A KINETIC MODEL OF SYNAPTIC TRANSMISSION ON INTERCELL INTERACTION

O.V. CHALYI, O.V. ZAITSEVA

UDC 577.3
©2009

O.O. Bogomolets National Medical University, Chair of Medical and Biological Physics
(13, Shevchenko Blvd, Kyiv 01160, Ukraine),

Taras Shevchenko Kyiv National University, Faculty of Physics
(6, Academician Glushkov Ave., Kyiv 03022, Ukraine; e-mail: zaitseva@hotmail.com)

We present a model of synaptic transmission on the intercell interaction in acetylcholine synapses. The following processes are considered: the time-dependent release of a mediator in a synaptic cleft, the binding of a mediator with a receptor, the formation of mediator-receptor complexes, and the release of a mediator from a cleft due to the diffusion, reversible capture by a presynaptic membrane, and, mainly, the decay in the presence of the enzyme acetylcholinesterase. To describe the changes of the concentrations of a mediator, receptors in the ground state, and excited mediator-receptor complexes, we have constructed and studied a system of three nonlinear differential equations and have proved that the singular point of a stationary state for the synaptic transmission is a stable node.

1. Introduction

The present work is devoted to the theoretical modeling of the process of synaptic transmission which underlies the intercell interaction. As known, this process plays the decisive role in the comprehension of the fundamental difference between the alive nature and the inorganic one which is mainly determined by the ability of highly organized living creatures to think. The purpose of the present work consists in the theoretical modeling of those real processes which are running in acetylcholine synaptic clefts, because just acetylcholine synapses are responsible for the processes of memorizing.

The intercell interaction possesses the dual nature. On the one hand, it is based on electric mechanisms of the propagation of a nerve impulse, the so-called action potential (AP), along nerve fibers (axons). The electric nature of the intercell interaction was first studied in works by A. Hodgkin and A. Huxley in the middle of the last century (see, e.g., [1–3]). On the other hand, the process of intercell interaction is characterized by the chemical nature of a sequence of phenomena which occur in synaptic clefts – contacts between axons and tree-like nerve endings (dendrites) of adjacent interacting cells. The linear sizes of synapses vary, depending on their nature, in the limits from several tens to hundreds of nanometers, i.e. they are typical mesoscale objects. In this case, the process of synaptic transmission is considered as a distinctive cooperative phase transition (see, e.g., [1]).

The first theoretical models, which used the idea of the isomorpism of the processes of synaptic transmission and phase transitions in spatially bounded liquid systems, were formulated in [4]. This work and the subsequent ones [5, 6] considered the systems of two kinetic equations for mediators and mediator-receptor complexes, i.e., in fact, for the first two stages of the process of synaptic transmission. Then works [7], [8], and [9] proposed and studied more realistic theoretical models of intercell interaction which took all three main stages of the synaptic transmission:

1. On the first stage, the synchronous release of molecules of biologically active substances, mediators, [e.g., acetylcholine (ACh)] through a presynaptic membrane of the first cell under the action of only one nervous impulse of AP occurs. The molecules of mediators, whose number can be very large (to 10^7), diffuse through a synaptic cleft and reach the postsynaptic membrane of the other cell.

2. On the following stage, the specific receptors located on a postsynaptic membrane recognize the corresponding molecules of mediators and form the "mediator-receptor" complexes with them for some time interval. This results in a distinctive structural (conformational) phase transition which yields the activation (opening) or inactivation (closure) of the relevant ion channels.

3. On the third stage, the "mediator-receptor" complexes are destroyed by specific enzymes [e.g., by acetylcholinesterase (AChE)]. As a result, the inactivated state is restored on a postsynaptic membrane. Receptors become able again to interact with a new diffusion wave of molecules of mediators.

In the present work, we will consider a kinetic model of intercell interaction. This model is based on the

hypothesis of the isomorphism of the process of synaptic transmission in the "mediator-receptor" model and the critical phenomenon of mixing in a binary liquid mixture and allows one to study: 1) the type of singular points of the kinetic model of intercell interaction by the Poincaré classification; 2) the times of relaxation characteristic of the basic mechanisms of synaptic transmission, 3) the diffusion coefficient of molecules of mediators in a synaptic cleft; 4) the effect of the diffusion kinetics on the times of relaxation of the processes of intercell interaction.

