^{31}P Magnetization Inversion Transfer Approach for Measurements of Dynamic Parameters of Creatine Kinase and ATPase Reactions in the Human Brain at 7T: Comparisons to the Multi-Single-site Saturation Transfer Experiments

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Introduction Magnetization saturation transfer (ST) [1] and inversion transfer (IT) [2] as the non-invasive NMR approach are popularly used for studies of creatine kinase (CK) and ATPase reactions in the human and animal models. We have developed a magnetization saturation transfer method named as the multiple-single-site saturation transfer (MSS) [3] based on the three-site chemical exchange model for measuring all the chemical exchange rate constants and fluxes among PCr, ATP and Pi in the human brain. Principally, these chemical exchange dynamical parameters also could be determined by the IT approach. However, to date, the IT measurement was processed by the two-site chemical exchange model in which ATPase reaction was ignored. In this study, we used three-site exchange model and full matrix analysis method to perform IT measurements and determine the phosphorus metabolic fluxes in the human brain. We also compared its results with that deduced by MSS method.

Method Equation (1) described the dependence of magnetizations of chemically coupled spins on the inversion recovery time when the magnetizations of chemically coupled spins are selectively inverted. In this equation, A is kinetic matrix and $\vec{M}$ is the magnetization vector, in which three components equal to the longitudinal magnetizations of PCr, γ-ATP and Pi, respectively. $\vec{M}^0 = \vec{M}(t=\infty)$ are longitudinal magnetizations of PCr, γ-ATP, Pi at completely recovery condition. Equation (2) is the universal solution of Equation (1), where *I* is the 3×3 unity matrix and $\vec{M}(0)$ is the initial condition of Equation (1) at t=0. In principle, all kinetic parameters including three intrinsic relaxation times (T_1) and four chemical exchange rate constants (k) can be deduced from magnetizations recovery time courses of three components when magnetizations of any chemically coupled spins are selective inverted. In our current abstract only PCr was inverted to be discussed.

$$\mathrm{PCr} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{ATP} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{Pi}$$
a b c

$$\frac{\partial \vec{M}(t)}{\partial t} = \mathrm{A}\left[\vec{M}(t) - \vec{M}^0\right] \quad (1)$$

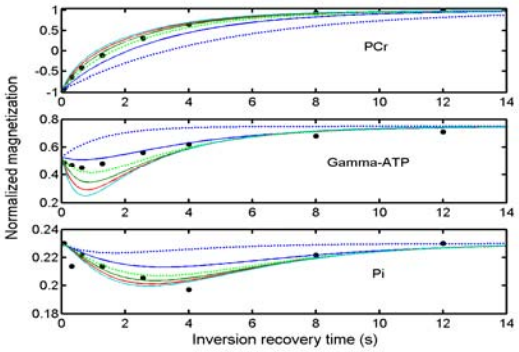
$$\mathrm{A} = \begin{Bmatrix} -(T_{1a}^{-1}+k_1) & k_{-1} & 0 \\ k_1 & -(T_{1b}^{-1}+k_{-1}+k_2) & k_{-2} \\ 0 & k_2 & -(T_{1c}^{-1}+k_{-2}) \end{Bmatrix}$$

$$\vec{M}(t) = (I - e^{t\mathrm{A}})\vec{M}^0 + e^{t\mathrm{A}}\vec{M}(0) \quad (2)$$

Experiments The experiments were performed at a 90-cm bore 7 T magnet with 6 healthy subjects. ^{31}P spectra from the human occipital lobe were acquired under full relaxation condition. Hyberbolic sech inversion RF pulse (180Hz exciting band) was used to selectively invert PCr peak.

