A Hypothesis for Cerebral Blood Flow Regulation and the Origin of the BOLD Effect

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Introduction: Functional MRI techniques provide a powerful tool for investigating the working brain by detection of changes in cerebral blood flow (CBF) and energy metabolism. However, the link between neural activity and CBF, and even the primary biological functions served by CBF regulation, are still poorly understood. In particular, the surprising decrease of the oxygen extraction fraction (E) with neural activation is the physiological basis of the BOLD effect. In addition, CBF increases strongly with inspired CO_2, but the biological function served by this response is unknown. Calculations of the transport kinetics of O_2 and CO_2 between blood and mitochondria in the brain suggest that experimental observations of the CBF response to changes in neural activation, inspired CO_2, and inspired O_2 can be quantitatively explained by a simple principle: maintenance of the concentration ratio $[O_2]/[CO_2]$ at the mitochondria.

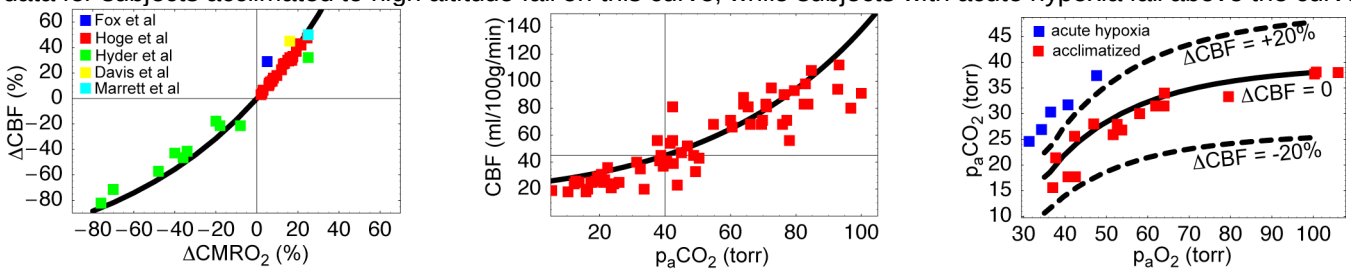
Theory: The limiting gradient for O_2 transport is taken to be that from end-capillary venous blood (p_vO_2) to the mitochondria (p_mO_2). Assuming diffusive transport with no capillary recruitment, we take $p_mO_2=p_vO_2-m\Delta pO_2$, where m is the metabolic rate of oxygen ($CMRO_2$) normalized to it's value at baseline, and ΔpO_2 is the partial pressure difference at baseline. A similar relationship is assumed to describe transport of CO_2 to the capillary: $p_mCO_2=p_vCO_2+m\Delta pCO_2$. For matched net delivery of O_2 and clearance of CO_2, the total CO_2 content of blood must increase by EY_aH_a in going from artery to vein, where Y_a is the arterial O_2 saturation, and H_a is the equivalent hemoglobin concentration. Because only a fraction of the total CO_2 is carried as dissolved gas, we take $p_vCO_2=p_aCO_2+\kappa EY_aH_a$, with κ defining that fraction. We assume: 1) p_vO_2 is modeled with the Hill equation, with p_{50}=26 torr and h=2.8; 2) $\Delta pCO_2=\Delta pO_2(s_{O2}/s_{CO2})$, where the solubilities are s_{O2}=0.00135 and s_{CO2}=0.030 mmol/l/torr; 3) $\kappa=[s_{O2}(1+10^{pH-6.1})]^{-1}$, due to conversion of CO_2 to bicarbonate; and 4) resting oxygen extraction is E_0=0.4, and blood hemoglobin is 8.9 meq/l. Then Eq [1] defines the $[O_2]/[CO_2]$ ratio at the mitochondria, and Eq [2] links f, the CBF normalized to its value at rest, with E and m (0 denotes baseline values):

$$\frac{[O_2]}{[CO_2]}=\frac{s_{O2}}{s_{CO2}}\frac{p_{50}\left[\frac{Y_a(1-E)}{1-Y_a(1-E)}\right]^{1/h}-m\Delta pO_2}{p_aCO_2+\kappa EY_aH_a+m\Delta pCO_2} \qquad [1]$$

$$E=E_0\frac{m}{f}\frac{Y_{a0}}{Y_a}\frac{H_{a0}}{H_a} \qquad [2]$$

The key parameter of the model is the O_2 diffusivity at baseline, represented by ΔpO_2.

Modeling Results: The figures illustrate how CBF must vary to keep the $[O_2]/[CO_2]$ ratio constant as other parameters are varied for ΔpO_2=16 torr, giving baseline values of p_vO_2=29 torr, p_mO_2=13 torr, and $[O_2]/[CO_2]$=0.014. The left figure shows how CBF increases with increased $CMRO_2$, compared with data from human activation studies and rat models with different levels of anesthesia [1-5]. The middle figure shows the dependence of CBF on p_aCO_2, compared with data in monkeys [6]. The right figure shows a contour map of the CBF change required when both arterial O_2 and CO_2 are varied, showing that if p_aCO_2 is reduced along with p_aO_2 the ratio can be maintained with no change in CBF. Note that blood gas data for subjects acclimated to high altitude fall on this curve, while subjects with acute hypoxia fall above the curve [7].



Discussion: Based on a simple model of O_2 and CO_2 transport, the function of CBF regulation in response to neural activation, inspired CO_2 and hypoxia can be understood as maintenance of the $[O_2]/[CO_2]$ ratio at the mitochondria. A possible explanation for the importance of preserving this ratio is that the thermodynamic free energy (ΔG) supplied by oxidative metabolism of glucose directly depends on this ratio. Early studies of mitochondria showed that, despite the fact that $[O_2]$ does not become limiting for oxygen metabolism until very low concentrations are reached, the ΔG is affected at much higher O_2 concentrations, manifesting in a degradation of the [ATP]/[ADP] ratio [8]. The proposed model accurately describes CBF changes under a range of conditions, and may serve as a basis for interpreting the BOLD effect.

References: [1] Fox and Raichle, PNAS 83:1140, 1986; [2] Hoge et al, PNAS 96:9403, 1999; [3] Hyder et al, J CBF Metabol 20:485, 2000; [4] Davis et al, PNAS 95:1834, 1998; [5] Marrett et al, Adv Exp Med Biol 413:205, 1997; [6] Reivich, Am J Physiol 206:25, 1964; [7] Rahn and Otis, Am J Physiol 157:445, 1949; [8] Wilson et al, Arch Biochem Biophys 195:485, 1979.