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Possible mechanism of flicking-induced short-term plasticity in retinal cone-LHC synapse: a computational study

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Abstract. In retinal cone-HC synapse, it has been found that repetitive stimulation could induce postsynaptic short-term responsiveness enhancement. However, the detailed mechanism underlying this short-term plasticity in the retinal graded neurons remains unclear. In this study, based on an ion-channel model described using Hodgkin–Huxley equations, the possible mechanism of repetitive-stimulation-induced short-term plasticity in the synapse between retinal cones and horizontal cells was investigated. The computational simulation results, together with evidence from experimental observations, suggest that the short-term modification of signal transmission between the retinal graded neurons is likely to be attributed to the regulatory effects that calcium-dependent process exerts on the single-channel properties of the postsynaptic AMPA receptors.

Keywords: Retina – Graded neurons – Short-term plasticity – Ion channels

1 Introduction

It has been observed in many spiking neurons of the central nervous system that a brief repetitive stimulation can result in a rapid modification of the synaptic strength, and the synaptic status can recover within a short period after the stimulation has ceased. This short-term synaptic plasticity is an important feature of synapses, which means that the synaptic output is not solely determined by the input stimulus, but also dependent on the recent and present activity status of relevant neurons (for a review see Zucker and Regehr 2002). It was previously found in this laboratory that in the synapse between retinal luminosity-type horizontal cell (LHC) and cone photoreceptors, where both the pre- and postsynaptic signals were graded potentials, the efficacy of synaptic transmission was dependent on the stimulus pattern and the activity of relevant neurons. Intracellular recordings made from carp LHC showed that repetitive red flashes were effective in inducing a short-term enhancement of the cell's responsiveness to the red light (Hu et al. 2000).

It is widely accepted that in the central nervous system, calcium plays a crucial role in the induction of synaptic plasticity. Lowering intracellular Ca^{2+} in the postsynaptic neuron actually prevented the development of activity-related response changes, which implicated the importance of postsynaptic Ca^{2+} (for a review see Linden 1999). In the graded neurons of carp retina, LHC expresses voltage-gated Ca^{2+} channels, which is believed to be a main source of membrane Ca^{2+} influx. However, it was also reported that a subtype of Ca^{2+}-permeable AMPA receptors was present in the horizontal cells of carp retina (Okada et al. 1999), the activation of which could be responsible for Ca^{2+} influx (Gu et al. 1996). Furthermore, it has been reported that in the CA1 region of the hippocampus, the elevation of intracellular Ca^{2+} can lead to modification of the single-channel conductance properties of the AMPA receptors and provides a fundamental mechanism for the alteration of synaptic efficiency (Benke et al. 1998).

However, the mechanism underlying the modification of synaptic transmission between the retinal graded neurons remains unclear and possible relevant calcium processes are poorly investigated. In this study, we attempted to pursue the mechanism(s) involved in the activity-dependent enhancement of the LHC's light responsiveness. The Hodgkin–Huxley ion-channel model was employed to describe the neuron's membrane potential changes in exposure to light stimulus (Usui et al. 1991, 1996). The dynamic changes of relevant components were examined to investigate the possible postsynaptic process involved in the repetitive-stimulus-induced synaptic transmission changes between the retinal photoreceptors and horizontal cells.

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2 Methods

2.1 Intracellular recording

Experimental procedure was described in a previous report (Hu et al. 2000). In brief, adult carp (*Carassius auratus,* body length 15–20 cm) retina was used. Basically, carp was maintained in aquarium under natural light/dark schedule. Experiment was conducted during daytime. The animal was kept in the dark for 20 min prior to the experiment to allow for the isolation of the retina and avoid a complete dark adaptation. After the animal had been decapitated, the eye was enucleated and the retina isolated under dim red light. The retina was then placed with the photoreceptor side up in a chamber with a volume of 1.4 ml and continuously perfused with oxygenated (95% O_2 + 5% CO_2) Ringer solution at a flow rate of 4.5 ml/min. The normal Ringer solution contained (in mM): NaCl 116.0, KCl 2.4, $CaCl_2$ 1.2, $MgCl_2$ 1.2, NaH_2PO_4 1.0, $NaHCO_3$ 30.0, and glucose 10.0 and had a pH value of 7.7 at room temperature.

The stimuli were originated from high-intensity light-emitting diodes (LEDs) with peak wavelength being 703 nm (referred to as red light). The LED output parameters, including intensity and time course of the light flash, were defined using a PC program. The light beam, projected through an optical system, formed an 8-mm-diameter diffuse light spot on the retinal surface. The maximal intensity of the 703-nm light ($\log I = 0$) was 2.16×10^{12} photons/(cm^2·s), measured using a photodetector (IL-1405, International Light, Newburyport, MA, USA). Stimulus intensities will be presented in relative log units (compared to the maximal intensity) in this paper. The light-on duration of the test flash was set at 500 ms and repetitive flashes with light-on duration of 500 ms were given at a frequency of 1 Hz, and lasted for 20 s.

