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Vitamin D and Intestinal Calcium Absorption

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Abstract

The principal function of vitamin D in calcium homeostasis is to increase calcium absorption from the intestine. Calcium is absorbed by both an active transcellular pathway, which is energy dependent, and by a passive paracellular pathway through tight junctions. 1,25Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) the hormonally active form of vitamin D, through its genomic actions, is the major stimulator of active intestinal calcium absorption which involves calcium influx, translocation of calcium through the interior of the enterocyte and basolateral extrusion of calcium by the intestinal plasma membrane pump. This article reviews recent studies that have challenged the traditional model of vitamin D mediated transcellular calcium absorption and the crucial role of specific calcium transport proteins in intestinal calcium absorption. There is also increasing evidence that $1,25(OH)_2D_3$ can enhance paracellular calcium diffusion. The influence of estrogen, prolactin, glucocorticoids and aging on intestinal calcium absorption and the role of the distal intestine in vitamin D mediated intestinal calcium absorption are also discussed.

Introduction

Studies in vitamin D receptor (VDR) null mice have indicated that the principal function of vitamin D in mineral homeostasis is to increase calcium absorption from the intestine (Li et al., 1997, Yoshizawa et al., 1997). This conclusion was made based on the findings that rickets and osteomalacia are prevented and serum calcium and parathyroid hormone (PTH) are normalized when VDR null mice are fed a rescue diet high in calcium and lactose. In the event of decreased calcium levels in the serum due to low dietary intake or increased demand of calcium due to growth, pregnancy or lactation, the synthesis of the hormonally active form of vitamin D, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is increased leading to increased intestinal calcium absorption. If normal serum calcium is unable to be maintained by intestinal absorption, then $1,25(OH)_2D_3$ together with PTH will mobilize bone calcium and increase reabsorption of calcium from the renal distal tubule.

$1,25(OH)_2D_3$ and Transcellular Calcium Absorption

In the intestine $1,25(OH)_2D_3$ affects the process of transcellular calcium transport which has been proposed to involve entry of calcium via the apical calcium channel, transient receptor potential vanilloid type 6 (TRPV6), translocation of calcium through the interior of the

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enterocyte (it has been suggested that the calcium binding protein calbindin-D_{9k} acts to facilitate calcium diffusion through the cell) and basolateral extrusion of calcium by the intestinal plasma membrane pump PMCA1b (Wasserman 2005) (Fig. 1). Previous studies provided indirect evidence for a role of TRPV6 and calbindin in intestinal calcium absorption. Both are co-localized in the intestine, they are both similarly regulated [induced at weaning (the time of onset of active intestinal calcium transport), under conditions of low dietary calcium and after $1,25(OH)_2D_3$ injection] (Song et al., 2003). TRPV6 and calbindin-D_{9k} are both induced prior to the peak of intestinal calcium absorption (Song et al., 2003). In addition, in vitamin D receptor (VDR) KO mice, where the major defect that results in rickets is the decrease in intestinal calcium absorption, there is a 50% reduction in intestinal calbindin-D_{9k} mRNA and a more marked decrease in TRPV6 mRNA (less than 5 – 10% of the levels in wild type (WT) mice) (Li et al., 1998, Van Cromphant et al., 2001). However, recent studies using calbindin-D_{9k} knock out (KO) mice and TRPV6 KO mice have challenged the traditional model of vitamin D mediated transcellular calcium absorption in the intestine (Kutuzova et al., 2006, Akhter et al., 2007, Benn et al., 2008, Kutuzova et al., 2008, Bianco et al., 2008). Calbindin-D_{9k} KO mice show no difference in phenotype compared to WT mice and they maintain normal serum calcium (Kutuzova et al., 2006, Akhter et al., 2007, Benn et al., 2008). Active intestinal calcium transport is similarly induced in both calbindin-D_{9k} KO mice and WT mice in response to a low calcium diet or $1,25(OH)_2D_3$, suggesting that calbindin-D_{9k} may be compensated by another calcium binding protein (Benn et al., 2008). Calbindin may have another role in the intestine. Calbindin-D_{9k} may be a modulator of the activity of TRPV6 and/or calbindin may act as a cytosolic buffer to prevent toxic levels of calcium from accumulating in the intestinal cell when there is an increase in apical calcium entry. TRPV6 KO mice also maintain normal serum calcium levels (Benn et al., 2008, Kutuzova et al., 2008). In response to $1,25(OH)_2D_3$ intestinal calcium transport is similar in WT and TRPV6 KO mice (Benn et al., 2008, Kutuzova et al., 2008). However, under conditions of low dietary calcium, compared to WT mice, intestinal calcium transport is less efficient in the TRPV6 null mice (Benn et al., 2008). Also, in response to restriction of dietary calcium, although impaired bone mass accrual is comparable in WT and TRPV6 null mice, there is an increase in osteoblast activity and osteoid abundance is more pronounced in the TRPV6 null mice, suggesting a role for TRPV6 under low calcium conditions in intestinal calcium absorption to maintain proper bone mineralization (Lieben et al., 2010). When dietary supply of calcium is normal, lack of TRPV6 did not affect bone mass, remodeling parameters or growth plate morphology in young adult or aging mice. Thus, under normal calcium intake, TRPV6 is redundant for intestinal calcium transport, suggesting compensation by another channel or protein. Although the phenotype is mild, studies in the TRPV6 null mutant mice suggest that TRPV6 does contribute to the calcium absorptive process during calcium restriction. Recent studies showed that TRPV6 can interact with other proteins including calmodulin, which facilitates rapid inactivation of TRPV6, S100A10-annexin 2 protein complex which maybe involved in constitutive trafficking of TPRV6 to the plasma membrane and Rab11a which plays a role in recycling of TPRV6 to the plasma membrane (Derler et al., 2006, Van de Graaf et 2003, Van de Graaf et al, 2006). These TRPV6 associated proteins may represent novel components of the regulation by $1,25(OH)_2D_3$ of calcium entry into the intestinal cell. Recent preliminary results show that transgenic mice overexpressing TRPV6 throughout the intestine (from duodenum to distal colon) of WT mice develop hypercalcemia, hypercalciuria and soft tissue calcification (Cui and Fleet, 2010). Although TRPV6 is not critical for $1,25(OH)_2D_3$ mediated intestinal calcium absorption and maybe compensated by another channel yet to be identified, these studies indicate that TRPV6 does have a role in the process of intestinal calcium absorption.

