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CONCEPTUAL MATHEMATICAL MODEL FOR CONVECTIVE MECHANISM OF BRAIN CORTEX OXYGENATION

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Normal physiological function of the brain cortex, one of the most intensively oxygen consuming tissues, absolutely depends on uninterrupted and adequate oxygen supply. The problem of brain cortex oxygenation mechanism presents an important issue from both theoretically and practically. At present, a dominating mechanism of the brain cortex oxygenation is based on the concept of oxygen diffusion [26]. According to this mechanism oxygen mass transfer from the capillary to cytochrome oxidase is driven by the oxygen partial pressure gradient established between the capillary blood and the interstitium.

A general progress in the area of non-invasive monitoring methods, physiology of the interstitium, water metabolism, and oxygen mass transfer resulted in accumulation of the experimental observations that are either hard to explain within the framework of the orthodox theory or are outright contradictory.

According to the diffusion theory, oxygen partial pressure goes down with increasing distance from the capillary [3]. But it is not the case with oxygen tension in the subarachnoid cerebrospinal fluid (CSF) in contact with the brain cortex peripheral structures and certainly furthest from the capillary network. The steady-state levels of oxygen partial pressure found there were close to the average capillary blood values. The fast changes of the oxygen tension observed there in response to changing ventilatory conditions were difficult to explain by diffusion, and a convectional oxygen mass transfer must be assumed [29]

The levels of oxygen partial pressure, also close to the capillary ones, were found on the dural aspect of the brain arachnoid [11], with its outer layer believed to be devoid of any capillaries [20]. A conflicting fact in the diffusion theory is that oxygen tension in the venous blood of the sagittal sinus is higher than that in the brain cortex venular blood [21].

The physics of the diffusion mechanism views the interstitium as immobile medium where convection is forbidden. It disagrees with the fact that the brain cortex vasculature is surrounded by perivascular water spaces [1] while oscillatory movements and directional flows in the interstitial fluid and CSF are well researched and documented [1, 40, 25, 35, 34].

A major fundamental breakthrough with important implication for the physiology of the interstitial space and the mechanism of tissue oxygenation was the discovery of the water channels, aquaporins, that catalyze transmembrane transport of water [14, 13]. The Arrhenius activation energy for this process is as low as 5 kcal/mole [12] and aquaporins are capable of providing 10 to 100 times faster water transport than diffusion [12].

The location of the aquaporins seems to have direct bearing to their function. Thus, they are invariably present in the plasma membrane of the cells involved in water transport between CSF and brain parenchyma and the functioning of the blood brain barrier. AQP4, the most active of the known aquaporins, is found in abundance in the astroglial end-feet in the immediate proximity to the endothelial basal membrane, in the ependymal cells lining the ventricles [45]. Another aquaporin present in quantity in the brain cortex, AQP1, is expressed in the plasma membranes of the arachnoid endothelium lining the subarachnoid channels and other structures, and mediates water transport across vascular cell membranes [32,33,37].

The aim of the present work was to develop a conceptual mathematical model for a convective brain cortex oxygenation mechanism and to explore its viability. It was believed that this mechanism should accommodate the latest relevant experimental findings on the interstitial space and water microcirculation along with blood circulation systemic and local features.

The concept of convectional transport of oxygen dissolved in tissue water is usually confronted by two main objections. Firstly, it is a comparatively slow ultrafiltration velocity of the capillary water due to high hydraulic resistance of the blood-brain barrier that goes with the physical-chemical diffusion and

that would be in the way of any significant solution of the problem. Now, with the discovery of aquaporins, this objection is obsolete.

Another argument is centered on a comparatively low oxygen-carrying capacity of water and, as a result, a necessity to engage large amounts of water for adequate oxygen delivery to the respiring tissue by convection [7]. This objection can be bypassed if one considers oxygen transport in terms of a small water volume oscillating between the capillary and the interstitium. In theory, the interstitial water oscillations could be driven by the capillary pulsatile hydrostatic pressure of systemic origin.

Within the framework of the convective mechanism, oxygen and water mass transfer are viewed as functionally coupled processes. Let us look into this process within the geometry of the tissue cylinder employed in the diffusion models [8].

Consider a tissue cylinder with the outer radius *R*, placed concentrically around a straight rigid wall capillary [10,18] with radius *r* and length *L*. At any time, *t*, the diastolic hydrostatic pressures at the arteriolar and venular ends of the capillary are $P_a(t)$ and $P_n(t)$ respectively. At $P_a(t) > P_n(t)$ there is an established longitudinal flow of blood (along the *x*-axis) directed toward the venular end of the capillary. At any point *x* (at $0 \le x \le L$) and time *t* on the cross-section of the model the capillary hydrostatic pressure is $P_{cap}(t,x)$ and the capillary oncotic pressure is $P_{onc}(t,x)$. Tissue hydrostatic pressure is P_t, while tissue oncotic pressure is assumed to be negligibly small [4].

