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Model of active transport of ions in biomembranes based on ATP-dependent change of height of diffusion barriers to ions

Alexey V. Melkikh*, Vladimir D. Seleznev

Molecular Physics Chair, Ural State Technical University, 19 Mira Street, 620002 Yekaterinburg, Russia

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Abstract

A closed model of the active transport was constructed taking into account ATP-dependent opening and closing of barriers to ions and the relationship between the membrane potential and the work of ionic pumps under the condition of electroneutrality inside the cell. The internal consistency of the model was verified by the fulfillment of Onsager's reciprocity relation. It was demonstrated that at the limit of large energy barriers the operation of the system of the active transport is equivalent to the "turning segment" model, which was proposed by the authors earlier. Values of the resting potential and the intracellular concentration of ions were obtained for different types of cells. These results were in qualitative agreement with relevant experimental data.

Keywords: Height of diffusion barrier; Active transport of ions; ATP-ase; Resting potential

1. Introduction

The active transport of ions through biological membranes ensures various vital processes in cells of organisms, creates a potential difference and an osmotic pressure on membranes of cells. The E_1E_2-like enzyme, which can transport H^+, K^+, Na^+/K^+, Ca^{+2} and H^+/K^+ ions, is the best-understood type of the ATP-dependent pump. Experimental studies of E_1E_2-like enzymes demonstrated that they are characterized by formation of a phosphorylated mediate (an intermediate complex), which is significant for the transport. The E_1E_2-like enzyme was called so because two conformational states E_1 and E_2 were detected in the experiment. In the states E_2 and E_1 the binding point of ions is directed to the outside and the inside of the cell, respectively. When the enzyme is saturated with ions and ATP, the reaction $ATP \rightarrow ADP + P$ takes place, which is accompanied by liberation of energy sufficient for the transition of the enzyme from the state E_1 to the state E_2. In the state E_2 an ion can pass to the solution surrounding the cell and the enzyme, which is released from the ion and $ADP + P$, comes into equilibrium with the environment. This equilibrium corresponds to the predominant state E_1. Although functioning stages and the structure of E_1E_2-like enzymes have been studied well, the theoretical description of the active transport and the prediction of the resting potential and the difference of ion concentrations at the membrane, which can be found in the literature, are far from enough.

Proceeding from the analysis of experimental operating characteristics of ionic pumps, in this paper we propose a model of the active transport of ions, which is based on ATP-dependent opening and closing of the ion barrier. The "turning segment" model, which was advanced by the authors earlier (Melkikh and Seleznev, 2005), does not consider this variable barrier and ions are carried as the conformon turns to the other side of the biomembrane.

2. Drawbacks of models of the active transport of ions

Models of the active transport of ions, which are currently available in the literature, can be divided into two groups. The first group includes models, which consider the active transport of ions from the viewpoint of thermodynamics of irreversible processes (see, for example, Kedem and Katchalsky, 1958; Caplan and Essig,

*Corresponding author.
E-mail address: mav@dpt.ustu.ru (A.V. Melkikh).

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1983; Kjelstrup et al., 2005). They yield, in the main, linear expressions for the flux of ions through the membrane J and the rate v_A of the reaction $\mathrm{ATP} \rightarrow \mathrm{ADP} + P$ associated with this ion transport:

$$J = L_{11}\Delta\mu_i^e + L_{12}\Delta\mu_{ATP}, \quad (1)$$

$$v_A = L_{21}\Delta\mu_i^e + L_{22}\Delta\mu_{ATP}, \quad (2)$$

where L_{11}, L_{12}, L_{21} and L_{22} are kinetic coefficients; $\Delta\mu_i^e$ is the difference of electrochemical potentials of ions at the membrane; $\Delta\mu_{ATP}$ is the difference of chemical potentials of the reaction $\mathrm{ATP} \rightarrow \mathrm{ADP} + P$.

The differences $\Delta\mu_i^e$ and $\Delta\mu_{ATP}$ are thermodynamic forces giving rise to the flux J and v_A in the cell. Specifically, if the equilibrium of the reaction $\mathrm{ATP} \leftrightarrow \mathrm{ADP} + P$ is displaced ($\Delta\mu_{ATP} \neq 0$) due to the synthesis of ATP in mitochondria in the cell, then, in accordance with (1), a flux of ions J through the membrane may arise although electrochemical potentials of ions at the membrane are not different ($\Delta\mu_i^e = 0$). If the equilibrium of the reaction $\mathrm{ATP} \leftrightarrow \mathrm{ADP} + P$ is not displaced ($\Delta\mu_{ATP} = 0$), then, in accordance with (2), ATP may be synthesized at the cell membrane thanks to the difference of electrochemical potentials of ions $\Delta\mu_i^e \neq 0$.

