Oxygen Effects in Tissue Preparation Neuronal Current MRI

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Introduction

Neuronal current MRI (ncMRI) is a promising technique which aims to produce brain function maps with more accurate localization and superior temporal resolution than BOLD fMRI. However, to date, the validity and reliability of neuronal current MRI (ncMRI) techniques are still controversial. Both positive[1-5] and negative[6] results have been reported in human subject studies. It is postulated that the conflicting results could have been due to hemodynamic contamination. To remove the hemodynamic effects, several groups have performed hemodynamic-free ncMRI experiments using tissue preparations, such as isolated snail ganglia[7-8] and rat brain slices[9], and have detected significant MRI signal changes when applying stimulation to the tissue preparations.

Although the potential hemodynamic artifacts are eliminated, the paramagnetic nature of oxygen poses another problem for tissue preparation ncMRI. In all previous tissue preparation ncMRI experiments, the tissue was submerged in oxygenated artificial cerebral spinal fluid (aCSF) which transported oxygen into the tissue to supply its energy metabolism. Additionally, when neuronal activity is enhanced or suppressed, the oxygen consumption and oxygen concentration (OC) in the tissue culture may change accordingly. Due to O_2's paramagnetic nature, the OC change alters the relaxation times and local magnetic fields, resulting in an MRI signal change. Unfortunately, this problem has been overlooked in previous experiments. To determine the validity of ncMRI experiments using animal tissue preparations, it is necessary to fully understand the nature of these oxygen effects and their impact on the ncMRI signal.

The work presented studies the mechanism of the oxygen-induced MRI signal in tissue preparation experiments and formulates it as a function of the fractional oxygen concentration of the gas dissolved in aCSF, tissue oxygen consumption rate, and imaging parameters. The impact of oxygen on ncMRI signal in a typical tissue preparation experiment is also estimated.

Methods

As shown in Fig. 1, in a tissue preparation ncMRI experiment, a brain tissue slice is submerged in oxygenated aCSF and attached to the bottom of a container. The oxygen in the aCSF diffuses into the tissue through its upper surface. When the tissue is at resting state or undergoing a block-designed stimulation, the OC will reach steady-state and can be expressed as a 1-D distribution along x, $C(x)$:

$$C(x)=\begin{cases}0 & (x\le -d_{\max})\\ \frac{V_{O2}}{2D_{BT}}(x+d_{\max})^2 & (-d_{\max}\le x\le 0)\\ \frac{C_b-C_0}{d_{DL}}x+C_0 & (0\le x\le d_{DL})\\ C_b & (x\ge d_{DL})\end{cases} \quad \text{where } C_b=kP_BF_{O2}, C_0=B-\sqrt{B^2-C_b^2} \text{ and } B=C_b+V_{O2}D_{BT}(\frac{d_{DL}}{D_{aCSF}})^2,\ d_{\max}=\sqrt{\frac{2D_{BT}C_0}{V_{O2}}} \quad [1]$$

C_b is the OC in the uniform aCSF, k (= 1.34×10^{-3} mM·mmHg^{-1}) is the solubility coefficient of oxygen in aCSF, P_B = 760 mmHg, F_{O2} is the fractional concentration of O_2 of the gas dissolved in the aCSF, D_{BT} (= 1.54×10^{-5} cm^2/s) and D_{aCSF} (= 2.48×10^{-5} cm^2/s) are the diffusion coefficient of oxygen in tissue and aCSF, respectively, V_{O2} is the tissue oxygen consumption rate, and at resting state V_{O2} = 3.38×10^{-2} ml O_2·cm^{-3}min^{-1}, $d_{\max}$ is the maximum diffusion depth, d_{DL} (≈ 0.20 mm) is the thickness of aCSF diffusion layer.