Results and Discussions The dependences of magnetizations of PCr, γ-ATP and Pi on the inversion recovery time after PCr was selectively inverted were displayed in Figure 1 and Figure 2, in which the dots or cycles indicated the averaged experiment data from 6 subjects (error bars were ignored). The sensitivity of each parameter to the curve fitting was simulated and partially displayed in Figure 1 starting with the blue dash line corresponding to the initial value of zero, then increasing the simulated kinetic parameter with a constant increment. The green dash lines are estimated using the results of MSS measurements [3]. It is clear that although each line of magnetizations of PCr, γ-ATP and Pi contains the information of chemical exchange of CK and ATPase, the sensitivity of curve fitting is different. The curves of PCr, γ-ATP and Pi are much sensitive to the variance of kinetic parameters of CK (intrinsic T_1s of PCr and γ-ATP have the similar behavior as that of k_1), while the curves of PCr and γ-ATP dominated the error generation for parameter fitting of ATPase and are not sensitive to the variance of the chemical exchange rates of ATPase and intrinsic relaxation time of Pi (intrinsic T_1 of Pi has the similar behavior as that of k_{-2}), which are mainly determined by the magnetization of Pi. This also was demonstrated by the results of three curve fitting using three-site exchange model and full matrix analysis (see Figure 2). The intrinsic T_1 of PCr, γ-ATP as 4.68±0.21 s, 1.08±0.05 s, respectively, as well as k_1= 0.32±0.01 s^{-1} are in good agreements with results of MSS measurements [3]. While the intrinsic T_1 (=5.90±0.11 s) of Pi and k_{-2} (=0.45±0.02 s^{-1}) have large deviations relative to MSS results (3.77±0.53 s and 0.18±0.05 s^{-1}, respectively). However, the T_1 (=4.52±0.5 s) of Pi and k_{-2} (=0.18±0.04 s^{-1}) deduced only by the magnetizations of Pi agreed well with the results of MSS. The current studies should provide some new horizons for the bioenergetics studies using in vivo ^{31}P-IT approach.

(a) k_1=0:0.15:0.75



(b) k_{-2}=0:0.09:0.45

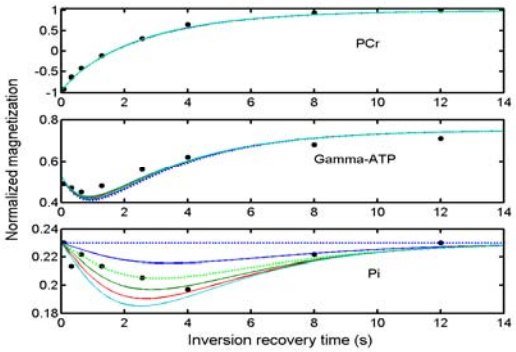


Figure 1. Curve fitting sensitivities of k_1 (a) and k_{-2} (b) for the PCr selective inversion experiments at chemical equlibrum condition (i.e., k_1×[PCr]=k_{-1}×[ATP] and k_2×[ATP]=k_{-2}×[Pi]). In each parameter fitting, the other parameters came from the MSS measurements.

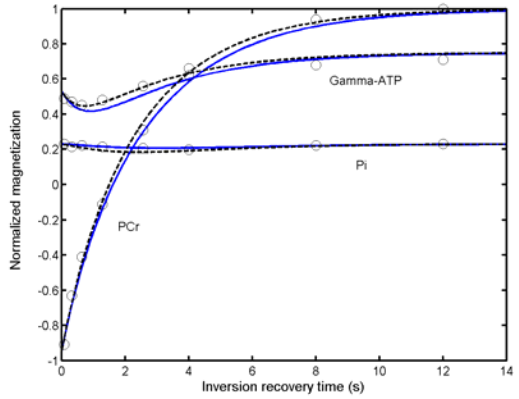


Figure 2. Five parameters curve fitting with the chemical balance. The straight blue line was obtained from MSS values and the black dash line was best fitting results.

Reference: 1. Sture F, et al. J. Chem. Phys. 1963. 2. Degani, H., et al. Biochemistry, 1985. 3. Du F. MRM 2006 (in press).

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