Effects of the cannabinoid agonist HU210 on BOLD response in rat brain as determined by fMRI

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Introduction

The hemp plant cannabis sativa (cannabis) has been used for over 4000 years as a medicinal and recreational drug. Its principle active constituent is delta-9 tetrahydrocannabinol (9-THC)(1). Extensive research has established number of characteristic properties for 9-THC and ligands displaying a similar pattern of response are deemed as cannabinoids . Mediation of cannabinoid effects occur through cannabinoid (CB) receptors (2). CB1 receptors are primarily localised to the central nervous system (CNS) and its distribution in the rat is well characterised .High density of CB1 receptors are localised in the basal ganglia ,cerebellum and hippocampus with intermediate/moderate levels of the receptor being observed in the nucleus accumbens (NAc), amygdala and the periaqueductal grey area (PAG) (3). Studies involving 2-deoxyglucose (2-DG) have shown that 2.0 mg/kg (i.p) of 9-THC increased 2-DG uptake in many cortical and limbic areas including the hippocampal formation and hypothalamus(4). Autoradiography studies have shown that 9-THC (1.0mg/kg i.p) causes a decrease of regional cerebral blood flow in areas such as the rostral NAc and prefrontal cortex (5).

Functional magnetic resonance imaging (fMRI) is a powerful technique used for the non-invasive study of brain structure and function.It is able to localise areas of neuronal activity and metabolism during physiological or pharmacological challenge. The technique is based on an assumed relationship between neuronal activity, metabolism and changes in blood flow. Blood flow and related changes may be caused by an increase in energy demand (invoked by neuronal activity) which is accompanied by an increase in parameters such as blood volume to meet the oxygen demand of neurons. The functional image produced is a result of changes in the volume of deoxygenated blood in a particular area post challenge (6). Although this technique is used mainly in humans to map regional neuronal activity , it has recently been extended to animal studies(7)

The aims of this study was to see if HU210 (a synthetic cannabinoid agonist) could invoke a significant BOLD response in brain regions associated with CB receptors and also in areas involved with reward phenomena as cannabis is widely used as a recreational drug.

Methods

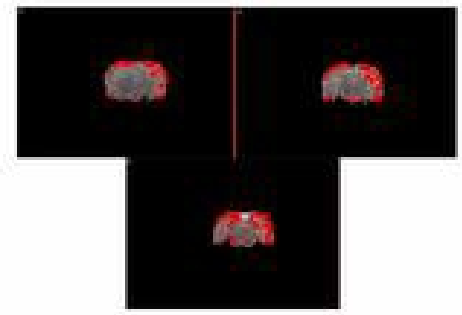
Hooded Lister (350-450g) were anaesthetised using chloral hydrate (650mg/kg i.p) and the jugular vein cannulated to allow administration of HU210. Temperature during surgery was maintained using a heater bed and throughout the experiment by means of a water jacket built into the rat body holder. The temperature of the rat was continuously monitored by means of a rectal probe. The rat body holder was placed into a horizontal bore 2.35T biospec avance imaging system and optimal positioning of the rat was determined using a pre-functional pilot scan. Once in position, functional images were acquired using RARE The parameters for this technique are as follows TR: 4356.0ms,TE: 62.7ms,NEX: 8,TA: 280s ,FOV: 50mm x 50mm , matrix dimensions : 64 x 64. This fast spin echo sequence was used to try and minimise any would be effects from large cerebral blood vessels. Each rat brain was covered using 30 1mm slices so as to record BOLD effects over all brain regions. Orientation of the slices were coronal. Pre-drug data was collected over a period of 12 scans (~60 minutes). On completion of the twelfth scan, HU210 was administered (10ul/kg i.v) and scanning continued over a ninety minute period. As an extra precaution, an angiogram was performed at the end of the experiment to locate large cerebral vessels so as to eliminate BOLD effects from these areas.

Statistical analysis

Group statistics were achieved using statistical parametric mapping (spm99) software. Using a box car design basal functional data obtained was compared with post-drug functional data. Significant changes in BOLD signal was determined using fixed effect analysis.

Results

Results show that HU210 was able to produce a significant BOLD response in a number of brain areas including areas shown below (fig 1a 1b and 1c).Fig 1a and 1b (top left) shows changes in areas of the hippocampus and amygdaloid nucleui.Fig 1c shows significant changes in the ventral tegmental area and hindbrain areas including the periaqueductal grey.Not all areas of the brain which showed significant BOLD respone are shown. Areas not shown include striatum and thalamic nucleui.



1a 1b 1c

Discussion

The group statistics show that HU210 was able to produce a significant BOLD response in a number of brain areas including areas involved with reward phenomena (ventral tegmental area-VTA) and regions known to contain a high density of cannabinoid receptors e.g hippocampus. Surprisingly, a number of brain areas shown in previous findings to contain only moderate levels of CB receptors showed significant changes in BOLD signal. These areas include amygdaloid nucleui and the PAG.

These surprise findings maybe due to a 'down stream' effect. For example, the amygdala has reciprocal projections to a number of brain regions including the hippocampus and the VTA. Changes in the BOLD response observed in the amygdala maybe as a result of HU210 acting on afferent projections to this area. This may also be true of the PAG.

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