Novel biased agonists at the mu opioid receptor - how do they work and what do they do?

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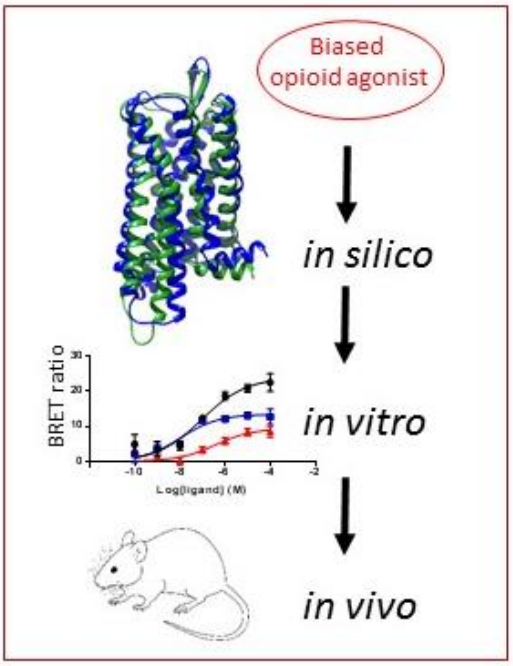
Project description:
A new generation of drugs that can activate G protein coupled receptors (GPCRs) has been discovered - these are called "biased agonists" and they stabilise different active conformations of the GPCR and so lead to different types of signalling. These drugs are exciting because it should be possible to design biased drugs that only trigger the GPCR signalling that leads to the beneficial effects of the drug whilst not activating the signalling that leads to the adverse and unwanted effects of the drug. In this project we will focus on the mu opioid receptor (MOPr), which is the target of opioid agonist drugs like morphine for the treatment of pain; such drugs are also heavily abused. In the past couple of years a series of novel G protein- or arrestin-biased MOPr agonists have become available and we are now in a position to test these ligands for mechanism and effectiveness. The question is whether biased agonists at MOPr are able to trigger signalling that leads to therapeutic effects (e.g. analgesia) but avoid signalling that leads to adverse effects (e.g. respiratory depression, tolerance). In this project you will seek to answer this in the following ways:

- in silico - investigate the structural mechanism of bias with advanced computing using Molecular Dynamics simulations of the MOPr with the novel biased agonists
- in vitro - confirm and extend studies on the bias of these ligands in cell signalling experiments, using Bioluminescence (BRET) technology to measure signalling via G protein and arrestin pathways in cultured cells
- in vivo - administer these drugs to mice acutely and chronically to determine their in vivo effects with relation to well characterised MOPr effects – analgesia and respiratory depression, and tolerance to these effects.

Using these advanced techniques, the project will answer the following questions:

- What conformational changes in the MOPr are triggered by biased agonists?
- Do biased agonists at MOPr actually function as biased agonsts in vivo, so fulfilling their promise as novel medicines of the future?

In summary this truly translational neuroscience project will allow the student to get to grips with a range of different techniques. Importantly it will equip the student with the means to undertake post-PhD research in a number of different subject areas.


Biased
opioid agonist
in silico
BRET ratio
30
20
10
0
-10
-8
-6
-4
-2
Log[ligand] (M)
in vitro
in vivo