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Commentary

Clinical utility of calcimimetics targeting the extracellular calcium-sensing receptor (CaSR)

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ABSTRACT

Calcimimetics, which activate the extracellular calcium (Ca_o^{2+})-sensing receptor in the parathyroid and other tissues participating in Ca_o^{2+} homeostasis, were the first described allosteric activators of a G-protein-coupled receptor. Cinacalcet, the only calcimimetic currently approved for human use, is used clinically for treating secondary hyperparathyroidism (e.g., overactivity of parathyroid glands) in patients being dialyzed for chronic kidney disease. By sensitizing the parathyroids to Ca_o^{2+}, cinacalcet lowers the circulating parathyroid hormone (PTH) level. It also reduces serum calcium and phosphate, changes increasing the percentage of patients achieving the guidelines recommended by the National Kidney Foundation (NKF) for these minerals. Studies are underway addressing whether better adherence to these guidelines in patients receiving cinacalcet reduces cardiovascular disease and related mortality, which are both common is the dialysis population. The second approved use of cinacalcet is for treating hypercalcemia in patients with inoperable parathyroid carcinoma. In this setting, it provides the first medical therapy chronically lowering serum calcium concentration in this condition, albeit not to normal in most patients. Its effect on the long-term prognosis of these patients, if any, is presently unclear. "Off-label" administration of cinacalcet [i.e., not yet approved by the US Food and Drug Administration (FDA)] effectively lowers serum calcium and/or PTH in various other forms of hyperparathyroidism and increases serum phosphate in renal phosphate-wasting syndromes by reducing PTH-induced phosphaturia. In the future, the drug could conceivably be utilized to modulate the activity of the CaSR in other tissues (i.e., kidney, colon) in therapeutically desirable ways.

1. Introduction

Calcimimetics are allosteric activators of the extracellular calcium (Ca_o^{2+})-sensing receptor (CaSR). Their development has provided an important advance in the treatment of disorders of mineral metabolism by sensitizing the receptor to its physiological agonist, the extracellular calcium ion (Ca_o^{2+}) [1]. This mode of action makes it possible to suppress the secretion of parathyroid hormone (PTH) from the parathyroid glands in patients with overactivity of these glands. The calcimimetic, cinacalcet® (or sensipar®), initially received approval from the US Food and Drug Administration (FDA) solely for treating two conditions: severe hyperparathyroidism in patients being dialyzed for chronic kidney disease (so-called stage 5 CKD) and hypercalcemia in patients with parathyroid cancer. It is the only calcimimetic currently approved for use in humans. Subsequently, cinacalcet has been utilized in a variety of clinical settings with a primary goal of reducing PTH secretion in order to decrease the serum calcium concentration and/or elevate the serum phosphate concentration. This review will cover this rapidly developing field, with the following

Abbreviations: CaSR, calcium-sensing receptor; Ca_o^{2+}, extracellular calcium concentration; PTH, parathyroid hormone; NKF, National Kidney Foundation; FDA, US Food and Drug Administration; CKD, chronic kidney disease; MGluR, metabotropic glutamate receptor; GABA, gamma aminobutyric acid; PLC, phospholipase C; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-jun N-terminal kinase; EGF, epidermal growth factor; $1,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; VDR, vitamin D receptor; EC_{50}, half-maximally effective concentration of a drug; KDOQI, Kidney Disease Outcomes Quality Initiative; ECD, extracellular domain; TMD, transmembrane domain; TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia; GFR, glomerular filtration rate; TP/GFR, renal threshold for phosphate corrected for GFR; ESRD, end stage renal disease; ADPKD, autosomal dominant polycystic kidney disease; PHEX, phosphate-regulating gene with homologies to endopeptidases on the X-chromosome; FGF-23, fibroblast growth factor-23; FHH, familial hypocalciuric hypercalcemia; NSHPT, neonatal severe hyperparathyroidism; PHPT, primary hyperparathyroidism; DCT, distal convoluted tubule; cTAL, cortical thick, ascending limb; BMD, bone mineral density; GPRC6A, G-protein-coupled receptor of family C, number 6A.

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aims: (1) to describe the properties and functions of the CaSR and its roles in maintaining Ca_o^{2+} homeostasis; (2) to briefly outline the pharmacology of the calcimimetics; (3) to describe both the approved and the "off-label" (i.e., not yet approved by the FDA for human use) applications of the drug to date, and finally (4) to comment on future prospects for this class of drugs. I will cite representative and important articles but not attempt to be exhaustive. As there are numerous reviews of the use of cinacalcet in patients with stage 5 CKD, this review will summarize this area succinctly. The primary focus will be on other potential applications of cinacalcet in order to highlight the therapeutic versatility inherent in being able to pharmacologically manipulate PTH secretion and, potentially, the functions of other tissues expressing the CaSR.

2. What is the CaSR?

To maintain near constancy of the blood Ca^{2+} level, a mechanism must exist that senses small changes in Ca_o^{2+} and responds appropriately so as to normalize Ca_o^{2+} [2]. The CaSR serves this function. It is a G-protein-coupled receptor (GPCR) that has Ca_o^{2+} as its principal physiological ligand. The cloning of the CaSR from bovine parathyroid was reported in 1993 [3]. Shortly thereafter, the receptor was cloned from human parathyroid [4] and, subsequently, from parathyroid and/or other tissues in a variety of other species.

The CaSR belongs to family C of the GPCRs, which also includes the metabotropic glutamate receptors (mGluRs), $GABA_B$ receptors, and receptors for taste and pheromones, as well as an amino acid- and divalent cation-sensing receptor called GPRC6A [5], which will not be discussed here. The human CaSR's 612 amino acid extracellular domain (ECD) [4] is followed by a 250 amino acid transmembrane domain (TMD) of 7 transmembrane helices, a signature of the GPCRs and, finally, by a ~200 amino acid carboxyterminal (C)-tail. The CaSR resides on the cell surface as a disulfide-linked dimer, involving cysteines 129 and 131 of each monomer [6].

Molecular modeling, utilizing the known 3-dimensional structures of the ECDs of several mGluRs, strongly suggests that the CaSR's ECD assumes a bilobed, venus flytrap (VFT)-like structure with a cleft between the two lobes [6] (Fig. 1). The CaSR responds over a much narrower range of Ca_o^{2+} than would be expected for a protein with a single binding site for Ca_o^{2+}. This marked positive cooperativity likely results from the presence of two or more binding sites for Ca_o^{2+} on each monomer [7]. One site is thought to reside in the crevice between the two lobes of each monomeric VFT. This cleft is postulated to be open in the absence of agonist and to close upon binding Ca_o^{2+}. Associated conformational changes in the TMDs and intracellular domains are presumed to initiate signal transduction. There are likely to be additional binding sites for Ca^{2+} that contribute to the steep slope of the CaSR's activation by Ca_o^{2+} [7]. As detailed later, calcimimetics bind at a different site within the receptor's TMD [8,9], where, by an unknown mechanism, they sensitize it to activation by Ca_o^{2+}.

The biologically active, cell surface CaSR, upon binding Ca_o^{2+}, activates the G-proteins, $G_{q/11}$, G_i, and $G_{12/13}$ (reviewed in [10]). These stimulate phospholipase C (PLC), inhibit adenylate cyclase and activate Rho kinase, respectively. The receptor couples to a variety of other intracellular signalling systems, including mitogen-activated protein kinases (MAPKs) [e.g., extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, and c-jun N-terminal kinase (JNK)], phospholipases A_2 and D, protein kinase B and the epidermal growth factor (EGF) receptor [10]. These various intracellular signalling systems mediate cell-specific regulation by the CaSR.

