Relation Between Cerebral Blood Flow and Metabolism
Revisited by a Model of Oxygen Exchange

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Purpose
Clear understanding of the relation between Cerebral Blood Flow (CBF) and Cerebral Oxygen Metabolic Rate (CMRO₂) during cerebral activation is a prerequisite for the physiological interpretation of the BOLD signal. We focus on a physiological model of oxygen transport through the capillary wall and tissue oxygen consumption to show a possible uncoupling between CBF and CMRO₂ if a tissue oxygen compartment is considered.

Context
There exists a good correlation between CMRO₂ and CBF at resting-state. However, there are great differences among experimental studies for the ratio of relative changes of CMRO₂ and CBF during activation (ΔCMRO₂/ΔCBF). Thus much attention has been paid to the problem of the so-called coupling between CBF and CMRO₂ [1]. It must be emphasized that this notion of coupling should not be reduced to a simple relationship.

Buxton et al. [2] derived a simple model of oxygen extraction by capillaries in which CBF and CMRO₂ were coupled by a nonlinear relationship so that during activation their model predicted CBF decreases whereas previous studies [3] pointed out that they could not explain such decreases in CBF. A study of such an approach is that of Davis et al. [4] where C, may vary depending on the oxygen extraction E = (C,- C,) / C,.

Hypotheses
- Oxygen extraction is limited by a diffusion barrier at the capillary wall.
- Passive oxygen exchange occurs between a single distributed capillary compartment and a well-mixed tissue compartment (total oxygen concentration depends on capillary axial direction).
- Blood is considered as a homogeneous solution of hemoglobin.
- Constant arterial pressure is set to 100 mmHg (no pre-capillary loss).
- The CMRO₂ may depend on oxygen tissue concentration and metabolic demand via a Michaelis Menten rate law.
- We only consider the stationary state.

Notations and parameter values
C(t, x), Cₐ(t, x), and C, respectively refer to: Total blood, plasmatic, and mean tissue oxygen concentrations (mmol.l⁻¹). Cₐ, C, arterial and venous total O₂ concentrations (capillary entry and capillary end). E: oxygen extraction E = (C,- Cₐ) / C, P: permeability, S: surface of capillary exchange. (PS = 7020 [S] or 3000 ml.min⁻¹(100g)⁻¹). x: coordinate along the capillary axis (normalized to the capillary length). (Hb) : hemoglobin concentration (2.2 mmol.L⁻¹). PO : oxygenic power (4). Km : Michaelis constant (0.1 mmol.l⁻¹). CMRO₄max : CMRO₂ at saturation C,.

The exchange model

Equations
Transport equations:
(1) \[ \frac{dC}{dx} = -\frac{PS}{CBF} (C_a(x) - C_t) \] and C(0) = Cₐ

(2) \[ CMRO₂ = PS \frac{C}{C_a(x) - C_t} \]

C, is the mean of C(t, x). C and Cₐ are related by the ODC (Hill equation): \[ C(x) = Cₐ(x) \cdot (1 + (\frac{aPo}{S}Cₐ(x))^{qn}) \]

Michaelis Menten rate law:

(3) \[ CMRO₂ = CMRO₂max \frac{C}{(1 + Km + C)} \]

Due to these three coupled equations, we can compute the oxygen extraction E. If E and CBF are known, a mass balance relation defines the CMRO₂ (CMRO₂ = CBF x E). Thus the coupling between CBF and CMRO₂ depends on the coupling between CBF and E.

Results and interpretation

Influence of parameters C, and PS: We first studied the effect of a fixed C, (eq. 3 is discarded). The capillary oxygen concentration (and thus E) is directly given by eq. 1 and depends only on CBF, PS, and C,.

There is a tight coupling as previously modeled [2, 3]. An increase in C, decreases the oxygen gradient as well as the oxygen extraction and CMRO₂. We define CMRO₂max as the maximal CMRO₂ (obtained for C, = 0). An increase in PS increases the CMRO₂ (Fig I).

Decoupling of CMRO₂ and CBF: We can also solve transport equations with CMRO₂ considered as an independent fixed parameter (below CMRO₂max) and C, as a variable. So, oxydative metabolism requirements need not match exactly CBF increases.

Discussion

The exact quantitative limitation of CMRO₂ by CBF is certainly model dependent [5] but our model proposes a physiological interpretation of the different CMRO₂ : CBF observed experimentally. It may predict a ratio from 0.1 up to 0.6:1. There are two possibilities which can account for large CMRO₂ relative changes: either PS increases or C, decreases. A variation in PS implies either capillary recruitment or dilatation which seems to be negligible in the brain [7].

Technological limitations make it impossible to obtain a clear representation of Cₐ repartition in the tissue. Anyhow Cₐ experimental studies have shown a mean tissue Cₐ of 15 mmHg [8, 9]. So it seems plausible that there are transient variations of tissue O₂ during activation.

Conclusion

Taking into account the tissue oxygen concentration has no negligible influence on oxygen transport, and allows a real decoupling between CBF and CMRO₂. This decoupling may explain the large rCMRO₂ : rCBF ratio observed experimentally.

References