2. A Kinetic Model of the Process of Intercell Interaction

Without consideration of physiological details of the process of intercell interaction, we note, in brief, that there exist two types of receptors of acetylcholine: nicotinic (N-cholinreceptors) and muscarinic (M-cholinreceptors) ones. It is known that the majority of central and nerve-muscle synapses contain N-cholinreceptors, whereas a cardiovascular system includes M-cholinreceptors. The mathematical model of the processes running in a synaptic cleft with cholinreceptors of the M-type which can be activated by only one molecule of acetylcholine was studied in [9]. The purpose of the present work is to study the other mechanism of synaptic transmission which involves cholinreceptors of the N-type. For their activation, two molecules of a mediator should be bound [10] according to the following scheme:

$$ACh + R \overset{k_1}{\leftrightarrow} AChR,$$

$$ACh + AChR \overset{k_2}{\leftrightarrow} ACh_2R,$$

$$ACh_2R \overset{k_3}{\leftrightarrow} ACh_2R^* \overset{k_4}{\leftrightarrow} R. \quad (1)$$

In other words, on the release in a synaptic cleft, a molecule of acetylcholine joins the molecule of a receptor (the first equation). Then another molecule of a mediator joins this complex (the second equation) which passes to the excited state at that (the ion channel opens, the permeability for ions Na^+ and K^+ enhances, and the depolarization of a membrane occurs). Further, the receptor returns to the initial state (the third equation). Obviously, each event happens with a certain rate, and the corresponding processes can run in one or another direction with different rates. We should not forget the fact that the process of removal of a mediator from a synaptic cleft is of importance for the renewal of the initial state of the postsynaptic membrane. The mediator leaves the cleft by a few ways: due to the diffusion, the reversible capture by a presynaptic membrane, and, mainly, the decay in the presence of the enzyme acetylcholinesterase.

In what follows, we will consider that the processes described in scheme (1) are irreversible. Then, in view of (1), we write the kinetic equations for the concentrations of acetylcholine (A), receptors in the ground state (X_1), and excited mediator-receptor complexes (X_2):

$$\dot{A} = M\delta(t) - k_1AX_1 - k_2AE - k_3A - k_4A(X_0 -$$

$$-(X_1 + X_2)) + k_5X_2 + k_6(X_0 - (X_1 + X_2)), \quad (2)$$

$$\dot{X}_1 = -k_1AX_1 + k_6(X_0 - (X_1 + X_2)), \quad (3)$$

$$\dot{X}_2 = k_4A(X_0 - (X_1 + X_2)) - k_5X_2. \quad (4)$$

In the first equation, we consider the concentration of acetylcholinesterase (E) to be constant, and the release of acetylcholine in a synaptic cleft is described by the Dirac δ-function [see the first term on the right-hand side of (2)]. The second and fifth terms describe the binding of a mediator with a free receptor and an inactive mediator-receptor complex, respectively; the third - hydrolysis of acetylcholine in the presence of acetylcholinesterase; the fourth – the removal of acetylcholine from a cleft due to the diffusion; and the sixth and seventh – the detachment of the mediator molecule from active and inactive mediator-receptor complexes, respectively. The terms in the second equation of the system have the following meaning: the first term describes the binding of a free receptor with a mediator molecule, and the second is analogous to the seventh term in Eq. (2). As for the third equation of the system, the first and second terms describe the transition of the inactive mediator-receptor complex in the excited state and the inverse process, respectively; and X_0 stands for the total concentration of cholinreceptors in a synaptic cleft.

In Eqs. (2)–(4), it is convenient to pass to dimensionless variables. To this end, we divide both sides of Eq. (2) by A_0 (the total concentration of molecules of the mediator at the time moment of the release) and those of Eqs. (3) and (4) by X_0. We obtain

$$\dot{a} = m\delta(t) - \tilde{k}_1ax_1 - k_2aE - k_3a - \tilde{k}_4a(1 - (x_1 + x_2)) +$$

$$+\tilde{k}_5x_2 + \tilde{k}_6(1 - (x_1 + x_2)), \quad (5)$$

$$\dot{x}_1 = -\tilde{\tilde{k}}_1 a x_1 + k_6(1 - (x_1 + x_2)), \quad (6)$$

$$\dot{x}_2 = \tilde{\tilde{k}}_4 a(1 - (x_1 + x_2)) - k_5 x_2, \quad (7)$$

where we used the following notation: $a = \frac{A}{A_0}$, $x_1 = \frac{X_1}{X_0}$, $x_2 = \frac{X_2}{X_0}$, $m = \frac{M}{A_0}$, $\tilde{k}_1 = k_1 X_0$, $\tilde{k}_4 = k_4 X_0$, $\tilde{k}_5 = \frac{k_5 X_0}{A_0}$, $\tilde{k}_6 = \frac{k_6 X_0}{A_0}$, $\tilde{\tilde{k}}_1 = k_1 A_0$, and $\tilde{\tilde{k}}_4 = k_4 A_0$.