The oxygen dissolved in the aCSF and tissue will affect the MRI signal through relaxivity and susceptibility effects, which will induce the decrease of relaxation time and magnetic field inhomogeneity, respectively. When the static magnetic field B_0 is perpendicular to x, the oxygen-induced MRI magnitude (δS) and phase ($\Delta\phi$) change for a T_2*-weighted gradient echo sequence with minimized T_1 effect will be:

$$\delta S=\frac{|S_{act}|-|S_{rest}|}{|S_{rest}|}=\frac{\sqrt{(\int_{x_1}^{x_2}E_1\cos\phi_1dx)^2+(\int_{x_1}^{x_2}E_1\sin\phi_1dx)^2}}{\sqrt{(\int_{x_1}^{x_2}E_2\cos\phi_2dx)^2+(\int_{x_1}^{x_2}E_2\sin\phi_2dx)^2}}-1 \quad [2] \qquad \Delta\phi=\phi(S_{act})-\phi(S_{rest})=\tan^{-1}\left(\frac{\int_{x_1}^{x_2}E_1\sin\phi_1dx}{\int_{x_1}^{x_2}E_1\cos\phi_1dx}\right)-\tan^{-1}\left(\frac{\int_{x_1}^{x_2}E_2\sin\phi_2dx}{\int_{x_1}^{x_2}E_2\cos\phi_2dx}\right) \quad [3]$$

where S_{act} and S_{rest} are the MRI signal at active and resting states, respectively, $|S|$ and $\phi(S)$ are the magnitude and phase of S, respectively, $x_1=x_{voxel}-\Delta x/2$ and $x_2=x_{voxel}+\Delta x/2$, where x_{voxel} is the x coordinate of the imaging voxel center (see Fig.1), and Δx is the voxel size in x; E_1=exp[$-r_2C_{act}(x)\cdot TE$], $\phi_1=\gamma f_\chi C_{act}(x)B_0\cdot TE$, E_2=exp[$-r_2C_{rest}(x)\cdot TE$], and $\phi_2=\gamma f_\chi C_{rest}(x)B_0\cdot TE$, where r_2 is the transverse relaxivity of oxygen and can be estimated by Solomon-Bloembergen-Morgan relations, f_χ = 4.0×10^{-8}mM^{-1}, $C_{rest}(x)$ and $C_{act}(x)$ are the OC distribution (Eq. [1]) for resting and active states, respectively, and TE is the echo time.

With Eqs. [2] and [3], the oxygen effects are evaluated for a typical tissue preparation ncMRI experiment, in which it is assumed that a steady-state electrical stimulation paradigm and a T_2*-weighted gradient echo sequence are used with TE = 30 ms and long TR to minimize T_1 effect, Δx = 0.01−2 mm and x_{voxel} = −2 to 2 mm (interval = 0.01 mm) which cover the combination of Δx and x_{voxel} corresponding to the maximum signal change, B_0 = 3, 4.7, 7, and 9.4 T and is perpendicular to x.

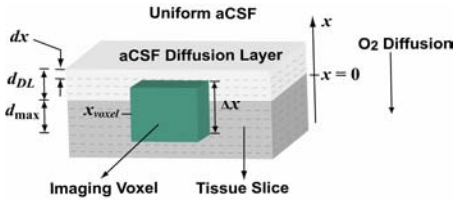

Fig. 1: The setup and oxygen diffusion in a tissue preparation ncMRI experiment. x is perpendicular to the upper surface of the tissue.

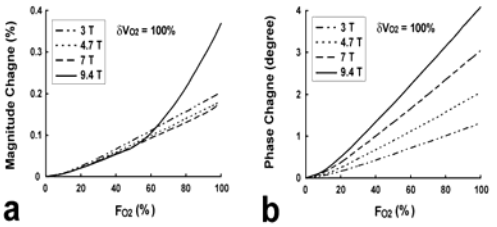

Fig. 2: The relationship of oxygen-induced magnitude (**a**) and phase (**b**) change with F_{O2} at B_0 = 3, 4.7, 7, and 9.4 T, and δV_{O2} = 100%. The magnitude and phase change in the figure are the maximum ones calculated with the corresponding F_{O2} for any imaging voxel size and position.

