Role of the Calcium Sensing Receptor (CaSR) in Divalent Mineral Ion Homeostasis

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About ten years ago Dr. Ed Brown and I cloned a G-protein-coupled receptor (CaSR) from bovine parathyroid that is sensitive to extracellular divalent minerals (Ca and Mg), and nutrients such as amino acids and polyamines. Since that time many studies in laboratories throughout the world have shown that the CaSR mediates many of the known effects of extracellular Ca on organ and tissue function. Genetic studies have shown that the CaSR is essential to extracellular Ca regulation of PTH and calcitonin secretion and renal Ca/Mg excretion. New evidence has emerged that divalent mineral and nutrient sensing by the CaSR plays important roles in regulating gastric, intestinal fluid transport and cell proliferation/differentiation, pancreatic and liver function.

The CaSR belongs to family C (or 3) of the superfamily of G protein-coupled receptors (GPRs) together with metabotropic glutamate and GABA receptors and pheromone receptors.

These receptors are characterized by the canonical 7-transmembrane domain of GPRs together with unique large extracellular domains of over 600 residues that form bi-lobed structures with a central cleft that binds ligands. The ligand-binding domain is reminiscent of bacterial periplasmic nutrient-binding proteins and suggests an early evolutionary appearance of the CaSR in primitive eukaryotic cells. Consistent with this long evolutionary timeframe, the CaSR appears to be essential for osmo-regulation in marine species that live in a world containing high concentrations of divalent minerals. The CaSR can couple to several different G proteins and an array of cell second messengers that modify cell function, proliferation and differentiation.

Several of the functions of the CaSR will be highlighted.

(1) Activation of the CaSR in parathyroid cells by Ca is essential for regulation of the secretion or parathyroid hormone (PTH). Individuals with uremic secondary hyper-parathyroidism have a reduced number of normal receptors on parathyroid cells leading to altered (elevated) secretion of PTH and its systemic consequences. Organic uncharged compounds have been developed by the pharmaceutical industry that act as allosteric modifiers of the CaSR and enhance its activation by Ca. Studies have demonstrated that these compounds can significantly reduce PTH secretion in uremic animals and in individuals with end-stage kidney disease on dialysis. These compounds may be useful in treating the hyperparathyroidism in end-stage disease.

(2) In the mammalian kidney, the expression and function of the CaSR along the nephron can account for the hypercalcemia-mediated reductions of NaCl and divalent mineral reabsorption as well as for the diminished urinary concentrating ability [hypercalcemic nephrogenic diabetes insipidus]. In general, Ca can be thought of as producing a loop diuretic-like effect in the TAL.

Polycationic aminoglycosides likely exert their natriuretic, calciuric and magnesuric effects by activating the CaSR in TAL. The CaSR is also present in APQ2 water channel-containing endosomes at the apical membrane in the terminal collecting duct. Increasing luminal Ca produces a rapid and reversible reduction in the water permeability of this nephron segment limiting the maximum rise in urinary Ca concentration during periods of increased Ca loss. These CaSR actions furnish a mechanism for integrating and balancing water and divalent mineral losses which minimizes the risk of stone formation and nephrocalcinosis.

(3) The CaSR is a potent activator of gastric H secretion and probably accounts for the rebound effect of Ca-containing antacids on gastric acidity. Recent studies suggest that the intestinal CaSR is also involved in the essential polyamine-mediated effects on epithelial proliferation-differentiation that is required for maintenance of normal GI epithelial cell function.

In fact, the CaSR has been suggested to mediate the effect of increased dietary calcium to reduce the risk of colon cancer. Moreover, the receptor in colonic epithelial cells is a potent regulator of cyclic-nucleotide-mediated fluid secretion as seen with cholera, suggesting that CaSR agonists like Ca and polyamines may be useful in oral rehydration therapy for secretory diarrheas.