Quantitative Analysis of the Feedback of the Robust Signaling Pathway Network of Myosin V Molecular Motors on GluR1 of AMPA in Neurons: A Networking Approach for Controlling Nanobiomachines

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Abstract. Acting as nanobiomachines within the cell, myosin V molecular motors contribute greatly to the LTP (Long Term Potentiation) in neural signaling, which transport the recycling endosomes from the dendrite to the spine of neurons and the GluR1 in AMPA receptors lead to the activities of memorization in brains. However it is unknown that how the restriction of GluR1 at the spine of neuron is caused by the signaling cascade of myosin V and Rab11/Rab11-FIP2 during the myosin V centered signaling process in neurons. Here we report that the feedback of the biochemical reaction for binding Myosin V and Rab11/Rab11-FIP2 plays a pivotal role to restrict the accumulation of GluR1 at the spine. We have investigated the feedback of myosin V and Rab11/Rab11-FIP2 on the convergence of GluR1 by using the computational model of intracellular signaling pathway networks we designed and the simulation software Cell Illustrator Professional Version 3.0 ®. The obtained results show that controllability of molecular motor based nanobiomachines is inevitable for exploring the molecular mechanism of neuroscience at the nanoscale.

Keywords: Signaling Pathway Network, Nanobiomachine, Molecular Motor.

1 Introduction

Based on the biophysics mechanism of molecular motors, modeling molecular movement in cells [1~5] is important for us to study the dynamics of genetic processes happening in cells, where the movement of motor proteins can be activated by the signaling pathways. Molecular motors that consist of motor proteins realize the molecular transportation and acts as nanobiomachine. Motor proteins are classified

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into three major categories: dynein [4], kinesin and myosin [1]. The microtubule and actin (actin filament) are the rails for molecular motors [6~8]. The biophysics and biochemistry features of molecular motors are the basis for analyzing the biological functions of (1) cell division, chromosome dynamics, and centrosome movement; (2) cytoskeleton and cytokinesis; and (3) the processes of transporting cargo molecule and vesicular transportation in cells. Research and development on molecular motors cover synthesis, analysis, simulation and applications (e.g., biosensor and actuator). One of the promising applications of molecular motors is expected in nano-medicine, e.g., molecular drug delivery systems [9~11]. The molecular mechanism of molecular motors for neuroscience is one of the latest themes in nanobioscience and nanobiotechnology [5].

As Wang et al. report [1], the myosin V molecular motors activated by Ca^{2+} through NMDA receptor and moves among actin filament to reach the dendrite of the neuron, where myosin V binds with Rab11/Rab11-FIP2. The Rab11/Rab-FIP22 and AMPA receptors are attached on the recycling endosomes. So the motor proteins myosin V transport AMPA receptors to the spine of neurons that causes the induction of the LTP (Long Term Potentiation) in neural signaling for memory function in neural networks [1,2].

In order to analyze the function of myosin V on LTP, the dynamics mechanism of Ca^{2+} and the pool of the spine have been taken into consideration [1], but the quantitative explanation of the asynchronous phenomena discovered by Wang et al. [1] on the accumulation of GluR1 and the transportation of recycling endosomes is not available yet. Here we answer the open problem pointed out by Y. Goda [2] on what is the pathway mechanism that causes the effect that "the extent of GluR1 accumulation on the cell surface could be restricted" by quantitative analysis and make it clear in theory that the feedback from the binding process of myosin V and Rab11/Rab11-FIP2 on the activation state of Rab11/Rab11-FIP2 is the reason in signaling dynamics of cellular pathways.

2 Methods and Results

Modeling the Cellular Signaling Process:

The pathway for the signal transduction process starting from Calcium ion (Ca^{2+}) and ending at the activation of LTP at the spine of the neuron is the basis for us to simulate. The signaling cascade consists of the following steps:

(a) Ca^{2+} activates the Myosin V through NMDA receptor;
(b) Myosin V moves along the actin filament from spine to dendrite ;
(c) Myosin V binds with Rab11/Rab11-FIP2 that is attached on the recycling endosomes with AMPA receptor in which GluR1 is included;
(d) Myosin V moves from dendrite to spine and carries the cargo molecule – AMPA including GluR1;
(e) AMPA and membrane activates the LTP.

