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A POOL MODEL OF THE MEDIATOR EXOCYTOSIS INTO THE SYNAPSE

A model describing the mediator release into a synaptic cleft and making allowance for the pool structure of the presynaptic region has been proposed. Namely, the presynaptic region is assumed to contain two pools with vesicles that accumulate the mediator. A nerve impulse stimulates the injection of mediator from the first pool into the synaptic cleft. Simultaneously, the mediator from the second pool diffuses into the first one. The replenishment of the second pool occurs by absorbing the mediator from the synaptic cleft. Various operational modes of this model are considered. In particular, specific features of the single-impulse transmission through the system are studied. The functioning of the system with a feedback (the output signal is supplied to the input of the system) is analyzed, and it is shown that, in this case, a parameter determining the feedback intensity has a critical character: at the parameter values not exceeding the critical value, the presence of feedback does not govern the functioning of the system at the qualitative level.

K e y w o r d s: neuron, synapse, mediator, presynaptic membrane.

1. Introduction

The chemical synapse is a contact between two neurons [1–3]. The synapse is confined by presynaptic and postsynaptic membranes, and the gap between them is called the synaptic cleft. The region in front of the presynaptic membrane contains vesicles [4–13] that accumulate a special substance, the *mediator*. When a nerve impulse arrives, the mediator is released into the synaptic cleft; this is the so-called *exocytosis* phenomenon [14–18]. Then the mediator diffusively moves to the postsynaptic membrane. The postsynaptic membrane contains special receptors, and the mediator interacts with them. As a result, the receptors become activated, and a new impulse is generated in the postsynaptic membrane. The receptor deactivation is accompanied by the release of the mediator and its removal from the synaptic cleft. Ultimately, the mediator returns back to the presynaptic membrane [1–4]. Thus, a cyclic process takes place here.

The relevant issues were studied in a number of researches. Here, we would like to distinguish an approach developed in works [19–24]. First of all, we are interested in the release of a mediator from the presynaptic membrane into the synaptic cleft and, in turn, of the mediator from the synaptic cleft back into the presynaptic membrane. Those processes are not trivial *per se*. In particular, vesicles in the presynaptic region combine with one another into groups, which are called *pools*. There can be two or three pools [25–27]. Let us consider a system consisting of two pools. The first pool is located immediately near the presynaptic membrane. The second pool, which is a reserve one, is located in front of the first pool. As a rule, the capacity of the second pool is much larger than the capacity of the first one.

The general scheme of pool organization in the system is illustrated in Fig. 1. When a nerve impulse is transmitted, the vesicles in the first pool become open, and the mediator is released into the synaptic cleft [25]. The replenishment of the first pool with the mediator occurs owing to the process, when the vesicles with the mediator from the second reserve pool move to vacancies in the first pool. The reserve pool, as was marked above, is replenished by the mediator released from the synaptic cleft, in which the mediator interacts with the receptors at the postsynaptic membrane.

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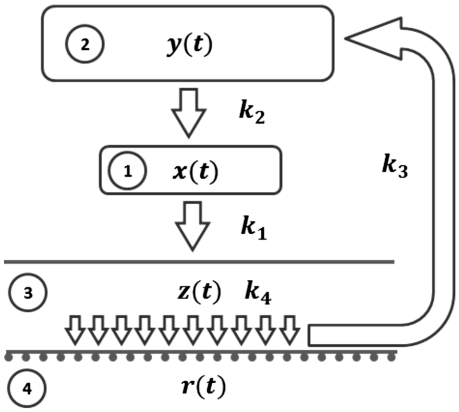

Fig. 1. General scheme of pool organization in the presynaptic region: first pool (*1*), second pool (*2*), synaptic cleft (*3*), and postsynaptic membrane (*4*). The arrows stand for the mediator transfer

In this work, a kinetic model that describes the corresponding processes is developed. The model makes it possible to consider various modes of nerve impulse transmission through the synapse. It should be noted that, in addition to a very obvious practical interest, the model can be interesting *per se*, because it can be used to determine the activation function of artificial neurons, while creating neural networks. It is also noteworthy that the proposed model is based on the approach that was earlier used for the creation of kinetic models to describe the synaptic information transmission [28, 29], in particular, at the stage of mediator exocytosis into the synapse [30].

