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Is the Facilitated Diffusion Exclusively a Passive Membrane Transport Mechanism?

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Abstract

Molecular transfer among cells occurs by means of a variety of transport processes. The membrane transport of hydrophobic ligands is facilitated by carriers - low molecular weight plasma membrane transport proteins. Particle transport is achieved by the reversible association of particles with the moving carriers. The velocity of a given particle transport is dependent on its affinity to the carrier. Analysis of the mathematical equations representing the concentrations of carriers and particles demonstrates that a traveling solution for the particle concentration is possible provided the chemical interaction between particles and carriers exhibits positive cooperativity. The permeability of the membrane depends on the rate constants of transitions between its two faces and, therefore, on energy profile in the membrane, because a concentration gradient in a solution represents stored chemical energy. The carrier-mediated transport exhibits passive transport if that chemical energy is dissipated spontaneously as the particles diffuse, i.e., the flow of particle is down its concentration gradient. We investigated a carrier model that can bind one or more than one substance, one of these can be transported up its concentration gradient. Such transport requires energy and exhibits active transport.

Keywords: facilitated diffusion, passive transport, active transport, carrier-mediated transport, concentration gradient, binding reaction.

Introduction

The carrier model that we propose represents a population of carriers that transports solute molecules. It exists in one of four states, which we label C^i, C^o, CS^i and CS^o. In the C state the solute S is free and in the CS state the solute is bound to the carrier. The carrier C communicates with the solution on the inner side of membrane in the C^i and CS^i states and on the outer side in the C^o and CS^o states. We assume that the binding of the solute to the carrier is so rapid that the reaction is at equilibrium at each instant of time [1]. So, the solute binds with the carrier rapidly with dissociation constant *k*, as shown in **(Figure 1)**. Suppose there is a number of such carriers in the membrane and let the concentrations of bound and unbound carriers in the membrane be c_{cs} and c_c, respectively. If the thickness of the membrane is *d*,

then the densities of bound and unbound carriers in the membrane, i.e., the number of moles of carrier per unit area of membrane, are $\sigma_{CS} = c_{CS} d$ and $\sigma_C = c_C d$. Let the concentration of solute be c_s. Then, at equilibrium, the binding reaction can be expressed in terms of the carrier densities as:

$$k = c_S \frac{c_C}{c_{CS}} = c_S \frac{\sigma_C}{\sigma_{CS}}. \quad (1)$$

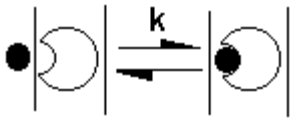

Figure 1. Kinetic diagram of the binding reaction of the carrier.

The bound complex translocates across the membrane according to a first-order reversible reaction with forward and reverse rate constants of α and β, respectively. If the density of bound carrier that is open to the left side in **(Figure 2)** is designated as σ_{CS}^i and to the right side is σ_{CS}^o, than the kinetic relation given by this model is:

$$\frac{d\sigma_{CS}^o}{dt} = \alpha \sigma_{CS}^i - \beta \sigma_{CS}^o. \quad (2)$$

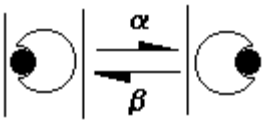

Figure 2. Kinetic diagram of the translocation step of the carrier.

The bound complex dissociates at the opposite side of the membrane with the same dissociation constant. The unbound carrier translocates across the membrane according to a first-order reversible reaction with rate constants that are the same as those for the translocation of the bound carrier.

We analyzed this model in the steady-state, which implies that the density of carrier in each of its four states is independent of time, i.e., the sum of the density of carrier over all of its states equals the total density of carrier:

$$\sigma_{CS} = \sigma_C^i + \sigma_C^o + \sigma_{CS}^i + \sigma_{CS}^o. \quad (3)$$

The only time the solute can cross the membrane is when it is bound to the carrier, so that the fluxes of bound and unbound carrier and the flux of solute are defined as follows:

$$\begin{aligned} \Phi_{CS} &= \Phi_S = \alpha \sigma_{CS}^i - \beta \sigma_{CS}^o \\ \Phi_C &= \alpha \sigma_C^i - \beta \sigma_C^o, \end{aligned} \quad (4)$$

all defined as positive when the flux is in the outward direction.

