Research Paper

Postsynaptic calcium pathway contributes to synaptic plasticity between retinal cones and luminosity-type horizontal cells

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Abstract: It was previously found that the efficacy of synaptic transmission between retinal cone systems and luminosity-type horizontal cells (LHCs) was activity-dependent. Repetitive activation of red-cone pathway increased the LHC's hyperpolarizing response to red light, and the response enhancement was reversible. In this study, intracellular recording and pharmacological method were applied to investigate the mechanism(s) underlying red-flickering-induced response enhancement. Lowering intracellular Ca^{2+} in the LHC by intracellular injection of Ca^{2+} chelator EGTA prevented the development of red-flickering-induced response enhancement, which implicates the importance of postsynaptic calcium signal. The response enhancement could also be eliminated by a potent antagonist of Ca^{2+}-permeable AMPA receptor (CP-AMPAR), which suggests the possibility that Ca^{2+} influx via glutamate-gated calcium channels is related to the changes of $[Ca^{2+}]_i$. Furthermore, the administration of ryanodine or caffeine also attenuated the phenomenon, which gives evidence that the local calcium signal caused by intracellular calcium-induced calcium release (CICR) may be involved. Taken together, our data implicate that postsynaptic CICR and CP-AMPAR are related to the activity-dependent response enhancement.

Key words: AMPA; calcium; neuronal plasticity; retina; ryanodine receptor/calcium release channel

突触后钙通路有助于视锥与 L 型水平细胞间的突触可塑性

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摘 要：我们实验室以前发现，视网膜视锥与亮度型水平细胞(luminosity-type horizontal cell, LHC)之间的突触传递效率具有可塑性。重复性刺激红敏视锥增加了 LHC 对红光的超极化反应幅度，而且这种增强作用是可逆的。在本文中，我们运用细胞内记录技术和药理学分析的方法来考察重复性红光刺激引起的反应增强的可能机制。当通过胞内注射 Ca^{2+} 的螯合剂 EGTA 来降低 LHC 内的 Ca^{2+} 浓度后，重复性红光引起的反应增强被抑制，提示突触后钙信号是反应增强的一个重要因素。另外，反应增强现象还可以被钙离子通透的 AMPA 受体(Ca^{2+}-permeable AMPA receptor, CP-AMPAR)的拮抗剂阻断，说明通过钙离子通透的谷氨酸受体内流的 Ca^{2+} 与胞内 Ca^{2+} 浓度的改变有关。进一步发现，胞外灌流 ryanodine 或 caffeine 也可以消除反应增强现象，说明由钙诱导的钙释放(calcium-induced calcium release, CICR)引起的钙信号可能也参与了反应增强现象的产生。结果提示，CICR 和 CP-AMPAR 与重复性红光刺激引起的 LHC 对红光的反应增强有关。

关键词：AMPA；钙离子；神经元可塑性；视网膜；ryanodine 受体 / 钙释放通道
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In the outer plexiform layer of the carp retina, luminosity-type horizontal cell (LHC) plays an important role in visual signal processing. It receives synaptic input from both red- and green-sensitive cones that tonically release *L*-glutamate during the dark. Light stimulus reduces the glutamate release and results in a hyperpolarization of the LHC's membrane[1]. Several reports have suggested that the LHC's light response can be regulated by the application of conditioning light. An increase of amplitude in turtle horizontal cell's light response could be induced by repetitive white light stimulation[2]. In goldfish retinal horizontal cells, a train of repetitive white flashes was able to change the cell's light response kinetics[3]. In this laboratory, it was previously found that repetitive activation of red-cone pathway progressively enhanced the LHC's responsiveness to red light, and the response recovered to its initial amplitude within 15 s after the repetitive stimulation had ceased[4]. These lines of evidence seem to suggest the existence of activity-dependent synaptic modification in the retinal graded neurons.

Postsynaptic calcium signaling is required for the induction of many forms of activity-dependent synaptic plasticity. It was reported that synaptic potentiation could be blocked by intracellular injection of Ca^{2+} chelator to the postsynaptic neuron[5]. Previous work indicated that postsynaptic calcium derived from calcium influx and calcium release from internal stores contributes to the activity-induced synaptic modification in hippocampus[6]. Morphological studies performed on teleost retinal horizontal cells also revealed that calcium signal is related to synaptic modifications and blocking calcium influx impairs the retraction of dendritic spinules induced by conditioning light[7].

