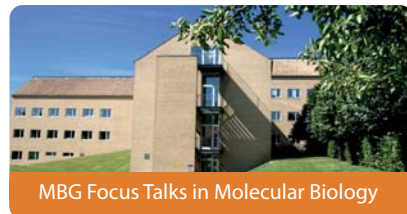


MBG FOCUS TALK

hosted by Section for Structural Biology



Tuesday 16th July 2018 from 10:15-11:00

MBG conference room (3130-303), Gustav Wieds Vej 10C, 8000 Aarhus C

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Structural insights into G protein activation

The crystal structure of beta2 adrenergic receptor ($\beta 2AR$) – Gs complex provided the first high-resolution snapshot of how agonist bound GPCR activates a heterotrimeric G protein. In this nucleotide-free complex (R^*-G^{empty}), the C-terminal α -5 helix of Gs undergoes a large structural change to penetrate the core of the $\beta 2AR$, into a space created by the outward movement of TM6. Recent single molecule experiments provide evidence for the existence of a transient complex between the $\beta 2AR$ and GDP bound Gs protein (R^*-G^{GDP}) that involves a smaller outward movement of TM6 and may represent an intermediate on the way to the formation of R^*-G^{empty} . R^*-G^{GDP} is not amenable to characterization by crystallography, as it appears to be a transient intermediate complex that is less stable than R^*-G^{empty} . However, we have been able to crystallize the $\beta 2AR$ fused to the carboxyl terminal 14 amino acids from Gs $\alpha 5$ helix (GsCT). Unexpectedly, we obtained a structure of GsCT interacting with active $\beta 2AR$ in a different mode compare to $\beta 2AR$ -Gs complex. The binding mode involves interactions between conserved E392 and R389 of Gs and the D and R of the conserved DRY sequence of the $\beta 2AR$. Of interest, in GDP-bound Gs, E392 and R389 are solvent exposed and accessible to the cytoplasmic surface of the $\beta 2AR$. Moreover, mutations of E392 and R389 alter interactions with Gs. These observations suggest that the structure presented here may represent an intermediate state in the formation of R^*-G^{empty} .

Host: Professor Poul Nissen