COCaine-INDUCED ACTIVITY IN THE RAT HIPPOCAMPUS USING PHMRI

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Introduction

The hippocampus (HF) is known to be involved in episodic memory and this brain region has increasingly been linked to drug-seeking behaviour in rodent behavioral models of substance abuse. Cocaine is a drug of abuse that can alter the magnitude of long-term potentiation (LTP) in the CA1 region of the HF (1). LTP is a form of synaptic plasticity that is thought to underlie learning/memory mechanisms at the molecular and cellular levels of information processing in the neural network. The psychostimulant effects of cocaine are thought to primarily result from its ability to block monoamine reuptake, including dopamine (DA) reuptake. This action increases DA levels in the brain and DA is known to facilitate LTP of glutamatergic synapses in the HF. Thus, cocaine actions in the HF will potentially facilitate the “memories of addiction” that persist following drug exposure. In terms of anatomical organization (especially efferent connectivity), the HF can be divided into two distinct sectors: dorsal hippocampus (dHF) and ventral hippocampus (vHF) (2). These sectors are also known to be dissociable at the functional level, with the dHF involved with spatial/cognitive processing and the vHF more concerned with motivational states (3). The BOLD activation following cocaine administration in laboratory rats has been reported, including the HF signal (4-5). However, an assessment has not been reported for discriminating between the dHF vs. the vHF. Our current study investigates such temporal responses in these two sectors in urethane anesthetized rats following systemic cocaine administration.

Methods

Male Sprague Dawley rats weighing 300–350 g were anesthetized with urethane anesthesia (1.25g/kg). Animals were secured to a custom built head holder using ear bars and nose cone and the body temperature was maintained with a thermostated circulating water heating element. Rectal temperature and breathing rate were monitored throughout MRI experiments. Rats received an i.p injection of either cocaine (10mg/kg) or saline. pHMRI experiments were conducted on a 7T Varian DirectDrive system using a 3 cm surface coil for transmission and reception. Anatomical MRI was collected using fast spin echo sequence with following parameters: TR=2, TE=48 msec, 12 slices and thickness =1.2 mm, field of view 40 x 40 mm and matrix size of 256 x 256, signal averaging of 6 resulting an acquisition time of 8 min. With similar parameters, spin echo EPI was acquired for 60-90 minutes with matrix of 64x64 pixels with TE/TR=16ms/1 sec. Animals received cocaine or saline injection after 15 minutes of baseline acquisition. Images were analyzed with SPM (6), Aedes and Stimulate (7) using a Student’s t-test (p<0.05). All motion correction, slice timing and co-registration were performed on the datasets. In a separate group of rats, brain slices from vHF and dHF were obtained for measuring LTP of field potentials using extracellular recording technique.

Results and Discussion

Continuous recordings of each physiological measure such temperature and breathing rate showed that few animals showed an increased in pulse rate after injection of cocaine. All the brain slices in the cocaine naive rats showed strong cocaine-induced activation, in contrast to the saline administration group. Minimal negative BOLD signal changes were observed in response to cocaine in both cocaine naïve and saline groups. In our initial studies, we have found significant cocaine-induced activation in both the dHF and the vHF of cocaine naïve animals. Figure 1 represents the change in BOLD signal intensity over 60 minutes that showed increased % BOLD change (> 6% in dHF and > 4% in vHF) after injection of cocaine, whereas the saline injection group remains non-significant during 60 minutes of acquisition. Figure 2 illustrates the BOLD MRI activation map of a cocaine-injected and a saline-injected animal and their corresponding dHF and vHF ROIs. Figure 3 shows that there is a significant increase in both the dHF and vHF sectors of cocaine-injected vs. saline-injected groups. The field potential recordings (right panel) demonstrate a significant difference between the effects of prior cocaine exposure on LTP assessed in dHF slices vs. vHF slices. These electrophysiological results support the hypothesis that the dHF and vHF sectors of hippocampus may respond differently to external stressors and drug exposure. Additional work is being undertaken using phMRI in cocaine experienced rats to determine if their BOLD response to cocaine challenge will also be different in the dHF and vHF, as demonstrated in the LTP experiments.

References