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TOPIC HIGHLIGHT

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Role of calcium and other trace elements in the gastrointestinal physiology

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Abstract

Calcium is an essential ion in both marine and terrestrial organisms, where it plays a crucial role in processes ranging from the formation and maintenance of the skeleton to the regulation of neuronal function. The Ca^{2+} balance is maintained by three organ systems, including the gastrointestinal tract, bone and kidney.

Since first being cloned in 1993 the Ca^{2+}-sensing receptor has been expressed along the entire gastrointestinal tract, until now the exact function is only partly elucidated. As of this date it still remains to be determined if the Ca^{2+}-sensing receptor is involved in calcium handling by the gastrointestinal tract. However, there are few studies showing physiological effects of the Ca^{2+}-sensing receptor on gastric acid secretion and fluid transport in the colon. In addition, polyamines and amino acids have been shown to activate the Ca^{2+}-sensing receptor and also act as allosteric modifiers to signal nutrient availability to intestinal epithelial cells. Activation of the colonic Ca^{2+}-sensing receptor can abrogate cyclic nucleotide-mediated fluid secretion suggesting a role of the receptor in modifying secretory diarrheas like cholera. For many cell types changes in extracellular Ca^{2+} concentration can switch the cellular behavior from proliferation to terminal differentiation or quiescence. As cancer remains predominantly a disease of disordered balance between proliferation, termination and apoptosis, disruption in the function of the Ca^{2+}-sensing receptor may contribute to the progression of neoplastic disease. Loss of the growth suppressing effects of elevated extracellular Ca^{2+} have been demonstrated in colon carcinoma, and have been correlated with changes in the level of CaSR expression.

Key words: Calcium; Trace elements; Gastrointestinal physiology

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INTRODUCTION

The gastrointestinal tract is in charge of handling the complex issues of nutrient, electrolyte and fluid absorption and the secretion of excess electrolytes and fluids. Body calcium homeostasis is regulated by the PTH and vitamin D feedback loop; additionally calcium plays a key role in many other mechanisms like intracellular signaling, cell differentiation, bone metabolism, *etc*. After identifying the calcium sensing receptor in several different tissues many studies were undertaken to characterize the role of extracellular calcium as a first messenger and the receptor as a calcium sensor of the cell. Ca^{2+}-sensing receptor transcripts and/or protein are expressed in the gastrointestinal tracts of fish[1], birds[2], amphibia[3,4] and mammals[5-10] including the human[5,11,12]. Tracings of the expression of the receptor in the gastrointestinal tract shows that the receptor goes back in evolution at least as far as cartilaginous fish (elasmobranchs), e.g., the dogfish shark[1]. In both cartilaginous and bony fish, the Ca^{2+}-sensing receptor has been shown to be expressed on apical surfaces of stomach and intestine[1]. More recent evidence suggests that the Ca^{2+}-sensing receptor may have evolved in the early marine environment in order to support osmo-adaptation. This notion is supported by the more general expression of the Ca^{2+}-sensing receptor in many other tissues outside the gastrointestinal tract that are involved in mono-and divalent ion transport both into and out of fish that live in a seawater environment that is rich in divalent minerals and sodium chloride[1,13]. This theme of the Ca^{2+}-sensing receptor linking divalent and monovalent metabolism is echoed in mammals (e.g., effects of the receptor on fluid transport by the colon; discussed later in this review).

In the amphibian, *Necturus maculosus*, Ca^{2+}-sensing receptor expression was detected on the basal surface of gastric epithelial cells[3]. Wherease in contrast the frog stomach, shows expression of the Ca^{2+}-sensing receptor

