Modulation of Synaptic Transfer between Retinal Cones and Horizontal Cells by Spatial Contrast

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ABSTRACT We studied the influence of steady annular light on the kinetics and sensitivity of horizontal cell (HC) responses to modulation of the intensity of small concentric spots in the turtle retina. As shown by previous investigators, when the intensity of the annulus was equal to the mean spot intensity, spot response kinetics were the same as those for the modulation of spatially uniform light. Turning off the annulus attenuated dramatically high-frequency flicker sensitivity and enhanced somewhat low-frequency sensitivity. This phenomenon reflects a modulation of synaptic transfer between cones and second-order neurons that is mediated by cones, and it will be referred to as cone-mediated surround enhancement (CMSE). Our main results are as follows: (a) The change in test-spot response sensitivity and kinetics upon dimming a steady surrounding annulus is a consequence of the change in spatial contrast rather than change in overall light level. (b) Introduction of moderate contrast between the mean spot intensity and steady surrounding light intensity causes a marked change in spot response kinetics. (c) The dependence of spot response kinetics on surrounding light can be described by a phenomenological model in which the steady state gain and the time constant of one or two single-stage, low-pass filters increase with decreasing annular light intensity (d) The effect of surrounding light on spot responses of a given HC is not determined by change in the steady component of the membrane potential of that cell. (e) Light outside the receptive field of an HC can affect that cell's spot response kinetics. (f) In an expanding annulus experiment, the distance over which steady annular light affects spot response kinetics varies among HCs and can be quite different even between two cells with closely matched receptive field sizes. (g) The degree of CMSE is correlated with HC receptive field size. This correlation suggests that part of the enhancement mechanism is located in the HC. Taken together, our results suggest the involvement of the inner retina in CMSE.

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INTRODUCTION

More than 25 years ago, Westheimer (1967) conducted psychophysical experiments to study spatial interaction in cone vision of human subjects. He measured the sensitivity to a flashed spot at the center of a uniformly illuminated circular patch in the fovea. He found that sensitivity first decreased as the diameter of the background patch was increased up to ~5 min of arc. But, as the diameter was increased further, sensitivity increased. The sensitizing effect of surrounding annular light was present from low to high photopic light levels, but was not as dramatic at the lower light levels. Similar results were obtained in peripheral areas of the retina, but on a broader space scale consistent with the decrease in visual acuity with retinal eccentricity.

Burkhardt (1974), in intracellular and extracellular recordings in the mud puppy retina, found apparent electrophysiological correlates of Westheimer's psychophysical results. He recorded action potentials of retinal ganglion cells and the proximal negative response with extracellular electrodes, and he also recorded intracellularly from bipolar and horizontal cells (HCs). Burkhardt found that when a steady background of constant illuminance was extended in diameter from 0.1 to 0.25 mm, responses to a flashed, concentrically placed test spot were attenuated. Extending the diameter of the steady background spot beyond 0.25 mm resulted in enhancement of responses to the test spot. Burkhardt (1974) also reported finding similar surround sensitization in extracellular recordings from frog and turtle retinas. More recently, similar results have been obtained in turtle HCs (Itzhaki and Perlman, 1984, 1987; Chappell, Naka, and Sakuranaga, 1985) and in catfish HC, amacrine, and ganglion cells (Kawasaki, Aoki, and Naka, 1984).

One of Burkhardt's (1974) experiments ruled out major rod involvement in the enhancement phenomenon in the mud puppy retina. In this experiment, conducted at a high photopic light level, the test spot and circular background were superimposed on a spatially uniform field bright enough to saturate rods. We therefore think it appropriate to refer to this spatial interaction as cone-mediated surround enhancement (CMSE). This term clearly distinguishes CMSE from suppressive rod-cone interaction (SRCI), in which a rod-effective background enhances the sensitivity of cone-driven responses (Frumkes and Eysteinsson, 1987; Frumkes and Wu, 1990; Eysteinsson and Frumkes, 1989; Witkovsky and Stone, 1987).

It is well established that under conditions of spatially uniform background illumination, the sensitivity of retinal neurons to a test stimulus that is spectrally matched to the background decreases monotonically with increasing background light level (Alpern, Rushton, and Torii, 1970; Baylor and Hodgkin, 1974; Werblin, 1974; Normann and Werblin, 1974; Fain, 1976; Naka, Chan, and Yasui, 1979; Purpura, Tranchina, Kaplan, and Shapley, 1990; see review by Shapley and Enroth-Cugell, 1984). Simultaneously, response kinetics speed up. Analogous findings have been obtained in human psychophysical studies (Kelly, 1971). These are traits of a form of light adaptation referred to as "field adaptation." A distinctly different form of light adaptation occurs in CMSE. In this case, despite the increase in overall light, sensitivity to the dynamic test stimulus paradoxically increases. In his early study of this phenomenon, Burkhardt (1974) pointed out that the latency of the ganglion cell
response to a test flash was reduced when the sensitivity was enhanced by surrounding light. More recent studies confirmed that surround sensitization is accompanied by a speeding up of response kinetics (Kawasaki et al., 1984; Chappell et al., 1985; Naka, Itoh, and Chappell, 1987).

CMSE is not present in the recorded voltage responses of cones (Normann and Perlman, 1979; Kawasaki et al., 1984; Itzhaki and Perlman, 1987; Naka et al., 1987). Thus, CMSE appears to involve the modulation of synaptic transfer between cones and second-order neurons.

Chappell et al. (1985) have shown that in the turtle retina, if a modulated test spot is surrounded by steady light with illuminance equal to the mean value of the spot, the kinetics of the HC spot response are very similar to those for modulation of spatially uniform light around the same mean. Naka et al. (1987) recorded both from red-sensitive cones and luminosity HCs in the turtle retina. They showed that, under conditions of spatially uniform mean light level, the kinetics of the HC response to spot or full-field modulation are almost identical to those of the red-sensitive cones that provide their major synaptic input. Turning off the light surrounding the test spot, thus introducing static spatial contrast, leads to a reduction in sensitivity and a slowing down of the kinetics of the response. Thus, under these conditions, the HCs exhibit slower response kinetics than the cones that provide their synaptic input. This is reflected in the time domain by a relatively slow impulse response function of reduced amplitude, and in the frequency domain by a decrease in high-frequency flicker sensitivity.

Several lines of evidence suggest that CMSE plays an important role in visual physiology. CMSE has been observed in all types of retinal neurons except photoreceptors in various nonmammalian vertebrates, in the off-subtype of P-type retinal ganglion cells in the primate retina (Benardete, 1994), and in human psychophysical experiments. Moreover, our results suggest that CMSE occurs under physiological conditions in which there is moderate spatial contrast in the retinal image. This suggests that it plays a role in detection and identification of objects on a background.

