tubule. Biochem J 257:259–264.

Schultz TD, Bollman S, Kumar R (1982): Decreased intestinal calcium absorption in vivo and normal brush border membrane vesicle calcium uptake in cortisol-treated chickens: Evidence for dissociation between calcium absorption and brush border vesicle uptake. Proc Natl Acad Sci USA 79:3542–3546.

Walters JRF (1989): Calbindin-$D_{9k}$ stimulates the calcium pump in rat enterocyte basolateral membranes. Am J Physiol 256:G124–G128.

Wasserman RH, Taylor AN (1966): Vitamin $D_3$–induced calcium-binding protein in chick intestinal mucosa. Science 152:791–793.

Wasserman RH, Fullmer CS, Shimura F (1984): Calcium absorption in the molecular effects of vitamin $D_3$. In Kumar R (ed): "Vitamin D, Basic and Clinical Aspects." Boston: Martinus-Nihoff, pp 233–258.

Wasserman RH, Chandler JS, Meyer SA, Smith CA, Brindak ME, Fullmer CS, Penniston JT, Kumar R (1992a): Intestinal calcium transport and calcium extrusion processes at the basolateral membrane. J Nutr 122:662–671.

Wasserman RH, Smith CA, Brindak ME, de Talamoni N, Fullmer CS, Penniston JT, Kumar R (1992b): Vitamin D and mineral deficiences increase the plasma membrane calcium pump of chicken intestine. Gastroenterology 102: 886–894.

Zhou LX, Nemere I, Norman AW (1992a): A parathyroid-related peptide induces transcaltachia (the rapid hormonal stimulation of intestinal $Ca^{2+}$-transport). Biochem Biophys Res Commun 186:69–73.

Zhou L-X, Nemere I, Norman AW (1992b): 1,25-Dihydroxyvitamin $D_3$ analog structure-function assessment of the rapid stimulation of intestinal calcium absorption (transcaltachia). J Bone Miner Res 7:457–463.