The microelectrode was pulled on a microelectrode puller (PD-30, Narishige, Japan) and had a resistance around 100 MΩ when filled with 4-M KAc and measured in Ringer solution. The LHC responses were recorded intracellularly using an amplifier system (MEZ-8300, Nihon Kohden, Japan) and monitored on an oscilloscope (TDS210, Tektronix, USA). A low-pass filter was applied to the recorded cell's membrane potential, with the cutoff frequency being 300 Hz. The data were digitized via an A/D interface (AD8111, Adlink Technology Inc., Taiwan) at a rate of 200 Hz and stored on an IBM-compatible PC for offline analysis. LHCs were identified by their light response characteristics and relative depth in the tissue. The efficacy of synapses between the LHC and cone photoreceptors was evaluated by measuring the amplitude of the LHC's response to test light.

2.2 Pharmacology

To investigate the possible synaptic and/or cellular mechanism(s) of the stimulus-dependent synaptic plasticity, the experiments were performed during normal Ringer perfusion and with administration of relevant chemical. In one protocol, 0.5 M EGTA was injected iontophoretically via the recording electrode into the LHC being recorded to keep the intracellular Ca^{2+} at a low level. A hyperpolarizing current within the range of 0.3–0.7 nA was applied, with an on-duration of 500 ms and frequency of 1 Hz, for 10 min. Repetitive light stimulus was given 10 min afterwards to allow for the intracellular diffusion of the injected chemical. The EGTA applied was purchased from Sigma Ltd., St. Louis, MO, USA.

2.3 Hodgkin–Huxley model description

The light responsiveness of the retinal LHC is measured by its membrane potential changes induced by the stimulus. The electrical properties of the LHC's membrane are governed by the voltage-dependent and ligand-gated currents in the cell soma (Tachibana 1983; Usui et al. 1996) and can be equated using Hodgkin–Huxley (H-H) equations (Hodgkin and Huxley 1952) in the following manner:

$$C_S \frac{\mathrm{d}V}{\mathrm{d}t} + \sum_j I_j = 0\,, \tag{1}$$

where V is the membrane potential, C_S represents the membrane capacitance, and I_j denotes the current passing the j-th channel, which is dependent on the membrane potential:

$$\begin{aligned} I_j(V,t) &= g_j\big(V - E_j\big) \\ &= \overline{g}_j \cdot m^p(V,t) \cdot h^q(V,t) \cdot \big(V - E_j\big)\,, \end{aligned} \tag{2}$$

where g_j is the conductance of the j-th ion channel; $\bar{g}_j$ is its maximal value; m and h denote the activation and inactivation variables of the channel, respectively; p and q are positive integers determining the dynamic properties of the activation and inactivation processes, respectively; and E_j stands for the equilibrium potential of the channel.

Since the LHC receives glutamatergic input from its presynaptic photoreceptors and the cell's membrane potential changes in response to light stimulus basically involve the activity changes of glutamate-gated channels and the subsequent changes of the voltage-gated cation channels, (1) can thus be reorganized as

$$C_S \frac{\mathrm{d}V}{\mathrm{d}t} + \big(I_{Na} + I_{Ca} + I_K + I_A + I_{anom} + I_{glu} + I_l\big) = 0\,, \tag{3}$$

where I_{Na} and I_{Ca} are sodium and calcium currents, respectively; I_K, I_A, and I_{anom} represent, respectively, delay time rectifying K^+ current, outward rectifying K^+ current, and anomalous rectifying K^+ current; and I_{glu} and I_l denote the glutamate-receptor-mediated current and leak current, respectively. The detailed descriptions for each ionic current are listed below. The parameters used in the equations mostly followed those put forth by Usui et al. (1991, 1996), which were based on voltage and current clamp results (Tachibana 1983; Yagi and Kaneko 1988).