METH O D S

Preparation

Intracellular recordings were obtained from luminosity horizontal cells in the isolated eyecup preparation of the turtle Pseudemys scripta elegans. The preparation and recording methods were similar to those described previously (Tranchina, Sneyd, and Cadenas, 1991). The eyecup was placed in a recording chamber that was supplied with moistened O2. A Peltier device controlled by a feedback circuit maintained the temperature of the preparation at 18°C.

Visual Stimuli

We used a two-channel optical system. One channel contained a monochromator (H10; Instruments SA, Metuchen, NJ) used to measure spectral sensitivity. The monochromator and projection lens system provided uniform light in the retinal plane with a flux of $2.6 \times 10^{13}$ photons s$^{-1}$ cm$^{-2}$ at 640 nm, as measured with an optometer (61CRT; United Detector Technology, Hawthorne, CA). A second channel was used to present images displayed on a
The images were generated by a computer-based visual stimulator (V-4; Laboratory of Biophysics and Electronics Shop, The Rockefeller University, New York). The image on the CRT measured 100 x 100 mm and consisted of 256 x 256 picture elements; the frame rate was 270 Hz. The mean luminance of the CRT, measured with the optometer above, was 100 candle/m². We determined the equivalent flux of monochromic light at 640 nm as follows. The flux of a step of light delivered by the monochromator (640 nm) was adjusted until the response elicited in a luminosity HC matched that given by a step of known luminance from the CRT. We concluded that the mean CRT intensity was equivalent to a retinal flux of $5.5 \times 10^{11}$ photons/s·cm$^{-2}$ at 640 nm. According to Baylor and Hodgkin (1973), this retinal flux would produce $\sim 5.5 \times 10^4$ photoisomerizations/s in a red-sensitive cone. The mean light intensity of the CRT hyperpolarized the HCs by $\sim 11$ mV from the dark adapted level. The HCs responded to square-wave modulation at 1 Hz of spatially uniform light from the CRT at 100% contrast with peak-to-peak amplitudes of 35–45 mV. Saturating responses to steps of light from the monochromator presented out of darkness were 40–50 mV in amplitude.

The visual stimulator (V-4) and CRT were used to generate drifting sinusoidal gratings, spots, and bars where the illuminance was sinusoidally modulated around a mean level and annuli of various fixed intensities. The CRT display was imaged onto the retina by a photographic lens (85 mm, f/1.4, Nikkor; Nikon, Garden City, NY); the object/image ratio was 16.

**Recording Techniques and Data Storage**

Recordings were obtained with microelectrodes pulled from 1.0 mm outer-diameter glass pipettes (B100; World Precision Instruments, Inc. [WPI], New Haven, CT) on a Brown-Flaming micropipette puller (P-77B; Sutter Instrument Co., San Francisco, CA). Typical electrode resistances were 150–300 MΩ. Intracellular signals were amplified with a WPI 707A amplifier and displayed on a storage oscilloscope (5103; Tektronix). Intracellular signals were further amplified (to range between $-5$ and $+5$ V) and sampled at the frame rate of V-4 by a 12-bit analogue-to-digital converter. The samples were stored in bins phased to the stimulus cycle and averaged for 15.2–60.8 s. The signal-averaged response was displayed continuously during an experimental run. The responses were stored in a file and analyzed later off line.

**Cell Identification**

Luminosity horizontal cells were identified by depth in the retina, waveform of the response, spectral sensitivity, and spatial sensitivity profile. We measured the spatial frequency response at a fixed temporal frequency of 4.2 Hz to determine the space constant of the cell's exponential spatial sensitivity profile (Tranchina, Gordon, and Shapley, 1983; Tranchina et al., 1991). Exponential space constants for cells in this study ranged between 74 and 812 μm.

**RESULTS**

**Temporal Aspects of the Interaction between Steady Annular Light and Spot Responses**

Spot response kinetics in presence and absence of steady annular light. Fig. 1A shows temporal frequency responses of a luminosity horizontal cell to sinusoidal modulation of the intensity of a spot (780 μm diameter) around a mean light level, $I_0$, under two different conditions, one in the presence of a contiguous annulus with steady light intensity $I_A$, where $I_A = I_0$ (open symbols), and the other with $I_A = 0$ (filled symbols). Response gain and phase are plotted in the upper and lower panels, respectively.
The data in Fig. 1A show the typical enhancement of sensitivity to high-frequency spot flicker and decrease in phase lag of the response caused by the addition of steady annular light. We refer to this phenomenon as cone-mediated surround enhancement (CMSE). Fig. 1A also shows that, for this cell, steady annular light had little effect on sensitivity at low frequencies. The increase in high-frequency gain and decrease in phase lag are reflections of the speeding up of response kinetics. The gain and phase together, according to linear systems theory, allow the computation of the linear regime response to any stimulus.

Fig. 1B shows the spot impulse response functions corresponding to the two temporal frequency responses in Fig. 1A. The impulse response function corresponds to the response that would be produced by a brief increment in spot illuminance above the mean level used to measure the temporal frequency response. Each impulse response function was computed by taking the Fourier transform of the corresponding frequency response in Fig. 1A. Note that we have elected to plot the computed impulse responses with positive polarity, despite the fact that the luminosity HCs hyperpolarize to increments in light. The amplitude of the impulse response for the annulus-on condition (solid line) is roughly four times larger than that for the annulus-off conditions (dashed line). The impulse response for the annulus-on condition is also faster and has a larger undershoot than that for the annulus-off condition. However, the integrals of the impulse response functions for the two stimulus conditions are about equal. According to linear systems theory, the integral of the impulse response function is equal to the frequency response evaluated at zero frequency. These data are consistent with those of previous studies (Kawasaki et al., 1984; Chappell et al., 1985).

Fig. 1C shows similar but more pronounced spatial interaction measured in the same cell with a spot of 195 μm in diameter.

The data in Fig. 1, A and C, can be used to demonstrate that spot response kinetics vary little with spot size in the annulus-on condition, but that in the annulus-off condition, spot response kinetics are slower for the smaller spot size. This point is illustrated in Fig. 1D, which plots normalized frequency responses (gain only) from Fig. 1, A and C, for the two spot sizes in the annulus-on (upper panel) and annulus-off (lower panel) conditions.

