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Research Article

Keywords:

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11508742/v1

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Additional Declarations: No competing interests reported.

Dedicated to The Memory of
Walter Jackson Freeman III

Commentary Article: A Drastically Simplified Model Concerning the Dynamic Mechanism of Ion-Channel Opening and Closing in Nicotinic Acetylcholine Receptors

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Abstract

In neuro- (brain-) science, several chemical substances called "neuro modulators (or neuro transmitters)" play very important roles in advanced functions of the brain, e.g., attention, memorising, wakefulness, etc. In particular, acetylcholine (ACh), nicotinic acetylcholine receptor (nAChR), and acetylcholinesterase (AChE, the enzyme responsible for ACh breakdown), constitute complex dynamical systems that are important for elucidating the underlying

mechanisms of higher brain functions. Herein, we briefly describe the microscopic physico-chemical phenomena involving ACh, nAChR, and AChE that regulate important neural activities, such as physiological excitation. Although, nAChR which opens or closes its sodium ion channel depending on the bound or unbound state of ACh, has been investigated for a long time but the channel mechanism is not clearly understood. In this paper, we propose a drastically simplified scheme to rationalise the mechanism of channel opening and closing, originating from three dynamically-coupled phenomena. First, ACh is released by cholinergic cells, second, the sub-unit configurations (five $\boldsymbol{\alpha}$-helix (named M2) belonging to each subunit) in nAChR are destabilized, and third, ACh is rapidly eliminated through AChE activity. The underlying mechanism can be illustrated through intuitive animations based on computational experiments if the theoretical formulation advances sufficiently.

Keywords: Biological macromolecules, Acetylcholine, Nicotinic-acetylcholine-receptor, Acetylcholine-esterase, Ligand-dependent-ionchannel, Ternary-&-Quaternary structure change

1 Introduction

Since Schrödinger's famous lecture in 1943, "What is Life? The Physical Aspect of the Living Cell", physicists have been increasingly attracted interdisciplinarily to biological systems or even to life itself from the perspective of physics. Currently, biological and life sciences have been remarkably developing and molecular biology, neuroscience, and brainscience are approaching levels that no one had imagined in Schrödinger's time. These developments have revealed serious difficulties not only in biological systems but also across a wide range of natural sciences, i.e., the complex dynamics exhibited by systems with finite but large degrees of freedom [1] $\sim$ [3]. Faced with these situations, a new trend in biological science has emerged since several decades ago, i.e., complex dynamics approaches to neuroscience, brainscience, and lifescience. Walter Freeman is one of the great pioneers of such new challenges in brain science who had focused on chaotic dynamics in the brain [4] from a functional point of view including philosophical thoughts [5]. Generally, the brain is a plentiful system full of natural-scientific phenomena. Freeman has classified them into three levels: "microscopic level", "mesoscopic level", "macroscopic level" [5]. He had been working mainly at the mesoscopic level, particularly in the field of neural activity stemming from a large-scale network of neural cells and how they are connected to macroscopic phenomena, i.e., advanced functions of the brain. One of his important contributions to mesoscopic dynamics of the brain is the perception of chaos and its functional role, especially in the olfactory system.

Together with Freeman's contributions, the complex dynamics approach to the brain- and the neuroscience has been advanced by many pioneering researchers [6] $\sim$ [10] and has grown into a substantial body of research [11] $\sim$ [14]. Starting from the perspective of such functional complex dynamics, one of the authors (S.N.) has been studying neural systems and/or brain systems, mainly with the use of computer

experiments to realise complex functions from simple rules [15] ∼ [19], while delving into visual hallucinations, a type of neurological symptom, in computer experiments [20]. In these studies, we encountered complex dynamics (chaos) of single neuron activities as well as simultaneous neural network activities, particularly related with non-equilibrium physico-chemical phenomena in neural networks of the brain [21]. For an example, single neuron firing is controlled by delicate balance between ion inflow resulting from ion channel protein on cell membrane and leakage of them, where ion channel protein seems to have complex chemical reaction mechanism and appears to be explainable within the framework of conventional chemical reaction theories.

