Evolution of the Dynamic Changes in Cerebral Oxidative Metabolism Evoked by Somato-sensory Stimulation

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Introduction: The cerebral metabolic rate of oxygen consumption (CMR_{O2}) is a key factor in brain function. Oxygen is consumed in the mitochondria of cells and it is delivered to tissue by blood, mostly at the capillary level. Hemoglobin-sensitive imaging methods, such as BOLD fMRI, partly rely on this sensitivity to map brain function. The dynamic relationship between brain function and oxidative metabolism remains largely unknown because direct measurements of tissue CMR_{O2} are very difficult. Changes in the intrinsic auto-fluorescence of tissue have been shown to stem from changes in metabolism since much of it stems from proteins that participate in the metabolic cascade (1,2,3). In this work, the temporal evolution of the changes in cellular oxidative metabolism, tissue oxygen tension and blood oxygenation were investigated using flavoprotein auto-fluorescence imaging (FAI), oxygen microelectrodes and deoxyhemoglobin-sensitive optical imaging of intrinsic signal (OIS), respectively. The impact of these findings on MRI-based CMR_{O2} measurements is discussed.

Methods: Nine Sprague-Dawley rats (200-500g) were used in this study with experimental protocols approved by the University of Pittsburgh's IACUC. The animals were anesthetized with isoflurane (5% for induction, 2% for surgery) via vaporizer. Catheters were inserted in the femoral artery and vein. An area 5x7mm on the skull centered over the somato-sensory cortex was thinned and removed. The dura was resected and the exposed area was resealed with 1% agarose gel. Upon completion of the surgeries, the isoflurane level was decreased to 1.1-1.4% for the remainder of the experiment. The default condition established after the surgery was considered to be the control condition in which stimulation evoked both vascular (CBF) and metabolic responses (CMR_{O2}). In order to evoke only metabolic responses, a vasodilator (sodium nitroprusside) was used to dilate the blood vessels and suppress the CBF and CBV responses (4,5). This condition has been demonstrated to not alter brain electrical activity (4,5) and the experimental data were recorded under this condition. To evoke a sensory response, two needles were inserted between digits 2 and 4 of the left forepaw. Forelimb stimulation consisted of 1ms, 1.5mA pulses delivered at a frequency of 3 Hz for 15 s every 45 s or at 12 Hz for 4 s every 16 s. FAI was performed by filtering excitation light (470±20nm) and recording the filtered emission (525±25nm) using a cooled CCD camera at 10fps. OIS was performed in separate, alternated experiments in the same animal using 620±5nm obliquely transmitted light. In all experiments, tissue P_{O2} and blood flow were simultaneously measured using an oxygen microelectrode and laser Doppler flowmetry. A preliminary OIS experiment was performed at the beginning of each experiment to map the forelimb area and place the P_{O2} and LDF probes.

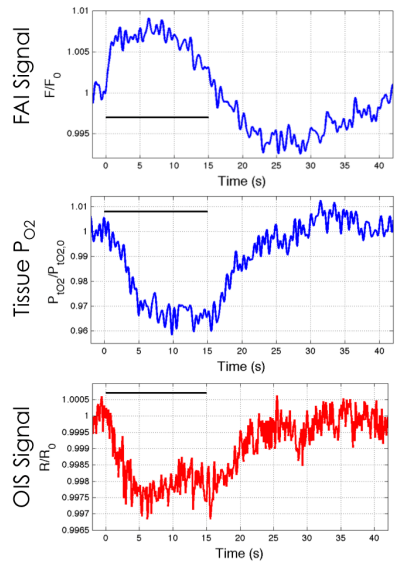

Fig. 1: Sample changes in FAI (top, A), tissue P_{O2} (mid, B) and OIS signal (bottom, C) due to stimulation (3Hz for 15s) under suppressed-CBF conditions.

Results and Discussion: A fast and robust increase in FAI signal was observed with stimulation onset due to increases in CMR_{O2} on average reaching 90% of its peak in 1.5s (Fig. 1A, 2). The increases were temporally sustained and spatially consistent during stimulation. A significant decrease was also observed following stimulation. Significant but slower decreases in tissue P_{O2} were observed during stimulation due to increases in CMR_{O2}, on average reaching 90% of its minimum in 4.1s (Fig. 1B). Significant decreases in blood oxygenation were observed using OIS during stimulation, similar to the decreases in tissue P_{O2}, and on average reaching 90% of its minimum in 4.4s (Fig. 1C). The FAI and OIS maps were found to be highly coincident although the FAI maps spanned a slightly larger area.

Fast increases in cellular oxidative metabolism were observed with increases in neural activity using FAI. The results showed that the increase in CMR_{O2} prompted the need for oxygen from the surrounding tissue and blood shortly after, indicating that, temporally, the dynamic changes in blood oxygenation (e.g. BOLD fMRI) reflect the average changes in tissue oxygen but less so the changes in cellular CMR_{O2}.

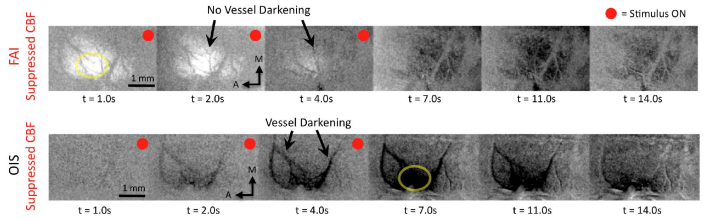

Fig. 2: Map of the changes in FAI (top) and OIS (bottom) due to somato-sensory stimulation (12 Hz for 4 s) under the suppressed-CBF conditions.

References: (1) Huang S, et al., Biophys J 82:2811,2002; (2) Shibuki K, et al., J Physiol 549:919,2003; (3) Reinert K, et al., J Neurophysiol 92:199,2004; (4) Fukuda M, et al., Neuroimage 30:70,2006; (5) Masamoto K, et al., Neuroimage 40:442,2008. This work was supported by NIH grants F32-NS056682, K01-NS066131, R21-EB006571, R01-NS044589 and R01-EB003375.