It is worth emphasizing that in a previous study of surround sensitization, Chappell et al. (1985) found that spot response kinetics in the presence of a steady annulus with the same light intensity as the mean spot intensity are the same as those for the response to modulation of a spatially uniform light. Our own data, like that in Fig. 1, indicating that spot response kinetics are similar for different spot sizes, provided that the mean retinal illuminance is spatially uniform, are consistent with the findings of Chappell et al. (1985). Thus, lowering the illuminance in the retinal field surrounding a test spot leads to a slowing down of spot response kinetics to varying degree, depending on spot size.

It is important to note that the effect of annular light on the sensitivity of spot responses is not always evident if one looks only at the amplitude of the spot impulse response function at peak response time. Fig. 2A plots the frequency responses of a different HC to modulation of a 390-μm diameter spot. Here, one can see that for this cell sensitivity to high-frequency flicker was increased and sensitivity to low-
FIGURE 1
frequency flicker was decreased by steady annular light. The corresponding impulse response functions for the annulus-on and -off conditions (Fig. 2 B) have roughly the same amplitude. However, the impulse response function for the annulus-off condition is much more spread out than that for the annulus-on condition, and the impulse response function for the annulus-off condition reaches its peak ~27 ms later than that for the annulus-on condition.

For a few cells (not shown), the amplitude of the impulse response function for a small spot (e.g., 195 μm in diameter) was larger for the annulus-off than for the annulus-on condition. These results indicate that CMSE could be defined in the broadest manner by the enhancement of sensitivity to high-frequency flicker caused by steady annular light, rather than by the enhancement of sensitivity of the impulse response function measured at peak time.

Dependence of CMSE on flicker frequency. Fig. 3 shows how the effect of steady annular light on spot flicker sensitivity depends on temporal frequency for a population of 27 cells. To prepare this figure, temporal tuning curves like those in Fig. 1 A were compared frequency by frequency. The response ratio $r$ plotted on the ordinate was obtained by dividing response gain for spot (780-μm diameter) flicker in the presence of a steady annular light ($I_A = I_0$) by that in the presence of a dark annulus ($I_A = 0$) for each frequency. Symbols plot the mean value of $r$ for the population of cells at each frequency, and the bar represents the standard error of the mean. The data in Fig. 3 show that $r$ increases monotonically with temporal frequency. At the lowest frequency of measurement (0.132 Hz), $r$ was usually somewhat less than 1, and at the highest frequency (16.9 Hz), $r$ had an average value of 5.

Figure 1. (opposite) (A) Temporal frequency responses of a luminosity horizontal cell measured under two different conditions with sinusoidal modulation of the illuminance of a 780-μm diameter spot around a mean level $I_0$. In one case, the illuminance $I_A$ of the annular field surrounding the spot was set equal to the mean spot illuminance (open symbols), and in the other case, $I_A$ was set equal to zero (filled symbols). The inner diameter of the annulus was equal to the spot diameter, and the annular field filled almost the entire retinal area complementary to the spot. Response gain (upper panel) was computed by dividing the Fourier component of the response at the input stimulus frequency by stimulus contrast ($U_{max} - U_{min}/ U_{max} + U_{min}$). Response phase (lower panel) is the phase difference between the stimulus sinusoid and the Fourier component of the response at the stimulus frequency. In this and other figures displaying frequency responses, the symbols that plot experimental data are connected with straight lines as a visual aid, unless otherwise indicated. (B) Impulse (brief flash) response functions corresponding to the two-frequency responses above for the annulus-on (solid line) and annulus-off (dashed line) conditions. Each impulse response is plotted in relative units by dividing by the peak amplitude of the response for the annulus-on condition. (C) Frequency responses measured with a smaller spot (195-μm diameter) from the same cell as in A above. Frequency responses for the annulus-on and annulus-off conditions are plotted with open and filled symbols, respectively. These data show that CMSE is greater with the 195-μm spot than with the 780-μm spot. (D) Normalized frequency responses (gain only) for the 780-μm diameter (closed symbols) and 195-μm diameter (open symbols) spots in the annulus-on condition (upper panel) and annulus-off (lower panel) conditions. These data are taken from A and C above.
Quantitative description of change in spot response kinetics. The change in spot response kinetics between the annulus-on and annulus-off conditions can be described quantitatively by a simple phenomenological model. The value of such a model is that the corresponding empirical equation provides a convenient method for testing specific physical models for surround enhancement. One simply has to compare the theoretical transformation in spot response kinetics between the two stimulus conditions given by the physical model to that described by the empirical equation.

It is well known that despite the nonlinear behavior overall of cones and HCs, these cells respond approximately linearly to stimuli consisting of moderate perturbations of light around a mean level (Tranchina, Gordon, Shapley, and Toyoda, 1981; Tranchina et al., 1983; Daly and Normann, 1985; Naka et al., 1987). In the

![Figure 2](image-url)
phenomenological model, the frequency response of the transformation between stimulus and response of the horizontal cell \( H(f) \) is represented by a cascade of linear filters. Let us define \( T(f) \) as the overall frequency response of the components with filtering properties that are independent of annular illuminance and \( G(f) \) as the frequency response of a component that is dependent on steady annular illuminance. With these definitions, \( H(f) = T(f) G(f) \). We found that under conditions where CMSE is substantial but not dramatic, for example, when measured with a 780-µm spot, the difference between frequency responses for the two stimulus conditions can be accounted for by changing the gain and time constant of a single-stage, low-pass filter. In this case, \( G(f) = k/(1 + i2\pi f\tau) \), where the steady state gain \( k \) and time constant \( \tau \) depend on annular illuminance. If the frequency response to spot flicker with annulus on is called \( H_L(f) \), and that with annulus off is called \( H_D(f) \), then, according to the model, the ratio of the two frequency responses \( H_D(f)/H_L(f) \) is given by

\[
\frac{H_D(f)}{H_L(f)} = \frac{k_D/k_L}{1 + i2\pi f\tau_L} \left( 1 + i2\pi f\tau_D \right).
\]  

where the subscripts \( L \) and \( D \) correspond to the light and dark annulus conditions, respectively. Fig. 4A is a plot of \( H_D/H_L \) computed from the data in Fig. 1A (symbols). The continuous line is drawn from Eq. 1 with \( k_D/k_L = 0.92, \tau_D = 79 \text{ ms} \), and \( \tau_L = 2.8 \text{ ms} \). The conclusion from the fit of Eq. 1 to the data in Fig. 4A is that turning off the annular light has an effect that is phenomenologically equivalent to changing the time constant of one stage of low-pass filtering between stimulus and response from 2.8 to 79 ms. In this particular experiment, the steady state gain, which determines the sensitivity to low-frequency flicker, was decreased slightly (i.e., \( k_D/k_L < 1 \)), but most cells showed an increase in steady state gain upon turning the annulus off (i.e., \( k_D/k_L > 1 \)). Note that according to this model, the ratio of response gains for the two stimulus conditions approaches \( \tau_L/\tau_D \) as \( f \to \infty \). The quantity \( k_D/k_L \) gives the asymptotic ratio of gains as \( f \to 0 \), which equals the ratio of time integrals of the two impulse responses.

