ABSTRACT
To investigate the charge effect of the endothelial surface glycocalyx on microvessel permeability, we extend the 3-D model developed by Fu et al. [2] for the interendothelial cleft to include a negatively charged glycocalyx layer at the entrance of the cleft. Both electrostatic and steric exclusions on charged solutes are considered within the glycocalyx layer and at the interfaces. Four charge density profiles are assumed for the glycocalyx layer. Our model indicates that the overall solute permeability across the microvessel wall including the surface glycocalyx layer and the cleft region is independent of charge density profiles as long as they have the same maximum value and the same total charge. Based on the experimental data, this model predicts that the charge density would be 25-35 mEq/l in the glycocalyx of frog mesenteric capillaries. An intriguing prediction of this model is that when concentrations of cations and anions are unequal in the lumen, the negatively charged glycocalyx would provide more resistance to positively charged solutes than to negatively charged ones.

INTRODUCTION
Adamson et al. [1] suggested that the microvessel wall contain negative charges, which enhance the transport of positively charged molecules but retard that of negatively charged molecules. In the current study, we have attempted to develop a 2-D model incorporating both size and charge effects so that it will provide, for the first time, a quantitative analysis of various experimental results expected to be associated with negative charges in transvascular pathways. Compared to the model in Fu et al. [2], this model features two new characteristics: (i) surface glycocalyx contains negative electric charge; (ii) there is an interface between the surface glycocalyx layer and the cleft entrance. This model will help to better understand both physical and electrochemical mechanisms of the selectivity in the endothelial surface glycocalyx layer and therefore provide a new method for controlling transport rates of charged or uncharged molecules in drug delivery.

MATHEMATICAL MODEL

Entrance Fiber Matrix Layer
The governing equation for solute transport in the fiber layer can be written as:

\[ \frac{d}{dx} \left[ -D_{i,f} \frac{dC_i'}{dx} + Z_i \frac{dy'}{dx} C_i + K_{i,f} J_i C_i \right] = 0 \]  

where \( \psi' = FE'/RT \) is the dimensionless electrical potential. \( R \) is the universal gas constant, \( F \) is Faraday constant and \( T \) is temperature. \( E' \) is the electrical potential and \( C_i \) the solute concentration within fiber matrix. \( D_{i,f} \) is the effective diffusion coefficient of solute \( i \) in fiber matrix.
matrix layer, which includes both steric hindrance and diffusive resistance of fibers. $Z_i$ is the molecular charge number of species $i$ and $K_{i,f}$ is the hindrance factor or retardation coefficient of solute $i$ in convection transport. The boundary and matching conditions for Eq. (1) are:

$$C_i'(x) = C_i(x) e^{[\psi(x)-\psi_0]} \text{ at } x=-L_d \text{ and } x=0 \quad (2)$$

$$D_{i,j} \left[ \frac{dC_i}{dx} + \frac{Pe_{j,k} C_i}{L_{i,j}} \right] = D_{i,j} \frac{dC_i^{(1)}}{dx} \quad (3)$$

where $C_i^{(1)}(x,y)$ is the solute concentration within the region 1 of the cleft and $P_{C_{i,avg}} = Z_i \frac{dC_i}{dx}\big|_{L_c}$.

**Cleft Region**

The governing equation for solute transport in the cleft region can be approximated by a steady two-dimensional diffusion equation averaged over the cleft height,

$$\frac{\partial^2 C_i^{(1)}}{\partial x^2} + \frac{\partial^2 C_i^{(1)}}{\partial y^2} = j = 1,3 \quad (4)$$

$C_i^{(1)}$, $j = 1,3$ are concentrations in regions 1 and 3 of the cleft. Boundary conditions for Eq. (4) are Eqs. 5(a-d) and Eq. (3) is the interface boundary condition, which represents conservation of mass from the fiber region to the cleft region.

$$C_i^{(1)} = C_i^{(3)} \quad \text{ at } x = L_1, |y| \leq d \quad (5a)$$

$$\frac{dC_i^{(j)}}{dx} = 0, j = 1,3 \quad \text{ at } x = L_1, d < |y| \leq D \quad (5b)$$

$$C_i^{(3)} = C_{i,b} \quad \text{ at } x = L, |y| \leq D \quad (5c)$$

$$\frac{dC_i^{(1)}}{dy} = 0, j = 1,3 \quad \text{ at } 0 \leq x \leq L, y = 0, D \quad (5d)$$

The diffusive permeability $P$ of the microvessel to a solute is defined as,

$$P = \frac{Q_{2D} L_c}{C_{i,b} - C_{i}} 2D \quad (6)$$

Here $C_{i,b}$ and $C_{i}$ are concentrations in the lumen and in the tissue space. $L_d$ is the total length of the cleft per unit surface area of the microvessel. $2D$ is the distance between adjacent junction breaks. $L_{1}/2D$ is the total number of the breaks per unit surface area of the microvessel. $Q_{2D}^1$ is the solute mass flow rate through one junction break period, which is

$$Q_{2D}^1 = 2B \int_0^{L_1} D_{i,j} \frac{dC_i^{(1)}(L_1, y)}{dx} \, dy \quad (7)$$

**RESULTS**

Figure 2 shows the ratio of microvessel permeability for charged molecules (ribonuclease $+$, and $\alpha$-lactalbumin $-$) to that for neutral solute with the same size $P/P_{neutral}$ as a function of charge density $C_{m_{0}}$ in the fiber matrix layer. Solid lines with circles and dashed lines with triangles are $P/P_{neutral}$ for constant $C_{m_{0}}$. Dotted lines with squares and dash-dot-dash lines with diamonds are $P/P_{neutral}$ for varied $C_{m}$ in the fiber layer. Three distributions of varied $C_{m}(x)$ have the same maximum value $C_{m_{0}}$ and the same total charge. When proteins exist in the plasma, there are unequal concentrations of cations and anions in the lumen, $C_+ = 155 \text{ mM}$ and $C_- = 138 \text{ mM}$. Fig. 2b shows that for small $C_{m_{0}}$, the $P$ of negatively charged $\alpha$-lactalbumin is higher than that of positively charged ribonuclease although the surface glycocalyx carries negative charges. This is due to the dependence of $P$ on not only on solute charge, charge density of the fiber matrix $C_{m}(x)$, but also on $C_+$ and $C_-$. In particular, if $C_{m_{0}}$ is small, the negative charge in the layer is not enough to overcome the favored electrical partition to negatively charged $\alpha$-lactalbumin due to the presence of negatively charged proteins in the lumen. This prediction may be used in controlled drug delivery by locally modulating $C_{m}(x)$, $C_+$, and $C_-$ for certain drug with fixed charge.

**REFERENCE**


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