

Color Opponency in Cone-driven Horizontal Cells in Carp Retina

Aspecific Pathways between Cones and Horizontal Cells

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ABSTRACT The spectral and dynamic properties of cone-driven horizontal cells in carp retina were evaluated with silent substitution stimuli and/or saturating background illumination. The aim of this study was to describe the wiring underlying the spectral sensitivity of these cells. We will present electrophysiological data that indicate that all cone-driven horizontal cell types receive input from all spectral cone types, and we will present evidence that all cone-driven horizontal cell types feed back to all spectral cone types. These two findings are the basis for a model for the spectral and dynamic behavior of all cone-driven horizontal cells in carp retina. The model can account for the spectral as well as the dynamic behavior of the horizontal cells. It will be shown that the strength of the feedforward and feedback pathways between a horizontal cell and a particular spectral cone type are roughly proportional. This model is in sharp contrast to the Stell model, where the spectral behavior of the three horizontal cell types is explained by a cascade of feedforward and feedback pathways between cones and horizontal cells. The Stell model accounts for the spectral but not for the dynamic behavior of the horizontal cells.

INTRODUCTION

In carp and goldfish retina three types of cone-driven horizontal cells exist. They are called the mono-, bi-, and triphasic horizontal cells (MHC, BHC, and THC) depending on their spectral sensitivity characteristics (MacNichol and Svaetichin, 1958; Norton et al., 1968). Stell and co-workers (Stell et al., 1975, 1982; Stell and Lightfoot, 1975; Stell, 1976) proposed a cascade model, which relates the spectral response properties of the horizontal cells (HC) to the structure of the ribbon synapse in the cone synaptic terminal. Stell's model is based on a morphological study of Golgi impregnated material from goldfish retina. In that study it was shown

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that the H1 cells make central as well as lateral contacts with the synaptic ribbons of the long wavelength sensitive cones (R-cones) and make lateral contacts only with the middle and short wavelength sensitive cones (G-cones, B-cones). The H2 cells, however, make central as well as lateral contacts in the G-cones and make lateral contacts only with the B-cones. Finally, the H3 cells make central as well as lateral contacts only with the B-cones.

Assuming that the central HC processes are the forward pathway from the cones to the HCs, that the lateral HC processes are a sign-inverting feedback pathway from HCs to the cones, and that the H1 cells correspond to MHCs, H2 cells to BHCs, and H3 cells to THCs, the color coding of the HCs could be explained simply.

However, three major problems exist with the Stell model: (a) The dynamics of the responses of all three cone horizontal cell types in carp retina to red light are equal except for latency differences (Spekreijse and Norton, 1970). According to the model of Stell, these responses are generated through different pathways, and hence should show latency as well as dynamic differences. (b) Our morphological studies on horseradish peroxidase (HRP)-stained HCs in carp retina (Kamermans et al., 1989b; Zweypfenning, R. C. V. J., manuscript in preparation) showed that a specialization in the dendritic contacts, found by Stell in goldfish, may not be present in carp retina. All electrophysiological HC types make contacts with all spectral cone types and both lateral and central contacts have presynaptic specializations near the synaptic ribbon. This would suggest that *all* HCs have direct input from *all* cone types. Furthermore, Yazulla and co-workers showed that there is no clear relation between the localization of the GABA_A receptor and the shape of the HC dendrites (Studholm et al., 1989; Yazulla et al., 1989). This finding contradicts the notion that the lateral contacts represent the feedback pathway as Stell suggests. (c) About 50% of the MHCs have been shown to receive input from the G-cones (Yang et al., 1982, 1983; Tauchi et al., 1984; Van Dijk, 1985; Kamermans et al., 1989a,c). In Stell's model there is no pathway for this input.

The data cited above suggest that the cascade model of Stell does not hold for carp. We shall present an alternative model that accounts fully for the dynamic as well as the spectral properties of the various types of cone-driven HCs. The model is based on the assumptions that all electrophysiological HC types receive input from all spectral cone types and that all electrophysiological HC types feed back to all spectral cone types.

The first part of this article deals with electrophysiological experiments. Results of chromatic adaptation and silent substitution experiments will be presented to test the above assumptions and to quantify the input from the various spectral cone types to the various electrophysiological HC types. In the second part of the article we present the model, and in the third part we simulate electrophysiological data, taken from this and earlier studies. Finally, in the last part we discuss some consequences of our model and its relevance for other retinas.

MATERIALS AND METHODS

Preparation

Eyes of grass carp (*Ctenopharyngodon idella*), 700–1,200 g, were enucleated and the retinas were isolated under dim light. The retina was placed with the receptor side up in a chamber that was

continuously perfused with oxygenated (97.5% O₂ + 2.5% CO₂) Ringer's solution containing (in mM): 102.0 NaCl, 2.0 KCl, 1.0 MgCl₂, 1.0 CaCl₂, 5.0 glucose, and 28 NaHCO₃. The temperature was kept at 17.5°C and the pH at 7.8. Light stimuli were projected from below. The fish were not exposed to light for at least 1 h before enucleation.

The Optical Stimulator

The experiments were performed on a setup described previously (Van Dijk and Spekreijse, 1984; Van Dijk, 1985). Briefly, the stimulator consisted of two stimulus beams from a 450-W xenon source (Heinzinger, Rosenheim, Germany) that was used to project spots, slits, and annuli on the retina. In one stimulus channel the wavelength was controlled by a monochromator 0.25m Ebert monochromator; Jarrell Ash Company, Waltham, MA; in the second stimulus channel it was controlled by interference filters (IRI filters; Ealing Corp., South Natick, MA). The intensity in each of the channels was set by a pair of circular neutral density filters (CND 3; Barr & Strout, Glasgow, Scotland) ranging over 6 log units. A third beam, from a second 450-W xenon source (Heinzinger) was used to project diffuse backgrounds on the retina. The wavelength of this channel was selected by interference filters (Schott; Mainz, Germany) and the intensity was set by a pair of circular neutral density filters (Eastman Kodak Co., Rochester, NY) ranging over 6 log units. Throughout the article intensity values will be expressed in relative log units. Zero log intensity equals 4×10^{16} quanta s⁻¹ m⁻². Between experimental runs and during the search for stable recordings of horizontal cells, a diffuse 517-nm background of -3.2 log units was used to maintain the retina at a constant adaptation level.

Recording

The microelectrodes were pulled on a Sutter puller (87-PC; Sutter Instrument Co., San Rafael, CA) and had a resistance of ~100 mΩ when filled with 3 M KCl and measured in Ringer's solution. Intracellular responses were amplified using an amplifier system with electrometer module (World Precision Instruments Inc., New Haven, CT; S7000A + S7071A). Data were recorded on magnetic tape (Ampex Corp., Redwood City, CA) and on chart paper (Graphtec Linearcorder; Tokyo, Japan).

Cells were classified as MHCs, BHCs, or THCs by standard criteria: spectral sensitivity and dependence on test spot diameter (Norton et al., 1968; Kaneko, 1970; Mitarai et al., 1974; Hashimoto et al., 1976; Kaneko and Stuart, 1980).

Stimuli

In the chromatic adaptation experiments stimuli were flashed on for 0.5 s and were off for at least 1.5 s. In the silent substitution experiments, responses to the exchange of two test fields were recorded. The intensities of the two stimulus spots and of the background were varied independently. In both types of experiments the test stimulus and the background covered the entire retina.

Model Simulations

All simulations were performed on an IBM-XT-compatible microcomputer. Differential equations 1, 5, and 9 were solved by the numerical method of Runge-Kutta (Hamming, 1962).

