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# Models of active transport of neurotransmitters in synaptic vesicles

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**Abstract**

Models of the active transport of neurotransmitters in synaptic vesicles were constructed. The models were used to determine the resting potential at membranes of synaptic vesicles: 40 mV (monoamines and acetylcholine) and −40 mV (glutamate). The potential at the membrane of a synaptic vesicle was almost absent for the transport of GABA and glycine. The neurotransmitter concentration of a cell was 0.1–18 mM at the concentration of neurotransmitters in a vesicle equal to 0.5 M. This result is in qualitative agreement with the relevant experimental data.


*Keywords:* Synaptic vesicles; Active transport of neurotransmitters; Resting potential

As is known, neurotransmitters represent molecules, which open channels that control the generation of a nerve impulse in neurons (see, for example, Nicholls et al., 2001). Neurotransmitters are stored in synaptic vesicles at dormancy. When a nerve impulse is produced, neurotransmitters leave the vesicles and open channels of the adjacent cell at the point of the synaptic contact.

A system of the active transport of neurotransmitters to synaptic vesicles is available. This system maintains the neurotransmitter concentration of the vesicles at 0.5 M (Nicholls et al., 2001). The concentration of neurotransmitters in the environment (a cell) is small and equals about $10^{-3}$ M (Wolosker et al., 1996). To understand the operating mechanism of neurotransmitters and the possibility to control their concentration inside and outside synaptic vesicles, we need models for prediction of the electric potential at the vesicle membrane and the internal concentration of ions. Also, it is necessary to construct such models because synaptic vesicles are small (about 50 nm in diameter) and, therefore, these quantities are difficult to measure.

However, although papers dedicated to experimental studies of synaptic vesicles and the transport of neurotransmitters in them are numerous (see, for example, Santos et al., 2006; Lachamp et al., 2006; Roz and Rehavi, 2003), models of the active transport of neurotransmitters, which allow predicting their concentration in vesicles and the potential at the vesicle membrane, are unavailable in the literature.

According to the literature data (Nicholls et al., 2001), neurotransmitters are transported to a synaptic vesicle by the proton gradient produced by the H-ATPase carrying protons to synaptic vesicles.

Let us construct a model of the active transport of ions for a synaptic vesicle on the basis of our earlier models of the active transport in different types of cells (Melkikh and Seleznev, 2005, 2006a, b).

In line with Melkikh and Seleznev (2005), model of the active transport of ions should have the following basic provisions:

1. A transport macromolecule capable of carrying ions has two conformational states corresponding to the location of the ion sorption center inside and outside a cell.
2. The motive force of the ion transport is the difference of the ATP–ADP chemical potentials (or the difference of chemical potentials of other ions for an exchanger). Almost all of the ATP energy is imparted to a transport molecule and this molecule passes with a high probability to the state corresponding to the location of the ion sorption center outside the cell.

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3. Once the ion passes to the solution, the macromolecule regains its initial state (the ion center is predominantly located in the cell).

The model of the active transport is based on the Boltzmann distribution for a two-level system and the probability of the macromolecule being in either state under nonequilibrium conditions (the difference of the ATP–ADP chemical potentials).

Relevant experimental data suggest that the flow of protons into a synaptic vesicle is due to the ATP energy. The H-ATPase carrying protons into vesicles refers to the family of V-ATPases, many of which participate in the transport of protons in bacterium cells and intracellular structures. According to the experimental data (Wagner et al., 2004), the stoichiometry of the proton transport by V-H-ATPases is 2–4 protons per one ATP molecule. The first value is characteristic of large ΔpH (of the order of 4), while the second value is typical of relatively small ΔpH (of the order of 2). It follows from experiments that ΔpH across the membrane of synaptic vesicles is about 2 (Gidon and Sihra, 1989; Tabb et al., 1992). We shall assume therefore that the number of carried protons is four.