The parathyroid glands, kidney and bone express the CaSR, enabling them to play key roles in Ca_o^{2+} homeostasis [2]. The CaSR is expressed in numerous other tissues (see http://biogps.gnf.org/#goto=genereport&id=846); however, most of these are uninvolved in mineral ion metabolism. The physiological significance of the receptor's expression in these "non-homeostatic tissues" is in most cases unclear [11].

3. Role of CaSR in Ca_o^{2+} homeostasis

The Ca_o^{2+} homeostatic system has three key components: (1) the cells, tissues and organs transporting Ca^{2+} out of or into the ECF [kidney, bone and intestine (and, in some stages of the life cycle, placenta and breast)]; (2) hormones regulating these fluxes [parathyroid hormone (PTH), calcitonin (CT), and $1,25(OH)_2D_3$]; and (3) Ca_o^{2+}-sensors (principally the CaSR) controlling the secretion/production of those hormones or the Ca^{2+} fluxes themselves [2,12]. Of these three Ca_o^{2+}-regulating hormones, PTH is a Ca_o^{2+}-elevating hormone whose secretion is stimulated by low Ca_o^{2+} and inhibited by high Ca_o^{2+}. $1,25(OH)_2D_3$ is also a Ca_o^{2+}-elevating hormone produced in the renal proximal tubule in response to PTH, hypocalcemia and hypophosphatemia [12]. $1,25(OH)_2D_3$ also feeds back to inhibit its own synthesis. CT is a Ca_o^{2+}-lowering hormone secreted by the thyroidal C-cells during hypercalcemia [12]. A more recently discovered hormone regulating both calcium and phosphate homeostasis is fibroblast growth factor (FGF)-23. It is a potent phosphaturic hormone released principally by osteocytes (osteoblasts encased in bone during bone formation) in response to $1,25(OH)_2D_3$ and hyperphosphatemia [13]. FGF-23 also inhibits both $1,25(OH)_2D_3$ production and PTH secretion. The rapid developments regarding the roles of FGF-23 in phosphorus and calcium metabolism are detailed in recent reviews and will be discussed below [13].

The integrated function of the homeostatic system is as follows, using its response to hypercalcemia as an example. High Ca_o^{2+} directly inhibits both PTH secretion and $1,25(OH)_2D_3$ synthesis by activating the CaSR, indirectly reduces $1,25(OH)_2D_3$ synthesis by decreasing PTH, and stimulates CT secretion. The decrease in PTH reduces the formation and activity of the bone-resorbing osteoclasts [14], producing net movement of Ca^{2+} into bone. At the same time, the decrease in PTH reduces renal tubular Ca^{2+} conservation by diminishing Ca^{2+} reabsorption in both the cortical thick ascending limb (cTAL) [2] and distal convoluted tubule (DCT) [15]. The decrease in $1,25(OH)_2D_3$ synthesis resulting from the lowering of PTH also suppresses Ca^{2+} reabsorption in the DCT [15], decreases bone resorption by diminishing $1,25(OH)_2D_3$-stimulated bone resorption, and reduces intestinal Ca^{2+} absorption [2,15]. The resulting reduction in net Ca^{2+} release from bone, combined with reduced intestinal absorption and renal tubular reabsorption of Ca^{2+}, will normalize Ca_o^{2+}. The homeostatic response to hypocalcemia entails largely opposite changes in the parameters just noted.

3.1. The CaSR in the parathyroid

In the parathyroid, the CaSR controls three important parameters, inhibiting (1) PTH secretion, (2) PTH synthesis and (3) parathyroid cellular proliferation [2]. Individuals homozygous for inactivating CaSR mutations and mice homozygous for targeted inactivation of the CaSR gene [2] have markedly elevated PTH levels and parathyroid hyperplasia in spite of their marked hypercalcemia. These observations prove the CaSR's key roles in tonically inhibiting PTH secretion and parathyroid cellular proliferation. Further studies have shown that the CaSR likewise controls expression of the PTH gene [16]. The receptor likely also indirectly inhibits parathyroid function by upregulating the

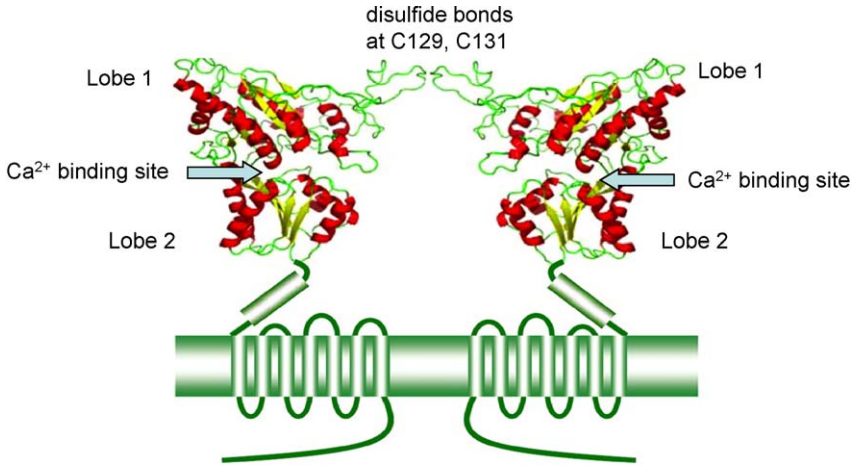


Fig. 1. Model of the CaSR based on the known structure of the extracellular domain of mGluR1. The two monomeric ECDs are linked by two disulfide bonds involving cysteines 129 and 131 in a flexible loop of the receptor (loop 2). Each monomeric ECD has a bilobed, "venus flytrap"-like configuration. A binding site for Ca^{2+} lies within the crevice between the lobes. Upon binding Ca^{2+}, the lobes are proposed to approximate one another and may interact with the transmembrane domains shown in green to initiate signal transduction. From Huang, et al., J Biol Chem 2007;282:19000–19010, with permission.

expression of the vitamin D receptor (VDR) [17], thereby potentially augmenting the inhibitory actions of $1,25(OH)_2D_3$ on parathyroid cellular proliferation and PTH gene expression. Calcimimetics produce the same effects by potentiating the actions of Ca_o^{2+} on the CaSR. $1,25(OH)_2D_3$ reciprocally upregulates expression of the CaSR, potentially enabling Ca_o^{2+} and $1,25(OH)_2D_3$ to coordinately inhibit several aspects of parathyroid function [18]. A recent study, however, has cast doubt on the physiological relevance of $1,25(OH)_2D_3$ in regulating parathyroid function in vivo under normal circumstances in that mice with knockout of the VDR only in the parathyroid show little, if any, perturbation in Ca_o^{2+} homeostasis [19]. This observation does not negate the fact, however, that exogenously administered $1,25(OH)_2D_3$ can effectively lower PTH levels in patients with renal insufficiency, as will be detailed later. The parathyroid is the sole target, to date, for the various applications of the calcimimetic, cinacalcet, to be discussed here.

3.2. The CaSR in kidney

In the kidney the CaSR (1) inhibits the synthesis of $1,25(OH)_2D_3$, at least in part, by upregulating the VDR in the proximal tubule, thereby promoting feedback inhibition of $1,25(OH)_2D_3$ formation, and (2) directly suppressing renal tubular Ca^{2+} reabsorption in the cTAL [2]. The second of these actions, in combination with decreased PTH secretion during hypercalcemia, maximize renal Ca^{2+} excretion.

