Metabolite Concentrations in the Basal Ganglia of Depressed Patients with High Inflammation

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Target Audience: The following presentation will be of interest to clinicians studying neurological and psychiatric disorders and scientists who employ magnetic resonance spectroscopy techniques for brain imaging.

Purpose: Interactions between the immune system and the brain contribute to the pathophysiology of many neurological and psychiatric disorders. Of particular interest has been the relationship between increased inflammation and major depression (MDD). Proinflammatory molecules including cytokines have been shown to target subcortical brain regions including the basal ganglia - a region known to participate in the regulation of mood and cognitive functions. Using single-voxel magnetic resonance spectroscopy (MRS), we previously showed that four-week administration of interferon (IFN)-alpha (a cytokine) for treatment of hepatitis C virus disease resulted in a significant increase in glutamate concentration in the left basal ganglia regions which in turn was associated with decreased motivation.[1] We hypothesized that similar changes would be seen in the basal ganglia of patients with MDD and high inflammation - a distinct subtype of MDD - leading to different treatment considerations.[2] Our secondary goal was to determine the utility of multivoxel MRS (chemical shift imaging, CSI) in quantifying brain metabolite changes resulting from inflammation in patients with MDD. Compared to single voxel techniques, CSI has the advantage of being able to simultaneously acquire metabolite concentrations from spatially segregated regions such as bilateral brain basal ganglia.

Methods: Fifty-three unmedicated human subjects diagnosed with MDD per DSM-IV criteria underwent blood draws, psychiatric symptom ratings, and CSI scans. Serum levels of C-reactive protein (CRP) were used as a measure of systemic inflammation and to categorize the subjects as follows: low (CRP <1 mg/L; 21 subjects), average (1 mg/L< CRP <3 mg/L; 11 subjects), and high inflammation subgroups (CRP >3 mg/L; 21 subjects). All magnetic resonance data was acquired on a 3.0 T Siemens Magnetom TRIO scanner (Siemens Medical Solutions, Malvern, PA). A T1-weighted 3D image of the brain was acquired with an MPRAGE sequence (TR = 2300 ms; TE = 3.02 ms; flip angle = 8°; 1 mm isotropic resolution). A double spin-echo point resolved spectroscopy (PRESS) sequence (TR = 1590 ms; TE = 30 ms; 10.3 x 10.3 x 15 mm^3 voxel size; 16x16 acquisition matrix; 1024 data points; 7 averages) was used to acquire CSI data. A 2x3 voxel area in bilateral subcortical regions at the level of basal ganglia was used to obtain metabolite concentrations (Figure 1A). LC Model (Version 6.3-1H)[2] was used to analyze CSI data using an 18 metabolite basis-set to estimate individual metabolite concentrations using a non-water suppressed water peak to scale the data. The metabolite concentrations were normalized to the sum of creatine and phosphocreatine concentrations (/Cr) to reduce structural heterogeneity effects. Concentration values with Cramér-Rao lower bound values >20% were not used in analysis. Significance was calculated using two-way ANOVA and characterized by p-values <0.05. A sample spectrum is shown in Figure 1B.

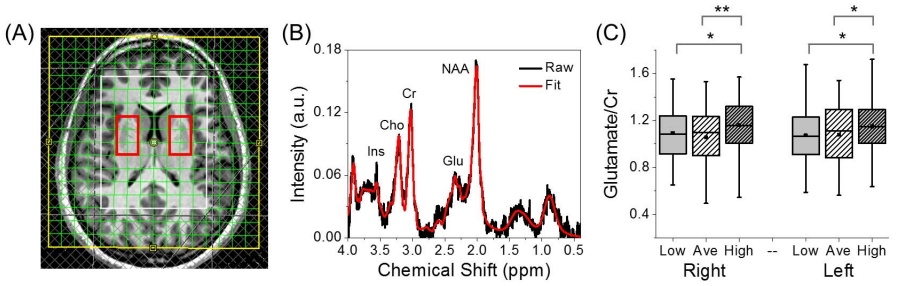

Figure 1. (A) CSI grid used for analysis. Red boxes indicate regions of the basal ganglia used to calculate metabolite concentrations. (B) Sample MR spectrum. (C) Mean (± standard deviation) glutamate concentrations normalized to creatine (Cr) in the basal ganglia as a function of low, average (Ave), or high inflammation.

Results: Basal ganglia metabolite/Cr concentrations are reported in Table 1. A significant increase in both glutamate (Glu/Cr, Figure 1C) and *myo*-inositol (Ins/Cr) were observed in both the left and right basal ganglia of subjects with high inflammation. Choline (Cho/Cr) concentrations in the basal ganglia decreased significantly in the average inflammation group compared to high and low inflammation groups. N-acetylaspartate (NAA/Cr) concentrations did not change significantly.

Table 1. Mean (± standard deviation) basal ganglia metabolite concentrations as a function of inflammation.

Metabolite	Low (n=21)	Average (n=11)	High (n=21)	F values
Right Glu/Cr	1.09 ± 0.23	1.06 ± 0.26	1.16 ± 0.21	F[2,310] = 5.63, p=0.004
Right Ins/Cr	0.64 ± 0.14	0.678 ± 0.14	0.75 ± 0.16	F[2,308] = 15.69, p<0.001
Right NAA/Cr	0.98 ± 0.22	0.99 ± 0.24	1.00 ± 0.22	F[2,282] = 0.21, p=0.814
Right Cho/Cr	0.23 ± 0.04	0.21 ± 0.36	0.23 ± 0.04	F[2,315] = 6.16, p=0.002
Left Glu/Cr	1.07 ± 0.23	1.11 ± 0.26	1.15 ± 0.22	F[2,310] = 3.82, p=0.023
Left Ins/Cr	0.66 ± 0.15	0.62 ± 0.17	0.75 ± 0.16	F[2,311] = 17.25, p<0.001
Left NAA/Cr	0.94 ± 0.35	0.90 ± 0.25	0.99 ± 0.24	F[2,272] = 2.85, p=0.06
Left Cho/Cr	0.23 ± 0.04	0.21 ± 0.39	0.23 ± 0.04	F[2,315] = 4.07, p=0.018

Discussion and Conclusions: The basal ganglia is a region known to regulate behavioral functions including motivation, affect regulation, and cognitive functioning. We observed a significant increase in Glu/Cr concentrations in the basal ganglia among depressed patients with high inflammation. These results are consistent with our previous studies.[1] At a synaptic level, glutamate concentrations are regulated and cleared by astrocytes through a high energy-dependent reuptake mechanism. It is likely that the ongoing inflammatory processes disrupt these reuptake mechanisms leading to decreased clearance of glutamate as astrocytic functions are highly regulated by cytokines under proinflammatory conditions. Ins/Cr is believed to be an astrocytic marker[4] and its increase lends support to the possibility of underlying glial dysfunction. Our previous findings on central nervous system changes following administration of IFN-alpha were specific to the left basal ganglia region as opposed to the bilateral changes seen in this study. We hypothesize that this might have resulted from the differences in the nature of the immune stimulation with IFN-alpha producing a more robust response as opposed to the low-grade activation seen in MDD. The differences observed between different grades of inflammation (high vs average vs low) seem to support this possibility. The directionality of the findings on choline might have been affected by the small sample of individuals with average inflammation available for this study. However, the current data lends support to our original hypothesis that chronic systemic inflammation might lead to selective targeting of basal ganglia functioning among patients with MDD. We expect these results will provide valuable insight into the role of inflammation in the underlying mechanism of behavioral disorders such as MDD.

References:

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