Then the flow of protons caused by the ATPase can be written as (the flow into a vesicle is assumed to be positive)

$$J_H = \phi_H\left[\exp(\Delta\mu_A)\left(n_o^H\right) - \exp(4\varphi)\left(n_i^H\right)\right], \quad (1)$$

where $C_H$ is a constant, while the subscripts $o$ and $i$ refer to a cell and a synoptic vesicle, respectively (since protons are pumped inwards, the barrier in the form of an electric potential appears during their inward movement). Here and henceforth we use dimensionless variables:

$$\frac{\Delta\mu_A}{kT} \equiv \Delta\mu_A, \frac{e\varphi}{kT} \equiv \varphi.$$

The total flow of protons is zero in the stationary state. Generally speaking, the total flow of protons consists of the active flow (1), the flow of protons through the exchanger during the transport of neurotransmitters, and the passive transport of protons. We shall neglect the passive transport of protons considering the requirement on the maximum efficient operation of molecular machines of cells. As for the flow of protons through the exchanger, in the subsequent discussion it will be shown to be independently zero. Therefore, $J_H$ also turns to zero under stationary conditions.

Then Eq. (1) gives the concentration of protons inside a synaptic vesicle:

$$\exp\left(\frac{\Delta\mu_A}{4} - \varphi\right) n_o^H = n_i^H. \quad (2)$$

Different neurotransmitters are carried by different systems of the active transport. Diagrams showing the transport of some neurotransmitters (Nicholls et al., 2001) are given in Figs. 1–3.

The transported neurotransmitters are charged differently and, therefore, we shall consider each case separately.

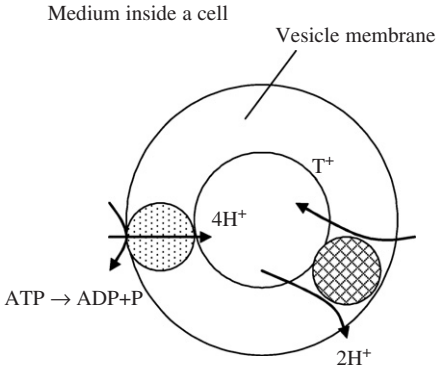


Fig. 1. Monoamines and acetylcholine transport.

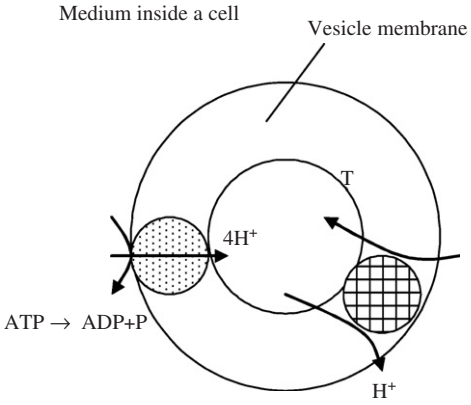


Fig. 2. GABA and glycine transport.

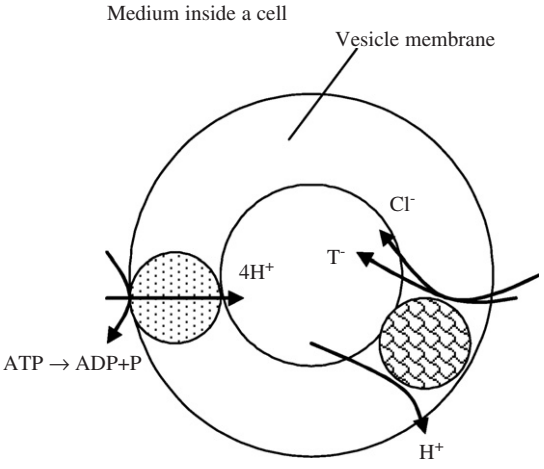


Fig. 3. Glutamate transport.

At the same time, for efficiency reasons, passive flows of all neurotransmitters through membranes of synaptic vesicles will be neglected.

Let us consider the first case (monoamines and acetylcholine). The active flow of positive neurotransmitters into a vesicle is written as

$$J_T = \phi_1\left(n_o^T \exp(\varphi)\left(n_i^H\right)^2 - n_i^T\left(n_o^H\right)^2\right). \quad (3)$$