Paracellular Calcium Transport

Calcium transverses the intestine by both the active transcellular pathway and the passive paracellular pathway (Hoenderop et al., 2005) (Fig. 1). The paracellular pathway functions throughout the entire length of the intestine and predominates in the more distal regions. This pathway is driven by the luminal electrochemical gradient and the integrity of the intercellular tight junctions (Tuskita et al., 2001). Recent evidence suggests that transjunctional transport of calcium by the paracellular pathway occurs in a regulated fashion, and may be coupled to active transcellular movement of calcium in a coordinated manner (Fujita et al., 2008). Tight junctions are specialized membrane domains located between the apical and basolateral membranes of the enterocyte, which form a barrier to the movement of ions, proteins, and other macromolecules across the intestine by maintaining a charge and size selectivity (Tuskita et al., 2001). Claudins are the major transmembrane components of tight junctions (Tuskita et al., 2001, Furuse et al., 1998) and it has been suggested that $1,25(OH)_2D_3$ can promote paracellular calcium diffusion by increasing junction ion permeability (Fujita et al., 2008, Kutuzova and DeLuca 2004). VDR knockout mice, known to exhibit reduced intestinal calcium absorption, have decreased levels of claudin-2 and claudin-12 mRNA and protein (Fujita et al., 2008). In addition, $1,25(OH)_2D_3$ has been shown to induce the expression of claudin-2 and claudin-12 in vitro in an intestinal epithelial cell line resulting in facilitated paracellular calcium conductance (Fujita et al., 2008). Gene array studies have shown that in addition to the known target genes, TRPV6 and calbindin-D_{9K}, $1,25(OH)_2D_3$ suppresses a number of intra- and intercellular matrix proteins including cadherin-17 (a cell adhesion protein) and aquaporin-8 (a tight junction channel), suggesting that vitamin D regulates intestinal calcium absorption via the paracellular pathway in addition to the transcellular pathway (Kutuzova and DeLuca 2004). It is possible that these other factors may compensate for the lack of TRPV6 in the TRPV6 KO mouse and thus may explain, in part, the mild phenotype of the TPRV6 KO mouse and the TRPV6/calbindin-D_{9k} double KO mouse. Future studies examining different regions of the intestine and the identification of novel $1,25(OH)_2D_3$ regulated proteins involved in transcellular and paracellular calcium absorption are needed.