It is relevant to say that the length of the pulse wave exceeds that of a brain capillary by several orders of magnitude. For example, if the pulse wave propagation velocity is 9.3 m/s [31] and systolic interval 0. 85 s (at 70 heart beats per min) then the pulse wavelength, the product of the two, is 8 m. For comparison, the brain cortex capillary length averages $1.2 - 2.5 \cdot 10^{-4}$ m [2]. It follows that quasi-steady state pulsatile hydrostatic pressure sets in simultaneously over the whole length of a capillary. The resulting magnitude and direction of the radial pressure gradient that drives capillary-interstitium water exchange is determined by the algebraic sum of the capillary pulse wave pressure, capillary hydrostatic diastolic pressure, and interstitial hydrostatic pressure. It should be noted that the changes in the pulse wave hydrostatic pressure proper do not generate any appreciable longitudinal hydrostatic gradients.

It is of interest to assess on this model what oscillating water volume should be engaged in the oxygen mass-transfer process to deliver an adequate oxygen supply to the respiring tissue. It is also possible to derive what would be an approximate value of the effective hydraulic conductivity coefficient, *k*. The ratio of the minute volume of the radial flow, ΔQ_r, to the minute volume of blood , ΔQ_c, passed through the capillary gives the fraction of the capillary water deflected into the radial oscillating volume:

$$\frac{\Delta Q_r}{\Delta Q_c} = \frac{V_t J_{O_2}}{a \overline{P}_{O_2} \overline{Q}_p \Delta t N_p}, \qquad (1)$$

where V_t –the volume of the respiring tissue that consumes oxygen at the rate J_{O_2}; a – is oxygen solubility in plasma; $\overline{P}_{O_2}$ – the luminal oxygen tension averaged over the length of the capillary ; Δt – duration of the pulse wave systolic phase; N_p – heart rate; $\overline{Q}_p$ – average volumetric blood flow velocity in the systolic phase.

The respiring tissue volume is determined from:

$$V_t = pL(R^2 - r^2) \qquad (2)$$

The following values for the above parameters were taken for the calculation:

$R = 2 \cdot 10^{-3}$cm ; $r = 3.5 \cdot 10^{-4}$ cm [2]; L = 0.01cm [2]; $\overline{P}_{O_2}$ = 50 mm Hg [3];

$\Delta t = 5 \cdot 10^{-3}$ min at N_p = 80 heart beats per minute; a = $2.6 \cdot 10^{-5}$ cm^3/(cm$^3 \cdot$ mm Hg) [41]; J_{O_2} = $2.1 \cdot 10^{-2}$ cm^3/(cm$^3 \cdot$ min) [28]. The volumetric blood flow velocity is the multiple of the capillary cross-section area and the linear blood flow velocity. The latter is taken to be within 12 ÷ 30 cm/min [9] .

It has been assumed that the ascending section of the pulse waveform, anacrota, is approximated by a straight line. The resulting ratio $\Delta Q_r / \Delta Q_c \approx 0.2 \div 0.5$ demonstrates that under the conditions described above from 20 to 50 per cent of the capillary water is redirected as an oscillating radial volume.

The effective hydraulic permeability coefficient can be obtained from the following expression:

$$k = \frac{Q_r}{SP_p} \qquad (3)$$

where S – capillary surface area and P_p – the capillary pulse wave pressure amplitude. For a rough estimate the pulse wave pressure amplitude is assumed to be 8 mm Hg [39] in which case $k \approx 0.011$–0.0044 cm^3/ (min·mmHg ·cm^2). This value is comparable to k$\approx$0.0025 cm^3/ (min·mm Hg.·cm^2) [4] for kidney glomerular capillaries where high filtration rate is due to the presence of aquaporins.

At present it is possible to monitor in both human and animal studies the physiological oscillations in the blood flow of the brain cortex microvasculature and in the interstitial fluid. In this connection, it is interesting to investigate the oscillatory effects arising from radial water mass transfer and the impact of the latter on the capillary blood flow.

Within this model it is assumed that the algebraic sum of all radial flows is zero, indicating that the radial oscillating water transport does not result in water accumulation in the interstitium and no swelling of the brain parenchyma occurs.

