Lateral Gain Control in the Outer Retina Leads to Potentiation of Center Responses of Retinal Neurons

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The retina can function under a variety of adaptation conditions and stimulus paradigms. To adapt to these various conditions, modifications in the phototransduction cascade and at the synaptic and network levels occur. In this paper, we focus on the properties and function of a gain control mechanism in the cone synapse. We show that horizontal cells, in addition to inhibiting cones via a “lateral inhibitory pathway,” also modulate the synaptic gain of the photoreceptor via a “lateral gain control mechanism.” The combination of lateral inhibition and lateral gain control generates a highly efficient transformation. Horizontal cells estimate the mean activity of cones. This mean activity is subtracted from the actual activity of the center cone and amplified by the lateral gain modulation system, ensuring that the deviation of the activity of a cone from the mean activity of the surrounding cones is transmitted to the inner retina with high fidelity. Sustained surround illumination leads to an enhancement of the responses of transient ON/OFF ganglion cells to a flickering center spot. Blocking feedback from horizontal cells not only blocks the lateral gain control mechanism in the outer retina, but it also blocks the surround enhancement in transient ON/OFF ganglion cells. This suggests that the effects of the outer retinal lateral gain control mechanism are visible in the responses of ganglion cells. Functionally speaking, this result illustrates that horizontal cells are not purely inhibitory neurons but have a role in response enhancement as well.

Introduction

To function optimally under a variety of adaptation conditions and stimulus paradigms, the retina must adjust the amplification factors or gains of the various interactions in and between retinal neurons. It is well known that photoreceptors reduce their gain with increasing light levels [see, for instance, Yau (1994)]. This gain change is called light adaptation. Amplification or gain control mechanisms are also functioning at the network and synaptic levels. Examples include spatial and temporal contrast adaptation, which seem to be generated in the inner retina (Kim and Rieke, 2001; Baccus and Meister, 2004; Manookin and Demb, 2006), presumably by interactions between bipolar cells (BC) and amacrine cells (AC).

Inner retinal gain control mechanisms have been studied extensively. In contrast, outer retinal synaptic gain control mechanisms have been suggested to exist, but have not been investigated in detail (Werblin, 1974; Attwell et al., 1987; Nelson et al., 1990;

Pflug et al., 1990; Lee et al., 2003; van Hateren, 2005, 2007), and their effects on the retinal output have not been well studied. Two effects have been described: gain decrease and gain increase. Attwell et al. (1987) showed that the gain of the rod synapse decreases with rod hyperpolarization. On the other hand, Nelson et al. (1990) studied the effect of background illumination on the enhancement of horizontal cell (HC) responses to flicker stimuli in cat. They reported an enhancement of the response to a flickering spot with HC hyperpolarization and called it background flicker enhancement. Although Witkovsky et al. (1997) and Cadetti et al. (2004) discussed mechanisms that could lead to a synaptic gain reduction, no mechanism that could account for both the gain reduction and gain increase simultaneously has been revealed nor has the effect of outer retinal synaptic gain control on the retinal output been studied. Given the strategic position of an outer retinal gain control mechanism, it is of great importance to gain insight into its origin and functional consequences.

In this paper, we will present direct evidence for a lateral gain control mechanism in the outer retina, a mechanism which was originally suggested by Kamermans and coworkers (Kamermans et al., 1998; Kraaij et al., 1998). It will be directly shown that, in addition to a subtractive component, feedback from HCs to cones also has a component that adjusts the gain of the photoreceptor synapse. Synaptic gain is defined as change in cone Ca current per millivolt change in cone membrane potential. The gain control mechanism in the cone synapse can be separated into two distinct components. The first is a synaptic gain reduction mechanism. The second component is a synaptic gain in-

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crease mechanism that is spatially extensive and cone type non-specific. This is a novel mechanism that might account for the HC response enhancement found by Nelson et al. (1990) and Pflug et al. (1990). Results will be presented that strongly suggest that this mechanism underlies, at least partly, the surround enhancement of transient ON/OFF ganglion cell (GC) responses. In light of these findings, one might consider HCs not as purely inhibitory neurons, but rather as neurons with a role in response enhancement as well.

Materials and Methods

Preparation

All animal experiments were performed according to the guidelines of the ethical committee of the Royal Netherlands Academy of Arts and Sciences acting in compliance with the European Communities Council Directive of 24 November 1986 (86/609/EEC). Animal housing and animal handling details have been described previously (Fahrenfort et al., 1999).

Goldfish, *Carassius auratus* (12–16 cm standard body length), were kept at 18°C under a 12 h dark/light cycle, and experiments were performed with fish that were between 6 and 9 h into their light phase. The fish were dark adapted for at least 3 min, and all further steps in preparation were performed in the dark under deep red light illumination. After decapitation, an eye was enucleated and hemisected, and most of the vitreous was removed with filter paper. The retina was isolated, placed receptor side up in a superfusion chamber (volume 0.75 ml), and superfused continuously (1.5 ml/min) with a Ringer's solution of which the pH was continuously measured. The Ringer's solution contained (in mM) 102.0 NaCl, 2.6 KCl, 1.0 MgCl₂, 1.0 CaCl₂, 28.0 NaHCO₃, and 5.0 glucose, and was continuously gassed with ~2.5% CO₂ and 97.5% O₂, yielding a pH of 7.8. Some Ringer's solutions contained drugs as indicated in the text and in the figure legends. All chemicals were obtained from Sigma.

Electrophysiological measurements

Three types of electrophysiological measurements were performed. Whole-cell voltage- and current-clamp techniques were used for the cones, intracellular recording techniques were used for HCs, and extracellular recording techniques were used for the GCs. Details about the recording equipment and recording procedure for the cone and HCs have been published previously (Fahrenfort et al., 1999). For the HC experiments, only monophasic HCs were used.

