Comparison between $TmDOTP^{5-}$ and $TmDOTMA^{-}$ temperature probes in rat brain

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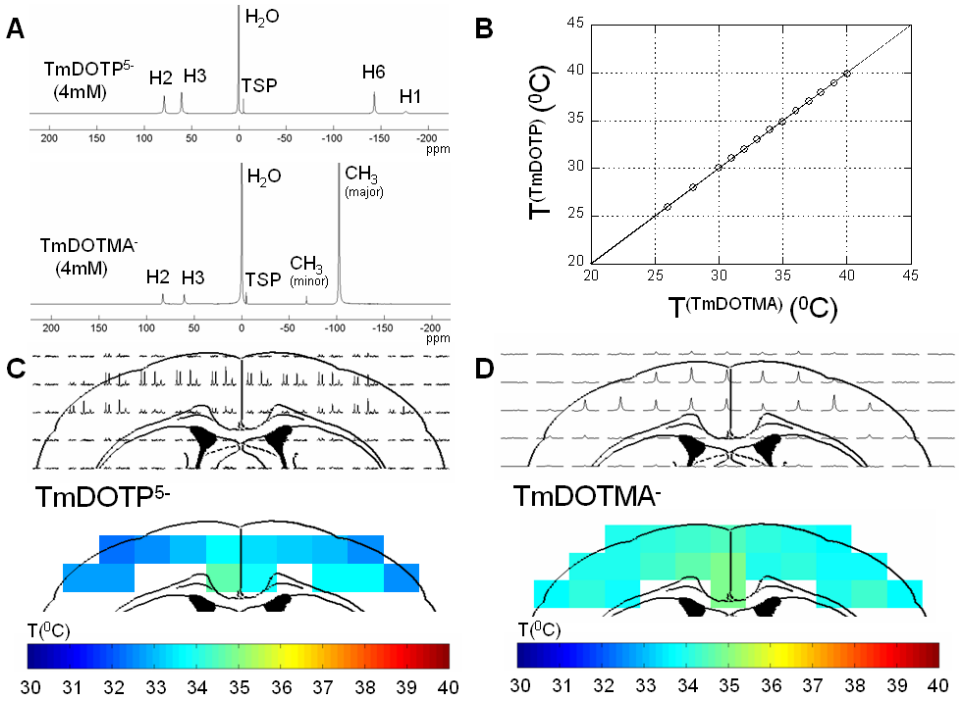
INTRODUCTION. A new non-invasive method for simultaneous measurements of temperature and pH – based on the strong dependence on temperature and pH of the proton chemical shifts from the complex between the thulium ion and the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra (methylene phosphonate) or $TmDOTP^{5-}$ (**A,** top**)** – has been developed [1-5]. Due to high sensitivity of each resonance on temperature and pH, models can be developed [2,3] to determine both temperature and pH simultaneously and with high accuracy in rat brain [4]. More recently, a new temperature-sensitive probe was introduced, using the same thulium ion integrated with a macrocyclic chelate of 1,4,7,10-tetraazacyclododecane-1,4,7,10- tetramethyl-1,4,7,10-tetraacetate or $TmDOTMA^{-}$ (**A**, bottom) where the methyl ^{1}H chemical shift of $TmDOTMA^{-}$ is pH-independent [6]. In the present work we compare the accuracy of temperature determination *in vitro* using these two temperature probes and discuss advantages and disadvantages of using these two complexes as non-invasive exogenous probes. Additionally we report detection of $TmDOTMA^{-}$ in the brain and we compare *in vivo* temperature distributions obtained using $TmDOTP^{5-}$ and $TmDOTMA^{-}$ complexes.