ELECTROPHYSIOLOGICAL RESULTS

Spectral Sensitivity Curves Under Intense Chromatic Background Illumination

To evaluate the various cone inputs to the HCs we recorded the responses to flashes of four wavelengths (670, 615, 560, and 500 nm). A background of 500 or 700 nm

was switched on 2.5 s before the test flash and switched off 2.5 s after stimulus offset. Using the spectral sensitivity curves of the R-, G-, and B-cones as given by Van Dijk and Spekrijse (1984), the test stimulus intensities for the various wavelengths were adjusted so that the G-cones were equally stimulated for all wavelengths. Fig. 1 gives the relative stimulus intensities for the R-, G-, and B-cone systems for these stimuli, assuming that all three cone systems have the same absolute sensitivity. If the response of a HC originated exclusively in the G-cones, all three stimuli would elicit the same response. Conversely, if additional inputs from the R- and B-cones were present, the responses for the three stimuli would be unequal.

Fig. 2 shows the responses of a MHC. For the zero log, 700-nm background (second row), the response to the 670-, 615-, and 560-nm stimuli are about equal, while the response to the 500-nm stimulus is much larger. The similarity of the responses to 670-, 615-, and 560-nm stimuli suggest strongly that with an intense 700-nm background, the R-cones do not contribute much to the responses, and that the G-cones generate the hyperpolarizing responses. Such a hyperpolarizing G-cone

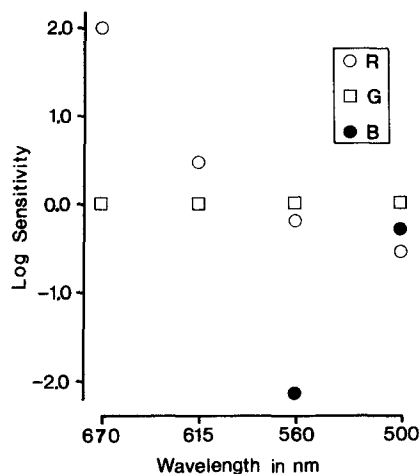


FIGURE 1. The relative sensitivity of the three cone systems to the stimuli used in the experiments of Figs. 2–4 as a function of wavelength. *Open circles*, R-cone system; *squares*, G-cone system; *filled circles*, B-cone system.

input to the MHCs has been unequivocally demonstrated previously (Kamermans et al., 1989a,c).

The large response to a 500-nm stimulus on a zero log, 700-nm background indicates hyperpolarizing B-cone input. We conclude that MHCs have hyperpolarizing G- and B-cone inputs in addition to a hyperpolarizing R-cone input.

Fig. 3 shows the response of a BHC. The inset shows the neutral point; i.e., the wavelength where, without background, the response changes from hyperpolarizing to depolarizing. The clearly hyperpolarizing response to the 670-nm stimulus (fourth row) suggests the presence of a hyperpolarizing R-cone input to the BHCs. Fig. 3 shows that for an intense 700-nm background (second row) the responses to 500-nm stimuli are larger than those to 560- or 670-nm stimuli. This suggests that BHCs receive hyperpolarizing B-cone input. These results suggest that BHCs receive hyperpolarizing R- and B-cone input in addition to the hyperpolarizing G-cone input.

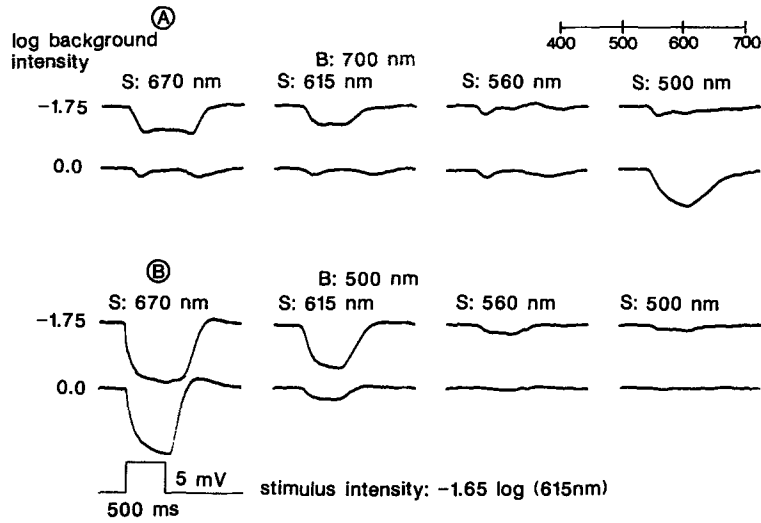


FIGURE 2. Responses of a MHC to full-field test flashes of 670, 615, 560, and 500 nm against a background of 700 or 500 nm for two background intensities. The intensities of the stimuli were equalized according to the G-cone fundamental (see Fig. 1).

Fig. 4 shows that the THC becomes hyperpolarizing to a 670-nm stimulus in the presence of a $-1.75 \log$ 500-nm background (fourth row). This hyperpolarization is probably due to input from the R-cone system because at this background both the G- and the B-cone systems are saturated. Although a hyperpolarizing input from the G-cones to the THCs could not be proven in these experiments, we assume that all three cone types can have a hyperpolarizing contribution to the THC response.

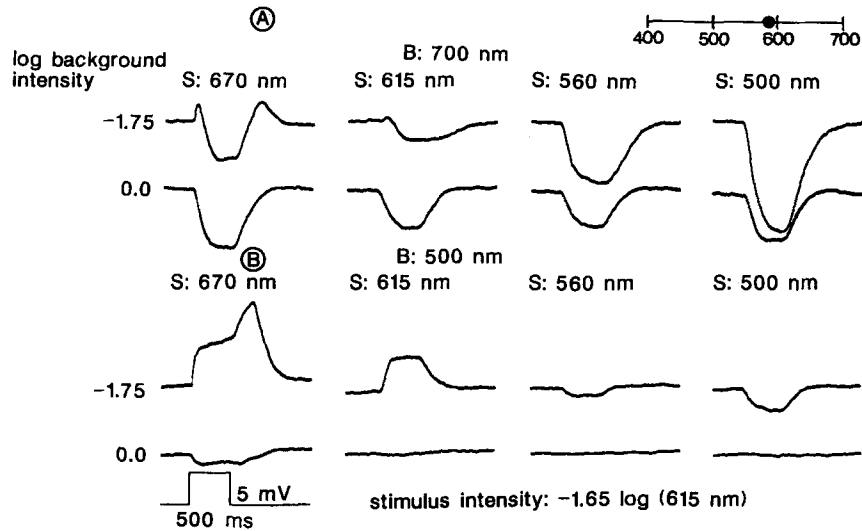


FIGURE 3. Responses of a BHC for similar stimuli as in Fig. 2. The inset indicates the neutral point of this cell in the absence of background illumination.