Structural Description:

The structure of the signaling pathway network is dynamical in space and time. As shown in Fig.1~3, the pathway is formulated by a direct graph where the node

corresponds to the molecule and the link corresponds to the biochemical reactions. Since the dynamics of Ca^{2+} [1,8] and movement of myosin V [1,6,7] is known and the function of AMPA on LTP is beyond the individual neuron, here the pathway we need to model is for the part "(c)", which is shown in Fig.1. The pathway consists of the interaction of myosin V and Rab11/Rab11-FIP2 and in consequent the accumulation of GluR1 of AMPA receptor. In order to clarify the dynamics function of the above pathway, the feedback from the interaction of myosin V and Rab11/Rab11-FIP2 to Rab11/Rab11-FIP2 as shown in Figure 2 and the fluctuation of myosin V and Rab11/Rab11-FIP2 as shown in Figure 3, are embedded into the pathway network.

Simulation:

The software Cell Illustrator Professional Version 3 ® is used for the implementation of the designed pathway model. The biochemical reaction of myosin V and Rab11/Rab11-FIP2 is calculated by Michaelis-Menten equation where K_m = 0.2 and $C(K_3,E_0)=K_3\times E_0=0.1$. The translation rate for myosin V and Rab11/Rab11-FIP2 are 0.1. The degradation rate of myosin V, the binding state of myosin V and Rab11/Rab11-FIP2 and the GluR1 is 0.1. The effector rate of the binding state of myosin V, Rab11/Rab11-FIP2 for the accumulation process of GluR1 is 0.9. The intrinsic degradation rate of Rab11/Rab11-FIP2 is 0.1 in the case without feedback. The feedback from the binding state of myosin V andRab11/Rab11-FIP2 on Rab11/Rab11-FIP2 enhances the degradation rate Rab11/Rab11-FIP2 by 0.4 so that it becomes 0.5 when feedback is embedded.

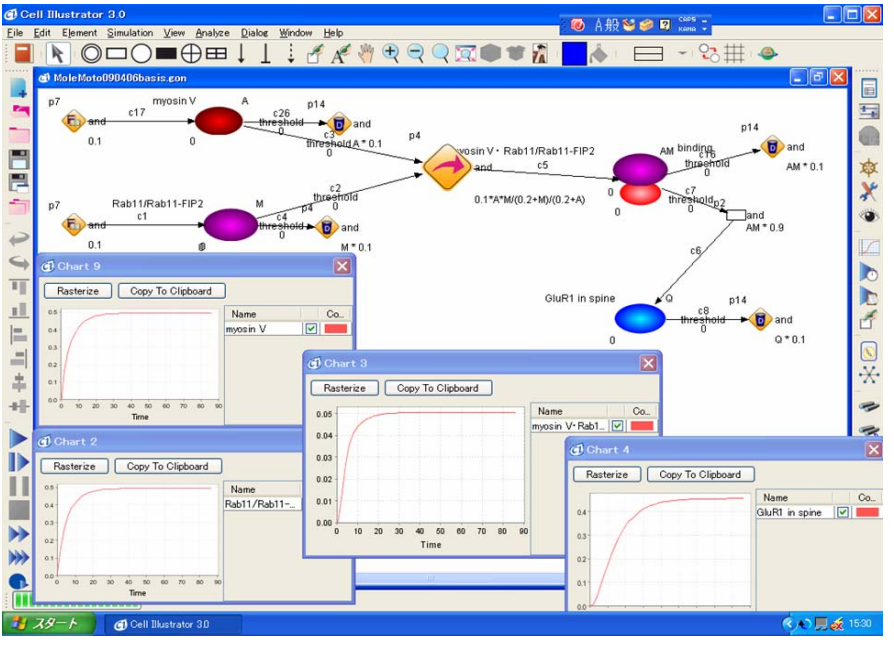

Fig. 1. Pathway of signaling cascade from myosin V to GluR1 without feedback and free of fluctuation