It was reported that in the carp retina, horizontal cell expresses AMPA-preferring glutamate receptors[8], which can be further classified into Ca^{2+}-permeable and Ca^{2+}-impermeable subtypes[9,10]. Calcium can enter the horizontal cell through the Ca^{2+}-permeable AMPA channel[7,9,11-13], and such calcium signals can be amplified by ryanodine-sensitive intracellular calcium stores, which in turn display a phenomenon of calcium-induced calcium release (CICR)[12,14,15]. In teleost retina, cone horizontal cells contain ryanodine-sensitive intracellular calcium stores, which could generate CICR triggered by Ca^{2+} entering through the plasma membrane[13,16]. The present study aims to investigate possible mechanism(s) involved in the red-flickering-induced LHC's response enhancement, particularly the details of the following aspects: (1) what's the role of postsynaptic intracellular Ca^{2+} in the modulation of synaptic transmission between cones and LHCs, (2) whether or not calcium-permeable AMPA receptor (CP-AMPAR) is related to the phenomenon, and (3) whether CICR has any effect on such modulation of synaptic transmission.

1 MATERIALS AND METHODS

1.1 *Preparation*

Experimental procedures followed a previous study carried out in this laboratory[4,17]. The adult carp (*Carassius Auratus*, body length 15~20 cm) retina was used. All procedures strictly conformed to the humane treatment and use of animals as prescribed by the Association for Research in Vision and Ophthalmology, and all efforts were made to minimize the number of animals used and their suffering. Briefly, carp was maintained in aquarium under natural light/dark schedule. Experiments were conducted during daytime and the animal was kept in the dark for 20 min prior to experiment to allow for the isolation of the retina and avoid being completely dark-adapted. Under dim red light, the eye was enucleated and the retina was isolated carefully after the animal had been decapitated. Immediately, the retina was 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 1.0 ml/min. The normal Ringer solution contained (in mmol/L): NaCl 116.0, KCl 2.4, CaCl$_2$ 1.2, MgCl$_2$ 1.2, NaH$_2$PO$_4$ 1.0, NaHCO$_3$ 30.0 and glucose 10.0 with a pH value of 7.7 at room temperature.

1.2 *Light stimulation*

The stimuli were originated from high intensity light-emitting diodes (LEDs) with peak wavelengths at 703 nm and 518 nm (referred to as red and green light) respectively. The LED output parameters, including wavelength, intensity and time course of the light flash, were defined via a PC program. The light beam projected onto the retinal surface formed an 8-mm-diameter diffuse light spot through an optical system. 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, USA). All stimulus intensities will be presented in relative log units in this paper.

To study the effect of repetitive stimuli on the short-term modification of cone-LHC synapses, we applied 20 repetitive red (703 nm, log I = –0.19) flashes with the light-on duration of 500 ms at a rate of 1 Hz for establishing the response enhancement. Test flash applied in this study was the alternation of red light (703 nm, log I = –0.19)

and green light (518 nm, log $I = -1.02$) with a light-on duration of 500 ms and a light-off interval of 4 500 ms.

1.3 *Recording and data analysis*

The glass microelectrode was made by pulling a pipette on a microelectrode puller (PD-30, Narishige, Japan) and had a resistance around 100 MΩ when filled with 4 mol/L KAc and measured in Ringer solution. The LHCs' responses were recorded intracellularly using an amplifier system (MEZ-8300, Nihon Kohden, Japan) and monitored on an oscilloscope (TDS210, Tektronix, USA). The electrode signal was filtered at 300 Hz using a low pass filter. The data were digitized via an A/D interface (AD8111, Adlink Technology Inc., Taiwan, China) at a rate of 200 Hz and stored on an IBM-compatible PC for off-line analysis. LHCs were identified by their response characteristics to red and green test flashes and their relative depth in the tissue. Statistical data will be presented as the mean±SD in the text and means±SEM in figures. Student's *t*-test was performed for statistical analysis and statistical significance was accepted when $P<0.05$.