$$I_{Na} \tag{4}$$

$$\alpha_{mNa} = \frac{40 \cdot (80 - V)}{\exp\left(\frac{80-V}{15}\right) - 1}$$
$$\beta_{mNa} = 10 \cdot \exp\left(-\frac{V}{20}\right)$$
$$\frac{\mathrm{d}m_{Na}}{\mathrm{d}t} = \alpha_{mNa} \cdot (1 - m_{Na}) - \beta_{mNa} \cdot m_{Na}$$
$$\alpha_{hNa} = 0.01 \cdot \exp\left(-\frac{V}{30}\right)$$
$$\beta_{hNa} = \frac{2}{\exp\left(\frac{70-V}{10}\right) + 1}$$
$$\frac{\mathrm{d}h_{Na}}{\mathrm{d}t} = \alpha_{hNa} \cdot (1 - h_{Na}) - \beta_{hNa} \cdot h_{Na}$$
$$\overline{g}_{Na} = 120 \quad [nS]$$
$$E_{Na} = 55 \quad [mV]$$
$$I_{Na} = \overline{g}_{Na} \cdot m_{Na}^3 \cdot h_{Na} \cdot (V - E_{Na})$$

$$I_K \tag{5}$$

$$\alpha_{mK} = \frac{10 \cdot (180 - V)}{\exp\left(\frac{180-V}{20}\right) - 1}$$
$$\beta_{mK} = 0.25 \cdot \exp\left(-\frac{V}{20}\right)$$
$$\frac{\mathrm{d}m_K}{\mathrm{d}t} = \alpha_{mK} \cdot (1 - m_K) - \beta_{mK} \cdot m_K$$
$$\overline{g}_K = 0.25 \quad [nS]$$
$$E_K = -60 \quad [mV]$$
$$I_K = \overline{g}_K \cdot m_K^4 \cdot (V - E_K)$$

$$I_A \tag{6}$$

$$\alpha_{mA} = \frac{40 \cdot (200 - V)}{\exp\left(\frac{200-V}{15}\right) - 1}$$
$$\beta_{mA} = 0.40 \cdot \exp\left(-\frac{V}{20}\right)$$
$$\frac{\mathrm{d}m_A}{\mathrm{d}t} = \alpha_{mA} \cdot (1 - m) - \beta_{mA} \cdot m_A$$
$$\alpha_{hA} = 0.0005 \cdot \exp\left(-\frac{V}{20}\right)$$
$$\beta_{hA} = \frac{2}{\exp\left(\frac{90-V}{10}\right) + 1}$$
$$\frac{\mathrm{d}h_A}{\mathrm{d}t} = \alpha_{hA}(1 - h_A) - \beta_{hA} \cdot h_A$$
$$\overline{g}_A = 2 \quad [nS]$$
$$I_A = \overline{g}_A \cdot m_A^3 \cdot (V - E_K)$$

$$I_{anom} \tag{7}$$

$$m_{anom} = \frac{1}{1 + \exp\left(\frac{V+60}{30}\right)}$$
$$\overline{g}_{anom} = 50 \cdot [1 - 0.5 \cdot Glu(t)] \quad [nS]$$
$$I_{anom} = \overline{g}_{anom} \cdot m_{anom}^4 \cdot (V - E_k)$$

$$I_{Ca} \tag{8}$$

$$\alpha_{mCa} = \frac{5 \cdot (70 - V)}{\exp\left(\frac{70-V}{28}\right) - 1}$$
$$\beta_{mCa} = 2 \cdot \exp\left(-\frac{V}{15}\right)$$
$$\frac{\mathrm{d}m_{Ca}}{\mathrm{d}t} = \alpha_{mCa} \cdot (1 - m_{Ca}) - \beta_{mCa} \cdot m_{Ca}$$
$$h_{Ca} = \frac{K}{K + [Ca^{2+}]_i}$$
$$\frac{\mathrm{d}[Ca^{2+}]_i}{\mathrm{d}t} = \frac{-I_{Ca}}{2 \cdot F \cdot v} + \frac{[Ca^{2+}]_{eq} - [Ca^{2+}]_i}{\tau_{trans}}$$
$$\tau_{trans} = 6 \cdot \exp\left(\frac{V}{100}\right)$$
$$\overline{g}_{Ca} = 135 \quad [nS]$$
$$E_{Ca} = 12.5 \cdot \log\left(\frac{[Ca^{2+}]_0}{[Ca^{2+}]_i}\right) \quad [mV]$$
$$I_{Ca} = -\overline{g}_{Ca} \cdot h_{Ca} \cdot m_{Ca}^3 \cdot (V - E_{Ca})$$

$$I_{glu} \tag{9}$$

$$\overline{I_{glu}} = 600 \cdot Glu(t)$$
$$I_{glu} = \overline{I_{glu}} \frac{\exp\left(\frac{V+60}{95}\right) - 1.5}{\exp\left(\frac{40-V}{125}\right) + 0.5}$$

$$I_l \tag{10}$$

$$g_l = 0.5 \quad [nS]$$
$$E_l = -60 \quad [mV]$$
$$I_l = g_l \cdot (V - E_l)$$

2.4 Calcium-dependent model

In all these voltage-dependent ion channels described, the Ca^{2+} channel is the most complicated one since the intracellular Ca^{2+} concentration can be regulated by a number of factors. It has also been frequently reported that synaptic modification involved intracellular Ca^{2+} activity. Stimulus-pattern-related synaptic weight changes could be eliminated when Ca^{2+} chelator EGTA was injected into the postsynaptic neuron (Malyshev and Balaban 1999), which implied that the postsynaptic Ca^{2+} concentration was crucial.