Intracellular recordings. Microelectrodes were pulled on a horizontal puller (Sutter P-80-PC) using aluminosilicate glass (OD = 1.0 mm, ID = 0.5 mm; Clark), and had impedances ranging from 300 to 400 MΩ when filled with 3 M KCl. The intracellular recordings were made with a WPI S7000A microelectrode amplifier system (World Precision Instruments), recorded on paper (Grathtec Linearcorder), and sampled using an AD/DA converter (CED 1401, Cambridge Electronic Design) coupled to a Windows-based computer system.

Whole-cell voltage- and current-clamp recordings. For the whole-cell voltage-clamp experiments, the pipettes were pulled from borosilicate glass (GC150TF-10 Clark) with a Sutter P-87 micropipette puller (Sutter Instruments); the impedances ranged from 3 to 6 MΩ when filled with pipette medium and measured in Ringer's solution. The standard patch pipette medium contained (in mM) 10 KCl, 96 D-gluconic-K, 1.0 MgCl₂, 0.1 CaCl₂, 5.0 EGTA, 5.0 HEPES, 5.0 ATP-K, 1.0 GTP-Na₃, 0.2 3':5'-cGMP-Na, 20 phosphocreatine-Na₂, 50 U/ml creatine phosphokinase. In experiments with the standard patch pipette medium, E_{Cl} was calculated to be −55 mV. The pH of the pipette medium was adjusted to 7.25 with KOH. The electrodes were mounted on a MP-85 Huxley/Wall-type micromanipulator (Sutter Instruments Company) and connected to a Dagan 3900A Integrating Patch Clamp (Dagan Corporation). The liquid junction potential was measured with a patch pipette filled with the pipette medium, and positioned in a bath filled with pipette medium. The reference electrode was filled with 3 M KCl. After the potential was adjusted to zero, the bath solution was replaced with Ringer's solution. The resulting potential change was considered the junction potential,

and all data were corrected accordingly. The liquid junction potential was 15 mV.

Extracellular recordings of action potentials. Action potentials generated by the GCs were recorded extracellularly with platinum/iridium electrodes (UEPMGGSGBP4M 10 mm/40 mm/10 mm from FHC Inc.). For the data acquisition, we used a 64-channel amplifier (FA-64-S-1000–0200–5000) and MC-Rack software (both from Multi Channels Systems). For the analysis, we used NeuroExplorer (Nex Technologies), Matlab (MathWorks), and OriginPro (OriginLab, MVB Scientific). Off-line wave form discrimination was performed with Offline Sorter (Plexon). GC responses were repeated 64 times, and the data were presented as peristimulus time histograms (PSTH; bin size 16.6 ms). The mean spike frequency minus the minimal spike frequency was used as a measure for the mean modulation of the spike frequency due to sinusoidal stimulation.

Optical stimulator

The optical stimulator for the cone recordings consists of a 450 W Xenon lamp which supplied two beams of light that were directed to the preparation after passing through Uniblitz VS14 shutters (Vincent Associates), neutral density filters (NG Schott), and a series of lenses and apertures. Feedback-induced responses to 500 ms, 3000 μm spot stimulation were measured in cones at different potentials while the cone light conductance was continuously saturated with a 20 μm spot. The 20 μm spots were projected through the 40× water-immersion objective (N.A. = 0.55) of the microscope, and the 3000 μm spots were projected through the microscope condenser (N.A. = 1.25). For experiments with cones, only white light stimuli were used; light intensities are expressed in log units of attenuation relative to the maximum luminance of 4 × 10³ cd/m².

The optical stimulator used for the HC measurements consisted of 2 beams from a 450 W Xenon light source and a pair of circular neutral density filters (Barr & Strout). The full-field chromatic light stimuli were projected onto the retina through a 2× objective lens (N.A. = 0.08) of the microscope. To classify the HC spectrally, a monochromator (Ebert) and interference filters with a bandwidth of 8 ± 3 nm (Ealing Electro-Optics) were used. The light intensities are expressed in log units relative to 4 × 10¹⁶ quanta · s^{−1} · m^{−2}. The intensities of the 550 nm and the 650 nm were respectively 0.4 and 0.2 log units lower than the intensity of the 600 nm stimuli. The contrast of the sinusoidal stimulation was 33% and was kept constant for all intensities.

The optical stimulator used for the GC experiments consisted of a digital light projector (DLP) (U2–1150 Projector Lamp, PLUS Vision). The DLP was driven by a PC with custom made software. Since the DLP has a high output above 700 nm, we used a low-pass filter with a cutoff wavelength of 700 nm to block this output (hot mirror filter No. 03MHG007, 50 mm², 0-degrees, Melles Griot). For the spectral classification of the GCs, all three color channels were used. For the experiments reported in this paper, only the red channel of the projector was used. This channel mainly stimulated the L-cones. Relative to the L-cones, M- and S-cones were stimulated 0.86 and 1.96 log units less, respectively. Light intensities are expressed in log units relative to 4 × 10¹⁶ quanta · s^{−1} · m^{−2}.

Receptive fields of GCs in Figure 4b were fitted with Equation 1, which describes the receptive fields of GCs as the difference of two Gaussians:

$$R = A_0 + \frac{1}{2} A_1 \cdot \operatorname{erf} \left(\frac{\frac{1}{2} \sqrt{2} x}{\lambda_1} \right) - \frac{1}{2} A_2 \cdot \operatorname{erf} \left(\frac{\frac{1}{2} \sqrt{2} x}{\lambda_2} \right),$$

where R is the GC response, A_0 is an offset, A_1 and A_2 are the amplitudes of the center and surround processes, respectively, λ_1 and λ_2 are the width of the center and surround Gaussians, respectively, and x is the radius of the stimulus spot.