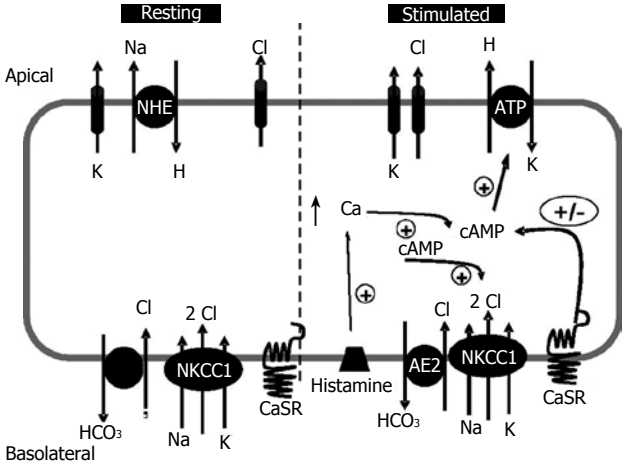

Figure 1 Simplified model of the parietal cell showing the current mechanisms involved in acid secretion in comparison to a resting cell. The Ca^{2+}-sensing receptor (CaSR) and the histamine receptor are located on the basolateral membrane. HCl secretion is mediated by H^+ extrusion *via* the H^+,K^+-ATPase coupled with Cl^- secretion *via* an apical channel. Activation of the CaSR causes acid secretion *via* the H^+, K^+-ATPase.

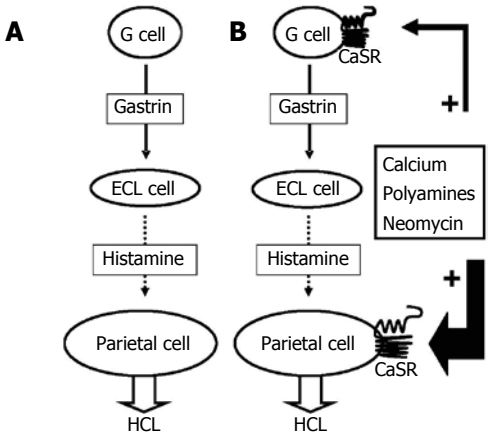

Figure 2 Schematic of acid secretion. **A**: Classically defined pathway of acid secretion: Gastrin released from the G cell binds to receptors on the ECL cell causing histamine release from the ECL cell. The histamine binds to receptors on the parietal cell and stimulates proton efflux; **B**: Modified model of acid secretion involving a functional CaSR on the basolateral membrane of both the G cell and parietal cell. Acid secretion can be activated directly by the CaSR on the parietal cell or *via* the G cell pathway.

on the apical membranes of acid-secreting oxyntic cells[4]. In the chicken, *Gallus domesticus*, the receptor was detected in the duodenum[2]. In mammals, a more complete exploration of Ca^{2+}-sensing receptor expression along the gastrointestinal tract has been performed[5-10,12]. Receptor transcripts and/or protein have been detected in: stomach, small intestinal, and colonic mucosal epithelia, as well as the underlying neural plexuses of Meissner and Auerbach. In addition, Ca^{2+}-sensing receptor expression has also been shown in several human intestinal cell lines (T84, HT-29, Caco-2, FET, SW480, MOSER and CBS;[8,14,15] in addition to primary cultures of human gastric mucosa and human parietal cells[11,16,17].

In mammalian stomach, the Ca^{2+}-sensing receptor has been identified on both apical and basolateral membranes of human G-cells (gastrin secreting cells;[16,17]) and mucous secreting cells[11] and on the basolateral membranes of parietal cells[4,6,18]. In small intestine, both apical and basolateral membranes of villus cells express the Ca^{2+}-sensing receptor[7]. In rat colon the receptor is expressed on both apical and basolateral membranes of surface and crypt epithelial cells[5,7]. A similar pattern of Ca^{2+}-sensing receptor immunostaining in rat was observed in both proximal and distal colon[5]. In the human large intestine, Ca^{2+}-sensing receptor has also been identified on both apical and basolateral membranes of crypts as well as in certain enteroendocrine cells at the base of crypts[7,12].

CALCIUM IN THE STOMACH

Overview

To produce the large quantities of 0.16 mol/L hydrochloric acid required for digestion of ingested food, the mammalian stomach has employed a complex series of neuronal, hormonal and/or paracrine[19]/autocrine feedback regulatory mechanisms[19-22] allowing for the continued production of acid. A model of acid secretion by the parietal cell is shown in Figure 1 summarizing data from many different studies[19,21-24]. Following stimulation, the H^+, K^+-ATPase (proton pump) is trafficked to the apical surface and is responsible for vectorial transport of protons[20-22,25-27]. Once at the membrane protons combine with secreted Cl^- ions to produce the concentrated acid. With the generation of a proton gradient enzymes such as pepsinogen are secreted into the lumen of the gland where they combine with the secreted acid and move from the gland into the interior of the stomach providing an effective solution that is capable of digesting proteins and processing them for amino acid or peptide reabsorption in the intestine.

