https://doi.org/10.15407/ujpe63.10.919

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# MODEL OF POSTSYNAPTIC MEMBRANE DEACTIVATION

*A model has been proposed to describe the deactivation of a postsynaptic membrane after its excitation by transmitting a nerve impulse across the synapse. In particular, the process of mediator release in the form of choline from the postsynaptic membrane and its diffusive excretion from the synaptic cleft are considered. The time dependence of the number of activated receptors, the dependence of the maximum number of activated receptors on the activation time, and the space-time distribution of the choline concentration in the synaptic cleft are calculated.*

*K e y w o r d s*: nerve impulse, synapse, mediator, receptor, postsynaptic membrane.

## 1. Introduction

The transmission of a nerve impulse across a synapse is a complicated multilevel process [1–3]. In particular, the matter concerns the transmission of a nerve impulse from one (transmitting) neuron to another (receiving) neuron. The synapse is a contact in the form of a cleft between two neurons. It is confined between two membranes: the presynaptic membrane of a transmitting neuron and the postsynaptic membrane of a receiving neuron.

When a nerve impulse approaches the presynaptic membrane of a transmitting neuron, the mediator, a special active substance that moves diffusively across the synapse toward the postsynaptic membrane of a receiving neuron, is injected through this membrane into the synaptic space [4–9]. At the postsynaptic membrane, the mediator interacts with receptors [10–13], and the latter become activated. As a result, an action potential is generated, which means the signal propagation along the receiving neuron.

After the postsynaptic membrane excitation (the transition of the receptors at this membrane into the active state), it is deactivated. Namely, the mediator that participated in the receptor activation is deactivated by acetylcholinesterase. The hydrolysis of acetylcholine produces choline. The latter is released from the postsynaptic membrane, excreted from the synapse, absorbed by the presynaptic membrane, and finally used again in the acetylcholine synthesis. It is important that the receiving neuron can receive the next signal only after the postsynaptic membrane has "relaxed" to the normal inactive state, i.e. a state when the receptors at the postsynaptic membrane are inactive. This process of postsynaptic membrane deactivation is an important link in the process of nerve impulse transmission, because it directly governs the ability of the synaptic contact to transmit sequences of impulses with various frequencies. The specific features of the relaxation processes that take place at the postsynaptic membrane affect the frequency characteristics of the synaptic channel for the information transmission. At least from this point of view, the study of the mechanisms of postsynaptic membrane relaxation invokes a certain practical interest.

In this work, a model is proposed that describes the process of postsynaptic membrane transition from

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the active to inactive state. Here, we continue the approach dealing with the modeling of the synaptic transmission of information, which was proposed and developed in a number of works [13–15]. The proposed model takes into account the main mechanisms and processes associated with the deactivation of a postsynaptic membrane. In particular, the mechanism of postsynaptic membrane relaxation in a synapse, for which the active substance (the mediator) is acetylcholine, is considered as the basic one. We proceed from the assumption that the activation-deactivation of a postsynaptic membrane has the following stages:

• Acetylcholine is released from the presynaptic membrane and diffusively moves to the postsynaptic membrane;

• At the postsynaptic membrane, acetylcholine interacts with the receptors and activates them;

• Acetylcholinesterase deactivates acetylcholine, which has interacted with the receptors; a product of the decay of acetylcholine is choline;

• The produced choline is released from the postsynaptic membrane and diffusively moves to the presynaptic membrane;

• The presynaptic membrane absorbs choline; later, choline is used to form acetylcholine.

In order to describe the transition of receptors at the postsynaptic membrane from the inactive to active state and the following deactivation of active receptors, a system of differential equations is used. The solutions of this system are required to determine the boundary conditions for the diffusion equation that describes the process of choline excretion from the synaptic cleft.

## 2. Mathematical Model

The synaptic cleft is considered as a layer located in between two planes (the pre- and postsynaptic membranes) [13]. The latter are arranged at the distance $L$ from each other. The coordinate axis $z$ is directed from the presynaptic membrane ($z = 0$) to the postsynaptic one ($z = L$). Let $U(z,t)$, where $0 \le z \le L$ and the time $t \ge 0$, denote the concentration of choline formed as a result of the interaction between acetylcholinesterase and acetylcholine that activated receptors at the postsynaptic membrane.

