

Gene Section

Review

CASR (Calcium-Sensing Receptor)

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Published in Atlas Database: September 2013

Online updated version : <http://AtlasGeneticsOncology.org/Genes/CASRID43977ch3q21.html>
DOI: 10.4267/2042/53534

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Abstract

Review on CASR, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CAR, EIG8, FHH, FIH, GPRC2A, HHC, HHC1, NSHPT, PCAR1

HGNC (Hugo): CASR

Location: 3q21.1

Local order: Chromosome: 3; NC_000003.11.

Note

Genbank Accession number: U20760; EMBL-Bank Accession number: X81086.

DNA/RNA

Description

The human CaSR gene maps to 3q13.3-21, is approximately 103 kb in length and contains 8 exons (exons 1A and 1B and exons 2-7) (Garrett et al., 1995; Janicic et al., 1995; Hendy et al., 2009). The full length CaSR protein is translated from part of exon 2, all of exons 3-6 and part of exon 7 (Figure 1). Exons 1A and 1B are not translated. An alternatively spliced, functional variant of the receptor lacking exon 5 has been reported (Rodriguez et al., 2005a). The CaSR gene has two promoters, an upstream promoter (P1) containing a TATA box and CCAAT box and an additional promoter (P2) with Sp1 sites that cluster near the transcriptional start site (Figure 1; Chikatsu et al., 2000; Canaff et al., 2008; Hendy et al., 2009). The two promoters yield alternative transcripts containing either exon 1A or exon 1B spliced to

exon 2 (Chikatsu et al., 2008; Hendy et al., 2009). Both promoters contain vitamin D response elements as well as response motifs for NF- κ B and glial cells missing-2 (Canaff and Hendy, 2002; Canaff and Hendy, 2005; Canaff et al., 2009). The upstream promoter region contains Stat1/stat3 elements which allow for response to interleukin-6 (Canaff et al., 2008). Use of differential polyadenylation signals in exon 7 appear to lead to at least two different-sized 3' untranslated regions (Figure 1; Garrett et al., 1995).

Protein

Note

The full length human CaSR mRNA encodes a protein of 1078 amino acids consisting of a 612 amino acid signal peptide/extracellular domain (ECD), a 250 amino acid seven transmembrane domain (7TM) and an unusually long 216 amino acid intracellular tail (Garrett et al., 1995; Hu and Spiegel, 2003) (Figure 1). The NH₂-terminal signal peptide is 19 amino acids in length and directs the nascent protein to the endoplasmic reticulum (ER) where it is subsequently removed (Hu and Spiegel, 2003; Pidasheva et al., 2005; Hendy et al., 2009). The ECD is composed of a bilobed Venus flytrap (VFT) domain followed by a cysteine-rich domain connected via a peptide linker region to the 7TM which in addition to the membrane α -helices also contains three intra- and three extra-cellular loops; the final TM α -helix is connected to the intracellular tail, the membrane proximal domain of which is important for receptor cell expression and intracellular signalling (Ray et al., 1997; Hu and Spiegel, 2003).

