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Modeling the pre- and post-synaptic components involved in the synaptic modification between cones and horizontal cells in carp retina

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Abstract In retinal synapses between cones and luminosity type horizontal cells (LHC), it was previously found in this laboratory that repetitive red flashes progressively strengthened the LHC's response to red flash, whereas weakened the LHC's response to green flash; repetitive green flash remarkably depressed the LHC's red response, but caused little changes in the cell's green response. However, the detailed mechanisms underlying these phenomena are not entirely clear. In the present study, based on an ion-channel model described mainly in the form of Hodgkin–Huxley equations, possible mechanisms of the short-term synaptic modification are investigated. The simulation results suggest that: (1) the auto-enhancement effect might be induced by the Ca^{2+}-dependent process on the post-synaptic AMPA receptors, which could lead to changes of the ionic channel's properties; (2) the asymmetric response to red- and green-flashes and the mutual-chromatic suppression effects might be attributed to the regulatory effects on the presynaptic glutamate release.

1 Introduction

It has been widely accepted that activity-dependent synaptic modification is fundamental to information processing and storage in the central nervous system (Miller 1996; Abraham and Bear 1996). In the carp retina, the activity of the luminosity-type cone-driven horizontal cell (LHC) is dependent on the recent and present activity status of the relevant neurons. The stimulus-pattern-related synaptic modification has also been observed in this laboratory in the LHC of isolated carp retina. Intracellular recordings made from isolated carp retinal LHC showed that repetitive red flashes progressively strengthened the LHC's response to red flash, whereas weakened the LHC's response to green flash; on the other hand, repetitive green flashes could also remarkably depress the LHC's red response, but caused little changes in the cell's green response (Hu et al. 2000). The different impacts between repetitive red and green flashes showed that the modification of synaptic efficacy between the cone systems and LHC of carp retina was closely related to the spectral configuration of the stimulation.

Calcium plays an important role in the induction of synaptic plasticity in the central nervous system (for a review see Linden 1999). Previous work carried out in this laboratory also suggested that the concentration of the intracellular Ca^{2+} might play a crucial role in the response enhancement induced by repetitive red light, with an assumption that the properties of AMPA-sensitive glutamate receptors in carp retinal horizontal cells could be regulated by Ca^{2+}-dependent phosphorylation process (Jin et al. 2004).

However, the mechanism underlying the mutual-chromatic depression effects still remains unclear. It has been reported that glutamate release from photoreceptors could be regulated by a number of factors, such as mGluRs-mediated suppression from neighboring cone-LHC pathways (Anwyl 1999; Mitchell and Silver 2000; Awatramani and Slaughter 2001; Luo and Liang 2003) and hemichannel-mediated feedback from postsynaptic LHC (Kamermans et al. 2001a,b). In the present study,

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these processes related to the modification of presynaptic glutamate release are introduced into an extended model to explain the mutual depression properties.

2 Models

2.1 Experimental results

The experimental recordings were made from LHC of adult carp (*Carassius auratus*, body length 15–20 cm) retina. The experimental procedures and observations were both reported in a previous paper (Hu et al. 2000). The stimulus-pattern-related response enhancement and depression results are plotted in Fig. 1 (see also Hu et al. 2000; Fig. 1), which gives an example of the LHC's response to red and green test light after a sequence of repetitive red or green flashes. It is clearly shown in Fig. 1 that repetitive red (703 nm) flashes (1 Hz, light-on duration 500 ms, 20 repeats) progressively enhanced the LHC's response to red test light, whereas depressed the cell's response to green test flash; on the other hand, repetitive green (501 nm) flashes (1 Hz, light-on duration 500 ms, 20 repeats) only caused little change of the cell's response to green test light, but also remarkably depressed the cell's response to red test light.

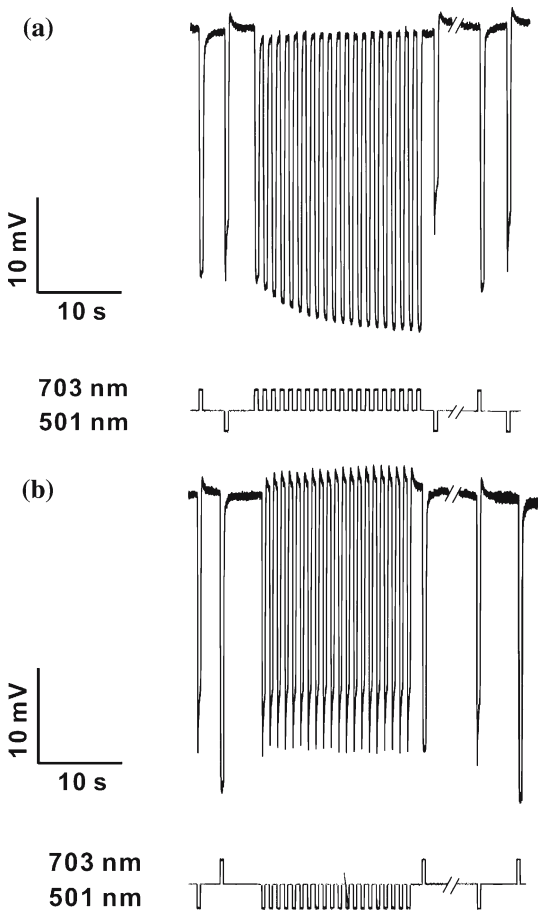

Fig. 1 LHC's responsiveness changes reported by Hu et al. (2000). **a** LHC's light response before, during and after a red flicking sequence (*upper panel* LHC's response; *lower panel* light flash). **b**. LHC's light response before, during and after a green flicking sequence (*upper panel* LHC's response; *lowerpanel* light flash)

2.2 Hodgkin–Huxley model description

The membrane potential of the LHC, which changes in response to light stimuli, is closely related to the voltage-dependent and ligand-gated ionic currents in the soma (Tachibana 1983; Usui et al. 1996), and can be equated reasonably using Hodgkin–Huxley model (Hodgkin and Huxley 1952):

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

where V and C_s represent the membrane potential and the membrane capacitance, respectively. I_j is the current passing through the j-th channel, which is dependent on both membrane potential V and the conductance of the relevant channel, and can be described as follows:

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

where g_j represents the conductance of the j-th channel with $\bar{g}_j$ being its maximal value; E_j denotes the equilibrium membrane potential of the j-th channel; m and h represent the activation and inactivation variables of the channel, respectively; p and q are positive integers determining the activation and inactivation dynamical properties. Since the total membrane current consists of several components, the H–H equation can thus be reorganized as

$$C_s \frac{\mathrm{d}V}{\mathrm{d}t} + (I_{\mathrm{Na}} + I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_{\mathrm{A}} + I_{\mathrm{anom}} + I_{\mathrm{glu}} + I_l) = 0 \tag{3}$$

where $I_{\mathrm{Na}}, I_{\mathrm{Ca}}, I_{\mathrm{K}}, I_{\mathrm{A}}, I_{\mathrm{anom}}, I_{\mathrm{glu}}, I_l$ are Na^+ current, Ca^{2+} current, delay time rectifying K^+ current, outward rectifying K^+ current, anomalous rectifying K^+ current, glutamate-receptor-mediated current and leak current, respectively. The detailed description for $I_{\mathrm{Na}}, I_{\mathrm{K}}$, $I_{\mathrm{A}}, I_{\mathrm{anom}}$ and I_l are following that forwarded by Usui et al. (1996).

Na^+ current

$$\begin{aligned}
&\alpha_{m\mathrm{Na}} = \frac{40\cdot(80-V)}{\exp\left(\frac{80-V}{15}\right)-1}\\
&\beta_{m\mathrm{Na}} = 10\cdot\exp\left(-\frac{V}{20}\right)\\
&\frac{\mathrm{d}m_{\mathrm{Na}}}{\mathrm{d}t} = \alpha_{m\mathrm{Na}}\cdot(1-m_{\mathrm{Na}}) - \beta_{m\mathrm{Na}}\cdot m_{\mathrm{Na}}\\
&\alpha_{h\mathrm{Na}} = 0.01\cdot\exp\left(-\frac{V}{30}\right)\\
&\beta_{h\mathrm{Na}} = \frac{2}{\exp\left(\frac{70-V}{10}\right)+1}\\
&\frac{\mathrm{d}h_{\mathrm{Na}}}{\mathrm{d}t} = \alpha_{h\mathrm{Na}}\cdot(1-h_{\mathrm{Na}}) - \beta_{h\mathrm{Na}}\cdot h_{\mathrm{Na}}\\
&\bar{g}_{\mathrm{Na}} = 120\,\mathrm{nS}\\
&E_{\mathrm{Na}} = 55\,\mathrm{mV}\\
&I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}\cdot m_{\mathrm{Na}}^3\cdot h_{\mathrm{Na}}\cdot(V-E_{\mathrm{Na}})
\end{aligned} \tag{4}$$

Delay time rectifying K^+ current

$$\begin{aligned}
&\alpha_{m\mathrm{K}} = \frac{10\cdot(120-V_{\mathrm{K}})}{\exp\left(\frac{120-V_{\mathrm{K}}}{20}\right)-1}\\
&\beta_{m\mathrm{K}} = 5\cdot\exp\left(-\frac{V_{\mathrm{K}}}{20}\right)\\
&\frac{\mathrm{d}m_{\mathrm{K}}}{\mathrm{d}t} = \alpha_{m\mathrm{K}}\cdot(1-m_{\mathrm{K}}) - \beta_{m\mathrm{K}}\cdot m_{\mathrm{K}}\\
&\bar{g}_{\mathrm{K}} = 0.25\,\mathrm{nS}\\
&E_{\mathrm{K}} = -60\,\mathrm{mV}\\
&V_{\mathrm{K}} = V - E_{\mathrm{K}}\\
&I_{\mathrm{K}} = \bar{g}_{\mathrm{K}}\cdot m_{\mathrm{K}}^4\cdot V_{\mathrm{K}}
\end{aligned} \tag{5}$$

Outward rectifying K^+ current

$$\begin{aligned}
&\alpha_{m\mathrm{A}} = \frac{40\cdot(140-V_{\mathrm{K}})}{\exp\left(\frac{140-V_{\mathrm{K}}}{15}\right)-1}\\
&\beta_{m\mathrm{A}} = 8\cdot\exp\left(-\frac{V_{\mathrm{K}}}{20}\right)\\
&m_{\mathrm{A}} = \frac{\alpha_{m\mathrm{A}}}{\alpha_{m\mathrm{A}}+\beta_{m\mathrm{A}}}\\
&\alpha_{h\mathrm{A}} = 0.01\cdot\exp\left(-\frac{V_{\mathrm{K}}}{20}\right)\\
&\beta_{h\mathrm{A}} = \frac{2}{\exp\left(\frac{30-V_{\mathrm{K}}}{10}\right)+1}\\
&\frac{\mathrm{d}h_{\mathrm{A}}}{\mathrm{d}t} = \alpha_{h\mathrm{A}}(1-h_{\mathrm{A}}) - \beta_{h\mathrm{A}}\cdot h_{\mathrm{A}}\\
&\bar{g}_{\mathrm{A}} = 2\,\mathrm{nS}\\
&E_{\mathrm{K}} = -60\,\mathrm{mV}\\
&V_{\mathrm{K}} = V - E_{\mathrm{K}}\\
&I_{\mathrm{A}} = \bar{g}_{\mathrm{A}}\cdot m_{\mathrm{A}}^3\cdot h_{\mathrm{A}}\cdot V_{\mathrm{K}}
\end{aligned} \tag{6}$$

Anomalous rectifying K^+ current

$$\begin{aligned}
&m_{\mathrm{anom}} = \frac{1}{1+\exp\left(\frac{V_{\mathrm{K}}}{30}\right)}\\
&\bar{g}_{\mathrm{anom}} = 50\cdot[1-0.5\cdot\mathrm{Glu}(t)]\quad(\mathrm{nS})\\
&V_{\mathrm{K}} = V - E_K\\
&E_{\mathrm{K}} = -60\,\mathrm{mV}\\
&I_{\mathrm{anom}} = \bar{g}_{\mathrm{anom}}\cdot m_{\mathrm{anom}}^4\cdot V_{\mathrm{K}}
\end{aligned} \tag{7}$$

Leak current

$$\begin{aligned}
&g_l = 0.5\,\mathrm{nS}\\
&E_l = -60\,\mathrm{mV}\\
&I_l = g_l\cdot(V-E_l)
\end{aligned} \tag{8}$$

