Project title: Drug discovery and design for the α_1-adrenoceptors

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Honours project available for ONE student

The α_{1A}- and α_{1B}-adrenoceptors (α_{1A}-AR and α_{1B}-AR) are closely related G protein-coupled receptors (GPCRs) that modulate the peripheral and central nervous systems in response to binding adrenaline and noradrenaline. While these receptors are known for their regulation of vascular tone and are targeted clinically to treat hypertension and BPH, the role of individual sub-types is unknown in the CNS and the periphery due to a lack of subtype-selective ligands. The α_{1A}-AR and α_{1B}-AR are putative drug targets for treating numerous diseases including depression, heart failure, epilepsy and Alzheimer's disease but their role as clinical targets for these diseases needs to be validated with subtype-selective tool ligands. Fragment screening is an approach for identifying and optimizing compounds for various protein targets but has been generally difficult to apply to GPCRs due to the instability of purified receptor preparations needed for biophysical screening methods. Our laboratory generated thermostabilized α_{1A}-AR and α_{1B}-AR variants suitable for biophysical studies, allowing the screening of a small, yet diverse fragment library with NMR spectroscopy and surface plasmon resonance. This screen identified two hits, the first of which exhibits a 10-fold selectivity for inhibiting α_{1B}-AR signalling and the second hit was a selective α_{1A}-AR agonist which also displayed a negative allosteric mode of action at the α_{1B}-AR. This project aims to understand the structural basis of binding and selectivity of these hits and understand the structure-activity relationships (SAR) of the hit molecules at each receptor. This will be probed using traditional molecular pharmacology techniques involving binding assays and measuring receptor activation using multiple signalling outputs on WT and mutant receptors. Computational ligand docking and ligand design will also be applied to guide SAR studies. The resultant information will be used to develop novel compounds to elucidate the individual physiological roles of α_{1A}-AR and α_{1B}-AR and their potential as targets for disease treatments. Students will be trained in: molecular cloning techniques, GPCR pharmacological assays including ligand binding and cell signalling assays, computational ligand docking and ligand design.