2. Kinetic Model for Determining the Mediator Distribution

First of all, we are interested in the kinetics of the processes indicated above. For this purpose, let us introduce some notations. For instance, the amounts of mediator in the first and second pools and in the synaptic cleft will be denoted as x, y, and z, respectively. Important is an indicator associated with the number of activated receptors at the postsynaptic membrane. This quantity will be denoted by r. All mentioned parameters are functions of the time t. Furthermore, we assume that the capacity of the first pool equals N, and this is a fixed parameter. The capacity of the second pool is considered to be infinitely large (here, we assume that the capacity of the second pool is much larger than the capacity of the first pool [25]). Finally, the total number of receptors at the postsynaptic membrane will be denoted as R.

The model is based on equations that describe how the amount of a mediator in the first and second pools and in the synaptic cleft varies in time. In addition, those equations also determine a change in the number of activated receptors. In particular, in the framework of the proposed model, the dynamics of the mediator amount in the first pool is determined by the following equation:

$$\frac{dx}{dt} = -k_1 x + k_2 (N - x(t)) y(t). \tag{1}$$

Here, the first term in the right hand side describes the transfer of the mediator from the first pool into the synaptic cleft. We proceed from the fact that the intensity of this transfer is proportional to the amount of a mediator in the first pool. The second term describes the occupation of vacancies in the first pool by a mediator released from the second pool. The basic assumption consists in that the probability of the corresponding transfer is proportional to the number of vacancies in the first pool and the amount of a mediator in the second pool. Hereafter, the kinetic coefficients k_m ($m = 1, 2, 3, 4$) are the phenomenological parameters of the model.

An important remark concerns the measurement units for the amount of a mediator. As was mentioned above, in the pools, the mediator is contained in vesicles. The release of the mediator into the synaptic cleft and the transfer of the mediator from the second pool into the first one occur at the level of vesicles. The both processes are quantized in the sense that a certain portion of the mediator can be released and transferred. Taking those effects into account would demand for a discrete model, which would be much more complicated than the proposed one, but would not produce essentially new effects at the qualitative level concerning the process of mediator transfer between the pools and the mediator exocytosis into the synaptic cleft [31]. Therefore, we do not consider the fact that the mediator in the pools is distributed over the vesicles and understand the actual number of mediator molecules as the mediator amount. This approximation gives rise to a relatively simple model and does not affect the results qualitatively.

As for the second term on the right-hand side of Eq. (1), it should be proportional to the product of the number of vesicles in the second pool and the

number of free vesicle vacancies in the first pool. However, after multiplying the corresponding expression by the amount of the mediator in a vesicle and rescaling the proportionality factor, we arrive exactly at the expression that was used in Eq. (1) (as well as in the next equation). Thus, the fact that the preservation of the mediator in vesicles is not taken into account does not qualitatively affect the model.

The following equation describes a change of the mediator amount in the second pool:

$$\frac{dy}{dt} = -k_2(N - x(t))y(t) + k_3 r(t). \tag{2}$$

The first term on the right-hand side describes the mediator transfer from the reserve pool into the first one. The second term corresponds to the process of reserve pool replenishment with the mediator, which is released as a result of the deactivation of receptors at the postsynaptic membrane. We suppose that the intensity of this process is proportional to the number of active receptors at the postsynaptic membrane.