3. Singular Point and Times of Relaxation

We will test the system of kinetic equations (5)–(7) for the steadiness of solutions. The corresponding system of stationary equations

$$-\tilde{k}_1 a x_1 - k_2 a E - k_3 a - \tilde{k}_4 a(1 - (x_1 + x_2)) +$$

$$+\tilde{k}_5 x_2 + \tilde{k}_6(1 - (x_1 + x_2)) = 0, \quad (8)$$

$$-\tilde{\tilde{k}}_1 a x_1 + k_6(1 - (x_1 + x_2)) = 0, \quad (9)$$

$$\tilde{\tilde{k}}_4 a(1 - (x_1 + x_2)) - k_5 x_2 = 0 \quad (10)$$

has the particular solution $a_0 = 0$, $x_{10} = 1$, $x_{20} = 0$ which corresponds to the real situation where no molecules of acetylcholine or mediator-receptor complexes are present in a synaptic cleft, and all receptors are free. We will limit ourselves by studying only this singular point. After the linearization, we get the following system of equations under small perturbations:

$$\delta\dot{a} = -(\tilde{k}_1 + k_2 E + k_3)\delta a - \tilde{k}_6 \delta x_1 + (\tilde{k}_5 - \tilde{k}_6)\delta x_2, \quad (11)$$

$$\delta\dot{x}_1 = -\tilde{\tilde{k}}_1 \delta a - k_6 \delta x_1 - k_6 \delta x_2, \quad (12)$$

$$\delta\dot{x}_2 = -k_5 \delta x_2. \quad (13)$$

The corresponding characteristic equation looks as

$$(\lambda + k_5)((\lambda + \xi)(\lambda + k_6) - \tilde{\tilde{k}}_1 \tilde{k}_6) = 0, \quad (14)$$

where

$$\xi = \tilde{k}_1 + k_2 E + k_3.$$

The last equation possesses the roots $\lambda_{1,2} = \frac{1}{2}[-(\xi + k_6) \pm ((\xi + k_6)^2 - 4k_6(\xi - \tilde{\tilde{k}}_1 X_0))^{1/2}]$, and $\lambda_3 = -k_5$.

In order to determine the type of a singular point by Lyapunov, we use the experimental data given in [11] and [12]: $\lambda_1 \approx -5$ ms^{-1}, $\lambda_2 \approx -3082$ ms^{-1}, and $\lambda_3 \approx -37$ ms^{-1}. It is clear that since the signs of all the solutions of the characteristic equation are negative, the singular point is a stable node.

Thus, the general solution of system (5)–(7) for the concentrations of acetylcholine a, free receptors x_1, and activated mediator-receptor complexes x_2 can be written as the following linear combinations of exponential functions with exponents equal to the above-presented roots of the characteristic equation:

$$a = a_0 + A_1 \exp(\lambda_1 t) + A_2 \exp(\lambda_2 t) + A_3 \exp(\lambda_3 t) + m,$$

$$x_1 = x_{10} + B_1 \exp(\lambda_1 t) + B_2 \exp(\lambda_2 t) + B_3 \exp(\lambda_3 t),$$

$$x_2 = x_{20} + C_1 \exp(\lambda_1 t) + C_2 \exp(\lambda_2 t) + C_3 \exp(\lambda_3 t). \quad (15)$$

It is obvious that the negative signs of all the roots of the characteristic equation ensure such a movement of the representative point in the space of the variables a, x_1, and x_2, at which the point approaches a stationary state.