Silent Substitution

It has previously been shown that MHCs receive G-cone input. However, a controversy exists about the sign of this input. If silent substitution stimuli are used, G-cone input to MHCs appears to be depolarizing (Van Dijk, 1985), whereas the results of Fig. 2 indicate that G-cone input to MHCs is hyperpolarizing. To settle this controversy we performed silent substitution experiments in combination with intense chromatic backgrounds. Fig. 5 shows data from such an experiment. The stimulus used was an abrupt replacement of a 700-nm test field with a 540-nm test field. The intensities of these two fields were adjusted according to the R-cone fundamental (Van Dijk and Spekreijse, 1984); thus the R-cones cannot contribute to the response. Without background illumination (Fig. 5A), responses to this silent substitution stimulus are depolarizing for low stimulus intensities and hyperpolarizing for high stimulus intensities. If these responses originate from the G- or B-cone

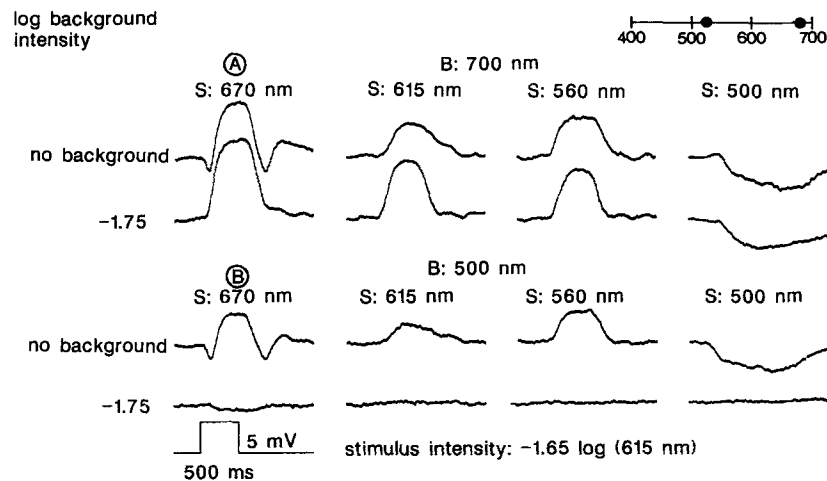


FIGURE 4. Responses of a THC for similar stimuli as in Fig. 2. The inset indicates the neutral points of this cell in the absence of background illumination.

systems, then adding a 645-nm background should hardly change the response amplitudes, whereas a 517-nm background should decrease the response amplitudes dramatically. The experimental results are just opposite: with a 645-nm background the depolarizing response to the -1.75 log stimulus becomes hyperpolarizing, while a 517-nm background leaves this response unaffected. For the higher stimulus intensities the response remains hyperpolarizing with a 645-nm background, whereas a 517-nm background makes the response first more depolarizing and finally transient-like.

These results indicate that the responses of a MHC to silent substitution stimuli are not due to depolarizing G- or B-cone input. Since the depolarizing response to a -1.75 log silent substitution stimulus (Fig. 5A) is not affected by a 517-nm background, but is affected by a 645-nm background, we conclude that this response must be mediated through the R-cone system although the R-cone light stimulus is constant. A possible pathway might be through feedback from the BHCs. The BHCs

are stimulated vigorously by the red/green exchange. If we assume that the BHCs feed back to the R-cones, then the MHCs will depolarize to the silent substitution stimulus. This feedback pathway can be silenced by a 645-nm background or by high stimulus intensities. Under these conditions the hyperpolarizing G-cone input will express itself in the response. A more detailed explanation of these findings will be presented in the simulation section.

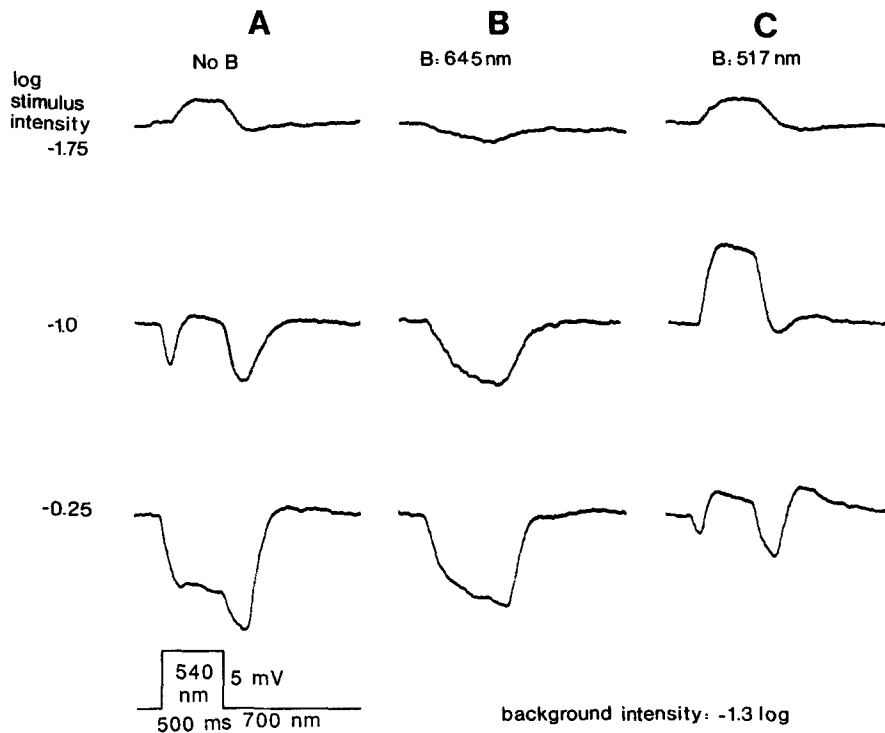


FIGURE 5. Responses of a MHC to substitution of a 700-nm test field with a 540-nm test field without and with background illumination of 645 or 517 nm at three different stimulus intensities. The intensities of the test fields were adjusted according to the R-cone fundamental and are specified for the 540-nm stimulus.

THE MODEL

Our model is based on the assumption that the wiring of the three types of cone-driven HCs is qualitatively identical. So one wiring scheme is sufficient, as presented in Fig. 6. In the following we shall name the various cone systems "*n*-cone" system, where *n* stands for R, G, or B; likewise, the various HC systems will be named "*q*HC," where *q* stands for M, B, or T.

The Cones

The inner and outer segments and the synaptic terminal are not modeled separately. We assumed that the dynamics of the R-, G-, and B-cones are equal (Spekreijse and Norton, 1970; Kaneko and Tachibana, 1985) and that only three types of ion

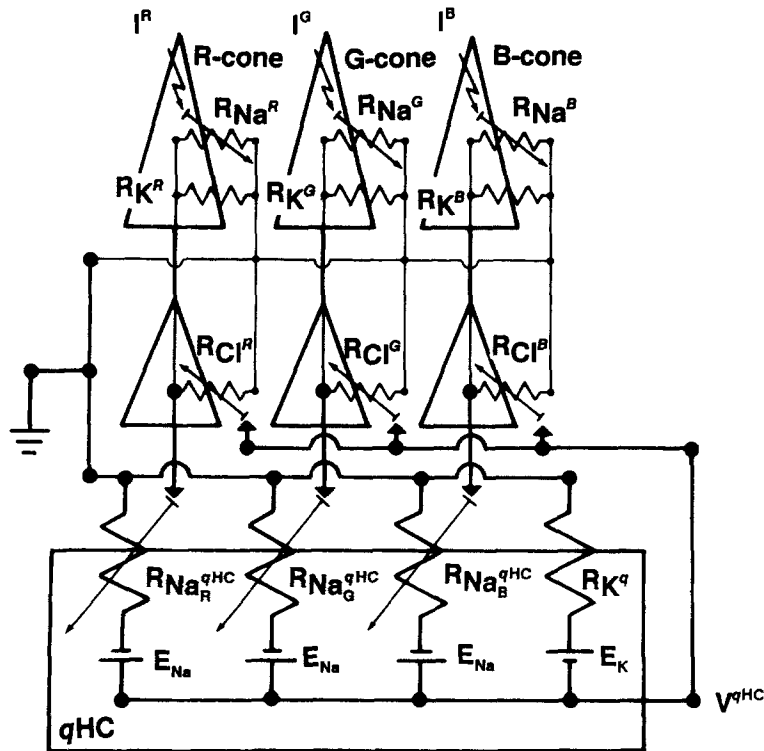


FIGURE 6. A schematic presentation of the proposed model. The following abbreviations have been used:

