MR Spectroscopic Measurement of Inhomogeneous Temperature Distribution in the Rat Brain

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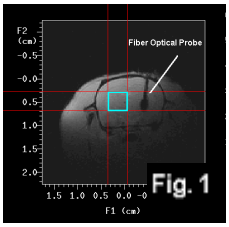
Introduction Proton magnetic resonance spectroscopy (MRS) determination of the water resonance frequency has been used for localized, non-invasive, brain temperature measurement with large animals (1). Application to small laboratory animals is challenged by the limiting SNR of the N-acetyl-aspartate (NAA) internal reference signal. We have extended this method and determined the brain temperature distribution in rat *in vivo*. Measurements employed a transmit/receive surface coil and modified Localization Adiabatic SelectivE Refocusing (LASER) sequence (2,3). Absolute brain temperature was calculated from the linear relationship between temperature and the water-NAA chemical shift difference. MRS results were compared with direct temperature measurements by thermocouple probes. We discuss our findings in light of a recently published theoretical model on brain temperature regulation (4).

Methods Non-invasive measurement by single voxel MRS: Imaging and spectroscopy were performed on an Oxford Instruments 4.7T/33cm horizontal-bore magnet with a 10cm inner-diameter, actively shielded Magnex Scientific gradient assembly controlled by a Varian NMR Systems INOVA console. Male Sprague-Dawley rats weighing approximately 300g were employed. Subjects were initially anesthetized with ketamine/xylazine (58.1mg/kg ketamine and 8.3mg/kg xylazine, i.p.). After 20min, subjects were restrained in prone position in a laboratory-constructed Teflon head holder and continuously supplied with 1.0% isoflurane in pure O_2 through a nosepiece. A single-turn, 3.0cm-diameter transmit/receive surface coil was placed on the head of each subject.



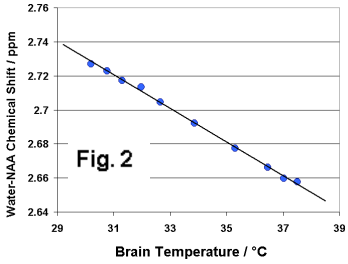
A temperature calibration curve was obtained via a Luxtron 1mm-diameter fiber-optical temperature probe placed vertically deep into left side of the brain through a drilled burr-hole (**Fig. 1**). The head was carefully insulated with cotton to diminish internal temperature gradients that would contaminate the calibration. The subjects torso was put on a circulating cold water pad (10°C), which decreased brain temperature at a rate of ~ 0.1 °C/min during the calibration measurement. A 4x4x3 mm^3 LASER voxel was placed at the right side of the brain (**Fig.1**) and spectroscopic data collected: 4kHz bandwidth, TR=1.6s, TE=75ms, 160 averages, 512ms acquisition time, and 2048 complex points.

Brain temperature distribution data was gathered from two cohorts of rats without surgical intervention, one cohort with (n = 4) and one cohort without (n = 5) cotton insulation about the head. Subjects were placed on a circulating 55-60 °C hot water pad. Deep rectal (7cm) temperature was continuously monitored by fiber optical probe. A pre-measurement temperature stabilization period of least 30min was employed following administration of isoflurane anesthesia. Field homogeneity was optimized over a localized 8x8x3 mm^3 rectangular voxel whose long axis extended from the brain surface to deep brain regions. A series of smaller voxels (1.5mm x 4.5mm in trans-axial plane, 3.0mm thickness) were then arrayed through the region defined by the large voxel for MRS temperature measurements. Starting at a location near the surface of the brain, six identical small voxels were set in positions increasing away from the surface (deeper) in 1mm increments. Spectroscopic parameters were the same as previously mentioned.