The common model of acid secretion (Figures 1 and 2) involves stimulation of the gastric glands *via* either neuronal or hormonal pathways which results in the release of gastrin, which in turn acts directly on the endocrine (ECL) cells of the gland. Following stimulation ECL cells secrete histamine causing the parietal cell to insert proton pumps (H^+, K^+-ATPase) into the apical pole of the gland[28] which occurs *via* an active tubular-vesicular insertion mechanism that is used to transport H^+, K^+-ATPases into the apical region of the parietal cell[26]. In conjunction with pump insertion activation of an apical K^+ channel(s) provides K^+ ions that act as the counter ion and exchange with H^+ on the pump[20,21,23,29] (Figure 1) to sustain acid secretion. In addition to cation secretion an additional action of histamine release is to activate and/or insert Cl^- channels into the apical membranes of the parietal cells which mediate Cl^- secretion that accompanies H^+ secretion[20,30,31] (Figure 1). Thus the entire acid secretory process relies on: (1) insertion of H^+, K^+-ATPase into the apical surface for H^+ secretion; (2) concurrent activation of apical Cl^- channels mediating Cl^- secretion which allows for the formation of HCl; and (3) activation of apical K^+ channel(s) for K^+ recycling to the lumen of the gland and thereby providing the counter cation K^+ to maintain H^+, K^+-ATPase activity.

Loss of feedback control of acid (HCl) secretion in the stomach causes symptoms ranging from mild heartburn, to lesions and ulcerations of the gastric mucosa[19,32]. Left

untreated gastric ulcers can lead to abdominal bleeding, hyperplasia of cells, and potentially tumor formation. The complexity of the tissue due to the mixed collection of cell types, as well an additional layer of surface cells (secreting a protective mucous gel layer rich in bicarbonate) has prevented a complete analysis of glandular cell function and the associated feedback loops.

Role of the Ca^{2+}-sensing receptor in acid secretion

Following hormonal or neuronal stimulation there is a transient rise in intracellular Ca^{2+} concurrent with the onset of acid secretion in the gastric gland[19,20,22,33], this process has been associated with activation of pump translocation to the apical pole of the cell , and the associated secretion of acid[34]. Following this stimulatory period intracellular Ca^{2+} levels fall, and acid secretion diminishes to basal levels.

Activation of basolateral CaSR in *Necturus* gastric antrum by elevating extracellular Ca^{2+}, or using other receptor agonists like NPS-467, or neomycin resulted in a rapid hyperpolarization and a decrease in resistance of the basolateral membrane. Circuit analysis of these data suggested that these electrophysiological effects were due to activation of a basolateral K^+ channel(s)[3]. In rat stomach elevating extracellular Ca^{2+} leads to a rapid increase in intracellular Ca^{2+} in parietal cells which can occur in the absence of conventional extracellular secretagogues (e.g. histamine;[6]). To confirm that this rise in Ca^{2+} was associated with activation of the receptor, studies have been conducted using either the potent agonist Gd^{3+}, or addition of an allosteric modifier of the receptor such as the amino acid phenylalanine which both lead to an increase in the rate of acid secretion through the apical H^+, K^+-ATPase in the absence of secretagogues[18,35]. Inactivation of the Ca^{2+}-sensing receptor by reducing extracellular divalent minerals can also down regulate acid secretion even in the presence of potent secretagogues like histamine[18]. From the results of these studies it has now become apparent that the Ca^{2+}-sensing receptor (CaSR) plays an important regulatory role in acid secretion in mammalian gastric glands.

