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(100 word abstract)

CONTRIBUTION OF Ca^{2+} TRANSPORTERS TO THE ELECTRICAL RESPONSE OF THE NON-SPIKING RETINAL NEURON

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Ion transporters of the neuron play important roles in regulating the intracellular ionic milieu. However, little is known about their contributions to the voltage responses. In the present study, effects of Ca^{2+} transporters on the voltage response of retinal horizontal cell, a typical non-spiking CNS neuron, was analyzed using a model reconstructed from physiological and morphological observations. The computer simulation showed that the Ca^{2+} transporters modulate the response to a flash via Ca^{2+} -dependent inactivation of the voltage-gated Ca^{2+} conductance. This also suggests that graded voltage change at the post-synaptic sites of spiking neurons might be modulated by Ca^{2+} transporters.

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(1000 WORD SUMMARY)

CONTRIBUTION OF Ca^{2+} TRANSPORTERS TO THE ELECTRICAL RESPONSE OF THE NON-SPIKING RETINAL NEURON

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Introduction: Ion transporters of the neuron are known to play important roles in regulation of the intracellular ionic milieu. They are often neglected when electrical responses of the neuron are analyzed since the ionic milieu is considered not to change significantly during the response. This may be reasonable for modeling the spiking neurons. However, in the non-spiking neurons, *e.g.* outer retinal neurons, the ion transporters are expected to contribute to the electrical responses since various types of voltage-gated ionic channel are activated tonically and thus the intracellular ionic concentrations should be dynamically regulated. The purpose of present study is to elucidate the contribution of Ca^{2+} transporters to the generation of electrical response in the horizontal cell, a typical non-spiking retinal

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neuron. Our previous experiments have revealed that the $\text{Na}^+/\text{Ca}^{2+}$ exchange and the Ca^{2+} pump extrude intracellular Ca^{2+} to regulate $[\text{Ca}^{2+}]_i$ in the horizontal cell (Hayashida et al. 1998). These Ca^{2+} efflux mechanisms are considered to affect the horizontal cell response, since the voltage-gated Ca^{2+} conductance is known to be inactivated by intracellular Ca^{2+} . In the present, we analyzed quantitatively how these Ca^{2+} efflux mechanisms can contribute to the voltage response of horizontal cell using a multi-compartmental cable model.

Model: Computer simulations were carried out using the simulation software “NEURON” (Hines and Carnevale 1997, 2000). The cellular morphology of horizontal cell was reconstructed by a combination of cylindrical and conical cables, as shown in Figure 1a. This cable model is composed of totally 388 cable compartments, each of which is divided into smaller segments. The physiological mechanisms relevant to $[\text{Ca}^{2+}]_i$ of the horizontal cell are the glutamate-gated cation conductance, the voltage-gated Ca^{2+} conductance, the $\text{Na}^+/\text{Ca}^{2+}$ exchange, the Ca^{2+} pump and the Ca^{2+} buffer. Intracellular Ca^{2+} diffusion in the radial and longitudinal directions of cables was taken into account. Other mechanisms relevant to calculate the membrane voltage were the passive leakage conductance, the membrane capacitance and the voltage-gated K^+ conductances, *i.e.* the anomalous rectifier, the delayed rectifier and the transient A-type conductances. These mechanisms were described by the model equations and the parameter values were estimated to reproduce the experimental observations in the isolated horizontal cells *in vitro*. The synaptic inputs onto the horizontal cells are known to be mediated by L-glutamate, which increases the glutamate-gated non-selective cation conductance. The glutamate-gated conductance was incorporated into the dendritic sites of the model according to previous morphological observations (Stell and Lightfoot 1975), as indi-

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cated by circles in Figure 1a. To simulate the synaptic inputs induced by a brief flash of diffuse light, the glutamate-gated conductances were modulated with a time course shown in Figure 1b. The membrane mechanisms except for the glutamate-gated conductance were assumed to distribute homogeneously over the entire cable model. The Ca^{2+} buffer was distributed evenly in the internal space of the all cables.