In carp retinal horizontal cells, in addition to the influx via voltage-dependent Ca^{2+} channel I_{Ca} and efflux via Ca^{2+} transporters (Usui et al. 1996), Ca^{2+} influx can occur via Ca^{2+} -permeable AMPA receptors on the plasma membrane (Okada et al. 1999). The Ca^{2+} concentration changes thus involve three components:

$$\frac{\mathrm{d}[Ca^{2+}]_i}{\mathrm{d}t} = \frac{-I_{Ca}}{2 \cdot F \cdot \mathrm{v}} + \frac{[Ca^{2+}]_{eq} - [Ca^{2+}]_i}{\tau_{trans}} + \eta \cdot I_{glu} \tag{11}$$

where $[Ca^{2+}]_i$ depicts the intracellular Ca^{2+} concentration; F is Faraday's constant (9.649×10^4 C/mol);v

reflects the volume of the cell; $[Ca^{2+}]_{eq}$ and τ_{trans} are the equilibrium concentration and the time constant of the transporter, respectively (Usui et al. 1996); and the third term, $\eta \cdot I_{glu}$, means that the Ca^{2+} concentration changes are also dependent on the activity of Ca^{2+}-permeable AMPA receptors (Okada et al. 1999). The value of the reversal potential for Ca^{2+} current is then determined by the Nernst equation:

$$E_{Ca} = 12.5 \cdot \log\left(\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}\right), \tag{12}$$

where $[Ca^{2+}]_o$ is the constant extracellular Ca^{2+} concentration (1.2 mM in Ringer's solution). The I_{Ca} component in the H-H equations (8) can thus be modified as follows:

$$I_{Ca} \tag{13}$$

$$\alpha_{mCa} = \frac{5 \cdot (70 - V)}{\exp(\frac{70-V}{28}) - 1}$$
$$\beta_{mCa} = 2 \cdot \exp\left(-\frac{V}{15}\right)$$
$$\frac{dm_{Ca}}{dt} = \alpha_{mCa} \cdot (1 - m_{Ca}) - \beta_{mCa} \cdot m_{Ca}$$
$$h_{Ca} = \frac{K}{K + [Ca^{2+}]_i}$$
$$\frac{d[Ca^{2+}]_i}{dt} = \frac{-I_{Ca}}{2 \cdot F \cdot v} + \frac{[Ca^{2+}]_{eq} - [Ca^{2+}]_i}{\tau_{trans}} + \eta \cdot I_{glu}$$
$$\tau_{trans} = 6 \cdot \exp\left(\frac{V}{100}\right)$$
$$\overline{g}_{Ca} = 135 \quad [nS]$$
$$E_{Ca} = 12.5 \cdot \log\left(\frac{[Ca^{2+}]_0}{[Ca^{2+}]_i}\right) \quad [mV]$$
$$I_{Ca} = -\overline{g}_{Ca} \cdot h_{Ca} \cdot m_{Ca}^3 \cdot (V - E_{Ca}).$$

It has been demonstrated that the LHC of carp retina expresses AMPA-sensitive glutamate receptors (Zhou et al. 1993), the properties of which can be regulated by Ca^{2+}-dependent phosphorylation processes (Liman et al. 1989; McMahon et al. 1994; Mammen et al. 1997). Therefore, the conductance of the glutamate channel is a function of intracellular Ca^{2+} concentration – $g_{glu} = \overline{g_{glu}} \cdot f([Ca^{2+}]_i)$ – and modification of the component I_{glu} (9) can be made accordingly:

$$I_{glu} \tag{14}$$

$$\overline{I_{glu}} = 600 \cdot Glu(t) \cdot f([Ca^{2+}]_i)$$
$$I_{glu} = \overline{I_{glu}} \frac{\exp(\frac{V+60}{95}) - 1.5}{\exp(\frac{40-V}{125}) + 0.5}$$
$$f([Ca^{2+}]_i) = \theta \cdot [Ca^{2+}]_i.$$

Glutamate is the neurotransmitter released by photoreceptors. The transmitter release is decreased when the retina is exposed to light stimulus, which causes a hyperpolarization of the photoreceptors. Glutamate activates I_{glu}, and in the meantime suppresses I_{anom} on the postsynaptic LHC (Ishida et al. 1984; Kaneko and Tachibana 1985; Tachibana 1985). In this study, we chose to set the glutamate index at 1.0 in the dark and 0.27 during light stimulation for simplicity.