In addition to the animal studies on gastric glands, the CaSR has also been identified in human gastric tissues[11,16,17,36-38]. In the mucous epithelial cells, activation of the receptor results in a rapid rise in intracellular Ca^{2+} as well as a proliferative response when the cells were placed in culture[11]. In G cells, stimulation of the receptor results in gastrin release[16] accompanied by activation of phospholipase C[16] and an increase in intracellular Ca^{2+}[16,17]. The associated histamine release due to CaSR-mediated secretion of gastrin by G cells could account for rebound acid secretion that occurs following exposure to calcium containing antacids. All of these data are consistent with the scheme that the CaSR in the stomach could play an important role in both acid secretion and in mucosal repair. Activation of the receptor may act to modulate the rates of acid secretion in response to total body calcium homeostasis. Should there be a deficiency in calcium receptor activation would increase acid secretion, or prolong acid secretion, thereby allow maximal ionization of calcium from ingested foodstuffs and produce increased calcium delivery to the intestine. Increased intestinal calcium will activate the CaSR on the apical surface of the cells and result in inhibition of fluid secretion and enhanced absorption of the delivered Ca^{2+}. Over time as serum calcium rises, gastric CaSR would either become internalized, or deactivated, leading to a down regulation in acid secretion. In patients with Zollinger-Ellison syndrome (ZES; characterized by ulcer disease of the upper gastrointestinal tract, increased gastrin secretion, and non-β-cell tumors of the pancreas, i.e., gastrinomas), gastrin secretion and serum levels appear to correlate with the activity of the frequently associated hyperparathyroidism. This result would be consistent with gastrin secretion paralleling high PTH-driven elevations in plasma Ca^{2+}. Significant albeit variable, CaSR expression has been detected in human gastrinomas[37,38], suggesting that the receptor could mediate the effect of extracellular Ca^{2+} on gastrin secretion. Consistent with this explanation, activation of CaSR by raising extracellular Ca^{2+} increased rapidly intracellular Ca^{2+} that was not altered by the Ca^{2+} channel blocker, nifedipine[38].

CALCIUM IN THE INTESTINE

Overview

The Ca^{2+}-sensing receptor is expressed in epithelial cells along the entire small and large intestine, but only in colon has the receptor been studied in sufficient detail to permit comment on potential roles in normal intestinal function, in diarrheal states, and the effect of oral Ca^{2+} intake on reducing the risk of colon cancer. The expression of CaSR in nerve plexi involved in smooth muscle function and coordination, however, suggests a potential role in modulating intestinal motility. The latter could be important in coordinating food delivery (Ca^{2+}, amino acids, polyamines) and modulating intestinal motility to maximize nutrient absorption. In addition, an effect of CaSR activation on intestinal motility may be one factor contributing to the constipation that is associated with hypercalcemic states.

Calcium modulates fluid transport in the colon

The primary function of the colon is to both absorb and secrete fluid and thereby maintain normal salt and water homeostasis. The colon is a complex epithelium that consists of both extensive invaginations of the surface which are designated as crypts which make up approximately 90% of the epithelial mass and the remaining 10% being surface cells. Although earlier studies suggested that only surface cells absorb and only crypt cells secrete fluid into the lumen of the colon, recent evidence has established that both surface and crypt cells absorb and secrete fluid (see review for details;[39]). As over 90% of the colonic epithelial surface area is occupied by invaginations or crypts, these structures constitute the major functional unit of the colonic epithelium[40, 41].

The direction of net fluid transport is determined by the relative magnitudes of the absorptive and secretory fluxes. Under basal conditions (absence of hormones, drugs or other factors), net fluid transport by crypts is absorptive[42]. However, colonic crypts alter the direction

of net fluid transport to secretion upon exposure to cell permeable cyclic AMP analogues, (forskolin, or other agents that activate adenylate cyclase), or modulators of cyclic AMP metabolism such as phosphodiesterase (PDE) inhibitors[42]. Addition of cyclic AMP-generating hormones/factors like 5-hydroxytryptophan or prostaglandin E2 to the blood/interstitial surface of the crypt will also increases fluid secretion by colonic crypts[40,41]. Modulation of these fluid transport processes in the colon by cyclic AMP can result in profound fluid and electrolyte losses with associated secretory diarrheas, as is the case during cholera exposure (Figure 3)[40].

Some previous physiological studies in rats, measuring Ca^{2+} fluxes in isolated colonic mucosa suggested that the colon had the capacity to respond to changes in extracellular Ca^{2+}. For example, the colon, as is true for the small intestine, can absorb and secrete Ca^{2+} in response to changes in extracellular Ca^{2+} as well as in levels of 1, 25-dihydroxy vitamin D3[43-45]. These latter observations indicate that colonic mucosal epithelium *per se* is equipped with a Ca^{2+}-sensing mechanism. Recent studies have suggested that this divalent mineral sensing mechanism in colonic epithelia is the CaSR, based on immunolocalization of the receptor in apical and basolateral membranes and receptor function assays[3,8,9,12].

