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SOME PRELIMINARY CONSIDERATIONS CONCERNING CONCENTRATION OF OXYGEN IN TISSUE

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An approximate expression for the average concentration of oxygen in vascular tissue is derived on the basis of certain assumptions. These assumptions are then analyzed, and the inadequacies of the approximate derivation are pointed out; possibilities as to the method and results of more exact derivations are briefly discussed.

The problem of what factors influence the concentrations in tissue of capillary-supplied substances, especially oxygen, was first suggested to the writer by Dr. Melvin H. Knisely of the University of Chicago, in connection with the variations in blood-flow rates during malaria. In this paper the writer is attempting merely to outline the quantitative aspects of capillary production of metabolites, and to derive an approximate expression for the average concentration of oxygen in a tissue. He realizes that the treatment here given is by no means complete, but hopes that it may, in the future, be made more exact and extended to concentrations of other substances than oxygen.

Oxygen is supplied to respiring cells in tissue by the blood; some of it exists in the blood in chemical combination with the hemoglobin in erythrocytes, while some is in solution in the plasma. While the blood is passing through a capillary, the dissolved oxygen diffuses through the thin capillary wall into the surrounding tissue, where it is consumed. Meanwhile, the oxidized hemoglobin in the blood cells is giving up some of its oxygen to help maintain the concentration of dissolved oxygen.

Obviously the rate of diffusion through the wall of a given capillary will depend on several factors:

x_1, x_2 = the concentrations, in gm. per cc. of blood, of oxygen in arteriolar and venular hemoglobin, respectively.

c_1 = the concentration, in gm. per cc., of dissolved O_2 in the arteriole.

c_2 = the concentration, in gm. per cc., of dissolved O_2 in the capillary just before it empties into the venule. We are not letting c_2 be venular concentration, because in the venule blood from several capillaries is mixed, and the effect of the capillary in question is no longer distinguishable.

h = the permeability of the capillary wall to diffusing O_2.

D = the average tissue diffusion coefficient for O_2.

$-q$ = the rate of O_2 consumption in gm. per cc. per sec., in the tissue.

v = the velocity of blood flow in the capillary.

l = the length of the capillary from arteriole to venule.

r_0 = the radius of the capillary.

d = the average distance to adjacent capillaries.

For the present, we simplify matters by making certain assumptions and approximations: We assume that the capillaries in this particular tissue are parallel (this condition is approximately realized in striated muscle). We further assume that a capillary supplies oxygen only to the tissue in a right circular cylinder, coaxial with the capillary of length l and radius $d/2$, within which cylinder we are neglecting the effect of other capillaries than the one in question. The tissue we assume to be homogeneous and isotropic. The oxygen consumption, $-q$, we assume to be the same at all points in the region of supply of the capillary we are discussing. We are letting the z-axis be parallel to the capillary, with $z = 0$ at the arteriole and $z = l$ at the venule. The concentration, $c_o(z)$, of dissolved O_2 in the capillary, is assumed to be constant over any cross section, and to vary linearly with z from c_1 to c_2; similarly, the concentration, $x_o(z)$ of oxygen in hemoglobin, is assumed to vary linearly with z from x_1 at $z = 0$ to x_2 at $z = l$. Finally the external radial concentration gradient is assumed constant over any plane through the region of supply and perpendicular to the z-axis. We neglect any flow of O_2 parallel to the z-axis in the tissue. We denote by $c'(z)$ the concentration of O_2 in the tissue immediately outside the capillary wall, while $\bar{c}''$ is the concentration at $r = d/4$, $z = l/2$, which we shall call the "average" concentration in the tissue. r here is the radius vector in cylindrical coordinates, measured from the axis of the capillary.

There are three relations, equations (1), (2) and (3) below, which are immediately suggested. First, the total efflux of oxygen from the capillary per second may be expressed in terms of arteriolar and venular oxygen content of the blood:

$$\text{efflux per sec.} = \pi\, v\, r_0^2 (c_1 - c_2 + x_1 - x_2).$$

This quantity must be equal to the total oxygen consumption per second in the region of supply, since we are dealing with a steady state:

$$\pi\, v\, r_0^2 (c_1 - c_2 + x_1 - x_2) = -\pi\, q\, l \left[\left(\frac{d}{2}\right)^2 - r_0^2\right]. \qquad (1)$$

A second relation arises from the fact that the efflux per second through a small element of the capillary wall between z and $z + dz$ may be expressed in terms of the permeability of the capillary wall and the internal and external concentrations of dissolved O_2:

$$\text{efflux per sec. through } dz = h[c_0(z) - c'(z)] \cdot 2\,\pi\, r_0\, dz\,.$$

This may be set equal to the difference in total oxygen content of the blood before and after passing through dz:

$$2\,\pi\, r_0 h[c_0(z) - c'(z)]\, dz = -\left[\frac{dc_0(z)}{dz} + \frac{dx_0(z)}{dz}\right] \cdot v \cdot \pi\, r_0^2\, dz$$

or

$$2h\, [c_0(z) - c'(z)] = -\left[\frac{dc_0(z)}{dz} + \frac{dx_0(z)}{dz}\right] \cdot v r_0\,. \qquad (2)$$

Since we are assuming that $c_0(z)$ and $c'(z)$ vary linearly between the arteriole and the venule,

$$\frac{dc_0(z)}{dz} = \frac{c_2 - c_1}{l}$$

$$\frac{dx_0(z)}{dz} = \frac{x_2 - x_1}{l}.$$

Also,

$$c_0(z) = c_1 - \frac{(c_1 - c_2)z}{l}.$$

Using these values and the result of (1), we obtain an expression for $c'(z)$, the concentration of dissolved O_2 immediately outside the capillary:

$$c'(z) = c_1 + \frac{qz\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{v r_0^2} + \frac{z}{l}\,(x_1 - x_2) + \frac{q\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2 r_0 h}.$$