Measuring “light-induced” changes in the cone Ca²⁺ current

Since the large light-driven conductance in cones masks the much smaller Ca²⁺-conductance in cones, it is not possible to directly measure light-induced changes in the cone's Ca²⁺ current. To overcome this problem, the cone membrane potential was clamped at −43 mV and

modulated with a 3 mV, 3 Hz sine wave stimulus protocol around this potential for 1000 ms. In addition, the cone was saturated with a small, intense spot of light to prevent interference from the phototransduction cascade. A leak subtraction protocol was used to isolate the Ca^{2+} current. Leak currents were measured by clamping the cone at -77 mV for 1500 ms. During these 1500 ms trials, the membrane potential was stepped for 50 ms to -87 mV. The resulting current change was used to calculate the leak conductance. Fahrenfort et al. (1999) showed that this procedure leads to a proper isolation of the Ca^{2+} current in the physiological membrane potential range.

Statistics

Data are presented as mean $\pm$ SEM. Significance was determined using the Wilcoxon test, paired Student's *t* test, or multiple regression analysis (SPSS version 16.0). The differences were considered significant for $p < 0.05$.

Results

Gain control in the outer retina

First it was established whether gain control at the cone–HC synapse was present by studying responses of HCs to full-field flashes of sinusoidally modulated or steady light. Monophasic HCs hyperpolarize to light over the entire visual spectrum. Full-field light flashes (Fig. 1*a*) induce an initial hyperpolarization, followed by a secondary depolarization or “roll-back” response is correlated with negative feedback from HCs to cones (Wu, 1994; Witkovsky et al., 1995; Kamermans et al., 2001*a,b*). Since feedback develops relatively slowly (Kamermans et al., 2001*b*), feedback will be weak early and pronounced late in the response. To test whether the synaptic gain changes in parallel with the strength of feedback, HCs were stimulated with a 1000 ms flash of sine wave-modulated light (Fig. 1*b*) of the same mean intensity as the full-field flash used in Figure 1*a*. The amplitude of the response to the sine wave component of the stimulus is small early in the HC response and larger toward the end of the response, consistent with the idea that the cone synaptic gain becomes higher when feedback becomes stronger. To quantify the increase in synaptic gain, the ratio of the amplitude of the sine wave component of the response (B or C) and the sustained response amplitude (A) was calculated (Fig. 1*b*). The ratio determined directly after light onset is the “early modulation coefficient” (B/A), and the ratio determined just before light offset is the “late modulation coefficient” (C/A). Figure 1*c* illustrates that the early modulation coefficient decreases with increasing intensity. Comparison of the early and the late modulation coefficients in Figure 1*d* shows that the late modulation coefficient, measured in 6 HCs at various light intensities, is always larger than the early modulation coefficient (paired *t* test, $p = 0.0001$; $N = 6$; $n = 31$). These experiments identify two changes in gain: (1) a gain reduction that correlates with increasing stimulus intensity and is independent of

Figure 1. Two synaptic gain modulation mechanisms. Sine wave-modulated surround stimulation increases the horizontal cell response but not the cone photocurrent. *a*, Response of a monophasic HC to a 1000 ms flash of 550 nm light. *b*, Response of a monophasic HC to a 1000 ms flash of full-field sine wave-modulated light of 550 nm. Directly after stimulus onset, the sine wave modulation of the stimulus yields only a small modulation of the HC membrane potential. The amplitude of the sine wave response component increases with stimulus duration. (A = the sustained response amplitude; B, C = the amplitudes of the sine wave response early and late in the HC response, respectively.) *c*, The early HC response (early modulation coefficient) to the sine wave stimulation decreases with increasing stimulus intensity. The early modulation coefficient is defined by the amplitude of the early sine wave response (*b*, B) divided by the sustained response amplitude (*b*, A). *d*, The relation between the modulation response early (*b*, B/A) and late (*b*, C/A) in the response. The late modulation coefficient is always larger than the early modulation coefficient, indicating that a relatively slow mechanism leads to an enhancement of the modulation coefficient (paired *t* test, $p = 0.0001$; $N = 6$; $n = 31$). *e*, The response of a voltage-clamped cone to sine wave-modulated light. The modulation coefficients are defined as B/A (early) and C/A (late). *f*, The early modulation coefficient in cones decreases with intensity as was observed in HCs. *g*, The late modulation coefficient is equal to the early modulation coefficient, indicating that no enhancement mechanism is working at the phototransduction level (paired *t* test; $p = 0.79$; $N = 4$; $n = 31$). *h*, The response of a current-clamped cone to sine wave-modulated light. The modulation coefficients are defined as B/A (early) and C/A (late). The early and late modulation coefficient did not differ from each other ($p = 0.29$; $N = 7$; $n = 7$). Error bars indicate SEM.

feedback and (2) a gain increase that correlates with the roll-back response and thus depends on the feedback strength. These gain modulation mechanisms could originate in the photoreceptor, or could be due to membrane properties or connectivity of HCs. To distinguish between these, the behavior of cones to a similar stimulus protocol was studied. Figure 1*e* shows the responses of a voltage-clamped cone (-68 mV) stimulated with a sine wave-modulated spot of light. As in HCs, the early modulation coefficient (B/A) decreased with increasing stimulus intensity (Fig. 1*f*). The late modulation coefficient (C/A) is plotted as function of the early modulation coefficient for 4 cones at various intensities in Figure 1*g* (paired *t* test; $p = 0.79$; $N = 4$; $n = 31$). Similar results were found in cones under current-clamp conditions (Fig. 1*h*). The early and late modulation coefficients do not differ from each other (paired *t* test; $p = 0.29$; $N = 7$; $n = 7$) showing that the gain enhancement does neither result from changes in the cone phototransduction cascade nor is due to nonlinear membrane properties of the cones. These experiments show that cones have an intrinsic gain reduction mechanism most likely originating in the phototransduction cascade (see for instance

