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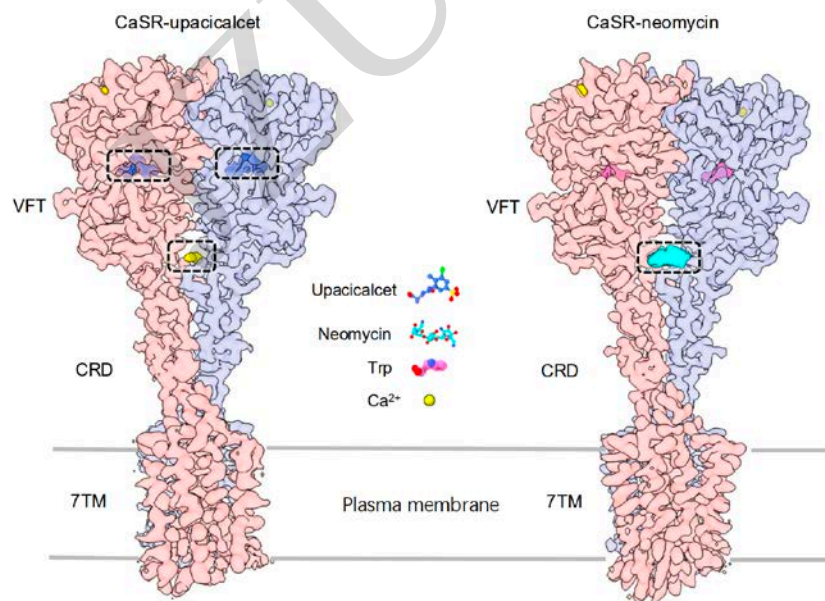
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Structural basis of calcium-sensing receptor activation by extracellular modulators

Key words: Calcium-sensing receptor (CaSR); Upacicalcet;
Neomycin; Cryo-electron microscopy (Cryo-EM)

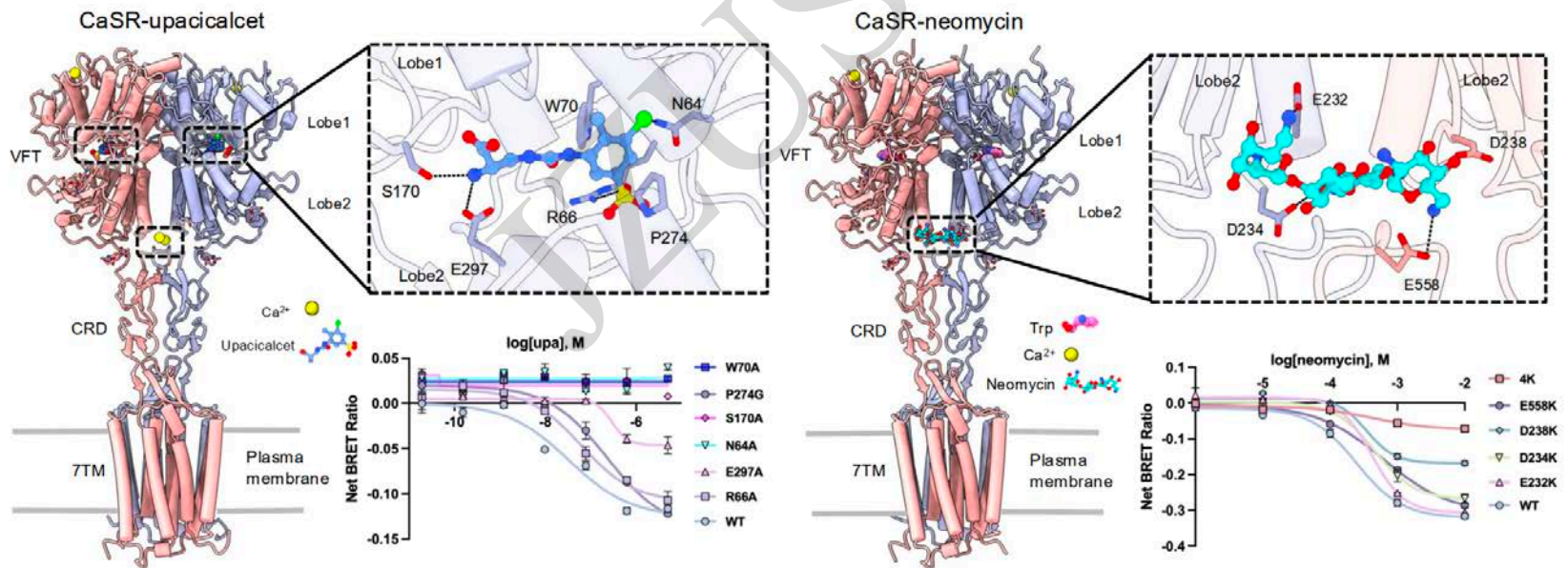
Research Summary

- Calcium-sensing receptor (CaSR) is a key drug target for the treatment of secondary hyperparathyroidism associated with chronic kidney disease and is clinically targeted by calcimimetics;
- We determined cryo-EM structures of the active-state Upacalcet-CaSR and Neomycin-CaSR complexes at 2.45 Å and 2.32 Å resolution respectively;
- Binding modes were validated with site-directed mutagenesis coupled with G protein signaling assays;
- Upacalcet binds at the extracellular Venus flytrap domain (VFT) amino-acid pocket and stabilizes an active closed VFT conformation;
- Neomycin occupies a Ca^{2+} binding site at the interface between the extracellular VFT and cysteine-rich domain (CRD), thus stabilizing the active-state conformation.
- The study defines multi-site extracellular allostery and provides insights into the design of next-generation CaSR modulators.



Innovation Points

- We utilized single-particle cryo-EM to determine structures of active-state CaSR bound to Upacicalcet or Neomycin at 2.45 Å and 2.32 Å resolution respectively.
- High-resolution structures coupled with functional assays reveal that Upacicalcet stabilizes a closed VFT by binding at the amino-acid pocket, whereas Neomycin occupies a Ca^{2+} pocket at the VFT–CRD interface.



Innovation Points

- CaSR harbors multiple allosteric modulation sites targeted by distinct modulators.
- The binding modes of Upacicalcet and Neomycin revealed by this study provide a structural foundation for the rational design of future CaSR-targeting therapeutics