3 Results

3.1 Repetitive-red-flash-induced LHC response enhancement

In the carp retina, LHC receives inputs from cones, and the efficacy of synapses between cones and the LHC is modifiable. It was previously observed in this laboratory that the LHC's responsiveness to red stimulus could be enhanced in exposure to repetitive red flashes, which reflected the synaptic strengthening induced by the stimulus (Hu et al. 2000).

Figure 1a gives a typical example of the LHC's responsiveness changes induced by repetitive red light flashes (light-on duration 500 ms, frequency 1 Hz, for 20 s). It is clear that the cell's response amplitude was gradually enhanced from the initial value of 18.1 to 20.5 mV toward the end of the 20-s period when the repetitive red flash sequence was applied.

3.2 Postsynaptic calcium concentration

The involvement of postsynaptic calcium processes in the induction of synaptic plasticity has been repeatedly reported (for a review see Linden 1999), and we thus tried a protocol in which intracellular injection of Ca^{2+} chelator EGTA was made to the LHC. The experimental result was that when the $[Ca^{2+}]_i$ was kept at a low level by EGTA, repetitive-flash-induced enhancement in the cell's red-light response was remarkably attenuated (18.1 vs. 18.2 mV, at the beginning and toward the end of the flickering sequence, respectively, Fig. 1b), which suggested that the intracellular Ca^{2+} concentration changes in the postsynaptic LHC played a crucial role in the synaptic modification that occurred in the outer retina.

3.3 H-H model output

The original model incorporating H-H equations was applied to describe the LHC's response elicited by light flash. The parameters were basically chosen following those suggested by Usui and coworkers (Usui et al. 1991, 1996). Although the model output fit the LHC's light responsiveness to a single flash reasonably well, it failed to describe the cell's behavior in response to repetitive light flashes. As illustrated in Fig. 2, the model cell's response to flickering red light was a sequence of membrane hyperpolarization with uniform amplitude.

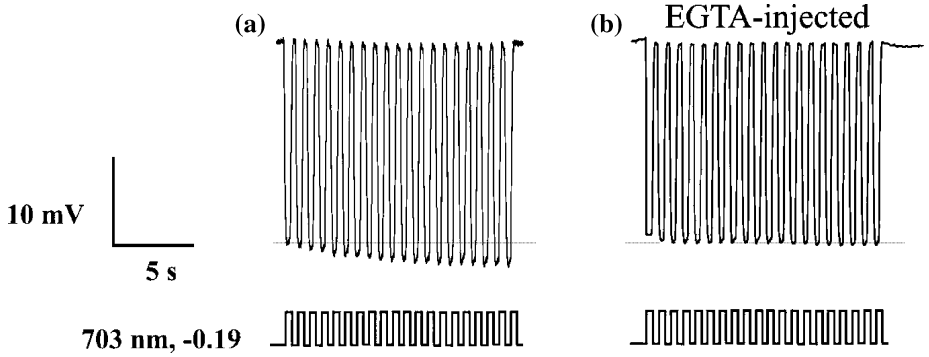

Fig. 1. Activity-dependent LHC light response enhancement and pharmacological result. **a** An LHC's light response during a red (703 nm, $\log I = -0.19$) flickering sequence (*upper panel*: LHC's response; *lower panel*: light flash). The repetitive red flashes increased the cell's light response amplitude (18.1 vs. 20.5 mV, at the beginning and toward the end of the repetitive flash sequence, respectively). **b** The response enhancement was remarkably attenuated after EGTA application (18.1 vs. 18.2 mV, at the beginning and toward the end of the repetitive flash sequence, respectively)

3.4 Calcium influx and possible postsynaptic mechanism

Experimental results revealed that the postsynaptic Ca^{2+} concentration change is crucial in the development of repetitive-light-induced LHC responsiveness enhancement. In LHC, Ca^{2+} influx can occur via Ca^{2+}-permeable AMPA receptors on the plasma membrane, in addition to the voltage-dependent Ca^{2+} channels (Okada et al. 1999). A glutamate-dependent component was thus introduced in (11).

Calcium can affect the postsynaptic neuron's behavior in several ways. Voltage-dependent Ca^{2+} current is one possible way. However, the simulation result showed that the change in the voltage-dependent Ca^{2+} current during the period of repetitive light stimulus was trivial and could not explain the LHC's response amplitude enhancement (Fig. 3).

