Targeted Project / AY 2023 -2024

Understanding the molecular basis of partial agonism and G protein selectivity in GPCRs

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Research area: Membrane protein biology

Project outline:

G protein-coupled receptors (GPCRs) are membrane-embedded signaling proteins that, when activated by agonists change their conformation, enabling transducers such as heterotrimeric G proteins or arrestins to bind. Structural and biophysical data have provided extensive insight into how agonists affect the function of GPCRs. However, how conformational changes in the receptor affect coupling and activation of intracellular transducers remains poorly understood. Major questions remain such as why certain agonists produce a less than full response (known as partial agonism), and why a given receptor binds selectively to one particular subtype of the G protein family over another (signal bias). Currently, we are reliant on information from static structures of immobilised proteins but to answer these questions we need additional insight on GPCR-G protein complexes that reveals their true dynamic nature.

The proposed project will investigate these aspects using NMR, to provide a much-needed dynamic explanation of how GPCRs and G proteins interact. A range of agonists and complexes with different G proteins will be investigated to establish how conformational variability arises. The molecular observations will then be related to various biophysical properties, such as binding affinity, kinetics of exchange and nucleotide exchange rates etc. that link to signaling function. Using the solution NMR data 3D model structures of b1AR-G protein complexes will be built. Overall, this work will provide a dynamic perspective of GPCR-G protein complexes and reveal key molecular features of partial agonism and G protein selectivity.

BBSRC DTP main strategic theme: Understanding the rules of life

BBSRC DTP secondary strategic theme: Bioscience for an integrated understanding of health