Data from the population of cells in Fig. 3 were processed in the same way as in Fig. 4A, and a statistical summary is provided by the following list, in which the mean ± standard deviation is given for each of the parameters: space constant \( \lambda = \)
When CMSE was measured with spot sizes < 780 μm in diameter, CMSE was more dramatic, and the empirical equation Eq. 1 often did not provide a good description of the ratio of the frequency responses for the annulus-on and -off conditions. In this situation, the relative gain curve given by Eq. 1 fails to fall off steeply enough to match the data. An embellishment of the model above, in which steady annular light alters the gain and time constant of two single-stage, low-pass filters, provides a better description of the data when CMSE is more dramatic. In this case,
\[ G(f) = \frac{k}{(1 + i2\pi f\tau_1)(1 + i2\pi f\tau_2)}, \]
and
\[ H_D(f) \frac{H_L(f)}{H_L(f)} = \frac{k_D}{k_L} \frac{(1 + i2\pi f\tau_{L_1})(1 + i2\pi f\tau_{L_2})}{(1 + i2\pi f\tau_{D_1})(1 + i2\pi f\tau_{D_2})}. \]

Note that Eq. 2 includes Eq. 1 as a special case \((\tau_{L_2} = \tau_{D_2} = 0)\). The data in Fig. 4 B (symbols) were computed by taking the ratio of frequency responses for the annulus-on and -off conditions from Fig. 1 C. Dashed and dotted lines were drawn from Eqs. 1 and 2, respectively. The dotted lines in Fig. 4 B were drawn from Eq. 2 with best-fit parameters \(k_D/k_L = 1.3, \tau_{L_1} = 4.8 \text{ ms}, \tau_{L_2} = 3.9 \text{ ms}, \tau_{D_1} = 47 \text{ ms}, \tau_{D_2} = 47 \text{ ms}\). Eq. 2 clearly provides a better description of the data in Fig. 4 B.

Note that the phase of \(H_D/H_L\) (Fig. 4, A and B, lower panels) first decreases as \(f\) increases up to a point, and that as \(f\) increases further, the phase approaches zero. This behavior provided the basis for considering the class of empirical equations for \(H_D/H_L\) that is a quotient of polynomials of the same degree in \(i2\pi f\). Eqs. 1 and 2 are variations on a model suggested by Naka et al. (1987).

**Spatial Aspects of Surround Enhancement**

The question of whether CMSE is mediated by a presynaptic mechanism, a postsynaptic mechanism, or both may be addressed by investigating the extent of CMSE in various cell types, its dependence on spatial aspects of the stimulus, and the spatial distribution of the change in sensitivity brought about by surround illumination. The basic idea is that if the target site for the modulation of response kinetics in CMSE were the cone terminal, then one would expect to find more-or-less the same degree of enhancement in cells postsynaptic to the cones, at least for small enough spot sizes.

The two morphological types of luminosity HCs in the turtle retina, axon terminals, and somata (Simon, 1973; Leeper, 1978) share a synapse with red-sensitive cones. Although luminosity HC receptive field sizes may not fall into two distinct categories in the turtle retina (Lamb, 1976), there is good evidence that cells with the smallest and largest receptive fields correspond to HC somata and axon terminals, respectively (Piccolino, Neyton, Witkovsky, and Gerschenfeld, 1982; Witkovsky, Owen, and Woodworth, 1983). Therefore, the question of whether CMSE is different in HC axon terminals and HC somata may be addressed by measuring the correlation between the degree of CMSE and receptive field size. If, for example, CMSE were observed in large-field but not small-field HCs, this would rule out the cone terminal as a site of enhancement.

**Dependence of CMSE on receptive field size.** In Fig. 5, we examine the dependence of CMSE on HC receptive field size. Fig. 5 is a scatter plot of surround enhancement at 8 Hz vs receptive field size for a spot of 780 \(\mu\text{m}\) in diameter. The frequency of 8 Hz was high enough to demonstrate robust modulation of high-frequency sensitivity and low enough to give HC responses with good signal-to-noise ratio. The response amplitude ratio \(r\) plotted on the ordinate (Fig. 5) is as defined above; the exponential space constant \(\lambda\) of the cell's one-dimensional spatial sensitivity profile is plotted on the abscissa. The space constant was determined by measuring the spatial frequency response of the cell and fitting it with the analytical expression corresponding to the
exponential spatial sensitivity profile (Tranchina et al., 1983). Fig. 5 shows a statistically significant correlation between degree of surround enhancement and receptive field size for a population of 54 cells when measured with a 780-μm spot. This conclusion is based on the results of a t test in a linear correlation analysis. The null hypothesis that surround enhancement (as measured by r) and receptive field size (as measured by λ) are not linearly correlated for a 780-μm spot can be rejected with P < 0.001, given the data in Fig. 5. The slope of the best-fit straight line in Fig. 5 is 6.5 × 10⁻³ μm⁻¹. In Discussion, we will use the data in Fig. 5 and the data below on the spatial distribution of sensitivity change within the test region to argue that at least part of the enhancement mechanism is located in the HC.

Spatial distribution of sensitivity change within test region. At first glance, the fact that large-field HCs show greater enhancement than small-field HCs argues against the idea that each cell type is simply reporting signals that are already enhanced in the cone terminal. The results seem to suggest that a target site for enhancement is located in the HC. However, the cone-terminal hypothesis can not be ruled out by the above result alone for the following reason. It is theoretically possible that signals in cone terminals far away from the center of the test region are enhanced more than those near the spot center. If this were the case, then large-field HCs would show more enhancement than small-field HCs because large-field HCs would give more weight to the distant, enhanced inputs than small-field HCs. We designed the following experiment to test this idea. The test region, a 780-μm diameter spot, was divided into two complementary parts by a circle with a diameter of 390 μm. The 780-μm spot had a mean light level of I₀ as above, and we modulated either the inner (390-μm diameter spot), the outer (annulus with a 390-μm inner diameter and a 780-μm outer diameter), or the entire test region. As above, the test region was surrounded by a steady annulus with intensity Iₐ = I₀ or Iₐ = 0. We asked whether the small inner spot or the contiguous inner annulus was more affected by Iₐ. We computed the gain factor for the small central spot, rₛ, and for the surrounding contiguous annulus, rₐ. For the purpose of statistical analysis, each of these gain factors was normalized by the gain factor r for modulation of the entire test region.
Let us call the normalized gain factors for the small spot and contiguous annulus $r_1'$ and $r_2'$, respectively. We computed the mean and standard error of the mean for the difference $d = r_2' - r_1'$. The mean value of $d$ for 11 cells was found to be $-0.1$. Thus, on average, the center part of the test region showed slightly more enhancement than the contiguous annular region. We performed a one-sided, paired-sample $t$ test to test the null hypothesis, $H_0: \mu_d > 0$, where $\mu_d$ is the population average of $d$. The probability corresponding to the computed $t$ value was 0.083. Thus, these data do not support the hypothesis that the test region near the border between the 780-$\mu$m spot and outer steady annulus is affected more by annular light than the region in the center of the receptive field, which is more distant from this border. In any case, the effect of steady annular light seems to vary little with position in the test region. We argue in Discussion that these data in conjunction with those in Fig. 5 suggest that at least part of the enhancement mechanism is located in the HC.

