Structural basis of the clinical candidates at muscarinic acetylcholine receptors

Mahmuda Yeasmin[1,2], Liudi Zhang[1], Jesse Mobbs[1,2], and David M. Thal[1,2]

[1]Drug Discovery Biology and [2]CCeMMP, Monash Institute of Pharmaceutical Sciences, Parkville, VIC

E-mail: mahmuda.yeasmin@monash.edu

The muscarinic acetylcholine receptors (mAChRs) are a five membered (M1–M5) subfamily of G protein-coupled receptors (GPCRs) that are activated by the neurotransmitter acetylcholine (ACh). The M1, M4, and M5 mAChRs have emerged as attractive drug targets for the treatment of various central nervous system disorders, such as Alzheimer's disease (AD) at the M1 mAChR. However, designing M1 mAChR selective ligands is challenging due to high sequence similarity of the ACh binding site (orthosteric site) that is present across all mAChR subtypes [1]. The agonist Xanomeline is an orthosteric mAChR agonist with clinical efficacy and was classically described as a M_1/M_4 preferring ligand with the potential to treat schizophrenia and AD [2]. However, more recent studies have shown the Xanomeline can bind to all five mAChR subtypes, but preferentially activate the M4 mAChR [3]. Recently, our group determined a cryo-EM structure of Xanomeline bound to the M4 mAChR, which revealed a novel binding mode with Xanomeline simultaneously binding to both the orthosteric and allosteric sites of the receptor [4]. To better understand the mechanism of action of this clinically relevant drug, we aim to determine cryo-EM structure of Xanomeline bound to the other mAChR subtypes. To that end, we have determined a cryo-EM structure of Xanomeline bound to the human M1 mAChR in complex with a G protein mimetic. Comparison to the M4 mAChR reveals a similar orthosteric binding pose, and notably there was no evidence of xanomeline binding to the allosteric site of the M4 mAChR.
Further aims of this project include the determination of Xanomeline-bound structures at other mAChR subtypes and determining structures of the M1 mAChR bound to subtype selective positive allosteric modulators.

References

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