1.4 *Pharmacology*

To investigate the possible synaptic and/or cellular mechanism(s) of the stimulus-dependent modulation of synaptic transmission, the experiments were performed during normal Ringer perfusion and with administration of relevant chemicals. All chemicals [EGTA, synthetic joro spider toxin (JSTX-3), ryanodine and caffeine] applied were purchased from Sigma Ltd., St Louis, MO, USA. EGTA of 0.5 mol/L in 4 mol/L KAc was injected iontophoretically into the neuron being recorded via the recording electrode. A hyperpolarizing current within the range of 0.3~0.7 nA was applied, with light-on duration of 500 ms and frequency of 1 Hz for 10 min. Test flashes were applied to ensure that the electrode was still positioned in the same cell when waiting for the intracellular diffusion of the injected EGTA. Repetitive light stimulus was given 10 min later. The control experiments were conducted by injecting hyperpolarizing currents of similar intensity through an electrode filled with 4 mol/L KAc. JSTX-3, ryanodine and caffeine were dissolved in Ringer solution with the final concentration of 1 μmol/L[18,19], 5 μmol/L[20,21] and 10 mmol/L[22] respectively for extracellular applications.

2 RESULTS

2.1 Activity-dependent response enhancement

In the carp retina, the LHC receives inputs from both red- and green-sensitive cones. LHC's spectral sensitivity can

be effectively modified by particular patterns of light stimulation. The cell's light response enhancement was observed during the application of repetitive red flashes[4].

Figure 1*A* gives an example of the typical process of an LHC's response sequence to repetitive red flashes (with light-on duration of 500 ms and frequency of 1 Hz, lasting for 20 second). It was shown that the cell's response was enhanced gradually in exposure to the repetitive red flashes, from the initial value of 19.7 to 21.6 mV towards the end of the 20-second flickering period, with the relative response amplitude (normalized against the response amplitude evoked by the first flash of the stimulus sequence) being 110% (Fig.1*A*). The enhancement was reversible, and the LHC's response to the red flash recovered to the initial level within 18 s after the repetitive red flashes had ceased,
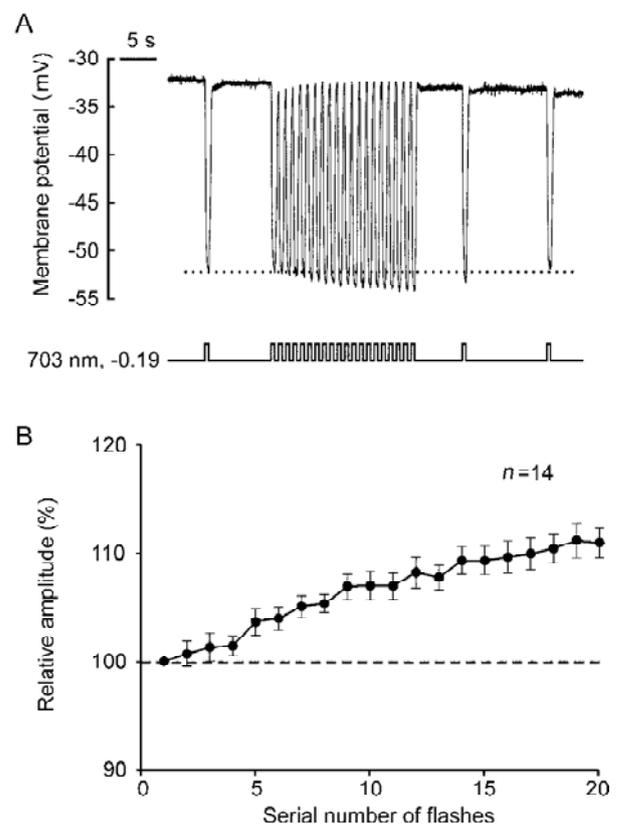

