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Further studies on membrane transport with time delay

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Abstract

A theory of cell membrane transport with a time delay which predicts under certain conditions overshoot or oscillatory permeation (Ohshima and Kondo, Biophys. Chem. 33 (1989) 303), is extended with the introduction of a parameter expressing a fraction of solutes inside the cell interior that suffer time delay. It is found that criterion for oscillation depends strongly on this parameter. Results will also be presented for the case of an exponential-type distribution of the delay time.

Keywords: Membrane transport; Time delay

1. Introduction

In a previous paper [1] we have proposed equations for solute transport through a cell membrane with a time delay in order to explain the phenomena of overshoot and oscillatory permeation that are often observed in biological cells (see, for example, refs. [2] and [3]) or their model systems [4]. On the basis of the fact that within the cell there are a number of small particles or sites which are expected to trap or accumulate diffusing solutes, we have introduced a time delay into the intracellular solute concentration. We have demonstrated that introduction of the time delay leads to, under certain conditions, overshoot or oscillatory permeation [1]. The reason for this can be explained as follows. During the time interval between $t = 0$ and $t = \tau$ only inward permeation (i.e., solute accumulation in the intracellular region) occurs. At the time instant $t = \tau$, in addition to inward permeation, outward permeation commences, i.e. solutes begin to diffuse out of the intracellular region into the extracellular region. Therefore, if τ is sufficiently large, the amount of solutes accumulated in the intracellular region may exceed the equilibrium value, resulting in overshoot or oscillation around the equilibrium value. In the previous work [1] we have assumed that all the solutes entering the intracellular region suffer time delay to the same extent. In the present work we eliminate this assumption and treat the situation that only a certain fraction of the solutes entering the cell interior suffer the time delay. Also we consider the case where the distribution of the delay time is expressed as an exponential function.

2. Basic equations

Consider permeation of diffusing solutes into cells through their membranes under quasi-steady-state conditions. The membrane transport equations with a time delay is generally given by [1]

$$V_o \frac{dC_o(t)}{dt} = -JA, \tag{1}$$

$$V_i \frac{dC_i(t)}{dt} = +JA, \tag{2}$$

with

$$J = P\left[C_o(t) - \int_0^\infty C_i(t-u) f(u)\, du\right], \tag{3}$$

where $C_o(t)$ and $C_i(t)$ denote the respective solute concentrations in the extracellular and intracellular regions at time t, J the solute flux directed from the outside to the inside of the cell, V_o and V_i the extracellular volume and total volume of the intracellular region, respectively, P permeability, A the total area of the cell surface, and $f(u)$ is the distribution function of delay time u, which satisfies

$$\int_0^\infty f(u)\, du = 1. \tag{4}$$

Let us obtain the solution to eqs. (1) and (2) (with eq. 3), subject to the initial conditions

$$C_o(0) = C_{o,0}, \tag{5}$$

$$C_i(0) = 0. \tag{6}$$

Note that the following conservation relation holds between $C_o(t)$ and $C_i(t)$:

$$V_o C_o(t) + V_i C_i(t) = V_o C_{o,0} E(t), \tag{7}$$

where $E(t)$ is a step function defined by

$$E(t) = \begin{cases} 1, & t > 0, \\ 0, & t < 0. \end{cases} \tag{8}$$

Equation (7) implies that the membrane volume is small so that the amount of solutes within the membrane can be neglected. Substituting eq. (3) into eq. (1) and using eq. (7), we obtain the following equation for $C_o(t)$:

$$\begin{aligned} \frac{dC_o(t)}{dt} &= -\alpha\phi\left[C_o(t) - \int_0^\infty C_i(t-u) f(u)\, du\right] \\ &= -\alpha\Big[\phi C_o(t) \\ &\quad + (1-\phi)\int_0^\infty C_o(t-u) f(u)\, du \\ &\quad - (1-\phi) C_{o,0} \int_0^\infty E(t-u) f(u)\, du\Big], \end{aligned} \tag{9}$$

with

$$\alpha = PA(1/V_o + 1/V_i), \tag{10}$$

$$\phi = V_i/(V_o + V_i), \tag{11}$$

where ϕ is the cell volume fraction. The intracellular concentration over time $C_i(t)$ is calculated via the conservation relation, eq. (7), which can be rewritten as

$$\frac{C_i(t)}{C_{o,0}} = \frac{1-\phi}{\phi}\left[E(t) - \frac{C_o(t)}{C_{o,0}}\right]. \tag{12}$$

