Decreased pHi and [ADP] in anterior cingulate cortex of bipolar disorder: further evidence of mitochondrial dysfunction

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Introduction:

Several investigators have hypothesized that mitochondrial dysfunction underlies the pathophysiology of bipolar disorder (BD). This hypothesis is supported by several magnetic resonance spectroscopy (MRS) studies.[1] Specifically, results of MRS studies report decreased intracellular pH values (pHi) in BD subjects,[2-6] a likely result of the expected shift toward glycolytic energy production. However, most studies found little associations with high energy phosphor compounds [i.e. ATP]. One recent study suggested that [ADP] is more strongly correlated with mitochondrial function than [ATP].[7] This work utilized 3D ^{31}P MRS to measure pHi and [ADP] *in vivo* in the anterior cingulate cortex (ACC) of BD subjects in an effort to examine whether the bioenergetics of this region are in congress with the theory of mitochondrial dysfunction. The results show that both pHi and [ADP] were found to be significantly decreased (p < 0.05) in manic BD subjects relative to healthy controls.

Methods:

All MR studies were performed on a Varian 4T whole-body MR system using a ^{31}P-^{1}H dual-tuned head coil. Twenty BD adolescents, ages 11 to 18 years, in manic or mixed state and seventeen age-matched subjects with no DSM-IV Axis I disorder in themselves or first-degree relatives participated in the study. All patients were unmedicated at the time of the scan. Diagnoses were made based on the Washington University at St Louis Kiddie Schedule of Affective Disorders and Schizophrenia. Manic adolescents met DSM-IV criteria for a manic or mixed episode and had a Young Mania Rating Scale score of greater than twenty.

3D MDEFT images were acquired for MRS voxel positioning as well as for the determination of tissue content within MRS voxels. The ^{1}H spectra were acquired from the ACC using the single-voxel PRESS sequence (2 x 2 x 2 cm^3 voxel size) and the ^{31}P spectra were acquired using a one-pulse 3D MRSI sequence with a three-dimensional spherical sampling scheme (13 x 13 x 13 data matrix, 24 x 24 x 24 cm FOV).[8] Analysis of the ^{31}P data was performed by the single voxel reconstruction method, which allows spatial positioning of the center of the ^{31}P MRSI voxels to be the same as that of the ^{1}H MRS voxels. Concentrations of creatine ([Cr]) and phosphocreatine ([PCr]) were determined via LCModel quantitation and subsequent T_1, T_2, [H_2O], and tissue segmentation corrections. The resulting [PCr] was used as a reference to determine absolute concentrations of other phosphor metabolites and thus [ADP] could be indirectly determined by the following equation.

$$[ADP] = \frac{[\gamma - ATP] \times [Cr]}{[PCr] \times K'_{CK}}$$

Where K'_{CK} is the adjusted creatine kinase equilibrium constant as derived by Golding, Teague, and Dobson assuming free magnesium concentration ([Mg^{2+}]) = 1 mM.[9]

Results:

pHi: ^{31}P MRS data were processed using AMARES quantitation in jMRUI. Metabolite peaks were discarded from pHi determination if Cramer-Rao bound errors exceeded 20%, five BD subjects and four healthy comparisons were eliminated in this way. A statistically significant decrease in pHi was found in manic BD subjects relative to healthy comparison subjects (p = 0.024). Figure 1A summarizes the results.

[ADP]: ^{31}P MRS and ^{1}H MRS data were excluded from consideration if Cramer-Rao bound errors exceeded 20% and 35% as determined by AMARES and LCModel, respectively. Nine BD subjects and seven healthy comparisons were eliminated in this way. [ADP] was significantly decreased in manic BD subjects relative to healthy comparisons (p = 0.026). Figure 1B summarizes the results.

Discussion:

Consistent with the results of a recent study by Wang et. al. in post-mortem BD subjects which found signs of increased oxidative stress in the ACC,[10] our results indicate decreased pHi in this brain region. Moreover, the reduction of [ADP] is directly tied to the decrease in pHi as K'_{CK} decreases with decreasing acidity. The reduction of pHi and subsequent increase in K'_{CK} and decrease in [ADP] are strong evidence in support of impaired oxidative phosphorylation in the ACC of BD adolescents – a primary facet to Stork's and Renshaw's hypothesis of mitochondrial dysfunction.

Determination of absolute concentrations of other phosphor metabolites in this study did not yield statistically significant differences. However, a trend (p<0.15) of decreased [ATP] in manic/mixed patients relative to healthy comparisons was found, a finding to be expected in a condition of energy shortage that would result from mitochondrial dysfunction.

The absolute quantitation of metabolite concentrations is an attractive advantage over many previous ^{31}P MRS studies in that it removes the need to report metabolic differences as ratios. Continuation and expansion of this work to include more subjects and brain regions will allow for the characterization of brain bioenergetics in BD to be supplemented with metabolic analyses, such as changes in [ADP], which have seen little or no attention to date.

References:

1. Stork, Renshaw. *Molecular Psychiatry*. 2005;10:900-919
2. Hamakawa, et al. *Psychiatry Clin Neurosci*. 2004;58:82-88
3. Kato, et al. *Eur Arch Psychiatry Clin Neurosci*. 1998;248:301-306
4. Kato, et al. *J Affect Disord*. 1994;31:125-133
5. Kato, et al. *J Affect Disord*. 1993;27:53-59
6. Kato, et al. *J Affect Disord*. 1992;26:223-230
7. Pan and Takahashi, Ann Neurol. 2005;57:92-7
8. Hetherington, et al. *Magn Reson Med*. 2001;45:46-52
9. Golding, Teague, Dobson. *J Exp Biol*. 1995;198:1775-1782
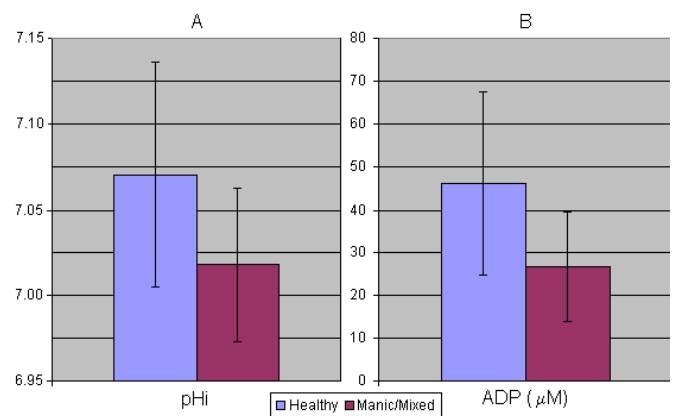10. Wang, Shao, Sun, Young. *Bipolar Disord*. 2009;11:523-529

Figure 1: (A) pHi and (B) [ADP] in the ACC of manic BD subjects are significantly decreased compared to healthy controls.