GPCR structures in drug design: a case study on the residence time of antimuscarinic drugs

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G-protein coupled receptors (GPCRs) are the largest superfamily of receptors and thus one of the most prominent classes of targets for drug discovery. In this talk basic current knowledge about GPCR biology, GPCR signalling and GPCR structure will be presented. In addition to this the use of GPCR structures and homology models will be discussed in the context of drug design. As specific example for the use of GPCR structures to gain deeper understanding of drug-receptor interactions, the interaction of the marketed drug tiotropium with the muscarinic receptor M3 is investigated. Antagonizing the human M3 muscarinic receptor (hM3R) over a long time is a key feature of modern bronchodilating COPD drugs aiming at symptom relief. The long duration of action of the antimuscarinic drug tiotropium and its kinetic subtype selectivity over hM2R are investigated by kinetic mapping of the binding site and the exit channel of hM3R. Hence, dissociation experiments have been performed with a set of molecular matched pairs of tiotropium on a large variety of mutated variants of hM3R. The exceedingly long half-life of tiotropium (of more than 24 h) is attributed to interactions in the binding site; particularly a highly directed interaction of the ligands' hydroxy group with an asparagine (N508) prevents rapid dissociation via a snap-lock mechanism. The kinetic selectivity over hM2R, however, is caused by differences in the electrostatics and in the flexibility of the extracellular vestibule. All these insights are gained from extensive molecular dynamics (MD) simulations (several microseconds) to support experimental results. Simulations are done for wild type hM3R, apo hM3R and for various mutated variants of hM3R and analyses are based on differences in spatial occupancy of the respective amino acids in different MD runs.