Simultaneous ^{1}H MRS measurement of temperature and pH with a lanthanide complex

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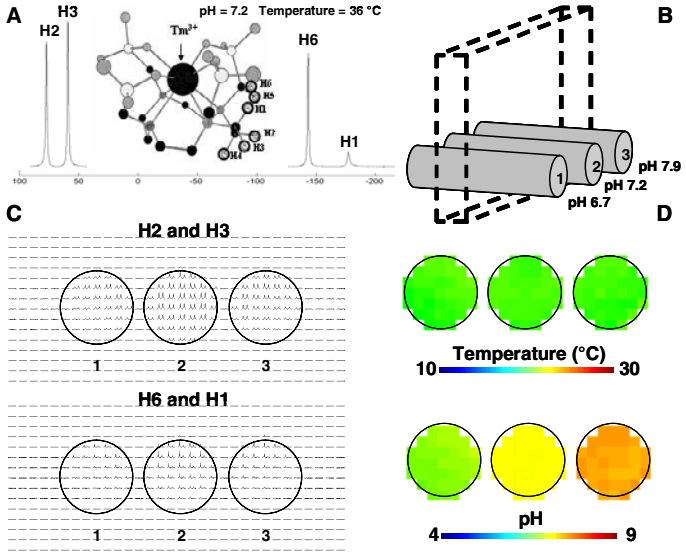
INTRODUCTION

In vivo measurements of brain temperature and pH distributions are scarce, mainly due to the lack of non-invasive methods. While thermocouple wires provide the most direct and absolute measure of brain temperature *in vivo* [1], measuring temperature across large brain regions are impractical. Near infrared spectroscopy is less invasive and therefore can provide temperature distribution assessments [2], however the methods are usually relative and do not provide measurements beyond the dorsal layers. In contrast, MRS can measure temperature and pH distributions non-invasively using temperature and pH based changes of chemical shifts from various molecules, both endogenous (e.g., water, NAA, P_i) and exogenous (e.g., shift reagents). The proton chemical shifts from the complex between the thulium ion and the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra (methylene phosphonate) – TmDOTP^{5-} a shift reagent **(A)** – are strongly dependent on temperature and pH [3,4]. Due to high sensitivity of each resonance on temperature and pH, models can be developed [3,4] to determine both temperature and pH simultaneously which basically exploit the sensitivities of two resonances with variable temperature and pH dependencies. Here we propose a new model which exploits the abundant temperature and pH information that is stored in all of the observable resonances of TmDOTP^{5-}. The variable temperature and pH interdependencies of at least three of the four resonances of TmDOTP^{5-} provide a highly redundant framework, which had not been exploited previously, to allow more accurate calibrations for temperature (±0.05 °C) and pH (±0.02) both *in vitro* and *in vivo*.



METHODS

Calibration: The data base for the model were obtained from various samples containing 5 mM Na[TmDOTP^{5-}] and 5 mM TSP at pH values between 6.5 and 8.0 and at various $CaCl_2$ concentrations from 0 to 5mM. For each sample, ^{1}H NMR spectra were acquired on an 11.7T Bruker vertical-bore spectrometer at various temperatures in the range from 25 to 45 ^{0}C. ***In vitro:*** Three adjacent samples containing 10 mM Na[TmDOTP^{5-}] at pH 6.7, 7.2 and 7.9 were used (**B**). The phantom 2D-CSI data were acquired on a modified 11.7T Bruker horizontal-bore spectrometer using a ^{1}H surface coil using the following parameters: TR = 11 ms, NS = 160, FOV = 4 cm, slice = 8 mm, and 16 or 32 encode steps in two dimensions. All spectra in a slice were line broadened (300 Hz) and baseline corrected (zero order) in a similar fashion. ***In vivo:*** Anesthetized rats were prepared with renal ligation for Na[TmDOTP^{5-}] as previously described [4] for 2D-CSI on the 11.7T horizontal-bore spectrometer.

RESULTS AND DISCUSSION

Since the chemical shifts of TmDOTP^{5-} protons have pseudo-linear temperature and pH dependencies [3,4], to improve accuracy of pH and temperature determination the non-linearity needs to be exploited fully. Moreover any given temperature/pH dependence on chemical shift has an additional dependency on pH/temperature and [Ca^{2+}] which has not been exploited previously. Therefore a multi-parametric solution exists in which a given chemical shift (of a proton) depends on specific values of temperature, pH, and [Ca^{2+}]. Preliminary results from *in vivo* experiments on rat brain indicate that the SNR for the H_1 proton is very low (data not shown) and therefore the chemical shift of this resonance is very difficult to measure. Therefore the maximum number of protons that can be used in the proposed model is reduced to three (H_2, H_3 and H_6) excluding the low SNR observable resonance (H_1). Using *in vitro* samples with high SNR and uniform (i.e., measured) temperature and pH within an NMR tube, at a given [Ca^{2+}], the equations that describe temperature and pH dependencies are

$$T = a_1 + a_2\,pH + a_3\ln(\delta_3) + a_4\ln(\delta_3) + a_5\ln(\delta_6) \text{ and } pH = b_1 + b_2 T + b_3\ln(\delta_2) + b_4\ln(\delta_3) + b_5\ln(\delta_6)$$

where T is the temperature and δ_2, δ_3 and δ_6 are the chemical shifts of H_2, H_3 and H_6 protons, respectively. The parameters a_i and b_i (i = 1 to 5) were obtained at each [Ca^{2+}] by multiple linear regression analysis. For example, at [Ca^{2+}] = 0, the error in temperature and pH predictions were ± 0.05 ^{0}C and ± 0.02, respectively. This approach to calculate temperature and pH distributions is demonstrated by a CSI experiment on three plastic tubes containing TmDOTP^{5-} at various pH values and all at room temperature (**B**). The result of the 2D-CSI experiment **(C)** for H_2 and H_3 protons (top) and for H_6 and H_1 protons (bottom) are shown separately since they were two independent experiments, one for the H_2 and H_3 protons and other for the H_6 and H_1 protons. The calculated temperature and pH maps (**D**) demonstrate the high accuracy of the method. The temperature is very homogenous in all three tubes, with average values of 19.1 ± 0.6, 19.2 ± 0.2 and 19.2 ± 0.6 °C for tube 1, 2 and 3, respectively, which are within 0.1 °C of bore temperature. The pH is also constant within each tube, with average values of 6.72 ± 0.08, 7.26 ± 0.03 and 7.94 ± 0.07 for tube 1, 2 and 3, respectively. The respective pH values calculated from the CSI data are within 0.06 of measured pH in each tube. The experimental errors associated with temperature and pH determination are slightly larger for the adjacent tubes in comparison to the central tube because of lower SNR for these compartments, which in turn caused inaccuracies of peak assignment. Therefore the small variations in temperature and pH values within each tube are not a result of the parameterization model used, but rather SNR limitations which can be improved upon further. While this multi-layered specificity on temperature, pH, and [Ca^{2+}] for each proton with respect to the chemical shift "space" of lanthanide complexes can be considered as a nuisance [5], here it has been exploited as an advantage because the TmDOTP^{5-} is an MR biosensor with high redundancy for both temperature and pH. In conclusion the current study introduces an improved model which combines magnetic properties of the TmDOTP^{5-} biosensor with high speed CSI to generate high resolution temperature and pH maps and opens the way towards a variety of non-invasive *in vivo* applications for the brain [6].

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