Calcium-sensing receptor, calcimimetics, and cardiovascular calcifications in chronic kidney disease

Pablo A. Ureña Torres[1] and Marc De Broe[2]

[1]Nephrology Dialysis, Clinique du Landy, Saint Ouen, France and [2]Department of Medicine, University of Antwerp, Antwerp, Belgium

Renal function impairment goes along with a disturbed calcium, phosphate, and vitamin D metabolism, resulting in secondary hyperparathyroidism (sHPT). These mineral metabolism disturbances are associated with soft tissue calcifications, particularly arteries, cardiac valves, and myocardium, ultimately associated with increased risk of mortality in patients with chronic kidney disease (CKD). sHPT may lead to cardiovascular calcifications by other mechanisms including an impaired effect of parathyroid hormone (PTH), and a decreased calcium-sensing receptor (CaR) expression on cardiovascular structures. PTH may play a direct role on vascular calcifications through activation of a receptor, the type-1 PTH/PTHrP receptor, normally attributed to PTH-related peptide (PTHrP). The CaR in vascular cells may also play a role on vascular mineralization as suggested by its extremely reduced expression in atherosclerotic calcified human arteries. Calcimimetic compounds increasing the CaR sensitivity to extracellular calcium efficiently reduce serum PTH, calcium, and phosphate in dialysis patients with sHPT. They upregulate the CaR in vascular cells and attenuate vascular mineralization in uremic states. In this article, the pathophysiological mechanisms associated with cardiovascular calcifications in case of sHPT, the impact of medical and surgical correction of sHPT, the biology of the CaR in vascular structures and its function in CKD state, and finally the role played by the CaR and its modulation by the calcimimetics on uremic-related cardiovascular calcifications are reviewed.

Kidney International (2012) **82,** 19–25; doi:10.1038/ki.2012.69; published online 21 March 2012

KEYWORDS: calcimimetics; calcium receptor; hyperparathyroidism; parathyroid hormone; renal osteodystrophy; vascular calcification

Correspondence: *Pablo A. Ureña Torres, Service de Néphrologie et Dialyse, Clinique du Landy, 23 Rue du Landy, 93400 Saint Ouen, France. E-mail: urena.pablo@wanadoo.fr*

Received 9 October 2011; revised 10 December 2011; accepted 13 December 2011; published online 21 March 2012

More than a century after its identification, secondary hyperparathyroidism (sHPT) is still observed in the majority of patients with chronic kidney disease (CKD) stages 4–5, and in more than one-third of patients treated by dialysis. Renal function impairment goes along with a disturbed calcium, phosphate, and vitamin D metabolism, resulting in sHPT. These mineral metabolism disturbances are associated with soft tissue calcifications, particularly arteries, cardiac valves, and the myocardium, which are ultimately associated with increased risk of morbidity and mortality.[1] Compared with age-matched subjects, CKD patients particularly present more atherosclerotic plaques and a more rapid calcification of these plaques and of the vascular media layer.[2] Besides mineral alterations, sHPT may also lead to cardiovascular calcifications by other less known mechanisms, including an impaired action of parathyroid hormone (PTH) and a decreased expression of the calcium-sensing receptor (CaR) on cardiovascular structures. The conventional therapy of sHPT, generally used until the past 5–10 years, consisting of calcium salts and supra-physiological doses of vitamin D analogs, increases serum calcium and phosphate concentrations and the risk of cardiovascular mineralization. Similarly, radical treatment of sHPT, by subtotal or total surgical parathyroidectomy (PTX), results in a permanent and irreversible state of hypoparathyroidism, low bone remodeling, and exposition to a high risk of hyperphosphatemia, hypercalcemia, and cardiovascular calcifications.[3] Thus, innovative therapies of sHPT such as calcium-free intestinal phosphate binders, lesser hypercalcemic vitamin D derivatives, and calcimimetics might control parathyroid gland hyperfunction, without significantly disturbing calcium phosphate metabolism, while preventing cardiovascular calcifications.

In this article, we review the pathophysiological mechanisms associated with cardiovascular calcifications in case of sHPT, the impact of medical and surgical correction of sHPT on the progression of cardiovascular calcifications, the biology of the CaR in vascular structures, and its function in CKD state, and finally the role played by the CaR and its modulation by the calcimimetics on uremic-related cardiovascular calcifications.