It should be noted that a number of substantial simplifications have been used in this case. For instance, the process of mediator release from the cleft and filling the reserve pool is extremely nontrivial (see, e.g., work [32]). However, in order to make the model simple and obtain a possibility to carry out its qualitative analysis, we assume that the corresponding processes can be generally described as a certain transition taking place with a certain probability. In this case, the intensity of the mediator transfer into the reserve pool is proportional to the number of activated receptors.

The next equation determines the dynamics of the mediator amount in the synaptic cleft:

$$\frac{dz}{dt} = k_1 x - k_4(R - r(t))z(t). \tag{3}$$

The first term on the right-hand side describes the process of mediator release from the first pool into the synaptic cleft. The second term describes the interaction of the mediator in the synaptic cleft with receptors at the postsynaptic membrane. We assume that the probability of this interaction is proportional to the mediator amount in the cleft and the number of receptors in the inactive state. Additionally, we assume that the mediator released as a result of the receptor deactivation is removed from the synaptic cleft.

Finally, a change in the number of activated receptors is described by the equation

$$\frac{dr}{dt} = k_4(R - r(t))z(t) - k_3 r(t). \tag{4}$$

It makes allowance for two competing processes. The first term on the right-hand side describes the interaction between the mediator and the receptors (resulting in the transition of receptors into the active state). The second term describes the process of receptor deactivation (the receptor deactivation intensity is proportional to the number of active receptors).

From Eqs. (1)–(4), it follows that

$$\frac{dx}{dt} + \frac{dy}{dt} + \frac{dz}{dt} + \frac{dr}{dt} = 0. \tag{5}$$

This relation means that the total amount of the mediator in the system (including its fraction participating in the interaction with the receptors),

$$M = x + y + z + r, \tag{6}$$

remains constant. Equations (1)–(4) and (6) are used to determine how the number of activated receptors and the amount of the mediator in the pools and in the synaptic cleft change in time.

Preliminarily, let us change the variables: $x \to Nx$, $y \to Ny$, $z \to Nz$, $r \to Nr$, and $t \to t/k_3$. We introduce new parameters: $\alpha = k_1/k_3$, $\beta = k_2 N/k_3$, $\gamma = k_4 N/k_3$, $\lambda = R/N$, and $m = M/N$. In the new notation, the equations for determining the amount of the mediator in the pools and the synaptic cleft, as well as the number of activated receptors, read

$$\frac{dx}{dt} = -\alpha x(t) + \beta(1 - x(t))y(t), \tag{7}$$

$$\frac{dy}{dt} = -\beta(1 - x(t))y(t) + r(t), \tag{8}$$

$$\frac{dz}{dt} = \alpha x(t) - \gamma(\lambda - r(t))z(t), \tag{9}$$

$$\frac{dr}{dt} = \gamma(\lambda - r(t))z(t) - r(t), \tag{10}$$

$$x + y + z + r = m. \tag{11}$$

This is a nonlinear system of equations which has to be solved numerically. However, under certain conditions, its qualitative analysis is also possible.

3. Mode of Equivalent Intensities

Proper qualitative results can be obtained, if a number of circumstances are taken into consideration. First, the parameters α, β, and γ determine the intensity of the processes associated with the mediator transfer from the first pool into the synaptic cleft, from the second pool into the first pool, and the interaction between the mediator and the receptors at the postsynaptic membrane, respectively. First of all, we are interested in the influence of the parameter α on the system characteristics. In the general case, this parameter can be a function of the time, because the probability of the mediator release into the synaptic cleft increases with the appearance of an impulse. Therefore, we may consider the parameter α as a control one. In this respect, the other parameters, β and γ, affect the quantitative characteristics of the processes (nevertheless, a theoretical model can be imagined, in which those parameters affect the system at the qualitative level). Let us assume that $\beta \approx \gamma \approx 1$. This relationship corresponds to the situation where the intensity of the mediator interaction with receptors and the intensity of the mediator transfer from the reserve pool into the first one have the same order of magnitude as the intensity of the mediator removal from the synaptic cleft.

