

Investigating the molecular and synaptic mechanisms which underlie the sustained antidepressant effects of NMDA receptor antagonists

Supervisory team:

Main supervisor: Prof Emma Robinson (University of Bristol)

Second supervisor: Prof Jack Mellor (University of Bristol)

Non-academic (CASE) supervisor: Prof Bastian Hengeler (Boehringer Ingelheim)

Host institution: University of Bristol

CASE partner: Boehringer Ingelheim

Project description:

In the last few years there has been a surge in interest in rapid-acting antidepressants arising from the discovery that ketamine induces both rapid and sustained clinical benefits following a single treatment. This has also led to new investment not only to study the clinical effects of these drugs but also to better understand their fundamental biology. Through this work, new treatments with better tolerability and wider clinical applications may be developed. Although ketamine is known to act as an NMDA receptor antagonist, not all NMDA receptor antagonists which have been tested clinically exhibit this same rapid-acting antidepressant profile. A unique characteristic of ketamine is that the effects of a single treatment are sustained beyond the initial pharmacological effects of the drug suggesting induction of some longer-term adaptive change which benefits mood. In this project we have established a collaboration with Boehringer Ingelheim and aim to integrate our combined expertise across molecular, electrophysiological and behavioural studies to try to understand the mechanisms which underlie these effects.

Capitalising on our validated rodent model of affective biases in depression, this project will use our affective bias test to compare the acute and sustained effects of different NMDA receptor antagonists comparing the results with clinical data and specific pharmacodynamic properties of the different drugs. In order to relate these behavioural findings to the underlying mechanisms we will also undertake studies using ex vivo electrophysiology in slices taken from the prefrontal cortex. Using fluorescent labelling we will identify specific neuronal populations which input to or receive inputs from key brain regions such as amygdala and hippocampus and investigate whether there are specific changes in synaptic physiology which correspond to the sustained antidepressant efficacy observed in the behavioural assays.

In collaboration with Boehringer Ingelheim we will undertake analysis of the RNA expression profile within these different neuronal populations following acute treatment with efficacious versus non-efficacious NMDA receptor antagonists. Using RNASeq and bioinformatics, these studies will generate new insights into potential mechanisms and novel drug targets which will be further explored as the project develops including using in vivo behavioural studies integrated with target brain infusions and DREADDs-based methods.