Metabolic Alteration of the Dorsolateral Prefrontal Cortex in Depressed Sprague-Dawley Rats by in vivo Proton MR Spectroscopy

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INTRODUCTION

The most common results in previous studies of depression patients were significantly increased Cho or Cho/Cr ratio in the dorsolateral pre-frontal cortex (DLPFC) of subjects with depression [1,2]. This change suggests that Cho plays a critical role for signal transduction in depression patients and indirect evidence from several pharmacological studies has revealed that Cho may have a "depressogenic" effect on the central nerve system (CNS) [3]. However, although there is an established depression animal model, the forced swimming test (FST) [4], initially invented by drug companies as pre-clinical screening tests to determine the effect of new antidepressant drugs, proton magnetic resonance spectroscopy (1H MRS) has been rarely performed in a depressed animal model versus their age- and sex-matched normal controls to the best of our knowledge. In view of this, the aim of this study was to measure metabolic difference, mainly Cho/Cr ratio, between the depressed rat models and the normal controls.

MATERIALS AND METHODS

Test-naive male Sprague-Dawley (Charles River) rats weighting 160 ~ 180g each were used for the MRI and in vivo 1H MRS study. The subject groups were composed of 10 depression model subjects and 10 healthy controls. The forced swimming test (FST) was performed for all subjects in the depression model group to induce a depressed mental status. The FST was performed for 2 days. Each of rats was placed into a vertical glass cylinder (height: 40 cm, diameter: 18 cm) that contained 25 cm of water maintained at 25 ^{0}C, and the rat was left for 15 min (Figure 1). After 15 min in the cylinder, the rat was removed and allowed to dry before being returned to its cage. Twenty four hours later, the rat was plunged again in the cylinder for 5 min. Water-suppressed proton MRI/MRS was conducted on a 4.7 T Bruker scanner (BioSpec, Ettlingen, Germany) with using a standard quadrature head coil. T2-weighted MR images were 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=256x192) to accurately place the voxel. The position of the voxel was visually adjusted in the left prefrontal regions, and it was predominantly done in the DLPFC. All the MR spectra were acquired using a point resolved spectroscopy (PRESS) pulse sequence (TR=3000 ms, TE=20 ms, 512 acquisitions, 2048 complex data points, voxel dimensions=3.5x3.5x3.5 mm^3 and an acquisition time of 25 min) to minimize the T1 and T2 relaxation effect to within an acceptable examination time and the global water suppression was achieved using the fast automatic shimming technique by mapping along projection (FASTMAP). All the acquired MRS spectra were analyzed by using Bruker TOPSPIN software and independent sample t-test for comparison of the two groups were performed by using SPSS (Windows Version 13.0, SPSS Inc., Chicago, IL). Animal anesthesia was induced by inhalation of isoflurane at a 4-6% concentration in a 5:5 mixture of N2O and O2, and this was maintained by inhalation of a 1.5-2% concentration of isoflurane in a 5:5 mixture of N2O and O2.

RESULTS

The typical MR spectra obtained from the depressed SD rats and the controls are shown in Figure 2 representing a substantial increase in Cho/Cr ratio in depressed subjects compared with healthy controls. Figure 3(A) present significantly higher Cho/Cr ratio of the DLPFC in the depressed SD rats than that of the normal controls (p=0.032). However, non significant metabolic change, in the NAA/Cr ratio (p=0.641), was observed between the two groups (Figure 3(B)).

Figure 1. Rat showing the typical posture of immobility during the second FST period.

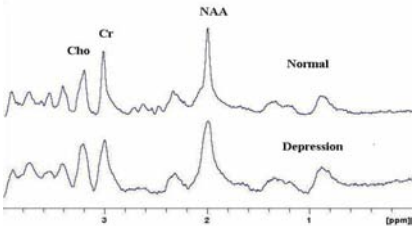

Figure 2. 1H MR spectra of the DLPFC from the normal control and the depressed SD rat after the FST.

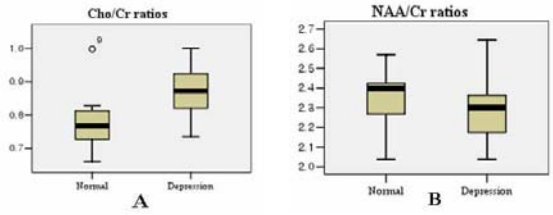

Figure 3. Effect of the FST on Cho/Cr (A) and NAA/Cr (B) ratio in SD rat DLPFC.

DISCUSSION

The previously reported increase in the Cho/Cr ratio of depression patients was replicated in SD rats with depressed status. This result indicates that the FST caused similar neurotransmitter alterations in depressed rats compared with depression patients. In addition, the NAA/Cr ratio had no statistical interaction between the healthy controls and the depression model group. These data reveal that the FST induce increased membrane degradation or synthesis but does not have an effect on regional neuronal loss or changes in neuronal metabolism. However, an increased left DLPFC Cho/Cr ratio may represent an epiphenomenon or even a compensatory response to illness. Therefore, further MRS studies of other brain regions are essential in order to prove the exact reason for an increased Cho/Cr ratio.

CONCLUSION

The present study demonstrates that 1H MRS has sufficient potential for measuring the metabolic changes in a manner of non-invasive and quantitative. Ultimately this non-invasive technique can be helpful for evaluating the newly developed antidepressant to animals in pre-clinical stage.

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