However, conventional theories are insufficient for understanding complex dynamical phenomena involving non-equilibrium reaction processes because of the following reasons [22]. First, these theories assume separation of timescales between reactive and nonreactive degrees of freedom, such that local equilibrium is established before the states change. They also assume that the characteristics of the degrees of freedom, that is, which degree of freedom represents the progress of the reaction, remains unchanged over the event. Second, usually such degrees of freedom are both microscopic and operate on the same spatial scale as the reacting molecule. When the timescales of each degree of freedom differ across several orders, faster degrees of freedom and/or environments such as solvents and fast degrees of freedom in proteins are a "bath" in a framework of (generalized) Langevin formulation. Here, explicit information or energy transfer from fast to slow degrees of freedom, even if it occurs, is often outside the scope of reaction-rate because these theories must incorporate the dynamic nature of the reacting system themselves, whereas macroscopic slow degrees of freedom could behave dynamically even under the existence of local equilibrium environments. In contrast, recent developments in dynamical reaction theories have demonstrated processes in which one reaction coordinate switches to another as the energy of the system is increased, i.e., the breakdown of the separation of time scales [23]. Moreover, certain degrees of freedom may exist that do not reach equilibrium within the time scale of the reaction. One of the outcomes is the chemical ratchet [24]. The chemical ratchet can provide a possible scenario of the antenna effect, which is experimentally observed in DNA-protein systems. In addition, even under in the presence of a (Langevin) thermal bath, the state space geometrical structure persists, as an analytic function of the positions and velocities of a reacting system embedded in the bath, as well as the friction constant and random force [25], [26]. Thus, in principle, the existence of a thermal bath and complicated nonlinear couplings among degrees of freedom does not necessarily imply spoiling of the dynamic perspectives of biological systems.

In line with our ongoing research, we have been particularly interested in the phenomenon where neuromodulators (neurotransmitters) modulate complex neural network dynamics, - ranging from converging attractor regimes to diverging chaotic regimes, - which are fundamental to advanced brain functions. To date, several ten such neuromodulators have discovered, more specifically, the histamine group, monoamine group (dopamine, noradrenaline, serotonin, etc.), amino-acid group (glutamic acid, GABA, etc.), and the acetylcholine group, which belong to the enormously large stream of neuro- and/or brain science research. All these neuromodulators are bound to corresponding receptors and regulate both intra- and inter-cell signal transfers,

which results in many of diverse manifestations of advanced functional brain activities. In particular, acetylcholine (ACh) and one of its receptors, i.e., nicotinic acetylcholine

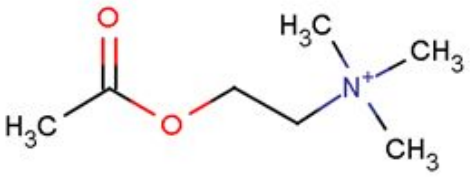


Fig. 1 Molecular structure of ACh

receptor (nAChR), acetylcholine esterase (AChE) as a resolving enzyme of ACh, have attracted substantial research interest, because ACh is simple molecule, as shown in Fig. 1. Nonetheless, it serves as a functional neuromodulator, and is related to the various advanced functions of the brain, such as perception, learning, memorising, or attention. These functional phenomena are thought to be associated with ACh binding to nAChR, where nAChR shows a transition between the open and closed states of a sodium-ion channel depending on whether ACh is bound or unbound (see Fig. 2 and Fig. 3). Furthermore in the brain, ACh is quickly eliminated by the action of AChE. Therefore, we should regard ACh-bound nAChR as short-lived form *in vivo*, although dependent on the concentration of AChE. Thus, the system consisting of these three elements, i.e., ACh, nAChR, and AChE, forms a highly dynamic system. However, despite the long history of investigation with respect to the ion-channel mechanism at the molecular scale, it is not yet fully understood.

