Cerebral Phosphorus Metabolites Profiling of Parkinson's Disease Patients at 7T

Xiao-Hong Zhu[1], Byeong-Yeul Lee[1], Susan Rolandelli[2], Paul Tuite[2], and Wei Chen[1]

[1]*CMRR, Department of Radiology, University of Minnesota Medical School, Minneapolis, MN, United States,* [2]*Department of Neurology, University of Minnesota Medical School, MN, United States*

Introduction The utility of the *in vivo* ^{31}P MRS technique has been enhanced significantly at high/ultrahigh fields owning to the high MR sensitivity, better spectral resolution and shorter longitudinal relaxation time (T_1), which allows non-invasive and reliable assessment of various phosphorus metabolites including the high-energy phosphate compounds within reasonable scanning time[1-2], thus, it is particularly important for studying impaired bioenergetics associated with various neurological diseases. Parkinson's disease (PD) is a common neurodegenerative movement disorder. It is believed that impaired energy metabolism due to mitochondrial dysfunction contributes to the pathogenesis of the PD[3-6]. However, better understanding of the underlying mechanisms of the disease requires reliable *in vivo* evidence from human patients. In this study, we aim to obtain cerebral phosphorus metabolites profiles in PD patients and matched controls (CT) with quantitative ^{31}P MRS measurements at 7T.

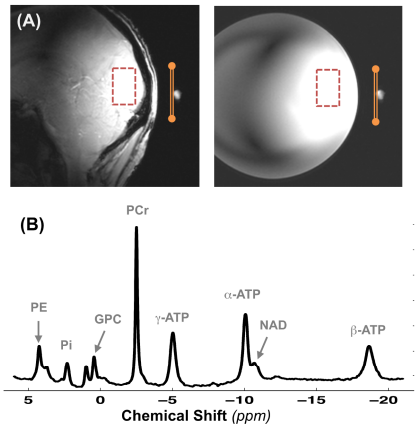

Figure 1. (A) ^{1}H MRI of human brain and phantom; and (B) a representative ^{31}P MR spectrum of human visual cortex at 7T. The positions of the ^{31}P surface coil with reference sphere at center and a typical ^{31}P-CSI voxel are displayed in the corresponding images.

Methods Seven PD patients (Age: 54-73 years, 4M/3F) and seven matched controls participated in this study. All MR measurements were conducted at 7 Tesla/90 cm actively shielded human scanner (Siemens) with a surface coil probe placed over the visual cortex for data acquisition. This probe consists of a quadrature ^{1}H coil for anatomic imaging and B_0 shimming and a single loop ^{31}P coil (Dia.=5cm) for collecting ^{31}P MRS and MRSI data. A small sphere containing reference phosphorus compound was placed at center of the ^{31}P coil for power calibration and optimization. For each subject, ^{31}P MR pulse-acquired spectra (NT=320, TR=3s and FA=84°) and 3D-MRSI data (FOV=12×12×9 cm, matrix=7×7×5, TR=1.2s, total NT=896 and FA=68°) were acquire with 300μs hard pulse. A 3D-MRSI data was also obtained after each human scan session from a spherical ATP phantom (containing 10mM ATP, 10.3mM [Mg^{2+}] and 45mM [Na^{+}] at pH of 7.0) with the same loading and position as the subject's head for calibration and quantification of brain metabolite concentrations. Software package jMRUI (v5.0) and AMARES method were used for spectral fitting and quantification of following phosphate resonances: phosphoethanolamine (PE); phosphocholine (PC); intracellular inorganic phosphate (Pi) and extracellular Pi (Pi^{ex}); glycerophosphoethanolamine (GPE); glycerophosphocholine (GPC); phosphocreatine (PCr); adenosine triphosphate (γ-, α- and β-ATP); and nicotinamide adenine dinucleotides (NAD). The resulted integrals were corrected for the saturation effects with relevant T_1 and flip angle (FA) information and were used to derive the metabolites concentrations based on [ATP] of the same subject as an internal standard. The ATP concentration of each subject was determined via comparing the ATP signals of identical 3D-MRSI voxels within the human brain and the ATP phantom, respectively. In addition, the brain tissue pH and free [Mg^{2+}] were also calculated. Student *t*-test was used for statistical analysis and a $p<0.05$ was considered statistically significant. All results were presented as Mean±SD.

