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Review Article

The calcium-sensing receptor: a comprehensive review on its role in calcium homeostasis and therapeutic implications

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Abstract: The calcium-sensing receptor (CaSR), a key member of the family C G protein-coupled receptors (GPCRs), plays a crucial role in regulating calcium homeostasis and parathyroid hormone (PTH) secretion. It responds to various physiological ligands, including calcium ions and amino acids, activating multiple signaling pathways through interactions with different G proteins and β-arrestin. This review focuses on the structural features of CaSR, emphasizing recent advances in understanding its activation mechanisms via agonists and allosteric modulators. CaSR holds significant therapeutic potential, particularly in treating calcitropic disorders such as hyperparathyroidism and hypoparathyroidism. Current pharmacological agents, including calcimimetics such as cinacalcet and etelcalcetide, have proven effective in managing secondary hyperparathyroidism (SHPT); however, they are associated with side effects such as hypocalcemia. Emerging investigational drugs, including palopegteriparatide and other small molecules, show promise in addressing various calcium-related conditions. Despite challenges that have led to the discontinuation of some drug developments, ongoing research is focused on refining CaSR-targeted therapies to improve efficacy, reduce adverse effects, and enhance patient outcomes.

Keywords: Calcium-sensing receptor, CaSR, G protein-coupled receptor, GPCR, allosteric modulator

Introduction

Ca^{2+} is crucial for the proper functioning of mammalian cells, both intracellularly and extracellularly. The intracellular Ca^{2+} concentration is typically maintained at around 100 nM, but it can rise to low micromolar levels upon activation of calcium channels in the cell membrane or endoplasmic reticulum. This increase in Ca^{2+} concentration serves as a critical second messenger in various cellular signaling pathways, emphasizing its role in cellular communication and function [1]. Furthermore, Ca^{2+} activates the calcium-sensing receptor (CaSR), which is instrumental in regulating free extracellular calcium levels, thus maintaining cellular homeostasis and physiological balance [2].

CaSR is a family C G protein-coupled receptor (GPCR), with a molecular weight of 120-160 kDa. It interacts with various endogenous agonists and allosteric modulators [3] and activates multiple heterotrimeric G proteins, including Gq/11, Gi/o, G12/13, and Gs. These interactions mediate a wide range of physiological and pathological functions [4, 5]. The CaSR is widely expressed in the parathyroid glands and kidneys [6], where it plays a pivotal role in calcium homeostasis. Mutations in CaSR and its signaling partners can result in disorders of calcium balance. Germline mutations causing loss- or gain-of-function in genes encoding CaSR chaperone proteins have significant implications for calcium regulation. These mutations can lead to inherited disorders like familial hypocalciuric hypercalcemia (FHH) or autosomal dominant hypocalcemia (ADH), characterized by abnormal calcium levels [7]. These disorders underscore the critical role of CaSR in regulating calcium homeostasis and highlight

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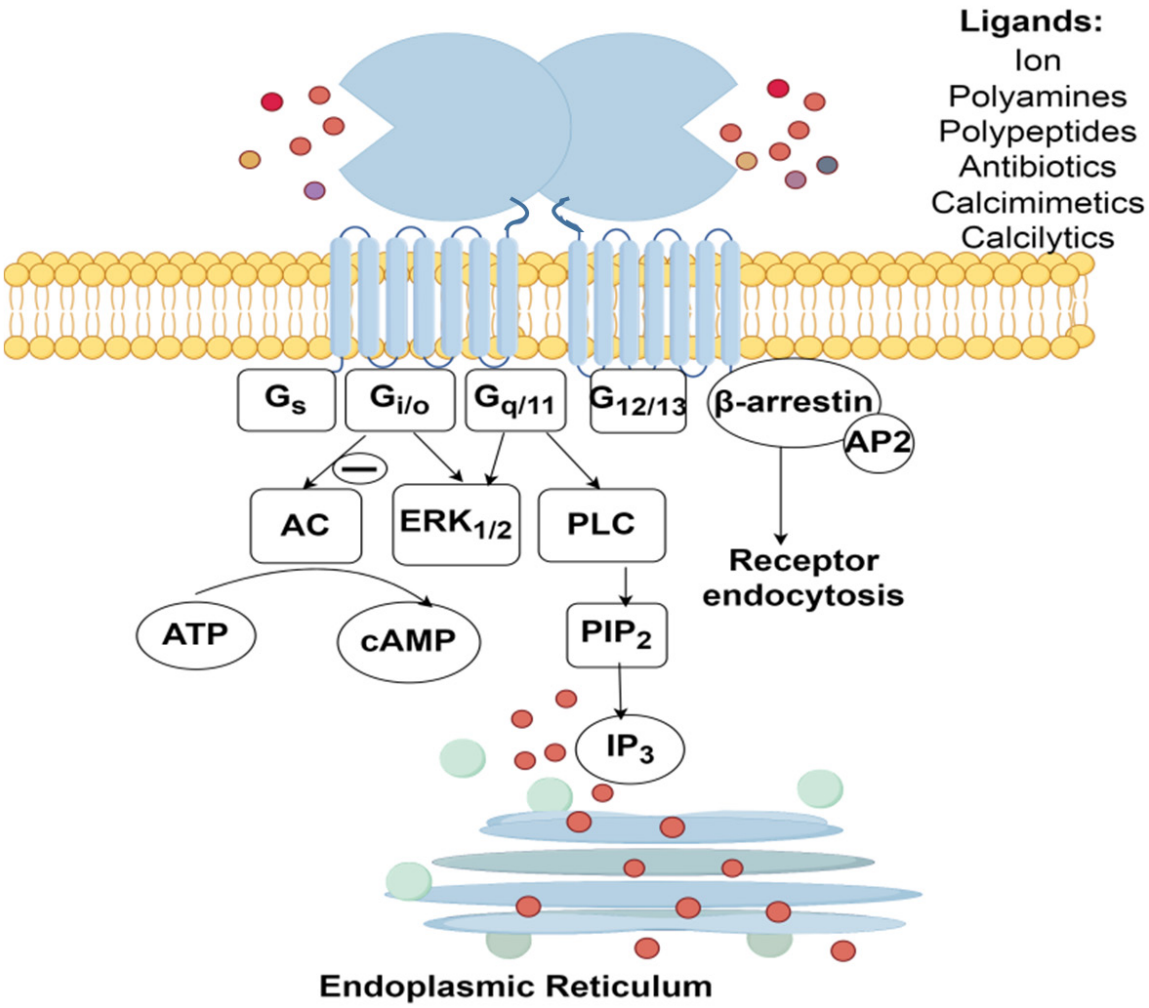