Methods

We derived the relation between the flux of solute and the concentration of solute implied by the kinetic diagram from Equations (1) – (4). This result can be accomplished if we use Equation (4) and express σ_{CS}^i and σ_{CS}^o in terms of the solute concentration:

$$\sigma_{CS}^{i} = \sigma_{CS}\left(\frac{\beta}{\alpha+\beta}\right)\left(\frac{c_S^i}{c_S^i+k}\right)$$
$$\sigma_{CS}^{o} = \sigma_{CS}\left(\frac{\alpha}{\alpha+\beta}\right)\left(\frac{c_S^o}{c_S^o+k}\right), \quad (5)$$

which indicate that the fractions of carriers on the inside and the outside faces of membrane are given by the quantities $\beta/(\alpha+\beta)$ and $\alpha/(\alpha+\beta)$, respectively.

The solute flux can be obtained by substitution of Equations (5) into Equation (4):

$$\Phi_S = \sigma_{CS}\frac{\alpha\beta}{\alpha+\beta}\left(\frac{c_S^i}{c_S^i+k}-\frac{c_S^o}{c_S^o+k}\right) = \Phi_S^{\max}\left(\frac{c_S^i}{c_S^i+k}-\frac{c_S^o}{c_S^o+k}\right) = \vec{\Phi}_S - \overleftarrow{\Phi}_S, \quad (6)$$

when $\vec{\Phi}_S$ and $\overleftarrow{\Phi}_S$ are, respectively, the outward unidirectional flux, or efflux and the inward unidirectional flux, or influx.

Results

The carrier mechanism can be understood more quantitatively with the aid of the more abstract diagram of carrier states shown in **(Figure 3)** and the results shown in **(Figure 4)**. Suppose there is no solute on either side of the membrane at initial instant of time, $c_S^i = c_S^o = o$. In that case, the interfacial binding reactions at two membrane surfaces are driven to the dissociated states and no solute is bound to carrier. Thus, all the carrier is found in the uncomplexed state on both sides of the membrane. For the case $\alpha = \beta$ and in according with Equations (5), this implies that $\sigma_C^i = \sigma_C^o = \sigma_{CS}/2$. Only two of the four possible carrier states are occupied and each is occupied with half the total carrier density. Since $\sigma_{CS}^i = \sigma_{CS}^o = o$, the solute flux through the membrane is zero.

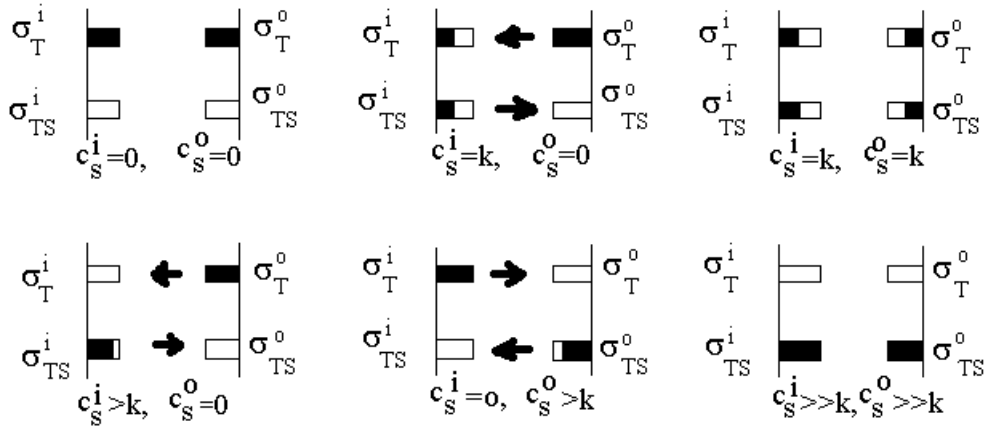

Figure 3. Schematic diagram of the carrier with four possible states. The size of each dark area is proportional to the fraction of the carrier density that is in that state. The arrows indicate the direction of the fluxes of the bound (TS) and unbound (T) transporters.