2.3 The Ca^{2+}-dependent processes

In carp retina, the Ca^{2+} current is much more complicated than other voltage-dependent ion current, this is because the intracellular Ca^{2+} concentration can be regulated by a number of factors. In addition to the influx via voltage-dependent Ca^{2+}channel and efflux via Ca^{2+} transporters, Ca^{2+} influx can occur via Ca^{2+}-permeable AMPA receptors on the membrane (Okada et al. 1999; Huang et al. 2004; Huang and Liang 2005). The Ca^{2+} current is then described in the following manner:

Ca^{2+} current

$$\begin{aligned}
&\alpha_{m\mathrm{Ca}} = \frac{5\cdot(70-V)}{\exp\left(\frac{70-V}{28}\right)-1}\\
&\beta_{m\mathrm{Ca}} = 2\cdot\exp\left(-\frac{V}{15}\right)\\
&\frac{\mathrm{d}m_{\mathrm{Ca}}}{\mathrm{d}t} = \alpha_{m\mathrm{Ca}}\cdot(1-m_{\mathrm{Ca}}) - \beta_{m\mathrm{Ca}}\cdot m_{\mathrm{Ca}}\\
&h_{\mathrm{Ca}} = \frac{\mathrm{K}}{\mathrm{K}+[\mathrm{Ca}^{2+}]_i}\\
&\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_i}{\mathrm{d}t} = \frac{-(I_{\mathrm{Ca}}+0.01\cdot I_{\mathrm{glu}})}{2\cdot F\cdot v} + \frac{[\mathrm{Ca}^{2+}]_{\mathrm{eq}}-[\mathrm{Ca}^{2+}]_i}{\tau_{\mathrm{trans}}}\\
&K = 0.002\,\mathrm{mM}\\
&\tau_{\mathrm{trans}} = 2\cdot\exp\left(\frac{V}{60}\right)\\
&v = 10^{-15}\,m^3\\
&F = 9.65\times10^4\,\mathrm{C/mol}\\
&\bar{g}_{\mathrm{Ca}} = 135\,\mathrm{nS}\\
&E_{\mathrm{Ca}} = 12.5\cdot\log\left(\frac{[\mathrm{Ca}^{2+}]_0}{[\mathrm{Ca}^{2+}]_i}\right)\quad(\mathrm{mV})\\
&\left[\mathrm{Ca}^{2+}\right]_o = 4\,\mathrm{mM}\\
&\left[\mathrm{Ca}^{2+}\right]_{\mathrm{eq}} = 0.05\,\mathrm{mM}\\
&I_{\mathrm{Ca}} = \bar{g}_{\mathrm{Ca}}\cdot h_{\mathrm{Ca}}\cdot m_{\mathrm{Ca}}^3\cdot(V-E_{\mathrm{Ca}})
\end{aligned} \tag{9}$$

It has been suggested that the properties of AMPA-sensitive glutamate receptor on LHC of carp retina could be regulated by Ca^{2+}-dependent phosphorylation processes (Mammen et al. 1997), the conductance of the glutamate-mediated current was therefore suggested to be related to the intracellular Ca^{2+} concentration in a previous model (Jin et al. 2004), and the enhancement of LHC's response in exposure to repetitive red flashes could be satisfactorily described. Therefore, the glutamate- receptor-mediated current can be equated as follows:

Glutamate-receptor-mediated current

$$\begin{aligned}
&I_{\mathrm{glu}} = 600\cdot\mathrm{Glu}\,(t)\cdot f\left(V,[\mathrm{Ca}^{2+}]\right)\\
&f\left(V,[\mathrm{Ca}^{2+}]_i\right) = 11\cdot[\mathrm{Ca}^{2+}]_i\cdot\frac{\exp\left(\frac{V+15}{95}\right)-1}{\exp\left(\frac{3-V}{125}\right)+1}
\end{aligned} \tag{10}$$

Following this model, the simulated changes in the membrane potential during the 20 s flicking can be computed and the LHC's responsiveness changes during this period are plotted in Fig. 2 (see also Jin et al. 2004; Fig. 4).

However, this simple model involving post-synaptic Ca^{2+}-dependent mechanism is not able to describe those aspects such as the LHC's response behavior during the application of repetitive green flashes and

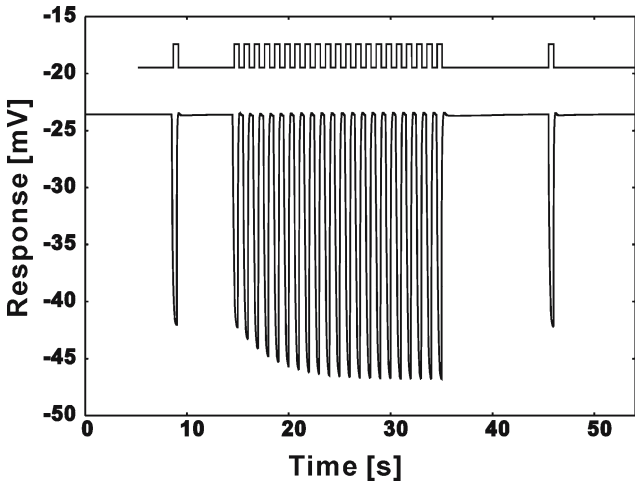

Fig. 2 Simulated result of LHC's responsiveness changes during the 20 s red flickering following the model forwarded by Jin et al. (2004)

the mutual-chromatic depression effect revealed in experimental recordings as illustrated in Fig. 1 (Hu et al. 2000, 2003).

2.4 The modulatory effect of the presynaptic glutamate transmitter release

2.4.1 Biological evidence

The status of presynaptic photoreceptors can be affected by a number of factors which in turn modulate glutamate release. Some lines of evidence suggested that metabotropic glutamate receptors (mGluRs) located on the presynaptic terminals are important in modulating the synaptic transmission (Anwyl 1999). Activation of mGluRs as autoreceptor may depress presynaptic release, and result in some negative regulation in synaptic signal transferring (Awatramani and Slaughter 2001). Photoreceptors of carp retina express mGluRs that located on the presynaptic terminals. In the dark, excessive amount of glutamate released from retinal cones may spill over and diffuse from the synaptic cleft and then activate the presynaptic mGluRs at the adjacent cones (Mitchell and Silver 2000; Luo and Liang 2003), which should result in a suppression of glutamate release. However, this local feedback pathway may be weakened when the retina is exposed to light stimulation (Luo and Liang 2003).