The space-time distribution of the choline concentration is described in the framework of this model by the following equations:

$$\frac{\partial U(z,t)}{\partial t} = D\frac{\partial^2 U(z,t)}{\partial z^2}, \tag{1}$$

$$U(z=0,t) = 0, \tag{2}$$

$$\frac{\partial U(z=L,t)}{\partial z} = \alpha N_a(t), \tag{3}$$

$$U(z,t=0) = 0. \tag{4}$$

Here, $D$ is the coefficient of choline diffusion, $N_a(t)$ is a function that determines the number of activated receptors at the postsynaptic membrane, and $\alpha$ is a phenomenological parameter that couples the choline flux from the postsynaptic membrane to the presynaptic one with the number of activated receptors on the postsynaptic membrane. Thus, we proceed from the assumption that the amount of choline released from the postsynaptic membrane is proportional to the number of activated receptors. This assumption seems to be quite natural, because the activated receptors are the "sources" of choline that is formed at the acetylcholine deactivation.

The zero boundary condition at the left boundary ($z = 0$) follows from the assumption that the entire choline that diffusively reaches the presynaptic membrane is completely excreted from the synaptic cleft. Finally, the zero initial condition means that, at the initial time moment, no choline is released from the postsynaptic membrane, and there is no choline in the cleft.

To solve the problem, we have to know the time dependence of the number of activated receptors, $N_a(t)$. In order to determine it, let us use the following considerations and introduce the following notations. Let $N$ be the total number of receptors at the postsynaptic membrane, and $N_n(t)$ a function that describes the number of receptors in the inactive state. We assume that, under the action of acetylcholine, the receptors transit from the inactive state into the active one. Then, as a result of the acetylcholinesterase action, they transit from the active state into the relaxation state. For the sake of simplicity (and without loss of generality), we also assume that, under the acetylcholine action, all receptors transit from the inactive into the active state, and the intensity $\eta$ of those transitions is determined by the equation

$$\frac{dN_n}{dt} = -\eta N_n(t). \tag{5}$$

Actually, we assume that the number of receptors activated per unit time is proportional to the number of still inactivated receptors. For the transition of receptors from the active state to the relaxation one, we use the following equation:

$$\frac{dN_a}{dt} = \eta N_n(t) - \alpha N_a. \tag{6}$$

The first term on its right-hand side describes an increment in the number of active receptors due to the transition of inactive receptors into the active state, and the second (with the minus sign) term describes a reduction in the number of activated receptors due to the transition of receptors into the relaxation state. The initial conditions for the functions $N_a(t)$ and $N_n(t)$ are as follows:

$$N_a(t=0) = 0, \tag{7}$$

$$N_n(t=0) = N. \tag{8}$$

(at the initial time moment, all receptors are inactive, and there are no active receptors, respectively).

The above equations together with the initial conditions make it possible to determine the time dependence of the number of activated receptors at the postsynaptic membrane and the space-time distribution of choline in the synaptic cleft.

## 3. Analysis of Results

It is convenient to make the model equations dimensionless. Therefore, the following dimensionless variables are introduced: the time $\tau = \eta t$ and the coordinate $x = z/L$, as well as the dimensionless functions $a(\tau) = N_a(t)/N$, $n(\tau) = N_n(t)/N$, and $u(x,\tau) = U(z,t)/(\alpha L N)$. Then the initial model equations read

$$\frac{\partial u(x,\tau)}{\partial \tau} = h^2 \frac{\partial^2 u(x,\tau)}{\partial x^2}, \tag{9}$$

$$u(x=0,\tau) = 0, \tag{10}$$

$$\frac{\partial u(x=1,\tau)}{\partial x} = a(\tau), \tag{11}$$

$$u(x,\tau=0) = 0. \tag{12}$$

Here, $h^2 = D/(\eta L^2)$. We also have the equations

$$\frac{dn}{d\tau} = -n(\tau), \tag{13}$$

$$\frac{da}{d\tau} = n(\tau) - \lambda a(\tau), \tag{14}$$

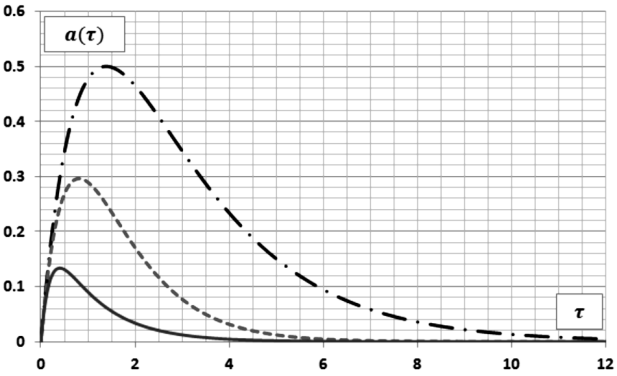


***Fig. 1.*** Dimensionless time dependences $a(\tau)$ of the number of activated receptors on the postsynaptic membrane for various values of the parameter $\lambda = 5$ (solid curve), 1.5 (dashed curve), and 0.5 (dash-dotted curve)