We can obtain a similar result, by using the linear homogeneous transformations from the old variables a, x_1, and x_2 to new ones $\tilde{a}$, $\tilde{x_1}$, $\tilde{x_2}$ by the following formulas:

$$\tilde{a} = \alpha_1 a + \alpha_2 x_1 + \alpha_3 x_2,$$

$$\tilde{x}_1 = \beta_1 a + \beta_2 x_1 + \beta_3 x_2,$$

$$\tilde{x}_2 = \gamma_1 a + \gamma_2 x_1 + \gamma_3 x_2.$$

These transformations allow us to reduce the initial system of differential equations (5)–(7) for the concentrations a, x_1, and x_2, as well as, respectively, system (11)–(13) for small perturbations δa, δx_1, and δx_2, to the canonical form

$$d\tilde{a}/dt = \lambda_1 \tilde{a},$$

$$d\tilde{x}_1/dt = \lambda_2 \tilde{x}_1,$$

$$d\tilde{x}_2/dt = \lambda_3 \tilde{x}_2. \quad (16)$$

The system of differential equations of the canonical form (16) involves three independent dynamical

variables $\tilde{a}$, $\tilde{x_1}$, and $\tilde{x_2}$ which (like the old dynamical variables a, x_1, and x_2) have three different times of relaxation τ_1, τ_2, and τ_3. These times are equal to reciprocal values of the roots of the characteristic equation (14), namely: $\tau_1 = 0.2$ ms, $\tau_2 = 3 \times 10^{-4}$ ms, and $\tau_3 = 2.7 \times 10^{-2}$ ms.

4. Diffusion Coefficient of Mediators in a Synaptic Cleft

The above-proposed kinetic model of synaptic transmission takes the diffusion into account in a rather formal manner, due to the introduction of the fourth term into the first differential equation of system (1) for the concentration of molecules of a mediator. Let us do it in a more sequential way, analogously to the consideration of the diffusion of M-cholinreceptors in the model considered in [9]. We recall that the removal of the "mediator-receptor" complexes from a synaptic cleft was described in [9] with the help of the diffusion-related term $D\Delta x$ in the approximation $\Delta x \approx x/L^2$, where L is the transverse thickness of the synaptic cleft. The characteristic times of relaxation $\tau_{\rm d} \approx L^2/D$ for the diffusion processes in the synaptic clefts are of the order of milliseconds. Therefore, the numerical estimation of the diffusion coefficient $D \approx L^2/\tau_{\rm d}$ for synaptic clefts with the thickness $L \approx (20 \div 100)$ nm gives the following value: $D \approx (4 \times 10^{-13} \div 10^{-11})$ m^2/s. By the order of magnitude, this result coincides with the typical value of the coefficient of lateral diffusion of phospholipid molecules in plasmatic membranes of cells $D_{lat} \approx 10^{-12}$ m^2/s (see, e.g., [1]– [3]). Using the above-presented numerical estimates for the kinetic coefficient k_3 in the model with N-cholinreceptors, we have $k_3 \approx 1/\tau_3 \approx 5 \times 10^3$ s^{-1}. Thus, the conclusion about the negative sign of the root λ_1 of the characteristic equation within the kinetic model of synaptic transmission, which is considered in the present work, is not changed, in principle. In other words, the proposed kinetic model of intercell interaction with the decisive role of N-cholinreceptors in a synaptic cleft is, in fact, a "rough" nonlinear dynamical system (by the Andronov's definition [13]), because all three Lyapunov exponents are negative. In such a case, the deviations of the concentrations a, x_1, and x_2 from stationary values will decay exponentially in the course of the time. Therefore, the singular point of the kinetic model under study is classified as a stable node or a simple attractor. As for the further studies, we plan to carefully investigate the question about the dimension dependence of the diffusion coefficient of mediators and its effect on the character of the singular point within the kinetic model of synaptic transmission. This can be made on the basis of the hypothesis of space-limited scaling in mesoscale systems, the example of which is given by just synaptic clefts.

5. Effect of the Diffusion Kinetics on Times of Relaxation of the Process of Intercell interaction

At the same time, if the hypothesis advanced in work [4] as for the isomorphism of the process of intercell interaction in synaptic clefts and the critical phenomena in binary liquid systems will be additionally corroborated experimentally and theoretically, we may expect the observation of certain specific features of the process of synaptic transmission which are foreseen by our model and are of interest, in our opinion. Going toward the critical (bifurcation) point, the numerical value of the diffusion coefficient and, as a result, that of the coefficient k_3 must decrease.