On the other hand, some previous work also suggested an electrical feedback pathway from HC to photoreceptors which is mediated by hemichannel (Kamermans et al. 2001a,b). In that model, hyperpolarization of HCs shifts the presynaptic Ca^{2+} current to a more negative potential, which in turn increases the Ca^{2+} influx and subsequently leads to an increase in glutamate release. A schematic model including mGluRs- and hemichannel-mediated local feedback processes which regulate the presynaptic glutamate release is presented in Fig. 3.

2.4.2 Model description

Since LHC receives glutamatergic inputs from both red- and green-sensitive cones, the glutamate-receptor-mediated current on LHC can then be separated into two parts based on Eq. (10), with each unit mediated by red- or green-sensitive cone system, respectively:

$$\begin{aligned} I_{\text{glu}} &= I_{\text{Red}} + I_{\text{Green}} \\ I_{\text{Red}} &= \bar{g}_{\text{glu}} \cdot \text{Glu}_{\text{R}}(t) \cdot f\left(V, [\text{Ca}^{2+}]_i\right) \\ I_{\text{Green}} &= \bar{g}_{\text{glu}} \cdot \text{Glu}_{\text{G}}(t) \cdot f\left(V, [Ca^{2+}]_i\right) \end{aligned} \tag{11}$$

where $\text{Glu}_{\text{R}}(t)$ and $\text{Glu}_{\text{G}}(t)$ stand for the amount of glutamate released by the red- and green-sensitive cones, respectively. Based on the stimulation-induced regulatory effects on presynaptic glutamate release, $\text{Glu}_{\text{R}}(t)$ and $\text{Glu}_{\text{G}}(t)$ can be described as follows:

$$\begin{aligned} \text{Glu}_{\text{R}}(t) &= 0.5 \cdot (1 - \xi_{\text{R}} + \xi_{\text{R}} \cdot K_{\text{R}}) \\ \text{Glu}_{\text{G}}(t) &= 0.5 \cdot (1 - \xi_{\text{G}} + \xi_{\text{G}} \cdot K_{\text{G}}) \end{aligned} \tag{12}$$

where, ξ_{R} and ξ_{G} represent the reduction of the glutamate amount released by red- and green-sensitive cones, respectively, when light is applied; K_{R} and K_{G} represent the presynaptic regulatory effects on red- and green-sensitive cones, respectively.

In carp retina, LHC receives excitatory glutamatergic inputs from both red- and green-sensitive cone photoreceptors which continuously release glutamate in the dark and induce a depolarization of the LHC (Yang et al. 1983; Kamermans et al. 1989). Light hyperpolarizes the photoreceptors and reduces their glutamate release, which results in a hyperpolarizing response in LHC (Copenhagen and Jahr 1989). It is revealed by Fig. 1 that the dark membrane potential of the LHC did not change much during the application of repetitive light flashes. In Eq. (12), ξ_{R} and ξ_{G} are therefore set as 0 in the dark, and positive values between 0 and 1 are chosen for these parameters during exposure to light flash. This means that the presynaptic regulatory effects on glutamate release are only taken into account during light stimulation, but not in the dark. Here, we assume that the amount of glutamate released by presynaptic cones in the dark is large enough, and the presynaptic regulatory effect is very small as compared to the base level and is therefore ignorable in the dark.

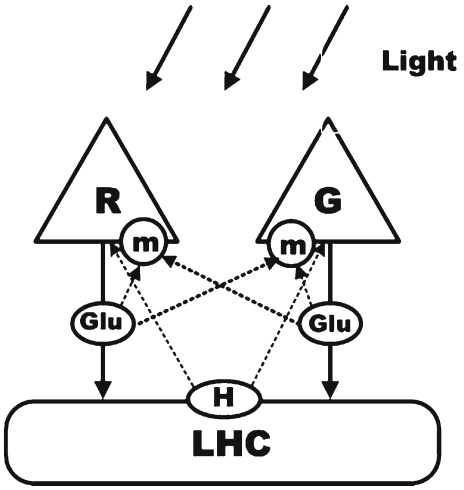

Fig. 3 A simple model describing the feed-forward and feedback pathways between retinal cones and horizontal cell. *R* and *G* stand for red- and green-sensitive cones, respectively; *LHC* is the luminosity-type horizontal cell; *m* represents the metabotropic glutamate receptors; *H* stands for hemichannel on LHC; *Glu* is the glutamate transmitter released by the cones

The mGluRs-mediated presynaptic effect between red- and green-sensitive pathways is closely related to the glutamate transmitter concentration in synaptic cleft while the hemichannel-mediated feedback from LHC to cone is dependent on the hyperpolarization of the postsynaptic LHC. In both cases, the presynaptic regulatory effects on glutamate release are positively related to the reduction of glutamate amount (ξ) in the relevant pathway. In the present model, this process is described as $\xi \cdot K$ in Eq. (12) with K being dynamically changing as follows:

$$\begin{aligned} \frac{dK_R}{dt} &= \eta_R \cdot \exp(-T/\tau_A) \\ \frac{dK_G}{dt} &= \eta_G \cdot \exp(-T/\tau_A) \end{aligned} \tag{13}$$

It is revealed by Fig. 1 that the LHC's response was recovered in a few seconds time after the repetitive flashes had ceased. This gives some evidence that the mechanism underlying the modulation of the LHC's response during repetitive flashes is not enduring. This property is further described in the recovery processes (14) in the present model. A time constant (τ_B) is chosen for this process according to the LHC's recovery performance presented in Fig. 1.

$$\begin{aligned} \frac{dK_R}{dt} &= -K_R \cdot \tau_B \\ \frac{dK_G}{dt} &= -K_G \cdot \tau_B \end{aligned} \tag{14}$$

2.4.3 Principles in choosing parameters

It is known that the chromatic properties of red- and green-sensitive cones are quite different from each other. The green-sensitive cones are significantly less sensitive than the red-sensitive cones in response to 703 nm (red) stimulus; on the other hand, the sensitivity of red-sensitive cones is fairly close to that of green-sensitive cones in response to 501 nm (green) light (Palacios et al. 1998). Based on this evidence, the reduction amount of glutamate released from red- and green-sensitive cones is different from each other when red and green light is applied. It is reasonable to assume that the amount of glutamate released by red-sensitive cones ($0.5 \cdot (1 - \xi_R)$) would be much less than that released by green-sensitive cones ($0.5 \cdot (1 - \xi_G)$) when the stimulus light is red; on the other hand, the glutamate released by red- and green-sensitive cones might be quantitatively similar when the stimulus light is green.

