Chapter 4

Extracellular Ca\(^{2+}\)-Sensing Receptor and Kidney Function

\(^1\)Daniela Riccardi, Ph.D., \(^2\)Steven C. Hebert, M.D.

\(^1\)School of Biological Sciences, University of Manchester, U.K; \(^2\)Yale University School of Medicine New Haven, CT, U.S.A.

INTRODUCTION

Changes in extracellular calcium concentration (Ca\(^{2+}\)) dramatically affect many aspects of kidney function under both basal and hormone-stimulated conditions. Normally about 60% of the plasma calcium (100% of the ionized calcium) is filtered through the glomerular capillaries and is reabsorbed virtually along the entire nephron, with the exception of the thin descending and ascending limbs of Henle’s loop (1,2). Sixty-five percent of the Ca\(^{2+}\) filtered at the glomerulus is usually reabsorbed in the proximal tubule (PT) with the remaining Ca\(^{2+}\) reabsorbed by the thick ascending limb of Henle’s loop (TAL) and more distal nephron segments (see figure 1A). Sodium and calcium transport by the kidney generally occur in parallel such that there is a codependence of calcium and sodium transport (3).

The molecular identification of the renal extracellular calcium-sensing receptor, CaR (4-9), has provided confirmation for a direct role of Ca\(^{2+}\) on kidney function (i.e., independent of calciotropic hormones) as a modulator of body calcium homeostasis. The bovine parathyroid and rat kidney CaRs are 1081 and 1079 amino acids long, respectively (4,5), and belong to the type III (or C) family of G-protein coupled receptors, which include the metabotropic glutamate receptors and vomeronasal organ (putative pheromone) receptors. The low affinity of the receptor for Ca\(^{2+}\) (i.e. millimolar range), as well as its positive cooperativity and its large ion-sensing apparatus indicate that the receptor is more sensitive to changes in net charge than to the specific ligand. Mg\(^{2+}\), trivalent cations of the lanthanide series, and polycations such as aminoglycoside antibiotics can all activate the
receptor *in vitro* with EC\(_{50}\) values ranging from the µM range (tri-, polyvalent cations) to millimolar concentrations (Mg\(^{2+}\)). In addition to true CaR agonists, CaR sensitivity to Ca\(^{2+}\) can be significantly shifted by allosteric modulating factors including polyamines such as spermine and spermidine (10), ionic strength (11) and L-amino acids (12). L-amino acids can stereoselectively activate the CaR, aromatic and small aliphatic amino acids being more effective than positively charged and branched chain amino acids (12).

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**Figure 1.** A) Sites of calcium transport by the kidney. B) Direct effects of calcium on kidney function

Pharmacological agents known as calcimimetic compounds (e.g., NPS R-467 and -568); (13), which are small phenylalkylamine derivatives, are also allosteric modifiers of the CaR and increase the sensitivity of the CaR to activation by Ca\(^{2+}\). One of these, NPS R-568, has been shown to mitigate renal osteodystrophy due to secondary hyperparathyroidism in rats with chronic renal failure (14).