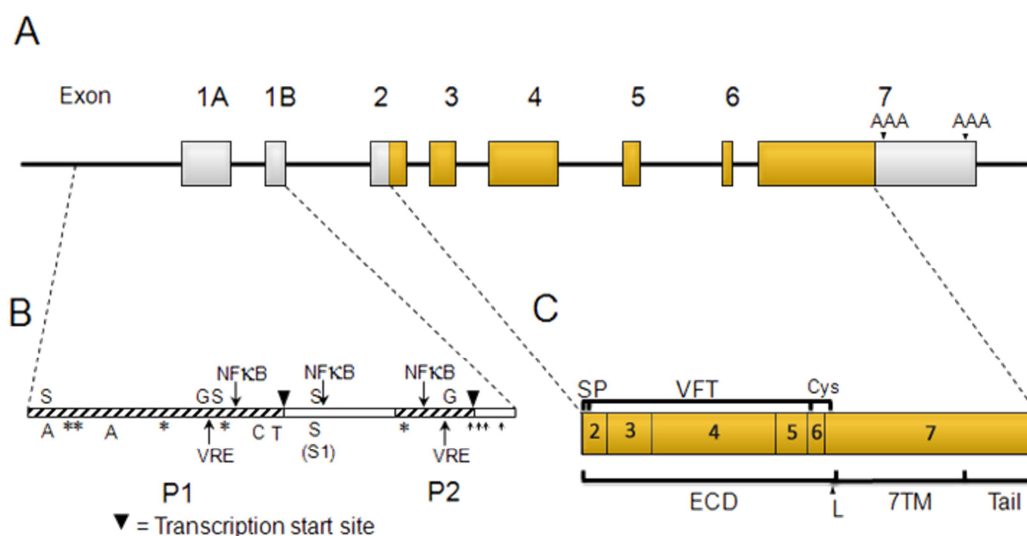


Figure 1. Schematic representation of the calcium-sensing receptor (CaSR) gene structure (A), promoter location and features (B) and protein structural arrangement (C). The CaSR mRNA is transcribed from part of exon 2, all of exons 3 to 6 and part of exon 7. Exons that comprise the CaSR protein are shaded yellow; untranslated exons are left unshaded. Note that intronic regions are not drawn to scale. The location of polyadenylation sites (AAA) within the untranslated region of exon 7 are arrowed. In B, the spatial relationship between promoters P1 and P2 (hatched) and untranslated exons 1A and 1B (unshaded) is highlighted along with the position of various transcription factor binding sites and regulatory elements: C, CCAAT box; T, TATA box; A, Ap-1 sites; *, serum response elements; VRE, vitamin D response elements; G, glial cells missing-2 response element; †, Sp1 sites; NFkB, NFkB response elements; S, STAT sites (S1 regulates IL-6 response). The CaSR protein (C) is composed of the extracellular domain (ECD) consisting of a signal peptide (SP), Venus Fly Trap (VFT) domain and cysteine-rich domain (Cys) connected by a small linker region (L) to the seven transmembrane domain (7TM) and intracellular tail, both encoded by exon 7.

The CaSR protein is processed as a dimer in the ER via covalent intermolecular disulphide bonds and hydrophobic interactions and functions as a dimer when mature (Bai et al., 1998; Bai et al., 1999; Zhang et al., 2001; Pidasheva et al., 2006). Essentially, agonist binding to a cleft between the VFT lobes of each monomer leads to their closure and rotation about the VFT dimer interface thus transmitting a conformational change to the cysteine-rich domain which in turn allows movement of the 7TM α -helices with respect to one another resulting in connection of G proteins to the intracellular loops and initiation of signalling pathways (Hu and Spiegel, 2003).

The CaSR contains 11 potential N-linked glycosylated sites in the ECD and is glycosylated in the ER with high mannose carbohydrates (immature receptor) after which it is transported to the Golgi where it is further modulated with complex carbohydrates (mature receptor) (Ray et al., 1998). Western blot analysis of protein extracted from cells containing mature and immature CaSR reveal bands at 150 kDa and 130 kDa, respectively.

The CaSR contains five potential sites for protein kinase C phosphorylation, two in intracellular loops 1 and 3 and three in the intracellular tail and two potential sites for protein kinase A phosphorylation in the intracellular tail (Garrett et al., 1995; Bosel et al., 2003).

Description

The CaSR was first cloned from bovine parathyroid cells by Brown and coworkers in 1993 and the human receptor was cloned from an adenomatous parathyroid gland in 1995 (Brown et al., 1993; Garrett et al., 1995).

The CaSR is a G protein-coupled receptor belonging to Group II of Family C, G protein-coupled receptors and conforms to a typical G protein-coupled receptor structure with a large extracellular domain, a seven transmembrane spanning domain and a rather large intracellular tail (Brown and MacLeod, 2001; Hu and Spiegel, 2003).

The CaSR is promiscuous, activating a variety of signalling pathways via a host of ligands (in addition to Ca^{2+}) in a cell/tissue type-specific manner (Brown and MacLeod, 2001; Magno et al., 2011b).

The receptor's primary function is in the maintenance of calcium homeostasis in the body, but other functions have more recently come to light (see below).

Expression

The CaSR has a widespread tissue distribution in the body including those tissues which are important in the maintenance of calcium

homeostasis, namely the chief cells of the parathyroid gland where it is responsible for regulating parathyroid hormone (PTH) secretion, the C cells of the thyroid whereby it controls calcitonin secretion, the kidney where it controls calcium reabsorption, the placenta whereby it controls calcium transport from mother to foetus and in cartilage and bone cells, (chondrocytes, osteoblasts and osteoclasts) in which it has important effects on the laying down and maintenance of the skeleton (Magno et al., 2011b; Riccardi and Kemp, 2012). The CaSR is also expressed in intestinal epithelial cells where it serves to regulate intestinal uptake of calcium by directly modulating responsiveness to 1,25-dihydroxyvitamin D (Egbuna et al., 2009). Apart from tissues which regulate calcium homeostasis, the CaSR is also expressed in many tissues outside this realm including the breast, ovary, uterus, testis, prostate and germ cells, the tongue, oesophagus, stomach and pancreas as well as the heart, various parts of the brain (including the subfornical organ and olfactory bulbs, hippocampus, hypothalamus and cerebellum), pituitary, lens epithelium and skin (Brown and MacLeod, 2001; Magno et al., 2011b; Riccardi and Kemp, 2012). The function of the CaSR in many of these tissues is still largely unknown.