In the experiment, the stimulus intensities were controlled to make sure that the amplitude of the LHC's responses to red and green flashes were similar (4.529×10^{12} photons/cm$^2 \cdot$ s for 703 nm light and 3.77×10^{11} photons/cm$^2 \cdot$ s for 501 nm light) (Hu et al. 2000). Here, we set ($\xi_r + \xi_g$) a fixed value for the cell's response to both red- and green-light, which reflects that when the presynaptic regulatory effects are not taken into account, the total reduction of glutamate release is identical in response to the red- and green-light with particular intensities.

Given the asymmetric properties of red- and green-sensitive cones in response to red- and green-light, the regulatory effects on red- and green-sensitive cones should also be different when red- and green-light is applied. When red flashes are applied, red-sensitive cones are much more hyperpolarized than green cones. The presynaptic inhibitory effect that the red-sensitive cones exert on the green-sensitive cone pathway is dramatically relieved, while that the green-sensitive cones exert on the red-sensitive cone pathway is relieved in a much less degree. Meanwhile, the hemichannel-mediated feedback to the green-sensitive cones is much stronger than that to the red-sensitive cones. When green flashes are applied, mGluRs-mediated presynaptic effects on both the green- and red-sensitive cone pathways are relieved in similar degrees, and this is also the case for the hemichannel-mediated feedback to both red- and green-sensitive cone pathways. Based on above consideration, a larger value is chosen for η_G than that for η_R when the flashes are red; on the other hand, η_R is slightly bigger than η_G when the flashes are green, where the summation of ($\eta_R + \eta_G$) is identical in both cases (Table 1).

3 Results

3.1 Simulated results of the repetitive red light induced changes

The simulated results of $\mathrm{Glu_R}(t)$, $\mathrm{Glu_G}(t)$ in response to repetitive red flashes are illustrated in Fig. 4a, b. The red- and green-sensitive-cone-mediated currents calculated using Eq. (11) are plotted in Fig. 4c, d. Changes of other currents are not presented in this paper since their contribution to the stimulus-pattern-induced responsiveness changes is not significant. The model output for the membrane potential is illustrated in Fig. 4e, which effectively mimics the previously reported experimental results as illustrated in Fig. 1a. The LHC's response to red test light after repetitive red flashes (D) is dramatically increased as compared to the initial status (A), and the LHC's response to green test light after repetitive red flashes (E) is dramatically decreased as compared to its initial response to green flash (B). The retina is kept in dark for recovery after repetitive flashes, and the LHC's responses to red flash (F) and green flash (G) are both recovered after a short period.

3.2 Simulated results of the repetitive green light induced changes

The simulated results of $\mathrm{Glu_R}(t)$, $\mathrm{Glu_G}(t)$ during repetitive green flashes are illustrated in Fig. 5a and b. The red- and green-sensitive-cone-mediated glutamate currents are changed consequently, the simulated results are illustrated in Fig. 5c and d, respectively. The LHC's responsiveness changes are plotted in Fig. 5e, which satisfactorily describes the experimental observation given in Fig. 1b. The LHC's response to green test light after repetitive green flashes (D) changes little as compared to the initial status (A), and the LHC's response to red test light after repetitive green flashes (E) is dramatically decreased as compared to its initial response to red flash (B). The retina is kept in dark for recovery after repetitive flashes, and the LHC's responses to both green flash (F) and red flash (G) are recovered after a short period.

3.3 Detailed analysis of the model's performance

The model's performance is sensitive to the glutamate released by both red- and green-sensitive-cones under stimulus. The presynaptic regulatory effects on glutamate release follow the dynamical processes determined by ξ_R, ξ_G, η_R and η_G. Values for ξ_R, ξ_G, η_R and η_G are different under red and green stimulus light (Table 1). For convenience, we use ξ_R, ξ_G, η_R and η_G for red light response and ξ'_R, ξ'_G, η'_R and η'_G for green light response in this section.

Table 1 Parameter values chosen for Eqs. (12) and (13)

Parameter value	ξ_R	η_R	ξ_G	η_G
Red-response	0.9990	0.0003	0.4610	0.1497
Green-response	0.5500	0.1110	0.9100	0.0390

According to Eq. (12), the total glutamate amount released during red light response is $1-(\xi_\mathrm{R}+\xi_\mathrm{G})+(\xi_\mathrm{R}\cdot K_\mathrm{R}+\xi_\mathrm{G}\cdot K_\mathrm{G})$. Since $(\xi_\mathrm{R}+\xi_\mathrm{G})$ is set as a fixed value (1.46) in the present model, the total glutamate amount is determined by the value of $(\xi_\mathrm{R}\cdot K_\mathrm{R}+\xi_\mathrm{G}\cdot K_\mathrm{G})$, and is therefore positively correlated to $(\xi_\mathrm{R}\cdot\eta_\mathrm{R}+\xi_\mathrm{G}\cdot\eta_\mathrm{G})$ according to Eq. (13). Similarly, the total glutamate released during green light response is positively correlated to $(\xi'_\mathrm{R}\cdot\eta'_\mathrm{R}+\xi'_\mathrm{G}\cdot\eta'_\mathrm{G})$.

It is illustrated in Fig. 1 that the LHC's response to repetitive red flashes was significantly enhanced, while the LHC's response to repetitive green flashes changed little. In the present model, the presynaptic regulatory effects increase the glutamate release and therefore weaken the LHC's response amplitude. So, the presynaptic regulatory effects on glutamate release during repetitive green flashes should be stronger than that during repetitive red flashes, and therefore the value of $(\xi'_\mathrm{R}\cdot\eta'_\mathrm{R}+\xi'_\mathrm{G}\cdot\eta'_\mathrm{G})$ should be larger than $(\xi_\mathrm{R}\cdot\eta_\mathrm{R}+\xi_\mathrm{G}\cdot\eta_\mathrm{G})$ (0.09654 vs. 0.06931 in the present model, following the parameters chosen).