Now we set up our third relation, which will lead us to an expression for $\bar{c}''$, the average O_2 concentration in the external tissue. First, we shall call $\bar{c}'$ the average value of $c'(z)$, which will exist at $z = l/2$:

$$\bar{c}' = c_1 + \frac{ql\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2vr_0^2} + \tfrac{1}{2}(x_1 - x_2) + \frac{q\left[\left(\frac{d}{2}\right)^2 - r_0^2\right]}{2r_0 h}.$$

Since we assume a linear fall of oxygen concentration along any radius vector, the radial gradient of concentration in the plane $z = l/2$ will be given by

$$-\frac{\bar{c}' - \bar{c}''}{d/4} = -\frac{\bar{c}' - \bar{c}''}{R}$$

where $R = d/4$. Hence the total flow outward through the surface of the cylinder of length l and radius R may be approximated by

$$\frac{2\pi R\, l(\bar{c}' - \bar{c}'')D}{R} = 2\pi l D(\bar{c}' - \bar{c}'').$$

Obviously this quantity is equal to the total flow outward through the capillary wall, *minus* the amount consumed in the cylinder:

$$2\pi l D(\bar{c}' - \bar{c}'') = \pi r_0^2 v(c_1 - c_2 + x_1 - x_2) - [-q\pi l(R^2 - r_0^2)]$$

or

$$\bar{c}' - \bar{c}'' = \frac{r_0^2 v(c_1 - c_2 + x_1 - x_2)}{2lD} + \frac{q(R^2 - r_0^2)}{2D}. \qquad (3)$$

On using values obtained above for $c_1 - c_2 + x_1 - x_2$ and $\bar{c}'$, and collecting terms, we obtain

$$\bar{c}'' = c_1 + \tfrac{1}{2}(x_1 - x_2) + q(4R^2 - r_0^2)\left(\frac{1}{2r_0 h} + \frac{l}{2vr_0^2}\right) + \frac{3qR^2}{2D}.$$

This expression is seen to be reasonable, since $\bar{c}''$ is an increasing function of r_0, h, q (the "rate of production" of oxygen in the tissue; $q < 0$), D, v, and $x_1 - x_2$; it is a decreasing function of l and d.

Although we have what seems a qualitatively reasonable expression for $\bar{c}''$, it remains to analyze our initial assumptions in order to investigate the possibility of a more exact and general approach to the problem.

The first assumption that appears to need refining is that of linear change in $c_0(z)$ along the capillary. It can be seen that, if there were no hemoglobin, all the oxygen being in solution, the concentration $c_0(z)$ would fall exponentially, since, roughly, the rate of fall of $c_0(z)$ would be proportional to $c_0(z)$ at any z.

The effect of the hemoglobin will, to first approximation, be to hold $c_0(z)$ nearly constant over quite a wide range of values of total oxygen $x_0(z) + c_0(z)$; this is due to the fact that the hemoglobin contains many times as much oxygen as does the plasma.

However, this approximation will be vitiated by at least two complicating factors. The first of these is the fact that the equilibrium constant of the dissociation of oxyhemoglobin is not fixed; the reaction is pushed in the direction of dissociation by the presence of free carbonic acid. The second complication is the time lag in the dissociation, which will prevent the existence of an equilibrium at any point along the capillary. These two effects will tend to neutralize each other, but just what the final result will be is not known at present.

Another assumption which will have to be altered is that of constant radial gradient of external concentration. Poisson's equation shows us that this gradient can never be constant in consuming tissue, and we intuitively feel that concentration ought to fall asymptotically to zero as r, the radius vector in cylindrical coordinates, increases.

In order to arrive at a more exact idea of the nature of the external gradient, we must first have consumption, $-q$, as a function of concentration, c. N. Rashevsky (1940) gives the following relation for oxygen consumption (the notation has been changed):

$$c = \alpha y + \frac{\beta y}{1 - y} \tag{4}$$

where

$c = O_2$ concentration outside a cell

α, β are constants

$y = q/q^*$, where $-q^* =$ limiting consumption for $c = \infty$.

If we solve Poisson's or an equivalent equation for c, having first substituted for $-q$ its value as given by equation (4), we should get an exact expression for oxygen concentration as a point function in consuming tissue.

Finally, it will be well to discuss another of the concepts employed in our approximate derivation of $\bar{c}''$. This is the concept of a "region of supply". In our approximation we assumed that the capillary in question supplied all the oxygen consumed in a region assumed to be cylindrical; we neglected the effect on concentration in this region of all other capillaries than the one under investigation. Although it is true that, if there are n capillaries supplying a volume V of tissue, the average capillary may be assumed to supply a volume V/n, and although it is further true that through any closed surface S constructed around any such volume V/n containing one capillary the net diffusion is zero, it is not true that the capillaries outside S have no effect on concentration inside S. It is obvious, for instance, that if one of the external capillaries stops flowing, S will, on the average, have to expand to include the volume $V/n - 1$; hence, concentration within S will be reduced.

The problem of determining the exact effect of distant capillaries may be approached in either of two ways: by summing, or integrating, the effect of a single capillary over all the capillaries in the tissue, or by finding the total diffusion out through S of products of the capillary within S. This quantity will be equal in magnitude to the diffusion inward from all other capillaries, the average value of which diffusion will thus be determined.

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