Anterior Cingulate Glutamate Concentrations as a Window to Study Impact of Inflammation on Behavior

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Target Audience Academic researchers, physicians and scholars who are interested in studying the impact of inflammation on behavior

Purpose Increased neural and glial activity in several brain regions including dorsal anterior cingulate cortical (dACC) regions has been reported to occur in response to inflammatory activation by infections, cancer and chronic psychological stress. Dorsal ACC activity has been associated with multiple behaviors including appraisal of threat, expending effort, error prediction and conflict monitoring, and its impairment in the face of ongoing inflammation can lead to behavioral disorders such as anxiety and depression [1, 2]. We designed a study to test the hypothesis that depressed patients with CRP > 3mg / L (high inflammation) will show an increase in the dACC glutamate (Glu / creatinine or Glu / Cr) and inositol (Ins / Creatine or Ins / Cr) levels indicating high levels of neuronal and glial activation and further that the neural metabolite changes will be directly and positively correlated with inflammatory biomarkers seen in plasma.

Methods Twenty-four subjects participated in this study. These subjects were divided into two groups based on their CRP: a Low CRP group (CRP < 3 mg / L, n=15) and a High CRP group (CRP > 3 mg / L, n=9). For each subject, T_1-weighted images were obtained on a 3.0 Tesla Siemens Magnetom TRIO scanner (Siemens Medical Solutions, Malvern, PA) with an MPRAGE sequence (TR = 2300 ms, TE = 3.02 ms, TI = 1100 ms, Flip Angle = 8°, voxel size = 1 × 1 × 1 mm^3). Single voxel H^1-MRS data were collected with a PRESS sequence (TR = 3000 ms, TE = 30 ms, sampling size = 1024, 128 averages). The voxel size for the dACC is 20 × 30 × 10 mm^3 (Fig. 1). The MRS data were analyzed with LCModel to assess concentrations of creatine (Cr), myo-inositol (Ins), choline (GPC), glutamate (Glu), and N-acetylaspartate (NAA). Concentration ratios of these metabolites over creatine were further analyzed with SPSS 20.

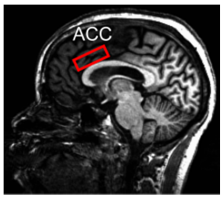

Fig. 1. Voxel location for the MRS scan.

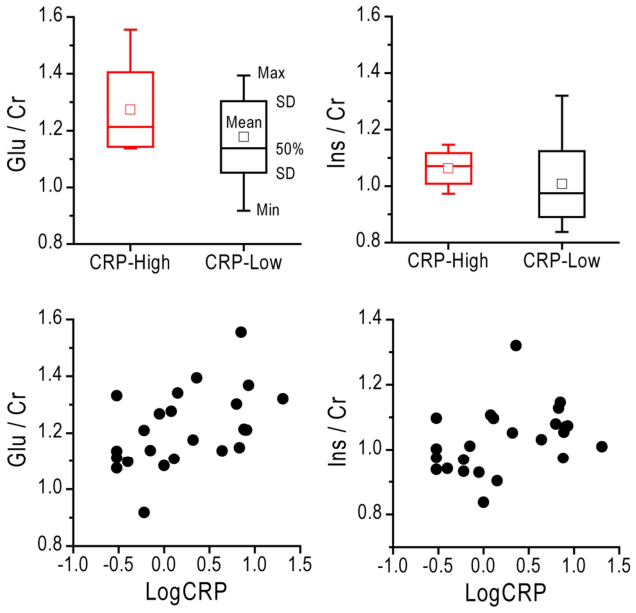

Fig. 2. Upper: Differences in Glu / Cr and Ins / Cr between the High and Low CRP groups. Lower: Correlation between the metabolites (Glu / Cr and Ins / Cr) and log of CRP.

Results Differences in metabolites' concentration ratios between the High and Low CRP groups were analyzed with independent-samples Mann-Whitney U test. The results showed that the Glu / Cr and Ins / Cr were higher in the High CRP group than in the Low CRP group, although the difference did not reach statistical significance (Fig. 2. Glu / Cr, p = 0.073; Ins / Cr, p = 0.073). The metabolites' concentration ratios also were correlated with log of the CRP score using Spearman's correlation analysis. As shown in Fig. 2, the Glu / Cr and Ins / Cr were significantly correlated with log of the CRP score (Glu / Cr: correlation coefficient = 0.540, p = 0.006; Ins / Cr: correlation coefficient = 0.405, p = 0.050).

Discussion The results reported in this study suggest that the metabolism of glutamate and myo-inositol in the anterior cingulate cortex may be altered by inflammatory status. These changes in the central nervous system may be the underlying mechanisms for the behavioral alterations induced by inflammation such as anxiety, fatigue and poor motivation. Further investigation with a larger sample size and correlation of behavioral outcomes with metabolic, functional and structural changes in these brain regions will improve our understanding of the impact of inflammatory status on the brain and behavior.

Conclusion A better understanding of mechanisms of glutamate elevation in inflammatory status might provide a better target for new drug development or repurposing previously developed agents.

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References

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