Pregnancy, Lactation, Estrogen and Prolactin and Intestinal Calcium Absorption

Although $1,25(OH)_2D_3$ is the principal hormone regulating active intestinal calcium absorption, other hormones have been shown to influence the process as well. Increased intestinal calcium transport has been observed in vitamin D deficient pregnant and lactating rats (Halloron and Deluca 1980, Boass et al., 1981, Brommage et al 1990). In addition, estradiol replacement in ovariectomized rats has been reported to result in an increase in intestinal calcium absorption without a stimulation of circulating $1,25(OH)_2D_3$ levels (O'Loughlin and Morris, 1998). Studies by Van Cromphaut et al (Van Cromphant et al., 2003) in VDR KO mice showed that estrogen treatment after ovariectomy as well as pregnancy and lactation result in an induction of TRPV6 in the duodenum. In addition, in estrogen receptor α (ERα) KO mice, TRPV6 is reduced (Van Cromphant et al., 2003). These findings suggest that estrogens, independent of vitamin D, may be important regulators of calcium influx into the enterocyte and that these effects are mediated by ERα. In addition to estrogen, prolactin, a lacotgenic polypeptide hormone that is elevated during pregnancy and lactation, has been shown to have calcium regulatory effects. Prolactin has been reported to stimulate active intestinal calcium transport in vitamin D deficient rats (Pahuja and Deluca 1981). In addition, a direct effect of prolactin on active duodenal calcium transport was shown in studies using the Ussing chamber technique and prolactin applied to the incubation solution (Charoenphandhu et al., 2001). Studies in our laboratory indicate that prolactin can regulate TRPV6 in the duodenum independent of vitamin D, and

also has cooperative effects with $1,25(OH)_2D_3$ in regulation of both the intestinal calcium transport proteins TRPV6 and calbindin-D_{9K} (Ajibade et al., 2010). Because both $1,25(OH)_2D_3$ and prolactin levels are elevated during lactation (Halloron and Deluca 1980, Halloron et al. 1979, Pike et al., 1979, Meites et al 1972), prolactin may act together with $1,25(OH)_2D_3$ to increase active intestinal calcium absorption. In addition, we found that prolactin has a direct effect on the transcription of the 1α(OH)ase gene, thus enhancing 1α(OH)ase protein expression and increasing levels of $1,25(OH)_2D_3$ during lactation when there is an increased calcium requirement for the neonate (Ajibade et al., 2010). It has been suggested that prolactin also has an effect on the paracellular pathway of intestinal calcium absorption through upregulation of claudin-15 (Charoenphandhu et al., 2009).

Glucocortiocoids and Intestinal Calcium Absorption

Because of their potent anti-inflammatory and immunosuppressive properties, glucocorticoids are effectively used to treat inflammatory conditions such as asthma and rheumatoid arthritis. However, long term treatment with glucocorticoids reduces bone mineral density leading to osteoporosis (Reid 1997). In addition to direct effects on bone, glucocorticoids can also induce bone loss through diminished intestinal calcium absorption (Reid 1997, Huybers et al., 2007). In mice it has been reported that treatment with pharmacological doses of glucocorticoids results in decreased intestinal calcium absorption which is associated with a decrease in TRPV6 and calbindin-D_{9K} (Huybers et al., 2007, Lee et al., 2006). Studies in cortisol treated chicks also noted an inhibition of intestinal calcium absorption which was associated with a decrease in calbindin (Feher and Wasserman, 1979). It has been suggested that the effect of glucocorticoids on calcium transport proteins can be independent of vitamin D (Huybers et al., 2007, Feher and Wasserman, 1979).

Effect of Aging

In aging, intestinal calcium absorption declines resulting in increased PTH which correlates to an age-related increase in bone turnover (Bullamore et al., 1970, Ledger et al., 1995). It has been proposed that the defect in intestinal calcium absorption is related both to low circulating levels of $1,25(OH)_2D_3$ and to intestinal resistance to the action of $1,25(OH)_2D_3$ (Wood et al., 1998). Either no change or a small decrease in intestinal VDR number has been reported with aging (Wood et al., 1998, Halloran and Portale, 2005). The expression of TRPV6 and calbindin-D_{9k} declines with age and this decline is correlated to the decrease in intestinal calcium absorption and serum $1,25(OH)_2D_3$ (Brown et al., 2005). In mice deficient in klotho (a multifunctional protein involved in phosphate and calcium homeostasis) a premature aging phenotype has been described (including short lifespan, infertility, atherosclerosis, skin atrophy and osteoporosis) (Kuro-o et al., 1997). Klotho functions as an essential cofactor for FGF23 which has been shown to regulate phosphate homeostasis and vitamin D biosynthesis (Kurosu et al). FGF23 and klotho, the FGF cofactor, suppress the expression of 1α(OH)ase and induce 24(OH)ase in kidney (Tsujikawa et al., 2003). Compared to WT mice, klotho KO mice have increased serum calcium and phosphate and decreased serum PTH (Kuro-o et al., 1997). Klotho KO mice also display increased serum levels of $1,25(OH)_2D_3$ and increased expression of 1α(OH)ase (Tsujikawa et al., 2003, Yoshida et al., 2002). In the intestine klotho KO mice show increased expression of TRPV6 and calbindin-D_{9k} and increased intestinal calcium absorption (Alexander et al., 2009) (in contrast to the decline observed in aging mice and rats; Brown et al., 2005). Thus the "aging" phenotype of the klotho KO mouse may reflect, at least in part, the effect of overproduction of $1,25(OH)_2D_3$ rather than an effect on intestinal calcium absorption which contributes to bone loss in aging.