On the other hand, when a flash of green light was applied immediately after the repetitive red flashes, the recovery dynamics determined by Eq. (14) are not fast enough to bring K_R and K_G back to zero during the 500 ms dark interval as shown in Fig. 6a and b, respectively. So, the total glutamate released during the 500 ms green light after 20 s repetitive red flashes is positively correlated to the value of $(\xi'_\mathrm{R}\cdot\eta_\mathrm{R}+\xi'_\mathrm{G}\cdot\eta_\mathrm{G})$ according to Eqs. (12) and (13). Mutual chromatic depression in the present model requires a higher glutamate level in response to green light after repetitive red flashes, therefore the parameter values should allow for a larger $(\xi'_\mathrm{R}\cdot\eta_\mathrm{R}+\xi'_\mathrm{G}\cdot\eta_\mathrm{G})$ as compared to $(\xi_\mathrm{R}\cdot\eta_\mathrm{R}+\xi_\mathrm{G}\cdot\eta_\mathrm{G})$ (0.13639 vs. 0.06931 in the present model).

Similarly, a larger value is also requested for $(\xi_\mathrm{R}\cdot\eta'_\mathrm{R}+\xi_\mathrm{G}\cdot\eta'_\mathrm{G})$ as compared to $(\xi'_\mathrm{R}\cdot\eta'_\mathrm{R}+\xi'_\mathrm{G}\cdot\eta'_\mathrm{G})$ to generate the LHC's depression effect to red flash after repetitive green flashes (0.12887 vs. 0.09654).

The parameter values chosen for $\xi_\mathrm{R},\xi_\mathrm{G},\eta_\mathrm{R},\eta_\mathrm{G}$ and $\xi'_\mathrm{R},\xi'_\mathrm{G},\eta'_\mathrm{R},\eta'_\mathrm{G}$ are crucial for the model's performance. Meanwhile, the parameter values are chosen according to the asymmetric response properties of red- and green-sensitive cone systems in the present model. Given

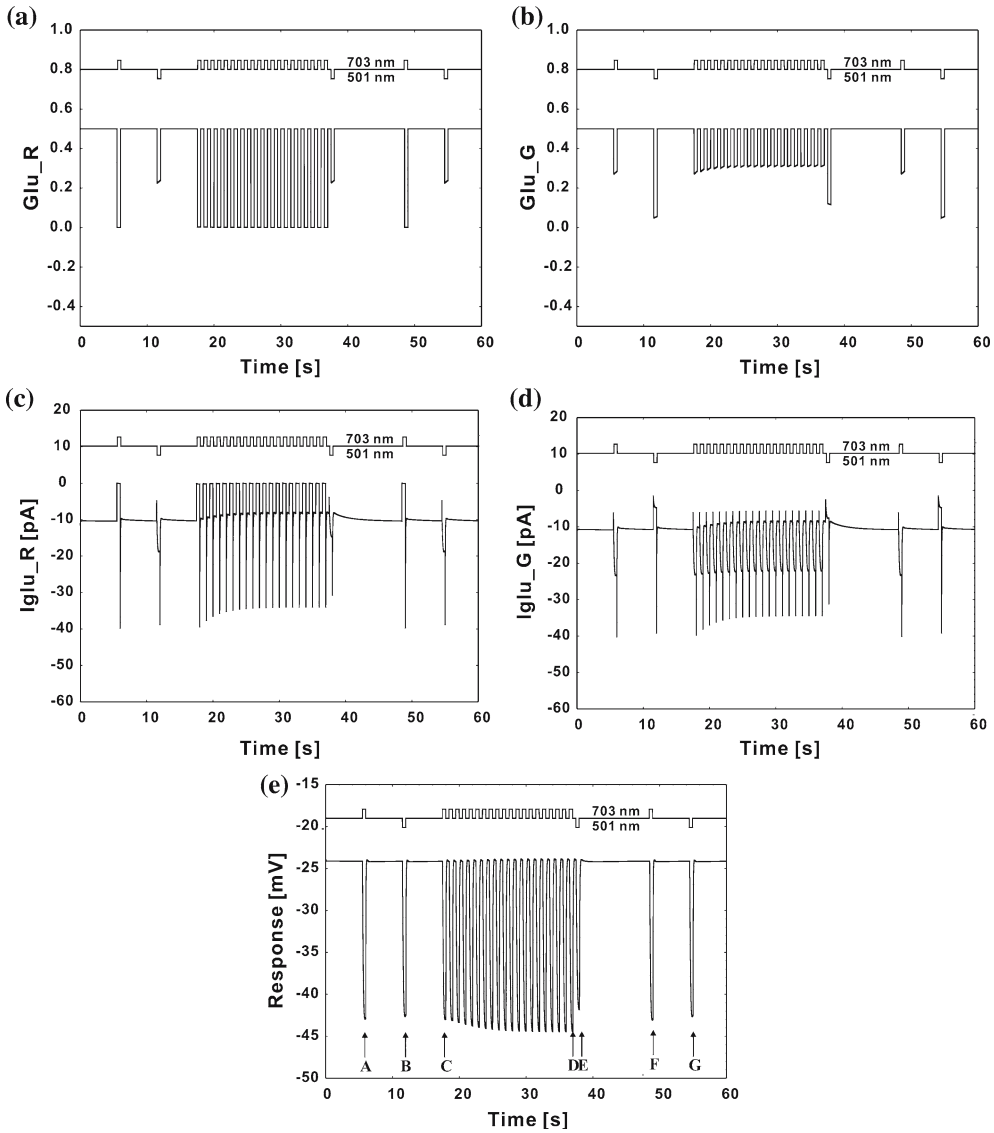

Fig. 4 Simulated results of the LHC's activity changes in response to repetitive red flashes. **a**, **b** $\mathrm{Glu_R}(t)$ and $\mathrm{Glu_G}(t)$ changes during repetitive red flashes. **c**, **d** The red- and green-sensitive-cone-mediated glutamate currents. **e** The model output of the LHC's light response changes induced by repetitive red flashes

reasonable parameter values, the model's performance mimics the experimental results satisfactorily.