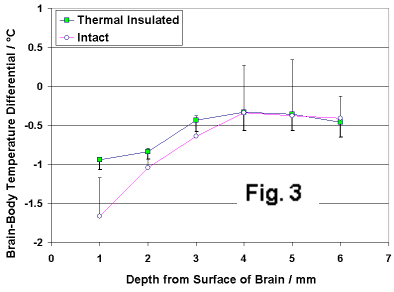
Post-process for frequency determination: All FIDs were Fourier transformed with 5Hz exponential window function via MestRe-C software. After automatic phase correction, water and NAA peak values were determined by the same program. Unless otherwise noted, results presented as mean ± SD.

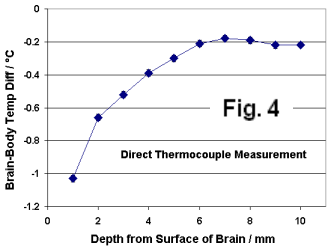
Direct measurement by thermocouple: Following the same surgical procedure as described above for temperature vs. MRS calibration, a Physitemp 36GA thermocouple probe was used to record brain temperature. The probe was vertically moved in 1mm steps from the brain surface to a 10mm deep location. At least 1min was allowed for temperature stabilization at each depth prior to measurement. The brain/body-core temperature differential at each brain depth was determined by averaging brain and body temperatures over a 1min period. The body core temperature was maintained at 37°C ± 0.5°C during the experiment.

Results and Discussion The water-NAA chemical shift vs. brain temperature relationship is shown in **Fig. 2**. The temperature calibration line was determined by fitting straight line to all data points: $T = -101.01 \times (\delta_{H2O} - \delta_{NAA}) + 305.77$ ($R^2 = 0.9982$), where T is temperature in °C, δ_{H2O} and δ_{NAA} are chemical shift values of H_2O or NAA in ppm.



The in-brain temperature gradient with and without thermal insulation of the head is shown in **Fig. 3**. Data are represented as brain-body temperature differential vs depth of measurement. The temperature difference between voxels close to surface vs center of brain (5mm apart) was 1.3 °C. In the thermally insulated situation, the temperature near the cortex was ~ 0.6 °C greater than in the non-insulated case, which decreased the brain-body differential to 0.7 °C. The temperatures monitored at all locations within the brain were lower than body core temperature, and the temperatures were consistently warmer in the brain center than in the peripheral (surface) area. Direct thermocouple measurements were in good agreement with MR single voxel temperature measurements (one example is illustrated in **Fig. 4)** and gave a 0.9 °C temperature differential between corresponding surface vs deep lying brain sites. An analytical model of temperature distribution in human brain has been reported recently (4). A blood flow dependent parameter "characteristic length, Δ", which represents the thickness of the surface layer with significant temperature gradient, is defined as: $\Delta=(\alpha_0/\rho_b c_b w_0)^{1/2}$, where α_0 is brain thermal conductivity, ρ_b and c_b are blood density and heat capacity respectively, and w_0 is blood flow. By modeling the temperature data from MRS (**Fig. 3**. red line) and thermocouple measurements (**Fig. 4**) to a single exponential function (4), the characteristic lengths were determined to be 1.8 ± 0.5 mm from MRS measurements and 2.3 ± 0.4 mm from thermocouple measurements. This is consistent with Δ=2mm – an estimate that can be obtained from the above theoretical expression employing known parameter values.





Conclusion Non-invasive measurement of brain temperature gradients in the isoflurane anesthetized rat was achieved using a transmit/receive surface coil and modified adiabatic pulse sequence. Results are consistent with direct brain temperature measurements with thermocouple probes. Both MRS and thermocouple measurements of brain temperature inhomogeneity are in agreement with a recently proposed theoretical model (4). Anticipated further optimization of this methodology will extend to multi-voxel MRS and real time monitoring of brain temperature gradient changes with small animal models under various physiologic challenges and sensory stimulation.

References [1] Corbett RJ, et al., J Neurochem 1995;64(3):1224. [2] Garwood M and DelaBarre L., J Magn Reson 2001;153(2):155. [3] Kroenke CD, et al., Magn Reson Med 2004;52(5):1052. [4] Sukstanskii AL and Yablonskiy DA., J Therm Biol 2004;29(7-8):583.

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