3.3. The CaSR in bone

The presence and functional significance of the CaSR in bone cells has been controversial (for review, [20]). However, recent studies provide strong evidence that the CaSR is expressed in osteoblasts, osteoclast precursors, and at least some mature osteoclasts [21]. In the osteoblast lineage, the CaSR is mitogenic for preosteoblasts, promotes their differentiation to mature osteoblasts and enhances bone formation and mineralization [21,22]. The CaSR appears to serve a permissive role in osteoclastogenesis, but high Ca_o^{2+} concentrations directly inhibit osteoclast activity and stimulate their apoptosis [23]. Thus high Ca_o^{2+}, via the CaSR, stimulates bone formation and inhibits bone resorption in a homeostatically appropriate manner, actions that at least theoretically could be mimicked by calcimimetics. The applications of cinacalcet to date, however, are thought to impact bone indirectly by suppressing PTH secretion.

4. Development of calcimimetics

The discovery of calcimimetics occurred as a result of screening organic compounds for their ability to mobilize intracellular calcium stores in bovine parathyroid cells by potentiating the action of Ca_o^{2+} on the CaSR [1]. Mobilization of intracellular calcium owing to activation of phospholipase C is a characteristic "signature" of activation of the CaSR. Inorganic polyvalent cations that are agonists of the CaSR, such as Ca^{2+}, Mg^{2+}, La^{3+} or Gd^{3+}, activate the receptor without the need for any other agonists and are termed type 1 agonists. Calcimimetics, on the other hand, require some level of Ca_o^{2+} (e.g., $\sim\geq$0.5 mM) to activate the CaSR [1]. They are positive allosteric modulators and are termed type 2 agonists. Calcimimetics were the first described allosteric modulator of a GPCR. The initial, "first generation" calcimimetics, NPS R-467 and R-568 (the S-isomers of these compounds are inactive), were supplanted by a second generation drug, called cinacalcet HCl® or sensipar® in the US and mimpara® in Europe (initially called NPS 1493 and subsequently AMG 073 prior to its use in humans) (Fig. 2). Cinacalcet was the first calcimimetic to enter the clinic. All three of these calcimimetics are phenylalkylamine derivatives, although other related calcimimetics have subsequently been identified, such as the naphthylalkylamine, calindol [24]. Cinacalcet has a more favorable pharmacokinetic profile than its predecessors owing to less inter-individual variation in its metabolism in vivo than with NPS R-568, for example. It was

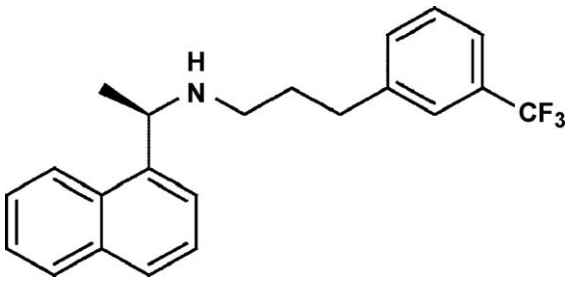


Fig. 2. Chemical structure of the calcimimetic, cinacalcet. From Nemeth, et al., J Pharmacol 2004;308:627-35, with permission.

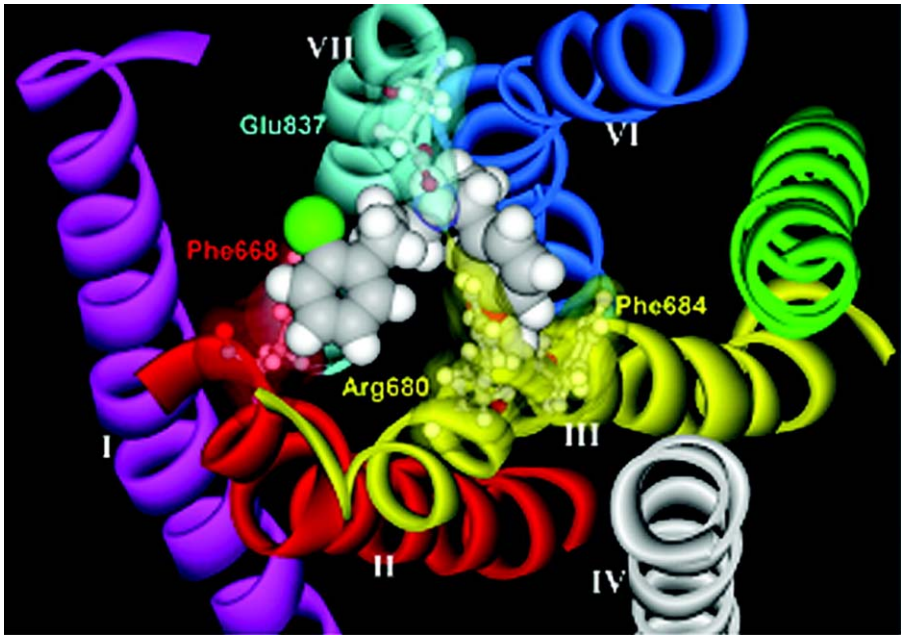


Fig. 3. Proposed model for the binding of the first generation calcimimetic, NPS R-568, to the transmembrane domain of the CaSR. The amino group is anchored to residue glu837, while the two hydrophobic ends of the molecule are postulated to interact with hydrophobic residues within the transmembrane helices, e.g., phe668 in helix 2 for the phenyl moiety and phe684 in helix 3 for the naphthyl moiety. By uncertain mechanisms, binding of the calcimimetic increases the apparent affinity of the ECD of the CaSR for Ca_o^{2+}. Reprinted from Miedlich, et al., J Biol Chem 2004;279:7254–63, with permission.

chosen, therefore, for subsequent clinical trials assessing its efficacy and safety in treating hyperparathyroidism in stage 5 CKD [25].

A combination of site-directed mutagenesis and molecular modeling has identified the likely binding pocket for calcimimetics in the TMD of the CaSR, although the models differ in their details. Glu837, at the outer end of TM7, plays a key role by binding to the amino group of the calcimimetic in a salt bridge [26]. Two published models propose that the hydrophobic "arms" of the calcimimetic bind to hydrophobic residues within the TMD. One group suggests that two such residues are Phe668 (transmembrane helix 2) and Phe684 (helix 3), which bind not only the calcimimetic, NPS R-568 [8] (Fig. 3), but also the CaSR antagonist, NPS 2143 (a so-called calcilytic [27]). The other group identified partially overlapping binding pockets for calcilytics and calcimimetics. In this model, both calcilytics and calcimimetics are predicted to interact with Trp818 and Phe821 in helix 6, while only the calcilytic interacts with Phe668 and Phe684 [9]. The discrepancies between these two models have not yet been resolved.

5. Clinical application of calcimimetics

5.1. Secondary hyperparathyroidism in stage 5 CKD

5.1.1. Studies in experimental animals

It remains to be proven that the actions of calcimimetics on rats with experimentally induced uremia are generally applicable to humans. Nevertheless, these animal studies have provided proof-of-principle that calcimimetics, as expected, sensitize the CaSR in the parathyroid to Ca_o^{2+} in vivo, thereby producing the expected changes in parathyroid function. In addition, the available data provide benchmarks for the subsequent investigation of potentially beneficial effects that the drug might have in humans.