**Spatial extent of the influence of surrounding light.** We asked whether the spatial scale for the influence of surrounding light matches the receptive field size in the recorded cell. Is it possible that the recorded cell itself mediates the enhancement measured in that cell? Fig. 6 shows the results of experiments designed to measure the spatial scale for the influence of annular light on spot responses. Fig. 6, A and B, are plots of normalized amplitude of response to spot flicker vs outer radius of the steady annulus, as measured with test spots of 780 and 390 $\mu$m in diameter, respectively. The first data point on the abscissa for each line graph, in which the outer radius of the steady annulus is equal to the spot radius, corresponds to a test spot surrounded by darkness, i.e., the annulus-off condition. Normalized response amplitude is defined as the amplitude of spot response with the annulus off divided by the amplitude with outer radius equal to 3,125 $\mu$m (i.e., spatially uniform mean light level). The first data point along the abscissa corresponds to the case where the outer radius of the annulus is equal to the spot radius, i.e., the annulus-off condition. The number labeling each data set refers to the space constant measured in micrometers of the corresponding HC. (B) Data from an experiment similar to that in A, except that the diameter of the spot was 390 $\mu$m.
spatially uniform mean light level). For the sake of figure clarity, results from only 3 out of 10 cells are plotted in Fig. 6A, and results from three out of eight cells are plotted in Fig. 6B.

We found that spot flicker sensitivity can change with the outer radius of the steady annulus at very different rates between two cells with similar space constants and with similar maximal enhancement. For example the two cells in Fig. 6A with space constants of 545 and 547 μm show sensitivities to spot flicker that saturate at low and high rates, respectively, as the outer annulus is expanded in radius. Two cells in Fig. 6B, both with space constants of 503 μm, also show differences in the dependence of enhancement on outer radius of the annulus. The cell in Fig. 6A with a space constant of 614 μm is an extreme example of a cell whose spot response amplitude saturates slowly with outer radius of the steady annulus. For this cell, the relative sensitivity to spot flicker was only about half-maximal, even when the outer radius of the steady annulus was ~ 1,200 μm.

Fig. 6B demonstrates that the addition of annular light in a region distant from the center of the receptive field of a small-field cell can have an appreciable effect on spot flicker sensitivity of this cell. For the cell in Fig. 6B with a 92-μm space constant (h), expanding the steady annulus from the outer radius of 390 μm (which is equal to 4.2 h) to 488 μm (which is equal to 5.3 h) increased the relative sensitivity to spot flicker from 0.72 to 0.94. For the sake of appreciating the electrotonic distance corresponding to 390 μm, we point out that the retinal area included in a spot with a radius of 390 μm would contribute 96% to the amplitude of the response to modulation of spatially uniform light for this cell, while the annulus with inner radius of 390 and outer radius of 488 μm would contribute <3%.

As the extent of signal spread in the network of electrically coupled HCs is determined by the space constant h, the data in Fig. 6 suggest that surround enhancement in a given HC is not mediated principally by electrical coupling between that cell and other HCs.

Graded Dependence of Surround Enhancement on Steady Annular Illuminance

The following experiment was designed to determine whether the mechanisms underlying CMSE might be operable under normal physiological conditions in which there is only moderate spatial contrast in the visual scene. This experiment also provides information on the question of whether rods play a major role in CMSE in the turtle retina.

Fig. 7 shows that CMSE is smoothly graded with annular light intensity. In Fig. 7, r is plotted as a function of temporal frequency for various values of I_A from 0.1 to 2 times the mean spot illuminance, I_0. Fig. 7 shows that there need not be a dramatic difference between mean spot intensity and annular intensity to see a significant change in flicker sensitivity from that measured under conditions of spatially uniform mean light intensity. Dimming the annulus by only a factor of 2, from I_A = I_0 to I_A = I_0/2 caused a substantial attenuation in spot flicker sensitivity at the higher frequencies. Note also that increasing the intensity of the annulus by a factor of 2 from I_A = I_0 to I_A = 2I_0 gave a substantial enhancement in high frequency sensitivity. We may conclude that moderate variations in static contrast in a region of retina can lead to significant changes in the kinetics of the response to a dynamic stimulus in that
it is important to note that the mechanism that determines spot response kinetics is sensitive to the sign of the contrast between spot and annulus. The brighter the annulus compared to the spot, the faster the spot response kinetics. When the annulus is brighter than the mean spot intensity, spot response kinetics are even faster than those under conditions of spatially uniform mean light level. These results support and extend those of Burkhardt (1974).

These data also provide evidence against major rod involvement in CMSE. According to a previous study (Tranchina et al., 1991), the mean illuminance \( I_0 \) of the spot used here puts red-sensitive cones into the Weber's law regime, where incremental sensitivity is inversely proportional to the background light level. We expect the green P31 phosphor to be a more effective stimulus for rods than for red-sensitive cones, based on the peak spectral sensitivities of \( \sim 515 \) and \( \sim 630 \) nm, respectively (Baylor and Hodgkin, 1973). Therefore, it is likely that the rods are saturated by the mean CRT illuminance \( I_A \). However, changes in the mean annulus illuminance \( I_A \) from \( I_A = I_0 \) to \( I_A = 2I_0 \) resulted in greater enhancement. Thus, it is unlikely that rods played a role in this effect of annular light.

