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Estimating the dissipative factors of synaptic exocytosis in Drosophila using a filter based reverse engineering method

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ABSTRACT

The SNARE-regulated exocytosis is an important molecular level mechanism for the persistent inter-neuronal communication via plasticity of neurons. Without considering the dissipation of synaptic vesicle, the explanation of the inter-neuronal communication via plasticity of neurons in existing models cannot fully account for the persistence of neuronal plasticity. In this paper the dissipative factors CPX and SYT corresponding to unbinding neurotransmitters fused with the membrane are estimated using a reverse engineering method where the dynamic flux is embedded in the filtering model of synaptic transmission. With the CPX and SYT in the corresponding regulation mechanism of exocytosis being estimated, the dissipation function of synaptic vesicle for the persistence of neuronal plasticity is explicitly expressed.

1. Introduction

The high-level cognitive function of the brain is normally measured directly by the region-level signal detection techniques such as brain imaging. With the advances of nanotechnology, this kind of macro-level detection can be used together with the micro-level detection for super-resolution measurement of molecules [1]. The more knowledge provided by the micro-level observation of the structure of cells, the more likely the "neuronal integration" mechanism, which refers to the signal transmission processes modeled by information transfer of neurons from pre-synapse to post-synapse, can be quantitatively explained. The synaptic vesicle releasing process of SNARE-regulated exocytosis is the kernel of the molecular signaling mechanism for the neurotransmitter signal transduction in nervous systems [2]. The function of synaptic vesicle exocytosis is activated by the SNARE factors in the synaptic exocytosis process. The synaptic plasticity of neurons in neuronal integration, which reflects the molecular signaling mechanism of the brain's function, may provide evidences to explain the high-level cognitive function such as learning and memory via the biochemical reactions at the receptors such as AMPA and NMDA [3].

As we know, docking and fusion through which the signal transmission occurs are fundamental processes in cell biology and are conserved among various species including the model organism *Drosophila*. The relationship between docking and fusion has captured attentions since Rothman's SNARE hypothesis was proposed. Technically, the two derived open questions by Goda [2] can be summarized as follows:

(1) Some fused neurotransmitters in synaptic vesicle releasing process can be measured, but some of those not bound cannot be identified by the current measurement techniques. The fusion state does not logically guarantee the bound state, which means that some fused ones cannot be detected because of their unbound state.
(2) To exactly calculate the minimum set of the binding neurotransmitters requires the prerequisite condition that all the neurotransmitters be bound. This is not feasible by the current technology when their regulation scheme of unbinding neurotransmitter release is not clear.

The above-mentioned (2) is based on the major experimental evidence by Südhof and Rizo [4] and leads to the extensive research reviewed by Rizo and Xu [5] as well as by Südhof [6] where they have outlined the current progresses of the SNARE-regulated exocytosis. The description of the dynamics of the neurotransmitters is limited to the binding neurotransmitters [7,8]. How to quantitatively measure the unbinding neurotransmitters still remains unsolved after reviewing to the state of the art of the molecular neuroscience related to neurotransmitter release [5–8]. There exists a gap between the task of molecular neuroscience aimed at the functions caused by the coupled proteins in synaptic

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exocytosis and the condition of single molecular measurement technology that requires the purified proteins [9].

In systems biology, direct methods for modeling robustness, stability, and sensitivity puts their main focus on the measurable signaling molecules. But this is not complete for the systematic description of the signal transduction involving docking and fusion processes of neurotransmitters when the attribute of the measurable object is "incomplete" for the functional interpretation, which requires that both the positive (i.e., bound SNAREs) and the negative (i.e., unbound SNAREs) factors be included in the modeling. Even though the theory of dissipative systems has been widely applied in various fields ranging from physics to economics [10], the existing numerical method for systematically modeling the dissipative systems is still limited to the binding factors in the field of systems biology. Also, the conventional description method for neurotransmitter releasing in systems biology and computational bioinformatics is limited to the constraint of binding neurotransmitters [11,12]. In order to include the dissipative factors into the model, in this paper we add the unbinding state to the theoretical explanation of the mechanism of the synaptic vesicle release process. The experimental evidence for the CPX–SYT pathway pointed by Jorquera and his colleagues [13] shows that the qualitative link between CPX and SYT exists, which support our method of quantitative analysis of the neurotransmitter releasing in synaptic exocytosis. In our study, the estimation method for blind system identification of the dissipative factors, i.e., the estimation of the variation of CPX in regulated exocytosis, is designed based on the observation on the dissipation characteristics of the synaptic vesicle release process, which has not been reported yet. With this method, we can explicitly describe the dependency of coupled CPX and SYT to analyze the signaling dynamics of SNARE-complexes regulated by CPX in exocytosis. The wet-experiment-unidentified-function of the unbound factors for the persistence of neurons, which is the very place for us to develop a numerical calculation method to estimate the unknown parameters, can help us not only to describe the phenomenon observed quantitatively but also to further improve the super-resolution measurement technology by multiple tools and methods.

