

Calcium-sensing

Overview: The calcium-sensing receptor (CaS, provisional nomenclature) responds to extracellular calcium and magnesium in the millimolar range and to gadolinium and some polycations in the micromolar range (Brown *et al.*, 1993). The sensitivity of CaS to primary agonists can be increased by aromatic L-amino acids (Conigrave *et al.*, 2000) and also by elevated extracellular pH (Quinn *et al.*, 2004) or decreased extracellular ionic strength (Quinn *et al.*, 1998).

Nomenclature	CaS
Other names	CaSR, CaR
Ensembl ID	ENSG00000036828
Principal transduction	G _{q/11} , G _{i/o} , G _{12/13} (Ward, 2004)
Cation rank order of potency	Gd ³⁺ > Ca ²⁺ > Mg ²⁺ (Brown <i>et al.</i> , 1993)
Polyamine rank order of potency	Spermine > spermidine > putrescine (Quinn <i>et al.</i> , 1997)
Amino-acid rank order of potency	L-Phe, L-Trp, L-His > L-Ala > L-Ser, L-Pro, L-Glu > L-Asp but not L-Lys, L-Arg, L-Leu and L-Ile (Conigrave <i>et al.</i> , 2000)
Positive allosteric modulators	NPS R568 (Nemeth <i>et al.</i> , 1998), calindol (Petrel <i>et al.</i> , 2004), cinacalcet (Nemeth <i>et al.</i> , 2004)
Negative allosteric modulators	NPS 2143, NPS 89636 (Nemeth <i>et al.</i> , 2001), Calhex-231 (Petrel <i>et al.</i> , 2004), 2-benzylpyrrolidine derivatives of NPS 2143 (Yang <i>et al.</i> , 2005)

Positive allosteric modulators are termed type II calcimimetics and can suppress parathyroid hormone (PTH) secretion (Nemeth *et al.*, 1998). Negative allosteric modulators are called calcilytics and can act to increase PTH secretion (Nemeth *et al.*, 2001).

The central role of CaR in the maintenance of extracellular calcium homeostasis is seen most clearly in patients with loss-of-function CaR mutations who develop familial hypocalciuric hypercalcaemia (heterozygous mutation) or neonatal severe hyperparathyroidism (homozygous mutation) and in CaR null mice (Ho *et al.*, 1995), which exhibit similar increases in PTH secretion and blood Ca²⁺ levels. A gain-of-function mutation in the CaR gene is associated with autosomal dominant hypocalcaemia.

Abbreviations: **Calhex-231**, (1S,2S,1'R)-N¹-(4-chlorobenzoyl)-N²-[1-(1-naphthyl)ethyl]-1,2-diaminocyclohexane; **calindol**, (R)-2-[1-(1-naphthyl) ethylaminomethyl]-1H-indole; **NPS R568**, (R)-N-(3-methoxy- α -phenylethyl)-3-(2-chlorophenyl)-1-propylamine hydrochloride; **NPS 2143**, N-[(R)-2-hydroxy-3-(2-cyano-3-chlorophenoxy)propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine

Further Reading

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