The pulse-wave-dependent hydrostatic pressure undergoes changes with time as:

$$P_a(t) = f(t), \qquad (4)$$

where P_a is hydrostatic pressure at the arteriolar end of the capillary and f is a given function of time, *t*.

In the capillary there is established a quasi-steady state hydrostatic pressure gradient, ΔP:

$$\Delta P = \Delta P_a(t) - P_n(t) \equiv P_a - P_n, \qquad (5)$$

where P_v is the hydrostatic pressure at the venular end of the capillary.

The volumetric velocity for the longitudinal flow, n_0, is obtained from Stocks equation for Newtonian fluid as:

$$n_0 = \frac{pr^4 \Delta P}{8hL}, \qquad (6)$$

where h – dynamic fluid viscosity, ΔP – longitudinal hydrostatic pressure gradient over the length of the capillary. The following inequality r<< L makes it possible to disregard the flow entry effects and consider the flow established over the whole length of the capillary.

The radial flow of water, J_v, is described by Kedem-Katchalsky equation:

$$J_n = L_p S(\Delta P - s_T \Delta \Pi), \qquad (7)$$

where L_p – the phenomenological proportionality coefficient, S – the water transfer surface area, ΔP– the oncotic pressure gradient, and s_T – the reflection coefficient which is unity for brain capillaries [4].

The phenomenological coefficient can be rewritten as:

$$L_p = a_{AQP} r_{AQP}, \qquad (8)$$

where a_{AQP} – the aquaporin molecular activity and r_{AQP} – aquaporin membrane density.

If $n(t, x)$ is capillary volumetric flow at point *x* and time *t* of the cardiac cycle then

$$\frac{\partial n(t,x)}{\partial x} = -2prL_a \left[P_{cap}(t,x) - P_{onc}(t,x) - P_t \right], \qquad (9)$$

where P_t is the interstitial pressure.

The hydrostatic pressure in the capillary lumen linearly decreases along *x* as:

$$P_{cap}(t,x) = P_a(t) - \frac{P_a - P_n}{L}x = f(t) - \frac{P_a - P_n}{L}x, \quad 0 \le x \le L. \qquad (10)$$

The capillary oncotic pressure, $P_{onc}(t,x)$, depends on protein concentration, $C_{pr}(t,x)$, and is derived from an empirical formula that gives its values in mm Hg [27] as:

$$P_{onc}(t,x) = 2.1C_{pr}(t,x) + 0.16C_{pr}^2(t,x) + 0.009C_{pr}^3(t,x), \qquad (11)$$

where C_0 is protein concentration at the arteriolar end of the capillary.

$$C_{pr(t,x)} = C_0 \frac{n_0}{n(t,x)} \qquad (12)$$

The radial water mass transfer is described by a system of equations:

$$\begin{cases} \dfrac{\partial n(t,x)}{\partial x} = -2prL_a \left[f(t) - \dfrac{P_a - P_n}{L}x - P_{onc}(t,x) - P_t \right], \\ P_{onc}(t,x) = 2.1C_{pr}(t,x) + 0.16C_{pr}^2(t,x) + 0.009C_{pr}^3(t,x), \\ C_{pr}(t,x) = C_0 \dfrac{n_0}{n(t,x)}. \end{cases} \qquad (13)$$

The numerical solution of this system was obtained with the use of *Mathematica* software. After transformation the system was computed in two stages. The equation was discretized using the fifth-order finite differences and the resulting system was solved by the NDSolve's built-in method (switching between Gear and Adams).

The volumetric velocity of water is derived from the formula:

$$\Phi(t) = \int_0^{g(t)} \frac{\partial n(t,x)}{\partial x} dx, \qquad (14)$$

where $x = g(t)$ is the solution of the following equation:

$$f(t) - \frac{P_a - P_n}{L}x - P_{onc}(t,x) - P_t = 0. \qquad (15)$$

Solution of the model yields the water volume that oscillates between capillary lumen and interstitium over one cardiac cycle:

$$V = \int_0^{t_{cyc}} \Phi(t) dt, \qquad (16)$$

where t_{cyc} is the duration of a cardiac cycle.

In Fig.1, there is a sequence of curves showing a change in the volumetric velocity over the length of the capillary with a linear increase in the pulse wave pressure.

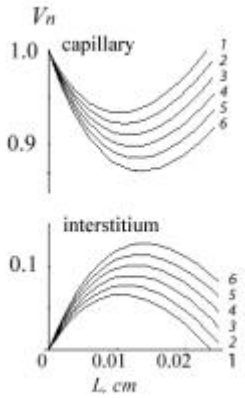

Fig. 1. Longitudinal profile of the normalized volumetric flow velocities in the capillary lumen and the adjacent interstitial region.