Equation (9) can easily be integrated numerically. In order to study the analytic nature of the solution to eq. (9), we use the Laplace transform of $C_o(t)$, viz.,

$$\overline{C_o}(p) = \int_0^\infty e^{-pt} C_o(t)\, dt. \tag{13}$$

We then obtain, from eq. (9),

$$\overline{C_o}(p) = \frac{p + \alpha(1-\phi)\bar{f}(p)}{p\left[p + \alpha\phi + \alpha(1-\phi)\bar{f}(p)\right]} C_{o,0}, \tag{14}$$

where

$$\bar{f}(p) = \int_0^\infty e^{-pt} f(t)\, dt \tag{15}$$

is the Laplace transform of $f(u)$. If $f(u)$ is expressed as Dirac's delta function, viz.,

$$f(u) = \delta(u - \tau), \tag{16}$$

then eq. (3) reduces to eq. (12) that has been treated in the previous paper [1]. In the present paper we shall consider the case in which $f(u)$ is given by

$$f(u) = \beta\delta(u-\tau) + (1-\beta)\delta(u), \qquad (17)$$

which expresses the situation that a certain fraction, which we denote by β, of the solutes entering into the cell interior suffer a time delay τ, while the rest faction $1-\beta$ is not subject to the time delay. If $f(u)$ is given by eq. (17), then we have

$$\bar{f}(p) = \beta\,\mathrm{e}^{-\tau p} + (1-\beta). \qquad (18)$$

Hence eq. (14) can be written as

$$\overline{C_o}(p) = \{p + \alpha(1-\phi)(\beta\,\mathrm{e}^{-\tau p} + 1 - \beta)\} \times \{p[p + \alpha\phi + \alpha(1-\phi) \times (\beta\,\mathrm{e}^{-\tau p} + 1 - \beta)]\}^{-1} C_{o,0}. \qquad (19)$$

3. Results and discussion

In addition to two parameters considered in the previous model [1], that is, the delay time τ (or the scaled delay time $\alpha\tau$) and the cell volume fraction ϕ, the present model involves β as the third parameter which is the fraction of solutes in the cell interior that suffers a time delay. Figure 1 depicts the results of some calculations for the extracellular solute concentration $C_o(t)$ as a function of the scaled time αt for three values of β at $\phi = 0.5$ and $\alpha\tau = 1.5$ As is seen in Fig. 1,

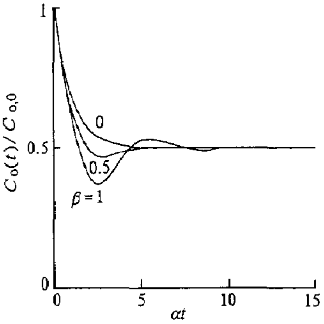

Fig. 1. Solute concentration $C_o(t)$ in the extracellular solution as a function of scaled time αt at $\phi = 0.5$ and $\alpha\tau = 1.5$ for three values of β (0, 0.5 and 1).

depending on the value of β, $C_o(t)$ exhibits monotonic exponential-type decay ($\beta = 0$), overshoot ($\beta = 0.5$), or oscillatory permeation ($\beta = 1$).

Now we obtain the criterion for oscillation. Let the time dependence of $C_o(t)$ (and $C_i(t)$) be $\exp(pt)$, where p may be a complex number. Then p can be given as the poles of $C_o(p)$, i.e., the solution to the characteristic equation obtained by setting the denominator of eq. (19) equal to zero, viz.,

$$p + \alpha\phi + \alpha(1-\phi)(\beta\,\mathrm{e}^{-\tau p} + 1 - \beta) = 0, \qquad (20)$$

which can be rewritten as

$$r + \gamma\,\mathrm{e}^{-r} = 0, \qquad (21)$$

with

$$r = [p + \alpha\{1 - \beta(1-\phi)\}]\tau, \qquad (22)$$

and

$$\gamma = \alpha(1-\phi)\beta\tau\,\exp[\alpha\tau\{1 - \beta(1-\phi)\}]. \qquad (23)$$

For the special case of $\beta = 1$, the present treatment reduces to the situation considered in the previous paper [1]. It thus follows that oscillatory permeation occurs when

$$\gamma > \mathrm{e}^{-1}(=0.368). \qquad (24)$$

This is the required criterion for oscillation. It should be emphasized that the criterion for oscillation is determined by only one parameter γ. Note that in our model overshoot is such that the amplitude of oscillation is damped so rapidly that all extrema, except for the first one, are negligible and, thus, that the oscillation is in practice observed as overshoot.

If the expression for γ (eq. 23 of ref. [1]) is replaced with eq. (23), then for the present case, all conclusions previously obtained apply [1], especially on the locations of extrema of $C_o(t)$ and $C_i(t)$ (see Fig. 7 of ref. [1]). Thus, we will not reproduce them here, but would like to add a crude approximation for the time instant at which $C_o(t)$ has its first minimum (or $C_i(t)$ has its first maximum), viz.,

$$t_m = \left[\tau + \frac{1}{\gamma - 0.368}\right], \quad (\gamma > 0.368), \qquad (25)$$

which is suggested from Fig. 7 of ref. [1].

Figure 2 demonstrates, on a ϕ–$\alpha\tau$ plane, two regions in which $C_o(t)$ (and $C_i(t)$) shows monotonic exponential-type change without oscillation (region I) and oscillation (region II) at several values of β. Regions I and II correspond to $\gamma < e^{-1}$ and $\gamma > e^{-1}$, respectively, and the boundary coincides with $\gamma = e^{-1}$. Note that for all values of β except the case of $\beta = 1$, region II corresponds to stable oscillation and only with $\beta = 1$ region II contains a certain region in which unstable oscillation is observed; this case has already been considered in the previous paper [1] (Fig. 5 of ref. [1]).

