Quantification and Differentiation of CK and ATPase Fluxes between Human GM and WM using 3D ^{31}P CSI and Saturation Transfer

X-H. Zhu[1], F. Du[1], Q. Xiong[1], H. Qiao[1], X. Liu[1], J. Zhang[2], X. Zhang[3], K. Ugurbil[1], and W. Chen[1]

[1]Center for Magnetic Resonance Research, Department of Radiology, Minneapolis, MN, United States, [2]Department of Medicine, University of Minnesota, Minneapolis, MN, United States, [3]University of California San Francisco, San Francisco, CA, United States

INTRODUCTION *In vivo* ^{31}P MRS combined with magnetization saturation transfer (ST) approach is unique for noninvasively assessing the cerebral metabolic fluxes of two important reactions of CK and ATPase involving high-energy phosphate (HEP) ATP, PCr and inorganic phosphate (Pi) (i.e., PCr↔ATP↔Pi) [1-4]. However, its utility, especially for chemical shift imaging (CSI) application, relies on the adequate SNR and the appropriate quantification for reliably measuring the rate constants and fluxes. In this study, we aim to image the fluxes in the human brain using 3D ^{31}P-ST CSI approach with a short repetition time (TR), and our results demonstrate the superior capability of this approach for quantifying and differentiating the CK and ATPase fluxes in human grey (GM) and white (WM) matters at 7T.

METHOD All 3D ^{31}P CSI data and anatomic brain images were acquired on a 90-cm bore 7T Magnex magnet with a Varian INOVA console for achieving higher sensitivity and improved ^{31}P spectral resolution at high field [5, 6]. A circular-polarized double-tuned (^{31}P-^{1}H, 8 elements each channel) TEM RF head coil was designed [7], and applied for obtaining whole brain *in vivo* ^{31}P CSI and ^{1}H MRI at 7T with fairly uniform RF field (B_1) and flip angle (β) distributions for ^{31}P measurements. 3D ^{31}P CSI data were acquired using the Fourier Series Window (FSW) CSI technique [8] with following acquisition parameters: 5000 Hz spectral bandwidth; β=36° with a 500-μs hard RF pulse; 20×20×22 cm^3 FOV; 15×15×13 phase encodes; 0.73 s TR; 10.1 ml (or 2.3 ml nominal) voxel size; and total acquisition time of 48 minutes. A saturation pulse train based on BISTRO scheme was incorporated into 3D ^{31}P FSW-CSI, and applied at the γ-ATP resonance for measuring steady-state saturated magnetization (M^S) of PCr (or Pi) or set at the mirror frequency of γ-ATP with respect to PCr for measuring steady-state control magnetization (M^C). Multiple-slice T_1-weighted images were acquired and used for GM and WM segmentation and for quantifying their fractions (f_{GM} and f_{WM}) in each ^{31}P CSI voxels.

Due to limited 3D ^{31}P CSI sensitivity, small voxel size and large k-space sampling number, a much shorter TR (comparing to the mixed T_1 values of PCr and Pi) is desired for obtaining a full 3D ^{31}P FSW-CSI data set with sufficient signal averages and adequate SNR. At meantime, constrain in measurement time for human study also suggests that the CSI version of conventional progressive ST measurement with long TR would not be feasible. However, when CSI acquisition with ***short TR*** is incorporated with ST measurement, the ratio between measured M^c and M^s is governed not only by the forward CK and ATPase rate constants (k_f) but also many other parameters including TR, β and intrinsic T_1 values of PCr and Pi, leading to a daunting challenge for quantifying k_f and fluxes for CK ($F_{CK}=k_{f,CK}\times[PCr]$) and ATPase ($F_{ATPase}=k_{f,ATPase}\times[Pi]$) reactions.

For the conventional ST data obtained under fully relaxed condition, there is a simple relation between the M^c/M^s ratio and k_f according to $M^c/M^s = 1+k_f\times T_1^{int}$, where T_1^{int} is the intrinsic T_1 for PCr or Pi and can be treated as constant at a given magnetic field and has been measured at 7T [2, 3]. In the present work, we applied a novel approach for quantifying k_f from the 3D ST-CSI data acquired with very short TR of < 1s. This new quantification method is based on a simple, linear relation of $M^c/M^s \approx 1+k_f\times T_1^{nom}$, where T_1^{nom} is a nominal T_1. The T_1^{nom} value for CK or ATPase reaction can be obtained via simulation using modified Bloch-McConeell equations incorporated with three-site chemical exchange model [9] and known TR, β and the T_1^{int} values at 7T [2, 3]. The major merit of this T_1^{nom} quantification method is generic and suitable for any TR and β values. The ST CSI data were analyzed using the region of interest (ROI) with multiple voxels from two types of tissues: GM-like ROI and WM-like ROI, and the outcomes of the CK and ATPase rate constants and fluxes were further processed for correcting the partial volume effect between GM and WM based on the segmentation results of f_{GM} and f_{WM} and linear regression, leading to the fluxes values of pure GM or WM.