Localisation

As expected for a G protein-coupled receptor, the CaSR localizes to the plasma membrane of the cells in which it is expressed. However, there is accumulating evidence for a large intracellular pool of receptor that localizes to the ER/Golgi awaiting agonist driven trafficking to the plasma membrane, a mechanism thought to regulate membrane CaSR abundance in the chronic presence of agonist (Grant et al., 2011). While the CaSR does undergo endocytosis and is targeted to the lysosome, it does not undergo substantial desensitization and recycling as occurs with many other G protein-coupled receptors (Grant et al., 2011). In the chief cells of the parathyroid gland, CaSR is located in caveolae, flask-like invaginations of the plasma membrane that contain various signalling molecules and scaffolding proteins such as filamin-A and caveolin-1 to which the CaSR is anchored (Kifor et al., 1998). In various parts of the kidney tubule (proximal tubule, cortical thick ascending limb, distal convoluted tubule, medullary collecting duct) the membrane bound CaSR may be located apically or basolaterally or both depending on its specific function(s) in these compartments (Riccardi and Kemp, 2012). For example, the apically located CaSR in the medullary collecting duct inhibits insertion of AQP2 water channels and promotes activation of the B1 subunit of the vacuolar H⁺-ATPase in the apical membrane, thus delivering a

less concentrated and more acidified urine (Sands et al., 1998; Procino et al., 2004; Riccardi and Kemp, 2012). Likewise in the gastrointestinal tract, the CaSR is expressed both on the apical and basolateral membranes of the gastrin secreting G cells of the stomach indicating that it can sense and respond to nutrient levels both in the lumen and in the blood, whereas CaSR in colonic epithelial cells, whether it is expressed apically or basolaterally, can mediate cAMP-mediated fluid secretion (Conigrave and Brown, 2006).

Function

The primary function of the CaSR is in the maintenance of calcium homeostasis through regulation of PTH secretion and reabsorption of calcium from the kidney tubules. PTH has effects on bone resorption, intestinal uptake of calcium (via production of 1,25-dihydroxyvitamin D) and calcium reabsorption from the kidney, all combining to restore calcium in the extracellular fluid to a concentration within the narrow range 1.1 - 1.3 mM Ca²⁺ (Tfelt-Hansen and Brown, 2005). However, the CaSR is now known to be a multifunctional receptor with important influences on major cellular processes that include not only entero-endocrine secretion but control of gene expression and cell differentiation, cellular proliferation, apoptosis, chemotaxis, cytoskeletal organization and the regulation of ion transport and the activity of ion channels (Tfelt-Hansen and Brown, 2005; Riccardi and Kemp, 2012). It achieves this enormous diversity of function by activating an array of cell signalling pathways in a tissue and ligand-dependent manner, with partner binding proteins also playing an important role (Brennan and Conigrave, 2009; Magno et al., 2011b). The CaSR can be activated not only by Ca²⁺ ions but by other di-, tri- and polyvalent cations including polyamines such as spermine, aminoglycoside antibiotics such as neomycin and polypeptides including amyloid β -peptide. Receptor activity is also modulated by pH and salinity and can be potentiated (in the presence of direct agonist) by allosteric activators such as L-amino acids and type II calcimimetics (Nemeth et al., 1998; Conigrave et al., 2000; Brown and MacLeod, 2001; Magno et al., 2011b). The receptor, upon activation, can couple to G_{q/11}, G_{i0}, G_{12/13} and G_s G protein families to regulate a variety of signalling molecules including phosphatidylinositol-specific phospholipase C (PLC) (and hence PKC and release of intracellular Ca²⁺ from intracellular stores), as well as phospholipase A₂, phosphatidylinositol 3-kinase (which in turn affects Akt signalling), phospholipase D and Rho and MAP kinases (including ERK1/ERK2) (Brennan and Conigrave, 2009; Magno et al., 2011b). When coupled to G_s and G_i the receptor can stimulate or

inhibit cAMP production, respectively (Mamillapalli et al., 2008).

The precise pathway(s) involved in CaSR-mediated inhibition of PTH have yet to be completely elucidated, however the associated reduction in PTH mRNA levels involves an increase in intracellular Ca^{2+} , suggesting a role for PLC activation (Ritter et al., 2008). The CaSR has several important homeostatic functions in the kidney depending on its location. In the proximal tubule, CaSR stimulation reverses the inhibitory effects of PTH on phosphate reabsorption via the phosphate transporters NaPi-IIa/NaPi-IIc and also blocks 2,5-hydroxyvitamin D₃-1 α -hydroxylase. In the thick ascending limb of Henle's loop, stimulation of basolaterally localized CaSR reduces potassium cycling (by decreasing the activity of the 70-pS channel) as well as NaCl transport and paracellular reabsorption of Mg^{2+} and Ca^{2+} . In the distal convoluted tubule, the CaSR is located both apically and basolaterally, in the former it is linked to the receptor potential vanilloid member 5 (TPRV5) and stimulation of the CaSR therefore increases uptake of Ca^{2+} ions. Basolaterally, CaSR activation inhibits the activity of plasma membrane Ca^{2+} -ATPase 1b and decreases expression of the K^+ channel, Kir4.1 resulting in inhibition of basolateral K^+ recycling. Activation of apically localized CaSR in the medullary collecting duct reduces osmotic water permeability (creating less concentrated urine) by inhibiting vasopressin-induced insertion of AQP2 water channels and increases the activity of H^+ -ATPase (making urine more acidic). These effects reduce the likelihood of kidney stone formation (see recent reviews that discuss the functional homeostatic role for the receptor in the kidney by Magno et al., 2011b and Riccardi and Kemp, 2012). The CaSR is also expressed in regions of the kidney that do not relate to Ca^{2+} or other mineral ion homeostasis. Activation of the CaSR expressed in the juxtaglomerular cells of the afferent arteriole of the kidney inhibits release of renin, thus exerting influence over the renin-angiotensin system that controls blood pressure (Atchison et al., 2010) while stimulation of the CaSR in the podocytes of the glomerular filter has been shown to effect the cytoskeletal integrity and viability of these cells suggesting an important role for the receptor in proper renal filtration (Oh et al., 2011).