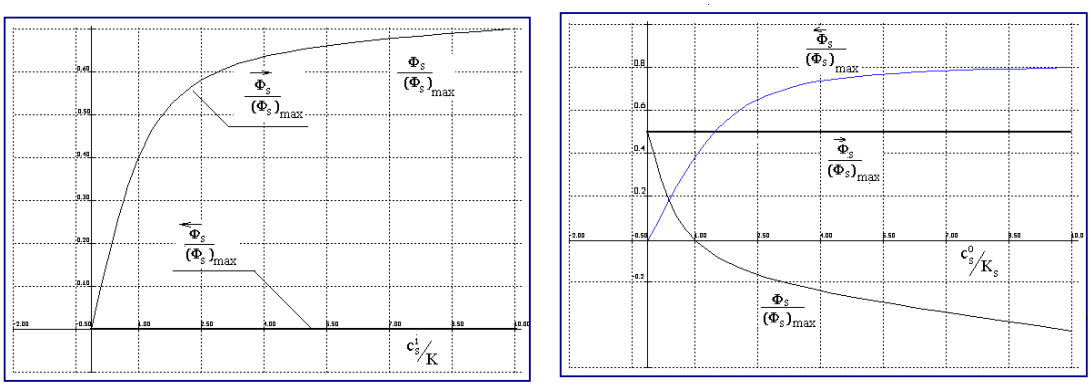

Figure 4. Dependence of the solute fluxes on solute concentrations: c_S^i for $c_S^o/k=0$ (left panel) and c_S^o for $c_S^i/k=1$ (right panel). $\vec{\Phi}_S$ and $\overleftarrow{\Phi}_S$ are the unidirectional efflux and influx of solute, defined in Equation (6).

If c_S^i is increased, then σ_{CS}^i increases and σ_C^i decreases. The carriers on the outer side of the membrane do not change state, so that σ_{CS}^o remains at zero. Therefore, $\sigma_{CS}^i > \sigma_{CS}^o$ and $\sigma_C^i < \sigma_C^o$. This state leads to an efflux of bound carrier and hence to an outward flux of solute. Since the influx of solute remains at zero, the net flux of bound carrier and solute increase as c_S^i is increased. That is, $\Phi_{CS} = \Phi_S = 0$. Also, there is an inward flux of unbound carrier, i.e., $\Phi_C < 0$.

If c_S^i is increases so that $c_S^i = k$, then $\sigma_C^i/\sigma_{CS} = \sigma_{CS}^i/\sigma_{CS} = \beta/(2(\alpha+\beta))$. Thus, half the carriers on the inside surface of the membrane are bound and half are unbound to solute. If, with $c_S^i = k$, c_S^o is increased from zero, then σ_{CS}^o will increase and σ_C^o will decrease. The increase in σ_{CS}^o will reduce the outward flux of solute until $c_S^o = o$, when half the carrier on the outer surface of the membrane is in the bound and half is in the unbound form. For the case shown, this implies that all four carrier states are occupied equally with one-quarter of the carriers. Under these circumstance the efflux of both bound and unbound carrier is zero. Further increases in solute concentration on either or both sides of the membrane drive the carrier into its bound states. The flux depends upon the relative number of carriers in the two bound states.

