MRS of Basal-Ganglia in Parkinson's Disease Reveals Higher GABA Levels

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Target audience: Clinicians and researchers interested in using GABA MRS as a biomarker in Parkinson's disorder or any other related movement disorder.

Purpose: The primary cause of Parkinson's disease (PD) is the loss of dopamine-producing neurons (DA) in the substantia nigra. A consequence of the reduced DA levels is believed to be an increase in the inhibitory input from the pallidal segment to the thalamus causing hypokinetic symptoms of PD[1]. MRS of the main inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), is of interest as a possible biomarker for PD; however, GABA may also be altered by many anti-Parkinson medicines. In this study, the utility of GABA MRS as a non-invasive biomarker of disease severity was explored in PD subjects, who temporarily withheld their medication, by evaluating the relationship between GABA and motor scores.

Methods: PD patients with mild-to-moderate symptoms (n=19; 3 medication-naïve, 16 withheld medication for at least 12 hours; age: 64.68 ± 9.12 y; 10 males) and controls (n=18; age: 58.44 ± 10.49 y; 12 males) underwent MRS on a Siemens 3-T Tim Trio scanner using a standard head coil. 3D T1-w MPRAGE and fast T2-w images were obtained for segmentation and planning of VOI, respectively. Single voxel short TE PRESS (TR/TE=2000/35 ms) and GABA-edited MEGA-PRESS[2,3] data (TR/TE=2000/68 ms, 256 averages, editing pulse BW=44 Hz, interleaved ON/OFF editing pulses at 1.9 and 7.5 ppm) was acquired in all subjects from a 25x30x25 mm^3 VOI placed in the right-side thalamus and striatum (Figure 1). A reference scan was also acquired for eddy current correction and water scaling. In addition, motor scores in all subjects were recorded using the motor sections of the MDS-Unified Parkinson's Disease Rating Scale (UPDRS-III) prior to MRS. LCModel[4] was used for quantification of metabolites including creatine, N-acetyl aspartate (NAA), myo-Inositol, glutamate + glutamine (Glx) and GABA (+macromolecules (MMs)). A cut-off criteria of CRLB < 20% was used for inclusion in further analysis. Segmentation was performed to account for partial volume effects in the voxel and the metabolites were expressed in absolute concentrations. Multi-variate analysis with age as covariate was performed in each VOI to calculate group differences. Pearson correlations were performed to assess the association between GABA and UPDRS-III scores.

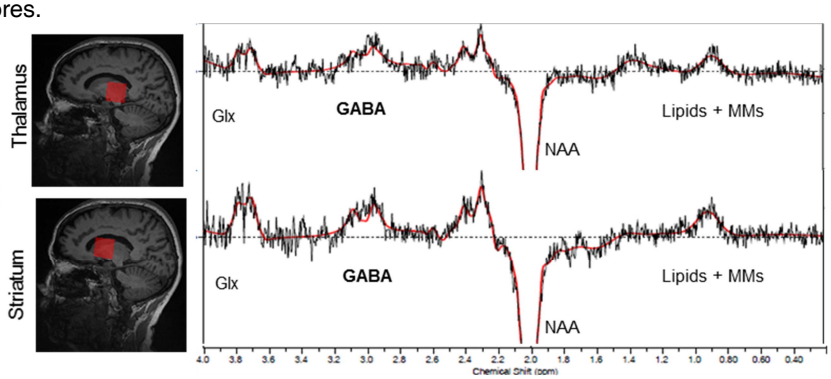

Figure 1. Representative VOI placement and GABA spectra from the thalamus (top) and striatum (bottom) of a PD subject.

Results and Discussion: Thalamic spectra were obtained with an average SNR of 20 and FWHM of 20 Hz whereas for the challenging striatum voxel, the average SNR was 18 and FWHM was 24 Hz over all participants. The shims were marginally better in controls than the PD subjects (p=0.05) due to the PD tremor. The voxel composition was not significantly different between groups in both the VOI. Significantly higher GABA (F=8.199, p=0.008) was detected in the thalamus of PD subjects (2.09 ± 0.39 mM) compared to controls (1.73± 0.29 mM) (Figure 2). No such differences was detected in other metabolites in the thalamus or in the striatum. The UPDRS scores of PD patients (33.34 ± 10.9) and controls (5.43 ± 3.36) were correlated with the GABA levels in the thalamus (R =0.459, p=0.006) (Figure 3).

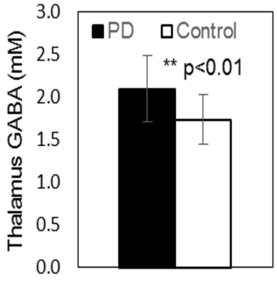

Figure 2. Thalamic GABA is higher in PD subjects.

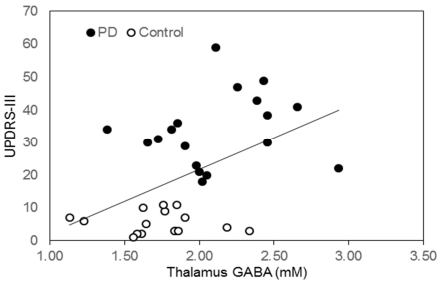

Figure 3. UPDRS scores are positively correlated with thalamic GABA in all subjects.

Conclusion: Elevated thalamic GABA in off-medication PD subjects is consistent with the known pathophysiology of PD; such that there is increased inhibition in the indirect pathway giving rise to hypokinetic symptoms. The correlation between thalamic GABA and disease severity measured by UPDRS-III highlights the possible utility of GABA MRS as a biomarker of disease severity. This study also lays a groundwork for a longitudinal study to assess GABA MRS as a biomarker of disease progression.

References: 1.DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol. 2007;64(1):20-24.2.Mescher M, Merkle H, Kirsch J, et al. Simultaneous in vivo spectral editing and water suppression. NMR in Biomedicine 1998;11(6):266-272.; 3. Edden RA, Barker PB. Spatial effects in the detection of gamma-aminobutyric acid: improved sensitivity at high fields using inner volume saturation. Magn Reson Med 58(6): 1276–1282; 4.Provencher SW. 1993. Magn Reson Med 30(6):672-679.

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