Fig. 1. Activity-dependent LHC's response enhancement. *A*: An LHC's light response to a red (703 nm, log $I = -0.19$) flickering sequence (upper panel: LHC's response; lower panel: light flash). The repetitive red flashes increased the cell's red response. The response amplitude gradually recovered to the initial level in about 17 s after the red flickering had ceased. The dotted line indicates the peak value of the light response evoked by the first flash of the repetitive stimuli. *B*: Averaged data from 14 LHCs' response amplitude (normalized against the response evoked by the first flash) measured during repetitive red flashes.

which was in agreement with the previous report by Hu *et al*[4]. Statistics was applied to a total number of 14 LHCs investigated. The cells' relative responsiveness amplitude measured during repetitive red flashes were given in Fig. 1*B*, which showed that the cells' response to the red flash was gradually increased during repetitive red flashes, and the relative response amplitude reached a final value (means±SEM) of (111±1.4)% at the end of the 20-second repetitive red-flash-stimulus period. The red responsiveness enhancement as a result of repetitive activation of red-cone pathway was significant ($P<0.05$, $n=14$, paired *t*-test).

2.2 Role of postsynaptic intracellular calcium signal

Calcium imaging experiments performed on the retinal slice and intact retina showed that $[Ca^{2+}]_i$ of the neurons changed following light stimulation[23,24]. Thus, it might be reasonable to speculate that $[Ca^{2+}]_i$ of the LHC fluctuated when the repetitive red flashes were applied to the retina. Since intracellular Ca^{2+} in postsynaptic neuron serves as a key regulatory factor for synaptic modification in the central nervous system[25], it is of interest to know whether or not the responsiveness enhancement elicited by repetitive red flashes in the LHC is related to the postsynaptic calcium signal. Therefore, we tried to keep the $[Ca^{2+}]_i$ at a low level by intracellular injection of EGTA into the LHC, so as to investigate this issue. Following the method introduced in the experimental procedures session, EGTA (0.5 mol/L) dissolved in 4 mol/L KAc was injected into the LHC through the recording microelectrode. Effect of EGTA on the LHC's response to repetitive red flashes was then compared to the control (injected with KAc). As illustrated in Fig.2*A*, in the control experiment, repetitive activation of red-cone pathway increased the LHC's red response from 22.6 to 25.1 mV, with the relative amplitude being 111%. In the EGTA-injected cells, red flickering-induced enhancement was remarkably attenuated, with the response increasing from 22.8 to 23.6 mV (measured at the beginning and towards the end of the red flash sequence, respectively) and the relative amplitude being 104%. Statistics was made in the normalized response amplitudes between the two groups (Fig.2*B*). The relative response amplitude measured at the end of the 20-second period in the EGTA-injected LHCs was (104± 0.8) % ($n=21$), which was significantly lower than that measured in the control cells [(109±1.7)%, $n =8$; $P<0.05$, unpaired *t*-test]. It thus seemed to suggest that the postsynaptic intracellular calcium signal may play an important role in the flickering-induced enhancement in
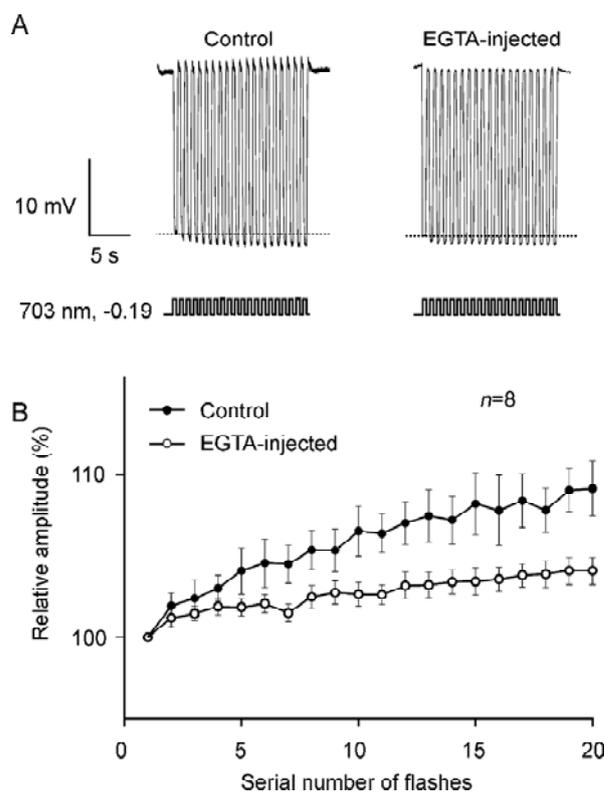