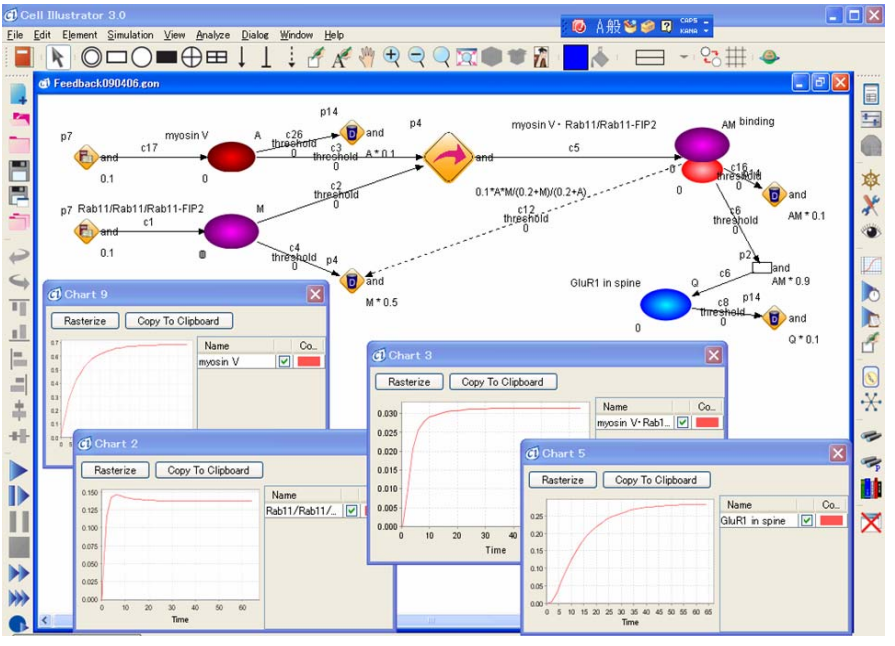

Fig. 2. Pathway of signaling cascade from myosin V to GluR1 with feedback and free of fluctuation

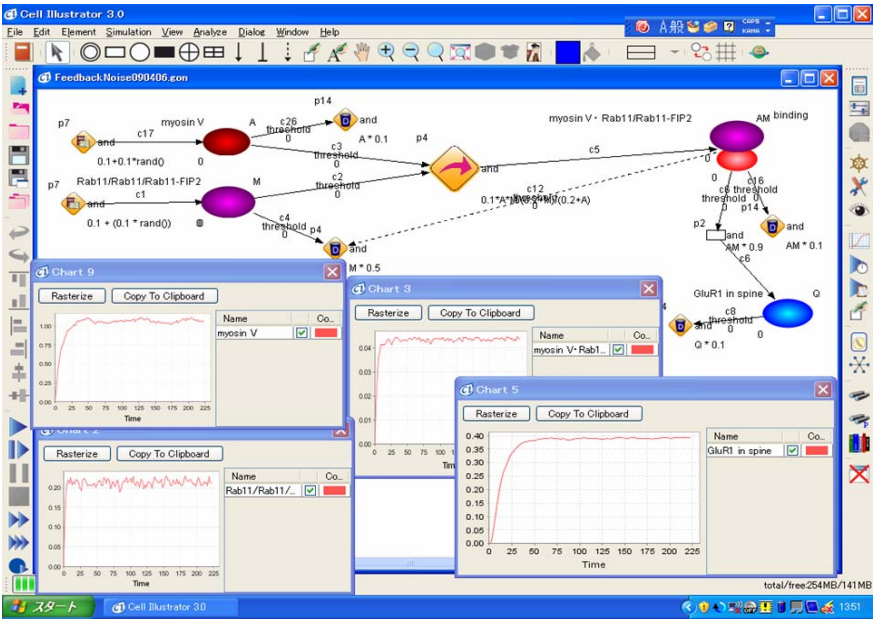

Fig. 3. Pathway of signaling cascade from myosin V to GluR1 with feedback and fluctuation

3 Conclusion

Based on the monotonic effect of myosin V and Rab11/Rab11-FIP2 on GluR1, which is consistent with the verified evidence [1,2], the obtained simulation results show that under the condition of feedback the quantity of FluR1 accumulation at the spine reduces as 64% of the one without feedback. Even though an additive fluctuation sampled from a uniform distribution in [0, 0.1] is added to myosin V and Rab11/Rab11-FIP2, we observe that the quantity of FluR1 accumulation at the spine still reduces as 81% of the one without feedback. It can be inferred in theory that the restriction of GluR1 is caused by the feedback of myosin V and Rab11/Rab11-FIP2. This provides us the theoretic basis for the investigation on the function of molecular motors within the cell with respect to neuroscience at the nano-scale.

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