where $\lambda = \alpha/\eta$. Taking the initial conditions in the form

$$n(0) = 1, \tag{15}$$

$$a(0) = 0, \tag{16}$$

it is easy to obtain the following solution for the number of activated receptors at the postsynaptic membrane:

$$a(\tau) = \frac{\exp(-\tau) - \exp(-\lambda\tau)}{\lambda - 1}. \tag{17}$$

This dependence completely corresponds to general concepts about the activation dynamics at the postsynaptic membrane: the number of activated receptors firstly increases from zero to a certain maximum value and, afterward, decreases to zero. In Fig. 1, the dependences $a(\tau)$ are shown for various values of the parameter $\lambda$.

The function $a(\tau)$ has the maximum value

$$a(\tau_{\max}) = \lambda^{-\frac{\lambda}{\lambda-1}} \tag{18}$$

at

$$\tau_{\max} = \frac{\ln(\lambda)}{\lambda - 1}. \tag{19}$$

It is easy to understand that, as the parameter $\lambda$ grows, this value monotonically decreases. Expressions (18) and (19) can be considered as a relationship between the time of activation of the maximum number of receptors, $\tau_{\max}$, and the maximum number of

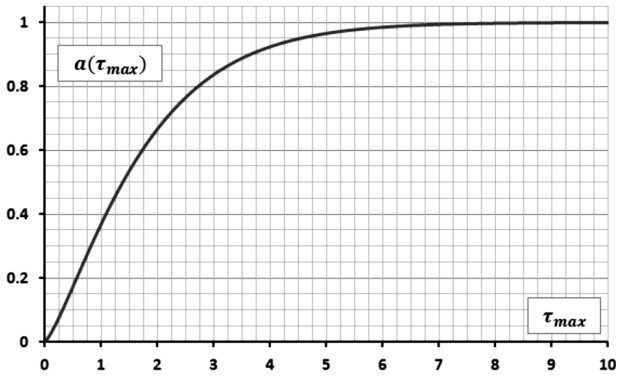


***Fig. 2.*** Dependence of the maximum number of activated receptors $a(\tau_{\max})$ on the time of activation of the maximum number of receptors $\tau_{\max}$

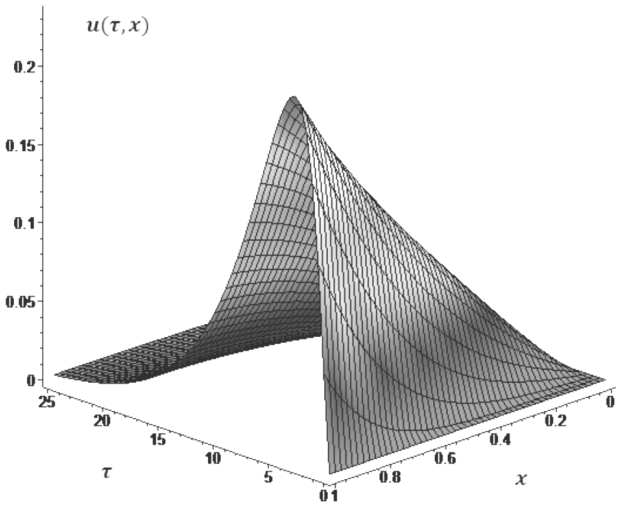


***Fig. 3.*** Dependence $u(\tau, x)$ calculated for the parameter values $\lambda = 0.5$ and $h = 0.3$

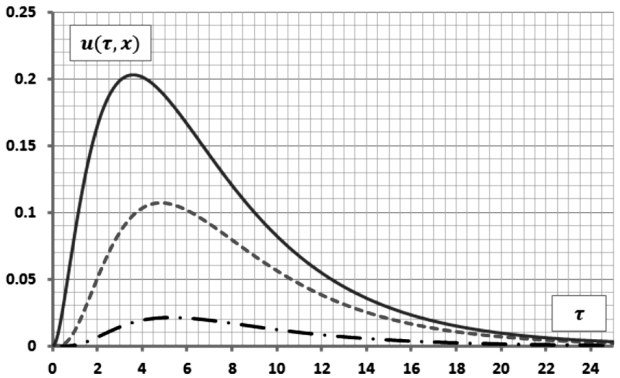


***Fig. 4.*** Dependences $u(\tau, x)$ at $x = 0.1$ (dash-dotted curve), 0.5 (dashed curve), and 0.9 (solid curve). The parameter values are $\lambda = 0.5$ and $h = 0.3$