Results: Figure 2 shows the light-induced responses to a diffuse flash calculated with the present cell model. The glutamate-gated conductance at all the post-synaptic sites were modulated simultaneously to mimic the response to the diffuse flash. The voltage responses calculated at the post-synaptic site (indicated by A in Figure 1a) and at the cell body (indicated by B) are shown in a and b, respectively. At the cell body, the membrane voltage is hyperpolarized from about -30mV to -54mV in response to the flash, as shown in Figure 2b. After the hyperpolarization, the membrane voltage rebounds to about -28mV (referred to as *after-depolarization*) and then gradually returns to the original potential. The time course of this voltage response provided a reasonable fit to the membrane potential change recorded experimentally from the soma of horizontal cell. As shown in Figure 2a, the voltage response at the post-synaptic site is quite similar to the one at the cell body. This indicates that the voltage response to the diffuse flash induced at the post-synaptic sites can conduct to the cell body through the dendrites without significant attenuation. In contrast to such voltage responses, $[\text{Ca}^{2+}]_i$ is regulated in different way at the post-synaptic site (c) and the cell body (d). At the post-synaptic site, $[\text{Ca}^{2+}]_i$ is maintained at about 550nM in the dark and decreased to 100nM in response to the flash. The time course of the change is not slower than but comparable with that of the voltage response. At the cell body, however, $[\text{Ca}^{2+}]_i$ is

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decreased from about 450nM to 340nM in response to the flash and its time course is much slower than that of the post-synaptic site.

To examine the contribution of the Ca^{2+} efflux mechanisms to the voltage response, the rates of Ca^{2+} efflux through the $\text{Na}^+/\text{Ca}^{2+}$ exchange and the Ca^{2+} pump were decreased by 1/10 times of the original values used in the simulation of Figure 2. The simulation results obtained with the slower rates of the efflux are shown in Figure 3. As shown in a and b (for the post-synaptic site and the cell body, respectively), the membrane voltage in the dark calculated with the slower efflux rates (solid lines) is 2mV lower than that calculated with the original efflux rates (dotted lines). Moreover, the *after-depolarization* seen in the response calculated with the original efflux rates (indicated by arrow heads) is completely suppressed. This indicates that $[\text{Ca}^{2+}]_i$ does not decrease enough for the voltage-gated Ca^{2+} conductance to be released from the Ca^{2+} -dependent inactivation during the hyperpolarizing response and the *after-depolarization* due to an activation of the voltage-gated Ca^{2+} conductance does not take place.

Conclusions: The present simulations indicated that the Ca^{2+} efflux mechanisms contribute to shaping the voltage response of the retinal horizontal cell, a typical non-spiking neuron. The Ca^{2+} efflux mechanisms might play a significant role in modulation of the electrical response of the post-synaptic sites of spiking neurons, *e.g.* synaptic spines.

