Quantitative Description of Proton Exchange Processes between Water and Endogenous and Exogenous Agents. The Sensitivity of pH Imaging Using Endogenous Amide Proton Transfer (APT) Contrast

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ABSTRACT

The proton exchange processes between water and solutes containing exchangeable protons have recently become of interest for monitoring pH effects, for detecting cellular mobile proteins and peptides, and for sensitivity enhancement of various low concentration endogenous and exogenous species. In this abstract, the analytic expressions for several types of experiments are derived using the Bloch equations with exchange terms. The case of endogenous amide proton exchange in the rat brain at 4.7 T is analyzed in detail.

INTRODUCTION

Proteins constitute 18% of the total mass of a typical mammalian cell. Although some of these proteins are MRS-detectable in cells and *in vivo*, it would be useful to have protein-sensitive image contrasts in the water signal to image spatial distribution of the protein content and related properties, such as pH and temperature. Imaging pH (intracellular and extracellular) using *in vivo* proton MR methods is an area of research that has recently become popular (1-6). One possible approach for this purpose is to perform low-power radiofrequency (RF) irradiation of the exchangeable solute protons and to follow the subsequent transfer of saturation to water. In such a chemical exchange dependent saturation transfer (CEST) approach (2), the proton exchange process (solute to water) is used as a means for detection sensitivity enhancement of low-concentration exogenous and endogenous agents, including small molecules (2), polymers (3), and paramagnetic Europium (III) and Lanthanide (III) complexes (4,5). In the recent *in vivo* amide proton transfer (APT) imaging experiments (6,7), the signals from endogenous protein/peptide amide protons are enhanced using this approach and used to assess cellular pH effects and protein/peptide content.

THEORY

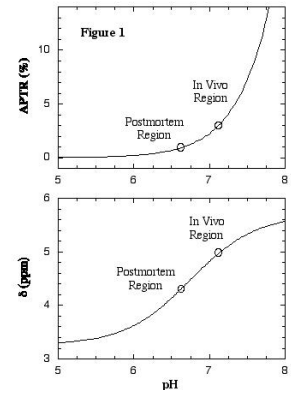
We used a two-pool proton exchange model: a small pool for water-exchangeable solute protons (s) and a large pool for bulk water protons (w). It is somewhat cumbersome to obtain the exact analytical solutions of the problem. As an approximation, we can separate the question into two steps, namely, the instant labeling/saturation process of pool s, followed by the transfer process of saturation to pool w. Therefore, the proton transfer ratio (*PTR*) in the water signal can be derived to be

$$PTR = \frac{M_{0w} - M_{zw}(t_{sat})}{M_{0w}} = \frac{k_{sw}\alpha M_{0s}}{(R_{1w} + k_{ws})M_{0w}}\left[1 - e^{-(R_{1w}+k_{ws})t_{sat}}\right],$$

where t_{sat} is the applied RF saturation time, α is the saturation efficiency for pool s, k_{sw} and k_{ws} are the exchange rates of protons from pool s to pool w and *vice versa*, $k_{sw}M_{0s} = k_{ws}M_{0w}$, $M_{0s} \propto$ [solute proton], $M_{0w} \propto$ [water proton]. *PTR* depends on the exchangeable proton concentration of the solute and chemical exchange rate of the particular protons, as well as on labeling/saturation efficiency for pool s and T_1 of the water. Under *in vivo* conditions, *PTR* is also related to the water content of tissue (*w*, [water proton] = 2 × 55 M × *w*). In addition, at fast exchange rates, high exchangeable proton concentrations, and a high magnetic field (low R_{1w}), k_{ws} (k_{ws} = k_{sw} ([solute proton]/[water proton]) may become comparable with R_{1w}, and back exchange (water protons to solute protons) may be of influence.

RESULTS AND DISCUSSION

Because water content and spin-lattice relaxation rates change for most pathologies, the prerequisite for proton exchange as specific image contrast is that the effects of exchangeable solute proton concentration and exchange rates in lesions outweigh those of water content and spin-lattice relaxation rates. When $k_{ws} >> R_{1w}$, *PTR* will become independent of the exchange rates and proton exchange will not work as a pH image contrast. We have demonstrated two important applications with the endogenous APT image contrast at 4.7 T, namely, non-invasive ischemia detection and cancer imaging. In these animal experiments, we found an *APTR* (*PTR* for amide protons) decrease of 1-3% in the affected areas of the rat brain during middle cerebral artery (MCA) occlusion (6) and an *APTR* increase of 3-4% in an experimental rat brain tumor (7), which were interpreted as being predominantly caused by decreased amide proton exchange rates (or decreased intracellular pH) and increased amide proton content in the lesions, respectively. We have calibrated the initial postmortem changes in APT for rat brain at 4.7 T (6), under the assumption that the effects were based on intracellular pH changes in the brain (base-catalyzed for pH values above ~5). The calibrated APTR-pH relationship was determined to be $APTR = 5.73 \times 10^{pH-9.4}$. Figure 1 shows the numerical calculation results, in comparison with ^{31}P spectroscopy. It can be seen that the sensitivity for measuring pH changes in the physiological range (pH 6.5-7.5) is quite good, showing an *APTR* reduction by 65% between normal (pH ~7.11) and postmortem (pH ~6.66) brain tissue. Fig. 2 shows the APT images (pH-weighted images and calculated pH maps) and diffusion-weighted images performed on a 4.7 T GE CSI animal imager for a rat following MCA occlusion (about 2 hours post-ictus). Several affected regions (caudate nucleus, cortex near caudate, cerebellum) were visible in all the images. There is a small core with very low calculated pH values in caudate nucleus of some animals.



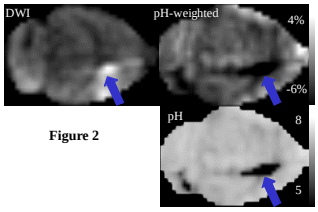


Figure 2

REFERENCES

(1) Helpern, et al. MRM 1987;5:302. (2) Ward, et al. JMR 2000;143:79. (3) Goffeney, et al. JACS 2001;123:8628. (4) Zhang, et al. JACS 2001;123:1517. (5) Aime, et al. MRM 2002;47:639. (6) Zhou, et al. Nature Med 2003;9:1085. (7) Zhou, et al. MRM In press.