Localization of Activated Ca^{2+}/calmodulin- Dependent Protein kinase II within a spine: Modeling and computer simulation

Kazuhisa Ichikawa
Corporate Research Laboratory, Fujixerox Co., Ltd.
Advanced Research Institute for Science and Engineering, Waseda University

Abstract

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) plays a crucial role in the induction of long-term potentiation (LTP). One form of LTP expression is thought to be the phosphorylation of glutamate receptor channels by CaMKII. The localization of activated CaMKII will affect the induction of LTP, and the translocation of activated CaMKII to PSD was reported. Here we investigated the localization of activated CaMKII in a model dendritic spine, and found that the diffusion of calmodulin and calcineurin but not CaMKII contribute to the localization of activated CaMKII.

1 Introduction

Long-term potentiation (LTP) and depression (LTD) of synaptic efficacy are thought to be controlled by the balance of activated kinases and phosphatases. The activation of kinases and phosphatases is triggered by the elevation of the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) mainly thorough NMDA receptors (NMDARs) [1, 2]. By the induction of LTP, Ca^{2+}/ calmodulin-dependent protein kinase II (CaMKII) phosphorylates AMPA receptors (AMPARs) [3] leading to the alteration of AMPAR channel kinetics. The translocation of CaMKII to the postsynaptic density (PSD) by the activation of NMDA receptors (NMDARs) is reported [4].

The translocation of CaMKII is an important mechanism for the localization of CaMKII. However, little is known about the mechanisms of the localization. In the present study, we constructed a biochemical and biophysical model for the activation of CaMKII within a 3D shape mimicking the morphology of a spine, and the spatio-temporal characteristics of activated CaMKII ($CaMKII^*$) were investigated by the simulation using a modeling and simulation tool, A-Cell-3D, which was developed for the construction and simulation of biochemical, electrical, and biophysical models within various morphologies including spines and whole neurons. The simulation results showed that the translocation of $CaMKII^*$ effectively localized its activity at PSD, and reduced its activity at the rest of the region within a spine. To our surprise, however, the diffusion of calmodulin and calcineurin without the translocation of CaMKII resulted in localization of $CaMKII^*$ within a spine head.

2 Biochemical reaction model

The present biochemical reaction models were constructed using A-Cell, which was

developed for the construction and simulation of biochemical reactions and/or electrical equivalent circuit models in a neuron [5].

2.1 Inward flow of calcium ions from the extracellular space

NMDARs open upon the combined events of the binding of transmitter molecules released from the presynaptic terminal and the sufficient depolarization of post synaptic membrane. Calcium ions flow into a spine through open NMDARs. In the present study, the increase in $[Ca^{2+}]_i$ was simulated using the following equation.

$$Ca(t) = Ca_0 (1 - \exp(-t/\tau_r)) \exp(-t/\tau_f) f(t) \quad (1)$$

The value of Ca_0 was so determined that the single release of glutamate resulted in 1 μM increase in $[Ca^{2+}]_i$. τ_r and τ_f are rising and falling time constant of $[Ca^{2+}]_i$. f(t) is a function simulating the desensitization of NMDARs. The stimulation frequency was 100Hz in the simulations.

2.2 Activation of calmodulin

Calmodulin (CaM) is known to be activated by the binding of four Ca^{2+} molecules, and the following scheme was employed in the present study.

$$CaM_0$$

$$CaM_1$$

$$CaM_2 \qquad CaM_3 \qquad CaM_4 \quad (2)$$

CaM_4, which is the four Ca^{2+}-bound CaM, is the activated state.

2.3 Activation of CaMKII

CaMKII is known to be activated by the binding of activated CaM, and this leads to the

autophosphorylation of CaMKII. The following scheme was employed.

K

$K.CaM_4$

$K^*.CaM_4$

K^*

(3)

K^* is the autophosphorylated CaMKII, and $K.CaM_4$, $K^*.CaM_4$ and K^* are the activated states.