I^n light stimulus

R_{Na}^n resistance of the Na^+ channels in the n -cone

R_{Cl}^n resistance of the Cl^- channels of the n -cone

R_{K}^n resistance of the K^+ channels of the n -cone

$R_{\text{Na}}^{\text{qHC}}$ resistance of the R-cone-modulated Na^+ channels of the qHC

$R_{\text{Na}}^{\text{qHC}}$ resistance of the G-cone-modulated Na^+ channels of the qHC

$R_{\text{Na}}^{\text{qHC}}$ resistance of the B-cone-modulated Na^+ channels of the qHC

$R_{\text{K}}^{\text{qHC}}$ resistance of the K^+ channels of the qHC

E_{Na} equilibrium potential of the Na^+ channels of the qHC

E_{K} equilibrium potential of the K^+ channels of the qHC

V^{qHC} membrane potential of the qHC

▲ transmitter concentration dependence of the variable resistances

● For clarity we have not drawn the equilibrium potentials of the cone channels E_{Na} , E_{K} , and E_{Cl} .

channels, permeable to Na^+ , K^+ , and Cl^- , respectively, are involved. For simplicity we assumed that none of these channels is voltage dependent. Finally, we assumed that the channels and equilibrium potentials for the relevant ions are identical for all three cone types.

With the above assumptions the behavior of the model cones can be described by the following equations. The light stimulus for the n -cone system, I^n , is filtered by a

first-order low pass filter with a time constant, τ^{photo} , representing the result of photon catch.

$$I^{n'} = I^n - \tau^{\text{photo}} \frac{dI^{n'}}{dt} \quad (1)$$

where $I^{n'}$ is the intrinsic light response of the n -cone to the light stimulus.

We have assumed that the resistance of the K^+ channels, R_K^n , is constant. The resistance of the Na^+ channels, R_{Na}^n , is modulated by $I^{n'}$ in such a way that the channels are open in the dark and closed by light (Trifonov, 1968; Werblin, 1975):

$$R_{Na}^n = R_{Na}^o + \alpha_1 I^{n'} \quad (2)$$

where R_{Na}^o is a constant representing the resistance of the Na^+ channels without stimulation, and α_1 is a constant indicating the resistance change of the Na^+ channels by one unit of light stimulation.

The resistance of the Cl^- channels in the cones, R_{Cl}^n , is modulated by the γ -aminobutyric acid (GABA) concentration near the cone. GABA is released upon depolarization of a HC (Ayoub and Lam, 1984) and opens the Cl^- channels in the cones:

$$R_{Cl}^n = R_{Cl}^o - \alpha_{[GABA]} [GABA]^n \quad (3)$$

where R_{Cl}^o is a constant indicating the resistance of the Cl^- channels when no GABA is present, $\alpha_{[GABA]}$ is a constant indicating the change in resistance of the Cl^- channels per unit GABA, and $[GABA]^n$ is the GABA concentration near the membrane of the n -cone.

Thus, the membrane potential of the n -cone, V^n , is given by:

$$V^n = \frac{g_{Na^+} E_{Na} + g_{K^+} E_K + g_{Cl^-} E_{Cl}}{g_{Na^+} + g_{K^+} + g_{Cl^-}} \quad (4)$$

with

$$g_{Na^+} = \frac{1}{R_{Na}^n}; g_{K^+} = \frac{1}{R_K^n}; g_{Cl^-} = \frac{1}{R_{Cl}^n}$$

where E_{Na} is the equilibrium potential for Na^+ in the cone, E_K is the equilibrium potential for K^+ in the cone, and E_{Cl} is the equilibrium potential for Cl^- in the cone.

The neurotransmitter released by the cones upon depolarization is presumably glutamate (Cervetto and MacNichol, 1972; Dowling and Ripps, 1972; Murakami et al., 1972). In the model the glutamate concentration near the HC dendrites is given by Eq. 5:

$$[Glu]^n = [Glu] - \alpha_v V^n - \tau^{\text{synapse}} \frac{d[Glu]^n}{dt} \quad (5)$$

where $[Glu]^n$ is the glutamate concentration near the q HC dendrites due to release from the n -cone system, $[Glu]$ is the glutamate concentration in the dark without feedback from the HCs to the cones, α_v is a constant indicating the number of units

of glutamate released by a 1-mV change in membrane potential, and τ^{synapse} is the time constant of the synapse from cone to horizontal cell.

The synapse from the cone to the HC behaves as a first-order low pass filter with a time constant of ~ 16 ms (Spekreijse and Norton, 1970; Schnapf and Copenhagen, 1982).

The Horizontal Cells

Tachibana (1985) has shown in isolated HCs that application of glutamate opens nonspecific cation channels in HCs. For simplicity we will refer to these channels as glutamate-modulated Na^+ channels. Although various voltage-dependent channels are present in goldfish HCs (Tachibana, 1981, 1983), we did not include these voltage-dependent nonlinearities in the model. R-, G-, and B-cones modulate separate Na^+ channels in the HC membrane, and therefore interact nonlinearly (Kamerlings et al., 1989a).

The HC membrane resistance in our model can thus be divided into four parallel resistances: (a) the nonsynaptic membrane resistance, R_{K_y} , which is the resistance between the inside of the HC and the surrounding medium, which is grounded; this resistance is associated with the K^+ channels; (b) the R-cone-driven synaptic membrane resistance, $R_{\text{Na}_k^{\text{qHC}}}$, which is the resistance of the Na^+ channels modulated by the glutamate release by the R-cones; (c) the G-cone-driven synaptic membrane resistance, $R_{\text{Na}_g^{\text{qHC}}}$, with properties similar to $R_{\text{Na}_k^{\text{qHC}}}$; (d) the B-cone-driven synaptic membrane resistance, $R_{\text{Na}_b^{\text{qHC}}}$, with properties similar to $R_{\text{Na}_k^{\text{qHC}}}$.

With these assumptions the HC membrane potential is given by the following equations. The resistance of the Na^+ channel of the qHC is modulated by the glutamate released by the n -cone system, $R_{\text{Na}_n^{\text{qHC}}}$:

$$R_{\text{Na}_n^{\text{qHC}}} = R_{\text{Na}_n^{\text{qHC}}}^{\circ} - \alpha_{[\text{Glu}]} [\text{Glu}]^n \quad (6)$$

where $R_{\text{Na}_n^{\text{qHC}}}^{\circ}$ is a constant indicating the resistance of the n -cone-modulated Na^+ channels when no glutamate is present, $\alpha_{[\text{Glu}]}$ is a constant indicating the change in resistance of the Na^+ channels per unit glutamate, and $[\text{Glu}]^n$ is the glutamate concentration near the dendrites of the qHC due to release of the n -cone system.

