Calcium-Sensing Receptor Activation in Chronic Kidney Disease: Effects Beyond Parathyroid Hormone Control

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Summary: Secondary hyperparathyroidism (SHPT) is an important complication of advanced chronic kidney disease (CKD). Cinacalcet, an allosteric modulator of the calcium-sensing receptor (CaSR) expressed in parathyroid glands, is the only calcimimetic approved to treat SHPT in patients on dialysis. By enhancing CaSR sensitivity for plasma extracellular calcium (Ca_0^{2+}), cinacalcet reduces serum parathyroid hormone, Ca_0^{2+}, and serum inorganic phosphorous concentrations, allowing better control of SHPT and CKD–mineral and bone disorders. Of interest, the CaSR also is expressed in a variety of tissues where its activation regulates diverse cellular processes, including secretion, apoptosis, and proliferation. Thus, the existence of potential off-target effects of cinacalcet cannot be neglected. This review summarizes our current knowledge concerning the potential role(s) of the CaSR expressed in various tissues in CKD-related disorders, independently of parathyroid hormone control.

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First identified by Brown et al[1] in bovine parathyroid glands, the calcium-sensing receptor (CaSR), a 121-kDa protein, plays a crucial role in the maintenance of Ca homeostasis, in particular the extracellular ionized calcium concentration (Ca_0^{2+}). This receptor belongs to class C of the G-protein–coupled membrane-bound receptor superfamily. Its structure consists of a long extracellular N-terminal domain (ECD), which is essential for interactions with its agonists, 7 hydrophobic transmembrane helices that anchor the receptor in the plasma membrane, and an intracellular C-terminal domain that has multiple regulatory protein kinase phosphorylation sites[2] (Fig. 1). At the cell surface, the CaSR is present constitutively in a dimeric configuration.[3] CaSR monomers can link covalently by creating disulfide bridges within their N-terminus domains. This homodimerized configuration is crucial for normal CaSR function.[4]

AGONISTS AND ANTAGONISTS

CaSR ligands usually are classified as orthosteric modulators (type I agonists), which can bind and directly activate the CaSR, thus inducing signal transduction into the cell, and allosteric modulators (type II agonists), which bind to allosteric sites of the CaSR and require the fixation of orthosteric modulators to produce their effects.[5] Allosteric modulators can either activate or inhibit the CaSR.

Orthosteric modulators bind the orthosteric fixation site of the CaSR, which is localized in the ECD (Fig. 1). The term *orthosteric* characterizes the primary ligand fixation site, in the absence of any change of conformation. Numerous divalent and trivalent cations can bind the orthosteric site of the CaSR, including Ca^{2+}, Mg^{2+}, Al^{3+}, Sr^{2+}, Mn^{2+}, Ni^{2+}, Gd^{3+}, and Ba^{2+}.[6] The orthosteric site also can bind polycationic compounds such as aminoglycoside antibiotics (neomycin, gentamycin),[7] polyamines (such as spermine),[8] and numerous amino acids.

Allosteric modulators bind outside the orthosteric site. Their fixation changes CaSR 3-dimensional conformation, which modulates the affinity of orthosteric CaSR modulators. Aromatic L-amino acids, which bind within the ECD to a site adjacent to orthosteric sites, have been shown to act as positive allosteric