Figure 2. The increase in modulation coefficient is not an intrinsic property of HCs but is present in the integrated output of the HCs. *a*, Responses of a monophasic HC to full-field light flashes of 1000 ms of green (550 nm) and red (700 nm) light. *b*, Relationship between the early- and late-modulation coefficient for green (550 nm) and red (650 nm) light stimulation. For both stimuli, the late modulation coefficient is always larger than the early modulation coefficient. However, multiple regression analysis shows that the increase in late modulation coefficients found with the red stimuli are significantly smaller than those found with the green stimuli ($p < 0.001$, $n = 36$). *c*, Procedure to isolate the sinusoidally modulated response component from HCs. HCs were stimulated with a 1000 ms flash of 550 nm light with or without sinusoidal modulation. The difference curve is the sinusoidally modulated component of the response. The black curve shows the actual data trace, and the red curve shows the fitted curve using Equation 2 (bottom, black trace: data; red trace: fit). *d*, The red trace gives the relation between the time constant of feedback responses in cones and stimulus intensity [based on Kamermans et al. (2001b)]. The black trace gives the time constants of the increase in amplitude of the sinusoidally modulated response in HCs as a function of stimulus intensity. To construct the graph, the procedure illustrated in *c* was used. *e*, HC responses to full field light flashes in control (black) and in the presence of $50 \mu\text{M Co}^{2+}$ (red). The roll-back response disappears in $50 \mu\text{M Co}^{2+}$, indicating a block of feedback (see also Fahrenfort et al., 2004). *f*, The increase in amplitude of the sinusoidally modulated response in HCs is present in control conditions (black trace) but absent in $50 \mu\text{M Co}^{2+}$. For better comparison, the responses are scaled such that the initial sine wave responses are equal. Error bars indicate SEM.

Yau (1994). The gain enhancement mechanism like the one visible at the HC level might thus originate either in the cone synapse or originates in the HC network.

Response enhancement is not due to nonlinear membrane properties of horizontal cells

Next it was tested whether the gain enhancement mechanism was an intrinsic membrane property of HCs. As in all animals with color vision, HCs in the goldfish retina receive and integrate input from various cone types, making the HC response dependent on the wavelength of the stimulus light. This spectral dependency of the HC response is illustrated in Figure 2*a*. HCs respond differently to green (550 nm, left) and red (700 nm, right) light. Responses to green light stimulation show a clear feedback-induced roll-back. In contrast, responses to red light show almost no feedback-induced roll-back, consistent with the finding that feedback is weaker when using red and stronger when using green light stimuli (Kamermans et al., 1989a,b; Kraaij et al., 1998).

The reason for the lesser effect of feedback in the long wavelength part of the spectrum is as follows. Monophasic HCs, studied in the present study, hyperpolarize over the whole visible

spectrum, receive input from both R- and G-cones and feed back to both the R- and G-cones. Biphasic HCs hyperpolarize in the blue/green part of the spectrum and depolarize in the red part of the spectrum, receive prominent G-cone input and feed back prominently to G-cones. For red light stimulation biphasic horizontal cells depolarize and monophasic horizontal cells hyperpolarize whereas they both hyperpolarize for green light stimulation. This means that the total feedback the G-cones receive in the red part of the spectrum is small relative to the feedback they receive in the green part of the spectrum. This accounts for the difference in roll-back seen for red light stimulation compared with green light stimulation. This characteristic was used to distinguish between features depending directly on membrane polarization and those depending on synaptic or network properties. If the change in modulation coefficient is due to nonlinear membrane properties of HCs, then the modulation coefficient should not depend on the spectral composition of the stimulus. The late modulation coefficients for both green (550 nm) and red (650 nm) stimuli are plotted as functions of the early modulation coefficient in Figure 2*b* for the 6 HCs tested at various intensities. For both stimulus wavelengths, the late modulation coefficient is larger than the early one. However, the difference between early and late modulation coefficient is larger for green light stimuli. Multiple regression analysis shows that this difference is significant ($p < 0.001$, $N = 6$; $n = 36$). This experiment shows that the increase in modulation coefficient does not depend on the HC polarization per se, thus ruling out intrinsic properties of HCs as the

source for the enhancement. Feedback from HCs to cones, therefore, most likely, underlies the increase of the late modulation coefficient relative to the early modulation coefficient. Consistent with this suggestion is that the difference between the early and late modulation coefficient is much larger in conditions where feedback is strong (550 nm light) than for conditions where feedback is weak (650 nm light).

Detailed analysis of the feedback responses in cones and the roll-back responses in HCs (Kamermans et al., 2001b) has shown that the feedback pathway is relatively slow and that the feedback-induced responses in both cones and HCs do not have a fixed time constant. The time constant of feedback-induced responses depends on the membrane potential of the cone and thus on the stimulus intensity (Kamermans et al., 2001b). If negative feedback from HCs to cones leads to gain enhancement, the amplitude of HC responses to the sinusoidally modulated spot of light should increase with a time constant similar to that of the feedback-induced responses. To determine the time constant of the gain increase, HCs were stimulated with full field flashes of sinusoidally modulated or steady light. The responses to the sine wave stimulus were separated from the sustained response by

subtracting the response to the steady light (Fig. 2*c*, middle) from the response to the sinusoidally modulated flash of light (Fig. 2*c*, top). To estimate the time constant of the increase in gain, Equation 2 was fitted to the difference response (Fig. 2*c*, bottom; black line: data; red line: fit).

$$\Delta V_{HC}(t) = [A_0 + A_1 \cdot (1 - e^{-t/\tau})] \cdot \sin(2\pi ft + \theta),$$

where ΔV_{HC} is the response of the HC to the sine wave part of the stimulus, A_0 is the initial amplitude of the sine wave response, A_1 is the maximal increase in amplitude of the sine wave response, t is time, τ is the time constant of the increase in amplitude of the sine wave component of the response, θ is the phase, and f is the temporal frequency. The red line in the bottom panel of Figure 2*c* shows the fit. These fits were used to estimate the time constant of the gain increase. These time constants are plotted in Figure 2*d* (black symbols). The red symbols show the time constant of the feedback signal measured in cones as a function of intensity. This curve is based on Kamermans et al. (2001*b*). They measured the relation between stimulus intensity and cone membrane potential and the relation between cone membrane potential and time constant of feedback. Combining these two datasets yields the red curve. The two curves are similar, indicating that the synaptic gain of the cone increases with the time constant of feedback from HCs to cones.