Figure 1. CaSR ligands and key signaling pathways. The CaSR functions as a homodimeric class C G-protein-coupled receptor that is essential for responding to a variety of different endogenous agonists and allosteric modulators. These modulators include ions, polyamines, polypeptides, antibiotics, calcimimetics, and calcilytics. When activated, the CaSR primarily activates the Gq/11 signaling cascade, which triggers the activation of phospholipase C (PLC) and leads to the production of diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3) from the membrane-associated phosphatidylinositol 4,5-diphosphate (PIP2). The rise in the IP_3 levels within the cell promotes the release of Ca^{2+} from stores such as the endoplasmic reticulum. Furthermore, the CaSR also activates the Gi/o protein; this action suppresses the production of cyclic AMP (cAMP) mediated by adenylate cyclase (AC). Concurrently, G-protein-dependent pathways involving Gq/11 and protein kinase C (PKC) can stimulate extracellular signal-regulated kinases (ERK) 1/2. Although CaSR may couple with G12/13, its physiological relevance remains unclear. Research involving immortalized malignant breast cells alongside pituitary tumor-derived AtT-20 cells revealed that the interaction between CaSR and Gs increases intracellular cAMP levels, which in turn activates PKA and promotes the production of PTHrP. The CaSR is known to have regulatory mechanisms that manage insertional signaling induced by agonists at the cell membrane, whereas a complex formed by β-arrestin and adaptor-associated protein Complex 2 (AP2) facilitates the retrograde trafficking of receptors.

its potential as a therapeutic target for conditions such as hyperparathyroidism, hypercalcemia, and osteoporosis.

Ligands and cellular signalling of CaSR

The major ligands and signaling pathways associated with the CaSR are shown in **Figure 1**. CaSR interacts with various physiological ligands, including cations (Ca^{2+}, Mg^{2+}), L-amino acids, polyamines, and γ-glutamyl peptides (e.g., glutathione) [8, 9]. Previous studies suggest that CaSR may also bind anions like phosphate (PO_4^{3-}) and sulfate (SO_4^{2-}) [8]. Calcimimetics and calcifications allosterically modulate CaSR activity by enhancing or inhibit-

ing its function, respectively [9, 10]. Several calcimimetic agents are in clinical use or under investigation for treating disorders related to abnormal CaSR expression or mutations [11, 12].

CaSR plays a crucial role in neurotransmission, nutrient perception, and Ca^{2+} homeostasis [13]. The receptor interacts primarily with the Gi/o and Gq/11 families of G proteins [14], triggering signaling pathways that inhibit parathyroid hormone (PTH) secretion. Activation of Gi/o proteins inhibits adenylate cyclase, reducing intracellular cAMP levels [15]. Mutations in this signaling pathway can lead to conditions such as hypoparathyroidism and familial hypocalciuric hypercalcemia. CaSR also activates the Gq/11 pathway, leading to phospholipase C (PLC)-β activation, generating inositol trisphosphate (IP_3) and diacylglycerol [16]. IP_3 releases Ca^{2+} from internal stores, while diacylglycerol activates protein kinase C (PKC), which regulates processes like cell survival, differentiation, and proliferation, including the activation of mitogen-activated protein kinases (MAPKs) [17]. Additionally, ERK1/2 activation is induced through both G protein-dependent and β-arrestin-dependent mechanisms [18].

CaSR has also been shown to interact with the G12/13 protein, activating RhoA, a small GTPase involved in gene expression regulated by the serum response element of CaSR [19]. In immortal malignant breast cell lines and pituitary tumor-derived AtT-20 cell lines, CaSR couples with Gs, leading to an increase in intracellular cAMP levels and activation of protein kinase A (PKA), which stimulates the production of parathyroid hormone-related protein (PTHrP) [20, 21]. The NanoBiT technique has proven effective in activating members of the Gαq/11 family and several Gαi/o proteins in HEK293 cells. However, it failed to activate Gαz. While CaSR can induce dissociation of Gα12/13 and Gαs from Gβγ subunits, this dissociation occurs at a slower rate compared to other Gα subunits, highlighting the unique behavior of Gαz and the complexity of G protein signaling.

In analyzing G protein cDNA expression, significant findings revealed high expression of Gα11, Gαz, Gαi1, and Gα13 in parathyroid tissues. This suggests a strong correlation between these specific Gα proteins and CaSR activity in those tissues. It is likely that CaSR activation in the parathyroid primarily involves Gα11 and Gαi1, implicating these proteins in the regulatory functions of calcium homeostasis in these glands [15].

Most family C GPCRs exhibit constitutive activity, though this remains underexplored. Our laboratory has demonstrated the importance of inter-subunit disulfide bonds in maintaining the inactive conformation of CaSR, setting it apart from other class C receptors. Ma et al. found that removal of these disulfide links leads to pronounced constitutive activity, enabling L-amino acids (L-AAs) to activate CaSR autonomously and enhance agonist potency [22]. These disulfide bridges contribute to constitutive activity, which is associated with ADH. These findings emphasize the potential for enhancing receptor activity in developing targeted therapeutics.

Role of CaSR in Ca^{2+} homeostasis

Ca^{2+} is crucial for numerous biological functions, including bone matrix mineralization, neuronal and neuromuscular function, blood clotting, and intracellular processes like signal transduction and hormone synthesis [1, 5, 23]. The Ca^{2+} level is tightly regulated through a homeostatic mechanism involving four key elements: the parathyroid gland, kidneys, small intestine, and bone [11], with CaSR expression in various tissues, including the parathyroid, kidney, bone, and breast (**Figure 2**). Below, we describe the role of CaSR in the calcification of these tissues.