Results Figure 1A displays the experimental setup and the ^{1}H MRI of human brain and corresponding ATP phantom. A typical *in vivo* ^{31}P spectrum of human visual cortex is shown in Fig. 1B which demonstrates excellent sensitivity and spectral quality achievable at 7T, thus, leading to reliable detection and quantification of the phosphorus metabolites *in vivo*. Direct comparison of the PD group (mean disease duration of 7 years) with age matched CT group (n=7) revealed almost identical metabolites profiles except a small trend of lower ATP and PCr in PD patients. However, as shown in Figure 2, when dividing the PD group according to gender, significant differences in PE, Pi contents and metabolites ratios of Pi/PCr and Pi/ATP were observed between the male and female PD patients, which was not the case in the CT subjects.

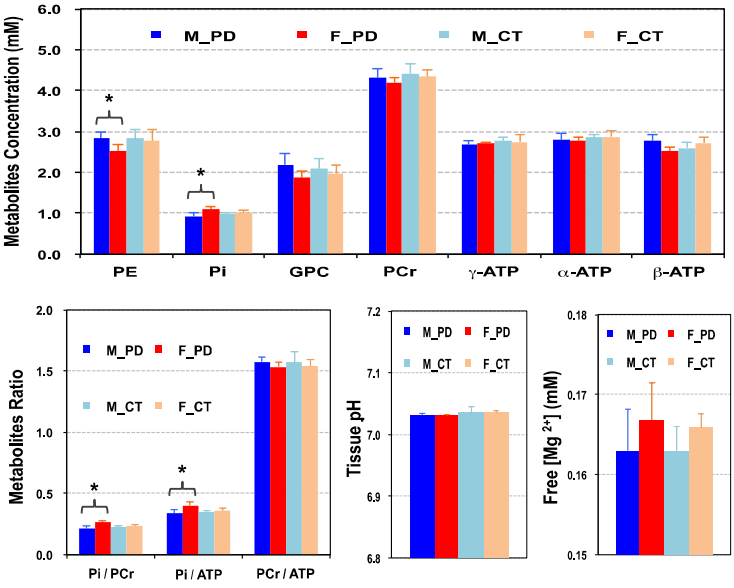

Figure 2. The human brain ^{31}P metabolites profiles, including metabolites concentration, metabolites ratio, tissue pH and free [Mg^{2+}] contents of Parkinson's Disease (PD, n=7) patients and matching control (CT, n=7) subjects are displayed and compared between male (M, n=4) and female (F, n=3) groups. Statistic significant differences ($p<0.05$) were observed in PE, Pi contents, Pi/PCr and Pi/ATP ratios between the male and female PD patients.

Discussion and Conclusion In the present study, although the number of PD patients being studied so far is relatively small (4M/3F), distinct phosphorus metabolites profiles in male vs. female patients have been revealed. This only becomes possible with the high sensitivity and reliability of the *in vivo* ^{31}P MRS achievable at high/ultrahigh field. The interesting observation of the metabolites differences between male and female PD groups has provided direct evidence regarding the involvement of altered energy metabolism and phosphorus lipid metabolism in the PD process. Further investigation is needed, which could give useful insights into the underlying mechanism and the potential contribution of the gender difference in the disease. In addition to demonstrate the superior sensitivity and quality of the 7T human ^{31}P MRS data, this work indicates that *in vivo* ^{31}P MRS at high/ultra-high field could provide an important and powerful tool for studying neurodegenerative diseases such as PD.

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References [1] Zhu et al. *Proc ISMRM* **20**:1781 (2012); [2] Lu et al. *Proc ISMRM* **20**:719 (2012); [3] Barbiroli et al. *JCBFM* **13:**469-474 (1993); [4] Rango et al. *JCBFM* **26:** 283-290 (2006); [5] Henchcliffe et al. *Ann. N.Y. Acad. Sci.* **1147:**206-220 (2008); [6] Hattingen et al. *Brain* **132:**3285-3297 (2009).