The activation of colonic CaSR by: Ca^{2+}, Gd^{3+} or neomycin, leads to rapid rises in intracellular Ca^{2+} in both surface and crypt cells[5]. The elevation in intracellular Ca^{2+} occurs within a few seconds, consistent with activation of the phosphatidylinositolphospholipase C-inositol 1, 4, 5-trisphosphate (PI-PLC-IP3) pathway by G protein-coupled cell membrane receptors. Ca^{2+}-sensing receptor-mediated increases in intracellular Ca^{2+} can be prevented by pre-treatment with U-73122, a specific inhibitor of phosphatidylinositolphospholipase C. This effect of PLC inhibition demonstrated that intracellular Ca^{2+} transients induced by Ca^{2+}-sensing receptor agonists were not the result of altered entry of extracellular Ca^{2+} into colonic epithelial cells but were rather due to receptor-mediated activation of PI-PLC. The receptor-mediated increase in intracellular Ca^{2+} concentration in colon was shown to be due to the release of Ca^{2+} from thapsigargin-sensitive cell stores[5].

The role of CaSR in modulating colonic fluid movement has been examined in isolated perfused colonic crypts using an in vitro micro-perfusion technique[5,46]. Under basal conditions (i.e., in the absence of forskolin, or other secretagogues), crypts exhibit net fluid absorption[47]. Following exposure to forskolin a net fluid secretion occurs[47]. Activation of either luminal or basolateral CaSR by Ca^{2+} and/or spermine reverses the forskolin-stimulated fluid secretion[5,46]. Further studies will be necessary to fully define the mechanism of CaSR effects on cyclic AMP-mediated fluid secretion. However, based on information recently obtained from the effects of CaSR activation on vasopressin-stimulated increases in cyclic AMP in the kidney thick ascending limb of Henle[48,49], we postulate CaSR-mediated elevation in intracellular Ca^{2+} would activate Ca^{2+}/calmodulin-sensitive phosphodiesterases that would metabolize intracellular cyclic AMP, and thereby abrogate fluid secretion (Figure 3).

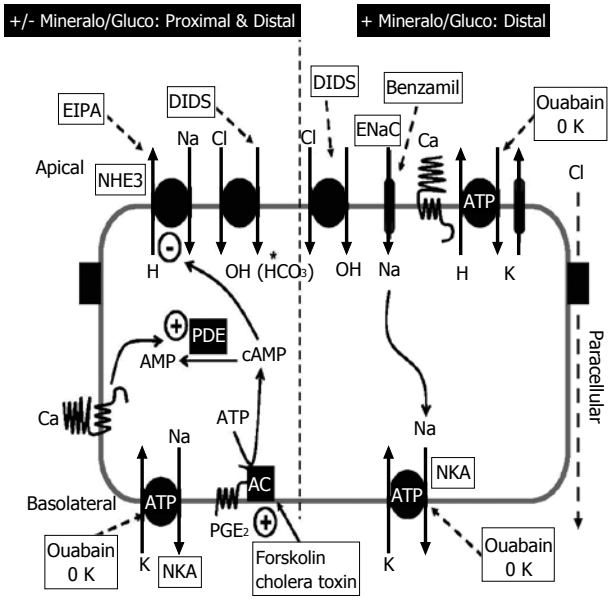

Figure 3 Cell model of proximal and distal colon. Shown are the known transport proteins in absence or presence of mineralocorticoid stimulation and their known inhibitors.

Increasing the levels of calcium on either the apical or basolateral membrane of the intact colon in Ussing chambers or in isolated perfused crypts leads to a decrease in fluid secretion. This decrease remains even in the presence of potent secretagogues such as forskolin; in fact there is enhanced absorption of fluid in the continued presence of potent secretagogues as long as the receptor remains activated[5,6]. In disease states or infectious states, fluid and electrolyte secretion can occur at pronounced levels and can cause dehydration and potentially death. By modulating the CaSR through increased delivery of calcium, or calcimimetic agents to the receptor, it appears possible that secretion could be stopped. This aspect of the CaSR could serve as an important new therapeutic target to modulate secretion and absorption of electrolytes along the intestine and combat secretory disease states.