V_n – the normalized volumetric flow velocity; abscissa, L, represents the capillary length. Curves from 1 to 6 have the time interval Δt = 50 ms. A linear rise of the pulse wave pressure amplitude is assumed throughout.

The following parameters are used in the numerical solution of the model:

L = 0.025cm [2]; r= 3.5 $\cdot 10^{-4}$ cm [2]; C_o= 7 g/100cm^3 [27] ; P_a = 35 mm Hg and P_v = 15 mm Hg [2]; P_t =-2 mm Hg [4]; $\Delta t = 5 \cdot 10^{-3}$min ; the capillary pulse pressure amplitude, ΔP=6 mm Hg [39]; the linear blood flow velocity at the arteriolar end of the capillary , the linear blood flow velocity is assumed to be 12 cm/min [2]; k= 2.5 $\cdot 10^{-3}$ cm^3/(min mmHg cm^2).

As is seen, each velocity curve passes through a minimum after which there is a rise toward the initial values. The plot clearly demonstrates the oscillatory nature of the water movements. The frequency of water oscillations coincides with the pulse wave frequency.

A 3D plot presented in Fig.2 shows the waveform profile as a function of time along with the capillary longitudinal distribution of the volumetric flow velocities.

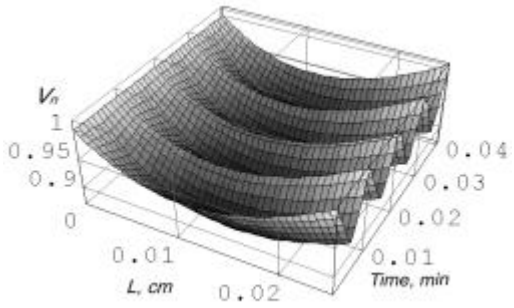

Fig.2. 3D plot of the normalized volumetric flow velocities against time and capillary length.
The parameter for solution of the model as in Fig 1. Pulse rate is 80. It is assumed that both the anacrotic and catacrotic changes in the capillary pulse pressure amplitude are linear functions of time. The systolic to diastolic time ratio is 0.48. The duration of the systolic phase is 0.3 s.

The oscillatory-convection model described in this paper gives an affirmative answer to the question of whether an oscillating volume of interstitial water can provide an adequate supply of oxygen to a respiring tissue volume defined by the geometry of the model. The parameters chosen for solution of the model are those found in the brain cortex or close to them, which gives more credit to the encouraging results thus far obtained. Contrary to the approach adopted in the oxygen-diffusion models, the interstitium here is viewed as a physiologically active medium where an important functional role in organizing tissue water microcirculation belongs to the aquaporin system [42].

When the transports of water and of oxygen are hypothesized to be coupled processes, implying the involvement of aquaporins, a question arises whether these water channels can themselves facilitate

transfer of oxygen, along with water, through the blood-brain barrier. As far as AQP1 and AQP4 are concerned, the answer so far is negative. But aquaglyceroporins, a group of aquaporins called so for their ability to transport low molecular weight substances, along with water, set a precedent which may suggest that such a possibility should not, at present, be entirely ruled out.

Any mediated mechanism of oxygen transport across the blood brain barrier (via aquaporins or otherwise) is of rather peripheral importance for the conclusions reached within the context of the oscillatory-convection model at this stage. Indeed, it has been revealed through direct measurements that in close proximity to the outer capillary wall a steady state level of oxygen tension is close to that found in the capillary lumen [6]. This outer region is involved into convective exchange which settles the issue of oxygen mass transport through the capillary wall and on to the interstitium. A very small trans-mural oxygen partial pressure gradient there might indicate that oxygen mass transfer is convection dominated. Incidentally, the convective microflow of water in the interstitium is enhanced due to a greater freedom with which water can move through parallel fiber bundles in the glial tissue and the extracapillary space freely communicating with CSF.

There is a number of systemic and local factors that influence oxygenation of the brain cortex. Among them are blood flow and pulse rate, pulse waveform and amplitude, water filtration coefficient. As far as the latter is concerned, it should be noted that according to the literature data water ultrafiltration velocities for CSF secretion and absorption may vary from 0.35 to 520 ml/min [16, 36]. The implycation here is that, provided the filtration surface area stays set, filtration coefficients should follow suit. Although the above data were obtained without any awareness of aquaporin function and what influences their activity, they give ample evidence for a possible wide range of the filtration coefficient values. In the light of the available information one might find an explanation to this in possible changes of aquaporin activity under the influence of some physiological agents and variation in the membrane density distribution of the water channels .