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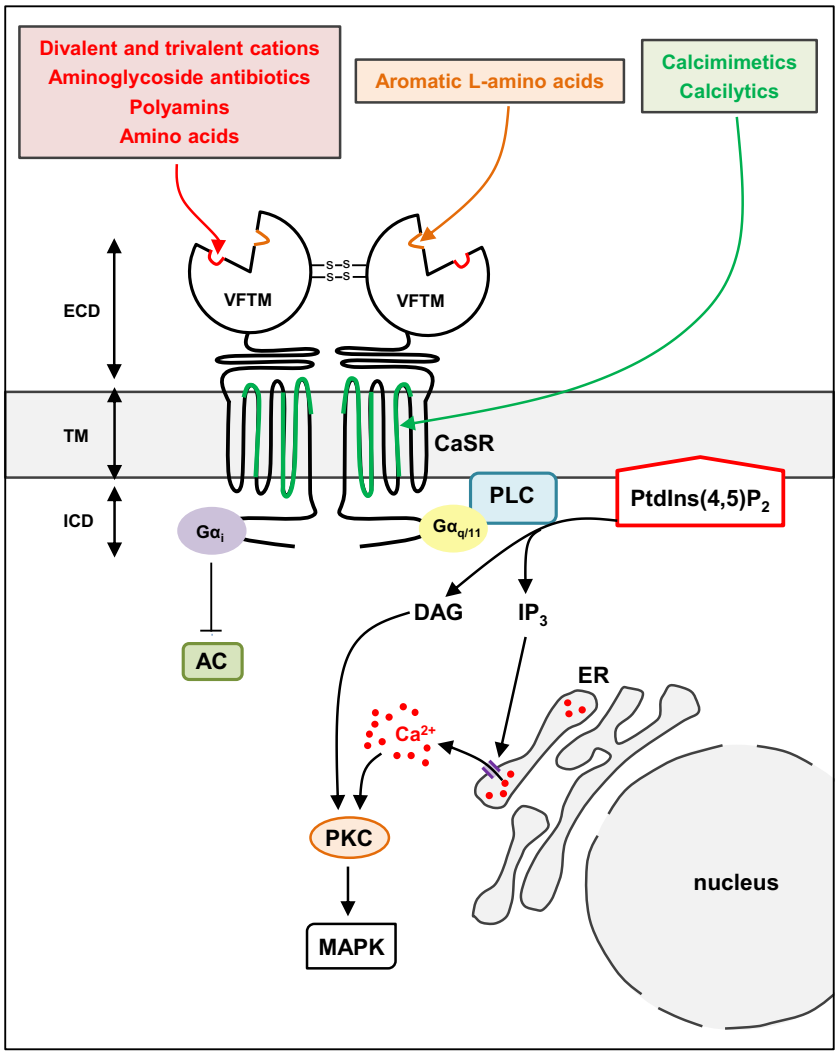

Figure 1. CaSR structure, agonist fixation sites, and general signaling. Ac, adenylate cyclase; DAG, diacylglycerol; Gαi and Gαq/11, α subunits of the i-type and q-type heterotrimeric G proteins; ICD, intracellular domain; IP3, inositol trisphosphate; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; PLC, phospholipase C; PtdIns(4,5)P, phosphatidylinositol-4,5-bisphosphate; ER, endoplasmic reticulum; TM, transmembrane domain; VFTM, Venus flytrap domain motif.

modulators of the CaSR[9,10] (Fig. 1). The recent design of synthetic allosteric modulators of the CaSR, calcimimetics and calcilytics, which increase and decrease, respectively, CaSR sensitivity for its orthosteric agonists, has opened new fields of research. These compounds share structural similarities with aromatic L-amino acids, with an aromatic ring and positively charged amine groups.[11] Their binding sites have been shown to be located in the transmembrane helices and extracellular loops of the CaSR[12,13] (Fig. 1). Currently, the most frequently studied allosteric modulators are as follow: (1) the first-generation calcimimetics NPSR-467 and R-568,[14] (2) the second-generation calcimimetic NPS 1493 (also named AMG 073), which is clinically known as cinacalcet HCl and is used to treat primary and secondary forms of hyperparathyroidism,[15] (3) calindol, which belongs to the naphtylalkylamine group, in contrast to the other calcimimetics that belong to the phenylalkylamine group,[13] (4) velcalcetide (AMG 416), a novel peptide agonist of the CaSR,[16,17] (5) the new chemical series of trisubstituted ureas,[18,19] and (6) the calcilytics NPS 2143[20] and Calhex 231.[21]

TRANSMEMBRANE SIGNALING

Stimulation of the CaSR by its agonists leads to the activation of multiple types of G-proteins (Fig. 1). Activation of Gαq/11 activates phospholipase C, producing inositol 1,4,5 trisphosphate and diacylglycerol, which in turn promotes the mobilization of intracellular calcium stores, the activation of protein kinase C, and the stimulation of mitogen-activated protein kinases. Activation of Gαi inhibits the adenylate cyclase signaling pathways and protein kinase A.[22] It is now widely accepted that the activation of the CaSR by different