Second, let us assume that the total number of receptors at the postsynaptic membrane is sufficient for the number of activated receptors to be much smaller than the total number of receptors.

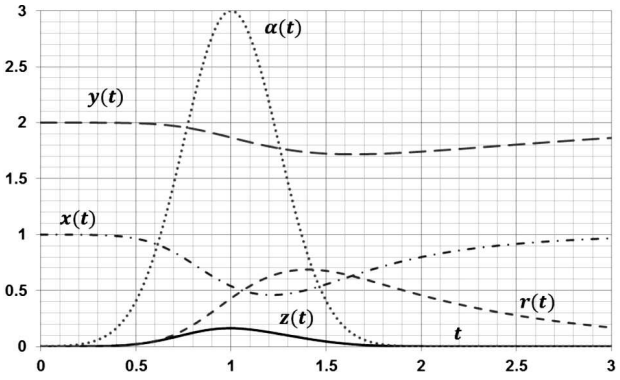

Fig. 2. Mediator distributions in the system in the case of a single impulse transmission: in the first pool ($x(t)$, dash-dotted curve), in the second pool ($y(t)$, dashed curve), and in the synaptic cleft ($z(t)$, solid curve); and the number of activated receptors at the postsynaptic membrane ($r(t)$, short-dashed curve). The dependence $\alpha(t)$ (dotted curve) is depicted for comparison. The parameter values used in calculations are $t_0 = 1$, $T = 0.25$, $A = 3$, $\lambda = 10$, and $m = 3$

Under those conditions, Eqs. (7)–(10) become strongly simplified:

$$\frac{dx}{dt} = -\alpha x(t) + (1 - x(t))y(t), \tag{12}$$

$$\frac{dy}{dt} = -(1 - x(t))y(t) + r(t), \tag{13}$$

$$\frac{dz}{dt} = \alpha x(t) - \lambda z(t), \tag{14}$$

$$\frac{dr}{dt} = \lambda z(t) - r(t). \tag{15}$$

We assume that $m > 1$, which corresponds to the situation where the amount of the mediator in the system is enough to completely fill the first pool.

In the absence of an impulse, the value of the parameter α can be considered as close to zero. In this case, a stationary solution is realized, which corresponds to the completely filled first pool, whereas the other mediator fraction is located in the second pool. In the framework of the model, the appearance of an impulse can be interpreted as a change in the parameter α. Below, several scenarios are considered. Let us begin with the case where a single impulse is transmitted through the system.

4. Transmission of a Single Impulse

When a single impulse is transmitted, the parameter α first increases from zero and then returns back to zero. The model time dependence of the parameter α is taken in the form

$$\alpha(t) = A \exp\left[-\frac{(t - t_0)^2}{2T^2}\right]. \tag{16}$$

Here, t_0 is the impulse arrival time, the parameter T can be interpreted as a characteristic impulse duration, and the parameter A determines the impulse amplitude. The corresponding dependences $x(t)$, $y(t)$, $z(t)$, and $r(t)$ are shown in Fig. 2. Everything is quite expected at the qualitative level. For instance, the amount of a mediator in the synaptic cleft first increases (when the impulse appears) and then returns back to the zero value. The time dependence of the number of activated receptors has a similar character. Thus, after the nerve impulse has been transmitted, the whole system returns to its initial state.

It is evident that, in this model, the redistribution of a mediator and the activation/deactivation of receptors are induced by a variation in the kinetic coefficient α in time. What is important here is how this coefficient changes (the law) rather than its magnitude. For example, if proceeding from relation (16) for $\alpha(t)$, the changes in the parameters T and A will affect the character of the processes in the synapse; it will take place, in particular, due to a change in the amount of a mediator released into the synaptic cleft.

