Class 3 GPCRs as broad-spectrum L-amino acid sensors

A.D. Conigrave, School of Molecular and Microbial Biosciences, University of Sydney, NSW 2006, Australia.

Class 3 G-protein-coupled receptors (GPCRs) are typified by a large extracellular domain that includes a nutrient sensing Venus Fly Trap domain (VFT) and a Cys-rich domain that couples nutrient binding in the VFT to the activation of G-proteins on the internal face of the 7-transmembrane domain motif. Class 3 GPCRs include receptors that are selective for the amino acid L-glutamate (mGlus) and the glutamate metabolite, γ-amino-butyrate; the so-called GABA(B) receptors. Recent work demonstrates that one subgroup of the class 3 receptors that includes the extracellular Ca^{2+}-sensing receptor (CaR), the T1R1/T1R3 taste receptor and the recently cloned ortholog of the fish 5.24 receptor, GPRC6A, are all broad-spectrum L-amino acid-sensing receptors that are coupled to phosphoinositide turnover, intracellular Ca^{2+} mobilization and, perhaps, other intracellular signalling pathways. CaR homodimers are selective for aromatic and aliphatic L-amino acids, GPRC6A homodimers are selective for basic and aliphatic L-amino acids and T1R1/T1R3 heterodimers are selective for aliphatic and polar L-amino acids. Although the amino acid residues required for ligating the α-amino and α-carboxylate functional groups are tightly conserved in many class 3 GPCRs, the side chain binding cleft of the broad-spectrum amino acid sensing receptors is predicted to be substantially larger and recent work suggests that short peptides may be developed as selective receptor activators. The physiological significance of amino acid sensing is known to include the regulation of growth promoting and metabolism-regulating signalling pathways and in appetite control. Expression of the CaR in endocrine tissue, the gut, kidney and hypothalamus of the brain, provides potential molecular explanations for various aspects of L-amino acid sensing.