The total change in Na^+ conductance, $g_{\text{Na}^{\text{qHC}}}$, is the sum of all the synaptic Na^+ conductances:

$$g_{\text{Na}^{\text{qHC}}} = g_{\text{Na}_k^{\text{qHC}}} + g_{\text{Na}_g^{\text{qHC}}} + g_{\text{Na}_b^{\text{qHC}}} \quad (7)$$

with

$$g_{\text{Na}_k^{\text{qHC}}} = \frac{1}{R_{\text{Na}_k^{\text{qHC}}}}; g_{\text{Na}_g^{\text{qHC}}} = \frac{1}{R_{\text{Na}_g^{\text{qHC}}}}; g_{\text{Na}_b^{\text{qHC}}} = \frac{1}{R_{\text{Na}_b^{\text{qHC}}}}$$

The membrane potential of the qHC, $V^{q\text{HC}}$, follows straightforwardly:

$$V^{q\text{HC}} = \frac{g_{\text{Na}^{\text{qHC}}} E_{\text{Na}} + g_{\text{K}^{\text{qHC}}} E_{\text{K}}}{g_{\text{Na}^{\text{qHC}}} + g_{\text{K}^{\text{qHC}}} \quad (8)$$

with

$$g_{\text{K}^{\text{qHC}}} = \frac{1}{R_{\text{K}^{\text{qHC}}}}$$

where E_{Na} is the equilibrium potential for Na^+ in the HC, E_K is the equilibrium potential for K^+ in the HC, and $R_{K^{qHC}}$ is the resistance of the K^+ channels in the HC membrane.

We have assumed that all HCs release GABA upon depolarization. For the MHCs this is a well-established fact (Lam et al., 1980; Ayoub and Lam, 1985; see Yazulla, 1986, for an overview). Despite the fact that no GABA or glutamic acid decarboxylase (GAD) is found in BHCs and THCs, there is strong evidence that the BHCs feed back to the cones (Spekreijse and Norton, 1970; Stell et al., 1975; Stell and Lightfoot, 1975; Toyoda et al., 1982; Toyoda and Fujimoto, 1983). A possible explanation for this controversy could be that another inhibitory transmitter is involved in the feedback from BHCs and THCs to cones. On the other hand, the absence of evidence for GABA in the BHCs and THCs might be due to a GABA concentration too low to be demonstrated in these cells.

To find an expression for the feedback strength we have assumed that the membrane potential of the qHC , on which the GABA release depends, is controlled by a first-order low pass filter:

$$V^{fb} = V^{qHC} - \tau^{fb} \frac{dV^{fb}}{dt} \quad (9)$$

where V^{fb} is the driving force for the release of [GABA] from the qHC and τ^{fb} is the time constant of the release and diffusion of GABA to the synaptic terminal of the photoreceptors.

Since Ayoub and Lam (1984) found that *l*-glutamate yields a [3H]GABA release that is logarithmically related to the external Na^+ concentration, and since GABA is released in a carrier-mediated manner (Yazulla and Kleinschmidt, 1983), we used the following expression for the GABA release by the qHC :

$$[GABA]^{qHC} = [GABA]^i \cdot \exp\left(\frac{V^{fb} \cdot F}{R \cdot T}\right) \quad (10)$$

where $[GABA]^{qHC}$ is the GABA concentration, $[GABA]^i$ is the intracellular GABA concentration, and F , R , and T have their usual meanings.

Finally, the GABA concentration near the n th cone, $[GABA]^n$, is determined by the total GABA release from the three types of HCs:

$$[GABA]^n = \sum_q \beta_{qHC}^n \cdot [GABA]^{qHC} \quad (11)$$

with

$$\sum_q \beta_{qHC}^n = 1$$

where β_{qHC}^n is a constant indicating the relative feedback strength of the qHC to the n -cone system.

The Model Parameters

The parameter values used for all simulations are listed in Tables I–IV. The parameters in Tables I and II are not very critical for the behavior of the model. The parameters of Tables III and IV, however, determine the spectral and dynamic

TABLE I
Cone Parameters

E_{Na}	20 mV
E_K	-80 mV
E_{Cl}	-80 mV
R_{K^+}	2,000 k Ω
R_{Na}^0	200 k Ω
R_{Cl}^0	1,500 k Ω
α_1	15 k Ω /unit
$\alpha_{[GABA]}$	70 k Ω /unit
α_V	1 unit/mV
τ^{photo}	50 ms
$\tau^{synapse}$	16 ms

TABLE II
HC Parameters

E_{Na}	20 mV
E_K	-80 mV
R_{K^+}	150 k Ω
[Glu]	60 units
[GABA] ⁻	50 units
$\alpha_{[Glu]}$	20 k Ω /unit
τ^b	60 ms

TABLE III
 $R_{Na}^{0,qHC}$

q^a	R	G	B
	k Ω		
MHC	1,000	1,400	1,600
BHC	1,900	960	1,700
THC	1,700	1,900	960

TABLE IV
 β_{qHC}^a

q^a	R	G	B
	units/mV		
MHC	0.84	0.51	0.01
BHC	0.13	0.36	0.28
THC	0.03	0.13	0.71

behavior of the model HCs. For each simulation the values of I^n are given in the figure legends. We have assumed that the various cone types have similar parameter values and that they differ only in their spectral sensitivities. For the three types of HCs we have chosen equal parameter values except $R_{\text{Naq}^{\circ}\text{HC}}$, which expresses the feed forward strengths from the various cone types to the HCs, and $\beta_{\text{qHC}}^{\circ}$, which expresses the feedback strengths from the HCs to the various cone types. These values are listed in Tables III and IV, respectively. The lowest values in Table III give the dominant cone input; so in our model the MHCs receive most input from the R-cones, the BHCs receive most input from the G-cones, and the THCs receive most input from the B-cones. The highest values in Table IV represent the strongest feedbacks; so in our model the MHCs feed back preferably to the R-cones, the BHCs to the G-cones, and the THCs to the B-cones.

Since the various HC types are electrically coupled, the parameters listed in Tables II–IV are related to the number of contacts between the various cone types and the various HC layers, and not to the number of contacts of individual HCs.

SIMULATIONS

In this section we will discuss the behavior of the model HCs for various stimulus conditions. First, we will discuss the responses of the model HCs to 500-, 600-, and 700-nm stimuli. Second, we will present simulations of silent substitution and current injection experiments. Finally, we will present the phase and frequency characteristics for two sets of parameters: (a) those used for all the simulations, and (b) those dictated by the Stell model.

Responses to 500-, 600-, and 700-nm Stimuli

In this section we introduce the model and show how combinations of membrane resistances determine the HC responses. Fig. 7 shows the responses of the model HCs to full-field stimuli at 500, 600, and 700 nm in the absence of background illumination. The stimulus intensities were adjusted according to the R-cone fundamental. The responses illustrate that a single wiring diagram can account for the responses of all three HC types.

To understand the behavior of the model and to predict the response shapes, one should concentrate on the lowest resistance for each cell since that one determines most of the total resistance in a parallel resistance network.