Let us consider the process, when the values of the parameters T and A change synchronously in such a way that the following integral remains invariant:

$$\int_0^\infty \alpha(t)dt = \text{const}. \tag{17}$$

Condition (17) means that, provided the same amount of a mediator in the first pool, the amount of a mediator released every time into the synaptic cleft is also the same irrespective of the functional dependence $\alpha(t)$. To satisfy condition (17), let us set

$$A = \frac{A_0}{\sqrt{2\pi T}}. \tag{18}$$

In this case, if the parameter T changes (within certain limits), but the parameter A_0 is fixed, the following relation will be valid:

$$\int_0^\infty \alpha(t)dt \approx A_0. \tag{19}$$

To illustrate how a change in the kinetic coefficient α correlates with a change in the mediator amount x in the first pool, let us consider the corresponding dependence as a parametric one, in which the time plays the role of a parameter. The results of corresponding calculations for various values of T are depicted in Fig. 3.

Analogous parametric dependences between the kinetic coefficient α and the number of activated receptors r are exhibited in Fig. 4. The corresponding curves are expectedly closed, because the system returns to its initial state after the impulse has been transmitted. At the same time, the presented dependences give an idea about how the system works as a whole. First of all, it may be of interest from the viewpoint of the creation of artificial synapse-type elements. It should also be noted that the obtained dependences are in good agreement with the results of a model applied in work [30] to solve a similar problem with the help of different methods.

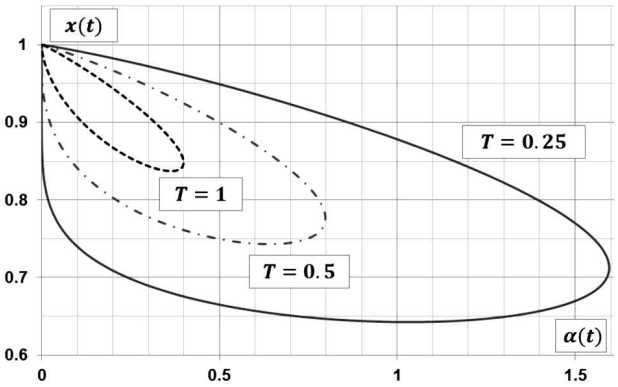

Fig. 3. Parametric dependences of the mediator amount in the first pool, x, on the value of the kinetic coefficient α for various values of the parameter $T = 0.25$ (solid curve), 0.5 (dash-dotted curve), and 1 (dashed curve). The parameter values used in calculations are $t_0 = 3$, $A_0 = 1$, $\lambda = 10$, and $m = 3$

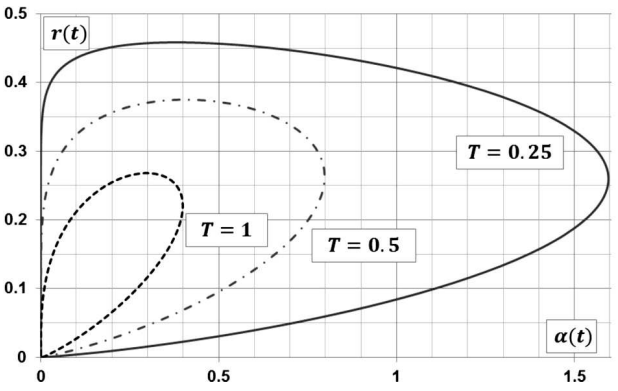

Fig. 4. Parametric dependences of the number of activated receptors, r, on the value of the kinetic coefficient α for various values of the parameter $T = 0.25$ (solid curve), 0.5 (dash-dotted curve), and 1 (dashed curve). The parameter values used in calculations are $t_0 = 3$, $A_0 = 1$, $\lambda = 10$, and $m = 3$

5. System with a Feedback

From the point of view of applications, not only the functional properties of a separate synapse can be a matter of interest, but also the properties of a synapse regarded as one of the elements in a complicated system like a neural network (artificial or natural). In