2.4 Activation of phosphatase

Calcineurin (CaN) is important phosphatase for the induction of LTD [6]. CaN is known to be activated by the binding of CaM [7]. This will affect the activation of CaMKII, because there is a possibility of competitive binding of CaM to both CaMKII and CaN. The scheme for the activation of CaN is shown below.

CaN

$CaN.CaM_4$

(4)

3 Morphological model of a spine

3.1 Morphology of a spine

Morphological model of a spine was constructed using A-Cell-3D. A-Cell-3D generates compartment models by the specification of small number of parameters.

Figure1 Compartment model of a spine using A-Cell-3D

The biochemical and biophysical models constructed by A-Cell are embedded to the shape generated by A-Cell-3D. Figure 1 shows the compartment model of a spine. The diameter of spine head and dendrite is 1 μm, and the length and the diameter of spine neck are 2 μm and 0.4 μm, respectively. The total number of automatically generated compartments is 3112, and the compartment size is $0.1016 \times 0.1016 \times 0.1016\ \mu m^3$. The membrane compartments are specified in light blue in Fig.1.

3.2 Diffusion of molecules

The diffusion of molecules within cytoplasmic space was calculated using Fick's low. The diffusion coefficients for Ca^{2+}, CaM, CaMKII and CaN were 10^{-10} m^2/sec, 10^{-10} m^2/sec, 3.4×10^{-11} m^2/sec, 10^{-10} m^2/sec, respectively.

4 Results

Figure 2 shows the simulation results of spatio-temporal characteristics of $[Ca^{2+}]_i$.

Figure 2 Spatio-temporal characteristics of $[Ca^{2+}]_i$ before (0sec), during (0.5 and 1sec), and just after (1.02sec) stimulation.

The peak $[Ca^{2+}]_i$ was 6.5 μM, and it decayed to basal level rapidly after the cessation of the stimulation (right most panel in Fig.2) as was suggested from experiments [8].

Next we investigated the localization of activated CaMKII by changing simulation conditions. These were combination of diffusion of molecules and translocation of $CaMKII^*$. The set of experiments are shown in Table 1.

Table 1 Experimental set for CaMKII* localization

experiment

diffusion

translocation of CaMKII*
#

CaM

CaN

CaMKII
Exp.1

no

no

no

no
Exp.2

yes

no

no

no
Exp.3

yes

yes

no

no

Exp.4

yes

yes

yes

no

Exp.5

yes

yes

yes

yes

Simulation results at 1sec after the cessation of stimulation are shown in Figure.3.

Exp.1

Exp.2

Exp.3

Exp.4

Exp.5

Figure 3 Spatial localization of activated CaMKII

In Exp.1, where there is no diffusible molecules except Ca^{2+}, the max [$CaMKII^{*}$] is located in

the spine neck but not in the spine head. CaMKII* is not localized within the spine head. In the condition where CaM diffuses (Exp.2), CaMKII* is localized within the spine head, and its peak is appeared at PSD. When both CaM and CaN diffuse (Exp.3), CaMKII* localizes within much smaller region than in Exp.2. When CaM, CaN and CaMKII diffuse (Exp.4), however, the localization of CaMKII* is completely abolished, and its concentration is almost uniform through the spine and the dendrite. When translocation of CaMKII* is introduced into the model (Exp.5), CaMKII* localized at PSD.

It was our surprise that the diffusion of CaM and CaN increased localization of CaMKII* (Exp.3). It is natural that the translocation of CaMKII* increased its localization (Exp.5). In the present study, we found that the diffusion of CaM and CaN localizes CaMKII* near PSD within a spine without its translocation to the membrane.

5 Conclusion

The localization of activated CaMKII was investigated in the model spine using modeling and simulation tool A-Cell and A-Cell-3D. We found that the diffusion of CaM and CaN localized activated CaMKII within the spine head near PSD, even if the translocation of CaMKII* is not involved in the model. This suggests the existence of additional mechanisms for the localization of CaMKII* other than the translocation.

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