DESCRIPTION FOR THE GENERAL PUBLIC

Depression is one of the major causes of ill health and economic burden. Around 30% of depressed patients do not benefit from antidepressant drug treatment. Recently, a number of novel and experimental treatments have been introduced into clinical practice that appear to be effective in these drug non-responsive patients. Among these is electrical stimulation of the prefrontal cortex (PFC), via implanted electrodes (deep brain stimulation: DBS). It is important to understand how and why DBS works in these patients when antidepressant drugs do not.

Animal models of depression are essential experimental tools for investigating how antidepressants work. The most valid, and most widely used, model for this purpose is the chronic mild stress (CMS) model, which we developed and have worked with over the past 30 years. In this model, rats (or sometimes, mice) are exposed to a constant barrage of very mild stressors. Over the course of several weeks, they begin to show a range of behavioural changes similar to those seen in depressed people, including loss of response to rewards (anhedonia), anxiety, and cognitive impairments. All of these changes are normalized by chronic (several weeks) but not acute (days) treatment with antidepressant drugs, or by the newer treatments such as DBS, which act rapidly, as they do in the clinic.

A problem with animal models of depression is that they cannot distinguish treatments that might be effective for drug-resistant patients from those that are simply antidepressant in responsive patients. We have developed two ways to address this issue. One is to use a particular strain of rat (Wistar-Kyoto: WKY) that is known not to respond to antidepressant drugs. The other is to identify empirically the small minority of standard (Wistar) rats that fail to respond to antidepressant drug treatment. In both models, a variety of antidepressant drugs were ineffective in restoring normal behaviour after CMS, but these non-responsive animals did recover when treated using DBS.

In this study, we aim to find out how and why DBS works in treatment-resistant WKY rats when antidepressant drugs do not. To do this we will use two additional experimental tools. One is a standard method: injecting drugs directly into the brain in order to ensure that they reach only the region of interest – in this case, the PFC. The other is a novel methodology, optogenetics. This is based on the observation that certain proteins exist that are sensitive to specific wavelengths of light. A virus is used to introduce these probes into specific brain regions, and after a few days they are found throughout the length of neurons located in the vicinity of the injection site. Subsequently, the probe can be activated via an optic fibre implanted into the brain, which promotes or inhibits (depending on the probe used) release of neurotransmitter from the infected neurons.

A particular focus of interest is in the neurotransmitter dopamine, because it is known from extensive earlier work that the dopamine input to PFC plays a major role in cognitive functioning. For example, we have studied the role of dopamine receptor subtypes in the rat PFC in a simple cognitive task: recognizing that one of two objects is novel, which rats normally do well but cannot do at all after exposure to CMS. Our first two series of experiments will investigate the extent to which dopamine receptors in PFC are involved in the effect of antidepressant drugs and DBS to rescue novel object recognition, and other behaviours impaired by CMS, in the WKY rat model of treatment-resistant depression.

Other studies will make a start on a much larger investigation to understand the pathways involved in the antidepressant effects of drugs and DBS, with an initial focus on one input pathway to, and one output pathway from, the PFC. The input pathway is from the hippocampus (HPC). This area has been identified as the major site of antidepressant action, and we hypothesize that differences in HPC-PFC activity may be responsible for the effectiveness of antidepressant drugs in some animals and their ineffectiveness in others. The output pathway is to the nucleus accumbens, which for many years has been considered as a ‘gateway’ through which motivational influences gain access to the motor output systems of the brain.

Through these studies, we aim to understand better the mechanism of action of DBS, and the mechanistic similarities and differences between DBS and antidepressant drug treatment, so as to shed light on the nature of antidepressant treatment-resistance and so open new avenues for the treatment of resistant depression.