Parathyroid gland

The parathyroid gland exhibits the highest expression of CaSR, which modulates PTH synthesis and secretion through a negative feedback mechanism [23]. When Ca^{2+} levels rise, CaSR inhibits PTH release, while a decline in Ca^{2+} levels stimulates persistent PTH secretion [23]. CaSR in the parathyroid constantly monitors Ca^{2+} levels, along with factors like plasma L-AAs, pH, ionic strength, and potentially locally synthesized polyamines [23-25]. The importance of CaSR in Ca^{2+} metabolism is evident in disorders such as hypercalcemia, neonatal severe hyperparathyroidism, FHH, hypocalcemia, ADH, and Bartter syndrome type V. CaSR's

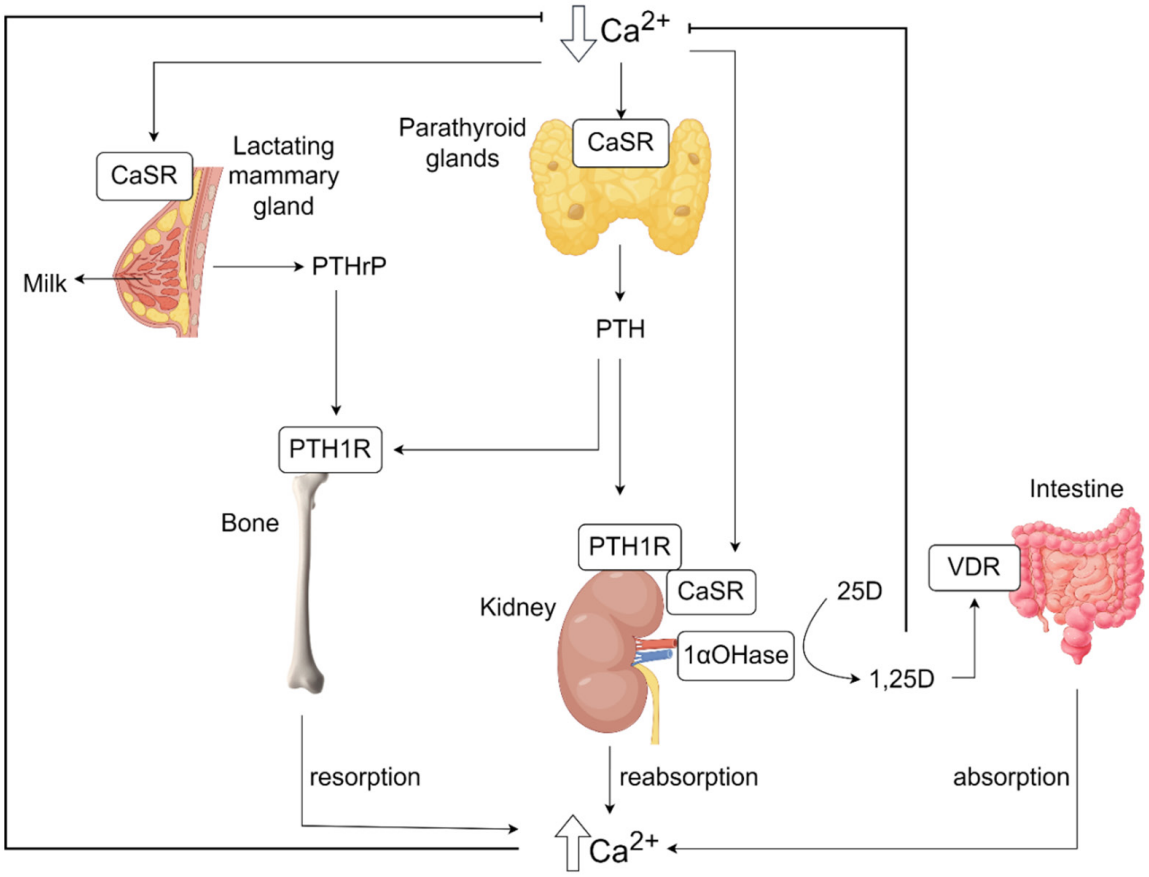

Figure 2. Role of the CaSR in Maintaining Calcium Homeostasis in the Human Body. The CaSR is essential for regulating calcium homeostasis within the human body. It is predominantly expressed on the surface of parathyroid cells, where it plays a critical role in responding to fluctuations in the blood calcium levels. When blood calcium decreases, CaSR stimulates the secretion of PTH, resulting in elevated PTH levels. PTH then binds to the PTH1R, initiating various physiological mechanisms to restore calcium levels, including: (i) Bone: Promotes the mobilization of calcium from bone stores. (ii) Kidneys: Enhances the renal reabsorption of calcium, thus reducing urinary calcium loss. (iii) Vitamin D Activation: Upregulates the expression of the 1αOHase enzyme in the kidneys, which is crucial for converting vitamin D into its active form, thus increasing the absorption of dietary calcium from the intestines. As blood calcium levels rise, a negative feedback mechanism is activated, leading to suppressed PTH release, maintaining the calcium balance, and preventing hypercalcemia. Beyond its role in the parathyroid gland, CaSR is additionally found in mammary epithelial cells, with its expression rising during the lactation period, facilitating the transport of calcium into breast milk while concurrently inhibiting the synthesis of PTHrP, which helps to prevent excessive calcium release from the bones.

effect on cell proliferation is particularly prominent in conditions like hyperplasia associated with primary hyperparathyroidism (e.g., adenomatous disease) and chronic kidney disease (CKD).

Cinacalcet, a calcimimetic agent, has demonstrated significant effects in reducing parathyroid gland size and serum PTH levels. These effects have been observed in CKD patients and in rat models simulating SHPT, where CaSR-targeted pharmacological agents are primarily used to treat SHPT caused by CKD [6, 26, 27].

CaSR signaling in parathyroid cells: CaSR in parathyroid cells is associated with various signaling pathways, particularly through Gαi/o and Gαq/11 [17]. Gαq/11 signaling is crucial for regulating PTH secretion via CaSR. A loss-of-function mutation in Gα11, which partially impairs signaling, is linked to a specific variant of FHH, termed FHH2 [28], while a gain-of-function mutation in Gα11 leads to ADH, termed ADH2 [29].

Kidney

CaSR expression in the kidney is among the highest in the body, serving both PTH-de-

pendent and PTH-independent roles in renal regulation [30, 31]. PTH interacts with the PTH type 1 receptor (PTH1R) to enhance calcium absorption from bones, promote calcium reabsorption from urine, and stimulate the production of 1-α-hydroxylase (1αOHase), which converts 25-hydroxyvitamin D (25D) into its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). This active form of vitamin D facilitates calcium absorption in the intestine via the vitamin D receptor (VDR) [11]. In the thick ascending limb of the renal cortex, CaSR independently regulates urinary calcium reabsorption, without PTH involvement [32, 33]. Additionally, elevated levels of Ca^{2+} and $1,25(OH)_2D$ provide negative feedback to the parathyroid gland, suppressing further PTH secretion.