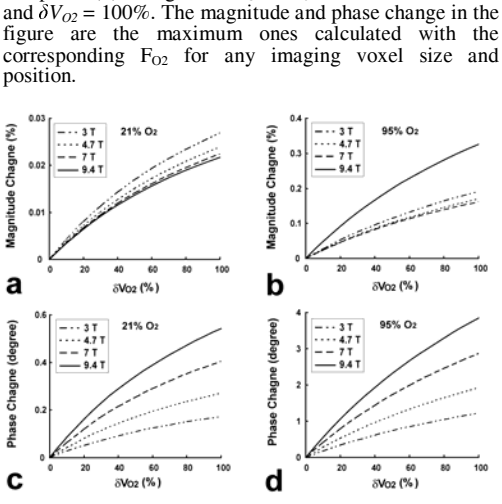

Fig. 3: The dependence of oxygen-induced magnitude (**a** and **b**) and phase (**c** and **d**) change on δV_{O2} at B_0 = 3, 4.7, 7, and 9.4 T. Either 21% or 95 O_2 gas is used. The magnitude and phase change in the figure are the maximum ones can be achieved with the corresponding δV_{O2}, regardless of the imaging voxel size and position.

Results and Discussion

Our results (Fig. 2) indicate that when the maximum change of oxygen consumption rate δV_{O2} (= $(V_{O2,act}-V_{O2,rest})/V_{O2,rest}$ =100%, $V_{O2,act}$, $V_{O2,rest}$ are the V_{O2} at resting and active states, respectively) is achieved, the maximum oxygen-induced magnitude (phase) change increases from 0 (0 degrees) to 0.37% (4.08 degrees) with the increase of F_{O2} from 0 to 100%. The results (Fig. 3) also show that when increasing δV_{O2} from 0 to 100%, the maximum magnitude (phase) change increases from 0 to 0.03% (0.54 degrees) and to 0.32% (3.85 degrees) for 21% and 95% O_2, respectively. Considering that 21%–95% O_2 are usually used in the tissue preparation ncMRI experiment, the maximum magnitude (phase) change induced by the oxygen effects will be in the range of 0.03% (0.54 degrees) to 0.32% (3.85 degrees).

In the previous ncMRI experiments using isolated snail ganglia[7-8] and 21% O_2, approximately 3-5% increase of ncMRI magnitude signals were found at 3T. It is estimated that the corresponding oxygen-induced magnitude change would be less than 0.03% (Fig. 3(a)), which is more than a hundred times smaller than the observed signal. In the ncMRI experiment using rat tissue cultures[9], ~ 0.8 and 1.7 degrees of phase change were detected at 3 (using 95% O_2) and 7 T (using 21% O_2), respectively. In this experiment the δV_{O2} is less than 4%, so the oxygen-induced phase change does not exceed 0.05 and 0.03 degrees at 3 and 7 T, respectively (Figs. 3d and c). Thus the oxygen-induced signals are 11-57 times smaller than the corresponding detected ncMRI signals. Therefore, the oxygen effects were negligible in all the previous tissue preparation ncMRI experiments[7-9].

References: 1. Xiong, et al. Hum Brain Mapp 2003;20:41. 2. Liston, et al. Magn Reson Imaging 2004;22:1441. 3. Bianciardi, et al. Magn Reson Imaging 2004;22:1429. 4. Chow, et al. NeuroImage 2006;30:835. 5. Chow, et al. Magn Reson Imaging 2006;24:681. 6. Chu, et al. NeuroImage 2004;23:1059. 7. Park, et al. NeuroReport 2004;15:2783. 8. Park, et al. Physiol Meas 2006;27:181. 9. Petridou, et al. Proc Natl Acad Sci U S A 2006;103:16015.