Stimulation-induced changes in temperature and pH measured simultaneously by ^{1}H CSI

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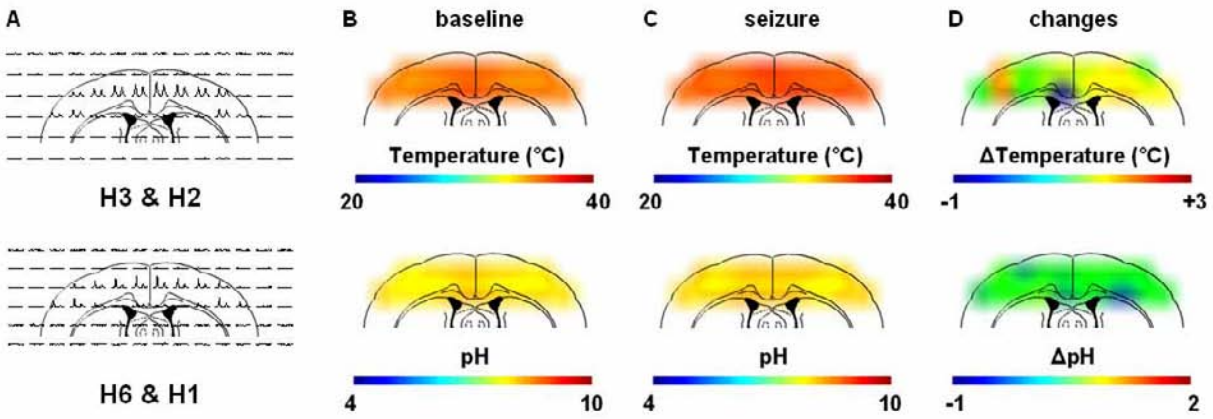
INTRODUCTION

Increased neuronal activity in the cortex leads to a rise in metabolic activity and blood flow [1] which results in a net change in brain temperature [2]. One of the most important neuromodulators in the brain is the H^+ ion which can affect neuronal function at the nanomolar level [3]. Changes in temperature have profound effects on the solubility of a range of solutes. Since a drop in temperature increases the solubility of gases like CO_2 in the tissue and CO_2 is a potential target for H^+, acid-base regulation is linked to temperature regulation [1]. It is important to note that pH has a vague meaning when temperature is varied, due to the fact that the water ionization constant varies with temperature. Thus measurement of both temperature and pH from the same compartment has great significance for determination of neuroprotective treatments (e.g., effects of hypothermia with selective brain cooling), interpreting neurophysiology of fMRI (e.g., contributions of temperature/pH induced changes in the MRI signal), tumor model diagnosis and understanding site-specific drug delivery (e.g., temperature/pH sensitive drug release systems). *In vivo* measurements of brain temperature and pH distributions are scarce, mainly due to the lack of non-invasive methods. In the present work, we demonstrate the feasibility of obtaining temperature and pH maps of rat brain for α-chloralose anesthetized rats, using an improved model which combines specific magnetic properties of the $TmDOTP^{5-}$ biosensor (such as short ^{1}H longitudinal and transverse relaxation times and a strong dependence of proton chemical shifts on temperature and pH) [4,5] with high speed CSI. The CSI data indicates that $TmDOTP^{5-}$ biosensor is accumulating mainly in the cortical area. Using this method, localized or global changes in temperature and pH associated with various stimulations (seizures, forepaw stimulations, whisker stimulations, etc.) can be directly measured. Preliminary results of temperature and pH distribution in rat cortex under various conditions are shown (Fig. 1).

MATERIALS and METHODS

Animal preparation: Sprague-Dawley rats (280-340 g) were tracheotomized and artificially ventilated (70% N_2O, 30% O_2). During the animal preparation, halothane (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), Na[$TmDOTP^{5-}$] (150-200 µmol/hr) and bicuculine (1 mg/kg). 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 for Na[$TmDOTP^{5-}$] as previously described [5]. ***In vivo (n=3):*** All CSI data were obtained on a modified 11.7 T Bruker horizontal-bore spectrometer (Billerica, MA) using a ^{1}H resonator/surface coil RF probe using the following parameters: TR = 11 ms, NS = 40, FOV = 2.56 cm, slice = 8 mm, acquisition time = 2 min and 16 encode steps in two dimensions. All spectra in a slice were line broadened (300 Hz) and baseline corrected in a similar fashion. The temperature and pH maps were calculated from the redundant information stored in the chemical shifts of H_2, H_3 and H_6 protons of $TmDOTP^{5-}$ (work submitted in a separate abstract).

Fig. 1



RESULTS and DISCUSSION

The CSI results from the rat brain shows rapid accumulation of $TmDOTP^{5-}$ in the extracellular space, where both the H_2 and H_3 as well as the H_6 and H_1 signals are easily detectable within 2 min of averaging (Fig. 1A). The temperature and pH distributions under normal conditions showed that the cortical values are near ~34 ^{0}C and ~7.3, respectively (Fig. 1B). Seizure events were induced in three rats using the competitive $GABA_A$ antagonist bicuculline and in all three cases, both temperature and pH are increasing during seizures relative to the baseline values (Fig. 1C). Temperature and pH distributions were calculated from the chemical shifts of H_2, H_3 and H_6 protons of $TmDOTP^{5-}$. The average temperatures in the three rat brains before infusion of bicuculine were 34.5 ± 0.8, 33.7 ± 0.7 and 34.7 ± 1.1 ^{0}C, respectively, and after infusion 38.4 ± 1.1, 35.1 ± 0.6 and 37.2 ± 0.9 ^{0}C, respectively. The pH average values before infusion were 7.35 ± 0.15, 7.30 ± 0.18 and 7.23 ± 0.26, respectively, and after infusion, 7.94 ± 0.37, 7.46 ± 0.19 and 7.53 ± 0.29, respectively. The average changes (Fig. 1D) in the temperature were 3.9 ± 0.9, 1.3 ± 0.8 and 2.5 ± 0.7 ^{0}C, respectively, while the average changes in the pH were 0.59 ± 0.35, 0.13 ± 0.19 and 0.34 ± 0.35, respectively. The results obtained for temperature changes during seizure are consistent with previous results using thermocouple wires [6], which indicated that brain temperature increases from 33.1 ^{0}C to 36.3 ^{0}C during seizure. We are currently validating the pH changes during seizure.

REFERENCES **[1]** Sokoloff L, *Feder Proc* 40:2311-2316, 1981. **[2]** Trubel HK et al., *J Cereb Blood Flow Metab,* 1-11, 2005. **[3]** Kaila K, Ransom BR, *pH and Brain Function,* Wiley: New York, NY, 1998. **[4]** Zuo CS et al., *Magn Reson Med* 36: 955-999, 1996. **[5]** Trubel HK et al., *J Appl Physiol* 94: 1641-1649, 2003. **[6]** Trubel HK et al., *Intensive Care Med* 30: 1829-1833, 2004.

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