Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad - 500107

Seminar

Peptide Ligand G Protein-Coupled Receptors are Dynamic Molecules in the Lipid Membrane

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G protein-coupled receptors (GPCRs) constitute a large group of membrane proteins, known to undergo a set of well-defined structural transitions upon activation and signaling. In our work, we address the molecular dynamics of peptide ligand GPCRs using solution and solid-state NMR. We work with human class A GPCRs that are activated by peptide hormones, such as neuropeptide Y (NPY) or ghrelin. The GPCRs are expressed in prokaryotic systems or by cell-free synthesis. In the talk, results on three research topics will be discussed. (i) Studies on the equilibrium dynamics of GPCRs using static ^{15}N CP NMR, ^{15}N NMR spectra acquired as a function of the CP contact time, and ^{13}C MAS NMR experiments confirm the high molecular dynamics of three peptide ligand GPCRs. Quantitative determination of ^{1}H-^{13}C order parameters through measurement of the ^{1}H-^{13}C dipolar couplings in separated local field NMR experiments revealed axially symmetric motions of the GPCRs and molecular fluctuations of large amplitude. (ii) Data will be reported that led to the development of structural models of NPY bound to the Y_1 and the Y_2 receptors. Isotope-labeled NPY was used to determine the secondary structure of the receptor bound ligand. Upon receptor binding, the C-terminal α helix of NPY, formed in membrane environment in the absence of receptor, is unwound starting at Thr^{32} to make optimal contact of the C terminal residues within the binding pocket. The NMR signals of several hydrophobic residues in the α-helical region of NPY were broadened upon receptor binding. The ligands are tethered to the second extracellular loop by hydrophobic contacts, with the N-terminal part of its helix facing the solvent. The C terminal pentapeptide of NPY inserts deeply into the transmembrane bundle, making optimal contacts to the Y_2 receptor including a contact NPY's amidated C terminus with $Gln^{3.32}$ in a polar cluster within helices 2 and 3 of the receptor. (iii) We will report data on the dynamics and ligand binding of the human GHS receptor, which plays a key role in the development of obesity.

Thursday, Apr 12th 2018

4:00 PM (Tea/Coffee at 03:30 PM)

Auditorium, TIFR-H