It has been shown that a low dose of Co^{2+} can inhibit feedback without affecting the Ca^{2+} current of the cones directly (Fahrenfort et al., 2004). If feedback from HCs to cones is the underlying mechanism of the increase of the response to sinusoidal stimulation, then blocking feedback should abolish this increase. Figure 2*e* shows that $50 \mu\text{M}$ Co^{2+} blocks the roll-back response of HCs. The difference curve in Figure 2*f* demonstrates that $50 \mu\text{M}$ Co^{2+} also blocks the increase in the amplitude of the response to the sine wave stimulus. The black trace (control) shows the increase in response amplitude to the sine wave stimulus. The red curve, recorded in $50 \mu\text{M}$ Co^{2+} , does not show this increase. In the 6 cells tested this way, the mean increase in amplitude in control conditions was $37.6 \pm 8.8\%$ ($n = 6$; $p = 0.0079$), whereas the increase was absent in $50 \mu\text{M}$ Co^{2+} ($0.2 \pm 3.2\%$; $n = 6$; $p = 0.95$). These experiments show that the synaptic gain change critically depends on an intact feedback pathway from HCs to cones.

Response enhancement originates in cone output

To directly test whether feedback is involved in the increase in synaptic gain, the effects of cone and HC polarization on the output of cones was studied. Cones release glutamate in a Ca^{2+} -dependent manner. The L-type Ca^{2+} channels are the main pathway for Ca^{2+} influx in the synaptic terminal and are directly linked to neurotransmitter release from the cones. Witkovsky et al. (1997) showed that there is a linear relation between the Ca^{2+} current and the release. This makes the Ca^{2+} current a good estimate for glutamate release from the cones. Therefore, the modulation of the Ca^{2+} current during stimulation was estimated using a protocol in which a voltage-clamped cone was saturated with a small spot of light to prevent interference from the phototransduction cascade (Fahrenfort et al., 1999). A leak subtraction protocol that adequately isolated the Ca^{2+} current, as described by Fahrenfort et al. (1999), was used.

First, it was tested how the modulation of the Ca^{2+} current of the cones depends on sustained membrane polarization of the cone. The cone membrane potential was modulated with a sine wave of 3 Hz and 6 mV (Fig. 3*a*, red trace) at various potentials. The resulting modulation of the Ca current is plotted in Figure 3*a*

Figure 3. Feedback from HCs to cones modulates the synaptic gain of the cone synapse. *a*, The Ca^{2+} current of the cone measured with a sine wave-modulated voltage-clamp protocol at different clamp potentials in the absence of surround stimulation. The sine wave stimulus elicited a larger modulation of the Ca^{2+} current at depolarized membrane potentials compared with hyperpolarized potentials. *b*, Surround illumination-mediated increases in response amplitude are present at the level of the cone output. The membrane potential of a cone clamped at -43 mV was sine wave-modulated, and the light response was blocked by a saturating spot projected on the cone. The top panel shows the response in the absence of surround stimulation, and the bottom panel shows the response when HCs are hyperpolarized with full-field light stimulation. *c*, Mean amplitudes of the modulation of the Ca^{2+} current in cones as a function of holding potential. At depolarized potentials, the amplitude is larger than at hyperpolarized potentials (* $p = 0.045$). *d*, Mean amplitudes of the modulation of the Ca^{2+} current in cones with and without surround illumination. On average, surround stimulation enhances the response amplitude to $168 \pm 15\%$ ($n = 5$; ** $p = 0.0095$). Error bars indicate SEM.

(black traces). The more hyperpolarized the cone was, the smaller the modulation of the Ca current became. In all 9 cells tested, the modulation of the Ca^{2+} current became smaller with hyperpolarization (Fig. 3*c*; * $p < 0.05$). This result illustrates that, apart from a gain reduction mechanism present in the cones (phototransduction), the gain of the output synapse decreases with hyperpolarization as well. This gain reduction strictly depends on the cone membrane potential and most likely arises from the voltage dependence of the L-type Ca channels of the cones (Thoreson et al., 2003; Heidelberger et al., 2005). Attwell et al. (1987) and Belgum and Copenhagen (1988) have described a similar phenomenon for rods.

Next, the effect of surround stimulation on the Ca^{2+} current of the cone was studied. Figure 3*b* shows the change in the Ca^{2+} current (black traces) evoked by modulating the cone's membrane potential with a sine wave of 3 Hz and an amplitude of 6 mV (red trace). The top and bottom panels of Figure 3*b* show the responses in the absence and presence of sustained surround illumination, respectively. In all 5 cones tested, the amplitude of the response to the sine wave modulation increased when HCs were hyperpolarized by surround illumination. On average, the amplitude increased to $168 \pm 15\%$ ($p = 0.0095$; $n = 5$) (Fig. 3*d*), showing that feedback from HCs to cones leads to a strong enhancement of the response. If one defines synaptic gain as the change in Ca^{2+} current per mV change in cone membrane potential, then one can conclude from these results (Fig. 3*a–d*) that the hyperpolarization of the cone leads to a synaptic gain reduction, and that feedback from HCs to cones leads to a synaptic gain increase.

