A Quantitative Model to Estimate Limited Permeability of Mitochondrial Membrane to Water in Brain

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Introduction and Theory It has been observed that the clearance rate of cerebral $H^{17}O$ in bolus injection experiment is significantly faster than that following $^{17}O_2$ inhalation[1]. When blood passes through the brain tissue, labeled water continuously diffuses across the blood brain barrier (BBB), driven by the water concentration gradient between the tissue and the blood, and is washed out of the brain tissue by the convective movement of blood flow. Therefore, the clearance rate of the labeled water from the brain tissue is determined by both the diffusion process and the convection process. Considering an elementary unit in a capillary between position z and z+dz shown in Fig.1, the mass balance relationship of labeled water in this unit is given by Eq.(1), where C_c is the concentration of labeled water in capillary, C_b is the concentration of labeled water in brain tissue, R_c is the radius of the capillary and P is the permeability of water across the BBB. Q is blood flow rate with the unit ml/sec and the relationship between Q and CBF is given in Eq.(2), where L is an average length of the capillary in the brain tissue, f is the volume fraction of capillary vessel in brain tissue (i.e. CBV), ρ is brain density, and the number 60 converts the unit of minute in CBF to second in Q. Eq. (1) can be rewritten as Eq.(3). Since capillaries only take a few percentage of the total tissue volume (~2% for rat), the dilution effect of blood flow on the concentration of the labeled water in the brain tissue can be negligible for a short period of transit time. Therefore, it is reasonable to assume C_b in Eq. (3) be a constant. The differential equation Eq. (3) can thus be solved as Eq.(4), where C_{c0} is the concentration of the labeled water in capillary when new blood enters the brain tissue. Based on Eq. (4), the concentration difference in the blood before it feeds in and after it flows out of the brain tissue ΔC can be given by Eq.(5), where C_{cL} is the concentration of the labeled water in the capillary blood when it leaves the tissue. The rate of the concentration change of the labeled water in brain tissue is the product of the ΔC and CBF shown in Eq. (6), based on the mass balance relationship of the brain-blood system, assuming the volume of the tissue does not change. Solving Eq. (6) gives the expression of concentration of brain tissue as a function of time given by Eq.(7), where $m = 1\text{-}e^{-2\pi RcPL/Q}$ and C_{b0} is the initial concentration of the labeled water in the brain tissue, i.e. brain concentration after the first passage of the injected bolus in the bolus injection experiment and/or the highest concentration after stopping inhalation in the oxygen inhalation experiment.

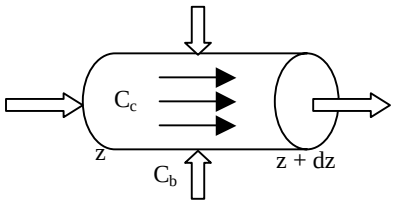

Fig. 1: Elementary unit in capillary at the position of z with the length dz

$$[Q\cdot C_c]_z - [Q\cdot C_c]_{z+dz} + 2\pi R_c dz P(C_b - C_c) = 0 \quad (1)$$

$$Q = CBF/[f/(\pi R_c^2 L)\rho]/60 \quad (2)$$

$$\frac{dC_c}{dz} = \frac{2\pi R_c P(C_b - C_c)}{Q} \quad (3)$$

$$C_c(z) = (C_b - C_{c0})(1 - e^{-\frac{2\pi R_c P}{Q}z}) + C_{c0} \quad (4)$$

$$\Delta C = C_{cL} - C_{c0} = (C_b - C_{c0})(1 - e^{-\frac{2\pi R_c P}{Q}L}) \quad (5)$$

$$\frac{dC_b}{dt} = -(C_b - C_{c0})(1 - e^{-\frac{2\pi R_c P}{Q}L})CBF \quad (6)$$