Studies in normal rats showed that oral administration of a single dose of cinacalcet lowered serum PTH, with a nadir at 1–2 h [27]. Serum calcium concentration also decreased with a maximal reduction at 1–4 h, depending on dose. While cinacalcet also elevated circulating calcitonin levels, the apparent in vivo EC_{50} values for lowering PTH and stimulating calcitonin were 0.5 and 16 mg/kg, respectively [27]. Therefore, doses suppressing PTH release would have minimal effects on calcitonin secretion in vivo. An extensive body of data then documented that NPS R-568 lowers serum PTH and calcium concentrations in rats with experimentally induced renal insufficiency, generally induced by subtotal (i.e., 5/6) nephrectomy [27]. A calcimimetic also reduced PTH mRNA [16], which likely contributes to the decrease in PTH secretion, and upregulated both the CaSR and VDR in parathyroid [17]. Increased CaSR expression would further sensitize the parathyroid to both Ca_o^{2+} and the calcimimetic. Since activating the VDR upregulates the CaSR [18] and inhibits PTH gene expression [28], increased VDR expression could also potentiate the action of the calcimimetic.

Administering calcimimetics to uremic rats also prevented the parathyroid hyperplasia that occurs with renal insufficiency [29], due, at least in part, to upregulation of the cyclin dependent kinase inhibitor, p21 [30]. Some studies have also shown regression of established hyperplasia [31]. While there is generally thought to be little apoptosis of the long-lived parathyroid chief cells, some evidence exists that calcimimetics induce apoptosis of this cell type, albeit at a high dose (10^{-4} M) [32]. Finally, treating uremic rats with a calcimimetic reduces the degree of hyperparathyroid bone disease, termed osteitis fibrosa cystica [33].

Subsequent studies in rats revealed additional actions of calcimimetics in tissues outside of the parathyroid glands and skeleton. Rats administered NPS R-568 showed a reduction in the rate of progression of renal failure that would otherwise occur in rats that have undergone subtotal nephrectomy [34]. This same study showed that the drug also decreased blood pressure and LDL cholesterol levels, which would be expected to have a favorable impact on the high prevalence of cardiovascular complications of uremia in animals and humans [35]. Indeed, the hearts of the treated animals exhibited less interstitial fibrosis and decreased arteriolar wall thickness relative to control animals. Subsequent studies also demonstrated reductions in the thickness and calcification of blood vessel walls outside of the heart, and the life span of calcimimetic-treated, uremic rats was significantly

longer than in controls [36]. The use of atherosclerosis-prone, apolipoprotein E-deficient mice made it possible to show directly that NPS R-568 retarded uremia-enhanced vascular calcification and atherosclerosis in this animal model [37]. Finally, the recently developed calcimimetic, AMG 641, promoted actual regression of preexistent aortic and soft tissue calcification in uremic animals [38]. The relative contributions of changes in PTH vs. serum mineral ions (i.e., Ca^{2+}, phosphate and calcium-phosphate product) vs. putative direct actions of calcimimetics on blood vessels are topics of current investigation.

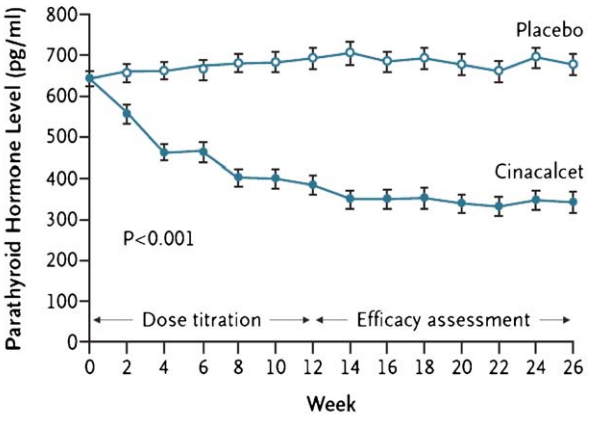
Active vitamin D compounds, such as $1,25(OH)_2D_3$ and its less calcemic analogue, paracalcitol, are a mainstay of the treatment of secondary hyperparathyroidism in uremic humans by virtue of their capacity to inhibit PTH gene expression and parathyroid cellular proliferation [28]. Preclinical studies in uremic rats have, in general, shown that the vitamin D analogues, particularly $1,25(OH)_2D_3$, are effective in lowering PTH, but can decrease survival as well as induce extraosseous calcification and the progression of renal failure [36]. These effects of the vitamin D analogues can be significantly ameliorated by the co-administration of a calcimimetic [39].

5.2. Studies in humans

A substantial body of evidence in humans with stage 5 CKD has shown effects of cinacalcet on parameters of mineral ion metabolism that are similar to those just described for animal models of uremia, although there are differences as pointed out below (the rats are not being dialyzed for one). This field will be summarized relatively briefly here, pointing out gaps in our knowledge or areas of controversy, as this area is covered in detail in recent reviews (e.g., [40]).

In randomized control studies, cinacalcet has lowered serum PTH (Fig. 4), calcium, phosphate and the calcium × phosphate product [25]. The reduction in serum phosphate was initially surprising. In a dialysis patient, there is minimal or no renal phosphate excretion, so the observed change in serum phosphate must result from other, as yet poorly defined, mechanisms. These reductions in indices of mineral metabolism have improved the achievement of biochemical targets established for these parameters in patients with stage 5 CKD. The National Kidney Foundation (NKF) of the U.S. provides guidelines [so-called NKF KDOQI (kidney disease outcomes initiative) guidelines] for the levels of serum calcium, phosphate, PTH and the calcium × phosphate product to be achieved in patients with CKD. These guidelines have as their goal to reduce morbidity and mortality in this patient population (http://www.kidney.org/Professionals/Kdoqi/guidelines_ckd/toc.htm). For stage 5 CKD, the goals for serum calcium, phosphorus, calcium × phosphate product and PTH are, respectively, 8.4–9.5 mg/dL, 3.5–5.5 mg/dL, <55 mg^2/dL^2 and 150–300 pg/mL.

The PTH levels referred to in this review are generally those obtained with so-called "intact" assays. These actually recognize not only the full length PTH1-84 molecule but also N-terminally truncated forms such as PTH7-84. The latter inhibits the activity of PTH on its receptor in kidney and bone and accumulates in the serum of patients with renal insufficiency. While newer, "whole" PTH assays recognize only PTH1-84, they do not provide a clearly superior assessment of the relative level of parathyroid overactivity. Cinacalcet has increased the percentage of patients achieving KDOQI goals, but the frequency with which the individual targets or all four together are achieved has remained suboptimal [25]. For example, addition of cinacalcet to standard therapy (principally phosphate binders and vitamin D analogues) increased the percentage of patients achieving the NKF guidelines for serum calcium (49% vs. 24% for controls), phosphate (46% vs. 3%), and PTH (56% vs. 10%), calcium × phosphate product (65% vs. 33%), as well as for both PTH and calcium-phosphate product simultaneously (41% vs. 6%) [41]. The effects of cinacalcet on serum minerals and PTH persist for at least 3 years, without a need for dose escalation. The commonest side effects of the drug are nausea and vomiting, occurring in ~30% of patients, although ~15% of the placebo-treated controls had the same symptoms [25].