Figure 4. Sustained surround illumination leads to potentiation of center responses of transient ON/OFF GCs. *a*, Response of an ON/OFF GC to a 500 ms flash of 520 nm light. *b*, Normalized ON-response amplitude of transient ON/OFF GC to spots of 520 nm light of various diameters in control (solid line; closed symbols) and in $25 \mu\text{M Co}^{2+}$ (dashed line; open symbols). Neither the response to a $500 \mu\text{m}$ spot nor spontaneous spike rate were significantly affected by $25 \mu\text{M Co}^{2+}$ application. The responses to spots larger than $500 \mu\text{m}$ were significantly larger in $25 \mu\text{M Co}^{2+}$ compared with control. The responses to spots smaller than $500 \mu\text{m}$ were similar in both conditions. *c*, Responses of an ON/OFF GC to a sinusoidally modulated spot of light without and with surround illumination. Timing of the center spot stimulus (C) and surround illumination (S) is given at the bottom of the figure. Note that surround illumination did not cover the center spot. Spike frequency was determined in the last second of either the dark surround (1–2 s) or light surround condition (3–4 s) as indicated by the gray bars. Sustained surround stimulation increases the responses of a GC to a sinusoidally modulated spot (100% contrast, 2.5 Hz) ($135 \pm 13\%$; $n = 19$; $p = 0.007$). Error bars indicate SEM.

Effect of cone synaptic gain modulation on ganglion cell responses

So far, it was shown that negative feedback from HCs to cones leads to an increase in synaptic gain of the photoreceptor synapse. Would such an effect be visible in GC responses? To test this, transient ON/OFF GCs, which respond with a burst of spikes at both light onset and light offset, were studied (Fig. 4*a*). These ON/OFF GCs have a well developed antagonistic surround, as is evident from their area response curve, which shows large responses for small spots and reduced responses for large spots (Fig. 4*b*, solid line; closed symbols). These transient ON/OFF GCs were stimulated with a $500 \mu\text{m}$ spot of sine wave-modulated light with a mean intensity of $-1.0 \log$ projected in the center of their receptive fields. Figure 4*c* shows the response to a sine wave-modulated center spot in the absence of (time window 0–2 s) and in the presence of (time window 2–4 s) sustained surround illumination. In both conditions, the sine wave stimulus leads to bursts of spikes in phase with the sinusoid. To prevent interference from the onset and offset responses to the sustained surround illumination, the spike frequency was determined in time windows from 1 to 2 s and from 3 to 4 s after sinusoid stimulus onset (Fig. 4*c*). Such analysis shows that the bursts of spikes in the presence of the sustained surround illumination were larger. To quantify this effect, the mean spike frequency was determined in both conditions. The mean modulation in the spike frequency increased to $135 \pm 13\%$ ($n = 20$; $p = 0.007$) in the presence of the sustained surround illumination compared with the condition without sustained surround illumination.

The results depicted in Figure 4*c* could originate either from an enhancement of the sustained spike rate during surround stimulation or to an increased response to the sine wave-modulated center stimulus. To test these possibilities, the sustained response to a flash of light in either the center or surround was analyzed. The experiments presented in Figure 4 demonstrate that in transient ON/OFF GCs with a well developed inhibitory surround, sustained surround stimulation leads to a potentiation of the center response to a flickering spot.

To test whether this enhancement of the ganglion center responses was generated in the inner or the outer retina, the feedback pathway from HCs to cones was inhibited by application of $25 \mu\text{M Co}^{2+}$. Figure 4*b* shows that application of $25 \mu\text{M Co}^{2+}$ leads to a reduction of the inhibitory surround of transient ON/OFF GCs. In control conditions, a pronounced inhibitory surround is present (solid line; closed symbols), whereas inhibition is reduced after Co^{2+} application (dashed line; open symbols). Neither the center responses ($107 \pm 24\%$; $n = 7$; $p = 0.75$) nor spontaneous spike rate ($113 \pm 13\%$; $n = 5$; $p = 0.40$) were significantly affected by $25 \mu\text{M Co}^{2+}$ application. Univariate analysis shows a significant interaction between the pharmacological condition (control vs $25 \mu\text{M Co}^{2+}$) and spot size ($F = 2.549$; $p = 0.019$; $n = 7$). The responses to spots larger than $500 \mu\text{m}$ were significantly larger in $25 \mu\text{M Co}^{2+}$ compared with control ($F = 10.283$; $p = 0.003$; $n = 7$). The responses to spots smaller than $500 \mu\text{m}$ were similar in both conditions.

c, Responses of an ON/OFF GC to a sinusoidally modulated spot of light without and with surround illumination. Timing of the center spot stimulus (C) and surround illumination (S) is given at the bottom of the figure. Note that surround illumination did not cover the center spot. Spike frequency was determined in the last second of either the dark surround (1–2 s) or light surround condition (3–4 s) as indicated by the gray bars. Sustained surround stimulation increases the responses of a GC to a sinusoidally modulated spot (100% contrast, 2.5 Hz) ($135 \pm 13\%$; $n = 19$; $p = 0.007$). Error bars indicate SEM.

μM were similar in both conditions ($F = 1.104$; $p = 0.363$; $n = 7$). Co^{2+} could potentially reduce the input to the GC by inhibiting the Ca^{2+} current of presynaptic neurons. Because Co^{2+} application did not significantly change the center response, it is unlikely that Co^{2+} had an appreciable effect on the output of presynaptic neurons. Kaneko and Tachibana (1986) reported that GABA_A receptors are also sensitive to Co^{2+} . Since surround mechanisms in the inner retina are reported to be GABAergic, Co^{2+} could potentially have blocked surround responses in GCs by blocking GABA_A receptors in the inner retina. We tested the effect of the GABA antagonist picrotoxin on GC responses and found that the spontaneous activity of transient ON/OFF GCs increased strongly and that the light responsiveness of these cells was lost. Since such effect was not found in $25 \mu\text{M}$ Co^{2+} , it was concluded that Co^{2+} did not block GABA_A receptors in the inner retina.