The CaSR is expressed along the whole length of the gastrointestinal tract where it plays important roles in nutrient sensing, the regulation of fluid secretion, hormone release and cell differentiation/apoptosis (Conigrave and Brown, 2006; Geibel and Hebert, 2009). Recent data show that taste buds contain the CaSR and that agonists of the CaSR enhance taste perception while antagonists of the CaSR suppress it (Ohsu et al.,

2010). The receptor is also expressed in the basal cells of the oesophagus where stimulation results in an increase in IL-8 secretion, the physiological importance of which is yet to be determined (Justinich et al., 2008). In the stomach, the CaSR plays a clear role in the regulation of gastrin and gastric acid release from G cells and parietal cells, respectively (Conigrave and Brown, 2006; Geibel and Hebert, 2009). In the duodenum, amino acid stimulation of the CaSR in I cells of the small intestine leads to release of cholecystokinin a hormone important for gall bladder contraction, pancreatic enzyme secretion and gastric emptying (Wang et al., 2011). CaSR expression in the acinar cells of the pancreas and in pancreatic duct cells suggests a role for the receptor in fluid secretion and/or the secretion of enzymes from the pancreas (Racz et al., 2002; Riccardi and Kemp, 2012). The proper regulation of fluid secretion from the pancreatic ducts by the CaSR is thought to be important in the prevention of pancreatic stones and pancreatitis (Riccardi and Kemp, 2012). In addition, activation of the CaSR expressed in the β -cells of the pancreatic islets of Langerhans can modulate insulin secretion and this has implications for the onset and progression of diabetes (Gray et al., 2006; Squires et al., 2000). CaSR expression in colonic epithelial cells is required for the transition of cells along the crypt from a proliferative to a differentiated state, thus the presence of receptor in these cells is thought to be important in preventing colon cancer (Whitfield, 2009).

Agonist activation of the CaSR in the colon can suppress cAMP-mediated fluid loss and is important in the control of NaCl and water absorption (Geibel and Hebert, 2009). It has been proposed that calcimimetics could be used to prevent diarrhoea/fluid loss associated with bacterial toxins in diseases such as cholera (Geibel et al., 2006).

In the lactating breast, expression of the CaSR in mammary epithelial cells can regulate parathyroid hormone-related protein (PTHrP) production and adjust uptake of calcium into milk according to calcium availability (VanHouten et al., 2004). In the normal breast the CaSR has tumour suppressor properties acting in concert with the BRCA1 tumour suppressor to decrease levels of the antiapoptotic protein, survivin, and increase sensitivity to paclitaxel, a drug commonly used in breast cancer treatment (Promkan et al., 2011). However, if expressed in malignant breast cells, the receptor may actually aid bone metastasis (see below under hypercalcaemia of malignancy). With relevance to its apparent role in metastasis, the CaSR has been shown to couple to integrins thereby promoting tumour cell adhesion and migration (Tharmalingham et al., 2011). The CaSR can also bind the focal adhesion protein, testin, that is

known to have important effects on cell spreading and motility (Magno et al., 2011a).

In the brain, The CaSR is highly expressed in the subfornical organ and potentiates neuronal, hyperpolarization-activated and inward currents, consistent with the bursting of action potentials in these neurons that has also been shown to be CaSR-potentiated (Washburn et al., 2000; Yano et al., 2004). The expression of the CaSR in the subfornical organ, which is a thirst control centre, suggests that the receptor plays a crucial role in fluid and electrolyte homeostasis. The CaSR also controls neuronal excitability in a number of other parts of the brain by regulating ion channels and this may contribute to its apparent role in epilepsy (Kapoor et al., 2008; Riccardi and Kemp, 2012). For example, in the hippocampus, CaSR-mediated activation of a voltage-independent Na^+ leak conductance channel leads to neuronal excitation (Lu et al., 2010). In the hippocampus, increasing expression of the CaSR during the first weeks of life correlate with long-term potentiation indicating that the CaSR may play a role in cognitive functions such as memory and learning (Brown and MacLeod, 2001; Yano et al., 2004). The CaSR has important regulatory effects on the developing nervous system, for example, activation of the CaSR appears to be critical for the expansion and differentiation of oligodendrocyte progenitor cells and the generation of myelin in preoligodendrocytes (Chattopadhyay et al., 2008). Stimulation of CaSR is required for the production of a cofactor, tetrahydrobiopterin, essential for the activation of nitrous oxide that is produced (in its inactive form) in response to amyloid β peptide-mediated activation of the receptor (Dal Pra et al., 2005). Hence, CaSR may play an important role in late onset Alzheimer's disease that is characterized by nitrous oxide-mediated neuronal damage. In the pituitary gland, activation of the CaSR stimulates cAMP production via coupling to G_{os} with subsequent secretion of PTHrP and ACTH (Mamillapalli and Wysolmerski, 2010).