Abnormal calcium levels in renal diseases do not arise from kidney dysfunction but rather from altered Ca^{2+} sensing by CaSRs in the parathyroid glands and kidneys. In chronic kidney disease (CKD), hyperphosphatemia and acidosis-due to impaired renal phosphate excretion-can lead to insufficient CaSR activation, resulting in secondary hyperparathyroidism (SHPT). Thus, similar to CaSR in the parathyroid, renal CaSR may serve as a potential drug target. Pharmacological CaSR-positive allosteric modulators (PAMs) are being explored to correct abnormal Ca^{2+} levels in the kidneys [32].

Bone

CaSR is expressed in various bone cell types, including osteoblasts, osteoclasts, and certain chondrocytes [34]. While research opinions vary, substantial evidence suggests that Ca^{2+} and CaSR play a key role in bone development and maintenance, with skeletal CaSRs influencing overall Ca^{2+} balance [15, 35]. Studies using CaSR knockout models and targeted deletions in bone show that CaSR is essential for both bone development and preservation.

Given the negative impact of CaSR loss on bone density and cellular vitality [36], targeting osteoblast CaSRs to promote bone anabolism presents a promising therapeutic approach [37, 38]. Research indicates that strontium ions (Sr^{2+}) are more potent than Ca^{2+} in osteoblasts, enhancing bone density and reducing clinical fractures [39]. Thus, targeted activation of CaSR in osteoblasts could be an effective strategy for treating osteoporosis, either alone or alongside other anabolic treatments, such as intermittent parathyroid hormone (iPTH), which stimulates osteoblast activity, enhances osteoclast function, and inhibits bone resorption [34]. Combining CaSR-PAMs with iPTH may reduce the risk of hypercalcemia while amplifying the anabolic effects of iPTH.

Breast

CaSR is present in mammary epithelial cells, where it plays a crucial role in regulating maternal Ca^{2+} metabolism by modulating calcium activity and usage [40]. During lactation, CaSR expression increases, regulating calcium transport into milk. CaSR also inhibits PTHrP synthesis by coupling with Gi, which suppresses adenylate cyclase activity and cAMP production [41]. During milk production, CaSR helps lactating mammary glands regulate Ca^{2+} levels and bone metabolism. The systemic function of breast CaSR ensures a steady influx of calcium ions, aiding in milk synthesis and preventing hypocalcemia in nursing mothers [42].

Structure of CaSR

The complete structure of CaSR was not determined until 2021, and much of our understanding comes from the crystal structures of its extracellular domain (ECD) in both its inactive and active [8, 43] states. Zhang et al. reported the first crystal structure of the CaSR ECD at a resolution of 2.1 Å, revealing how magnesium ions (Mg^{2+}) and the ligand TNCA (a tryptophan derivative) synergistically activate the receptor [43]. Geng et al. found that calcium ions do not directly activate CaSR; instead, they can lead to inactivation in both the presence and absence of calcium ions (PDB: 5K5T); however, calcium ions only fully activate CaSR when combined with amino acids. In the active conformation (PDB: 5K5S), the binding site for agonists is occupied by L-Trp within the interdomain gap, playing a crucial role in triggering ECD closure for receptor activation [44]. This structure revealed multiple binding sites for Ca^{2+} and phosphate ions, with calcium stabilizing the active state and phosphate ions preserving the inactive state.

In 2021, several research groups published near-full-length cryo-electron microscopy (Cryo-EM) structures of CaSR, including the ECD, seven transmembrane (7TM) regions, and