In such a case, the character of the dynamical behavior of the process of synaptic transmission, which is described by the proposed kinetic model, should be sharply changed. If the root λ_1 will take the zero value, the model will stop to be "rough", because the phase portrait of the system will possess the limiting cycle, which is, generally speaking, an atypical situation. With the further approaching to the critical (bifurcation) point, a numerical value of λ_1 can become positive, which will lead to the appearance of a strange attractor. We note that the reality of such a scenario should not be considered exceptional, because a similar dynamical behavior was already foreseen on the study of the model of synaptic transmission, in which the main role was played by M-cholinreceptors [9]. In conclusion, it is worth to note that a decrease of the diffusion coefficient with approaching the critical point was first indicated theoretically by M.A. Leontovich [14], and this fact obtained a reliable experimental confirmation (see, e.g., the study of the diffusion coefficient for liquid systems by methods of neutron and optical spectroscopies [15], [16]).

1. M.V. Vol'kenshein, *Biophysics* (Nauka, Moscow, 1982) (in Russian).
2. P.G. Kostyuk, V.L. Zyma, I.S. Magura, M.S. Miroshnychenko, and M.F. Shuba, *Biophysics* (Oberegy, Kyiv, 2001) (in Ukrainian).
3. *Medical Biological Physics*, edited by O.V. Chalyi (Kniga Plyus, Kyiv, 2004) (in Ukrainian).

4. *Dynamical Phenomena at Interfaces, Surfaces and Membranes*, edited by D. Beysens, N. Boccara, and G. Forgacs (Nova Science Publ., New York, 1993).

5. A.V. Chalyi, K.A. Chalyi, L.M. Chernenko, and A.N. Vasil'ev, in *Nonlinear Dielectric Phenomena in Complex Liquids*, edited by S.J. Rzoska and V.P. Zhelezny (Kluwer, Dordrecht, 2004), p. 143.

6. A.V. Chalyi and A.N. Vasil'ev, Phys. Alive **10**, 32 (2000).

7. O.V. Chalyi and O.V. Zaitseva, Phys. Alive **13**, 51 (2005).

8. A.V. Chalyi, L.A. Bulavin, K.A. Chalyi, L.M. Chernenko, A.N. Vasil'ev, and E.V. Zaitseva, in *Critical Properties of Soft Matter at Restricted Geometry as Emerging Problem: Fundamentals and Biological Applications*, edited by S.J. Rzoska and V.A. Mazur (Springer, Berlin, 2007), p. 475.

9. A.V. Chalyi and E.V. Zaitseva, J. Phys. Stud. **11**, 322 (2007).

10. A.J. Gibb, in *Neurotransmitters, Drugs and Brain Function* edited by R.A. Webster (Wiley, New York, 2001), p. 57.

11. A.I. Skorinkin and A.P. Shaikhutdinova, Biofiz. **49**, 872 (2004).

12. N.R. Nigmatullin *et al.*, Neirofiz. **20**, 390 (1988).

13. A.A. Andronov, A.A. Vitt, and S.E. Khaikin, *Theory of Oscillations* (Nauka, Moscow, 1981) (in Russian).

14. M.A. Leontovich, *Statistical Physics* (Nauka, Moscow, 1981) (in Russian).

15. L.A. Bulavin, T.V. Karmazina, V.V. Klepko, and V.I. Slisenko, *Neutron Spectroscopy of Condensed Media* (Akademperiodyka, Kyiv, 2005) (in Ukrainian).

16. E.L. Lakoza and A.V. Chalyi, Usp. Fiz. Nauk **26** 573 (1983).

Received 10.07.08
Translated from Ukrainian by V.V. Kukhtin

КІНЕТИЧНА МОДЕЛЬ СИНАПТИЧНОЇ ПЕРЕДАЧІ ПРИ МІЖКЛІТИННІЙ ВЗАЄМОДІЇ

О.В. Чалий, О.В. Зайцева

Р е з ю м е

У роботі представлено модель синаптичної передачі при міжклітинній взаємодії в ацетилхолінових синапсах. Було враховано такі процеси: вивільнення медіатору в синаптичну щілину, яке залежить від часу, зв'язування медіатору з рецептором, утворення медіатор-рецепторних комплексів, видалення медіатору зі щілини за рахунок дифузії, зворотного захвату пресинаптичною мембраною, а також, головним чином, розпаду в присутності фермента ацетилхолінестерази. Для опису змін концентрацій медіатору, рецепторів у незбудженому стані, а також збуджених медіатор-рецепторних комплексів було побудовано та досліджено систему з трьох нелінійних диференціальних рівнянь та доведено, що особлива точка стаціонарного стану для синаптичної передачі є стійким вузлом.