The CaSR is expressed and plays a functionally important role in various bone cells including osteoblasts/osteocytes and osteoclasts and their precursors, bone marrow derived stromal cells, monocyte-macrophage cells, chondrocytes and haematopoietic stem cells (Yamaguchi, 2008). Targeted depletion of the CaSR induced in mouse embryonic chondrocytes and osteoblasts has revealed that the CaSR is absolutely required for growth plate and skeletal development (Chang et al., 2008). Activation of the CaSR in osteoblasts is required for osteoblast differentiation, proliferation and mineralization (Yamaguchi, 2008; Dvorak-Ewell et al., 2011). In addition, high Ca^{2+} -induced apoptosis of osteoclasts is mediated through nuclear translocation of NF- κ B which in turn is dependent

on CaSR stimulation and activation of PLC (Mentaverri et al., 2006). The CaSR also appears to be important in osteoclastogenesis as shown in studies with bone marrow cells from CaSR knockout mice (Dvorak-Ewell et al., 2011). The CaSR is required for haemopoietic stem cells to lodge in the endosteal niche of the bone marrow - this has implications for the proper functioning of erythropoiesis (Adams et al., 2006). The CaSR appears to contribute, albeit indirectly, to the formation of teeth and the development of dental alveolar bone (Sun et al., 2010).

The CaSR also has established roles in other organs and tissues including the heart and circulatory system. In the heart, the receptor can augment angiotensin II-mediated cardiac hypertrophy in cardiomyocytes, while CaSR-mediated production of nitrous oxide can lead to vasodilation in human aortic epithelial cells with subsequent effects on blood pressure (Ziegelstein et al., 2006; Wang et al., 2008). The CaSR has also been shown to mediate the cardio-protective effects of ischaemic preconditioning (Sun and Murphy, 2010). Expression of the CaSR in vascular smooth muscle cells of human arteries appears to be important in preventing arterial calcification (Alam et al., 2009). The CaSR appears to play an important role in the differentiation of keratinocytes and their survival (Tu et al., 2008). Lens epithelial cells express CaSR mRNA and protein and stimulation of the receptor regulates a calcium-activated potassium channel - it is likely that the receptor contributes to lens integrity (Chattopadhyay et al., 1997; Brown and MacLeod, 2001).

The receptor also has functional effects on reproduction and development (Riccardi and Kemp, 2012). The CaSR is expressed in ovarian surface cells and ova (where it is important for development and maturation), sperm (where it is important for maturation, motility and fertilization) and uterus (where it plays roles in implantation and embryonic development). Hence its proper expression has important implications for fertility. In addition the receptor plays a critical role in the placenta and in embryonic and foetal development of organs such as the lung, brain and nervous system (Riccardi and Kemp, 2012).

Homology

The human and bovine CaSR share significant homology (greater than 90% at the amino acid level) with CaSRs from other mammals such as rodents, rabbits and cats (Garrett et al., 1995; Brown and MacLeod, 2001; Gal et al., 2010). Even CaSRs from chickens and the mudpuppy (an amphibian) share approximately 80% amino acid identity underscoring the functional importance of this receptor throughout the animal kingdom (Brown and MacLeod, 2001). The CaSR belongs to

Family C of the G protein-coupled receptors, members of which share at least 20% amino acid homology in their seven transmembrane domains (Brauner-Osborne et al., 2007). Group I of Family C comprise the metabotropic glutamate receptors (mGluR 1-8) whereas the CaSR belongs to Group II which also contains the vomeronasal and taste and odorant receptors and various orphan receptors including GPRC6A (the most closely related to the CaSR).

Group III comprises the gammabutyric acid (GABA_B) receptors). Interestingly, the CaSR can heterodimerize with mGluR and GABA_B receptors resulting in receptor units with unique pharmacological profiles (Gama et al., 2001; Cheng et al., 2007).

The ECD including the VFT of the Family C GPCRs shares homology with bacterial periplasmic nutrient-binding proteins (PBPs) and Family C GPCRs are thought to have evolved from fusion of an ancient PBP-like structure (forming the ECD) with an independently derived seven transmembrane domain entity (Brown and Macleod, 2001).

