A Seven Year Longitudinal ^{31}P MRS Study of Schizophrenia

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Introduction Membrane phospholipid abnormalities have been implicated in the pathophysiology of schizophrenia.(1) Our phosphorus MRS longitudinal study of the first 30 months of schizophrenia revealed an increase in glycerophosphocholine (GPCh) in the anterior cingulate in patients as compared to controls, a decrease in glycerophosphoethanolamine (GPEth) in the left thalamus in patients over time and an increase in GPCh in the left superior temporal lobe in patients over time.(2) In our chronic schizophrenia study [length of illness = 21.6 +/-7.3 yrs] a decrease in GPEth was observed in both the anterior cingulate and left thalamus in patients as compared to controls.(3) These studies suggest an interruption in phospholipid turnover as the illness progresses. In a continuation of our first episode longitudinal study, a third scan [LOI =7 +/-2.1 yrs] has been acquired for both patients and controls. This scan permits the observation of metabolite changes 7 years into disease progression and allows the examination of the influence of age, medication and length of illness (LOI) on metabolite concentrations in the early years of psychosis. We hypothesized that at the 7 year time point, a decrease in GPCh will be revealed in the anterior cingulate in patients as compared to controls and will correlate with LOI; a decrease in GPeth will occur in the left thalamus in patients as compared to controls and will correlate with LOI; and an increase in GPCh in the left superior temporal gyrus will occur in patients as compared to controls and will correlate with LOI.

Methods To date, 8 patients (3 neuroleptic free) who met the DSM IV diagnosis of schizophrenia and 6 healthy controls have undergone the 7 year scan. These scans were included in the correlation analysis, along with 42 patient scans acquired in our previous first-episode studies.(2,4) Only 39 scans were used for the left superior temporal gyrus correlations. For 19 of the scans, patients were neuroleptic free. Forty-eight control scans, from 22 subjects, were used to determine if there were effects of aging on membrane metabolites.

Data was acquired with a 4.0 T whole body research scanner (Varian/Siemens/UnityINOVA). A ^{1}H quadrature head-coil was used for shimming and to acquire sagittal, coronal images (2D-FLASH-TR=11ms, TE=6ms, 256 phase-encodes, 0.93x0.93 mm pixels) and 32 T_1-weighted transverse images (3D-FLASH-TR=11 ms, TE =6.2 ms, nominal slice thickness = 4.375 mm and 1.09X1.09 mm in-plane resolution) for ^{31}P voxel location and to determine the grey matter, white matter and CSF fraction within these voxels. The ^{1}H coil was replaced with a ^{31}P quadrature head-coil, without moving the patient. Localized ^{31}P spectra were acquired from 15cc effective spherical voxels using an optimized 3D chemical shift imaging sequence with a spherically bound, random point omission, weighted k space. (TR = 500ms; pre-acquisition delay time = 1.905 ms; tip angle = 32°; matrix size (x, y, z) = 14X14X14 (zero-filled to 16X16X16); FOV (x, y, z) = 280 mm; data readout time = 400 ms).(4) Spectra were analyzed from of the left thalamus, left superior temporal gyrus and the anterior cingulate. After left shifting 5 time domain points to remove the broad membrane baseline component, unfiltered spectra were fit in the time-domain using a non-linear, iterative fitting program based on the Marquardt-Levenberg algorithm using prior spectral knowledge.(5) There was no T_2 weighting in the fitted data, since the fitting algorithm automatically extrapolated metabolite amplitude values back to t=0. Millimolar concentrations for each metabolite were determined after correction with literature T_1 values and an external reference standard (methylene diphosphonic acid (270mM)) mounted inside the ^{31}P coil.

All statistics were performed using SPSS version 10.0 for Windows. To determine metabolites differences between patients and controls at the time of the third scan a MANOVA was performed for each region, followed by an ANOVA for each metabolite. For the correlation of metabolite concentration vs. LOI a two-tailed Pearson correlation was performed on the specified metabolite vs. medication for the patients and metabolite vs. age for both patients and controls. Based on the directional hypotheses, a one-tailed Pearson correlation was performed on metabolites vs. LOI.

Results In the anterior cingulate the MANOVA was not significant (p=0.064, F=7.358, df=3). Due to our directional hypothesis, the ANOVA was still performed and revealed a significant decrease in GPCh in patients as compared to controls (p=0.015, F=8.014, df=1) and a decrease in PEth (p=0.050, F=4.761, df=1) in patients as compared to controls. In the left thalamus the MANOVA was significant (p=0.047, F=9.143, df=10,3) and the ANOVA for GPEth revealed a trend towards a decrease in patients as compared to controls (p=0.064, F=3.751, df =1). Neither the MANOVA nor ANOVA were significant in the left superior temporal gyrus.

The control subject correlation of metabolites vs. age was insignificant. The patient correlation analyses of metabolite vs. medication and age were, also insignificant. Glycerophosphocholine was negatively correlated with LOI in the anterior cingulate (r = -0.527, p= 0.0004, df=50) and GPEth was negatively correlated with LOI in the left thalamus (r=-0.326, p=0.01, df=50) and the correlation of GPCh, although positive, was insignificant in the left superior temporal gyrus. (r=0.032, p=0.425, df = 39).

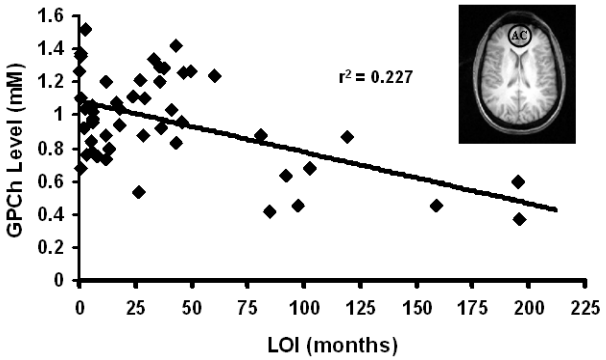

Figure 1. Level of glycerophosphocholine vs. length of illness in the anterior cingulate in the early years of schizophrenia. The solid line is the regression line with coefficient of determination $r^2 = 0.227$.

Discussion The preliminary results of patients vs. controls at 7 years revealed a significant decrease in GPCh in patients as compared to controls in the anterior cingulate, which is consistent with our previous findings.(2,3,4) The observed decrease in PEth, in patients as compared to controls, is consistent with our chronic findings.(3) The trend of decreased GPEth in the left thalamus of patients as compared to controls is consistent with our previous findings.(2,3) The correlation analysis of metabolite dependence on length of illness in both the anterior cingulate and left thalamus and are consistent with our longitudinal study results.(2) The lack of significance in the correlation of the left superior temporal gyrus with length of illness could result from the lower sample size as compared to the left thalamus and anterior cingulate analyses. The lack of significance of the correlation of metabolites vs. age in each of these regions in the control subjects suggests the observed metabolite changes in patients are not due to the effects of aging. These changes may represent an interruption in phospholipid membrane turnover as the disease progresses.

Limitations of this study include exposure to different types of atypical antipsychotic medications, which may have a different effect on phosphorous membrane metabolism at the time of scan. Even with T_1 correction, the phosphorous spectra may be T_1 weighted due to the short repetition time, which could be a potential source for the observed changes in metabolite concentrations in schizophrenia. In addition, the small sample size may account for some of the insignificance in our hypothesized changes. Other limitations of this study are described in Jensen et al, 2002.(5)

References

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