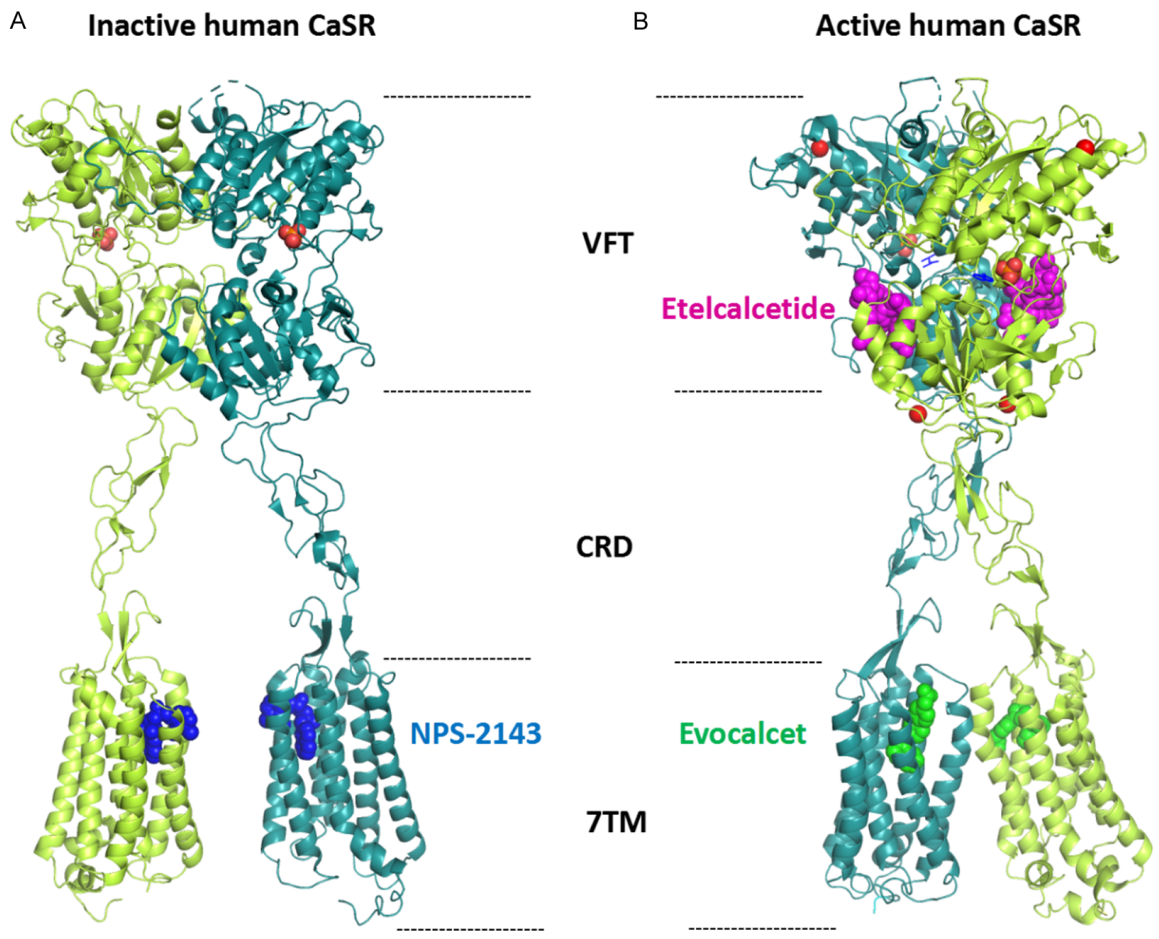

Figure 3. Structure of the CaSR. A. CaSR in the inactive state bound to the negative allosteric modulator (NAM) NPS-2143 (PDB 7M3J), which binds to the 7TM domain of the CaSR, inhibiting its activity. B. CaSR in the active state engaged by positive allosteric modulators (PAMs) evocalcet and etelcalcetide (PDB 7M3J). The PAM cinacalcet binds similarly to evocalcet, interacting with the CRD-ECL2-ECL3 region in the active state of CaSR. Etelcalcetide interacts with the active-state VFTs, enhancing the functionality of the receptor.

extracellular and intracellular loops (ECL and ICL) (**Figure 3**). These studies demonstrated how agonist binding induces structural changes in the extracellular domain of CaSR, leading to G protein activation and how allosteric modulators influence these dynamics [45-50]. Three commercial drugs act as PAMs, targeting CaSR, Etelcalcetide, Cinacalcet, and Evocalcet, with Etelcalcetide binding to the ECD and Cinacalcet and Evocalcet interacting with the 7TM domain [51]. These medications are used to treat SHPT and FHH1, and a negative allosteric modulator (NAM) is currently in Phase II clinical trials for treating ADH1 [52].

Cryo-EM studies also explored the binding mechanisms of allosteric regulators [53, 54]. Gao et al. revealed a 2.5 Å structure showing that two Etelcalcetide molecules covalently bind to the C482 site on the C-terminal LB2 promoter, stabilizing the active ECD conformation [47]. The efficacy and potency of Cinacalcet and Evocalcet in treating CaSR-related conditions share a similar skeletal structure from the arylalkylamine family of PAMs, which allows them to bind to their respective receptors in a similar manner [47]. In the ggCaSR structure, Evocalcet binding reduces the distance between the extracellular ends of the two TM6 helices, while increasing the distance in the cytoplasmic region, a conformational change akin to the activation mechanism observed in the metabolic GABAB receptor [55].

Studies on NAM NPS-2143 showed that in the 7TM state, the CaSR exhibits symmetry, differ-

Table 1. CaSR related diseases and marketed clinical trial drugs

Therapeutic field	Drug	Stage (year, country)
SHPT	Upacicalcet Sodium Hydrate	Marketed (2021, Japan)
	Evocalcet	Marketed (2018, Japan)
	Etelcalcetide	Marketed (2016, The European Union)
Postmenopausal osteoporosis	Strontium Ranelate	Marketed (2004, The European Union)
SHPT; Hypercalcemia	Cinacalcet Hydrochloride	Marketed (2004, America)
Hypoparathyroidism	Palopegteriparatide	Applied to list
Hypocalcemia; ADH1	Encaleret sulfate	Phase III
Hyperparathyroidism	LNP-1892	Phase II
Osteoporosis	RT-102	Phase I
	DS-9194b	Phase I
Parathyroid diseases	[18F]F-cinacalcet	Preclinical
Hypoparathyroidism	Long-acting parathyroid hormine (ProLynx)	Preclinical
Diabetes; Obesity	GSK-3004774	Preclinical
Osteoporosis	ATF-936	Termination
Hyperparathyroidism	Tecalcet Hydrochloride	Termination
SHPT	ASP-7991	Termination
Postmenopausal osteoporosis	AXT-914	Termination
	Colecalciferol/Strontium Ranelate	Termination
Bone marrow transplant rejection	Ronacaleret Hydrochloride	Termination
Asthma	B2.1-E1	Stagnation
Osteoporosis	SB-423557	Stagnation
	Recombinant human PTH	Stagnation

ing from the Ca^{2+}-L-Trp binding configuration [47]. Park et al. reported that NPS-2143 binds to sites similar to those of PAMs [48]. In the ggCaSR, two NPS-2143 molecules bind cooperatively to each promoter, resembling previous findings on human CaSR [56, 57]. Cui et al. found that the negative allosteric nanobody NB-2D11 stabilizes CaSR in a fully inactivated state and discovered a new Ca^{2+} ion binding site that, when complexed with L-amino acids, stabilizes ECD closure [58]. These results highlight the importance of LB2 domain interactions in CaSR activation.

In 2020, Liu et al. developed a cell-free FRET method to measure receptor conformational changes, demonstrating that calcium ions alone can induce a full conformational change in CaSR [51]. This method, along with other functional experiments, suggests that calcium ions activate the receptor, whereas amino acids enhance this activation as PAMs. These findings have been supported by subsequent structural analyses.

Drug development of CaSR

Several active molecules that regulate CaSR function through allosteric modulation have been optimized and are commercially available. As shown in **Table 1**, some of these molecules are already approved for clinical use, while others are still undergoing preclinical and clinical research. These drugs, including calcimimetics and calcilytics, modulate CaSR activity by either enhancing or inhibiting its function, depending on the disease being treated. Various cellular signaling pathways are involved in their action.

The primary signaling pathway activated by calcimimetics (such as Cinacalcet and Etelcalcetide) is the Gαq/11 pathway. These drugs enhance CaSR activity by increasing its sensitivity to calcium, leading to the activation of this signaling pathway, which suppresses parathyroid hormone (PTH) secretion. This pathway is crucial for managing diseases such as secondary hyperparathyroidism (SHPT) and hypercalcemia, where PTH levels are dysregulated. In contrast, calcilytics (such as Encaleret) inhibit CaSR activity via the Gαi/o pathway, reducing the receptor's sensitivity to calcium and thereby increasing PTH secretion. This makes calcilytics beneficial for treating hypoparathyroidism, where insufficient PTH is produced.