Mutations

Note

Heterozygous, germinal mutations in the CaSR may be activating or inactivating leading to the familial conditions of altered calcium sensing, autosomal dominant hypocalcaemia (ADH) and familial hypocalciuric hypercalcaemia (FHH), respectively (Pollak et al., 1993; Pollak et al., 1994). These disorders are usually benign and may often be asymptomatic, although in rare cases severe activating mutations of the CaSR may give rise to Bartter's syndrome subtype IV (Vargas-Poussou et al., 2002). On the other hand, the homozygous presence of inactivating mutations or compound heterozygous mutations affecting both alleles of the CaSR gene give rise to the rare, but much more serious condition, neonatal severe hyperparathyroidism (NSHPT), that normally requires surgical intervention (usually sub-total parathyroidectomy) in the neonate (Pollak et al., 1993; Ward et al., 2004; Ward et al., 2012). Reported mutations leading to ADH and FHH/NSHPT number around 65 and 140, respectively and may occur almost anywhere in the CaSR gene coding region, although there is a particular preponderance in exons 3 and 4 which encode part of the extracellular ligand-binding domain that includes the VFT, and the 5' end of exon 7 which encodes the seven transmembrane, signalling domain, including the extra- and intracellular loops (Hendy et al., 2009 and see database: CASRdb).

Implicated in

Breast cancer

Note

Increased dietary calcium has been shown to be protective against the development of breast cancer (Negri et al., 1996) and by contrast to the CaSR's positive role in breast cancer metastasis, the CaSR in general plays a tumour suppressor role in the development of breast cancer. This apparent paradox may best be explained by differences in the properties of primary as opposed to metastasising breast cancer cells (Ward et al., 2012). Agonist activation of the CaSR in breast cancer cells down-regulates cell proliferation, cell invasion and anchorage-independent growth as well as expression of the anti-apoptotic protein, survivin, and affords an increase in sensitivity to paclitaxel, an important drug used in the treatment of breast cancer (Liu et al., 2009a). Interestingly, the BRCA1 tumour suppressor gene which mimics these effects in breast cancer cells has been shown to do this by regulating the expression of the CaSR and therefore its effect on survivin expression and paclitaxel sensitivity (Promkan et al., 2011).

Colon cancer

Note

As for breast cancer, calcium has been shown to be chemopreventative for colon cancer with high levels being inhibitory and low levels favourable to human colonic cell proliferation (Lipkin, 1999; Kallay et al., 2000). Moreover, the CaSR is expressed in human colonocytes and has been shown to mediate these proliferative events (Kallay et al., 2000; Kallay et al., 2003). This becomes significant within the colonic crypts where a concentration gradient which increases from the base to the apex of the crypt allows for early proliferation of stem cells at the base of the crypt and their subsequent differentiation to functional colonic epithelial cells and finally their apoptogenesis at the apex of the crypt (reviewed by Whitfield, 2009; Ward et al., 2012). This process is regulated in part by the CaSR which is expressed in cells in response to calcium as they move up the crypt. In turn, stimulation of the CaSR signals cells to stop dividing and start differentiating. This occurs primarily by CaSR-mediated suppression of components of the wnt signalling pathway such as β -catenin/TCF-4 which control nuclear cell cycle activators such as c-myc and cyclin D1 (Chakrabarty et al., 2003; Whitfield, 2009). CaSR stimulation also produces E-cadherin which links up with β -catenin to form adherens junctions allowing cell-cell connections and at the same time sequestering β -catenin away from the nucleus (Bhagavathula et al., 2007). CaSR stimulation also

leads to increased expression of the cyclin-dependent kinase inhibitors, p21 and p27, and down-regulates expression of the anti-apoptotic protein, survivin (Chakrabarty et al., 2005; Liu et al., 2009b). Taken together, it has been concluded that low levels of Ca^{2+} in the colon and/or a poorly expressed or functionally compromised CaSR could lead to a lack of control of cell proliferation in colonic crypt development leading to potential malignancy (Whitfield, 2009; Ward et al., 2012).

Pancreatitis

Note

Chronic pancreatitis develops largely as a result of a build-up of trypsin resulting in tissue injury and inflammation. Hypercalcaemia associated with inactivating mutations of the CaSR might be expected to lead to high exposure of pancreatic acinar cells to Ca^{2+} leading to the activation of trypsinogen to trypsin and a reduction in chymotrypsin C-mediated degradation of trypsin (Racz et al., 2002; Whitcomb, 2010). Although inactivating CaSR mutations are sometimes associated with pancreatitis, no causal link between CASR/FHH and pancreatitis could be demonstrated (Stuckey et al., 1990; Pearce et al., 1996). However, there is a stronger association between concurrent mutations in the SPINK1 and CaSR genes and pancreatitis (reviewed by Whitcomb, 2010). The SPINK1 gene encodes a protein (serine protease inhibitor Kazal 1) that blocks trypsin in response to tissue inflammation. The current belief is that neither CASR nor SPINK1 gene mutations act alone to cause pancreatitis but together and/or in association with other factors appear to contribute to the pathogenesis of this disease (Whitcomb, 2010).

