Lower Glutathione Levels in the Anterior Cingulate Cortex of Patients with Schizophrenia: A preliminary 3T 1H-MRS Study

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Target audience: Radiologist and psychiatrist

Purpose: Glutathione (GSH), a dominant antioxidant in the brain, exhibits modulatory effects on glutamatergic neurotransmission through the redox-sensitive modulatory site of N-methyl-D-aspartate receptor (NMDAR). Dysfunction of the NMDAR has been implicated in the pathophysiology of schizophrenia (Sz). Therefore, GSH has been target of research exploring biological mechanisms of Sz.

One postmortem study reported lower GSH level in the caudate of patients with Sz [1]. Emerging proton magnetic resonance spectroscopy (1H-MRS) techniques allow us to measure the GSH levels in-vivo. The previous 1H-MRS studies reporting GSH levels in the brain of patients with Sz have shown inconsistent results [2-5]. While few studies did not find any difference in GSH levels patients with Sz and healthy controls in the anterior cingulate cortex (ACC) [2] and posterior medial frontal cortex [3], a study reported higher levels of GSH in medial temporal lobe in Sz [4] and another study reported lower levels of GSH in medial prefrontal cortex in Sz [5]. Accordingly, further research is needed to examine the role of GSH in schizophrenia.

Our current study is aimed to compare GSH levels between in patients with Sz and healty controls (HC) quantified in the ACC employing a validated J-editing quantification method.

Methods: GSH levels were quantified with 1H-MRS. The scans were performed with an in-house 3-Tesla GE instrument. GSH was obtained using standard PRESS-based J-edited spin echo difference method (TE = 68 ms, TR = 1500 ms, and 256 interleaved excitations, total 512 with the editing pulse on/off 250/2000 Hz for a scan time of 13 min). The GSH spectra was obtained by setting the frequency of the editing pulse to the □-cysteinyl resonance of GSH at 4.56 ppm to detect the □-cysteinyl resonance at 2.95 ppm. The voxels had a size of 24 ml centered over the ACC extending to medial prefrontal cortex. The PRESS spectra for the quantification of creatine (Cr) was analyzed with the Linear Combination Model included in the LCModel software.

Results: Eighteen patients with Sz (3 females, 43.1 ± 11.0 years) and 9 HC were included in this study. GSH/H2O and GSH/Cr levels in the ACC were significantly lower in patients with Sz than HC (11.86 ± 2.70 vs. 7.45 ± 3.68, $t(25) = 3.46$, $p = 0.0002$ and 2.76 ± 1.38 vs. 4.21 ± 0.96, $t(25) = 3.15$, $p = 0.004$). Cr levels in the ACC were not different between the patients with Sz and HC (282.50 ± 22.76 vs. 278.14 ± 42.12, $t(25) = 0.35$, $p = 0.73$)

Discussion: Our pilot data demonstrated lower levels of GSH in ACC in patients with Sz compared with HC. The main limitations of this study include the small sample size, the lack of stratification of patients according with the illness stage and severity.

Conclusion: Our results suggests that the NMDAR hypofunction previously described in schizophrenia may be partially explained by a decrease in GSH concentration. The results open a new potential therapeutic strategy in Sz using compounds that modules GSH levels. The present results provide a compelling rationale for larger investigations to clarify the role of GSH in schizophrenia.

Reference:

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