No. of Patients														
Cinacalcet	371	354	338	333	315	305	297	298	293	280	276	266	257	257
Placebo	370	354	342	344	328	321	323	315	312	308	291	287	291	289

Fig. 4. Suppression of circulating PTH levels by cinacalcet in patients being dialyzed for stage 5 CKD. There is a ~40% suppression of the PTH level at steady state, which persists for the duration of the study. The average level of PTH in the cinacalcet-treated patients is around 300 pg/mL, which is at the upper limit of the NKF KDOQI guidelines for stage 5 CKD, indicating that a substantial fraction of the treated patients were within the recommended range of 150–300 pg/mL. From Block et al., New Engl J Med 2004;350:1516–25, with permission.

In addition to its effects on serum mineral ions and PTH, one study showed a reduction in the size of the hyperplastic parathyroid glands in cinacalcet-treated dialysis patients [42], especially in those glands weighing less than 500 mg. In addition, a small study showed that cinacalcet produced a reduction in the degree of osteitis fibrosa cystica (hyperparathyroid bone disease) in dialysis patients [43]. There has been some concern, however, that overly aggressive treatment with cinacalcet reducing PTH below the recommended levels could produce so-called adynamic bone disease, thought to result from the presence of insufficient levels of PTH to promote a normal rate of bone turnover [43]. Further studies are needed to clarify the impact of treatment with calcimimetics on bone mineral density and bone histology in patients with stage 5 kidney disease.

There has been considerable interest in determining whether vitamin D metabolites alone, cinacalcet alone, or a combination of both would be most effective in treating secondary hyperparathyroidism in stage 5 CKD [40]. While vitamin D analogues and cinacalcet given singly lower PTH to a similar degree, there are several notable differences between the two. (1) Vitamin D can produce both hypercalcemia and hyperphosphatemia at high doses, while cinacalcet lowers both modestly. Symptomatic hypocalcemia does occur in a minority of patients receiving cinacalcet [40]. (2) There is a higher incidence of side effects with cinacalcet, principally nausea and/or vomiting. (3) Observational studies (randomized control trials have not been carried out to date) have suggested that vitamin D analogues prolong survival [44], while no such data are yet available for cinacalcet (see below). A growing body of evidence suggests that a combination of both agents has advantages over either given by itself: (a) The combination provides better control of SHPT than does vitamin D alone and (b) combined therapy enables the use of a lower dose of vitamin D, thereby reducing the risk of vitamin D-induced elevations in serum calcium and/or phosphate [40].

Will therapy with cinacalcet, alone or in combination with vitamin D analogues, reduce cardiovascular disease and associated mortality? Answering this question will impact heavily on the assessment of whether cinacalcet therapy is cost-effective. The high cost of cinacalcet (estimated to range from $300/mo for 30 mg/day to ~$2000/mo for 180 mg/day) has suggested that the drug would not be cost-effective without a substantial reduction in price. There has been one small meta analysis of 4 randomized, double-blind, placebo-controlled clinical trials utilizing cinacalcet or placebo in patients already receiving vitamin D and phosphate binders to assess its impact on end-points other than serum mineral ions and PTH [35]. This study found that relative to patients not receiving cinacalcet who were on standard care, cinacalcet-treated patients had a >90% reduction in the rate of parathyroidectomy and about a 40% reduction in cardiovascular hospitalizations. The study was underpowered, however, to assess the effect of the drug on "hard" cardiovascular end-points, such as myocardial infarction or death. Two large randomized controlled studies are underway to address this latter point, the ADVANCE ("A randomized study to evaluate the effects of cinacalcet plus low dose vitamin D on vascular calcification in subjects with chronic kidney disease (CKD) receiving hemodialysis") and EVOLVE studies (EValuation Of Cinacalcet HCl Therapy to Lower cardioVascular Events). The latter has as its primary end-points all-cause mortality and first nonfatal cardiovascular event in 3800 chronic dialysis patients being treated with a flexible regimen of traditional therapies, who will additionally receive either cinacalcet or placebo [45].

5.3. SHPT in children

In addition to the application of cinacalcet to the treatment of adult patients with stage 5 CKD, the drug has also been utilized in pediatric dialysis patients, although it has not yet been approved for use in children. One such off-label study showed an 86% reduction in PTH after treatment for up to 3 years, although the achievement of targets for serum mineral levels was unaffected [46]. Therefore, whether the calcimimetic will impact long-term complications related to abnormal serum mineral levels is uncertain. Although there are no data to substantiate it, there might be theoretical concerns regarding issues such as excessive reduction in bone turnover or other unwanted side effects with more prolonged use of the drug in the pediatric setting than in adult patients.

5.4. Recurrent hyperparathyroidism after parathyroidectomy for severe secondary or tertiary hyperparathyroidism in patients with ESRD

Some dialysis patients develop marked secondary hyperparathyroidism with elevations of intact PTH to 1000–1500 pg/mL or higher that are not effectively treated with phosphate binders and vitamin D analogues. Furthermore, some of these patients progress from severe secondary, albeit normocalcemic, hyperparathyroidism to a state called "tertiary" hyperparathyroidism, in which frank PTH-dependent hypercalcemia develops. The progression from severe secondary to tertiary hyperparathyroidism generally occurs coincident with a transition from polyclonal hyperplasia of the parathyroid glands to nodular hyperplasia, with each nodule representing a separate monoclonal growth that behaves functionally like a parathyroid adenoma, the cause of most cases of primary hyperparathyroidism [47]. When such nodular parathyroid glands are studied either in vivo or in vitro, they exhibit an increase in "set-point" (the level of Ca_o^{2+} half maximally suppressing PTH secretion) similar to that seen with adenomas in PHPT. This increase in set-point produces an elevation in serum calcium concentration to the frankly hypercalcemic level seen in tertiary hyperparathyroidism. There is reduced expression of the CaSR and VDR in such cases, which likely contributes to the associated functional abnormality [47]. The genetic defects in the parathyroid nodules of patients with tertiary hyperparathyroidism, however, are usually different from those associated with parathyroid adenomas [48].

Prior to the development of calcimimetics, if secondary or tertiary hyperparathyroidism in dialysis patients could not be adequately controlled by phosphate binders and vitamin D analogues, subtotal parathyroidectomy was standard therapy (or, in some centers, total parathyroidectomy with reimplantation of a small amount of the patient's own parathyroid tissue) [49]. Even in patients treated successfully in this manner, however, there is a risk of recurrence of the severely hyperparathyroid state that ranges from about 10% at 3 years to 30% after 7 years. The use of cinacalcet in this setting might provide a non-surgical approach to the problem of recurrent hyperparathyroidism. In one off-label study utilizing the drug in this setting in a small number of patients ($N = 6$), there were substantial reductions in mean PTH (1388–435 pg/mL), serum calcium (9.6→8.3 mg/dL), serum phosphorus (5.5→31.3 mg/dL) and calcium-phosphate product (53→31 mg^2/dL^2) [50]. In additional case reports, cinacalcet has effectively lowered serum calcium to or toward normal in this setting. While the results to this point suggest the utility of the drug in this setting, additional experience in CKD patients with recurrent hyperparathyroidism after prior parathyroid surgery is clearly needed to further validate the application of calcimimetics to these patients.