Calcium processes have been proved to be important in the induction of synaptic modification. It has also been reported that an AMPA receptor's properties can be regulated via Ca^{2+}-dependent phosphorylation processes (Liman et al. 1989; McMahon et al. 1994; Barria et al. 1997; Mammen et al. 1997). The glutamate current in the model was thus suggested to be Ca^{2+}-dependent. It is illustrated in Fig. 4 that this modification effectively changed the model prediction for the glutamate current and also remarkably changed the total current on the cell's membrane. The model output eventually fit well the experimental observations that the repetitive light flashes enhanced the LHC's light response amplitude.

4 Discussions

4.1 Synaptic plasticity in the outer plexiform layer of retina

To describe the stimulus-pattern-related responsiveness changes in the LHC of carp retina, self-organizing models were developed (Hu et al. 2003) in which the synaptic weight changes were suggested to be the mechanism underlying the cell's responsiveness changes. However, the model did not actually indicate whether pre- or postsynaptic process is responsible for this short-term plasticity.

In the outer plexiform layer of retina, bipolar cells (BCs) are also postsynaptic to photoreceptors, and they can be further divided into ON and OFF types by the cells' response properties. It is widely acknowledged that the glutamate receptors of ON and OFF BCs are of different subtypes (Nakanishi 1995). OFF BC possesses an ionotropic-type glutamate receptor, which is AMPA preferring. When light reduces glutamate release from cones, OFF BC hyperpolarizes. On the other hand, ON BC contains a metabotropic glutamate receptor. Glutamate actually hyperpolarizes the ON BC; thus light-induced decrease of glutamate release causes a depolarization of the cell. Experimental observations made in this laboratory showed that the repetitive light-induced response enhancement occurred only in LHC and OFF BC, both of which possess ionotropic glutamate receptors. The phenomenon was not observed in ON BC, which contains metabotropic glutamate receptors (Hu and Liang 2002). It therefore seems to suggest that the light response enhancement that occurred in the retinal graded neurons involves some postsynaptic receptor mechanism(s).

Further experiments conducted in this study revealed that the repetitive-flash-induced responsiveness enhancement was very much attenuated when Ca^{2+} in the postsynaptic neuron was chelated by intracellular injection of EGTA. It thus suggests that the postsynaptic $[Ca2+]_i$ is involved in the induction of the phenomenon.

4.2 Synaptic plasticity and postsynaptic calcium hypothesis

The activity-dependent modification of synaptic connection strength is thought to be fundamental to information processing and storage in the neuronal circuitry (for a review see Miller 1996). In many spiking neurons, the changes of synaptic efficacy are dependent on the past and present activity status of relevant neurons, and it is widely accepted that Ca^{2+} plays an important role (for a review see Zucker 1999). Some theoretical hypotheses and mathematical models have also been proposed, and the

