The mechanisms of neuronal functions

Brain function depends on the complex dynamic interactions of large numbers of neurons connected into networks by synapses. Each neuron is structurally complex, receiving up to 10,000 inputs onto its dendritic tree. Even the simplest task uses many thousands of neurons operating in a coordinated manner on timescales from milliseconds (synaptic transmission, action potentials) up to days, weeks and longer (synaptic plasticity, structural plasticity/growth, neuronal migration). Analysing how these neurons and networks operate requires a multidisciplinary approach, including molecular biology, histology, anatomy, physiology and behaviour. Examples of the kinds of problems being investigated include mechanisms of epilepsy, roles of cortical oscillations in mental retardation and ageing, disease processes in dementia, and pathophysiology of prion diseases such as BSE.

The imaging aspects of these investigations fall into at least four broad categories.

Neuronal morphology - The specific shapes of neurons are important to function, and the location of molecules such as synaptic receptors and ion channels are crucial to patterns of neuronal activity. Teams in the Medical School are looking at changes in the detailed structure and localisation of neurons in health and disease. Specific projects include: intellectual disability resulting from well-defined genetic mutations, epilepsy (where connections between neurons change substantially and neurons may die or be mis-positioned), dementia, and normal ageing. Methods include histology and various kind of histochemistry as well as filling individual neurons with fluorescent or other labels for reconstruction in 3-D by confocal microscopy, or by conventional microscopy, allowing the quantitative analysis of their structure.

Visualisation of live neurons - In many studies neurons are visualised in small pieces of brain tissue in vitro. Infra-Red Differential Interference Microscopy allows the cell body, which houses the nucleus, and the larger dendrites to be seen well enough to position recording electrodes on their surfaces. Injecting dyes then allows the neuron to be seen more clearly, allowing, for instance, recordings from two parts of the same cell to help understand the coupling process between inputs on the dendrites to the outputs starting near the junction between the axon and cell body. This is used for many studies of neuronal function, including work on the properties of synapses, normal functions of prion protein, changes with normal ageing, and the pathophysiology of epilepsy.

Optical measurements of dynamic processes - Dyes can be injected into neurons or their esters can be taken up from the bathing medium. Depending on the specific dye, this allows measurements of biologically relevant factors such as membrane potential, intracellular calcium ions and free radicals. Specific projects include: the potential role of prion protein in controlling free radicals, changes in calcium homeostasis during ageing and following genetic modification.

Non-invasive imaging plays a major role at the holistic end of the reductionist spiral. At the moment the facilities in Birmingham are restricted to human work (see Imaging in Neuroscience and Clinical Imaging).

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