METHODS. ***In vitro:*** The ^{1}H NMR spectra of $TmDOTP^{5-}$ and $TmDOTMA^{-}$ were obtained using samples at pH values between 6.9 and 7.7, containing 4mM $TmDOTP^{5-}$ or 4mM $TmDOTMA^{-}$, respectively, and 3mM TSP in 10%D_2O. ***In vivo:*** Sprague-Dawley rats were prepared as previously described [4]. The rats were similarly anesthetized (1 to 2 % halothane for induction, then 40 mg/kg/hr α-chloralose). *In vivo* ^{1}H 16×16 CSI data were acquired on a modified 11.7T Bruker spectrometer using a ^{1}H surface coil. A gaussian pulse of 200 μs was used for excitation of a 4 mm slice with FOV of 2.56 cm×2.56 cm using previously described parameters [4,5].

RESULTS. Temperature-dependent redundancy of three $TmDOTP^{5-}$ protons, H2, H3 and H6, (**A**, top) can be used to increase the accuracy of temperature (and pH) prediction [3]. The temperature can be calculated from the chemical shift values δ_2, δ_3 and δ_6 of the protons using the equation: $T^{(TmDOTP)} = a_1 + a_2\delta_2 + a_3\delta_3 + a_4\delta_6 + a_5\delta_2^{\,2} + a_6\delta_3^{\,2} + a_7\delta_6^{\,2} + a_8\delta_2\delta_6 + a_9\delta_3\delta_6$, where nominal values of the parameters a_1 – a_9 were estimated by linear regression. For the $TmDOTMA^{-}$ complex, the chemical shifts of proton resonances do not depend on pH or Ca^{2+} concentration (data not shown). Therefore, temperature determination requires only the measurement of the methyl group only, for which the signal-to-noise ratio (SNR) is much larger than the SNR for the other proton resonances (**A**, bottom). Temperature can be calculated from the chemical shift of the methyl group of $TmDOTMA^{-}$ according to the equation: $T^{(TmDOTMA)} = b_1 + b_2\delta_{CH_3} + b_3\delta_{CH_3}^{\,2}$, where nominal values of the parameters b_1 – b_3 were also estimated by linear regression. To compare the accuracy of temperature determination using these two thulium agents, the temperature calculated using the chemical shifts of H2, H3 and H6 protons of $TmDOTP^{5-}$ ($T^{(TmDOTP)}$) was plotted against the temperature calculated using the chemical shift of $TmDOTMA^{-}$ methyl group ($T^{(TmDOTMA)}$) (**B**). All data points measured *in vitro* fell along the line of identity, demonstrating that there is no significant difference between temperature calculated using the three $TmDOTP^{5-}$ protons and temperature calculated using the $TmDOTMA^{-}$ methyl group. Although the SNR of the $TmDOTMA^{-}$ methyl group is much larger than the SNR of all $TmDOTP^{5-}$ protons under similar conditions (**A**), the temperature sensitivity of the $TmDOTMA^{-}$ methyl group is only 0.67 ppm/^{0}C, compared to the H6 proton of $TmDOTP^{5-}$ which has a temperature sensitivity of 1 ppm/^{0}C (at 35 ^{0}C and pH 7.4). Therefore the gain in accuracy of temperature determination due to higher SNR for the $TmDOTMA^{-}$ methyl group is partially compensated by its lower temperature sensitivity, resulting in very similar accuracies for temperature predictions for both $TmDOTMA^{-}$ and $TmDOTP^{5-}$ methods. The *in vivo* results suggest that both methods can be used successfully to calculate temperature distributions in the rat brain (**C** and **D**). The main advantage of the $TmDOTMA^{-}$ method is that it uses only one proton resonance, avoiding therefore the scanning of two different spectral regions (as in the case of the $TmDOTP^{5-}$ method). Although the linewidth of the $TmDOTMA^{-}$ methyl group is ~ 150 Hz *in vitro*, our *in vivo* results show a linewidth of ~ 450 Hz for this resonance, most likely because of inhomogeneous temperature distributions in the rat brain. The advantage of the $TmDOTP^{5-}$ method is that it can simultaneously provide temperature and pH measurements, which are extremely important in a large number of physiological and pathological situations.



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