$$C_b = C_{c0} + (C_{b0} - C_{c0})e^{-mCBFt} \quad (7)$$

$$\frac{1}{P_o} = \frac{1}{P_m} + \frac{1}{P_c} + \frac{1}{P_b} \quad (8)$$

$$m' = 1 - e^{-\frac{2\pi R_c P_o}{Q}L} = mn \quad (9)$$

Results For the bolus injection experiment, P in Eq. 3 is the permeability of water across BBB. Eq. 7 indicates that the decay rate of the labeled water is the product of m and CBF rather than CBF as used in some old publications. The dependence of m on CBF is shown in Fig. 2, with the parameters: $Rc \approx 1.7\times10^{-4}$ cm, and L≈0.8 cm (ref. from literature), assuming brain density $\rho \approx 1 gram/cm^3$, and volume fraction of capillary in brain tissue f ≈ 2%. Permeability of water across BBB is estimated as $P \approx 9.29\times10^{-5}$ cm/s, based on the measurement of the product of permeability and surface area of capillaries[2]. The calculated curve of m versus CBF is in excellent consistence with the experimental data[3]. Fitting the curve of ln(1-m) as a function of 1/CBF should give a linear line with the slope $2\pi R_c LpCBF/Q = 2\pi R_c LpR = 1.31$, which is also in excellent accordance with the experimental measurement results of 1.26 min·ml/gram in rat[3] and 1.38 min·ml/gram in monkey[4].

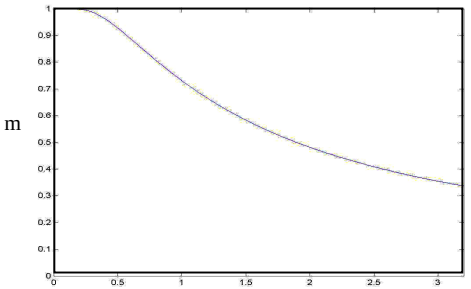

Fig. 2: Dependence of m on CBF

For the oxygen inhalation experiment, the metabolic water has to diffuse out of mitochondria membranes, cellular membrane, as well as BBB to be washed out of the brain. Overall permeability cross these three barriers can be expressed in Eq. 8, where P_o is the overall permeability, P_m is the permeability of water across mitochondria membranes, P_c is the permeability of water across cellular membrane, and P_b is the permeability across BBB. Replacing P with P_o in the expression of m gives Eq. 9, where n is the ratio between the decay rate in $^{17}O_2$ inhalation experiment and that in bolus injection experiment. More layers of limitation in permeability of the metabolic water explain significantly slower transport in the oxygen inhalation experiment. With Eq. 8, and Eq. 9, permeability of water across mitochondria membranes (i.e., P_m) can be estimated as 7.6×10^{-5} cm/s, based on our experimental data, in which n is approximately 0.7 when CBF = 0.53 ml/g/min, as well as $P_c = 2.7\times10^{-4}$ cm/s from literature[5]. Simulated dependence of n on mCBF is consistent with the experimental results as shown in Fig. 3 indicating the validity of the model.

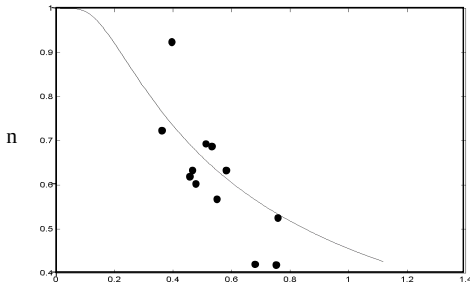

Fig. 3: Dependence of n on mCBF

Discussion The expression of m gives the same result as the model for the clearance of diffusible substances from a single capillary proposed by Renkin[6] and Crone[7]. Their model assumes extreme low concentration in the tissue so that the diffusible material leaving the capillary is quickly diluted with none of it returning to the capillary. The relation developed is given by: $1\text{-}E = e^{-PS/CBF}$, where E is the extraction fraction of the diffusible material. This extraction fraction is equivalent to m in our model, both of which measure the normalized transportation of the diffusible material across BBB in the condition of convective blood flow. Furthermore, the water permeability across mitochondria membrane is limited in brain and the degree of the limitation depends on CBF. In summary, the results of this study suggest the feasibility of utilizing the tool of ^{17}O NMR to measure the permeability of mitochondria to water. This feasibility may be important for studying the permeability change in mitochondria during pathological perturbations.

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