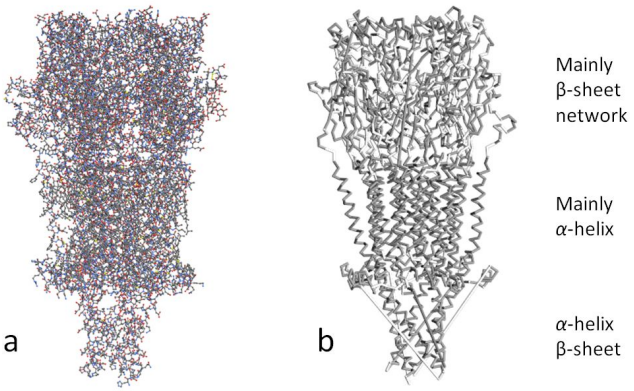


Fig. 2 Atomic molecular structure of nAChR in resting state (no bound ACh), where the data are taken from PDB ID:7SMQ; [27]. (a) All atoms are shown as points except for the hydrogen atoms and each atomic point is connected by a line. (b) Only C_α are considered, and the ribbon representation is employed and shown with the use of Mathematica. A more detailed structure can be found in the references, e.g., in [28], [29], [30]

Here, we describe the molecular structure and microscopic physico-chemical phenomena of ACh, nAChR, AChE, more in detail. Using a simplified scheme, we propose a novel possible mechanism of channel opening and closing, which originates from the dynamically coupled three-factor phenomenon shown later. First, nAChR belongs to a group of proteins called "ion channel proteins", which have molecular weights of 250 kDa $\sim$ 350 kDa and take quaternary structure consisting of five subunits. Each subunit has the conformation of a 4-transmembrane protein. The molecular weight of each subunit is 50 kDa $\sim$ 70 kDa. Experiments demonstrated that, as quaternary structure, nAChR has pentameric structure and makes up a quite large family depending on different combinations of various kinds of subunits, which are classified into five types according to their amino-acid-sequences: $\alpha, \beta, \gamma, \delta$, and ϵ. Of these amino acid sequences, the first two have intra-subunit variations, i.e., $\alpha 1 \sim \alpha 10$ and $\beta 1 \sim \beta 4$. The others, γ, δ, and ϵ, do not have distinct subtypes [31] [32] [33]. Depending on the combination of subunits in the pentamers, the permeabilities of ions differ under acetylcholine binding. They may cause well-turned regulation of advanced functions in the brain [34].

One of the reasons why they attract considerable research interest is that they *regulate neuron firing* by switching their functional state to allow sodium ions to pass from the outside to the inside of the cell through tiny hollow channel, whose diameter is on a sub-nanometre scale; the channel has two states, i.e., "the open state" or "the closed state". Notably, the both states are controlled by binding or unbinding of ACh to the two specific sites on nAChR, where the molecular weight of ACh is only 146 (see Figs. 1 & 2), moreover, the two binding sites are far from the channel position at the molecular scale [35] [36] [37] [38]. That is, from the perspective of dynamical systems, rationalising why such small-molecule ACh bound at remote can trigger opening/closing events across the channel without dissipation of binding energies to the surrounding environment as heat is far from trivial.

A further detailed discussion of this problem is beyond the scope of this paper. Readers interested in further details, including extensive experimental evidence, in-depth analyses, and the historical development of the field, are referred to the excellent book by Changeux and Edelstein [39].

2 Conformational Transition Hypothesis of a β-Sheet Network & Drastically Simplified Model of the Ion-Channel Mechanism

As shown in Fig. 2, ternary and quaternary structures of nAChR are classified into three parts, i.e., outside of the cell, within the membrane (lipid bilayer), and inside of the cell. From the N-terminus of each subunit, the initial long strand of the amino-acid mainly consists of hydrophilic residues forms many β-sheets, and their network entangled together with those from other subunits. After the β-sheet network, the transmembrane alpha-helix called "M1" appears, which consists mainly of hydrophobic residues. M1 is followed by M2-, M3-, and transmembrane alpha-helixes spanning the cell membrane. Between M3 and M4, the other β-sheet network exists in inside of cell and is succeeded by the final transmembrane alpha-helix, M4 that ends at C-terminus

in outside of cell. One such important points with respect to ternary and quaternary structures of nAChR is the existence of an entangled β-sheet network together with those from the other subunits.