Fig. 2. Intracellularly injected EGTA inhibited the LHC's response enhancement. *A*: Intracellular injection of EGTA did not change the LHC's response to test flash, and the amplitude of light response elicited by the red flash was almost the same in EGTA-injected cell as in KAc-injected (control) cell. However, the activity-dependent reasponse enhancement was significantly attenuated after EGTA injection. The dotted lines indicate the peak value of the light response evoked by the first flash. *B*: Averaged data of the LHCs' response amplitude (normalized against the response evoked by the first flash) during the 20-second repetitive red flashes, recorded from 21 cells injected with EGTA (open circles) and 8 cells with KAc (filled circles).

the LHC's response to red light.

2.3 Effect of Ca^{2+} influx through AMPA type channels

In the carp retina, glutamate receptors located on the LHC's membrane are of AMPA type[7,8]. Previous work has shown that CP-AMPAR is located on horizontal cells[7,9]. To test the possibility that calcium influx through these channels contributed to the flickering-induced responsiveness enhancement, JSTX-3, which specifically blocked CP-AMPAR was applied. As illustrated in Fig.3*A*, in normal Ringer solution, the repetitive red flashes increased the amplitude of the LHC's response to red light from 20.3 to 22.8 mV, with the relative response amplitude being 112%. The extracellular application of 1 μmol/L JSTX-3 depolar-

ized the cell's resting membrane potential by about 9.9 mV. At the mean time, repetitive red flashes changed the cell's response amplitude from 24.7 to 24.5 mV, with the relative response amplitude being 99%. Statistics performed on 5 cells showed that, during JSTX-3 perfusion, the flickering-induced change of the LHC's response amplitude was negligible, with the end-flickering relative response amplitude being $(100\pm0.7)\%$, which was significantly different from that measured in normal Ringer solution $[(109\pm1.7)\%, n=5; P<0.05$, paired *t*-test, Fig.3*B*]. This result suggested that CP-AMPAR should be involved in the response enhancement induced by repetitive red flashes.

2.4 Effect of intracellular CICR

It has been reported that CICR may be involved in the induction of synaptic modification[6,15], and cone-driven

horizontal cells contain ryanodine-sensitive intracellular calcium stores[13]. Ryanodine at a concentration of 5 µmol/L was thus used to test the potential role of CICR in the flickering-induced response enhancement. As illustrated in Fig.4*A*, the extracellular application of ryanodine hyperpolarized the cell's resting membrane potential by about 5.3 mV. Repetitive red flashes did not change this LHC's response to red flash (from 7.8 to 7.7 mV, with a relative response amplitude being 99%) during the drug application, which was different from that in normal Ringer solution (10. 5 *vs* 11.3 mV, with the relative amplitude being 108%). The statistical result showed a significant difference, with the relative response amplitude being $(98\pm3.3)\%$ during the application of ryanodine and $(110\pm2.3)\%$ in normal Ringer solution $(n=6, P<0.05$, paired *t*-test, Fig.4*B*), respectively. This result suggested that CICR from ryanodine-sensitive calcium stores was an important factor in the flickering-induced enhancement of LHC's re-
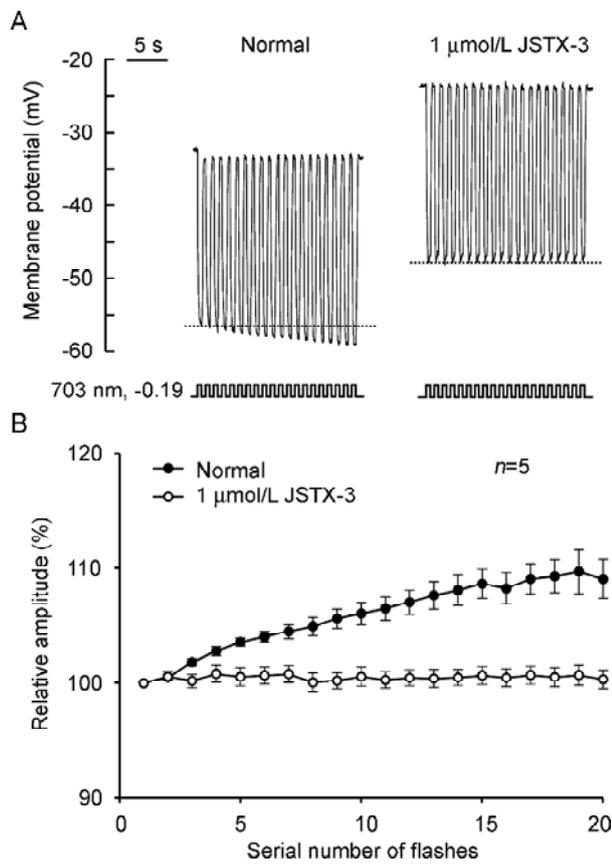