In accordance with Onsager's principle, cross kinetic coefficients, which are responsible for the ion flux by the difference $\Delta\mu_{ATP}(L_{12})$ and the ATP synthesis by the difference $\Delta\mu_i^e(L_{21})$, should be equal. The requirement that the second law of thermodynamics is fulfilled (the entropy production $\geqslant 0$) leads to the known inequality

$$|L_{12}| \leqslant \sqrt{L_{11}L_{22}}, \quad (3)$$

which limits the absolute value of the cross kinetic coefficients.

However, thermodynamics of irreversible processes cannot give expressions for kinetic factors and, therefore, the resting potential of a cell. Nonlinear thermodynamics models represent the generalization of linear models to the region far from the equilibrium. But in this case, it is also impossible to obtain values of kinetic factors or fluxes and their dependence on parameters of a cell and the environment.

Models of the second group consider the active transport in terms of the chemical kinetics and the Brownian motion (Gordon and Macknight, 1991a,b; Kabakov, 1994, 1998; Tsong and Chang, 2003; Sagar and Rakowski, 1994; Hopfer, 2002; De Weer et al., 2001; Faber and Rudy, 2000; Fahraeus et al., 2002; Bustamante et al., 2001; Oster and Wang, 2000, 2003). These models have drawback that, firstly they disregard the relationship between the active flux and the difference of chemical potentials $\mathrm{ATP} - \mathrm{ADP}$ as the main thermodynamic force.

Thus, models of the active transport of ions, which are available in the literature, do not answer the question about the value of the resting potential and its dependence on cell parameters. Also, intracellular concentrations of ions cannot be predicted from these models.

On the other hand, the literature reports models relating the intracellular potential φ ($\varphi = 0$ is assumed in the environment) to concentrations of main types of ions inside and outside a cell and to penetrability of biomembranes by various types of ions. For example, for the transport of Na^+ and K^+ ions, φ is given by the Goldman–Hodgkin–Katz formula (Goldman, 1943; Hodgkin and Katz, 1949)

$$\varphi = -\frac{kT}{e}\ln\left(\frac{P_K n_K^i + P_{Na} n_{Na}^i + P_{Cl} n_{Cl}^o}{P_K n_K^o + P_{Na} n_{Na}^o + P_{Cl} n_{Cl}^i}\right). \quad (4)$$

However, this formula was deduced on condition that the cell was filled by some means (for example, thanks to the work of ionic pumps) with a solution, whose composition differed from the composition of the environment. Then a quasistationary regime corresponding to a zero passive electric current can be established in this system. The formula (4) was obtained just on this condition. Clearly, if the problem is stated this way, the potential will drop to zero or the Donnan potential (if we take into account the presence of ions incapable of penetrating through the membrane) as ionic compositions of the environment and the cell become equal.

The formula (4) agreed well with relevant experimental data on potentials of some types of cells. It is obvious however that the formula (4) does not reveal mechanisms of the active transport. This formula cannot predict intracellular concentrations of ions. Oppositely, these concentrations need be known to predict the potential. However, intracellular concentrations of ions change if changes occur in the environment. In this case, the formula (4) may be used if concentrations of ions inside a cell are measured continuously as ion concentrations outside the cell change. Such measurements are difficult to perform and are inefficient in living cells. If intracellular concentrations of ions can be predicted, it is much easier to obtain the dependence of the cell potential on environmental conditions.

The authors (Melkikh and Seleznev, 1998, 1999, 2001, 2005) proposed a basic model of the active transport, providing the dependence of the resting potential and intracellular concentrations of ions on the difference of the chemical potentials $\mathrm{ATP} - \mathrm{ADP}$ and concentrations of ions outside a cell.

The model has the following main provisions:

1. Some part of the transport ATP-ase, which contains the ion sorption center, can turn through 180°. The extreme turning points correspond to two positions of the ion sorption center: the left (inside a cell) and the right (outside a cell) positions. This part of the ATP-ase is simulated as the "conformon 1", i.e. as a subsystem with two states. When it is in the equilibrium with the thermostat, the conformon-1 is mostly in the state having a smaller potential energy and the ion sorption center is inside the cell.
2. The reaction $\mathrm{ATP} \leftrightarrow \mathrm{ADP} + P$ can be conveniently presented as a subsystem with two states or the