Calcium absorption, vitamin D and the distal intestine

In the calcium absorptive process the duodenum has been the major focus of research due to its highly active transport system. However, it is the distal intestine where 70- 80 % of the ingested calcium is absorbed (mostly in the ileum) (Wasserman 2005). Thus, it is important to understand the process by which the distal segment transports calcium. The vitamin D dependence of calcium absorption in the ileum and the colon has been shown (Petith et al., 1979, Lee et al., 1981, Favus et al., 1980, Favus, 1985, Vergne-Marini et al., 1976). VDR is expressed in all segments of the small and large intestine (highest levels have been reported in the cecum and colon) and in patients with extensive resection of the small intestine, calcium absorption has been reported to be significantly higher when the colon is preserved (Hirst and Feldman 1981, Stumpf et al., 1979, Xue and Fleet 2009, Hylander et al., 1990). $1,25(OH)_2D_3$ has been shown to convert regions of net secretion of calcium in ileum and colon to net absorption (Favus 1985). The cecum has also been reported to be involved in $1,25(OH)_2D_3$ mediated active transport (Favus and Angeid-Backman 1985). TRPV6 protein and calbindin-D_{9k} protein are present in all segments of the mouse and rat intestine (immunocytochemical studies have indicated that the strongest expression of TRPV6 is in the cecum and colon) (Teerapornpuntakit et al., 2009, Zhang et al., 2010). Together these findings indicate that the distal segments of the intestine, in addition to the duodenum, play an important role in $1,25(OH)_2D_3$ mediated calcium homeostasis. Our studies in the TRPV6/ calbindin-D_{9k} double KO mice indicate that we are missing important information related to the mechanisms involved in the regulation of intestinal calcium transport by $1,25(OH)_2D_3$. Identification of multiple mechanisms by which $1,25(OH)_2D_3$ acts to increase calcium absorption in different segments of the intestine is needed in order to identify new approaches to sustain calcium balance.

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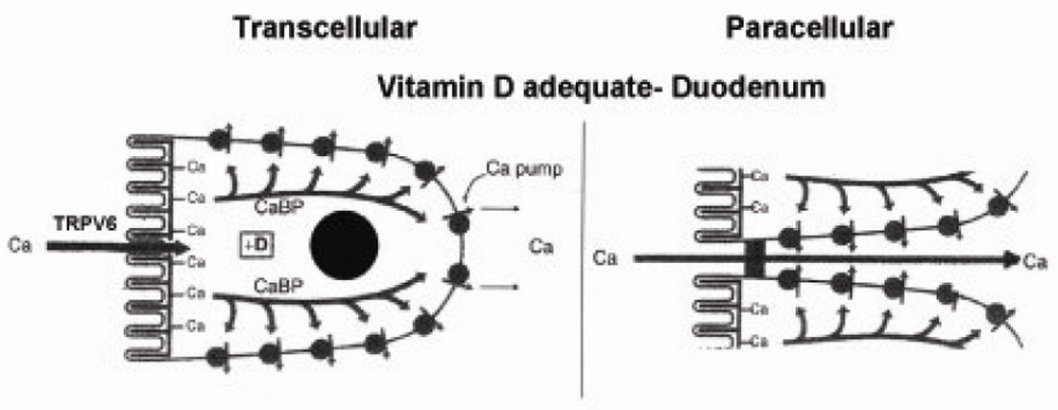

Figure 1.

Models of vitamin D mediated intestinal calcium absorption. Left panel: Transcellular intestinal calcium absorption. $1,25(OH)_2D_3$, through its genomic actions, stimulates active intestinal calcium absorption. The traditional model of transcellular calcium transport involves calcium influx through TRPV6, intracellular calcium transfer by calbindin (CaBP) and calcium extrusion by the plasma membrane calcium ATPase (Ca pump). Recent studies using KO mice have suggested that TRPV6 and calbindin are not critical for $1,25(OH)_2D_3$ calcium absorption and maybe compensated by another channel or protein. Right panel: Paracellular pathway. There is increasing evidence that $1,25(OH)_2D_3$ can enhance paracellular calcium diffusion by regulating tight junction proteins. (Reproduced with permission from Wasserman RH, 2005).