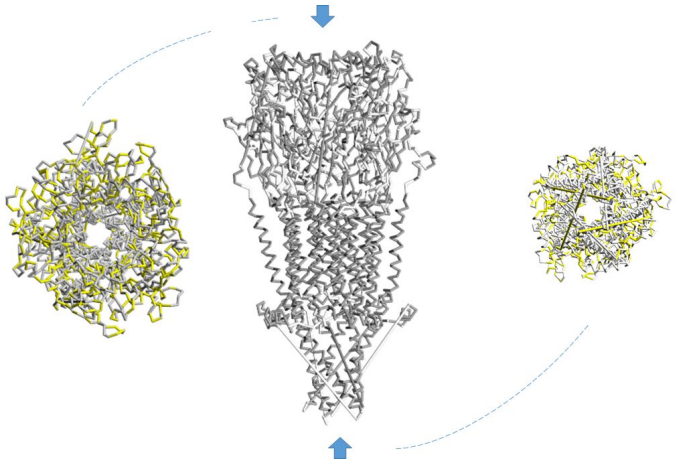


Fig. 3 Top view and bottom view of nAChR. One can observe that the 5-subunits form a quasi pentamer configuration. There is a tiny hollow along the cetral axis, but it is too small to make sodium ions pass through it, so it is considered closed ion channel.

Next, the configurations of M1-M4 in the cell membrane supplied from each of the five units are discussed, where the five subunits exhibit a pseudo-fivefold-symmetrical overall arrangement, form a central pore lined by M2 helices (see also Fig. 4). With respect to the more accurate configurations, many experimental reports are based on electron microscopy or X-ray diffraction etc., as *in vitro* environments. However, accurate observation of the configuration is difficult when nAChR is existing in membrane, i.e., in an *in vivo* environment. Therefore, we have to rely on certain working hypotheses concerning the *in vivo* ternary and quaternary arrangement of M2 helices in a pentamer conformation. We employ the configuration of M2 shown in Fig. 3, in which M2 (α-helix) is regarded as a cylinder, whose diameter is approximately determined based on a large amount of data reported by now, also the interval of each cylinder as well [29]. The five twisted cylinder in a pentamer configuration gives a tiny hollow part, which we regard as a "channel-closed" state because the cylinder shape is a very rough approximation of a practical α-helix that has many uneven residues. When this configuration is somewhat distorted, then the hollow part is expanded considerably, and the situation becomes a "channel-opened" state, as shown in Fig. 4 and 5.

It is generally accepted that the *two binding positions* of ACh exist in the β-sheet network as if the pocket-like space was surrounded by residue from several amino-acids [40] $\sim$ [42], in which the binding affinity is reported to be approximately -5 kcal/mol in terms of ΔG [43]. This affinity is not particularly strong and is presumed to be result from hydrogen-bonding between ACh and surrounding residues, so that the bound ACh promptly dissociates from nAChR if the free ACh concentration in the surrounding region decreases rapidly in response to the action of AChE. This process

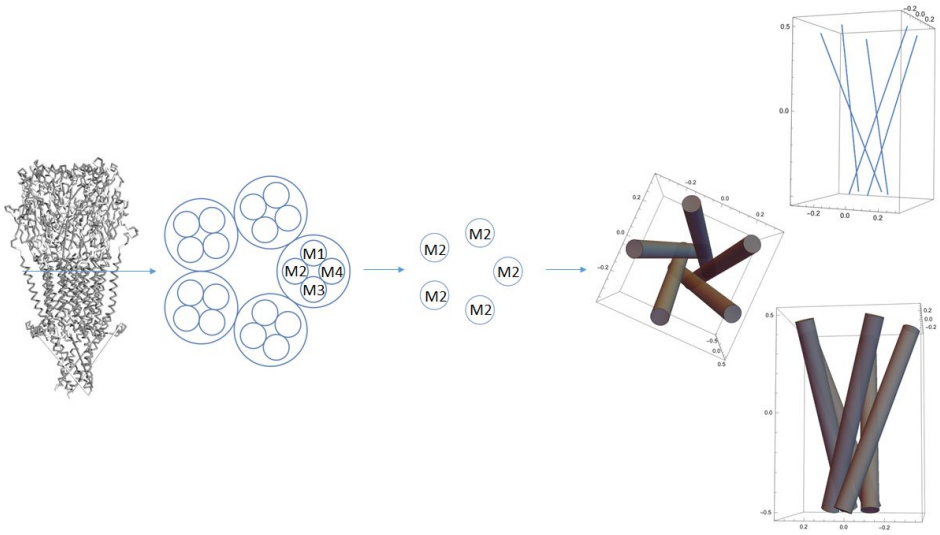


Fig. 4 Our configuration model of α-helix (M2) in the five subunits within the membrane. The dimension of each cylinder are approximately estimated with the use of those in actual data, and the twisted angle of cylinders is chosen to make the image of the configurations easier to visualise.