**The Role of Overall Light Level: Dimming the Annulus Versus Overall Dimming**

We asked whether the attenuation in high-frequency sensitivity upon dimming the annulus from a light level equal to that of the mean spot intensity is a consequence of the overall lower light level. Previous studies of temporal frequency sensitivity of cones (Daly and Normann, 1985; Tranchina et al., 1991) and HCs (Tranchina et al., 1984; Chappell et al., 1985) have shown that lowering spatially uniform light, or the intensity of a spot surrounded by darkness, can only increase sensitivity at any given frequency. The results below confirm these findings. The sensitivity of the HC to spot flicker at 13 Hz was measured under four different conditions for mean spot illuminance, \( I_0 \), and steady annular illuminance, \( I_A \). The light levels in units of percent maximal CRT illuminance were as follows: (a) \( I_0 = 50, I_A = 50 \), (b) \( I_0 = 50, I_A = 0 \), (c) \( I_0 = 50, I_A = 25 \), (d) \( I_0 = 25, I_A = 25 \). For each condition, relative sensitivity was computed by dividing the measured sensitivity by that measured for condition a. The relative sensitivities for conditions a–d were 1, 0.2, 0.8, and 1.1, respectively. Thus, the sensitivity to spot flicker at 13 Hz was reduced when the
intensity of only the annulus was reduced by a factor of 2, but not when the mean intensity of the spot and annulus were both reduced by a factor of 2.

The Role of Membrane Polarization

A previous investigation of surround enhancement in catfish HCs by Kawasaki et al. (1984) suggested that it might be mediated by changes in membrane potential of the HC. They reported that in experiments not shown in their paper, the sensitization produced by a background field was dependent on the amplitude of the steady hyperpolarization but not on the size of the illuminated area. Our results on turtle HCs are not consistent with this claim for catfish HCs. We present several lines of evidence here that membrane potential in the cell from which one is recording is not strictly related to the enhancement measured in that cell.

The experiments above showed that dimming the steady annulus surrounding a test spot led to an attenuation of sensitivity to high-frequency flicker, while dimming the entire field of light by the same factor did not. This was despite the fact that the depolarization of the HC was greater for the overall dimming than for the dimming of the annulus. One might argue that the frequency response of synaptic transfer between cones and HCs is in fact affected by voltage or light level, but that the decrease in high-frequency sensitivity of synaptic transfer upon dimming the spot and annular field simultaneously was masked by an increase in sensitivity of the cones in the test region caused by light adaptation. This can not be the case because a previous study (Tranchina et al., 1991) has shown that the sensitivity of cones to high-frequency flicker (e.g., > 12 Hz) is independent of mean light level over a broad range of light levels including the light levels used in this study.

Still, another experiment suggesting that neither change in the steady component of HC membrane potential per se in the recorded cell nor change in the gradient of membrane potential in the HC network plays a critical role in surround enhancement involved the use of a test bar (390 μm wide) that was centered 390 μm eccentric to the center of the HC receptive field (recording site). The purpose of the experiment was to examine the effects of two different voltage profiles and voltage gradients between the test region and the recording site. As in the case of the spot experiments above, the intensity of the bar was modulated with a sinusoidal time course around a mean level $I_0$. In this experiment, the test bar by convention was said to be to the right of the receptive field center, so the region to the left of the test bar included the receptive field center, and the region to the right covered only a peripheral part of the HC receptive field. We measured sensitivity to modulation of the test bar under four different conditions of steady light in the retinal area to the right and left of the test bar. The four stimulus conditions were (a) darkness on both sides of the test bar; (b) steady light with intensity $I_0$ on both sides of the bar; (c) steady light with intensity $I_0$ on the left and darkness on the right; (d) steady light on the right and darkness on the left. Conditions b and c produced two different membrane voltage profiles and membrane voltage gradients between the test region and recording site. We found that steady light presented on both sides of the test bar simultaneously enhanced the flicker response to the bar, and the effect was similar to that of annular light on spot responses. Steady light on one side of the test bar alone enhanced flicker responses to a lesser degree. However, the enhancement produced by light on the left only was
approximately equal to that produced by light on the right only. This was despite the fact that when steady light was placed on the side of the test bar where it covered the receptive field center (left), the hyperpolarization was greater (at the recording site) than when the steady light was on the other side, in the periphery of the receptive field. In one typical cell, for example, the enhancement in flicker sensitivity when steady light was on the right of the test bar ($r = 2.3$) was about the same as that when the light was on the left ($r = 2.1$), despite the fact that the membrane potential at the recording site was more hyperpolarized by $2$ mV when the light was on the left. Of course, because of the symmetry of the stimulus configuration, HCs located in the center of the test bar were polarized to the same degree by light on the left or on the right. Similar results were obtained on $10$ cells.

Our final evidence that level of polarization in the cell from which one is recording does not determine high-frequency flicker sensitivity is contained in the results of an experiment presented above, where expanding an annulus virtually outside the receptive field of a small-field cell (Fig. 6B) led to a change in flicker sensitivity, despite the fact that there was no change in membrane potential in the center of the test region.

We wish to emphasize that our data do not show that the membrane potential of HCs plays no role in CMSE; rather, the data show that there is not a strict relationship between membrane potential in the recorded HC and the degree of CMSE in that cell. It is possible to alter high-frequency sensitivity in the recorded cell without changing the steady component of its membrane potential. Furthermore, a change in steady membrane potential in a given HC does not necessarily alter its high-frequency sensitivity.

**DISCUSSION**

We have extended previous work on CMSE in HCs (Burkhardt, 1974; Kawasaki et al., 1984; Chappell et al., 1985) by characterizing in more detail its spatial and temporal aspects. The kinetics and sensitivity of HC responses to modulation of the intensity of a test spot around a mean level $I_0$ are dramatically affected by the steady light intensity $I_A$ of an annulus surrounding the spot. In our study, $I_0$ was high enough to put luminosity HCs and red-sensitive cones into the Weber's law regime, where sensitivity to an incremental stimulus presented on a spatially uniform background is inversely proportional to the background light level. Weber's law behavior is observed both in sensitivity as measured by the amplitude of the impulse response function at peak response time and also in sensitivity as measured by the amplitude of the response to low-frequency sinusoidal flicker (Tranchina, Gordon, and Shapley, 1984; Tranchina et al., 1991). When $I_A = I_0$, spot response kinetics are the same as those for modulation of spatially uniform light around $I_0$ (Chappell et al., 1985). Under these conditions, the HC response kinetics resemble those of the red-sensitive cones (Naka et al., 1987), which provide the major synaptic input to luminosity HCs. Either dimming a steady annulus surrounding a test spot or reducing its outer radius leads to an attenuation in high-frequency spot-flicker sensitivity, and this is sometimes accompanied by a modest increase in low-frequency sensitivity. This alteration in response kinetics is reflected in the time domain by a slower impulse response function with little or no biphasic behavior. The slower impulse response waveform is
usually but not always accompanied by a reduction in amplitude at the time of the peak. Previous studies (Kawasaki et al., 1984; Normann and Perlman, 1979; Itzhaki and Perlman, 1987; Naka et al., 1987) indicate that such interactions between spot and annulus are not observed in the membrane potential of cones. Thus, under conditions where an adapting spot of light is surrounded by dimmer steady light, HC responses to modulation of the spot exhibit slower kinetics than the cones that drive the HCs. We may conclude that CMSE reflects a modulation of synaptic transfer between cones and HCs. We use the term synaptic transfer in this context to refer to all mechanisms involved in the cone voltage to HC voltage signal transduction. A recent review of modulation of photoreceptor synapses was provided by Wu (1991).