Discussions and Conclusions

Equation (6) can be rewritten in the form:

$$\Phi_S = k\,\Phi_S^{\max}\,\frac{c_S^i - c_S^o}{\left(c_S^i + k\right)\left(c_S^o + k\right)} \qquad (7)$$

Note that $\Phi_S > 0$ if $c_S^i > c_S^o$, i.e., flow of solute is down its concentration gradient as for diffusion of solute. At low solute concentrations, $c_S^i < k, c_S^o < k$, Equation (6) can be approximated as:

$$\Phi_S \approx \frac{\Phi_S^{\max}}{k}\left(c_S^i - c_S^o\right), \qquad (8)$$

so that the transport of solute cannot be distinguished from diffusion and the effective permeability of the membrane for the solute is:

$$P_S = \Phi_S^{\max}/k. \qquad (9)$$

However, even under these conditions, for which the relation of flux to concentration obeys Fick's law for membranes [2], the transport can show structural specificity not seen for diffusion processes. The structural specificity of P_S results from its dependence on the dissociation constant. Note that P_S depends inversely on k so that as *k* increases, P_S decreases.

As we shown, Equation (6) contains two terms that result from the binding reactions at the two membrane interfaces, which were assumed to have the same dissociation constant. Suppose the two dissociation constants differ, so that:

$$\sigma_{CS}^{i} = \sigma_{CS}\,\frac{c_S^i}{c_S^i + k_i} \text{ and } \sigma_{CS}^{o} = \sigma_{CS}\,\frac{c_S^o}{c_S^o + k_o} \tag{10}$$

Then it is easy to show that:

$$\Phi_S = \Phi_S^{\max}\left(\frac{c_S^i}{c_S^i + k_i} - \frac{c_S^o}{c_S^o + k_o}\right) = \Phi_S^{\max}\,\frac{c_S^i k_o - c_S^o k_i}{\left(c_S^i + k_i\right)\left(c_S^o + k_o\right)} \tag{11}$$

Suppose $c_S^i > c_S^o$, but $(c_S^i / k_i) < (c_S^o / k_o)$; then $\Phi_S < 0$. So, the model can result in transport up a concentration gradient. Such transport requires energy and is called active transport. If that energy is coupled to metabolism, then this form of transport is called primary active transport. Another type of active transport is that in which one solute S is transported up its concentration gradient because it shared a common transport mechanism with a second solute L and for which the energy comes from the stored chemical energy of the second solute. This type of active transport is called secondary and its schematic diagram is shown in **(Figure 5)**.

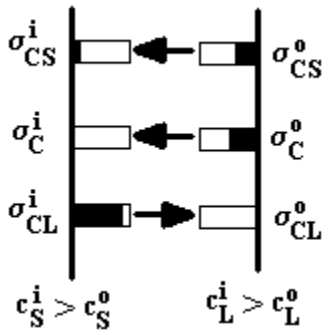

Figure 5. Schematic diagram for the state of the carrier for secondary active transport of solute. The size of each dark area is proportional to the fraction of the carrier density that is in that state. The arrows indicate the direction of the fluxes of the bound (CS and CL respectively) and unbound (C) carriers.

For example, neurotransporters, that are essential components in the recycling of neurotransmitters released during neuronal activity, works by coupling the downhill movement of small ions such as Na^+, Cl^-, K^+, and H^+ to the uphill transport of neurotransmitter [3, 4]. Plasma membrane transporters move the transmitter into the cytoplasm by cotransport with Na^+ [5]. The presence of glucose transport proteins is essential to supply glucose to the neurons and glia within the brain [6]. At least three glucose transporter isoforms have now been identified, and are thought to play a significant role, in the brain [7]. Transporters for glutamate couple influx of this excitatory amino acid to Na^+ and H^+ influx and K^+ efflux [8]. Transporters in synaptic vesicles couple H^+ efflux to neurotransmitter transport from the cytoplasm to the vesicle lumen [9].

Also, transport of bile acids across the canalicular membrane of the hepatocyte provides the primary motive force for generation of bile flow and is rate limiting in the vectorial movement of bile acids from blood to bile. Several distinct carriers for bile acids

have been defined based on physiological studies in isolated hepatocytes, membrane vesicles, hepatocyte couples and the perfused rat liver including membrane potential-driven and ATP-dependent mechanisms [10, 11].

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