is an important factor of the system to maintain the dynamic properties. The reason is as follows, in the resting state of nAChR, the binding of two ACh molecules to the two specific sites in β-sheet network opens the ion-channel within approximately sub-millisecond latency but if, within approximately 10 millisecond, two bound ACh molecules are dissociated from nACh, and then ion-channel is expected to be closed, and the state returns to the resting state. In contrast, when the concentration of ACh is maintained high enough in *in vitro* experiments without AChE, then the ACh-bound nAChR is moved to a more stable conformation and ion-channel closes together with fall into unsensitized state to ACh, in which the ΔG vallue of this state is calculated to be approximately -11 kcal/mol [43]. The existing time scale of weakly bound state of ACh is experimentally estimated to be $\lesssim 10$ msec or so, and in the latter case, to be ~ 100 msec or so [39].

Considering these underlying reported phenomena, We propose the following two novel hypotheses,

(1) When two ACh are bound to the two specific site in the β-sheet network, then network causes conformational transition and the initial resting state becomes unstable.
(2) A conformational transition in the β-sheet network drives a contractile and rotational/torsional deformation of the adjacent pentamer-configuration of the five M2 helices, simultaneously altering the central pore formed by these M2 structures.

These hypotheses are our key idea, and may be derived to explain the two important phenomena observed by recent experiments. First, *in vivo* phenomena, i.e.,

temporally dynamic state of ion-channel opening and closing in which, immediately after cholinergic cells release a large amount of ACh, two ACh molecules are bound to nAChR and are unbound within approximately 10 milliseconds by the action of AChE, allowing nAChR to return to the resting state (channel closing). Second, *in vitro* experiments on nAChR under high concentration of ACh "without" AChE, in which resting state (ion-channel closed) ⇒ ACh bound nAChR (ion-channel opend) ⇒ stable state (ion-channel closed and unsensitized to ACh) as discussed in the next section.

3 Results & Discussion

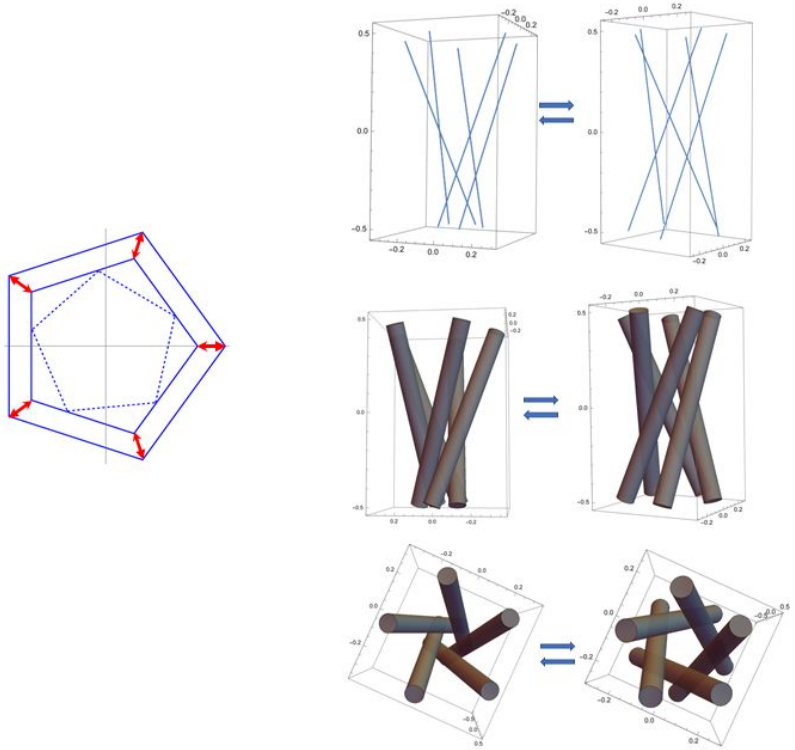


Fig. 5 Configuration model of five M2 in a pentameric state and their associated movements with a conformational transition in the β-sheet network, i.e., contractive displacements. (a) Illustration of top view. In the resting state, the top points of five cylinders form a larger pentagon, and by contractive displacement because of the conformational transition in the β-sheet network, the top points of five cylinders changes to a small pentagon. When ACh is dissociated by AChE, the configuration returns to the resting state. (b) 3-D illustration of reciprocating dynamics between ion-channels closed and opened.