**Similarities and Differences between CMSE and Suppressive Rod–Cone Interaction**

The effects of steady annular light on gain and kinetics of the response to flicker of a concentric spot of light are qualitatively similar to the effects of a diffuse rod-effective background on the cone-driven response to flicker of red light. This sort of rod–cone interaction has been reported in HCs in *Xenopus, Necturus* (Frumkes and Eysteinsson, 1987, 1988; Frumkes and Wu, 1990; Eysteinsson and Frumkes, 1989), and in HCs in the cat (Pflug, Nelson, and Ahnelt, 1990; Nelson, Pflug, and Baer, 1990). Similar interactions between rods and cones were observed with a different stimulus protocol in *Xenopus* HCs by Witkovsky and Stone (1987), who measured responses to weak red flashes in the presence and absence of a steady green background light. Thus, dark-adapted rods exert a suppressive influence on cone-driven responses. This type of rod–cone interaction measured electrophysiologically and analogous interactions measured psychophysically (Goldberg, Frumkes, and Nygaard, 1983; Coletta and Adams, 1984; Alexander and Fishman, 1984) have been referred to as suppressive rod–cone interaction (SRCI). The similarities between CMSE and SRCI suggest the possibility that they share a common mechanism at some level, such as a common neuromodulator and receptor.

Although there are some similarities between CMSE and SRCI, there are important mechanistic differences between the two phenomena. The experimental protocol of Burkhardt (1974) clearly eliminated the possibility that rods played any significant role in surround enhancement, as measured in his experiments in the mud puppy retina. His result is confirmed by our experiment on the graded dependence of CMSE on annular illuminance. It showed that spot response kinetics were altered by changing the annular illuminance between two levels, both bright enough to saturate rods. Furthermore, we have shown that in CMSE, a change in sensitivity to high-frequency flicker requires a change in contrast between the mean light level in the test region and that in the surrounding region. SRCI differs in that sensitivity to high-frequency flicker of diffuse red light is increased by addition of a diffuse rod-effective background (Frumkes and Wu, 1990), despite the fact that there is no spatial contrast under either stimulus condition.

**Mechanisms Underlying CMSE**

Because CMSE is most prominent at high frequencies, it does not seem likely that CMSE is mediated by an effect of annular light on feedback interaction between HCs.
and cones (Baylor, Fuortes, and O'Bryan, 1971; O'Bryan, 1973; Burkhardt, Gottesman, and Thoreson, 1988). One would expect an alteration in the feedback loop between HCs and cones to be reflected most prominently at low frequencies rather than at high frequencies. This is because, on general principle, one expects the gain of the feedback loop to decrease at high frequencies. Any transduction mechanism that is not instantaneous and does not involve a pure delay would have the property of monotonically decreasing gain at high frequencies. The mechanisms linking presynaptic voltage to postsynaptic current is no exception. Thus, feedback should be least effective at high frequencies. Consequently, altering its strength or kinetics should have a minimal effect on HC gain at high frequencies. CMSE, however, is most pronounced at our highest experimental frequencies. If we assume that the gain of the feedback loop is substantially attenuated under all stimulus conditions at our highest experimental frequency of 16.9 Hz, it is not possible for alterations in feedback to account for the enhancement of sensitivity at this frequency. This argument does not exclude the possibility that feedback plays a role in determining differences in gain at low frequencies between the annulus-on and annulus-off conditions.

One obvious question is whether CMSE involves presynaptic or postsynaptic mechanisms or both. Are the effects of annular light already present at the stage where the transmitter is released from the cone terminal or, alternatively, not until one of the steps linking the released transmitter to the HC membrane potential? Our data on the correlation of surround enhancement and HC receptive field size and data on the distribution of sensitivity within the circular test region suggest that at least part of the mechanism of CMSE is located in the HC.

Our results indicating that CMSE is not determined by the HC membrane potential in the recorded cell, coupled with the result that steady light located many space constants away from the HC receptive field center can affect spot responses, make it seem unlikely that CMSE in a particular HC is mediated solely by that HC and the cells to which it is electrically coupled. A suggestion that CMSE involves neural elements in addition to cones and HCs is provided by our experiments showing that spatial contrast plays a key role in CMSE. Although cones and small-field HCs can exhibit antagonistic center-surround organization under certain experimental conditions, they do not seem to be effective detectors of spatial contrast in the retina. Thus, our attention is directed to bipolar cells and/or the inner retina. If the inner retina is involved in CMSE, the link between the inner and outer retinas might be either via diffusion of a neuromodulator (Iuvone, 1986) and/or via interplexiform cells (Dowling, Ehinger, and Hedden, 1976; Eldred and Cheung, 1989).

Detailed information about the onset of sensitization upon presentation of surrounding light would be useful in determining the plausibility of a mechanism for CMSE that involves a diffusible messenger. Kawasaki et al. (1984) have shown that sensitization is already present at ~0.5 s after the surround light is turned on, but sensitization might occur even sooner.

Although the mechanism mediating CMSE in the HC is unclear, arguments can be made against several possibilities. Modification of the resistance of gap junctions between HCs can be ruled out as the sole mechanism because the effect on sensitivity
would not be opposite at low and high temporal frequencies, as we observe in CMSE.