activated receptors, $a(\tau_{\max})$, written in the parametric form. This dependence is depicted in Fig. 2. It is monotonic and substantially nonlinear. With the activation time growth, the maximum of the normalized number of activated receptors saturates at unity. In effect, this means that there is no sense to activate the postsynaptic membrane too long.

The solution $u(x, \tau)$ for the space-time distribution of choline in the synaptic cleft looks like

$$u(x,\tau) = \frac{h}{\lambda - 1}\Big(\varphi(\tau, x; 1) - \varphi(\tau, x; \lambda)\Big) - \\ - \sum_{m=0}^{\infty} u_m \exp\left(-\mu_m^2 h^2 \tau\right) \sin(\mu_m x), \tag{20}$$

where

$$\mu_m = \frac{(2m+1)\pi}{2}, \tag{21}$$

$$\varphi(\tau, x; s) = \frac{\exp(-s\tau)\sin\left(\frac{\sqrt{s}x}{h}\right)}{\sqrt{s}\cos(\frac{\sqrt{s}}{h})},$$

and the series coefficients

$$u_m = \frac{2h^2(-1)^m}{\lambda - 1}\left(\frac{1}{\mu_m^2 h^2 - 1} - \frac{1}{\mu_m^2 h^2 - \lambda}\right). \tag{22}$$

The calculated dependence $u(\tau, x)$ describes how the spatial distribution of choline in the synaptic cleft changes with the time. This dependence is exhibited in Fig. 3.

Finally, Fig. 4 demonstrates how the choline concentration changes with the time at some fixed spatial coordinates (in particular, at $x = 0.1$, 0.5, and 0.9). At the qualitative level, the scenario is as follows: the choline concentration firstly increases, reaches a certain maximum value, and then vanishes. The maximum value of the choline concentration is higher, if the point, at which the concentration is measured, is closer to the postsynaptic membrane.

## 4. Conclusions

The model proposed above to describe the deactivation of a postsynaptic membrane is rather simple. Nevertheless, with regard for the basic mechanisms and the stages of postsynaptic membrane relaxation and mediator excretion (in the form of choline) from the synapse, it allows analytical expressions to be obtained for the main system parameters.

It should also be noted that the relationship between the activation time of a postsynaptic membrane

and the maximum number of activated receptors, on the one hand, and the presence of a lower limit for the minimum number of activated receptors required to generate the action potential, on the other hand, imposes a restriction on the frequency of impulses that can be transmitted across the synapse.

Finally, it is generally accepted that the release of a mediator from the presynaptic membrane into the synapse space (when a nerve impulse approaches the presynaptic membrane) is a cooperative process, which lasts for a relatively short time interval (see, e.g., works [1, 2, 4]). The results obtained above allow us to assume that, under definite conditions (i.e. definite values of phenomenological model parameters), the process of mediator excretion from the synaptic cleft can also be considered as a cooperative process localized in the time.

We hope that the results obtained can be useful at performing the physiological and biophysical experiments with synapses and when modeling neural networks composed on the basis of elements of the synaptic type.


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Received 29.05.18.
Translated from Ukrainian by O.I. Voitenko

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МОДЕЛЮВАННЯ ПРОЦЕСУ
ДЕАКТИВАЦІЇ ПОСТСИНАПТИЧНОЇ МЕМБРАНИ

Р е з ю м е

Пропонується модель, яка описує процес деактивації постсинаптичної мембрани після збудження, що виникає внаслідок передачі нервового імпульсу через синапс. Зокрема, розглядається процес вивільнення медіатору (холіну) з постсинаптичної мембрани та виведення його із синаптичної щілини через механізм дифузії. Отримано часову залежність для кількості активованих рецепторів, залежність між часом активації постсинаптичної мембрани та максимальною кількістю активованих рецепторів, а також розраховано просторово-часовий розподіл концентрації холіну в синаптичній щілині.