Primary and secondary hyperparathyroidism

Note

Primary hyperparathyroidism (PHPT) is most commonly caused by a single adenomatous parathyroid gland, although it can occasionally arise from double adenomas or hyperplasia of all four glands. The condition arises from suppression of the Ca^{2+} -induced negative feedback mechanism that controls PTH secretion - essentially there is a higher set point for Ca^{2+} -induced inhibition of PTH secretion (Cetani et al., 2000). Unlike the inherited disorders of calcium homeostasis described in the above section, CaSR mutations have not been associated with the adenomas that give rise to PHPT, rather mutations in other genes such as the MEN1 tumour suppressor and cyclin D1 oncogene predominate (Hosokawa et al., 1995; Sharretts and Simonds, 2010). However, adenomas associated with PHPT have been shown to express low levels of CaSR compared to normal parathyroid tissue

(Kifor et al., 1996; Ward et al., 2012). While the reason for this reduced expression is unclear, it does lead to an exacerbation of the condition since the CaSR contributes to the altered set point for PTH release. In addition, there is further evidence for the involvement of the CaSR in PHPT: impaired CaSR-mediated amino acid sensing (as well as calcium sensing) can cause loss of negative feedback of PTH release (Mun et al., 2009) and specific allosteric activators of the CaSR (calcimimetics) have been used successfully in the treatment of PHPT (Peacock et al., 2009). Finally, various polymorphisms in the CaSR gene or its regulatory region have been linked to PHPT and/or the severity of its clinical manifestations (reviewed in Ward et al., 2012). Secondary hyperparathyroidism (SHPT) which most commonly arises from chronic kidney disease (CKD) is controlled by the CaSR as well as other factors that regulate calcium and phosphate homeostasis (Rodriguez et al., 2005b, Ward et al., 2012). Essentially, in CKD, decreased phosphate excretion and decreased output of 1,25-dihydroxyvitamin D (leading to decreased intestinal Ca^{2+} absorption) and skeletal resistance to PTH, result in hypocalcaemia which, through activation of the CaSR, leads to increased secretion of PTH (note that a decrease in both phosphate excretion and vitamin D production may also directly lead to increased PTH secretion). Parathyroid gland hyperplasia may then develop, leading to decreased expression of CaSR and further exacerbation of the hyperparathyroidism. As for PHPT, a rise in set point for Ca^{2+} -induced control of PTH suppression occurs making SHPT amenable to treatment with calcimimetics (Cunningham et al., 2011).

Hypercalcaemia of malignancy

Note

The CaSR plays a central role in hypercalcaemia of malignancy through the capacity of malignant cells expressing the CaSR to secrete PTHrP in response to agonist stimulation of the receptor (for reviews see Chattopadhyay, 2006, Ward et al., 2012). PTHrP acts like PTH to stimulate bone resorption and renal calcium reabsorption generating high Ca^{2+} concentrations which further stimulate the CaSR to secrete PTHrP, creating a vicious cycle. There are two types of hypercalcaemia resulting from malignancy, osteolytic hypercalcaemia and humoral hypercalcaemia (HHM), the former associated with bony metastases that act to directly resorb bone and the latter with solid tumours that secrete circulating factors that act to increase bone resorption. CaSR activation has been demonstrated to stimulate PTHrP in both breast and prostate cancer cell lines that metastasize to bone as well as in various solid tumours which are known to be associated with HHM: H-500 rat Leydig testicular cancer cells, a

human lung squamous cell carcinoma cell line and a human pancreatic cell line, (FA-6) (Sanders et al., 2000; Sanders et al., 2001; Tfelt-Hansen, 2003; Morgan et al., 2006; Lorch et al., 2011). Expression of the CaSR appears to be an important predisposing factor for the generation and continued growth of bony metastases. Both breast and prostate cancer cells that express the CaSR at high levels have a greater tendency to metastasize to bone than those that express the receptor at low levels (Liao et al., 2006; Mihai et al., 2006). High Ca^{2+} concentrations act as a chemoattractant for breast cancer cells and this CaSR-dependent response positively correlates with the in vivo metastatic potential of several breast cancer cell lines (Saidak et al., 2009). In addition, high Ca^{2+} at bony metastases signalling through the CaSR may stimulate further growth of malignant cells, for example by activation of choline kinase and production of phosphocholine (Huang et al., 2009) or by regulating estrogen receptor- α expression and activity (Journe et al., 2004). In the prostate cancer cell line, PC-3, knockdown of the CaSR blocked Ca^{2+} -enhanced proliferation and reduced metastatic progression in an athymic mouse model while Ca^{2+} stimulation enhanced PC-3 cell attachment, a critically important step in metastasis (Liao et al., 2006).