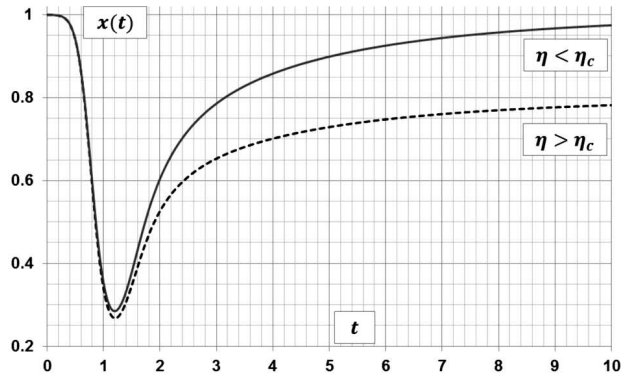

Fig. 5. Time dependences of the mediator amount in the first pool, $x(t)$, when the system has a feedback with the intensities $\eta = 0.15 < \eta_c$ (solid curve) and $\eta = 0.25 > \eta_c$ (dashed curve). The critical feedback intensity value is $\eta_c = 0.2$. The parameter values used in calculations are$t_0 = 1$, $A_0 = 5$, $\lambda = 10$, and $m = 3$

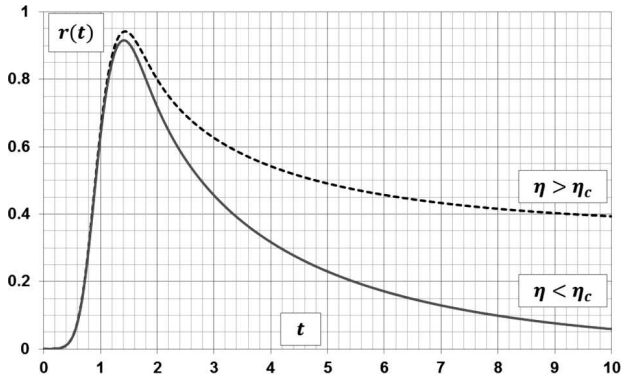

Fig. 6. Time dependences of the number of activated receptors in the first pool, $r(t)$, when the system has a feedback with the intensities $\eta = 0.15 < \eta_c$ (solid curve) and $\eta = 0.25 > \eta_c$ (dashed curve). The critical feedback intensity value is $\eta_c = 0.2$. The parameter values used in calculations are$t_0 = 1$, $A_0 = 5$, $\lambda = 10$, and $m = 3$

such systems, neurons transmit signals to a large number of other neurons and, in turn, receive signals from the latter. Very important is the case where a neuron has a feedback, i.e. a signal generated by a neuron is transmitted to the same neuron following a definite scheme [33–36]. In this case, there arise a number of important questions concerning the functioning of the neuron and the network as a whole. The main question is: How stable is this system?

Let us apply the model proposed above to study the feedback influence on the synapse functioning. For this purpose, let us consider the time dependence of the parameter α in the form

$$\alpha(t) = A\left\{\exp\left[-\frac{(t-t_0)^2}{2T^2}\right] + \eta r(t)\right\}. \tag{20}$$

The first term in this dependence describes a change in the kinetic coefficient induced by the impulse appearance, and the second term corresponds to the feedback. In particular, we use the approximation where the kinetic coefficient is determined by the number of activated receptors at the postsynaptic membrane, $r(t)$. In this case, the parameter η can be interpreted as a numerical characteristic of this feedback.