Fig. 3. Perfusing JSTX-3 inhibited the LHC's response enhancement. *A*: The application of JSTX-3 depolarized the LHC's dark membrane potential and slightly increased the amplitude of the cell's response to red test flash. However, the activity-dependent light response enhancement was eliminated during JSTX-3 perfusion. The dotted lines indicate the peak value of the cell's light response evoked by the first flash. *B*: Averaged data of the LHCs' response amplitude changes (normalized against the response evoked by the first flash) in exposure to the 20-second repetitive red flashes, recorded during the JSTX-3 (open circles) and normal Ringer's perfusions (filled circles).
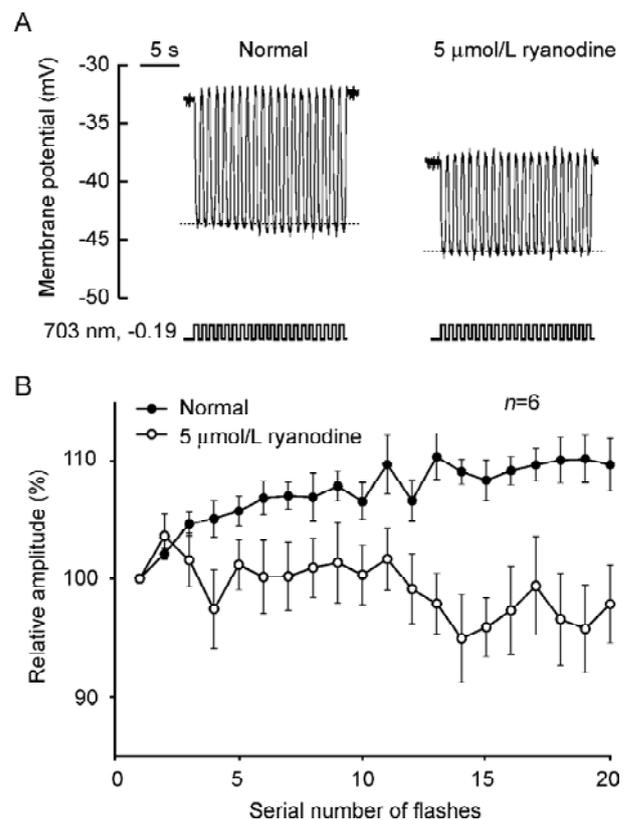

Fig. 4. Effect of ryanodine on the LHC's response enhancement. *A*: Light response to repetitive red flashes before and after the application of ryanodine in a typical LHC. The dotted lines indicate the peak value of the light response evoked by the first flash. *B*: Averaged data of the LHCs' response amplitude (normalized against the response evoked by the first flash) during the 20-second repetitive red flashes, recorded from the cells superfused with 5 µmol/L ryanodine (open circles) and normal Ringer solution (filled circles).

sponse to red flash.

