British Pharmacological Society Vacation Studentship Report

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Background

Rapid-acting antidepressants (RAADs) are a new class of treatments for major depressive disorder (MDD) that show both rapid and sustained effects following a single dose. Both serotoninergic psychedelics (5HT2A agonists) and non-competitive NMDA antagonists show potential as RAADs, in vitro, in vivo and ex vivo, however, the mechanisms by which they work are unconfirmed. Understanding the underlying mechanisms would enable the design of novel RAADs with less potential for abuse so this is a key focus of current research for pharmaceutical companies.

The main hypotheses surrounding RAAD mechanisms of action are increased glutamatergic signalling causing increased brain connectivity, decreased serotoninergic signalling, and induced neuroplasticity such as neurogenesis, synaptogenesis and dendritogenesis which would explain the sustained effects of RAADs.

Many of the experiments published are at higher doses than those which are clinically relevant and are not administered systemically. This leads to questions of how translatable these studies are to the clinically demonstrated antidepressant effect. Furthermore, much of the research has not highlighted the neural circuit and therefore key brain regions underpinning negative affective biases – a key characteristic of MDD.

Therefore, the experiment was designed to investigate the compare the neuronal activation in brain regions associated with affective biases and sensorimotor processing between clinically relevant doses, high doses used in the literature and a vehicle (saline).