Hippocampal Neurochemical Findings in Medication-Free, Euthymic Bipolar Disorder: 1H MRSI Study

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Introduction: Mood dysfunction in bipolar disorder could be related to metabolite abnormalities in specific brain regions. To date, ^{1}H MRS investigations have focused on the prefrontal cortex, basal ganglia, cingulate cortex, but only few studies of hippocampus have been reported. The hippocampus plays an important role in memory, and stress and emotional regulation. In this work, we investigate the metabolism of hippocampus in medication-free, euthymic bipolar disorder (BD) patients using 2D ^{1}H MRSI.

Methods: Six medication-free, euthymic BD patients were studied (M3/F3; age: 20.2±4.7). Nine healthy volunteers (M5/F4; age: 27.7±9.5) served as the comparison group. All MRSI and MR scout images were acquired with a 4T Varian INOVA system using a volume TEM head coil. Spectra were localized to a 10x80x100 voxel angulated along the temporal pole using a 3D localized adiabatic LASER sequence with 2D phase encoding. Shimming was optimized by automatic B_0 mapping.[1] Water suppression was provided by an initial broad-band semi-selective excitation pulse and frequency selective DANTE pulse applied to the water resonance. Data were acquired using TE/TR of 62/2000ms, FOV 192x192mm^2 with 24x24 encodes. Additional MRSI data with a long TE=144ms were also acquired at the same slice for lactate measurements. To provide consistent voxel size and positions in different subjects, an automated co-registration, selection and reconstruction routine was used (Fig. 1). Five non-overlapping voxels from each hippocampus (10 per study) were automatically reconstructed by translating along the hippocampal midline with voxel #3 placed at the level of the aqueduct (Fig. 1). Metabolite data were presented in terms of metabolite ratios after curve fitting (NAA: N-acetyl aspartate; Cr: creatine; Ch: choline).

Results: BD patients' data were compared with healthy subject measurements, and the number of voxels with significantly higher ratios at various hippocampal regions are summarized in Fig. 2. All 3 ratios showed abnormalities at one or more positions. The most frequently observed abnormality was Cr/Ch, which was found in 7 voxels at 6 different positions. L5 (left anterior hippocampus) was the voxel most commonly exhibiting abnormalities, i.e. elevated Cr/NAA. The mean values of 10 hippocampal voxels in the two groups are summarized in Table 1. Lactate signals were also observed in patients at various positions (Fig. 3 and Table 2), but not in healthy subjects. Lactate was most commonly observed in voxels from mid and posterior hippocampus.

Fig.1

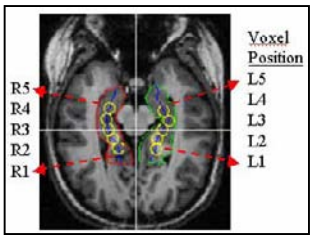

Fig.2

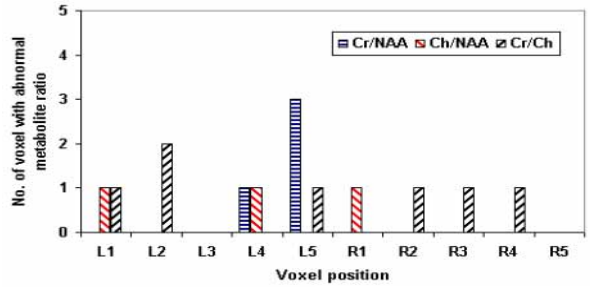

Fig.3

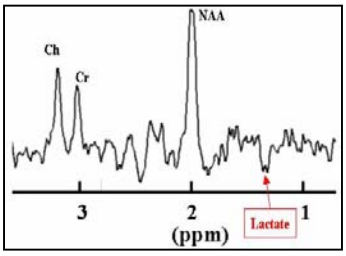

Table 1

	Cr/NAA	Ch/NAA	Cr/Ch
Control Group	0.62±0.14	0.63±0.16	1.04±0.29
Patient Group	0.88±0.15	0.83±0.17	1.47±0.16

Table 2

	L1	L2	R2	R3	R5
Number of voxel showed lactate	1	2	2	2	1

Discussion: Previously published studies had reported contradictory Cr/Ch results from lithium-treated bipolar patients.[2,3] Other investigations of temporal lobes also reported lower Ch/Cr in lithium-treated bipolar patients.[4] The current preliminary study found significantly higher hippocampal Cr/Ch (or lower Ch/Cr) in medication-free, euthymic BD patients. These contradictory data raise two issues. First, if it is true that lithium can alter *in vivo* brain choline metabolism, although lithium increased *in vitro* choline in human erythrocytes had been reported. Second, if it is possible that these different findings are attributed to tissue and/or region dependence since all reported measurement areas are not the same. The latter suggestion may be supported by the current study since we have found subregional differences in hippocampus. These will need to be clarified. In the current work, lactate signals were found primarily in the voxels #2 and #3, which are near the parahippocampal cortex. A recent positron emission tomography (PET) study reported that regional cerebral blood flow in euthymic BD patient's parahippocampus was different from healthy subject during a memory task.[5] Although our study was under resting conditions, our data suggest that lactate in parahippocampus reflects regional metabolic abnormalities, namely a shift from oxidative phosphorylation to glycolysis. Future studies using ^{31}P MRSI may help to clarify these hypotheses.

References: 1) Hetherington HP. *ISMRM* 2005,p730. **2)** Ohara K. *Psychiatry Res* 1998, 55. **3)** Sharma R, *Schizophr Res* 1992, 43. **4)** Wu RH, *Ann Gen Hosp Psychiatry* 2004, 13. **5)** Deckersbach T, *Biol Psychiatry* 2005, *in press*.