POTENTIAL ROLES OF THE CaSR IN INTESTINAL EPITHELIAL CELL GROWTH AND DIFFERENTIATION AND NUTRIENT SENSING

Overview

The epithelium of the colon and the small intestine remains in a constant state of renewal. In the colon cells proliferate and become differentiated as they migrate from the base of the crypt towards the surface. Therefore cells at the base of the crypt are highly proliferative but less differentiated, whereas cells along the surface of the colon are highly differentiated and are in a non-proliferative state. Alterations of this tightly regulated process may lead to the development of hyperplastic events (polyps) and/or tumors. A potential role for the Ca^{2+}-sensing receptor in colonic epithelial cell proliferation, differentiation and development is suggested by the observations that receptor

activation reduces proliferation and induces differentiation of a variety of different cell types in addition to the intestinal epithelium. For example, activation of CaSR enhances cell differentiation in both mouse[50,51] and human[52,53] keratinocytes[54]. Moreover, activation of the Ca^{2+}-sensing receptor in other cells modulates proliferation and inhibits apoptosis[55-57].

The Ca^{2+}-sensing receptor responds not only to changes in divalent minerals but also to changes in organic nutrients (such as polyamines)[58] and amino acids[59,60]. Recently this effect was demonstrated in isolated rat gastric glands, whereby stimulation of the Ca^{2+}-sensing receptor by L-amino acids induced acid secretion in vitro[35]. In addition to activation of CaSR, there is evidence that certain amino acids can stimulate gastric acid secretion *via* the system L-amino acid transporter [Kirchhoff] which illustrates an increased layer of complexity in the process of acid secretion. Organic nutrients function primarily by altering the EC_{50} of the CaSR for Ca^{2+}, although direct agonist effects have been demonstrated. These nutrients could potentially alter the conformational structure of the Ca^{2+}-sensing receptor thereby enhancing the affinity for divalent ions and attenuating the cellular effects of receptor stimulation. The potential roles for these nutrients in coordinating protein and divalent mineral metabolism and in providing information on nutrient delivery to intestinal cells will be discussed in the following section.

Role in intestinal cell growth and differentiation

In small rodents such as rats and mice , dietary polyamine intake plays an essential role for normal gastrointestinal tract cell growth and development[61-65]. In humans, the postulated mechanisms for the pro-differentiation and anti-cancer effects of dietary Ca^{2+}/polyamines include: (1) formation of insoluble salts of Ca^{2+} with otherwise tumorigenic fatty acids and bile salts; and (2) modulation of the rates and/or fates of biologically active molecules such as nucleic acids, proteins and phospholipids[66-69]. The presence of CaSR on the plasma membranes of both surface and crypt epithelial cells raises the intriguing possibility that this receptor could mediate some of the dietary effects of Ca^{2+}, polyamines, and other nutrients on tissue modeling of intestinal epithelia.

Increases in polyamines, specifically spermine, results in the generation of IP3, raises intracellular Ca^{2+}, and modulates forskolin-stimulated fluid secretion, all consistent with activation of the colonic epithelial CaSR[46]. Polyamine (spermine > spermidine > putrescine)-mediated augmentation of intracellular IP3 and Ca^{2+} accumulation requires the presence of, and is potentiated by, extracellular Ca^{2+}. The EC_{50} for $Ca^{2+}{}_o$- mediated activation of the CaSR was also reduced by polyamines[46]. These results demonstrate that the colonic epithelial CaSR also positively responds to polyamines.

In cultured intestinal cell lines, CaSR has been shown to increase E-cadherin and reduce β-catenin production which are markers for intestinal differentiation[14,70,71]. In Caco-2 cells expressing the CaSR activation of this receptor by extracellular Ca^{2+} increases thymidine incorporation into DNA as a marker of cell proliferation[72]. Low concentrations of extracellular Ca^{2+} cause a PKC-dependent increase in c-*myc* protooncogene expression in Caco-2 cells and this pro-proliferative effect is abrogated by activation of the CaSR by increasing concentrations of extracellular Ca^{2+}[15]. The CaSR in keratinocytes and certain other cells has been shown to alter proliferation/differentiation and to modulate the activities of MAP and tyrosine kinases associated with cell proliferation[50-52,57,72-77]. All of these data, when taken together, support a potential role for the CaSR as a modulator of cell proliferation and differentiation in intestinal epithelial cells.