5.5. Patients with CKD prior to the institution of dialysis therapy

There is a very limited number of studies on the effects of cinacalcet on indices of mineral metabolism in patients with CKD not yet requiring dialysis [51]. In an off-label, placebo-controlled study of 404 patients (75% receiving cinacalcet and 25% placebo) cinacalcet lowered PTH by 43% (vs. −1.1% in controls) and serum calcium by 8.9% (vs. +0.8%) and elevated serum phosphorus by 21% (vs. +6.8%), resulting in a 21% increase in calcium × phosphorus product. However, the calcium × phosphate product also increased (by 17%) in the placebo group and was 40 mg^2/dL^2 or less in both groups, well within the NKF KDOQI guidelines [51]. At this point, there is no consensus regarding the use of the drug in this setting. On a theoretical basis, given its capacity to inhibit parathyroid cellular proliferation, it might have utility in limiting parathyroid hyperplasia, particularly if there were an accurate way to measure parathyroid gland volume non-invasively early in the development of the hyperplastic process. In addition, in patients with stage 3 and 4 CKD with unusually large elevations in serum PTH, it could provide a means of lowering serum PTH to levels within the KDOQI guidelines (35–70 pg/mL in stage 3 and 70–110 pg/mL in stage 4). It would likely be used in combination with a vitamin D analogue and phosphate binder in this setting. Finally, further studies could determine whether cinacalcet slows the progression of renal failure in stages 3 and 4 CKD, as it does in experimental animals.

5.6. Hypercalcemia and hyperparathyroidism following renal transplantation

After renal transplantation, the improvement in renal function, with an attendant reduction in serum phosphate concentration and increase in renal production of $1,25(OH)_2D_3$, is accompanied by the development of PTH-dependent hypercalcemia in about 10% of patients [52] and persistent, albeit normocalcemic, hyperparathyroidism in additional patients. Hypercalcemia and/

or an elevated calcium × phosphate product post-renal transplant have been associated with increased mortality and risk of loss of the transplanted kidney through unknown mechanisms [53]. Because of the limited capacity of hyperplastic parathyroid glands to involute, on the order of 50% of such hypercalcemic patients remain so after 12 months. Cinacalcet has provided a novel approach to treating the persistent normocalcemic or hypercalcemic hyperparathyroidism in these patients. The largest study to date utilized the drug off-label in 48 transplant patients who were hypercalcemic or had persistent secondary hyperparathyroidism [54], but did not include untreated control groups. 91% of the hypercalcemic patients became normocalcemic and 70% of the normocalcemic hyperparathyroid patients achieved a target PTH level of 75–125 pg/mL. 10 patients in this study developed hypocalcemia. In several other studies, similar decrements in PTH and serum calcium were observed in frankly hypercalcemic patients post-renal transplantation [55].

Some studies have reported hypercalciuria [56], which could potentially damage the transplanted kidney, or modest reductions in renal function [57]. Most reports, however, have not reported hypercalciuria, and, in those in which there were reductions in renal function, they were modest (~10% increase in serum creatinine) and were reversible following discontinuation of the drug [57]. Increases in bone mineral density have also occurred during cinacalcet treatment of post renal transplant patients (e.g., in the femoral neck [58]). While this action of the drug would be very beneficial in this patient population, caution is warranted in ascribing this effect to cinacalcet, as there were no control groups in these two studies.

One study reported that 8 of 9 patients whose serum calcium concentration normalized during 12 months treatment with cinacalcet remained normocalcemic when treatment was stopped [57]. Given the lack of a control group in this study, it's unclear whether cinacalcet improved the outcome in these patients, although spontaneous resolution of hypercalcemia in this setting has been estimated to be only ~50%. Thus it is possible that the drug might hasten resolution of hypercalcemia and decrease the need for parathyroidectomy post-renal transplant, but additional studies are needed to address these points. Finally, a very recent study suggested that discontinuing cinacalcet therapy prior to renal transplantation did not adversely affect graft survival [59]. This finding and the stable renal function in most patients receiving cinacalcet post renal transplantation are of note, as parathyroidectomy after renal transplantation can be associated with deterioration in graft function.

5.7. Parathyroid carcinoma

In the largest study to date, Silverberg et al. utilized cinacalcet to treat 29 patients with inoperable parathyroid cancer (en bloc removal of the entire parathyroid cancer is the preferred treatment of parathyroid cancer at the time of first parathyroid surgery) [60]. This is the only FDA approved use of the drug other than in stage 5 CKD. Patients received escalating doses of the drug with an initial dose of 30 mg/day twice daily for 16 weeks or until serum calcium was no more than 10 mg/dL. The mean serum calcium concentration in these patients decreased from 14.1 mg/dL to 12.4 mg/dL, with 62% showing a decrement in serum calcium of 1 mg/dL or more at the time when a maintenance dose of the drug had been reached [60]. The patients with the highest initial serum calcium concentrations showed the greatest decrease in serum calcium concentration during treatment (a drop of 25% in patients in the highest tertile of serum calcium concentration). Although it was not stated explicitly how many patients became normocalcemic during treatment, it appears to have been about 10% from the graphical representation of the data.

Perhaps surprisingly, serum PTH levels, which were measured in the morning before the first daily dose of the drug, did not change significantly (−4.6%). This observation may reflect the fact that the biological half-life of the drug is such that serum PTH has increased from its nadir 2–4 h after a dose to levels in some cases approaching the baseline level by 12–24 h after the last dose [61]. Ideally, monitoring the area under the PTH curve over the course of the day would provide a better assessment of the full impact of cinacalcet on parathyroid function, but is impractical in routine clinical care. Finally, activation of the CaSR in the kidney, producing an increase in urinary calcium excretion (urinary calcium was not determined in the study), or in bone cells resulting in net movement of calcium into bone, could not be ruled out as contributory factors. In summary, meaningful reductions in serum calcium concentration were achieved with cinacalcet in patients with inoperable parathyroid cancer, although this was not associated with any change in quality of life as assessed with the SF-36 instrument. Therefore, while at least some degree of biochemical control of hypercalcemia can be achieved with cinacalcet in the majority of patients with parathyroid cancer for months or longer, the role that the drug will play in the longer-term management of this disease is not yet clear.

5.8. Other forms of primary hyperparathyroidism

The off-label use of cinacalcet in patients with primary hyperparathyroidism (PHPT) has been reported in two settings: (1) Mild primary hyperparathyroidism, as a means of lowering serum calcium and/or PTH [62] levels, and (2) persistent, "intractable" PHPT in patients with failed parathyroid surgery or in those with contraindication(s) to surgery [63]. PHPT is caused by one or more abnormal parathyroid glands that are less sensitive than normal to the suppressive effect of Ca_o^{2+} on PTH secretion, leading to a resetting upward in the patient's serum calcium concentration [12]. Definitive treatment is surgical removal of the abnormal parathyroid gland(s), although in mild asymptomatic cases, criteria have been developed for identifying patients in whom non-surgical follow up can be safe [64]. By monitoring such untreated patients, who must be 50 years or older, for progression of disease, as manifested by increases in serum calcium concentration or reductions in renal function or bone mineral density, medical follow-up can be carried out with relatively low risk of irreversible complications. Recent data indicate, however, that close to 40% of these patients develop progression of disease over 15 years of follow up, calling into some question the utility of a non-operative approach to managing this disease over the long term [65]. Prior to the development of calcimimetics, there was no medical therapy that effectively lowered serum calcium concentration in PHPT on a chronic basis. However, the calcimimetics address the primary functional abnormality in this condition by sensitizing pathological parathyroid glands to Ca_o^{2+} through a direct action on the CaSR. In most cases, the CaSR in PHPT does not harbor the inactivating mutations that are the cause of familial hypocalciuric hypercalcemia (see below), and so the calcimimetics are acting upon an intrinsically normal CaSR.