These experiments indicate that feedback from HCs to cones contributes to surround responses of GCs. Next the effect of sustained surround illumination on the response to a flickering spot was studied. In control conditions, the steady surround illumination enhanced the response significantly to $165 \pm 21\%$ of the control value ($n = 9$; $p = 0.00684$). In the presence of $25 \mu\text{M}$ Co^{2+} , on the other hand, such an enhancement was not present ($111 \pm 15\%$; $n = 9$; $p = 0.24$). A paired t test reveals that surround induced enhancement of the response is significantly larger in control conditions than in the presence of cobalt ($p = 0.00697$, $n = 9$). Furthermore, in the absence of the surround illumination, application of Co^{2+} did not affect the response to the sinusoidal modulation (control: 38.6 ± 8.2 spike/s; cobalt: 35.5 ± 8.9 spike/s; paired t test: $p = 0.797$, $n = 9$), suggesting that Co^{2+} does not strongly alter inner retinal processing. Although we cannot fully exclude that Co^{2+} has some unknown effects in the inner retina, the most simple explanation for the Co^{2+} dependent enhancement of the center response by steady surround illumination at GC level is the outer retinal gain control mechanism described in this paper.

Discussion

In this study, two mechanisms that affected the gain of the photoreceptor synapse have been identified: a gain-decreasing mechanism, and a gain-increasing mechanism. The gain-increasing mechanism leads to response enhancement in HCs and GCs. This gain-increasing mechanism has a time constant similar to that of feedback from HCs to cones. Blocking feedback from HCs to cones abolished the synaptic gain-increase and the resulting response enhancement in HCs and GCs.

The gain-decreasing component we identified in the cone synapse is spatially restricted and cone-type specific. Hyperpolarizing cones lead to a reduction in synaptic gain (Fig. 3). Since we manipulated in this experiment a single cone the observed effects must be cone specific and therefore spatially restricted. We cannot fully exclude that additional gain reduction occurs in the HCs layer it selves. Such additional gain reduction mechanism would be cone-type nonspecific and spatially extensive. The gain-increasing component is spatially extensive and cone-type non-

Figure 5. The proposed gain control mechanism. **a**, A schematic representation of the Ca^{2+} current of a cone. If one modulates the membrane potential of the cone a few millivolts around -35 mV (*i*), a relatively large modulation of the Ca^{2+} current occurs (*ii*). When the cone membrane potential is modulated at more hyperpolarized potentials (*iii*), the resulting modulation of the Ca^{2+} current is much smaller (*iv*). **b**, A schematic representation of the Ca^{2+} current without feedback (solid line) and with feedback (dashed line) from HCs. The modulation of the cone membrane potential by a few millivolts around -35 mV (*i*) leads to a smaller modulation of the Ca^{2+} current when HCs are at their resting membrane potential (*ii*) compared with the condition when HCs are hyperpolarized (*iii*).

specific. Hyperpolarizing HCs leads to a synaptic gain increase in cones (Fig. 3). HCs are strongly electrically coupled and have large receptive fields making the gain-increasing component spatially extensive. Since HCs receive input from more than one cone type and the spectral sensitivity of feedback from HCs to cones differs significantly from the spectral sensitivity of cones (Kraaij et al., 1998), the gain-increasing component is cone-type nonspecific. The notion that synaptic gain increase and synaptic gain decrease are driven differently has major implications for the function of cone/HC complex.

The gain control mechanism of the cone synapse

We propose the following gain control mechanism. Figure 5a shows a schematic representation of the Ca^{2+} current of a cone. If one modulates the membrane potential of the cone a few mV around -35 mV (*i*), a relatively large modulation of the Ca^{2+} current occurs (*ii*). When the cone membrane potential is modulated at more hyperpolarized potentials (*iii*), the resulting modulation of the Ca^{2+} current is much smaller (*iv*). This prediction was fully supported by our experimental results (Fig. 3a,c). Although this model suggests that the gain reduction is due to the shallower slope of the Ca^{2+} current at negative potentials, as already suggested earlier (Attwell et al., 1987; Belgum and Copenhagen, 1988), additional gain reduction will occur in the phototransduction cascade as well. Together, they can account for the intensity-dependent reduction of the initial modulation coefficient seen at the HC level (Fig. 1c). Note that this modulation mechanism is an intrinsic cone mechanism and is therefore local and cone specific.

Negative feedback from HCs to cones shifts the Ca^{2+} current to negative potentials (Verweij et al., 1996; Hirasawa and Kaneko, 2003). Although feedback from HCs to cones is subtractive, the cone output is modified in a multiplicative manner as well. Figure 5b shows the same schematic of the Ca^{2+} current as depicted in Figure 5a, but now in a condition when HCs are at their resting membrane potential (solid line) and when they are hyperpolarized (dashed line). Modulation of the cone membrane potential by a few mV around -35 mV (*i*) leads to a smaller modulation of the Ca^{2+} current when HCs are at their resting membrane potential (*ii*) compared with the condition when HCs are hyperpo-

larized (iii). Consistent with experimental findings, feedback from HCs to cones increases the cone synaptic gain (Fig. 3*b,d*). Note that this mechanism is spatially extensive, not cone specific, and fully accounts for the increase of the modulation coefficient with increased HC to cone feedback (Fig. 1*b,d*). This is a lateral gain control mechanism.

