Chronic effects of G protein-biased mu-opioid receptor agonists in the brain

Supervisory team:
Main supervisor: Dr Chris Bailey (University of Bath)
Second supervisor: Prof Eamonn Kelly (University of Bristol)
Prof Steve Husbands (University of Bath), Prof Graeme Henderson (University of Bristol)

Host institution: University of Bath

Project description:
G-protein coupled receptors (GPCRs) are the largest family of targets for approved drugs, with ~35% of current drug treatments targeting GPCRs. However, very few of these are GPCR agonists - drugs that directly activate the receptor. A primary reason for this is that chronic treatment with GPCR agonists can lead to a progressive loss of drug response, known as tolerance. Drug tolerance hinders the development of novel GPCR agonists as future drug treatments, and limits the clinical effectiveness of current GPCR agonists.

The discovery of "biased agonists" at G protein-coupled receptors (GPCRs) has revolutionised the field. Conventional GPCR agonists activate the receptor to cause cellular effect, but then the receptor is desensitized. This desensitization is the predominant mechanism underlying drug tolerance. One advantage of biased agonists is that they can allow GPCRs to signal to cause the desired cellular effect, but the receptors then may evade the usual mechanisms leading to desensitization and tolerance.

Mu-opioid receptors (MOPrs) are one of the few types of GPCR where agonists are already used in the clinic (eg. morphine for pain relief), as well as being abused on the street (eg. heroin). Tolerance is a significant problem when these drugs are taken long-term. Novel biased agonists at MOPr have recently been discovered, with some entering clinical trials, but, the long term effects of these drugs are yet to be studied.

Although the field of biased GPCR agonists is relatively new, the supervisory team of researchers has many years of experience in studying bias, desensitization and tolerance, particularly at MOPrs. For the first time, we can now bring together in this application the necessary expertise, experimental approaches and a number of novel biased mu-opioid receptor agonists to study tolerance to biased MOPr agonists.

This project takes a co-ordinated transdisciplinary approach, using a combination of in vivo and ex vivo techniques: behaviour, brain slice electrophysiology, phosphoproteomics. By studying the effects of biased MOPr agonists at a cellular, receptor and whole-animal level we will uncover the mechanisms by which biased agonists induce desensitization and tolerance.

This study is of profound importance for the future of biased agonists as novel and effective drugs, as well as offering a truly translational neuroscience PhD project, using a range of different techniques.