Figure 2 shows that the ϕ dependence of the boundary between regions I and II (i.e., that of the criterion for oscillation) is not very strong unless ϕ is close to 1. On the other hand, it depends strongly on the value of β, as is seen in Fig. 3, which shows the boundary between regions I and II on a β–$\alpha\tau$ plane at $\phi \to 0$. In this limit, which may correspond to the situation where one cell is suspended in a solution of an infinitely large volume, one obtains

$$\gamma \to \alpha\beta\tau \exp[\alpha\tau(1-\beta)]. \tag{26}$$

Equation (25) again shows that γ, that is, the criterion for oscillation depends strongly on the

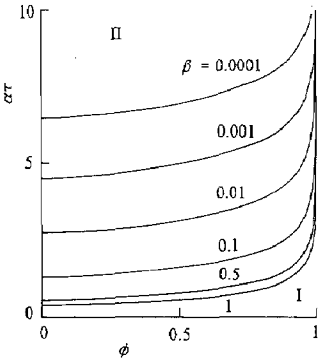

Fig. 2. Two regions I and II (on a $\phi - \alpha\tau$ plane) in which different types of time course of $C_o(t)$ and $C_i(t)$ appear for several values of β. I (over each curve), monotonic exponential-type change without oscillation; II (below each curve), oscillation. The boundary between I and II corresponds to values of ϕ and $\alpha\tau$ satisfying $\gamma = 1/e$ (= 0.368) for each β.

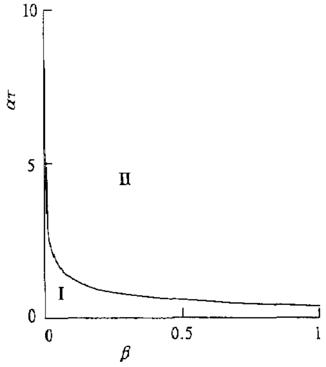

Fig. 3. Two regions I and II (on a $\beta - \alpha\tau$ plane) in which different types of time course of $C_o(t)$ and $C_i(t)$ appear in the limit of $\phi \to 0$. I, monotonic exponential-type change without oscillation; II, oscillation. The boundary between I and II corresponds to values of β and $\alpha\tau$ satisfying $\gamma = 1/e$ (= 0.368) in the limit $\phi \to 0$.

value of β; for small β, in particular, γ becomes proportional to β, viz.,

$$\gamma \approx \alpha\beta\tau \exp(\alpha\tau). \tag{27}$$

We would like to mention that the parameter β should be closely related to the concentration or number of the sites that trap and accumulate diffusing solutes entering the cell interior. If, therefore, one can measure the time course of $C_o(t)$ (or $C_i(t)$) at different values of β, then a rough estimation of the delay time τ may be possible by analyzing the experimentally-observed first minimum of $C_o(t)$ via eqs. (25) and (27).

The Laplace transform of $C_o(t)$, eq. (14), generally holds for arbitrary distributions $f(u)$ of the time delay other than eq. (17). As an example, we consider the case where $f(u)$ is an exponential function, viz.,

$$f(u) = \frac{1}{\tau} e^{-u/\tau}, \tag{28}$$

the Laplace transform of which is

$$f(p) = \frac{1}{1+\tau p}. \tag{29}$$

As will be shown below, an analytic expression for $C_o(t)$ can be obtained for this case. By using eq. (29), the Laplace transform of $C_o(t)$ becomes

$$\overline{C_o}(p)=\frac{\tau p^2+p+\alpha(1-\phi)}{p\left[\tau p^2+(\alpha\phi\tau+1)p+\alpha\right]}C_{o,0}. \quad (30)$$

Then we obtain

$$\frac{C_o(t)}{C_{o,0}}=1-\phi+\phi\exp\left[-\frac{(\alpha\phi\tau+1)t}{2\tau}\right]\times\left[\cosh\left(\frac{\omega t}{2\tau}\right)+\frac{1-\alpha\tau(2-\phi)}{\omega}\times\sinh\left(\frac{\omega t}{2\tau}\right)\right] \quad (31)$$

for $\quad \omega^2\equiv(\alpha\phi\tau+1)^2-4\alpha\tau>0, \quad (32)$

and

$$\frac{C_o(t)}{C_{o,0}}=1-\phi+\phi\exp\left[-\frac{(\alpha\phi\tau+1)t}{2\tau}\right]\times\left[\cos\left(\frac{\tilde{\omega} t}{2\tau}\right)+\frac{1-\alpha\tau(2-\phi)}{\tilde{\omega}}\times\sin\left(\frac{\tilde{\omega} t}{2\tau}\right)\right] \quad (33)$$

for $\quad \tilde{\omega}^2\equiv4\alpha\tau-(\alpha\phi\tau+1)^2>0. \quad (34)$

Thus we again see that $C_o(t)$ (and $C_i(t)$, which is calculated via eq. (12) can exhibit damped oscillation under certain conditions (i.e., if the condition 34 is satisfied).

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