Role in colon cancer

Ingestion of high dietary Ca^{2+} promotes colonic mucosal epithelial cell differentiation, decreases cell growth, and reduces the risk for development of colorectal cancer (see recent summaries[78,79] and[14,15,77,80,81] and review by Karen Roland Cell Calcium special issue). Cancer of the colon and rectum is the second most frequently diagnosed malignancy in the United States in addition to being the second most common cause of cancer-related death (>56 000 American deaths this year). Observations that demonstrate that increases in dietary calcium reduce the risk of developing colon adenomas are noteworthy. Specifically, by increasing dietary calcium intake there has been: (1) a reduced risk for colorectal cancer by three-fold in men consuming 1400-1500 mg calcium per day, 19 year prospective study of men working at the Western Electric Co., Chicago[82]; (2) a significant reduction in colonic crypt cell proliferation and enhanced markers of cell differentiation in human subjects at increased risk for colon cancer[81,83,84]; (3) a reduced risk of colorectal adenomas in humans[85] also see[86-89]; (4) decrease in the incidence and number of carcinogen-induced colonic tumors in virtually all studies in rats, see[90] for a review; (5) significantly reduced recurrence of colorectal adenomas in a randomized, double-blind trial of 930 subjects[85]; (6) long term calcium supplements significantly suppressed colonic cell proliferation in adenoma patients[80]. Activation of the CaSR in human carcinoma cell lines by raising extracellular Ca^{2+} promotes E-cadherin expression while suppressing β-catenin activation[14], both markers of cell differentiation[70,71]. In addition, there has also been a correlation between CaSR expression and the stage of differentiation n human colon tumors[14]. These observations provide a significant body of evidence that increases in dietary Ca^{2+} reduce the risk of colon cancer and are mediated by activation of the CaSR.

Role of the receptor as a nutrient sensor

The ability of the CaSR to be activated by l-amino acids has been suggested as a link between protein and calcium metabolism[60]. This was suggested by the direct relationship between dietary protein intake and renal Ca^{2+} excretion[91,92]. A diet high in protein acutely increased urinary Ca^{2+} excretion[91,92] and a low protein intake induces elevated parathyroid hormone levels[93]. The increased urinary Ca^{2+} excretion associated with high protein intake appears due to elevations in intestinal Ca^{2+} absorption[91-93], although this has not been a universal finding[94]. As discussed in previous sections of this review, activation of the CaSR by Ca^{2+} stimulates gastric acid secretion, which

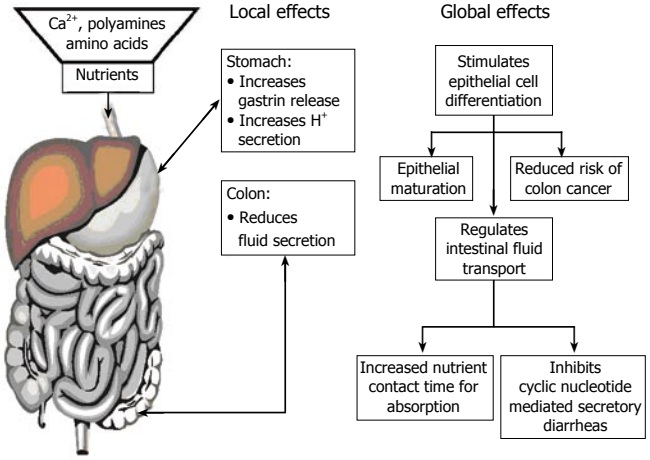

Figure 4 Current theory of roles for the Ca^{2+}-sensing receptor (CaSR) in the gastrointestinal tract.

in turn would promote acid digestion of proteins (together with peptidases). The release of l-amino acids would then promote Ca^{2+} absorption in small and large intestine by their synergistic activation of the Ca^{2+}-sensing receptor.

In summary, Figure 4 presents a current summary of the potential roles of the CaSR in gastrointestinal biology. Because of the unique properties of the CaSR in recognizing and responding to extracellular $Ca^{2+}{}_o$ and nutrients, this receptor presents a potential mechanism linking dietary metabolism (i.e., food digestion and nutrient absorption) to: (1) nutrient availability for epithelial growth and differentiation; and (2) protein and divalent mineral metabolism; (3) dietary Ca^{2+} intake and the associated reduction in risk of colon cancer; and (4) nutrient, salt and fluid homeostasis. In addition, the potential effects of nutrient activation of the CaSR on intestinal motility, coupled to the demonstrated reduction in fluid secretion, would increase nutrient-epithelial contact time and thereby enhance absorption. Finally, the potent ability of CaSR agonists to abrogate cyclic AMP-mediated fluid secretion by the colon has important implications for development of novel oral therapies of cyclic nucleotide dependent diarrheas like cholera.

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