Response to 700-nm Stimuli

A 700-nm stimulus hyperpolarizes the R-cone but does not affect the membrane potential of the G- and the B-cones. As a result, the glutamate release of the R-cone will be reduced and the $R_{\text{Naq}^{\circ}\text{HC}}$ of all HCs will increase. The MHC will hyperpolarize to this stimulus since, in this cell, $R_{\text{Naq}^{\circ}\text{MHC}}$ is the lowest of the three synaptic membrane resistances (Fig. 7, lower left panel). Hyperpolarization will reduce the GABA release from the MHC. Since the MHC feeds strongly back to the R- and the G-cones, reduction in the GABA release from the MHC results in an increase of both $R_{\text{Cl}^{\circ}\text{R}}$ and $R_{\text{Cl}^{\circ}\text{G}}$ (Fig. 7, upper left and upper middle panels). The increase in $R_{\text{Cl}^{\circ}\text{R}}$ restricts the hyperpolarization of the R-cone and the increase in $R_{\text{Cl}^{\circ}\text{G}}$ causes the G-cone to

depolarize. The depolarization of the G-cones results in an increase of glutamate release from the G-cones and therefore a decrease of $R_{Na_g^{BHC}}$ in all HCs. Since $R_{Na_g^{BHC}}$ is the lowest synaptic membrane resistance (Fig 7, lower middle panel) in the BHCs, the BHCs will depolarize. This leads to an increase in the GABA release from the BHC and finally results in a decrease in R_{Cl^B} . Since the feedback from the BHCs to the

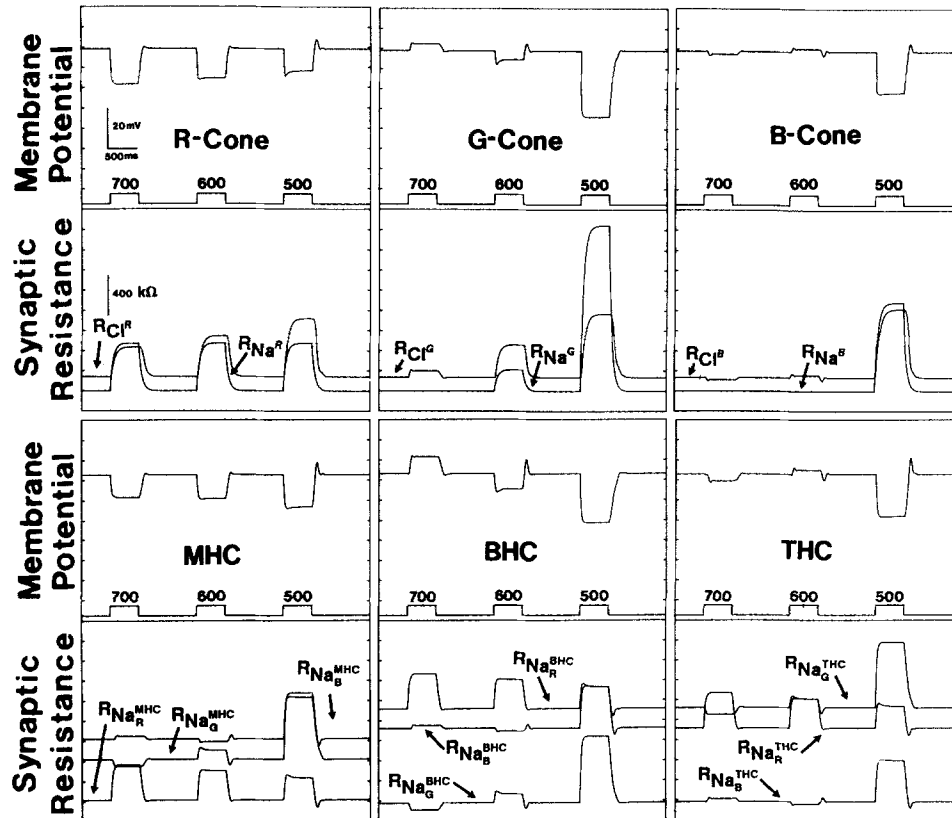


FIGURE 7. Responses of the model cells to 500-, 600-, and 700-nm stimuli in the absence of a background. The figure consists of six panels. The three top panels deal with the cone responses and the three bottom panels with the HC responses. Each panel consists of two parts. The top part depicts the membrane potential and the bottom part depicts the relevant synaptic membrane resistances. Timing and stimulus conditions are indicated on the figure. The values for I^n are for 700 nm: $I^R = 31.6$, $I^G = 0.01$, $I^B = 0.00$; for 600 nm: $I^R = 31.6$, $I^G = 14.1$, $I^B = 0.01$; and for 500 nm: $I^R = 31.6$, $I^G = 109.6$, $I^B = 58.9$.

B-cone is stronger than the feedback from the MHCs to the B-cone, R_{Cl^B} decreases and thus the B-cone hyperpolarizes slightly (Fig. 7, upper right panel) and $R_{Na_g^{BHC}}$ increases. The THC hyperpolarizes strongly (Fig. 7, lower right panel) because $R_{Na_B^{THC}}$ increases due to feedback and $R_{Na_g^{THC}}$ increases due to direct light stimulation (Fig. 7, lower right panel).

Response to 600-nm Stimuli

For the 600-nm stimuli, both the R- and the G-cone hyperpolarize and reduce transmitter release. Due to the resulting increase of both $R_{Na^+_{MHC}}$ and $R_{Na^+_{G}}$, the MHC will hyperpolarize (Fig. 7, lower left panel). The BHC hyperpolarizes too (Fig. 7, lower middle panel) since both $R_{Na^+_{BHC}}$ and $R_{Na^+_{R}}$ increase. The resistances $R_{Na^+_{BHC}}$ are decreased by feedback from the MHC and BHC to the B-cone. Therefore, the THC will depolarize and $R_{Na^+_{BHC}}$ will shunt the BHC response (Fig. 7, lower right panel). Since both the MHC and the BHC hyperpolarize, feedback to the R-cone will be stronger for 600-nm stimuli than for 700-nm stimuli. This expresses itself in a slight repolarization and an overshoot in the MHC response.

Response to 500-nm Stimuli

For 500-nm stimuli all cones hyperpolarize and decrease their transmitter release. The MHC, BHC, and THC responses (Fig. 7, lower left, middle, and right panels) are therefore hyperpolarizing because $R_{Na^+_{MHC}}$, $R_{Na^+_{BHC}}$, and $R_{Na^+_{G}}$ all increase. Since all HCs hyperpolarize, the feedback to all cone systems is maximal, resulting in a repolarizing phase and an overshoot in the MHC response. For this wavelength the MHC response is no longer shunted by $R_{Na^+_{G}}$ or $R_{Na^+_{BHC}}$ and thus the response amplitude is larger than for 600- or 700-nm stimulation.

Silent Substitution

The model can also account successfully for the response of a MHC to silent substitution stimuli with different backgrounds. In Fig. 8 three simulated MHC responses to low intensity silent substitution stimuli are shown, without background illumination, with 645- and 517-nm background illumination. The top row of Fig. 8 gives the membrane potentials and the bottom row gives the changes of the various synaptic membrane resistances.

The silent substitution stimulus has two effects on $R_{Na^+_{MHC}}$: (a) $R_{Na^+_{MHC}}$ is tonically increased by the continuous stimulation of the R-cones, and (b) $R_{Na^+_{MHC}}$ is decreased during the 540-nm phase of the stimulus due to feedback from the BHC to the R-cones. At the same time $R_{Na^+_{G}}$ is increased by the 540-nm stimulus. For low stimulus intensities without background illumination $R_{Na^+_{MHC}}$ dominates the response and consequently the MHC depolarizes during the 540-nm stimulus.

The intense 645-nm background increases $R_{Na^+_{MHC}}$ but has little effect on $R_{Na^+_{G}}$. Therefore, at some background intensities $R_{Na^+_{MHC}}$ will become larger than $R_{Na^+_{G}}$ and the MHC will hyperpolarize due to modulation of $R_{Na^+_{MHC}}$. A 517-nm background will increase $R_{Na^+_{G}}$ and $R_{Na^+_{BHC}}$ more than $R_{Na^+_{MHC}}$. Thus, irrespective of background intensity $R_{Na^+_{MHC}}$ will remain the lowest resistance and therefore the response will remain depolarizing.