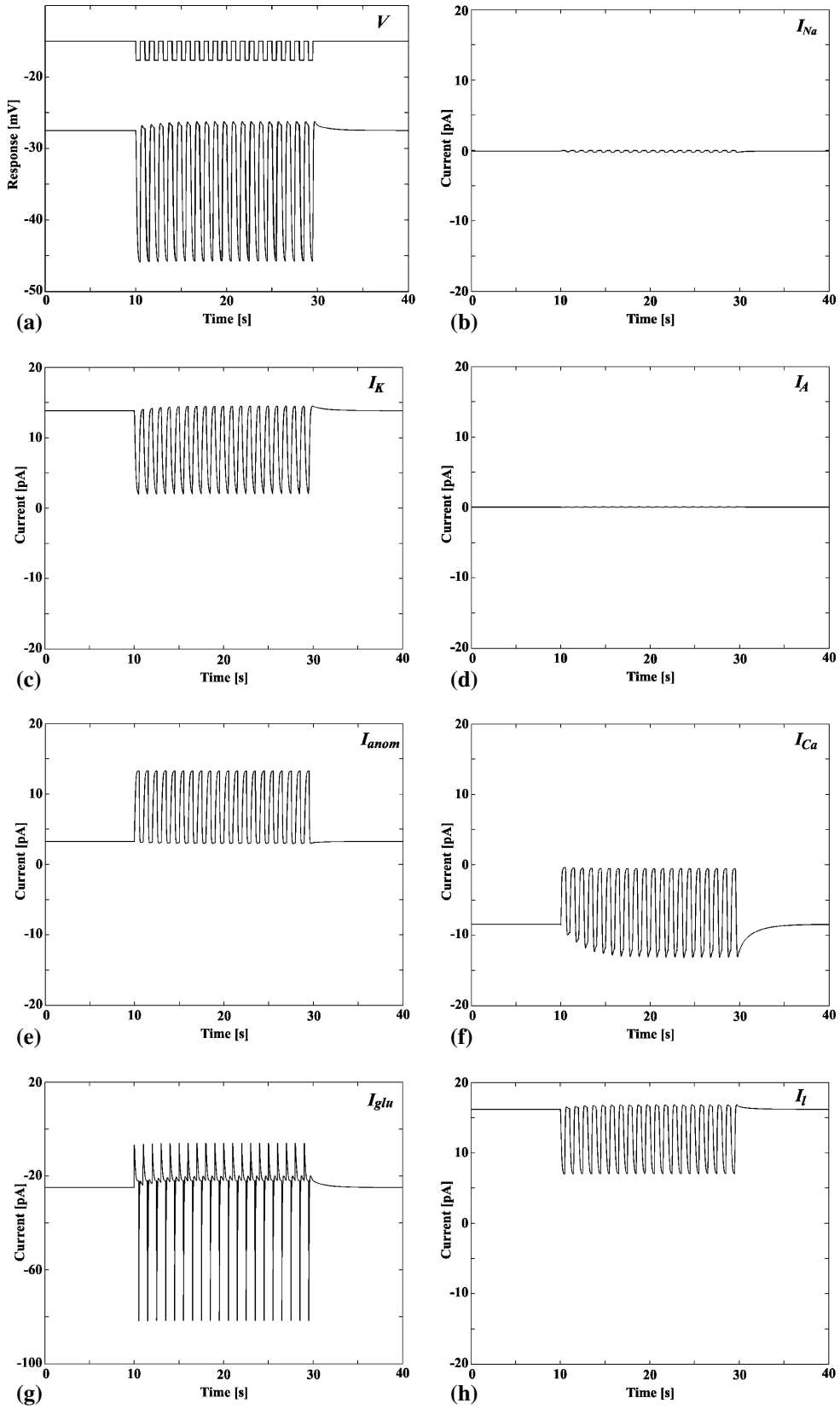

Fig. 2. The original H-H model's output to repetitive light stimulation. The model cell's input was defined as glutamate index, which was set at 1.0 in the dark and 0.27 during light stimulation, for simplicity. **a** LHC membrane potential response changes in exposure to repetitive stimulation (*upper panel*: glutamate index changes related to the repetitive light flashes, 1.0 and 0.27 for the higher and lower levels, respectively; *lower panel*: LHC's membrane potential changes). The model cell's response to flickering light was a sequence of membrane hyperpolarization with uniform amplitude. **b**–**h** The relevant changes of the model cell's single ionic currents (I_{Na},I_K,I_A,I_{anom},I_{Ca},I_{glu},I_l, in that order) occurred in response to the repetitive stimulation

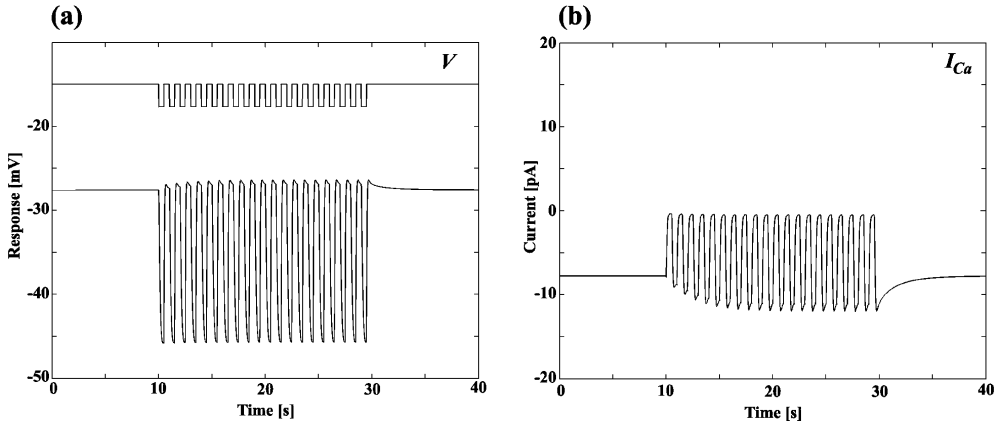

Fig. 3. The model cell's output to repetitive light flashes after incorporating an additional component for glutamate-dependent calcium influx. **a** The model cell's membrane potential changes in exposure to the repetitive stimulation. **b** The changes of the voltage-dependent calcium current during the period of repetitive stimulation. The changes in the voltage-dependent calcium current were trivial and could not induce the LHC's response amplitude enhancement

