Implications of temperature changes in the brain for fMRI

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SYNOPSIS
Brain temperature is one of the many critical factors for BOLD signal because changes in CBF and CMR_{O2} during perturbation are involved in heat removal/production. We examined temperature changes (by thermocouple) in localized regions of rat cortex with several perturbations which demonstrate a positive BOLD signal-change (i.e., $\Delta S/S>0$). When $\Delta S/S>>0$ (hypercapnia challenge, bicuculline-induced seizure) the temperature changes were significant (0.9-1.2°C), whereas during sensory stimulation the temperature changes were small (~0.1°C). Thus, local changes in temperature could be an indicator of the degree of the mismatch between CBF and CMR_{O2} during perturbations. Influence of brain temperature for BOLD signals is discussed.

INTRODUCTION

A net change in brain temperature is believed to depend on two dominant processes: heat production during increased CMR_{O2} and heat removal or delivery by increased CBF [1]. Thus a perturbation which raises CBF and CMR_{O2} in an uncoupled manner from rest would likely cause localized changes in brain temperature. The origin of the BOLD signal is believed to be primarily due to a mismatch between changes in CBF and CMR_{O2} during functional activation [2]. However the degree of the mismatch between changes in CBF and CMR_{O2} during functional activation has been a topic of controversy where the ratio for $(\Delta CMR_{O2}\%)/(\Delta CBF\%)$ is believed to range from 0.1 [3] to 0.8 [4]. An indirect test of the CBF-CMR_{O2} mismatch during functional activation could be obtained by measuring local temperature changes. The use of CO_2 in calibration of the BOLD response [5] (i.e., where CBF changes significantly and CMR_{O2} remains constant) also poses a similar problem with temperature changes in brain tissue. Changes in brain temperature can affect the fMRI signal directly by affecting the total magnetization of tissue water (M_o), transverse relaxation time of tissue water (T_2), and/or diffusion coefficient of tissue water (D_c). In this study we examined different perturbations (hypercapnia, seizure, sensory stimulation) to determine the temperature changes that occur with concomitant changes in the BOLD signal (S). Given these concerns about the unknown effects of temperature on the BOLD effect, we examined a variety of perturbations (hypercapnia challenge, bicuculline-induced seizure, and sensory stimulation) which show a T_2 decrease in the somatosensory region (i.e., $\Delta S/S>0$) to determine if temperature changes occurred as well. We measured changes in BOLD signal (by fMRI), absolute temperature (by thermocouple wires), and relative CBF (by laser-Doppler probe) in localized regions of the α-chloralose anesthetized rat brain.

MATERIALS and METHODS

Animal preparation: Sprague-Dawley rats were tracheotomized and artificially ventilated. Intraperitoneal lines were inserted for administration of α-chloralose (40 mg/kg/hr) and *D*-tubocurarine chloride (0.5 mg/kg/hr). Arterial and venous lines were respectively used for monitoring physiology (blood pH, pO_2, pCO_2) throughout the experiment and infusion of bicuculline which is an antagonist of γ-ammino butyric acid (GABA) – the major inhibitory neurotransmitter in the mammalian cortex. The body temperature was maintained (37.0±0.5 °C) with a heating blanket. For both fMRI and topical measurements with a dual thermocouple and laser-Doppler probe the same stimuli were used. For sensory stimulation a 2-minute forepaw stimulation (2 mA; 0.3 ms; 3 Hz) protocol in a block design was used. For the CO_2 challenge the blood pCO_2 was raised (to 50-60 mm Hg) by either additional CO_2 into the inhalation mixture or by reduction of the ventilation rate. For the bicuculline-induced seizure the GABA antagonist (bicuculline; 1 mg/kg; Sigma-Aldrich) was infused. Each perturbation was at least repeated twice with ~20 minute resting periods in each rat. *fMRI measurements (n=15):* All fMRI data were obtained on a modified 7T horizontal-bore spectrometer (Bruker, Billerica, MA) with a ^1H resonator/surface-coil radio-frequency probe. $\Delta S/S$ was measured in the forelimb somatosensory region with ~0.1 μL voxels [4]. *Temperature and CBF measurements (n=27):* A dual (thermocouple, laser-Doppler) probe (Oxylite, Oxford Optronix, UK) was used to measure changes in absolute temperature and relative CBF in the forelimb somatosensory region (layer 4), as guided by fMRI results, from a ~0.05 μL tissue volume. In some cases the temperature of the blood entering the brain was inferred from another probe inserted into the aortic arch.

RESULTS and DISCUSSION

In the forelimb somatosensory region, hypercapnia challenge and bicuculline-induced seizure (where $\Delta S/S>>0$) increased the brain temperature by 0.9-1.2°C, whereas sensory stimulation induced (where $\Delta S/S>0$) a smaller increment in temperature (~0.1°C). The changes in CBF were 2 to 3 times higher with hypercapnia challenge and bicuculline-induced seizure than the CBF change detected with sensory stimulation. The large increase in brain temperature with bicuculline-induced seizure was expected since large changes in CMR_{O2} occur with seizure activity [1]. The temperature increase during a hypercapnia challenge was surprising because the classical interpretation of an increase in CBF with constant CMR_{O2} is that the tissue becomes cooler [1]. However, the current finding is explained by the slightly warmer (~0.5°C) incoming blood (as measured by the blood temperature in the aortic arch) into the brain. The small increase in temperature with functional activation is in good agreement with previous reports in anesthetized rats [6], although in the awake human brain very small decrease has also been reported [7].

CONCLUSIONS

The current results do provide reasons for caution in using hypercapnia challenges for the calibration of the BOLD experiment [5]. Since a 0.9-1.2°C increase in brain temperature as a result of mild hypercapnia challenges can significantly change the temperature of the exiting venous blood, the oxygen binding affinity of hemoglobin is greatly affected. This temperature effect shifts the hemoglobin saturation curve in the same direction as does decreased pH (due to hypercapnia) and increased pCO_2 which altogether facilitate unloading of oxygen from hemoglobin.

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