GPCR Activation: What moves where?

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Introduction

G Protein-Coupled Receptors(GPCRs) are the single most important target in the pharmaceutical industry. They are crucial for vision, smell, taste, hearing and many mental processes related to addiction, depression, love and hate.

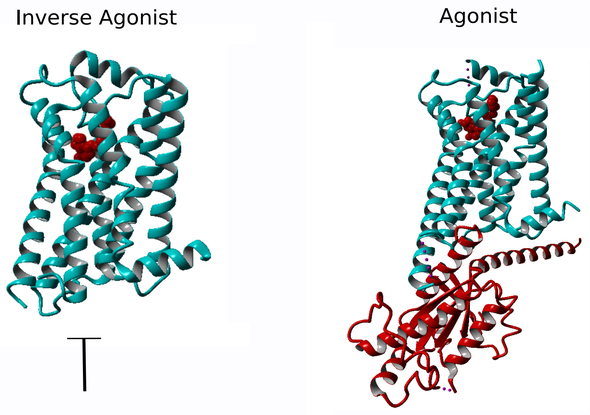


Figure 1 When they bind a ligand at the extracellular side of the membrane, residues and even whole helices move over large distances ultimately leading to binding and activation of a G protein.

Many GPCR structures recently became available, but unfortunately all of them contain artefacts that were needed to obtain good crystals. We filter out these artefacts by studying the mobility in distance space.

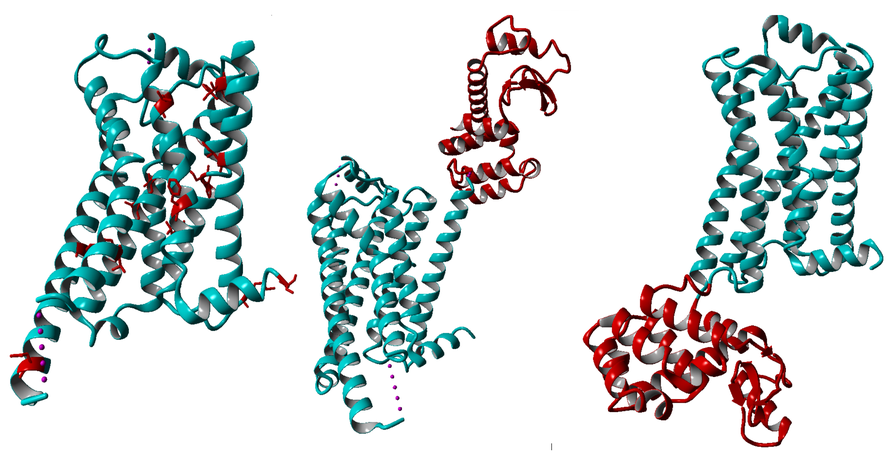


Figure 2 Mutations and T4 Lysozyme fusion to induce crystallization.

Methods

Many hypotheses for the function-mobility relation have been put forward. The 42 GPCR structures were captured in 12.561 vectors that each represent one inter Cα distance, and the Random Forest method (2) was used to correlate hypotheses with distances.

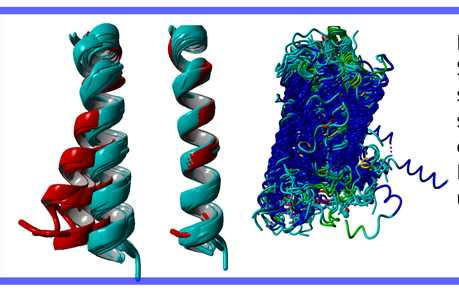
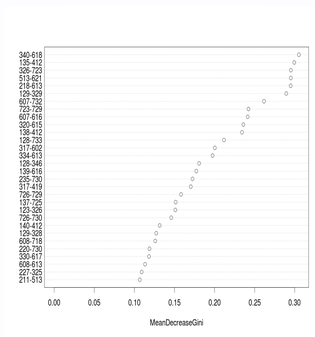


Figure 3 Superposition is relative.
Superposition of TM6. Left: extracted from superposing complete structures. Middle: the same helices superposed outside of the structural context.
Right: all 42 GPCR structures superposed provide unsurmountable visualization problems...



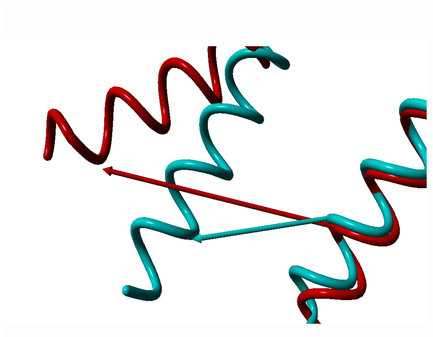


Figure 3 Variable importance score to visualize (3) significant differences between structures.