Our study on neurotransmitter release regulated by signaling pathways of synaptic exocytosis is to quantitatively identify the dissipative factors of unbinding neurotransmitters in synaptic exocytosis. Calculating the minimum set of the binding neurotransmitters is equivalent to finding the maximum set of the unbinding neurotransmitters (the dual form of the minimum set of binding neurotransmitters) to be identified by mathematical models. Because these mathematical models designed can fully capture the feature of the signaling dynamics of exocytosis of neurons, the neurotransmitters involved in the synaptic exocytosis can be directly estimated whether they are bound or not.

The organization of the paper is as follows. Section 2 presents a filtering method in which the dynamics of flux is embedded for estimating the dissipative factor—CPX and SYT in neural pathways. Section 3 discusses the results on the signal estimation of the unbound dissipative factor—CPX and SYT.

2. Dynamic flux embedded filtering model for the estimation of the dissipative SNARE factors in neuronal pathway

2.1. Synaptic exocytosis in synaptic plasticity

(1) Neuronal synaptic plasticity: Plasticity of neurons expressed in short-term plasticity [14] directly affects the memory of the brain which is the basis of the cognitive behavior such as learning. The mechanism of plasticity at the molecular level is just being unveiled recently with the advances of molecular measurement technology. Now it is known that the postsynaptic connection affects the LTP. The neuronal communication is a molecular signal generation mechanism for memory. To explain the role of neurotransmitters in SNARE-regulated exocytosis pathways that directly affects the neuronal plasticity, we need to investigate the mechanism for how the neurotransmitters are released and transmitted, which leads to activation and inactivation of neurons tightly connected to the signaling process of molecules from the kinase PKC to the receptor NMDA in the sub-nodes of the DMN (default mode network) [3].

Experimental evidence on the relationship between the neurotransmitters and synaptic exocytosis makes it possible to establish a universal computational biology theory of exocytosis among different species. Investigation on this relationship is to find a physiologically plausible mapping among the well-studied model organisms such as *Drosophila* to describe the generic signal mechanism of SNARE-regulated exocytosis. Eric Kandel's work [15] on neuronal exocytosis creates a bridge between the neurotransmitters and synaptic exocytosis. The crucial aspect for the universal description of exocytosis among different species is to make the theoretical interpretation of the phenomenon of neuronal exocytosis.

(2) Synaptic exocytosis: There are two types of synaptic exocytosis, signal triggered non-autonomous type and autonomous type—without any triggering signal. In molecular neuroscience, the former is called evoked mode and the latter is called spontaneous mode. These two types of signal transmission processes should be taken into consideration in modeling the mechanism of exocytosis. For SNAREs synaptic transmission, the SNARE synaptic transmission pathway for synaptic exocytosis consists of two consequent processes of biochemical reactions—(1) the cellular biochemical process that generates the SVs (synaptic vesicles) fusion within the neurons, and (2) the cellular biochemical process that releases the neurotransmitters among neurons.

(3) Formulation of neurotransmitter releasing by informatics.

In contrast to the biological representation of neurotransmitter releasing by signal pathways, information representation of the neuron-to-neuron communication is formulated by Malak and Akan [16] in which the neuron acts as a sender or a receiver and the neuron-to-neuron communication process is regarded as a channel. The compounds of signaling molecules trigger the signal cascade at the molecular level. The information encoded in these compounds is analyzed by nano-communication networks [17]. As shown in Fig. 1, the signaling pathway controls the synaptic vesicles (denoted as SV) which are stored in the pool and later released through the membrane. The cellular signaling process of SV occurs within the neuron and the signal transmission process of neurotransmitter release between neurons corresponds to the channel in [16,17]. The reverse model given in Fig. 1 formulates the dynamics of unbinding neurotransmitters of the synaptic exocytosis whose mathematical formulation of the biochemical reactions is given in Section 2.2.

Among the SNAREs, the interplay between the CPX (complexin) and SYT (synaptotagmin) whose pathway is given in Fig. 1 is the kernel of the mechanism of the SNARE-regulated synaptic exocytosis, which determines the neuronal plasticity. We select Neuron's CPX–SYT pathway [13] as a benchmark to study the dissipative factors in synaptic exocytosis.

2.2. Mathematical model

The problem of the estimation of the dissipative factors in the signaling process of neuronal exocytosis is deduced as follows:

minimum of bound SVs

vs.

maximum of unbound SVs

s.t. $F(.)$.