Table 2. Comparison of clinical drugs for CaSR

Drug	Advantages	Disadvantages
Cinacalcet	Effective in reducing PTH levels, FDA-approved for SHPT and hypercalcemia, treats genetic CaSR mutations like FHH	Hypocalcemia, gastrointestinal side effects (nausea, vomiting), drug-drug interactions (CYP2D6 inhibition), daily administration
Etelcalcetide	Longer half-life (3-5 days), less frequent dosing, FDA-approved for SHPT, injectable form	Hypocalcemia, gastrointestinal side effects, injectable form may affect adherence
Evocalcet	Oral administration, fewer gastrointestinal side effects compared to Cinacalcet, effective for SHPT	Hypocalcemia risk, currently only approved in Japan, daily dosing still required
Upacicalcet	Minimal metabolism, sustained pharmacological effects, effective for SHPT, longer excretion period	Hypocalcemia risk, limited approval in Japan only
Strontium Ranelate	Dual mechanism (promotes bone formation and inhibits resorption), effective for osteoporosis, increases bone density	Cardiovascular risks (myocardial infarction, thromboembolic incidents), severe side effects, limited approval in Europe due to safety concerns

Clinical drugs

Clinical agents targeting CaSR are primarily used in treating SHPT, a common early complication of chronic kidney disease (CKD) that is characterized by elevated serum PTH levels in individuals undergoing hemodialysis [59]. The characteristics of these clinical drugs are summarized in **Table 2**. CaSR is a target for calcimimetics like Cinacalcet, Evocalcet, Etelcalcetide, and Upacicalcet in hyperparathyroidism [60].

Cinacalcet was the first allosteric modulator of GPCRs to receive clinical approval in 2004. It is specifically approved by the FDA for treating primary hyperparathyroidism in patients who are not candidates for parathyroidectomy, a procedure that removes the parathyroid glands. Cinacalcet is also indicated for managing hypercalcemia in adults who have undergone parathyroidectomy, providing a therapeutic option for postoperative complications. Furthermore, it is FDA-approved for patients with SHPT undergoing renal replacement therapy, making it versatile for various conditions related to PTH regulation. Notably, Cinacalcet has been shown to effectively address loss-of-function mutations in CaSR, underscoring its importance in managing genetic abnormalities associated with calcium metabolism. However, clinical issues such as hypocalcemia and gastrointestinal side effects, including nausea and vomiting [61-64], as well as drug-drug interactions due to the inhibition of cytochrome P450 (CYP) 2D6, have been reported [65].

To mitigate these issues, a new CaSR PAM, Etelcalcetide, was developed as an injectable drug consisting of D-amino acid peptides [66]. It was FDA-approved in 2017 for treating SHPT in patients on dialysis for CKD. Similar to Cinacalcet, Etelcalcetide is associated with gastrointestinal side effects and the risk of hypocalcemia [67]. However, Etelcalcetide has a longer half-life (3-5 days) than Cinacalcet, which allows for administration three times a week, in contrast to Cinacalcet's daily dosing regimen [68, 69]. In Japan, Evocalcet was approved in 2018 for treating SHPT in dialysis patients. Although both Cinacalcet and Evocalcet can cause hypocalcemia in patients, Evocalcet, being an oral drug, appears to cause fewer gastrointestinal side effects in both rat and human studies compared to Cinacalcet [61, 70].

Upacicalcet (UPASITA®), an intravenous calcimimetic agent developed by Sanwa Kagaku Kenkyusho, received its first approval in Japan on June 23, 2021, for treating SHPT in adults undergoing hemodialysis. It is marketed under a license from EA Pharma [71]. A recent study indicated that Upacicalcet exhibits good resistance in healthy Japanese individuals, with minimal metabolism and rapid urinary excretion [72]. Consequently, when administered to SHPT patients after dialysis, the drug may have a longer excretion period and sustained pharmacological effects.

Strontium ranelate, a small molecule marketed compound, targets the CaSR and is currently used in Europe to treat severe osteoporosis in postmenopausal women and men [73]. Its molecular structure consists of two non-radioactive components: Sr^{2+} and a ranelate ion. It exerts dual mechanisms: promoting bone formation and inhibiting osteoclast activity [74,

75]. However, long-term use of strontium ranelate has been associated with a range of adverse effects. In 2013, the European Medicines Agency issued a directive limiting its use for treating severe osteoporosis due to the elevated risk of myocardial infarction, thromboembolic incidents, severe skin reactions, and various other health issues [76, 77].

Clinical investigational drugs

Palopeogenic parathyroid hormone (TransCon PTH) is a drug aimed at treating hypoparathyroidism by targeting both CaSR and PTH1R. TransCon PTH is a prodrug that continuously releases active PTH, providing a sustained release mechanism for the treatment of adult hypoparathyroidism [78, 79]. This drug mimics physiological PTH release, offering an ideal approach for managing hypoparathyroidism [80, 81].

Several other CaSR-targeting medications are in development, including: 1. Encaleret sulfate, a small molecule developed to treat hypocalcemia, is currently in Phase 3 clinical trials by Japan Tobacco (Hong Kong) Limited. 2. LNP-1892, another small molecule for hyperparathyroidism, is in Phase 2 clinical studies. 3. RT-102 (Rani), an investigational recombinant protein targeting both CaSR and PTH1R for osteoporosis treatment, is in Phase 1 clinical trials, developed by Rani Therapeutics Holdings, Inc. 4. DS-9194b, a small molecule in Phase 1 development for osteoporosis, developed by Daiichi Sankyo Co., Ltd., Tokyo, Japan.

Preclinical drug

Significant advancements have been made in the development of preclinical drugs for calcium-related diseases. Surgical removal of the parathyroid gland remains the standard treatment for parathyroid hyperplasia, which requires accurate preoperative localization. However, current imaging modalities suffer from limited sensitivity. Radiopharmaceuticals have been developed as early diagnostic tools for parathyroid diseases. For example, Cinacalcet undergoes 18F radiolabeling to create [18F] F-cinacalcet, a more sensitive imaging tracer for positron emission tomography (PET) [82].