Results

We found several trends comparing the structures: transmembrane helices(TMs) 5, 6 and 7 move towards each other upon agonist binding en away from each other upon inverse agonist binding. This also correlated with an upward movement of TM3.

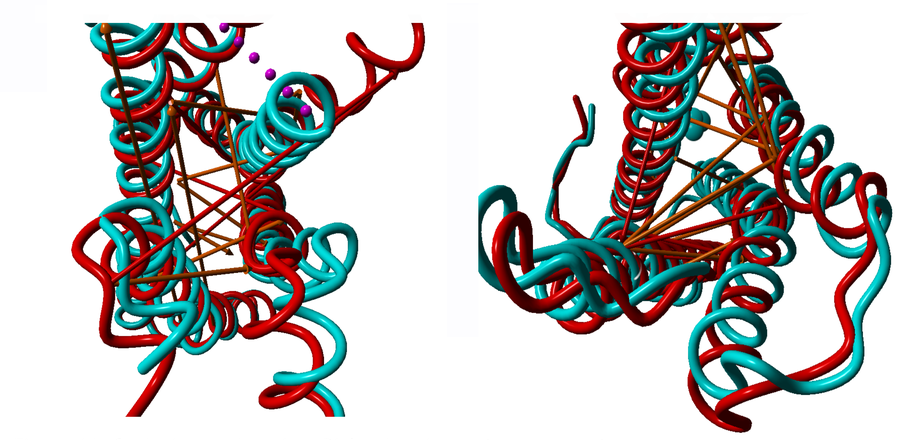


Figure 4 Left: Active vs. Inactive. Right: Agonist vs. Inverse agonist.

Fusion of GPCRs with T4 Lysozyme appeared to have no consistent influence on the TM bundle apart from a few disturbances of the intracellular loops. The structure stabilizing antibodies, on the other hand, lead to significant disturbances.

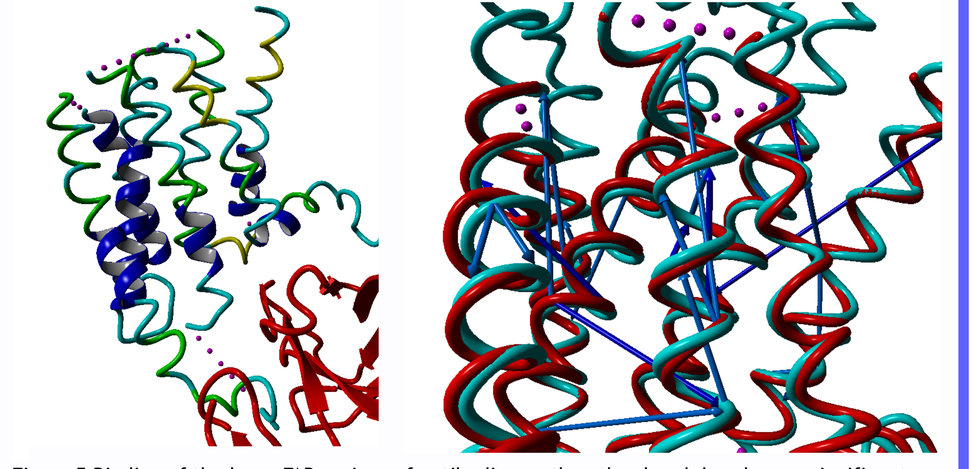
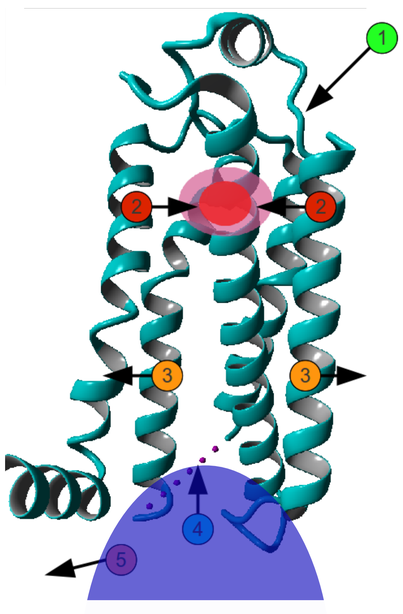


Figure 5 Binding of the large FAB regions of antibodies on the other hand does have a significant (artificial) influence on helical packing.

Conclusions

The RF method detects important distances and is resistant to noise: Agonist binding (1) induces inward motions (2) of the extracellular side of TM5-7 resembling a clothespin like motion. This is followed by an outward movement of the cytosolic side of TM5-7 (3), allowing the G protein to bind (4) and become activated (5). Large antibodies induce changes that ruin helical packing.



Future

Please talk to me if you want me as a PhD student in your lab soon. robvanderkant@hotmail.com

References

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3) Krieger E, Vriend G (Feb 2002). "Models@Home: distributed computing in bioinformatics using a screensaver based approach". Bioinformatics 18 (2): 315–8.

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