A placebo-controlled study has examined the effects of cinacalcet treatment for up to 5 years on patients with mild primary hyperparathyroidism [62]. While the use of cinacalcet in PHPT (other than in parathyroid cancer) has not been approved in the US, it has been approved in Europe. After 1 year, 73% of the cinacalcet-treated patients normalized their serum calcium concentration, compared with 5% of the placebo group. As in the studies on parathyroid cancer, and likely for the reasons noted earlier, PTH decreased modestly in the cinacalcet group (7.6%), although the level achieved was significantly less than in the placebo group. Patients who undergo successful surgical treatment

for PHPT show an increase of about 10% in their BMD within 1–2 years after their surgery [62]. Cinacalcet-treated patients showed no such increase in BMD, although it remained stable over the 5-year duration of the study. Thus the drug does not produce a true "medical parathyroidectomy" [62]. About 20–30% of the patients receiving cinacalcet withdrew from the study during the first year, and a further 25% withdrew during the 4-year extension of the study, due in part to nausea and vomiting, which occurred in ~30% of patients; 16% of the placebo group also experienced nausea in the 12-month study [62].

Treatment of 17 patients with intractable PHPT, which was of substantially greater severity than in the study just described (mean serum calcium concentrations of 12.7 mg/dL vs. 10.7 mg/dL, respectively), with cinacalcet for a mean duration of 270 days produced a 1 mg/dL or greater reduction in serum calcium concentration in 88% of the patients, with 53% achieving normocalcemia [63]. While the use of the drug in primary hyperparathyroidism has been approved in Europe, it has not been submitted for FDA approval in the U.S. Off-label treatment of PHPT with cinacalcet is expensive (several hundred dollars per month depending on dose) and does not provide the equivalent of a surgical parathyroidectomy, as just noted, with regard to the skeleton. In addition, regular clinical and biochemical follow-up of the patients, and the associated medical expense, would be needed. Therefore, the role of the drug in PHPT (outside of its approved role in parathyroid cancer) is uncertain. Most likely, its use in the U.S. will be limited to patients who are unwilling/unable to undergo parathyroidectomy.

5.9. Other forms of hyperparathyroidism

While not currently approved for use in forms of PTH-dependent hypercalcemia other than parathyroid carcinoma and primary hyperparathyroidism in the U.S, cinacalcet has shown efficacy in several such disorders. All have in common an increase in the set-point for Ca_o^{2+}-regulated PTH secretion. This abnormality in secretory control is what is corrected to, or toward, normal by calcimimetic treatment, in association with a resetting downward of the serum calcium concentration.

5.9.1. Lithium-induced hyperparathyroidism

PTH-dependent hypercalcemia develops in 10–20% of patients treated with lithium for psychiatric disorders, principally bipolar disorder, although the reported prevalence of this complication varies widely from <10% to >50% in different series [66]. The fact that PTH levels in these patients are normal or frankly elevated, and not suppressed, as would be expected with normal parathyroid glands, indicates that a PTH-dependent form of hypercalcemia is present. The mechanism by which lithium induces abnormal parathyroid function is not known. However, lithium-treated patients consistently show an increase in set-point for Ca_o^{2+}-regulated PTH secretion, which presumably reflects some direct, but currently unknown, pharmacological action of the drug on the parathyroid. Some patients with lithium-induced hyperparathyroidism harbor a parathyroid adenoma when subjected to parathyroid surgery, while others have generalized parathyroid hyperplasia. Lithium also has a hypocalciuric action, which can produce a picture of acquired, hypocalciuric, PTH-dependent hypercalcemia reminiscent of familial hypocalciuric hypercalcemia (see next section).

Treatment of lithium-induced hypercalcemia/hyperparathyroidism can be problematic, because psychiatrists often prefer not to discontinue lithium therapy in lithium-treated patients who develop hypercalcemia, which has some risk of exacerbating the underlying psychiatric disorder. Many of these patients have relatively mild hypercalcemia and can simply be followed expectantly without surgical intervention. Several case reports or small series of patients have described off-label treatment of lithium-induced hyperparathyroidism with cinacalcet. Serum calcium concentration decreased from an average of 10.8 to 10.0 mg/dL in three such patients in one study [67] and from an average of 10.9 to 10.1 in two further patients [68]. Therefore, in patients with lithium-induced hyperparathyroidism in whom parathyroid surgery is indicated but refused by the patient or contraindicated for other reasons, cinacalcet potentially provides an alternative form of treatment. Additional experience in the use of the drug in this setting should shed further light on its clinical utility.

5.9.2. Familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism

While the autosomal dominant disorder, familial hypocalciuric hypercalcemia (FHH), can be confused with primary hyperparathyroidism, in most cases it is a related but clearly distinct entity, with a totally different pathogenesis [2]. As in PHPT, there is resistance of the parathyroids to suppression by Ca_o^{2+}, leading to an increase in the set-point for Ca_o^{2+}-regulated PTH release. Unlike PHPT, there is also "resistance" of the kidney to the usual hypercalciuric action of hypercalcemia, producing the characteristic hypocalciuria observed in this condition (reabsorption of ≥99% of the calcium filtered by the glomeruli of the kidneys) [2]. The combined parathyroid and renal resistance to calcium in FHH results from germline, heterozygous inactivating mutations of the CaSR in more than 90% of patients with this syndrome. FHH is a mild, asymptomatic condition generally not requiring any specific medical or surgical therapy, while, as noted above, about 40% of patients with mild PHPT eventually develop skeletal or renal complications after 15 years of observation, necessitating parathyroid surgery [65].

Occasional families with FHH, however, present with a more severe clinical picture, including neonatal hyperparathyroidism with overt bone disease, hypercalcemia more severe than the norm, pancreatitis, or even renal stone disease [69]. Some such patients have been subjected to parathyroid surgery, providing a rationale for utilizing a calcimimetic as an alternative means of lowering serum calcium concentration and PTH in such atypical cases. Most FHH mutations exhibit some capacity for "rescue" of their function by a calcimimetic, providing a theoretic basis for the drug having a Ca_o^{2+}-lowering effect in vivo [70]. However, it is likely that the action of the calcimimetic on the patients' normal CaSRs encoded by the remaining normal CaSR gene may also be a major contributor to any therapeutic effect of the drug in this setting. To date only a single case of FHH has been treated off-label with cinacalcet, which reduced serum calcium concentration from ~11.4 mg/dL to an average of 9.7 after 12 months of therapy [71]. Therefore, while the number of FHH patients in whom this approach is warranted is small, the use of a calcimimetic in unusually severe cases of this condition could: (1) help to assess whether symptoms (such as pancreatitis) can be related to the hypercalcemia, and (2) offer an alternative to surgery in the rare case in which the latter was felt to be indicated.

Another disorder arising from inactivating mutations in the CaSR, neonatal severe hyperparathyroidism (NSHPT), usually represents the homozygous form of FHH [72]. In this situation, there are no normal CaSRs, resulting in severe hyperparathyroidism, since the parathyroid glands are no longer suppressed by increases in Ca_o^{2+} [72]. Consequently, there is severe hypercalcemia, not infrequently greater than 15 or even 20 mg/dL, accompanied by hyperparathyroid bone disease caused by the markedly elevated PTH levels. In severely affected infants whose condition does not improve with intensive medical therapy, such as administration of fluids and a bisphosphonate, total parathy-

roidectomy can be life-saving. While the use of cinacalcet has not been reported in this setting, even partial rescue of the function of the mutant CaSRs might be of therapeutic benefit. That is, if a calcimimetic lowered serum calcium even moderately, this might stabilize the infant's condition, affording more time to consider the relative merits of medical or surgical therapy.