RESULTS and CONCLUSIN Figure 1 shows the simulation result indicating a perfect linear relation between M^c/M^s and k_f with a T_1^{nom} value of 3.11 s for CK reaction (and 2.45 s for ATPase reaction) for the human brain at 7T. Figure 2 illustrates the 3D ^{31}P ST-CSI (Fig. 2c) and ^{1}H MRI (Fig. 2b) data acquired from a representative healthy volunteer using the ^{31}P-^{1}H double-tuned RF head coil (Fig. 2a), and the saturated and control ^{31}P spectra from GM-like ROI (Fig. 2d) and WM-like ROI (Fig. 2e), respectively. These spectra demonstrate excellent ^{31}P sensitivity; they also indicate a higher PCr concentration and stronger ST effect in GM-like ROI than that of WM-like ROI. The overall CK results are summarized in the table below. Here we outline the major findings from this study. First, the average $k_{f,CK}$=0.30±0.03 s^{-1} and F_{CK} = 59.4±0.7 μmol/g/min from GM-like ROI measured in the present study are in excellent agreement with the literature values obtained with conventional progressive ST method [2, 3, 10]. Secondly, both the CK rate constant and flux are significantly higher in GM than WM, indicating a higher enzyme activity (or neuroenergetics) in GM for supporting intense neuronal activity. After the partial volume correction using linear regression (see Fig. 3), we determined F_{CK} = 82.1 μmol/g/min in pure GM tissue and F_{CK} = 27.9 μmol/g/min in the pure WM tissue in healthy human brain (n=7), indicating a 3-folds higher CK activity in GM. This result is supported by the literature reports based on the measurements of cerebral metabolic rates of glucose and oxygen or cerebral blood flow. Finally, the values of $k_{f,ATPase}$=0.19±0.22 s^{-1} and estimated F_{ATPase} = 8.5 μmol/g/min from GM-like ROI in this study are again consistent with the progressive ST results [2, 3]. However, there was a large uncertainty in determining the ATPase kinetics in WM-like ROI due to limited sensitivity for detecting Pi signal. In conclusion, with advanced ST-CSI techniques and new quantification method, we have successfully imaged and differentiated the CK and ATPase fluxes in the human GM and WM noninvasively at high field. Such an imaging capability opens up new opportunities for studying the brain metabolism and neuroenergetics associated with brain function and dysfunction.

REFERENCES [1]Shoubridge et al, *FEBS Lett* 1982; [2]Lei et al, *PNAS*, 2003; [3]Du et al, *MRM*, 2007; [4]Du et al, *PNAS*, 2008; [5]Lei et al, MRM, 2003; [6]Qiao et al, *MRI*, 2006; [7]Zhang et al, *ISMRM*, p. 423, 2003; [8]Hendrich et al, *JMR*, 1994; [9]Xiong et al, *AJP*, 2009; [10]Bottomley at al, *JMR*, 1992.

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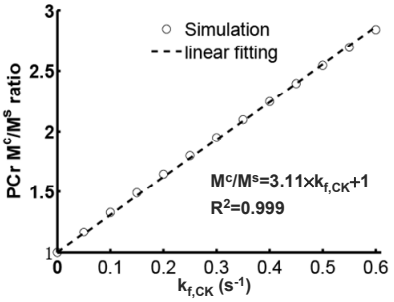

Figure 1 Simulation and linear regression results for determining T_1^{norm} of the CK reaction.

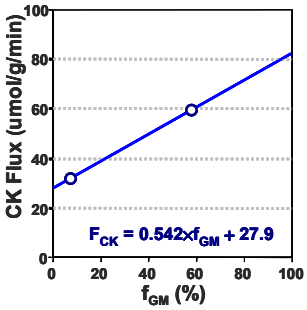

Figure 3 Linear regression to determine the CK fluxes in pure GM and WM tissue.

ROI (n=7)	f_{WM} (%)	f_{GM} (%)	[PCr] (mM)	$k_{f,CK}$ (s^{-1})	F_{CK} (μmol/g/min)
GM-like	35.7 ± 5.8	58.0 ± 5.1	3.65 ± 0.40	0.30 ± 0.03	59.4 ± 0.7
WM-like	88.6 ± 2.2	5.1 ± 1.8	2.86 ± 0.39	0.20 ± 0.03	31.8 ± 0.6

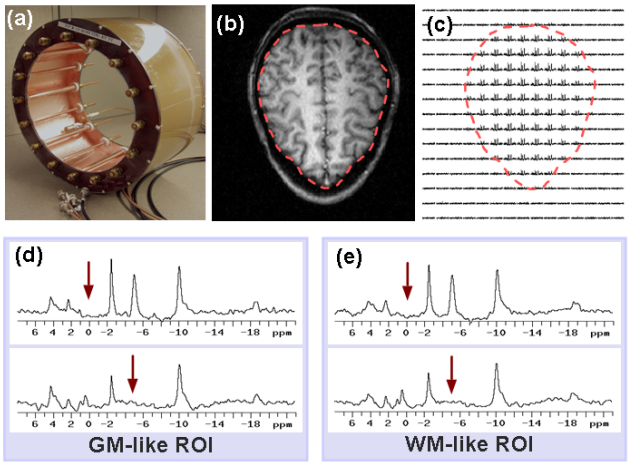

Figure 2 (a) ^{31}P-^{1}H double-tuned RF head coil; (b) T_1-weighted anatomic image; (c) 3D CSI; the γ-ATP-saturated and control ^{31}P spectra acquired from (d) GM-like and (e) WM-like ROI, respectively.