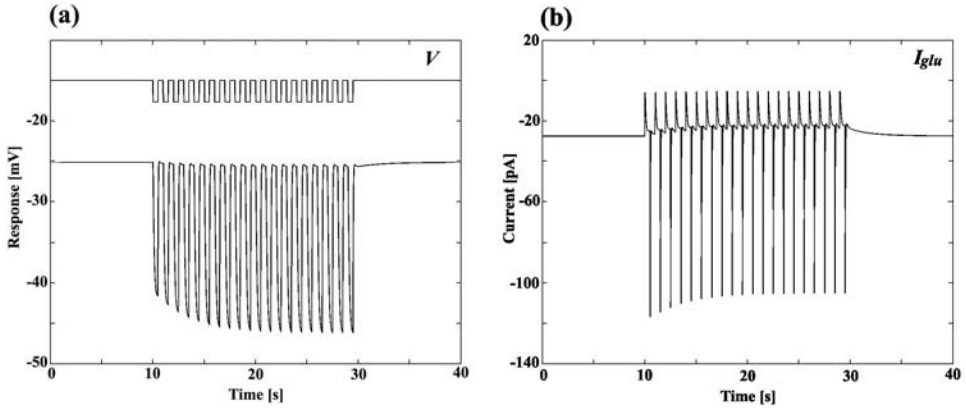

Fig. 4. Model cell's output to repetitive stimulation after introduction of a component related to the calcium-dependent modification effect on the single-channel conductance of AMPA receptors. **a** The model cell's response to the repetitive stimulation. **b** Changes of glutamate current during period of repetitive stimulation. It is shown that the model cell's response amplitude enhancement was closely related to the calcium-dependent modification of the glutamate current

synaptic strength was supposed to be directly related to the intracellular Ca^{2+} concentration (Liman et al. 1989; Shouval et al. 2002).

The changes of intracellular Ca^{2+} may directly act on the receptor-channel complex of the postsynaptic neuron. However, another possibility is that some second-messenger-mediated intracellular mechanisms are involved in the modification of receptor function or single-channel conductance of receptor via Ca^{2+}-dependent phosphorylation processes (Liman et al. 1989; McMahon et al. 1994; Derkach et al. 1999).

AMPA receptors mediate rapid synaptic transmission in the central nervous system. The activity and synaptic distribution of these receptors can be dynamically regulated under certain circumstances, and these changes are crucial for the modification of synaptic efficacy (for a review see Song and Huganir 2002). It has been reported that the activation of protein kinase and Ca^{2+}/calmodulin-kinase II (CaM-KII) can induce the phosphorylation of AMPA receptors, which should contribute to the postsynaptic mechanism for synaptic plasticity in many neurons (for reviews see Soderling 2000; Song and Huganir 2002).

4.3 Possible mechanism of repetitive-stimulus-induced response enhancement in LHC

Our experimental results revealed that the Ca^{2+} concentration changes in the postsynaptic neuron were crucial in the efficacy changes in the synapse between retinal photoreceptors and LHC. However, such Ca^{2+} concentration changes might influence the synaptic weight in a number of ways. One possibility is that Ca^{2+} can exert some direct regulatory effects on the voltage-dependent currents (Linn and Gafka 2001; Hayashida and Yagi 2002). Nevertheless, the calculation results of the model analysis suggested that this effect was trivial and could not explain the experimental observations.

Protein kinase and Ca^{2+}/CaM-KII-mediated phosphorylation of AMPA receptors could be achieved in other ways. Since the postsynaptic modification of AMPA receptor function is related to an increase in the number, open probability, and/or kinetics of the receptors, the modification of the single-channel properties of AMPA receptors via second-messenger-mediated phosphorylation provides a fundamental mechanism for the alteration of synaptic efficiency (Liman et al. 1989; McMahon et al.

1994; Schmidt 1996; Benke et al. 1998). However, previous reports suggested that PKC was not involved in the modulation of glutamate receptors in horizontal cells of fish retina (Schmidt 1996). On the other hand, our experimental results showed that the application of exogenous dopamine, which is believed to be linked to the PKA process in the teleost retinal horizontal cells (Liman et al. 1989; McMahon et al. 1994), exerted no effect on the LHC's response enhancement induced by repetitive stimulation (data not shown). This suggests that the PKA process might not be a candidate. Thus, our model simulation result might suggest that in the retinal neurons with graded potentials, the short-term modification of signal transmission between the retinal cone photoreceptors and LHC is likely to be attributed to the regulatory effects of Ca^{2+}/CaM-KII on single-channel properties of postsynaptic AMPA receptors.

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