5.9.3. Phosphate-wasting disorders

A novel application of calcimimetic therapy is to mitigate the hypophosphatemia that occurs in patients with excessive circulating levels of the phosphaturic hormone, FGF-23 [13]. The resultant hypophosphatemia, primarily by reducing the calcium × phosphate product, compromises the structural integrity of bone, causing the characteristic bowing of the lower extremities and other bony abnormalities of rickets in children. In adults who develop phosphate wasting after bone growth is complete, hypophosphatemia causes osteomalacia (poorly mineralized bone), associated with bone pain and, in some cases, fractures.

Two disorders caused by FGF-23 excess are X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO) [13]. The former is caused by inactivation of the gene encoding PHEX (phosphate-regulating gene with homologies to endopeptidases on the X-chromosome), an endopeptidase whose substrate in unknown [13]. Through an unclear mechanism, loss of PHEX results in overproduction of FGF-23 by the osteoblast-derived osteocytes embedded within bone during bone formation. The resultant increase in circulating FGF-23 produces hypophosphatemia and rickets/osteomalacia via renal phosphate wasting and, through a separate direct action of FGF-23, inhibits the formation of $1,25(OH)_2D_3$. TIO results from overproduction of FGF-23 by tumors of mesenchymal origin, usually benign, which are termed phosphaturic mesenchymal tumors of the mixed connective tissue type. The elevated FGF-23 levels produce rickets in children and osteomalacia in adults as described above [13].

Treatment of both XLH and TIO entails phosphate supplementation in doses of 250–500 mg, generally 4 times daily, which is often accompanied by increased GI motility leading to gastrointestinal distress, combined with $1,25(OH)_2D_3$ (1–2 μg daily) [13]. The latter increases gastrointestinal phosphate absorption and mitigates the secondary hyperparathyroidism associated with the hypocalcemic action of phosphate supplementation. Despite therapy with $1,25(OH)_2D_3$, however, secondary (and rarely tertiary) hyperparathyroidism may ensue, aggravating the hypophosphatemia owing to the phosphaturic action of PTH. It is the latter complication that has prompted the use of cinacalcet off-label in XLH [73] and TIO [74]. Administration of a single dose of cinacalcet and 20 mg/kg phosphate to 8 subjects with XLH produced a decrease in serum PTH (from 34 to 23 pg/mL) in association with a substantial increase in TP/GFR (a measure of the renal phosphate threshold, i.e., the level of serum phosphate at which phosphate first spills into the urine) from 1.7 to 2.5 [73]. In contrast, patients receiving phosphate alone exhibited an increase in PTH (from 36 to 53 pg/mL) and an unchanged TP/GFR.

Chronic administration of cinacalcet to 2 patients with TIO markedly reduced PTH (from 20 to <10 pg/mL in one patient and 24 to <10 pg/mL the other), substantially increased serum phosphate (from 2.8 to 3.7 mg/dL and from 2.8 to 3.4 mg/dL, respectively) and permitted a lowering of the dose of phosphate administered to one better tolerated by the patients [74]. Thus these admittedly preliminary studies suggest a possible role for calcimimetics as an adjunct to supplementation with phosphate and $1,25(OH)_2D_3$ in patients with XLH or TIO. By mitigating secondary hyperparathyroidism they could favorably impact renal phosphate handling, thereby increasing serum calcium × phosphate product and promoting better mineralization of bone.

5.9.4. Calciphylaxis

Calciphylaxis (sometimes called calcific uremic ateriolopathy) is a rare but potentially life-threatening condition encountered predominantly in patients with chronic renal insufficiency, particularly those with end stage renal disease receiving dialysis treatment [75]. The condition has also been reported in patients with normal renal function, e.g., in primary hyperparathyroidism, but this is rare. Patients present with cutaneous necrosis of variable extent that is painful and can progress and become life-threatening. There is thrombosis of the small cutaneous blood vessels in association with calcification of the media of the vessel wall, which causes the necrosis of the skin [75]. One of the strongest predictors of the development of calciphylaxis is hyperphosphatemia, associated with the high calcium × phosphate product characteristic of patients with ESRD. While an elevated level of PTH per se is not thought to be a risk factor for calciphylaxis (e.g., the very low incidence of calciphylaxis in PHPT), some consider it a tissue sensitizer predisposing to development of the condition in the presence of other factors initiating the disease, i.e., in ESRD.

Given the uncertainty about the pathogenesis of calciphylaxis, it is not surprising that treatment is empiric and suboptimal. Indeed, the relative rarity of the condition renders prospective, controlled studies of various therapies difficult, if not impossible. In addition to local care of skin ulcers, measures directed at reducing serum phosphorus (and the calcium × phosphate product) using non-calcium-based phosphate binders is a cornerstone of therapy [75]. Bisphosphonates have facilitated healing of skin lesions in some studies, through an uncertain mechanism(s). Some studies have shown that parathyroidectomy prolongs life in patients with calciphylaxis [75]. This has provided a rationale for administering cinacalcet off-label as a pharmacological means of lowering the PTH. This use of cinacalcet has been reported in about a dozen articles, generally single case reports [76]. While uncontrolled, these studies have reported some efficacy of cinacalcet in this setting, although the administration of several other therapies concurrently renders it difficult to definitively ascribe the observed therapeutic benefit to the calcimimetic. Nevertheless, the apparent therapeutic benefit of cinacalcet in these cases provides a rationale for its use in additional patients.

6. Future prospects

In addition to the conditions for which cinacalcet is approved in the U.S. and Europe, the results reviewed here indicate that there are additional disorders for which the drug could be useful therapeutically. They have in common overactivity of the parathyroid glands or the desirability of lowering PTH in order to mitigate hypophosphatemia, i.e., in XLH and TIO. The next frontier of calcimimetic therapy will likely be their application to CaSR-expressing tissues other than the parathyroid glands. A few examples are as follows: (1) As noted earlier, the beneficial effects of calcimimetics on vascular calcification may be due, at least in part, to their direct actions on blood vessels [77]. (2) There are several possible targets of CaSR-based therapeutics in the kidney, where cinacalcet-mediated activation of the receptor could be used, for instance, to promote calcium excretion (e.g., in hypercalcemic patients). Recent data also indicate that the juxtaglomerular cells, which under normal conditions secrete renin in states of extravascular volume deficiency (to promote sodium conservation and vasoconstriction) express the CaSR. Furthermore, a calcimimetic inhibited renin secretion [78]. Thus a calcimimetic might be useful in hypertensive states characterized by an inappropriately elevated renin concentration. (3) The CaSR promotes engraftment of hematopoietic stem cells in the bone marrow [79]. A calcimimetic might be useful, therefore, in

stimulating such retention following bone marrow transplantation. (4) Calcimimetics markedly suppress fluid secretion by colonic crypts and, therefore, have the potential to be effective anti-diarrheal drugs [80]. (5) A recent study showed that a calcimimetic retarded late stage cyst growth in an animal model of autosomal dominant polycystic kidney disease (ADPKD), a condition in which progressive cyst enlargement eventually causes kidney failure, suggesting a potential use of the drug in human ADPKD [81]. All of these putative uses of calcimimetics for non-parathyroid disorders, however, will likely require the development of calcimimetics with some specificity for the tissue of interest to avoid alterations the function of the parathyroid or other CaSR-expressing tissues. This may be a challenging undertaking, but success would provide novel means of modulating in therapeutically desirable ways the functions of the wide variety of tissues expressing the CaSR.

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