Based on the hypothesis presented in the previous section, and under *in vivo* conditions, where AChE concentration is markedly high, the binding of two ACh molecules

to the two specific points (pockets) in the β-sheet network triggers collective and compressive displacements in the network. These displacements cause a contractive deformation of the adjacent pentamer-configuration of the five M2's and result in opening of the ion-channel, but the opened state does not persist for long ($\lesssim 10$ msec) because AChE quickly resolve ACh and the two bound ACh molecules are dissociated from nAChR which results in a conformational transition stop and allows nAChR to return to the resting state together with close of ion-channel. The hypothesized process is illustrated in Fig. 5, where (a) indicates that a pentagon defined by the top ends of five M2 cylinders undergoes a contractile displacement, driven by a conformational transition within the β-sheet network.

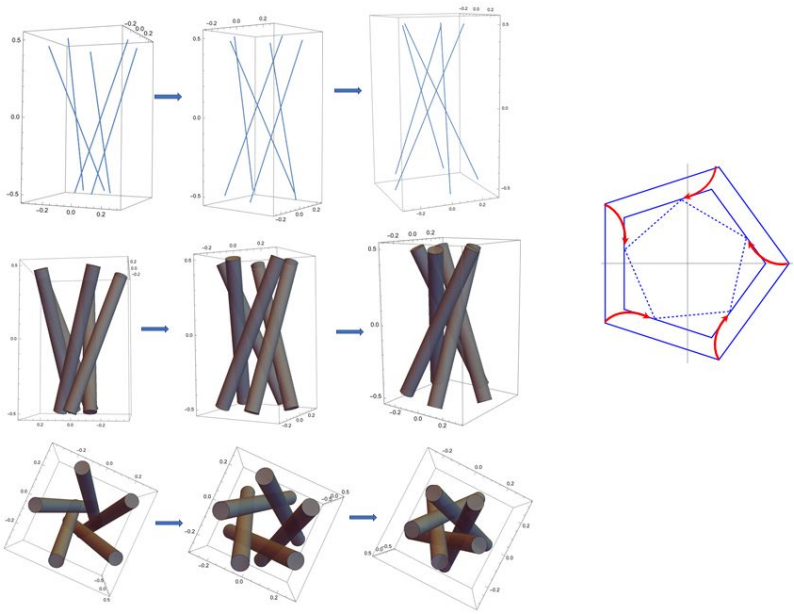


Fig. 6 Configuration displacements of five M2's in the *in vitro* experiment, where the concentration of ACh is kept sufficiently dense without AChE. A pentameric state contracts and is subsquently twisted to the dotted line pentagon, which is associated with a conformational transition in the β-sheet network.

We considered the *in vitro* experiments conducted in the absence of AChE. Initially, the previously described phenomena occur, with ACh binding to nAChR and opens the ion-channel, after which further movements of network and the resulting displacement of the M2 helix continues, which may eventually contract and lead to tortional displacements, as shown in Fig. 6. In Fig. 6, (a) the pentagon contracts and undergoes tortional rotation, as indicated by the dotted-line. Experimental validation of both hypotheses remains necessary. However, this might be very difficult because experimental technologies have not matured to a stage of *in situ* observation concerning the functional dynamics of biological macromolecules *in vivo*.

With respect to the mechanism of ion-channel opening and closing, Changeux and his collaborators developed the MWC-model (Monod, Wyman, Changeux) that was proposed in 1965. Their central idea is "allosteric effect" due to ACh. However, the allosteric effect is not yet clearly understood. Notably, Changeux & Edelstein stated, in their excellent book, that *convergent biochemical, biophysical, and electron microscopy data convincingly demonstrate the occurrence of conformation transitions in the receptor protein. But they are nonetheless too fragmentary to support firm conclusions of more detailed nature. A great deal of additional structural data will be required to fully describe the mechanisms responsible for the allosteric transitions of activation and desensitization in the nAChR.* [39]. Our two hypotheses might be useful for stimulating of experimental planning, but the most important and difficult subject is to develop *in situ* observation technology for *in vivo* dynamic processing of nAChR activity in the cell membrane.