Gain control mechanisms

Lee et al. (1999, 2003) used a sinusoidally modulated full field test stimulus on top of a sinusoidally modulated full field vehicle to study macaque HCs. Their main result was that hyperpolarization of cones and HCs with the vehicle leads to a decrease in response amplitude due to a test stimulus. They found that this sensitivity regulation has a finite time course rather than being based on an instantaneous nonlinearity, such as response compression. They suggested that the mechanism should be localized before the cone signals are summed in the HCs, either in the cone itself or in the cone–BC–HC synaptic triad. Since Lee et al. (1999, 2003) used full-field stimulation, both the gain reduction and the gain enhancing component of feedback will be activated. Since, for such a stimulus, the gain reduction component is always larger than the gain-increasing component, the mechanism shown by Lee et al. (1999, 2003) is most likely dominated by the cone-specific gain-decreasing mechanism described in this paper.

In cat, strong light stimulation leads to a gain reduction in HCs. They found a similar gain reduction with increasing light stimulation as Lee et al. (1999, 2003) and as we describe in the present paper. In contrast to the present paper, Lankheet et al. (1993) suggested that the gain reduction mechanism was based on a spatially extensive mechanism. The main difference between the experiments of Lankheet et al. (1993) and the experiments presented in this paper is that they used slits to stimulate the center and half circular stimuli positioned at each side of the slit for surround stimuli instead of spots and annuli. Due to the spatial configuration of this stimulus, it is less effective in separating center and surround and, it is likely that such stimulus configuration has induced considerable stray light in the center. This might have led them to the conclusion that the process was spatially extensive.

Nelson et al. (1990) reported an enhancement of the response of HCs to a flickering spot with HC hyperpolarization. They argued that the mechanism must account for at least two of the following findings: (1) it must generate an antagonistic surround and (2) it must induce surround facilitation. They acknowledged that these two requirements might be self-opponent if not mutually contradictory. They proposed that the gain control mechanism was located in the cone synapse. The present study makes this gain control mechanism explicit and shows that the antagonistic surround and surround-induced facilitation are neither mutually exclusive nor self-opposing. The gain increase is due to a spatially extensive feedback pathway from HCs to cones (lateral gain control) and the gain reduction is due to a cone specific and spatially restricted mechanism within the cones.

Inhibitory surround of ganglion cells

The classical receptive fields of retinal bipolar and GCs are organized into antagonistic center and surround regions. Stimulation of the surround leads to a reduction of the response to a center spot. A large variety of inhibitory, adaptive and gain control mechanisms are known to influence the responses of GCs (Shapley and Victor, 1978; Victor, 1987; Kim and Rieke, 2001; Baccus and Meister, 2004; Manookin and Demb, 2006). In this paper, we

show that surround illumination enhances the response of transient ON/OFF GCs to a flickering center spot and that the mechanism responsible for this enhancement has, most likely, an outer retinal origin. The conclusion that HCs contribute to the GC surround is in line with other reports (Flores-Herr et al., 2001; McMahon et al., 2004; Ichinose and Lukasiewicz, 2005).

Although inhibition of GCs by sustained surround stimulation has been described by various researchers (Thibos and Werblin, 1978; Ichinose and Lukasiewicz, 2005), enhancement of GC responses due to sustained surround stimulation is not unprecedented (Burkhardt, 1974). Burkhardt (1974) suggested an outer retinal origin. How can we reconcile these findings of the various researchers? In the present paper, we show an outer retinal mechanism that induces response enhancement when the surround is stimulated, lateral gain control. Since all cones receive feedback from HCs, the output of all cones will be affected by the lateral gain control mechanism. The implication is that all GCs would be influenced as well. Why does it seem that this mechanism is visible in some studies and not in others?

In general terms, responses of inner retinal neurons become more and more transient. Some have a purely transient nature, whereas others have a transient onset response followed by a sustained phase. In this study, we have identified two aspects of outer retinal lateral communication: (1) inhibition and (2) synaptic gain control. These two aspects will, most likely, affect sustained and transient responses differently. In first approximation, purely transient responses can be thought of as the first derivative of the sustained photoreceptor response. Sustained surround stimulation will induce an inhibitory signal and a gain enhancement. Additions and subtractions are lost after differentiation, but multiplications or divisions remain prominently present. The implication is that sustained inhibition will have only minor effects on the transient responding GCs whereas gain changes will affect these GCs strongly. On the other hand, sustained responding GCs will most likely be influenced strongly by both the inhibitory and the gain enhancement component. The overall result is that, depending on the dynamic characterization of inner retinal neurons, lateral processing in the outer retina can either lead to suppression or enhancement of responses.

The functional role of horizontal cells

The organization of receptive fields into an excitatory center and an inhibitory surround is an important principle of sensory system design, and is especially prominent in the retina. A variety of functions have been ascribed to this retinal organization including edge enhancement, image deblurring, and redundancy removal. Srinivasan et al. (1982) demonstrated that most of these views are formally equivalent and can be subsumed in the idea of “predictive coding” (see also Atick, 1992; Barlow, 2001; van Hateren, 2005, 2007). The essence of the predictive coding or related concept is that the antagonistic surround, consisting of a weighted average of signals in neighboring neurons, “the predicted value,” is subtracted from the response of the central neuron. In this way the central neuron only transmits information that differs from the predicted, leading to redundancy reduction and allows the neuron to use its entire response range of the postsynaptic neuron for the remaining signal.

To function optimally, predictive coding needs two steps: (1) subtraction of the predicted value from the center response and (2) amplifying the remaining response such that it optimally uses the dynamic range of the postsynaptic neuron. Without prominent gain control, predictive coding will hardly lead to more efficient use of the dynamic range of the postsynaptic neuron,

except for conditions close to saturation. In this study both transformations have been shown to function at the cone photoreceptor synapse, suggesting that indeed the coding step in the outer retina might be considered to be a “predictive coding” step.

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