Cardiovascular disease/hypertension

Note

There is mounting evidence that the CaSR plays an important role in the regulation of blood pressure. Stimulation of human aortic epithelial cells with spermine enhanced the production of nitrous oxide and this effect was prevented by siRNA- specific targeting of the CaSR, strongly suggesting a role for the receptor in vasodilation (Ziegelstein et al., 2006). In addition, activation of the CaSR expressed in the juxtaglomerular cells of the afferent arteriole of the kidney inhibits release of renin, thus exerting influence over the renin-angiotensin system that controls blood pressure (Atchison et al., 2010). Further to this, angiotensin II stimulates cardiac hypertrophy and this results in increased expression of the CaSR in the cardiomyocytes which, when activated, further drives angiotensin II-mediated hypertrophy (Wang et al., 2008; Magno et al., 2011b). The CaSR may also contribute to cardiac hypertrophy by IP3-mediated increases in nuclear Ca^{2+} and engagement of the CaN/NFAT pathway (Zhong et al., 2012). External stresses such as hypoxia-reoxygenation, ischaemia-reperfusion and the application of atherogenic agents have also been shown to increase CaSR expression in cardiac myocytes (reviewed in Magno et al., 2011b). Interestingly, the CaSR has been demonstrated to mediate the cardio-protective effects of ischaemic

preconditioning (Sun and Murphy, 2010). The CaSR is also expressed in vascular smooth muscle cells of human arteries where its increased activation is associated with decreased mineralization (Alam et al., 2009). This is consistent with reduced expression of the CaSR in the atherosclerotic, highly calcified arteries found in patients with hypercalcaemia associated with secondary hyperparathyroidism and end stage CKD (Alam et al., 2009; Cunningham et al., 2011).

Brain disease

Note

The CaSR is implicated to play a role in Alzheimer's disease (AD), with polymorphisms in intron 4 and exon 7 of the CaSR linked to AD status (Conley et al., 2009). Both amyloid- β peptide as well as apolipoprotein E protein can activate the CaSR with the former shown to have effects on calcium permeable, non-selective cation channels in hippocampal pyramidal neurons (Ye et al., 1997; Conley et al., 2009). Nitrous oxide is responsible for the neuronal cell death characterizing late onset AD and the CaSR is necessary for the generation of a cofactor (tetrahydrobiopterin) important in the activation of nitrous oxide that is produced (in its inactive form) in response to amyloid- β peptide-mediated stimulation of the receptor (Dal Pra et al., 2005; Chiarini et al., 2009). The CaSR has also been linked to other brain diseases such as epilepsy with a mutation in the CaSR (R898Q) reported to cosegregate with idiopathic epilepsy in a family from Southern India (Kapoor et al., 2008). The CaSR appears to be critical for the expression of mRNA for myelin basic protein in preoligodendrocytes and therefore for proper myelination (Chattopadhyay et al., 2008) - in this respect it is likely that a non-functional CaSR could lead to impaired neurodevelopment.

Bone disease

Note

The CaSR is expressed in osteoblasts/osteocytes and osteoclasts and their precursors, bone marrow derived stromal cells, monocyte-macrophage cells, chondrocytes and haematopoietic stem cells (reviewed by Yamaguchi, 2008). Expression of a functional CaSR is critical for growth plate development/endochronal bone formation, postnatal bone development and osteoblast differentiation and the effects on these processes are independent of CaSR-mediated PTH secretion (Brown and Lian, 2008; Chang et al., 2008; Dvorak-Ewell et al., 2011). The CaSR also appears to be important postnatally for proper teeth and dental alveolar bone formation (Sun et al., 2010) and upregulation of the CaSR in chondrocytes may contribute to the progression of osteoarthritis (Burton et al., 2005). While the CaSR has not been linked to the

development of osteoporosis, therapeutic agents such as strontium ranelate and calcilytic compounds which act through the CaSR have been used or proposed for its treatment (Trivedi et al., 2010; Marie et al., 2011).

Other disease associations

Note

Activation of the CaSR expressed in the β -cells of the islets of Langerhans of the pancreas can modulate insulin secretion and hence the receptor may play a role in diabetes mellitus (Gray et al., 2006; Squires et al., 2000). For example, L-histidine activation of the CaSR appears to negatively modulate glucose-induced insulin secretion from β -cells through changes in spatial arrangement of the CaSR and L-type voltage-dependent calcium channels that are important for Ca^{2+} -dependent triggering of insulin release (Parkash and Asotra, 2011).

Amino acid activation of the CaSR expressed in the I cells of the duodenum results in secretion of the hormone, cholecystokinin, which is important for the regulation of gall bladder contraction, pancreatic function, gastric emptying and satiety with the latter two having implications for obesity (Wang et al., 2011).

In the kidney, proper regulation of AQP2 water channels and vacuolar H^{+} -ATPase through activation of the CaSR in the collecting ducts is important for preventing kidney stones (Sands et al., 1998; Procino et al., 2004; Riccardi and Kemp, 2012) and stimulation of the CaSR expressed in podocytes of the Bowman's capsule of the kidney glomerulus, helps maintain their cytoskeletal integrity and overall survival thus preventing glomerular disease including proteinuria (Oh et al., 2011).

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- This article should be referenced as such:*
- Ward B, Magno A, Ratajczak T. CASR (Calcium-Sensing Receptor). *Atlas Genet Cytogenet Oncol Haematol*. 2014; 18(4):247-259.
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