2-JAL JPS-ASCEPT Lecture

The structural basis of peptide GPCR activation and signalling

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G protein-coupled receptors (GPCRs) are the largest family of cell surface drug targets. Consequently, there is high interest in understanding the structure of members of this receptor superfamily and molecular detail of how ligands and transducer proteins interact with them. Our laboratory has been applying single particle cryo-EM to determination of active GPCR structures, using minimally modified receptors. Our work has been principally focused on the class B GPCR subfamily that bind large peptide hormones and are well established clinical targets for the treatment of major disease, including migraine, irritable bowel syndrome, diabetes, obesity and neurodegeneration. We have now solved structures of multiple different receptors, providing wide structural coverage of the major subfamilies of class B GPCRs. Included within this are structures of the same receptor bound to native peptide agonists, biased peptide agonists and non-peptide agonists and receptors in complex with accessory proteins that allosterically modulate receptor function. In combination with molecular pharmacology and molecular dynamics simulations, we are gaining substantial insights into diverse modes of ligand binding, receptor activation and modulation that lead to G protein coupling and downstream signalling.