 Specifically, the objectives are:

1. To characterise brain function in the offspring of dams previously exposed to the psychostimulant drug, methylenedioxymethamphetamine (MDMA, “Ecstasy”).

2. To characterise brain function in animals where genetic modification alters central serotonergic systems, either directly or indirectly.

3. To characterise the mechanisms by which altered cerebrovascular physiology might contribute to changes in brain function induced by both genetic and environmental manipulation of central serotonergic systems.

Unipolar major depression is common and a leading cause of morbidity and mortality. In developed countries it is twice as common in women as men, affecting 20% of women at some time in life. The global burden of disease survey found it will be the fourth most prevalent cause of disability adjusted life years, accounting for about 20% of the burden of disease (Murray 1997). This is greater than the burden of common causes of death such as cardiovascular disease. In addition to its economic consequences, depression is a direct cause of death through suicide. There are important cohort effects – the age of onset of depression is steadily decreasing each decade and it no longer a disease of middle age. Furthermore, there has been a remarkable increase in the rate of suicide in young males over the last 15 years in the EU. Indeed suicide is second only to road traffic accidents as the cause of death in the 15 to 25 age band. Female gender and social and familial factors increase risk of depression but little is known about how these influences work in the brain, least of all at the molecular level. Antidepressant treatment has improved in terms of tolerability and thus treatment adherence but drugs currently in use have the same primary

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**Figure 1:** Functional imaging in coronal sections of mouse brain using colour-coded [14C]2-deoxyglucose autoradiograms. Generalised decreases in metabolic activity induced by the 5-HT1A agonist 8-OH-DPAT in wild type female mice (bottom) are attenuated in mice over-expressing the 5-HT transporter (top). No such differentiation between genotypes was found in male mice, indicating a significant gender x genotype interaction.
mechanisms of action as 30 years ago and their downstream molecular actions are obscure. Furthermore, at most 65% of new episodes respond to drug-treatment and chronic, treatment-resistant depression is a major health burden.

The link between pathological cerebrovascular dysfunction and the development of affective disorders is well established. Less well established is any physiological link whereby cerebrovascular insufficiency might contribute to either the aetiology or symptomology of affective disorders, or conversely how the neurochemical imbalances of affective disorders might impinge upon cerebrovascular control.

Over the past 8 years, our research group has worked in this field as part of two European research consortia, funded under the 5th and 6th Framework Programmes. Most recently, we were part of a major collaboration between 13 academic groups in 10 EU countries, together with 2 Small/Medium Enterprises. This grouping represented an integrated clinical - basic science project that is capitalising on state-of-the-art neuroscience expertise across the EU, including molecular genetics and functional brain imaging.

The contribution to this integrated programme from our laboratory concentrated on models of altered serotonin transporter function including:

(i) The characterisation of acute MDMA-induced cerebrovascular dysfunction (Quate et al., 2004) and altered circadian behaviours related to serotonergic function (Balogh et al., 2004), aggression (Kirilly et al., 2006), and social interaction (Ando et al., 2006).

(ii) The characterisation of persistent MDMA-induced cerebrovascular dysfunction (Ferrington et al., 2006) and long-term changes in behavioural responses to the specific serotonin reuptake inhibitor (SSRI) class of antidepressants (Ando et al., 2009).

(iii) The characterisation of cerebrovascular dysfunction induced by acute dietary tryptophan depletion (vanDonkelaar et al., 2009).

(iv) The characterisation of central serotonergic pharmacology and function in hSERT over-expressing and SERT knock-out mice with particular emphasis on gender differences (Dawson et al., 2009) (Figure 1).

SELECTED REFERENCES