Furthermore, based on spatiotemporal models for the HC syncitium (Krausz and Naka, 1980; Tranchina et al., 1983), it can be shown that the effect of changing gap junctional resistance on the temporal frequency response to modulation of the illuminance of a thin bar would be to multiply the gain by a uniform scale factor across all frequencies. In experiments not shown, we have found that thin bar temporal frequency responses in the surround-on and surround-off conditions do not differ in this manner. Instead, the differences are like those observed for small spots. A change in the resistance of the HC membrane can also be ruled out as the sole mechanism because it would have greatest effect at low frequencies, rather than at high frequencies, as we observe in CMSE. As an illustrative example, consider a parallel resistance and capacitance circuit with impedance $Z(f) = R/(1 + i2\pi f RC)$, where $R$ is resistance, $C$ is capacitance, and $f$ is temporal frequency. At low frequencies, $Z \sim R$, and, at high frequencies, $Z \sim 1/(i2\pi f)$, which is independent of $R$. Furthermore, the experiment by Kawasaki et al. (1984), in which current was injected at one site into the HC network and the membrane voltage recorded at another, indicated that transmission of signals within the HC network in the catfish retina is not affected by a background light that enhances HC spot responses. Moreover, they found that signals generated by modulation of a small spot surrounded by darkness propagate within the HC network with no substantial temporal filtering. These results indicate that the modulation of the network properties of the HC syncytium does not underlie CMSE. Corroborative experiments in other retinas that exhibit CMSE have not yet been reported. A number of additional plausible mechanisms that might underlie CMSE are discussed below.

In recent years, a number of neuromodulatory mechanisms in the retina have been studied in pharmacological experiments. The functional roles of these mechanisms in which response sensitivity and/or response kinetics are altered are not entirely clear. We discuss some of these mechanisms below in hopes of encouraging discussion and experiments on the possible involvement of one or more of these mechanisms in CMSE. The hypothesis that a particular transmitter or neuromodulator mediates CMSE could be tested by blocking the appropriate receptor and checking whether the differences between spot responses for the annulus-on and annulus-off conditions are largely eliminated.

The findings of Knapp, Schmidt, and Dowling (1990), that dopamine modulates the opening and closing rates of glutamate channels in teleost HCs, raises the possibility that this mechanism is involved in CMSE. The changes in opening and closing rates elicited by dopamine that were reported by Knapp et al. (1990) are not nearly great enough to account for the modulation of response kinetics reported in the present study. However, dramatic effects of dopamine on the kinetics and amplitude of cone-driven responses in *Xenopus* HCs have been reported by Witkovsky, Stone, and Tranchina (1989). They found that dopamine, as well as $D_1$ and $D_2$ agonists, sped up the kinetics and increased the amplitude of the cone component of the HC response to a flash of light. The details of these dopaminergic mechanisms have yet to be discovered. Recently, Reifsnider and Tranchina (1994) reported that in the superfused turtle eyecup preparation, addition of 100 $\mu$M
dopamine to the superfusate uncoupled large-field HCs and reduced CMSE. However, dopamine antagonists had no effect on CMSE. Thus, a dopaminergic mechanism does not seem to play a major role in CMSE.

Perlman and Normann (1990) found that superfusion of the isolated turtle retina preparation with GABA, a known inhibitor of dopamine release (Gerschenfeld, Neyton, Piccolino, and Witkovsky, 1982; Kirsch and Wagner, 1989) caused a dramatic slowing down of the HC response to light. In addition, they found that bicuculline, a GABA_α receptor antagonist, caused a slight speeding up of the HC response to light. These results raise the possibility that GABA is involved in CMSE. These results are not inconsistent with the notion that GABA affects HC response kinetics through dopamine in turtle, but another possibility is that GABA affects response kinetics more directly. Effects of GABA on synaptic transfer between cones and HCs in salamander (Yang and Wu, 1989) and _Xenopus_ (Witkovsky and Stone, 1987) have been reported previously. Kamermans and Werblin (1992) have developed a mathematical model that accounts for that transformation in HC response kinetics in the presence of GABA. The main feature of the model is a positive feedback loop involving voltage-dependent release of GABA by an electrogenic GABA/Na⁺ cotransporter (Malchow and Ripps, 1990) and GABA-gated chloride channels in the HC membrane. The experiments of Perlman and Normann (1990) suggest the existence of a positive feedback loop in turtle HCs, even in the absence of GABA-gated chloride channels.

An alternative mechanism for modulating the kinetics of the synaptic response to glutamate is suggested by experiments showing that non-N-methyl-D-aspartate (NMDA) glutamate receptors in HCs can mediate a membrane conductance increase that is sustained in response to kainate but transient in response to glutamate or quisqualate (Ishida and Neyton, 1985). This behavior is accounted for by a model for the glutamate receptor in which a sensitized and a desensitized state have different affinities for various glutamate agonists (Patneau and Mayer, 1991). Thus, CMSE could involve a modulation of one or more of the rate constants for the transition of the glutamate receptor between its various states.

Another possible mechanism for CMSE is raised by recent findings in several laboratories. There is evidence for the coexistence of NMDA and non-NMDA glutamate receptors on HCs of the turtle (Miyachi and Murakami, 1989) and catfish (O'Dell and Christensen, 1989) retinas. Mittman et al. (1990) showed that excitation in both on and off ganglion cells is mediated by concomitant activation of NMDA and non-NMDA glutamate receptors in the salamander retina. They also found that the kinetics of the response mediated by the NMDA receptors were substantially slower than those mediated by the non-NMDA receptors. Thus, it is conceivable that the kinetics of HCs in CMSE are modulated by alteration of the relative weights of the NMDA and non-NMDA components of the response. A possible intermediary for the modulation of NMDA channels in HCs is provided by glycinergic interplexiform cells in the turtle retina (Eldred and Cheung, 1989).

Recent experiments by Anderton and Millar (1993) suggest that NMDA channels are involved in modulating HC response kinetics in a different way, through a mechanism involving alteration of intracellular calcium ion concentration.
Functional Role of CMSE

The purpose served by the retinal mechanisms reflected in CMSE is not entirely clear. However, it appears that the mechanisms of field adaptation and CMSE work in concert to match the kinetics of the responses of second-order neurons to a measure of light level that is not completely local. Field adaptation produces Weber's law behavior and is accomplished primarily in the photoreceptors in the turtle retina. Although adaptation spreads to some extent in the network of electrically coupled cones (Itzhaki and Perlman, 1987; Copenhagen and Green, 1987), adaptation in cones is a fairly local phenomenon. In the Weber's law regime, a change in background light affects primarily the sensitivity at low temporal frequencies, where the gain is inversely proportional to background light intensity (Daly and Normann, 1985; Chappell et al., 1985; Naka et al., 1985; Tranchina et al., 1984, 1991). One measure of overall sensitivity, the time integral of the impulse response function per photon, is also inversely proportional to background light intensity in the regime of Weber's law.

Steady light surrounding a modulated test area, on the other hand, affects primarily the sensitivity at high temporal frequencies. Consequently, the integral of the impulse response per photon is affected minimally. In both field adaptation and CMSE, more light gives faster response kinetics. However, overall gain appears to be determined primarily by the light level falling directly on the modulated area, while kinetics are determined both by this light and by surrounding light. Thus, CMSE appears to have a special role in adjusting response kinetics.

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