Long-acting PTH (ProLynx), a recombinant protein with a long half-life and continuous release, is primarily used to treat hypoparathyroidism in endocrine and metabolic disorders [83]. This drug targets both CaSR and PTH1R and is currently undergoing preclinical development.

Studies suggest that the CaSR is closely associated with the onset and progression of endocrine and metabolic diseases like diabetes and obesity. Therefore, compounds modulating CaSR activity may offer therapeutic potential in these conditions. GSK-3004774, a small-molecule drug targeting CaSR, is currently in preclinical development for treating diabetes and obesity, developed by GSK Plc [84, 85].

Experimental discontinued drugs

Despite the promising prospects of CaSR-targeting drugs, challenges during research have led to the discontinuation of some experimental drugs. For example:

ASP-7991, a small-molecule drug targeting CaSR for SHPT, was developed by Astellas Pharma, Inc. [86], but its global development has been terminated. The reasons for this decision remain unclear, with no information available on clinical trial performance or potential side effects.

ATF-936, developed by Novartis Pharma AG, is another small-molecule drug intended for endocrine and metabolic diseases, as well as skin and musculoskeletal disorders [87]. Its development has been halted, possibly due to unsatisfactory clinical trial results or other commercial factors.

Tecalcet Hydrochloride (NPS R-568), a precursor to Cinacalcet developed by Shire Pharmaceutical Services, Ltd., was designed for treating immune system diseases, endocrine and metabolic disorders, and skin and musculoskeletal conditions [34, 88, 89]. This development was terminated due to various research challenges or unmet expectations.

AXT-914, another small-molecule drug targeting CaSR, developed by Novartis Pharma AG, had applications in endocrine and metabolic diseases as well as skin and musculoskeletal disorders [90, 91], but its development has also been discontinued.

Cholecalciferol/strontium ranelate, a small-molecule drug developed by Les Laboratoires

Servier SAS, targets both CaSR and VDR. It was intended for endocrine and metabolic diseases as well as skin and musculoskeletal disorders, but its development was halted, likely due to poor clinical trial outcomes, safety concerns, or other reasons.

Ronacaleret Hydrochloride, developed by Shire Pharmaceuticals Services Ltd., targets a range of diseases including endocrine and metabolic disorders, as well as skin and musculoskeletal conditions [90]. Global development of this drug has been terminated.

Stagnant drugs

CaSR-targeting drugs have shown promise in various therapeutic areas, yet development progress is often hindered by substantial challenges. For instance:

B2.1-E1 (calcylytic), a small-molecule drug [91], has not made progress due to significant challenges faced by Cardiff University, the original research institute.

SB-423557 (NPSP-790) [92], targeting a similar therapeutic range, has also seen halted development.

Recombinant human PTH, developed by Beijing Shuanglu Pharmaceutical Co., Ltd., targets both CaSR and PTH1R [93]. This recombinant polypeptide drug is intended for the treatment of endocrine and metabolic diseases as well as skin and musculoskeletal disorders. However, due to a lack of relevant research and development information, its clinical applications, efficacy, and safety remain unclear.

In conclusion, drugs targeting the CaSR are vital for managing a variety of calcium-related diseases by either enhancing or inhibiting CaSR activity, depending on the specific condition. Clinical drugs such as calcimimetics (Cinacalcet, Etelcalcetide, Evocalcet, and Upacicalcet) are primarily used to treat SHPT and hypercalcemia. These drugs increase CaSR sensitivity, thereby enhancing its activity and inhibiting PTH secretion. For example, Cinacalcet is FDA-approved for SHPT in patients on hemodialysis and has proven effective in managing hypercalcemia associated with parathyroid carcinoma. Etelcalcetide, an injectable drug, has a longer half-life, allowing for less frequent dosing compared to Cinacalcet, while Evocalcet has fewer gastrointestinal side effects. Strontium ranelate, another clinical drug, targets CaSR to treat severe osteoporosis by promoting bone formation and inhibiting osteoclast activity. However, its use is limited due to potential cardiovascular risks.

Preclinical drugs such as TransCon PTH, which targets both CaSR and PTH1R, are designed to treat hypoparathyroidism by continuously releasing active PTH. Additionally, compounds like GSK-3004774 are under development for treating metabolic diseases, such as diabetes and obesity, by modulating CaSR activity to regulate insulin secretion and glucose metabolism. These drugs, along with others in early-stage trials, represent the next frontier in targeting the CaSR for calcium homeostasis disorders and metabolic diseases, with the potential for more personalized and effective therapies. Overall, the specificity and function of these drugs underscore their pivotal role in treating calcium-related and metabolic diseases, with ongoing advancements toward safer and more effective treatment options.

Conclusion and discussion

The CaSR plays a pivotal role in calcium homeostasis and has significant implications for various physiological processes and diseases. Its complex signaling pathways, particularly in relation to PTH secretion, underscore its importance in maintaining calcium balance within the body. Given that calcium regulation is central to many biological functions, CaSR dysfunction can lead to disorders such as SHPT, osteoporosis, and hypoparathyroidism. Thus, understanding the signaling mechanisms of CaSR is essential for the development of targeted therapies for these conditions. A summary of the structural features, functions, and drug development related to the CaSR is provided in **Table 3**.

As research in this area progresses, future studies are expected to significantly impact clinical practice by developing new pharmacological interventions, such as targeted calcimimetics and calcilytics, which hold the potential to provide novel therapeutic options for calcium-related disorders. Drugs like Cinacalcet and other CaSR modulators have already demonstrated efficacy in regulating PTH secretion