CICR can also be abolished when the intracellular calcium stores were depleted by caffeine[13,16]. Therefore, caffeine was extracellularly applied to confirm the role of CICR in the flickering-induced response enhancement in the LHC. The application of caffeine (10 mmol/L) hyperpolarized the LHC's dark resting membrane potential. When the resting membrane potential was hyperpolarized to a steady level during the continued application of caffeine, repetitive red flashes were applied to activate the red-cone pathway. As a result, the flickering light changed the cell's response amplitude from 5.0 to 4.8 mV, with relative response amplitude being 96%, which was remarkably lower than that measured in normal Ringer solution (12.1 *vs* 13.1 mV, with relative response amplitude being 108%) (Fig. 5*A*). Statistics were made on 5 cells investigated. The relative response amplitude was measured as (97±1.6)% at
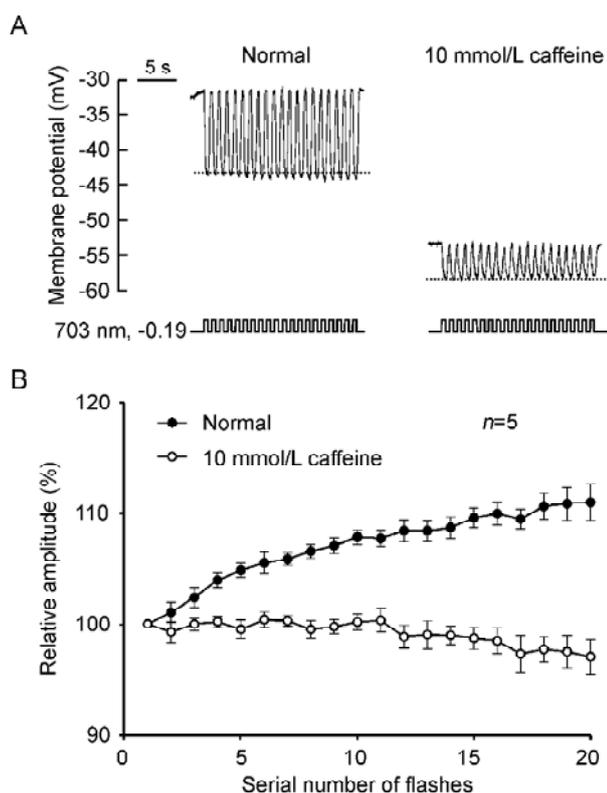

Fig. 5. Effect of extracellularly applied caffeine on the LHC's response enhancement. *A*: An LHC's light response to repetitive red flashes measured during normal Ringer perfusion and during continuous caffeine application. The dotted lines indicate the peak value of the cell's light response evoked by the first flash. *B*: Averaged data of the LHCs' response amplitude (normalized against the response evoked by the first flash) during 20-second repetitive red flashes, recorded from the cells perfused with 10 mmol/L caffeine (open circles) and normal Ringer solution (filled circles).

the end of the red flash sequence during continuous caffeine perfusion, which was significantly different from that measured in normal Ringer solution [(111±1.6)%, *P*<0.05, paired *t*-test, Fig.5*B*]. This result also confirmed that CICR was involved in the development of activity-dependent response enhancement in the LHC.

3 DISCUSSION

In this study we showed that the LHC's response to red light was progressively increased during repetitive red-flash stimulation. Such modulation of synaptic transmission was effectively eliminated when postsynaptic intracellular calcium pathways were disrupted, which suggests that postsynaptic calcium was an important factor in the visual activity-dependent response enhancement of LHCs.

During the repetitive red flash stimulation, following repetitive hyperpolarization of the membrane potential, $[Ca^{2+}]_i$ in the LHC fluctuated within a certain range. EGTA lowered the level of $[Ca^{2+}]_i$ and inhibited the change of $[Ca^{2+}]_i$ in the LHC when the retina was in exposure to the repetitive stimuli. However, the cells injected with EGTA still showed red-flickering-induced response enhancement to some extent. The explanation might be that EGTA chelates calcium with a slow dynamics so that it may not be effective enough to inhibit the rapid change of intracellular calcium during the repetitive red flash stimulation.

Two calcium pathway contributed to the change of $[Ca^{2+}]_i$. One is the calcium influx from the extracellular environment. The other is the calcium release from the inner calcium store with CICR.