EPIDEMIOLOGY AND CONSEQUENCES OF CARDIOVASCULAR CALCIFICATIONS

Vascular and cardiac valve calcifications are more prevalent and severe in CKD patients compared with healthy subjects of the general population.[4,5] Indeed, autopsy and clinical studies have found an increased intima layer thickness and areas of mineralization in coronary, renal, aorta, radial, and epigastric arteries in >90% of CKD patients compared with only 30% in age-matched control subjects. Similarly, media layer thickness and calcifications are also more frequently found in CKD patients than in control subjects, roughly 60% vs. 20%, respectively.[2,6–9] Vascular calcifications also consistently share the same five classical risk factors associated with the presence and extent of these calcifications in the general population, including advanced age, diabetes, hyperlipidemia, inflammation, and tobacco use. In addition, dialysis treatment itself exponentially accelerates the process of vascular mineralization.[2,8,10–12]

Once cardiovascular calcifications are installed, their consequences can be overwhelming as suggested by their association with an increased risk of fatal outcomes in CKD patients, more than 50% of whom die from cardiovascular complications including myocardial infarction, heart failure, and sudden death.[13] The consequences differ depending on the type of calcification, arterial intima or media, and in the heart, valvular or myocardial. Arterial intima calcification is mostly secondary to calcification of atherosclerotic plaques, which may increase the risk of arterial thrombosis, plaque instability, and myocardial infarction. Arterial media calcification leads to vessel stiffness, loss of vascular compliance, increased wave pulse velocity, left ventricular hypertrophy, diastolic dysfunction, coronary hypoperfusion, and finally heart failure.[14] It is also responsible for the rather exceptionally observed calcifying uremic arteriopathy, which often leads to necrotizing lesions of distal extremities and an extremely high mortality rate. In the heart, myocardial calcification is a rare cause of severe heart failure. Calcification of cardiac valves is an important cause of both native and prosthetic and mitral and aortic valve dysfunction. CKD patients with cardiac valvular calcifications may also die, as do non-uremic patients, from myocardial infarction, heat failure, and sudden death.[15]

CALCIUM-SENSING RECEPTOR

The CaR is a 121-kDa protein with three main structural domains characteristic of G-protein-coupled receptors. It has a long extracellular N-terminal domain essential for the interaction with its principal agonist ionized calcium, seven hydrophobic membrane-spanning helices, which anchor it in the plasma membrane, and an intracellular C terminus, which has multiple regulatory protein kinase phosphorylation sites.[16] The CaR is a low-affinity receptor, as millimolar concentrations of the agonists (3 mmol/l for calcium) are needed for its activation. It is also of limited selectivity as it can be activated by numerous divalent or trivalent cations in addition to calcium, and in order of potency, such as $La^3 > Gd^3 > Be^2 > Ca^2 > Ba^2 > Sr^2 > Mg^2$, and by other polycationic compounds such as neomycin, spermine, and numerous amino acids. It should be reminded that in clinical practice many of these cations would never reach the necessary plasma concentration to exert a calcimimetic effect except Gd^3 and Mg^2. The activation of the CaR by any one of the agonists leads to the stimulation of Gi protein, phospholipase C, inositide triphosphate cascade, the mobilization of intracellular calcium, and the activation of PKC. Its activation also inhibits the adenylcyclase signaling pathway and PKA.

The CaR is expressed in organs principally regulating systemic calcium homeostasis, including kidney, intestine, bone, thyroid, and the parathyroid glands. However, it is also expressed in a variety of organs usually not thought to be involved in calcium metabolism, such as brain, skin, breast, testes, placenta, heart, and vessels. The consequence of the activation of the CaR and the cascade of intracellular signal pathways in parathyroid cells is the inhibition of PTH secretion, whereas in the thyroid C cells it increases calcitonin secretion, both effects leading to a reduction in serum calcium concentration. Its activation in the other three organs may also contribute to a further decrease in serum calcium; hence, in the kidney it increases urinary calcium excretion, in bone it decreases bone turnover, and in the intestine it decreases intestinal absorption of calcium. The same CaR is also present in the cardiovascular structures including aortic endothelial and smooth muscle cells where it may exert multiple and not yet fully elucidated physiological functions.[17,18]

COMPOUNDS MODULATING THE CALCIUM-SENSING RECEPTOR

The molecular characterization of the CaR also led to the discovery of several compounds capable of modulating its function.[19] The first ones have been called 'type I calcimimetics' because they mimic the effects of extracellular calcium ($_eCa^{2+}$). The second ones are called 'type II calcimimetics' because they change the structural conformation of the CaR and stereoselectively increase its sensitivity to $_eCa^{2+}$. Thus, when tested in *in vitro* studies, type II calcimimetics appear to lose their effects in the absence of $_eCa^{2+}$; they do not really mimic the effect of $_eCa^{2+}$. The third ones have been called 'calcilytics' because they inhibit CaR function and stimulate PTH secretion. The mode of action of calcimimetics and calcilytics resides on their binding to distinct but overlapping regions of the extracellular loops of the transmembrane domain. Besides changing the structural conformation, calcimimetics can also enhance CaR function by increasing its expression; inversely, the calcilytics decrease parathyroid CaR expression. Several calcimimetics have already been made. The first-generation compounds, including NPS R-567, NPS S-567, NPS R-568, and NPS S-568, were retired from clinical development because of a low bioavailability (<1%). The second generation includes AMG-073 and Calindol. These compounds decrease the secretion of PTH in a dose-dependent