While the postsynaptic Ca^{2+}-dependent regulatory process on AMPA receptors was suggested to be responsible for the repetitive-flashes-induced response enhancement (Fig. 2, see also Jin et al. 2004), we propose in the present model that the presynaptic regulatory effects on glutamate release are the main course for the asymmetric response to red- and green-flashes as well as the mutual-depression phenomenon. The model's performance with only the presynaptic regulatory effects included is demonstrated in Fig. 7a and b. It could be seen that without the postsynaptic Ca^{2+}-dependent regulatory process, the LHC's response amplitudes are gradually decreased in response to repetitive flashes (C and D, in both plots), and the response amplitudes are asymmetric. The mutual chromatic depression effects could also be seen (B and E, in both plots).

4 Discussions

To describe the stimulus-pattern-related responsiveness changes in the LHC, self-organizing model was developed (Hu et al. 2003), in which the synaptic weight changes were suggested to be the underlying mechanism.

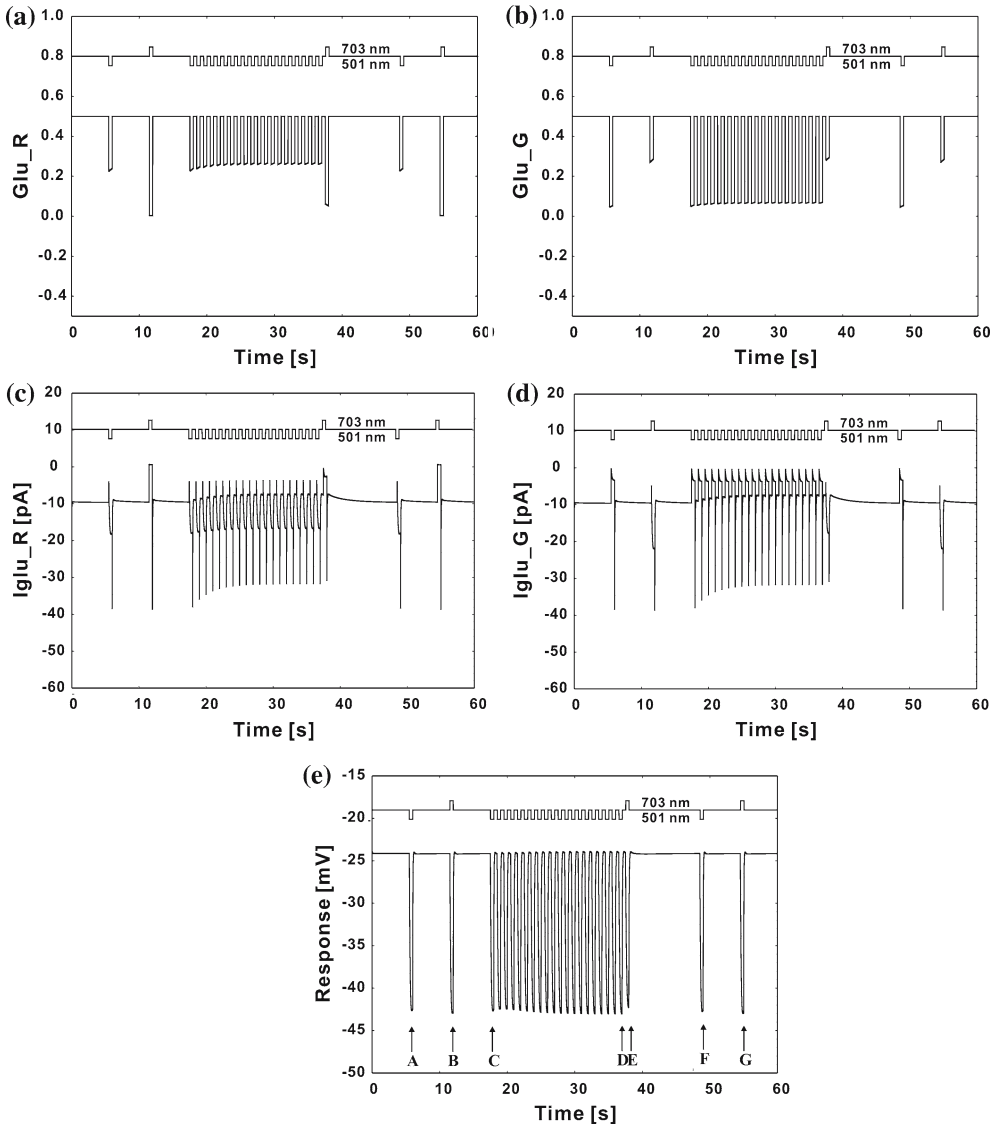

Fig. 5 Simulated results of the LHC's activity changes in response to repetitive green flashes. **a**, **b** $\mathrm{Glu_R}(t)$ and $\mathrm{Glu_G}(t)$ changes during repetitive green flashes. **c**, **d** The red- and green-sensitive-cone-mediated glutamate currents. **e** The model output of the LHC's light response changes induced by repetitive green flashes

However, the model did not actually indicate whether pre- or post-synaptic process is responsible for the short-term synaptic modification.

It is widely accepted that calcium plays a crucial role in the induction of synaptic regulation in the central nervous system (for a review see Linden 1999). However, the mechanism underlying the modification of synaptic transmission efficiency between retinal graded neurons and relevant calcium processes are poorly investigated. In the LHC of carp retina, apart from the influx via voltage-dependent Ca^{2+} channels, Ca^{2+} can also enter into the cell through Ca^{2+}-permeable AMPA receptors (Okada et al. 1999). The increase of intracellular Ca^{2+} concentration might in turn modify the single-channel conductance properties of the AMPA receptors and thus result in some modification of synaptic efficiency (Benke et al. 1998). It is therefore reasonable to make an assumption that the synaptic modification between the retinal neurons is related to the changes of intracellular Ca^{2+} concentration (Jin et al. 2004).