Four AMPA receptor subunits (GluR1-4) have been identified via molecular cloning. The AMPA receptors lacking of GluR2 subunit are highly permeable to calcium ions[10]. CP-AMPAR and CIP-AMPAR (calcium-impermeable AMPA receptor) co-exist on horizontal cells[9]. Consistently, the observation made in this study was that while JSTX-3 partly inhibited the horizontal cell's response to light stimulation, it completely blocked the flickering-induced response enhancement. This seems to support the notion that calcium influx through CP-AMPAR is an important factor for the fluctuation of $[Ca^{2+}]_i$.

It is unexpected that in our experiment, the application of JSTX-3 did not hyperpolarize the horizontal cells but rather depolarized it. The explanation might involve several aspects. One is that the proportion of calcium current through CP-AMPAR is small as compared to the total glutamate-gated cationic current, which was previously proposed by Hayashida and Yagi[22], and was confirmed by

our result given in Fig.3. As for the cell's membrane potential, the contribution of CP-AMPAR is trivial as compared to that of the other channels. Inhibition of CP-AMPAR would result in a mild reduction of the calcium influx from extracellular environment. However, it would induce a subsequent inhibition of the cell's secondary calcium process, such as CICR from the inner store. On the other hand, one important thing in the nervous system is that changes of $[Ca^{2+}]_i$ is linked to a number of events that modulate membrane excitability and cellular function[26,27]. In isolated horizontal cells, it has been demonstrated that glutamate application could keep $[Ca^{2+}]_i$ at a high level which was accompanied by a voltage-gated Ca^{2+} conductance inactivation[11]. Lowering $[Ca^{2+}]_i$ would relieve the inhibitory effect that $[Ca^{2+}]_i$ exerts on the voltage-gated Ca^{2+} channels, which in turn results in a depolarization of the membrane potential. Taken together, these factors may affect the membrane potential of LHC during the application of JSTX-3.

CICR is an amplification process related to the release of calcium from intracellular calcium stores when calcium enters across the plasma membrane and activates the calcium-sensitive receptors located on the membrane of intracellular calcium stores[14]. Horizontal cells in the teleost retina contain ryanodine-sensitive intracellular calcium stores[13]. Application of exogenous ryanodine causes the inhibition of CICR[13,20,21]. In our experiments, the application of ryanodine effectively eliminated the flickering-induced response enhancement, suggesting that ryanodine-sensitive calcium store is crucial to the modulation of synaptic transmission.

Caffeine can deplete the ryanodine-sensitive calcium store[14,28,29]. In our result, continuous extracellular application of 10 mmol/L caffeine effectively eliminated the flickering-induced response enhancement. The effect was similar to that resulted from ryanodine application, which confirms the notion that CICR from ryanodine-sensitive calcium store contributes to the modulation of synaptic transmission.

One argument is that in the retina, ryanodine/caffeine sensitive stores are located in both photoreceptors and horizontal cells. Since ryanodine/caffeine was extracellularly applied to the tissue via perfusion in our experiment, it might also act on the presynaptic photoreceptors to change the transmitter release, and thus change the activity of the postsynaptic horizontal cells. It has been reported by Krizaj and his coworkers that in retinal photoreceptors, extracellularly applied ryanodine had no effect on glutamate release[30], which seems to suggest that the ryanodine mechanism might be attributed to its effect on the postsynaptic

horizontal cells. However, presynaptic mechanism can not be entirely excluded since Krizaj *et al*. did not test ryanodine effect on the glutamate release in exposure to repeated stimuli. Thus, whether presynapse contributes partially to response enhancement is still an open question.

In summary, during repetitive activation of red-cone pathway, calcium flux into horizontal cells waved in the light-on and light-off periods. This calcium signal was amplified by CICR from ryanodine-sensitive intracellular calcium stores. A possible consequence of the fluctuation of intracellular Ca^{2+} concentration is a direct action of Ca^{2+} on the receptor-channel complex and/or initiation of second-messenger-mediated intracellular processes that modify the functioning of ion channels by phosphorylating or dephosphorylating them[13,31,32]. These might help explain the possible mechanism related to our observation of the activity-dependent response enhancement in LHCs.

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