In summary, for silent substitution stimuli without or with 517-nm background illumination the responses are generated via feedback from the BHC to the R-cones, whereas for silent substitution stimuli with a 645-nm background the responses are generated via direct hyperpolarizing G-cone input to the MHC.

Fig. 9 shows the simulated responses to silent substitution stimuli of three stimulus

and three background intensities. This figure is the model equivalent of Fig. 5. The responses for the low stimulus intensity (Fig. 9, top row) are the same as in Fig. 8.

The change in response sign at high stimulus intensity without background illumination (Fig. 9A) can be accounted for as follows: Increasing the intensity of the silent substitution stimulus has two effects: first, $R_{Na_R}^{MHC}$ is increased tonically; and second, $R_{Na_G}^{MHC}$ and $R_{Na_B}^{MHC}$ are more strongly modulated. The result is that $R_{Na_R}^{MHC}$ may exceed $R_{Na_G}^{MHC}$ during the 540-nm phase. If this happens, the MHC hyperpolarizes due to direct G-cone input. Adding a 645-nm background makes the response even more hyperpolarizing since $R_{Na_R}^{MHC}$ is increased further and thus $R_{Na_G}^{MHC}$ becomes more

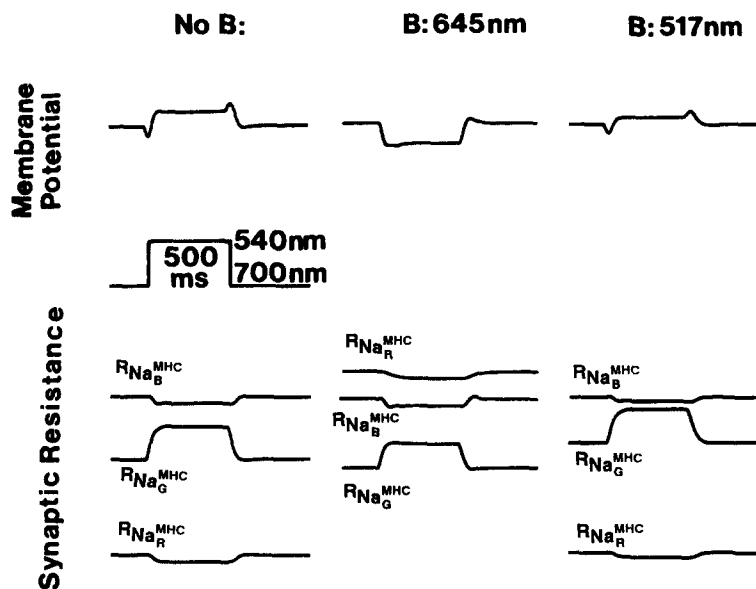


FIGURE 8. Responses of the model MHC to silent substitution stimuli with and without background illumination. *Top panel*, membrane potential; *bottom panel*, synaptic membrane resistances. Timing and stimulus conditions are indicated on the figure. The values of I^n are for 700 nm: $I^R = 3.38$, $I^G = 0.00$, $I^B = 0.00$; and for 540 nm: $I^R = 3.38$, $I^G = 8.13$, $I^B = 0.34$. The values of I^n for the background illumination are for 645 nm: $I^R = 100.0$, $I^G = 4.24$, $I^B = 0.00$; and for 517 nm: $I^R = 1.33$, $I^G = 4.36$, $I^B = 0.84$.

dominating. Adding a 517-nm background also increases $R_{Na_G}^{MHC}$ and results in a reduction of the direct hyperpolarizing G-cone input revealing the feedback from the BHC to the R-cones.

Some details of the simulated responses differ from the experimental findings (Fig. 5). For instance, the secondary hyperpolarization for the -1.0 log silent substitution stimulus without background (Fig. 5A) could not be simulated. This may be due to the assumption that the membrane resistance is linearly related to the glutamate concentration. It is likely that the changes in membrane resistance are smaller at high membrane resistances. If so, then the effective modulation of $R_{Na_G}^{MHC}$ will be smaller

and $R_{Na^+}^{MHC}$ and $R_{Na^+}^{BHC}$ could interact such that a double-peaked response would be generated.

Current Injection

The current injection experiments of Toyoda and Fujimoto (1983) in carp have been presented as strong support for the cascade model of Stell. They reported that current injection in a MHC polarized the BHCs; current injection in a BHC did not polarize the MHCs and polarized the THCs; and that current injection in a THC did not polarize the MHCs and the BHCs.

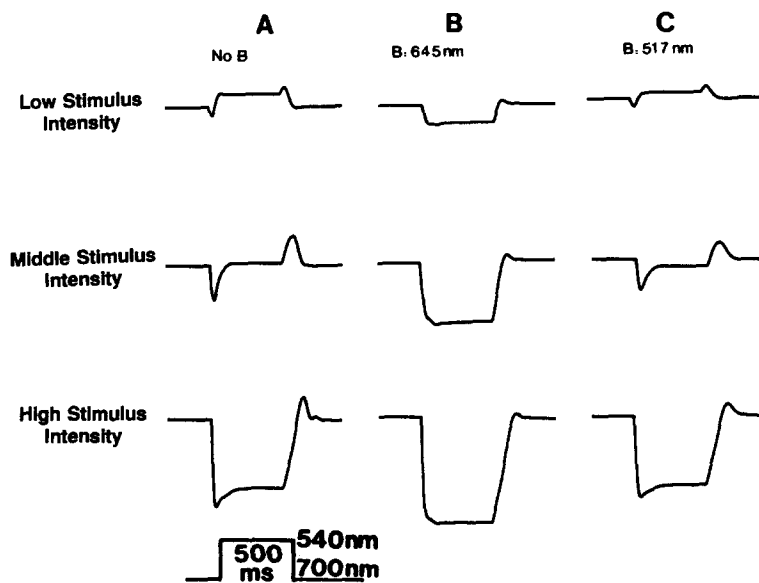


FIGURE 9. Model MHC responses to substitution of a 700-nm stimulus with a 540-nm stimulus without and with background illumination of 645 or 517 nm at three different stimulus strengths. The strengths of the stimuli were adjusted according to the R-cone fundamental. The values of I^n for low stimulus intensity and the background illumination are given in the legend to Fig. 8. For the medium stimulus intensity the values of I^n are for 700 nm: $I^R = 12.6$, $I^G = 0.01$, $I^B = 0.00$; and for 540 nm: $I^R = 12.6$, $I^G = 30.2$, $I^B = 1.26$. For the medium stimulus intensity these values are for 700 nm: $I^R = 39.8$, $I^G = 0.02$, $I^B = 0.00$; and for 540 nm: $I^R = 39.8$, $I^G = 95.5$, $I^B = 3.40$.

Fig. 10 shows that current injection in the HCs in our model yields similar results. Depolarizing current injected in a MHC hyperpolarizes the G-cone due to feedback from the MHC to the G-cones and thus the BHC will hyperpolarize. Injection of a depolarizing current in the BHC will modify $R_{Na^+}^{MHC}$ in the MHC only slightly because feedback from the BHC to the R-cone system is relatively weak. Therefore, the MHC will hyperpolarize slightly and the THC will hyperpolarize strongly due to the strong feedback from the BHC to the B-cone system. Current injected in the THC will modify $R_{Na^+}^{MHC}$ and $R_{Na^+}^{BHC}$ in the MHC and BHC only slightly since the THC does not feed back strongly to those cone systems. Thus, our simulations show that the

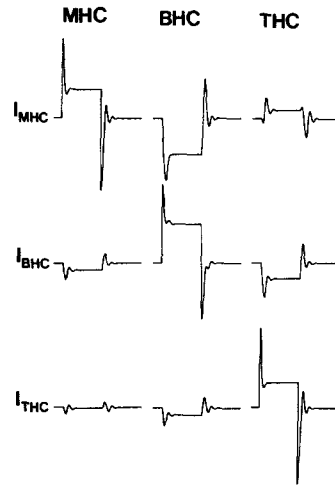


FIGURE 10. Model HC responses to injection of depolarizing current in a MHC, a BHC, and a THC.

experimental data of Toyoda and Fujimoto (1983) are compatible not only with Stell's model, but also with the model presented in this article.