However, while the model incorporating the post-synaptic calcium processes nicely described the LHC's response to repetitive red flickering, it failed to represent the LHC's response to repetitive green

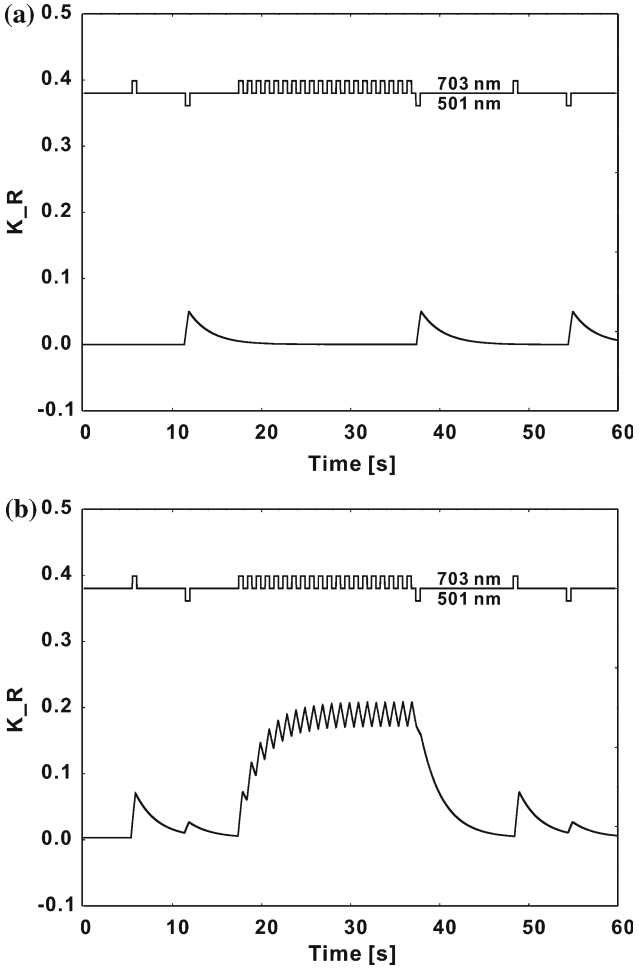

Fig. 6 **a**, **b** Dynamic changes of K_R and K_G induced by repetitive red-flashes

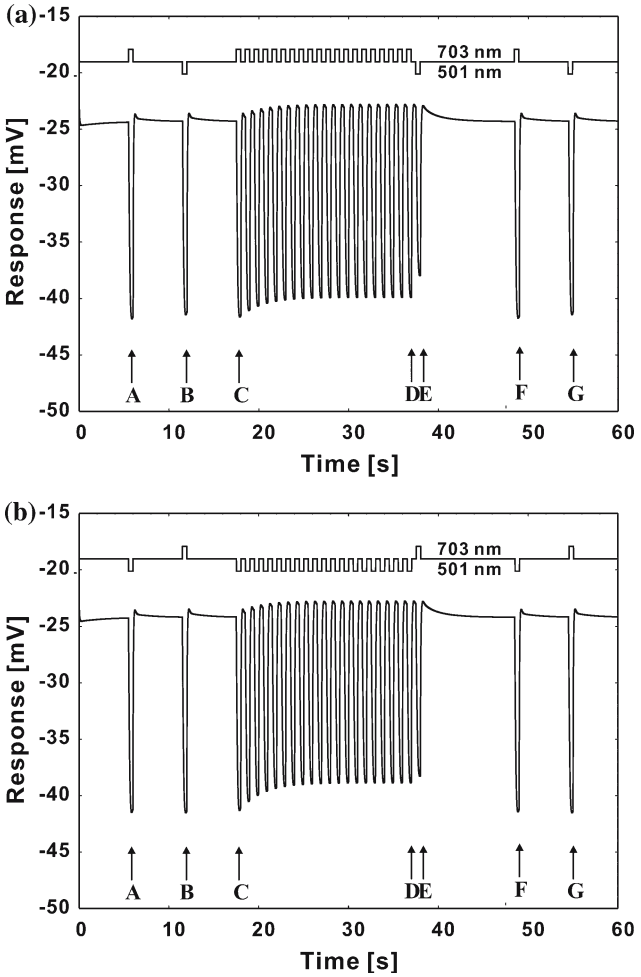

Fig. 7 **a**, **b** Model output of the dynamic changes of LHC membrane potentials induced by repetitive red- and green-flashes, respectively, while the model does not include the calcium-dependent post-synaptic regulatory process

flickering as well as the depressive effects between the red- and green-sensitive-cone pathways observed by Hu et al. (2000).

On the other hand, some factors can affect the status of the presynaptic photoreceptors, which in turn modulate the glutamate release. It has been reported that in the central nervous system, the intersynaptic diffusion of transmitter could mediate some modification of synaptic properties (Vogt and Nicoll 1999). Evidence also suggested that mGluRs located in the presynaptic terminals were crucial for tuning the synaptic transmission (Anwyl 1999; Awatramani and Slaughter 2001). Photoreceptors of carp retina express mGluRs that located on the presynaptic terminals, which act as autoreceptors and adjust the amount of transmitter release. In the dark, the retinal photoreceptors have tonic release of glutamate transmitter, which depolarizes the postsynaptic LHC. Meanwhile, the activation of the presynaptic mGluRs partly suppresses the release of glutamate transmitter, and in turn causes a modest reduction in the glutamate current on the LHC membrane. When the cone phototransduction is activated by light stimulus, the glutamate transmitter released by the photoreceptors will be dramatically decreased, and consequently relieves the mGluR-mediated presynaptic inhibition (Luo and Liang 2003). This process provides a mechanism for sensing activity in neighboring neural circuits and adjusting the efficacy of synaptic transmission.

Apart from the mGluR-mediated feedback in transmitter release from the cone systems, it was also suggested that hemichannel-mediated electrical feedback pathway from horizontal cell to cone should also be effective in regulating the glutamate release from the cones (Kamermans et al. 2001a,b). Based on the electrical feedback hypothesis, hyperpolarization of HCs shifts the Ca^{2+} current to more negative potentials, which

increases the Ca^{2+} influx and subsequently leads to an increase in glutamate release.

Inspired by these biological evidences, an extended model combining a feedback-mediated presynaptic modulation of glutamate release component together with a calcium-mediated postsynaptic enhancement component is developed in this study, to describe the repetitive-stimulus-induced transmission modification in the cone-LHC synapses and the suppressive effect across different cone pathways. The model output represents the experimental observations satisfactorily.

The simulation results suggest that: (1) the auto-enhancement effect might be induced by the Ca^{2+}-dependent process on the postsynaptic AMPA receptors, which could lead to changes of the ionic channel's properties; (2) the asymmetric response to red- and green-flashes and the mutual-chromatic suppression effects might be attributed to the regulatory effects on the presynaptic glutamate release.

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