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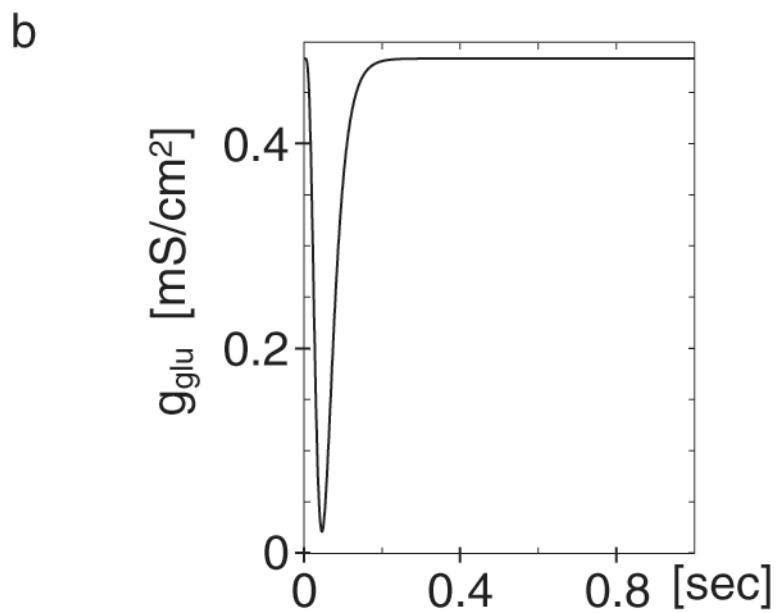
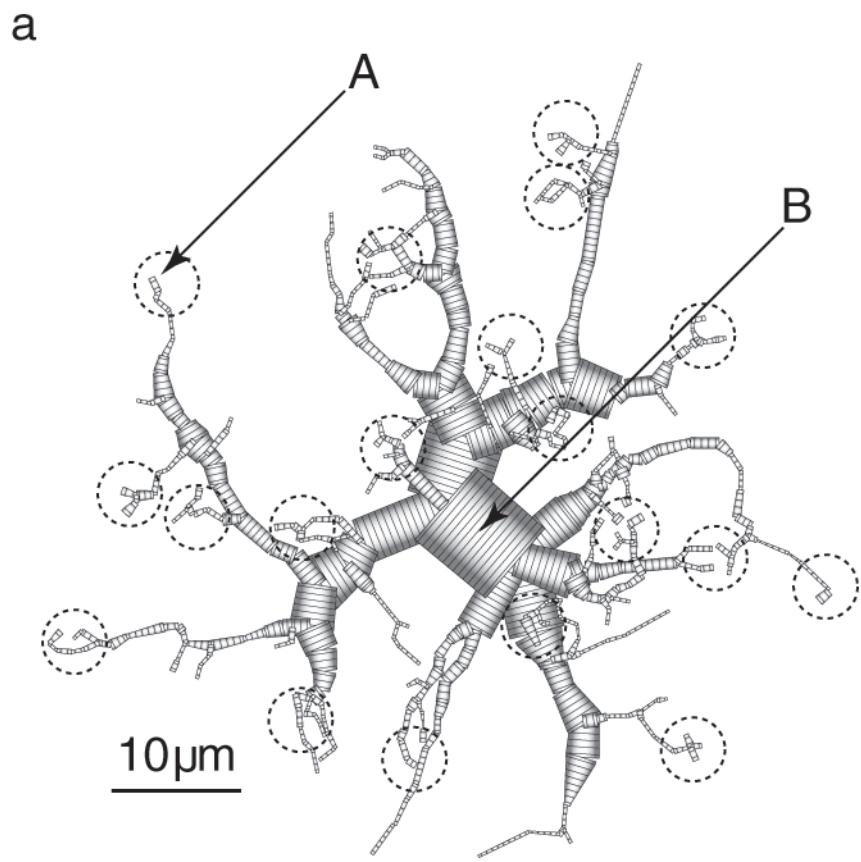


Figure 1:

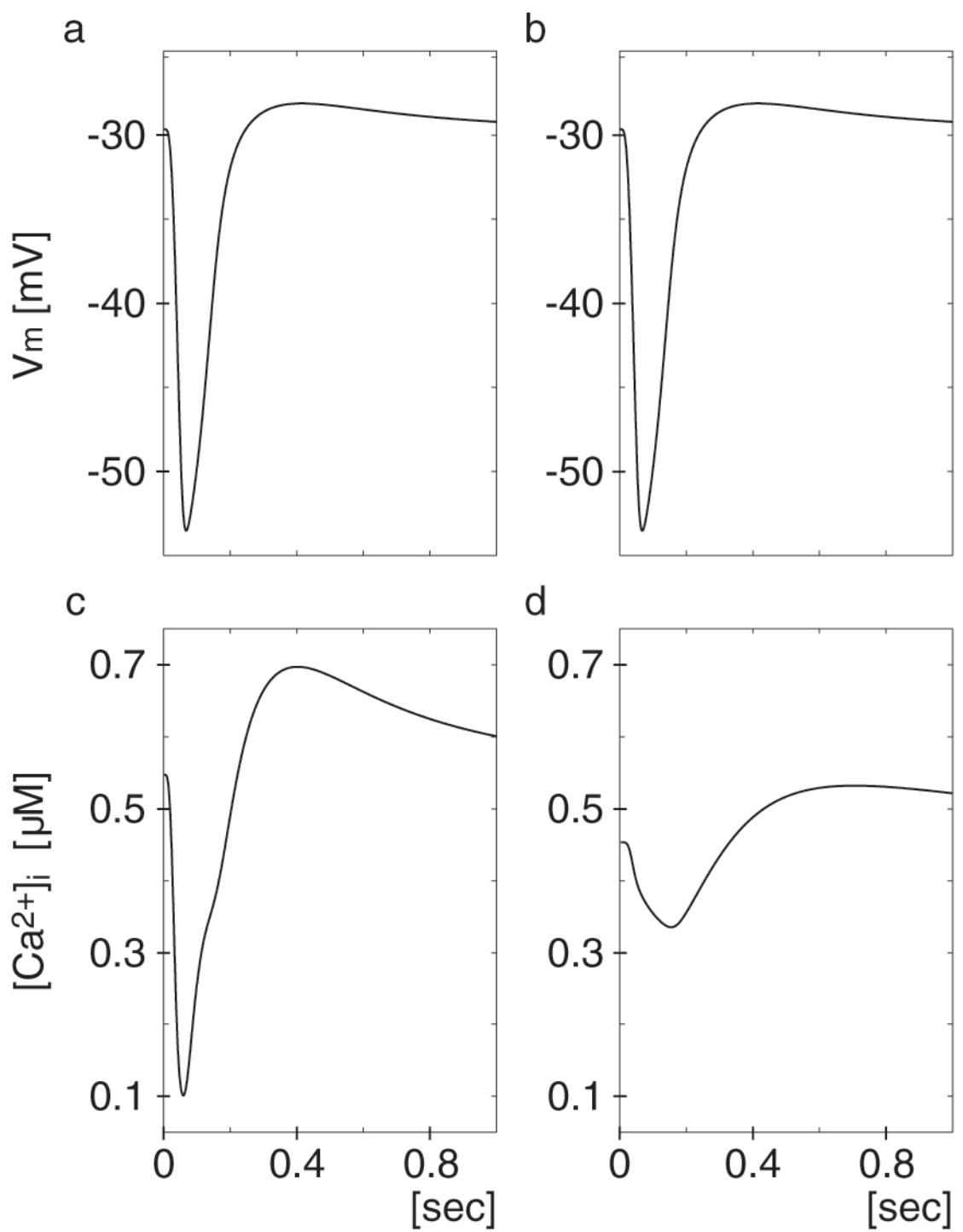


Figure 2:

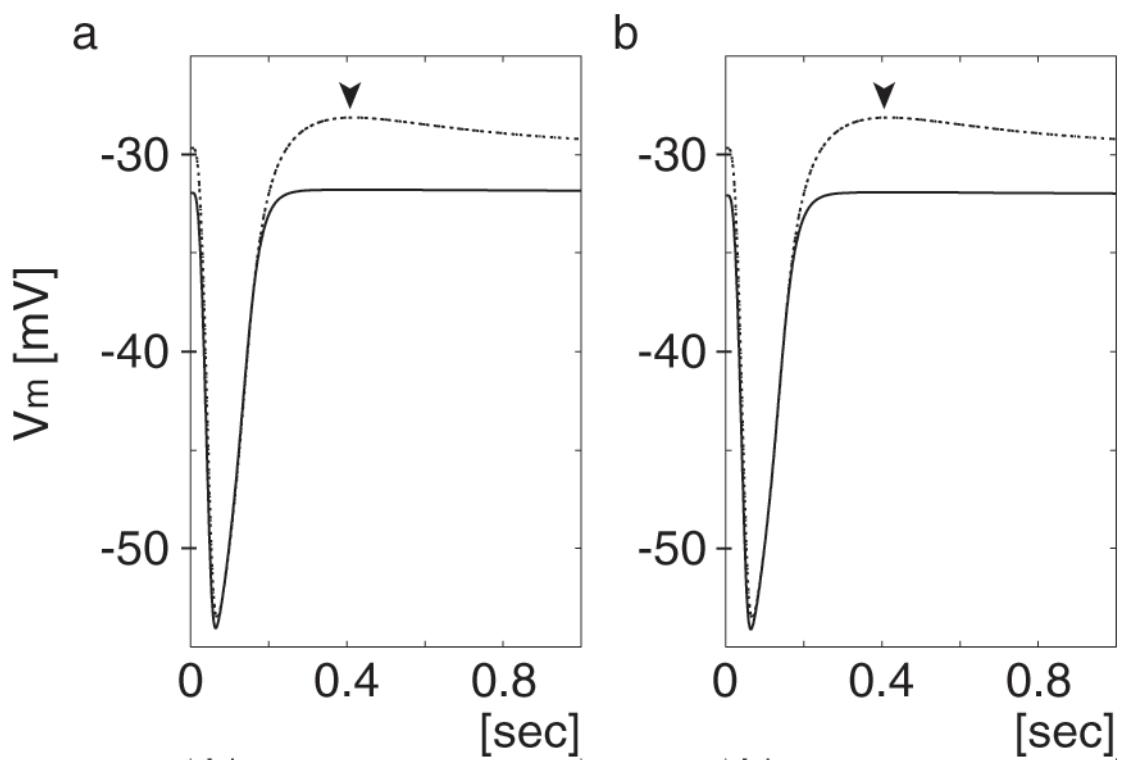


Figure 3: