Interferon-alpha Induced Metabolic Alterations in Basal Ganglia and Anterior Cingulate Cortex

Xiangchuan Chen[1], Reena Anand[2,3], Xiaoping Hu[1], and Ebrahim Haroon[2,3]

[1]*Biomedical Imaging Technology Center, Emory University, Atlanta, GA, United States,* [2]*School of Medicine, Emory University, Atlanta, GA, United States,* [3]*Winship Cancer Institute, Atlanta, GA, United States*

Introduction

Chronic administration of interferon (IFN)-alpha (a pro-inflammatory cytokine) for the treatment of hepatitis C virus (HCV) infection is associated with depression and fatigue in 40-50% of patients [1]. These behavioral outcomes have been correlated with alterations in glucose metabolism in basal ganglia (BG) and in neural activation patterns in anterior cingulate cortex (ACC) [2,3]. Based on these results, we hypothesized that the IFN-alpha induced metabolic changes in the abovementioned brain regions might underlie those changes in behavior. This hypothesis was investigated with H^1-magnetic resonance spectroscopy (MRS) in this study.

Methods

After all patients with associated primary psychiatric disorder (including depression), unstable medical conditions and active intake of psychotropic medications were excluded, twenty-one patients with HCV infection participated in this study. These patients were divided into two groups: (1) an IFN-alpha treated group (IFN group, n=7) who underwent two MRI sessions, one before and another after a 4-week treatment; (2) a control group (who was waiting for the same treatment procedure, n=14) who underwent the same two MRI sessions with a 4-week interval. In each MRI session, 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 ACC and BG (Fig. 1) is 20 × 30 × 10 mm^3 and 17 × 30 × 17 mm^3, respectively. The MRS data were analyzed with LCModel to calculate concentrations of creatine (Cr), myo-inositol (Ins), choline (GPC), glutamate (Glu), and N-acetylaspartate (NAA). Concentration ratios of these metabolites over creatine were further compared between the two groups and two scan sessions with ANOVA and t-test in SPSS 19.

Results

A 2 × 2 (two participant groups × two scan sessions) ANOVA showed that the ACC and left BG exhibited the same pattern of treatment effect of IFN-alpha on Glu / Cr (Fig. 1, right), while the ACC and right BG demonstrated similar influences of the treatment on GPC / Cr and Ins / Cr (Fig. 1, left). For Glu / Cr, both ACC and left BG showed a marginally significant interaction effect of group × session (ACC: $F_{1,19} = 3.42$, P = 0.080; left BG: $F_{1,19} = 3.75$, P = 0.068). For Ins / Cr, both ACC and right BG showed significant group difference (ACC: $F_{1,19} = 4.986$, P = 0.038; right BG: $F_{1,19} = 4.442$, P = 0.049). For GPC / Cr, the ACC demonstrated significant group difference ($F_{1,19} = 4.512$, P = 0.047), while the right BG exhibited marginally significant session difference ($F_{1,19} = 3.495$, P = 0.077). Further t-test showed that there were significant group difference in GPC / Cr and Ins / Cr (all P's < 0.05) in scan session 2, but not in session 1 for both ACC and right BG.

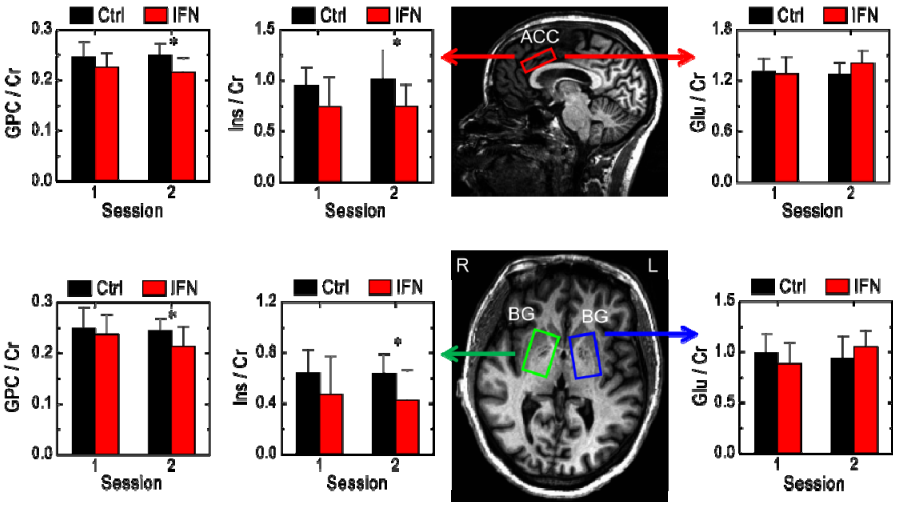

Fig. 1. Concentration ratios of GPC, Ins and Glu over Cr for the control (Ctrl) and IFN groups in scan sessions 1 and 2. Error bars are SD. *: significant group difference (p < 0.05).

Discussion and Conclusion

The results reported in this study support our hypothesis that the metabolisms of glutamate, myo-inositol and choline in the anterior cingulate cortex, left and right basal ganglia are altered by the treatment with IFN-alpha. These changes in the central nervous system may be the underlying mechanisms for the behavioral alterations (e.g., depression) induced by the treatment. Further investigations with a larger sample size and by correlating behavioral outcomes with metabolic, functional and structural changes in these brain regions will improve our understanding of the impact of inflammatory cytokine on brain and behavior.

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