Table 3. Structural features, functions, and drug development of CaSR

Category	Details
Structural Features	- Extracellular Domain: Contains the calcium-sensing region that binds extracellular calcium ions, crucial for activating the receptor.
	- Transmembrane Region: Seven α-helices that form a transmembrane domain; couples with G proteins to mediate intracellular signaling.
	- Intracellular Domain: Associated with G-protein signaling, interacts with Gαq/11 for activation of phospholipase C (PLC) and Gαi/o for inhibition of adenylyl cyclase.
	- Allosteric Sites: Distinct binding sites for calcimimetics (positive modulators) and calcilytics (negative modulators), enabling diverse therapeutic targeting.
	- Conformational Flexibility: The receptor's ability to undergo structural changes upon ligand binding is essential for its function in regulating calcium homeostasis.
Functions	- Calcium Homeostasis: Regulates calcium levels by modulating parathyroid hormone (PTH) secretion, playing a pivotal role in calcium-sensing at various tissues.
	- Bone Metabolism: Influences osteoblast and osteoclast activity, contributing to bone remodeling and mineralization.
	- Kidney Function: Regulates calcium reabsorption and phosphate handling in the kidneys.
	- Gαq/11 Pathway: Activated by calcimimetics (e.g., Cinacalcet), this pathway enhances PTH sensitivity and reduces its secretion, pivotal in managing hyperparathyroidism.
	- Gαi/o Pathway: Activated by calcilytics (e.g., Encaleret), this pathway inhibits CaSR sensitivity, promoting PTH secretion, useful in conditions like hypoparathyroidism.
	- Regulation of Insulin Secretion: Recent findings suggest CaSR involvement in regulating insulin release from the pancreas.
Drug Development	Calcimimetics (Enhance CaSR Activity):
	- Cinacalcet: The first FDA-approved calcimimetic; used to treat secondary hyperparathyroidism (SHPT), hypercalcemia, and disorders caused by CaSR mutations.
	- Etelcalcetide: FDA-approved injectable for SHPT treatment in dialysis patients; more stable pharmacokinetics compared to Cinacalcet.
	- Evocalcet: Approved in Japan for SHPT in dialysis patients; fewer gastrointestinal side effects compared to Cinacalcet.
	- Upacicalcet: A novel intravenous calcimimetic developed for SHPT in Japan, with promising resistance and minimal metabolism in trials.
	Calcilytics (Inhibit CaSR Activity):
	- Encaleret: Investigational drug that inhibits CaSR activity, designed to treat hypoparathyroidism by increasing PTH secretion.
	- Other Investigational Calcilytics: Compounds in preclinical stages targeting the Gαi/o pathway to promote PTH release in hypocalcemia-related disorders.
	Preclinical and Experimental Drugs:
	- TransCon PTH: Prodrug for adult hypoparathyroidism that continuously releases active PTH, targeting both CaSR and PTH1R.
	- GSK-3004774: A small-molecule drug in preclinical development for diabetes and obesity treatment by targeting CaSR.
	- LNP-1892: Investigational molecule for hyperparathyroidism in Phase 2 clinical trials.
	- RT-102: Recombinant protein targeting both CaSR and PTH1R for osteoporosis treatment, currently in Phase 1 trials.
	- DS-9194b: In Phase 1 trials for osteoporosis treatment, developed by Daiichi Sankyo.
	Experimental Drugs (Discontinued/Inactive Development):
	- ASP-7991: A small-molecule CaSR-targeting drug for SHPT, terminated globally due to unknown reasons.
	- ATF-936: Small molecule for endocrine/metabolic disorders, development ceased.
	- Tecalcet Hydrochloride: Precursor of Cinacalcet for immune system diseases; discontinued due to research challenges.

	- Strontium Ranelate: Used in Europe for osteoporosis, targets CaSR and osteoclast activity; concerns over cardiovascular risks led to regulatory restrictions.
	Stagnant Drugs:
	- B2.1-E1 (Calcylytic): A small-molecule calcilytic in development at Cardiff University, facing significant challenges.
	- SB-423557 (NPSP-790): A similar compound to B2.1-E1; development stalled.
	- Recombinant Human PTH: A polypeptide drug targeting both CaSR and PTH1R for metabolic diseases; development is currently unclear.
Clinical Applications	- SHPT (Secondary Hyperparathyroidism): Targeted by both calcimimetics (Cinacalcet, Etelcalcetide) and calcilytics (Encaleret).
	- Hypercalcemia: Managed with calcimimetics, particularly in cancer-related hypercalcemia and primary hyperparathyroidism.
	- Osteoporosis: Strontium ranelate used in Europe; ongoing exploration of CaSR-targeted therapies for bone health.
	- Hypoparathyroidism: CaSR modulators like TransCon PTH are under development to treat this disorder by increasing PTH secretion.
Challenges in Drug Development	- Side Effects: Common adverse events include hypocalcemia, gastrointestinal disturbances (e.g., nausea, vomiting), and potential drug-drug interactions.
	- Long-Term Safety: Issues such as cardiovascular risks with strontium ranelate and metabolic side effects from prolonged calcimimetic use.
	- Pharmacokinetic Issues: Variability in drug half-life and dosing frequency, e.g., Cinacalcet versus Etelcalcetide.
Future Directions	- Structural Insights: Detailed structural data will support rational drug design and improved therapeutic specificity.
	- Personalized Medicine: Genetic screening of CaSR variants could optimize treatment strategies for individual patients.
	- Expanded Therapeutic Applications: role of CaSR in metabolic diseases (diabetes, obesity) could open new avenues for treatment beyond calcium homeostasis.

and calcium levels in patients with endocrine disorders. Advances in structural insights into the CaSR will further aid in rational drug design, leading to more selective and effective treatments. Reducing side effects, such as hypocalcemia and gastrointestinal disturbances, is a crucial next step in drug development.

Furthermore, investigating the expression of CaSR in diverse biological contexts, including reproductive health and metabolic bone diseases, may reveal new regulatory mechanisms and therapeutic targets. The emerging role of CaSR in bone metabolism, along with its potential impact on insulin secretion and glucose metabolism, suggests that CaSR-targeted therapies could extend beyond traditional calcium disorders and provide new treatment options for metabolic diseases. Additionally, integrating genetic screening for CaSR variants could pave the way for personalized medicine, optimizing treatment strategies based on individual patient profiles. This approach may lead to more effective interventions, particularly for patients with genetic CaSR mutations, such as those with FHH or ADH.

Continued exploration of CaSR's role in calcium homeostasis regulation and its broader implications across various systems will deepen our understanding of calcium regulation and provide substantial advancements in patient care. Personalized treatment plans utilizing CaSR-targeted drugs will likely lead to more efficient and safer therapeutic strategies, improving patient outcomes in calcium-related and potentially other metabolic and endocrine disorders. As we continue to uncover the complexities of CaSR signaling, we are likely to witness significant innovations in therapeutic approaches that will have a meaningful impact on the management of calcium imbalances and associated diseases, ultimately enhancing the quality of life and long-term health outcomes for patients. In summary, ongoing research into the multifaceted roles of CaSR will not only advance our understanding of calcium regulation but also improve treatment outcomes and patient care.

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Disclosure of conflict of interest

None.

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