142P fMRI IN ANIMALS TO STUDY NEURAL PATHWAYS AND DRUG ACTION

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Since 1991 the emphasis on MRI for human studies has shifted from structural analysis to measurement of changes in regional cerebral blood flow in response to specific stimuli or tasks, as a measure of brain neuronal activation under non-invasive conditions. Functional MRI (fMRI) signal intensity can be measured with the T2*-weighted blood oxygenation level-dependent (BOLD) contrast method. With improvement in the speed of image collection and the resolution attainable, conditions used in humans can be applied to animal studies of fMRI. This talk considers the application of fMRI methods to the identification of changes in regional brain function in response to peripheral noxious stimulation and cannabinoid drug administration in rats.

The studies described were made using a 2.35T Bruker Biospec Avance imaging system with anaesthetised rats (core temperature maintained with a customised water bed within the imaging system). Basal scans were obtained before physiological or pharmacological intervention; evoked BOLD responses were compared to vehicle-injected controls.

Intraplantar injection of formalin (5%) into the hind paw was associated with significant increases in BOLD response in specific supraspinal brain regions associated with somatosensory processing, including the periaqueductal grey (PAG), thalamus, amygdala and areas of the somatosensory cortex. The peak increase in response was observed 40 min after formalin administration. In contrast, saline produced no effects in these regions apart from a small increase in the thalamus.

These data demonstrate that fMRI in the rat can be used to monitor CNS processing of noxious stimuli and offer the opportunity to investigate drug-induced alterations. The BOLD method has also been used to detect drug-induced changes (pharmacological MRI) in regional activation, as demonstrated with the results using both amphetamine and the CB receptor agonist HU210. The cannabinoid agonist increased BOLD response in the ventral tegmental area (VTA), PGA and the dentate gyrus, but not other areas of the hippocampal region, while BOLD response in the somatosensory cortex was reduced. These data help to provide anatomical explanations for some of the varied behavioural effects observed with cannabinoids.

fMRI and phMRI should lead to an improvement of our understanding of brain mechanisms and allow closer comparison between rodent and human brain in relation to the use of animal models for the study of human brain disorders.

143P GENERATION AND APPLICATIONS OF HIGH DENSITY PROTEIN ARRAYS

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A full understanding of the expression profile of a tissue or organism requires the screening of many genetic and or protein samples in parallel as rapidly as possible. Those steps which have been automated and miniaturised in our laboratory to enable a high-throughput and highly parallel approach to large-scale cDNA and protein analysis will be described. Specifically the generation and picking of cDNA expression libraries, and arraying of clones into microtitre-plates.

A technique known as oligonucleotide fingerprinting which has been developed to characterise cDNA libraries, which allows the generation of a non-redundant, human Unigene-Uniprotein set, will be described. The hEx1 library has been oligo-nucleotide fingerprinted to generate a non-redundant set, which contains over 10 000 non-redundant genes and proteins obtained from a human brain cDNA expression library. We have clonally expressed proteins from this library and produced high density protein arrays on filters and glass (chips).

These protein arrays have been screened with antibodies, which detected specific protein products. This approach makes translated gene products directly amenable to high-throughput experimentation, allowing a link between expressed protein and sequence.

Initial results of characterising antibody specificity and profiling auto-immune sera on protein arrays will be presented. Applications of high density protein and antibody arrays in proteomics will be discussed.