1H MR Spectroscopic Measurement of Neurochemical Alterations in the Hippocampus of a Rat Model of Depression

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INTRODUCTION

The forced swimming test (FST) is considered one of the most widely used and reliable animal models of depression for the assessment of antidepressant activity and for examining the pathophysiology of depression pre-clinically [1]. The impaired synaptic efficacy due to the FST procedure involving severe physical and emotional stress has been reported in the rat hippocampus, and the synaptic efficacy shows significant improvement after being treated with repetitive transcranial magnetic stimulation (rTMS) [2]. We recently reported a significantly increased Cho/Cr ratio in the dorsolateral pre-frontal cortex (DLPFC) of rats exposed to the FST compared with control animals [3], which is similar to results obtained from investigations of patients with depression [4]. To extend our previous findings and characterize the variation of the hippocampal Cho/Cr ratio in an animal model of depression, we systematically examined the Cho/Cr ratio in the hippocampus of rats exposed to the FST and controls by using relatively small volume-of-interest (VOI) compared with our previous study that specifically focused on the homogeneous hippocampus tissue.

MATERIALS AND METHODS

Experimentally naive male Sprague-Dawley rats (Charles River, Japan) weighting 160–180g were used as subjects. The FST was executed to induce a depressed mental status and was performed on each rat just a single time according to an original version of the FST [1]. MR experiments were conducted using a 4.7T BIOSPEC scanner (Bruker Medical GmbH, Ettlingen, Germany) with a 400 mm bore magnet and 150mT/m actively shielded gradient coils. To execute the MRS measurements, rats were initially anesthetized by inhalation of isoflurane at a 4–6% concentration in a 5:5 mixture of N_2O and O_2, and this was maintained by inhalation of a 1.5–2% concentration of isoflurane in a 5:5 mixture of N_2O and O_2. A scout image was initially obtained to verify the position of the subject and the image quality. The position of the volume-of-interest (VOI) was carefully selected from multislice axial T2-weighted MR images obtained using rapid acquisition with a relaxation enhancement (RARE) sequence (TR = 5000 ms, TE = 22 ms, slice thickness = 1.0 mm, NEX = 2, matrix size = 256 x 192) and a rectangular VOI was placed in the left and right dorsal hippocampus of the rat brain (Figure 1). As a single technique, ^{1}H MR spectra were obtained with use of a point resolved spectroscopy (PRESS) localization sequence performed according to the following parameters: repetition time, 2500 ms; echo time, 144 ms; 512 average; 2048 complex data points; voxel dimensions, 1.5 x 2.5 x 2.5 mm^3; acquisition time, 25 min. Adjustment of all first- and second-order shim terms was accomplished with the fast automatic shimming technique by mapping along the projections (FASTMAP). Water suppression was accomplished by variable power RF pulses with optimized relaxation delay (VAPOR) by controlling the transmit gain to maximize water suppression. Raw data were processed using the TOPSPIN data analysis program (Bruker) by an unbiased analyzer who was experienced in MRS data processing. Statistical analysis was performed with commercial SPSS software (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL USA). The paired samples t-test was used to test for the significant FST effect, that is, before and after exposing the same rats to the FST.

RESULTS

The typical proton MR spectra obtained after exposing the rats to the FST from the left hippocampus exhibited a marked reduction in the relative intensity for the Cho signal as compared with the spectra obtained before the FST (Figure 2). The paired samples t-test for metabolite signals before vs after the FST revealed that NAA/Cr ratio remained stable (p = 0.819), Cho/Cr ratio was significantly decreased (p = 0.037), and Cho/NAA ratio was also significantly decreased (p = 0.048) in the left hippocampus (Figure 3). However, no significant differences in the Cho/Cr ratio (p = 0.754), Cho/NAA ratio (p = 0.936) and NAA/Cr ratio (p = 0.349) were observed between the control animals and rats subjected to the FST in the right hippocampal region.

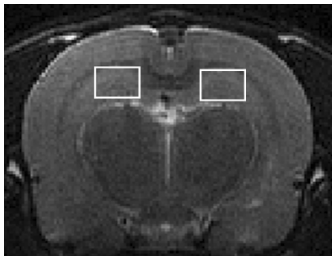

Figure1. Axial imaging with the superimposed location of the voxel in the left and right hippocampal regions.

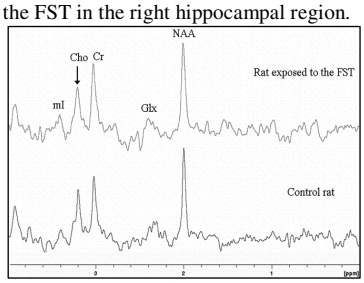

Figure 2. Representative ^{1}H MR spectra of the left hippocampus obtained before and after exposing the FST.

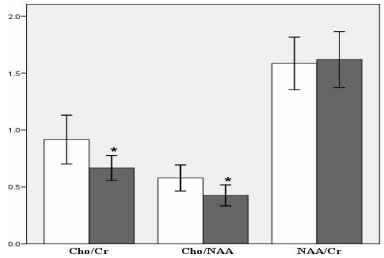

Figure 3 Metabolite ratios in the controls (white) and rats with depression (grey). *p<.05 as compared with the control subjects.

DISCUSSION

The present study is the first to demonstrate a decreased hippocampal Cho/Cr ratio in rats subjected to the FST as compared with control animals by the use of ^{1}H MRS as a general method for exploring the pathophysiology of depression. This result is consistent with early findings from ^{1}H MRS studies demonstrating decreased hippocampal levels of Cho in patients with depression [5], implying that decreased Cho/Cr and Cho/NAA ratios in the hippocampal regions might represent neurobiological markers of both patients with depression and rats with depressive characteristics induced by the FST. Based on the fact that left hemispheric lesions may be more linked to depression, while right hemispheric lesions are more general in mania [6], the present study observing metabolite differences in the left but not right hippocampal region may suggest a similar pathophysiology between major depression and FST-induced depression.

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