Finally, our hypotheses propose that contractive movements occur collectively in the β-sheet and cause the simultaneous displacement of the five M2's. This means that somewhat coherent motion arises, which is reminiscent of the Frörich coherent mode of macromolecules in biological systems. The idea of an allosteric effect is plausible with respect to information transfer to distant points inside molecules, but the energy source problem remains unsolved, i.e., the conformation change associated with ion channel opening is a slight but meaningful distortion and shifting of the five M2-α-helices belonging to each subunit. Thermal fluctuation energy or physicochemical energy (adsorbing or binding energy) of ACh is probably not enough to cause such movement of five helices. Our hypotheses also raise questions related to the origin of coherency (conformation transition in the β-sheet network) and the energy problem.

4 Concluding Remarks

(1) In light of recent developments in neuroscience and brainsciences, we support the view that functional complex dynamics provide scientific understanding of mechanisms underlying biological functions. Particularly, neuromodulators (or neurotransmitters) are one of our interests in such functional complex dynamics related to the advanced functions of the brain via their receptors.

(2) nAChR is one such receptor and a biological macromolecule belonging to the ion-channel-proteins. More specifically it is a ligand-gated ion-channel protein that exhibits functional complex dynamics, transitioning between open and closed states of sodium-ion channels depending on the binding and unbinding status of ACh (neuromodulator).

(3) We focus on such neurotransmitters (or neuromodulators), particularly to a system consisting of ACh, nAChR, and AChE, which is one of the most important functional systems to control the neuron firing over a wide range of fields of the brain and is thought to regulate advanced functions, such as perception, learning, memorizing, or attention.

(4) Employing a drastically simplified scheme, we propose a novel channel mechanism of opening and closing, which originates from the dynamically coupled three factor-phenomena. First, ACh is released by cholinergic cells, second, the destabilization

of sub-unit configurations (five α-helices (named M2) belonging to each subunit) in nAChR, and third, quick elimination of ACh by AChE actions.

(5) Our two hypotheses (the key ideas) are as follows:

(i) When two ACh are bound to the two specific site in the β-sheet network, then network causes conformational transition and the initial resting state becomes unstable.

(ii) A conformational transition in the β-sheet network drives a contractive and rotational/torsional deformation in the adjacent pentamer-configuration of the five M2, altering the central pore lined by the pentameric M2 structures simultaneously.

(6) When there is a high density of AChE (*in vivo* environment), released ACh is bound to nAChR and ion-channels open while through the actions of AChE, bound ACh quickly dissociates from nAChR within $\lesssim 10$ msec and nAChR returns to the resting state together with closing of the ion-channel. In contrast, during *in vitro* experiments under conditions with sufficiently high concentration of ACh without the presence of AChE, the following processes successively occur, i.e., the resting state (ion-channel close) $\Rightarrow$ ion-channel open $\Rightarrow$ a fixed stable state (ion-channel close and unsensitized to ACh), which is plausible as confirmed in many experiments [39].

(7) Verifying the proposed mechanism is necessary, however, this may be difficult because *in situ* observation of such dynamic processes in *in vivo* environments remains limited. Recent advances of quantitative measurement technologies, e.g. NMR-spectroscopy, NV-center spectroscopy, cryo-electron-microscope, etc., could facilitate such observations.

Acknowledgements. This research was funded by the Cooperative Research Program of "Network Joint Research Center for Materials and Devices", and the contribution of S.N. to this research was partly funded by JSPS KAKENHI Grant Number 25K03189, also by JSPS KAKENHI Grant Number 26K15000. M.T. is supported by a Grant-in-Aid for Scientific Research (C) (No. 23K03265 and 19K03653) from JSPS, and the Research Program of "Dynamic Alliance for Open Innovation Bridging Human, Environment and Materials" in "Network Joint Research Center for Materials and Devices".

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