The presence of a feedback can qualitatively change the behavior of the system. In particular, a new stationary solution may emerge in the system. For instance, in the absence of both the feedback ($\eta = 0$) and the signal, the following solution is stationary (the condition $m > 1$ has to be satisfied):

$$x_s = 1, \tag{21}$$

$$y_s = m - 1, \tag{22}$$

$$z_s = r_s = 0. \tag{23}$$

In the presence of a feedback, there exists a critical value of the parameter η, so that the system has a different stationary solution, if this value is exceeded. The critical value is determined by the following relation:

$$\eta_c = \max\left(\frac{1}{A}, \frac{2+\frac{1}{\lambda}}{Am}\right). \tag{24}$$

If the condition $\eta < \eta_c$ is satisfied, then soultion (21)–(23) is stationary. When transmitting an impulse, the system goes out from this stationary state and afterward returns to the same state. Actually, it is the initial state of the system before the pulse arrives and provided that $\eta > \eta_c$. However, the system does not return into the stationary state (21)–(23) in this case. There arises a new stationary state with the following parameter values:

$$x_s = \frac{1}{A\eta}, \tag{25}$$

$$y_s = \frac{(A\eta m - 1)\lambda}{2A\eta\lambda + A\eta - \lambda - 1}, \tag{26}$$

$$z_s = \frac{(A\eta - 1)(A\eta m - 1)}{A\eta(2A\eta\lambda + A\eta - \lambda - 1)}, \tag{27}$$

$$r_s = \frac{\lambda(A\eta - 1)(A\eta m - 1)}{A\eta(2A\eta\lambda + A\eta - \lambda - 1)}. \quad (28)$$

After the impulse has been transmitted, the system transits from state (21)–(23) into state (25)–(28). Figure 5 demonstrates the dependence $x(t)$ for the mediator amount in the first pool for various values (sub- and supercritical) of the parameter η.

A principal difference between the corresponding dependences consists in the stationary value, to which the mediator amount in the first pool returns after the impulse has been transmitted. The same trend can also be observed for the number of activated receptors. The corresponding dependences are shown in Fig. 6. One can see that, under the condition $\eta > \eta_c$, the number of activated receptors does not return to its initial zero value.

6. Results and Conclusions

In this work, a model was proposed, which describes the process of mediator redistribution, when a nerve impulse is transmitted through a synapse. The model, among other things, involves the pool structure of the presynaptic region and the interaction of a mediator with receptors at the postsynaptic membrane. On the basis of this model, it is shown that, during the impulse transmission, the system goes out from the equilibrium state; then, after the impulse has been transmitted, it returns to the equilibrium state. In the framework of the developed model, it is calculated how the amount of a mediator in the pools and in the synaptic cleft, as well as the number of activated receptors, changes in time. The results obtained are in a qualitative agreement with experimental data and the results of other studies.

An important result was obtained concerning the properties of the examined system with a feedback. As was shown above, the researched system is stable in the sense that the presence of a low-intensity feedback does not change the mode of its functioning. This fact may be important for the analysis of the results of physiological experiments dealing with the transmission of nerve impulses and for the simulation of synaptic-type elements developed for artificial neural networks.

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ПУЛОВА МОДЕЛЬ
ЕКЗОЦИТОЗУ МЕДІАТОРУ В СИНАПС

Р е з ю м е

Пропонується модель, яка описує вивільнення медіатору в синаптичну щілину і враховує пулову структуру пресинаптичної області. Припускається, що пресинаптична область містить два пули з везикулами, які акумулюють медіатор. Під час надходження нервового імпульсу з першого пулу в синаптичну щілину виділяється медіатор. При цьому з другого пулу медіатор дифундує в перший пул. Поповнення другого пулу відбувається за рахунок поглинання медіатору із синаптичної щілини. Всі ці процеси враховуються в запропонованій моделі. Також ми розглядаємо різні режими функціонування системи. Зокрема, досліджено особливості передачі системою окремого імпульсу, а також проаналізовано ситуацію, коли в системі має місце зворотний зв'язок (вихідний сигнал подається на вхід системи). Показано, що в такому режимі існує граничне значення для параметра, котрий визначає інтенсивність зворотного зв'язку. Якщо значення даного параметра не перевищує граничне, наявність зворотного зв'язку якісно не впливає на функціонування системи.