Dynamics and distributions of temperature changes during pharyngeal selective brain cooling by ^{1}H CSI

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INTRODUCTION

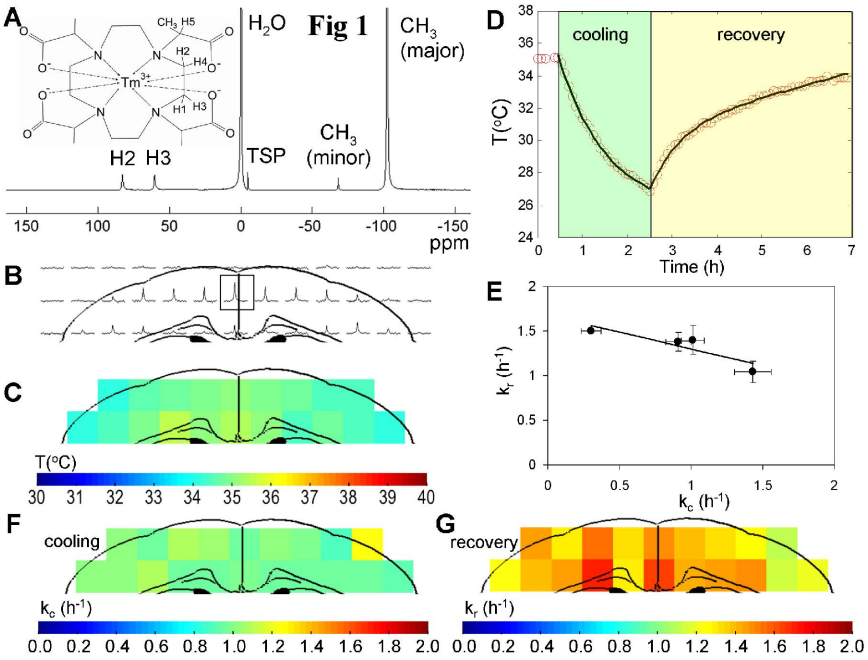
Therapeutic hypothermia is generally used to improve neurological outcome after either generalized [1] or focal [2] ischemic events affecting the brain. There are two different ways in which hypothermia can be applied: as whole body cooling [3] or as selective brain cooling (SBC) [4, 5]. However, the method of whole body cooling to decrease the brain temperature is associated with potential side effects such as infections, coagulopathy, cardiac arrhythmia and arterial hypotension [2]. Therefore, selective brain cooling has been suggested as a more suitable alternative [6]. Recently, we described a new approach to obtain pharyngeal selective brain cooling (pSBC) [7, 8]. In this method a cooling coil is inserted into the pharynx in order to cool the brain selectively. Temperature distributions in rat brain can be obtained within minutes by using a new temperature-sensitive probe which is based on the complex between the thulium ion (Tm^{3+}) and the macrocyclic chelate 1,4,7,10-tetraazacyclododecane-1,4,7,10- tetramethyl-1,4,7,10-tetraacetate or $DOTMA^{4-}$ **(Fig. 1A)** [9]. The methyl ^{1}H chemical shift of $TmDOTMA^-$ shows relatively high temperature sensitivity [9] and is pH-independent [10]. In the present study we use $TmDOTMA^-$ agent to measure time-dependent temperature distributions and from these we calculate the corresponding cooling rate constants in rat brain. In order to estimate the effect of local net heat contribution on the rate constants for cooling, we also measured the rate constants of recovery after cooling was stopped.

MATERIALS AND METHODS

Animal preparation: Sprague-Dawley rats (220-315 g) were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation, isoflurane (1 to 2 %) was used for induction. An intraperitoneal line was inserted for administration of α-chloralose (46 ± 4 mg/kg/hr) and an intravenous line for administration of D-tubocurarine chloride (1 mg/kg/hr) or $TmDOTMA^-$ (150-200 µmol/hr). An arterial line was used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment. The anesthetized rats were prepared with renal ligation as previously described [9]. pSBC was achieved by running ice-cold water for 2 hours through the cooling coil inserted into the pharynx. ***In vivo (n=4):*** All CSI data **(Fig. 1B)** were obtained on a modified 11.7 T Bruker horizontal-bore spectrometer (Billerica, MA) using a ^{1}H resonator/surface coil RF probe. A gaussian pulse of 200 µs was used for excitation of a 6 mm slice with FOV of 2.56 cm x 2.56 cm. The following parameters were used: 16x16 encode steps, TR=11 ms, 100 averages and 4 min 40s acquisition time. The spectra were line broadened (150 Hz), phased (zero order) and baseline corrected (first order) in a similar fashion in Matlab 5.3. The temperature maps **(Fig. 1C)** were calculated from the chemical shifts of $TmDOTMA^-$ methyl group according to the equation: $T=346+4.6\cdot\delta_{CH3}+0.0152\cdot\delta_{CH3}^2$ [9]. For each animal, the cooling and the recovering rate constants were calculated by fitting the temperature variation over time to a single exponential **(Fig. 1D, cooling)** or, if the fit was not good, to a sum of an exponential and a linear function **(Fig. 1D, recovery).** In the second case, the two different functions represent two separate processes which contribute to temperature changes, such as metabolic heat production and cerebral blood flow, as previously shown in our laboratory [11].

RESULTS AND DISCUSSION

The results in **Fig 1** represent the results for one animal. As an example, the temperature variations during the experiment for the central voxel, boxed in **Fig. 1B,** is shown in **Fig. 1D,** with the cooling period highlighted in light green and the recovery period in light yellow. For this experiment, the average brain temperature before cooling was 34.8 ± 0.4 ^{0}C and decreased to 26.7 ± 0.2 ^{0}C after 2 h of cooling. Therefore, the pSBC decreased the brain temperature by 8.1 ± 0.4 ^{0}C. After the cooling was stopped, the temperature was allowed to recover for ~ 4 h to 33.6 ± 0.3 ^{0}C. The average cooling rate constant was 1.01 ± 0.08 h^{-1}, while the average recovering rate constant was 1.40 ± 0.16 h^{-1}. The results for all the animals investigated indicate that there is a negative correlation (correlation coefficient R=0.88) between the average cooling rate constants (k_c) and the average recovering rate constants (k_r) in each animal **(Fig. 1E)**. This correlation is probably mediated by the local net heat contribution, which includes metabolic heat production, heat due to changes in cerebral blood flow or conductive heat exchange with the neighboring regions [11]. An increased net heat contribution will result in a decrease of the cooling rate constant and, correspondingly, an increase of the recovering rate constant. In all experiments, the temperature maps show a relatively homogenous temperature distribution across the entire cortical region, with standard deviations of less than 0.4 ^{0}C **(Fig. 1C)**. The distribution of the cooling rate constants is also relatively homogenous within the same animal **(Fig. 1F)**, although somewhat larger variations are observed between different animals **(Fig. 1E).** These results are in good agreement with a previous pSBC study in our laboratory using thermocouples, which indicate also similar cooling rates for various cortical depths [12]. In each animal, the recovering rate constants show a distribution which is slightly more dispersed than that of the cooling rate constants **(Fig. 1G)**. This could be due to different contributions from local net heat, process that is reflected more pronounced in the dispersion of the recovering rate constants. However, the range of the recovering rate constants for different animals investigated is relatively small (between 1 and 1.5 h^{-1}), compared with a relatively larger range for the cooling rate constants (between 0.3 and 1.43 h^{-1}) **(Fig. 1E).** In summary, our results indicate that the pSBC rate constants are tightly dependent on the local net heat contribution, measured indirectly by the recovering rate constants.



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