Local brain cortex metabolic activity and blood flow velocity are known to be functionally related. The non-destructive optical monitoring methods like dynamic capillaroscopy [38], laser Doppler flux motion [19], two-photon laser scanning microscopy [24, 23, 44] make it possible to conduct an ***in situ*** research for the parameters of blood flow in the brain cortex both in man and animal studies [23]. The capillary blood flow velocity in individual capillaries, as revealed through the erythrocyte movements, is extremely variable as is the erythrocyte density. [22]. Erythrocyte oscillations feature the systemic heart rate and respiratory movements [43, 15]. Also, the interstitial fluid and CSF demonstrate the same frequencies of variation [40].

The oscillatory-convective model supplies an explanation for the relationship between the observed changes in the capillary blood flow rates, the flow oscillations, and the oscillations in the capillary hydrostatic pressure. According to the model, at any position x along the length of the capillary the sum of the volumetric flow rates in the capillary lumen and the interstitial region is the total volumetric flow rate which is equal to the volumetric flow rate at the entry of the capillary. When the loss of capillary water due to radial filtration is negligible the linear and volumetric flow velocities would be linearly related. The situation changes when there is an increase in the filtration velocity. This would result in retardation of the capillary linear flow rate generally timed with the systolic phase of the cardiac cycle. In the diastolic phase the radial flow will be reversed with an accompanying increase in the capillary blood linear flow velocity. As the radial water flux is driven by the pulsatile hydrostatic pressure the latter must manifest itself in the blood flow oscillations bearing the rate of the heart activity. Indeed, the sharp changes in the linear blood flow thus found constitute up to 50 per cent of the average blood flow, with the frequency 0.5-3 Hz [8].

Both the changes in the linear velocities of capillary blood flow and in the linear erythrocyte density (observed through oscillations in the axial plasma gaps) may a further support the oscillatory-convective mechanism for the brain cortex oxygenation.

In theory, oxygen mass transfer proper might be sensitive to the oscillation of the capillary hydrostatic pressure. That can be revealed through changes in brain cortex hemoglobin levels and tissue oxygen partial pressure provided the monitoring methods allow to observe fast changes in the pulse rate. With the use of near-infrared spectroscopy to non-invasively monitor cerebral hemodynamics in a human subject it was possible to observe oxyhemoglobin oscillations at a frequency ~1 Hz, as that of the pulse rate [17].

Brain cortex capillary network with its largely T- branching and tortuosity is extremely variable and virtually lacks symmetry and ordered orientation of the capillaries [30]. In view of that radial oscillatory water exchange is easily visualized as taking place between individual capillaries. The direction of the water flux will depend on the instantaneous hydrostatic and oncotic pressure difference in the engaged capillaries, with an obvious implication to the character of oxygen mass transfer in the intercapillary region.

Apart from the capillaries, other microvessels of the metabolic group are involved in water exchange with the interstitium and the water of the perivascular spaces, with the venular regions being most absorption effective. At the same time the arterioles serve as a source of oxygen for the adjacent interstitial regions [5]. This creates conditions for intervascular oxygen mass transport via convection at the arteriolar-venular level. Thus the controversial issue of the "paradoxical" increase in oxygen tension in the sagittal sinus [21] can well find its simple explanation within the framework of oscillatory-convection mechanism of oxygen mass transfer.

The concept of convective mode of interstitial transport employing aquaporins, considered here in respect to oxygen mass transfer and brain cortex oxygenation, may have general implications concerning the physiology of the brain interstitium. Viewed in broader terms as a transport system, it may encompass other molecules like carbon dioxide, releasing factors, hormones, neurotransmitters, metabolites, to be involved in heat transfer, etc. Oscillatory convection may play an important role in the physiology of the interstitial space providing fast distance communications and intercellular exchange of information, thus performing an integrative function in relation to the brain cortex cell population.

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Summary

The orthodox diffusion mechanism of brain cortex oxygenation is reviewed in the light of the latest experimental observations. Data are given that are difficult to explain within the framework of the diffusion mechanism. As an alternative, a conceptual mathematical model for a convective mechanism of brain cortex oxygenation has been developed. In this model, oxygen mass transfer is viewed as coupled to the interstitial water transport, with aquaporins playing an important role in maintaining high water mass transfer rates and organising vectorial microflows of water. Oxygen transport is realized through a limited volume of water oscillating between the capillary lumen and the interstitium. A numerical solution of the model is given to demonstrate its validity.