INTRODUCTION

The extracellular calcium (Ca\textsuperscript{2+}_o)-sensing receptor (CaR), originally cloned from bovine parathyroid, is a G protein-coupled receptor (GPCR) (1). The CaR is expressed on the plasma membrane of a variety of cell types, including those involved in maintaining systemic calcium homeostasis, such as parathyroid chief cells, renal cells, as well as thyroid C-cells, and those not participating in systemic calcium homeostasis, such as brain and breast cells (2). The CaR is well conserved across species (3-8). For instance, the amino acid sequences of CaRs from human, rat, and rabbit are more than 90% identical to that of the bovine CaR.

As illustrated in Figure 1, the human homologue of the CaR consists of 1,078 amino acid residues. It has three major structural domains (4): a large, extracellular amino (N)-terminal domain (ECD) of 612 amino acid residues containing an initial hydrophobic, 20-amino-acid segment characteristic of eukaryotic signal sequences and 11 potential N-linked glycosylation sites; a central core of 250 amino acid residues containing a 7-transmembrane domain (TMD); and a hydrophilic, 216-amino-acid-containing carboxy (C)-terminus (C-tail) predicted to be cytoplasmic (4). Protein sequence analysis of the isolated ECD of the receptor has revealed that the putative signal peptide at the N-terminus of the CaR has been cleaved (9). Thus, the first residue encountered is the tyrosine predicted at amino acid position 20 of the human CaR cDNA. Sequence analysis predicts that the receptor will have five phosphorylation sites for protein kinase C (PKC) and two sites for protein kinase A (PKA) within its intracellular loops and C-tail.
The CaR belongs to a unique subfamily of GPCRs called family C, which includes five groups of receptors: the metabotropic glutamate receptors, mGluRs 1-8 (10-12); the metabotropic GABA\(_B\) receptors (13-16); the CaR; a subgroup of putative pheromone receptors (17-20); and the taste receptors (21). All of these receptors possess unusually large (500- to 600-residue) ECDs consisting of a bi-

**Figure 1: Schematic representation of the principal structural features of the predicted human CaR protein.** The large N-terminal domain is located extracellularly, and the C-terminal domain is located intracellularly. Symbols are provided in the key. SP, predicted signal peptide; HS, hydrophobic segment. Amino acid residues that are conserved in all mGluRs and the CaR are shown as filled circles and triangles. Modified from Bai, et al. (36) with permission from the Journal of Biological Chemistry.