Dynamics

One of the major problems with the Stell model is the fact that the amplitude characteristics of the responses to red sinusoidally modulated stimuli of a BHC and a THC are equal to that of a MHC. The differences in the phase characteristics were interpreted as an extra latency of ~ 25 ms for the BHC response and ~ 50 ms for the THC response (Spekreijse and Norton, 1970). However, according to Stell's cascade model the MHC response to red stimuli is generated via one synapse, the BHC response via three synapses, and the THC response via five synapses. Differences in dynamics should thus be expected.

We have simulated the experiments of Spekreijse and Norton (1970) with our model for two sets of parameters. One set of parameters is based on our electrophysiological work (Tables II–IV). The other set of parameters is based on the morphological study of Stell, in which the MHCs receive only R-cone input, the BHCs receive G-cone input, and the THCs receive B-cone input (Table V), while the MHCs feed back to the R-, G-, and B-cones, the BHCs to the G- and B-cones, and the THCs to the B-cones (Table VI). To make a fair comparison between the two models, the relative feedback strength from the MHC and BHC to the G-cones and the relative feedback strength from the MHC, BHC, and THC to the B-cones have been adjusted

TABLE V
 $R_{Na}^{0,qHC}$ Used in the Simulation of the Stell Model

q^r	R	G	B
	$k\Omega$		
MHC	1,100	10,000	10,000
BHC	10,000	1,100	10,000
THC	10,000	10,000	1,100

TABLE VI
 β_{qHC}^n Used for the Simulation of the Stell Model

q^n	R	G	B
	<i>units/mV</i>		
MHC	1.00	0.59	0.01
BHC	0.00	0.41	0.28
THC	0.00	0.00	0.71

to our model. The resting membrane potential of the various HCs had to be equal for both sets of parameters. To achieve this we reduced $\alpha_{[GABA]}$ to 60 k Ω /unit.

Fig. 11 gives the amplitude and phase characteristics of the model MHC, BHC, and THC to 700-nm, sinusoidally modulated red stimuli for the two sets of parameters: our model (Fig. 11, *A* and *C*), and the model of Stell (Fig. 11, *B* and *D*). The peak-to-peak amplitude is used as a measure for response amplitude. For our set of parameters, the behavior of the amplitude characteristics of the MHC, BHC, and THC are highly similar, while the phase characteristics of the BHC and THC show additional phase shifts resulting in latency differences of 21 ms between the MHC

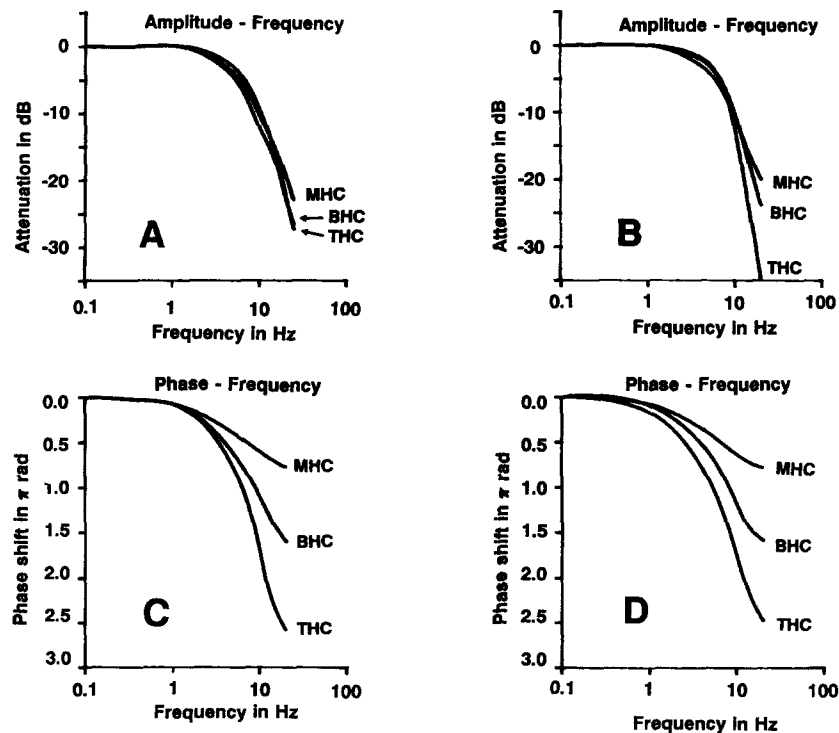


FIGURE 11. Amplitude and phase characteristics of the various model HCs for 670-nm, full-field, sinusoidally modulated light. *A* and *C*, the presented model; *B* and *D*, the Stell model. The mean stimulus intensities for the various cone systems were $I^R = 18.74$, $I^G = 0.21$, and $I^B = 0.00$.

and BHC responses and of 48 ms between the MHC and THC responses. These values are in close agreement with the latency differences in the various HCs to red stimuli found in literature, which range from 14–25 ms (BHC) and 53 ms (THC) (Yamada et al., 1985) to 22 ms (BHC) and 55 ms (THC) (Spekreijse and Norton, 1970).

Fig. 11, *B* and *D*, show that the set of parameters given by the Stell model does not generate identical amplitude characteristics for the three types of HCs. This simulation shows that the pathways we added to the Stell model have dramatic effects on the amplitude characteristics of the HCs.

The latency differences are due to the sign-inverting synapses and are therefore dependent on the ratio of the feed forward and feedback strengths for the various cone systems. It is important to keep in mind that there is no genuine delay in the model. The values for the delay as given by Spekreijse and Norton (1970) are based on linear filter theory. As we have shown in this paper, linear filter theory may not be applicable to this system, since the various cone inputs to the HCs interact nonlinearly.

Spekreijse and Norton (1970) found a high frequency fall-off of 24 dB/octave. In our simulations the fall-off is weaker, presumably due to the absence of membrane capacitances in the model.

DISCUSSION

It is commonly accepted that the spectral opponency of HCs in goldfish retina is generated by a cascade of feed forward and feedback pathways between cones and HCs (Stell et al., 1975; Stell and Lightfoot, 1975; Stell, 1976). In this cascade model each HC type is wired differently. In this paper we have shown that in carp the spectral and dynamic behavior of all cone-driven HC types can be explained by a single wiring scheme for all HC types. Further, we have shown that the strength of the feedback from a HC type to a cone type is roughly proportional to the input to that HC type.

Parameter Values

In this section we will discuss the dependence of the model on the parameter values. All simulations were performed with a single set of model parameters. Modest changes in most of these parameters will not severely influence the behavior of the model. Most critical are the parameters describing the input strength of the various cones to the HCs, $R_{Na_q^{qHC}}^o$ and the feedback strength of the HCs to the various cones, β_{qHC}^n .

$R_{Na_q^{qHC}}^o$ (Table III) is a measure of the input strength of the n -cone system to the q HC. The lower the value of $R_{Na_q^{qHC}}^o$, the stronger the direct cone input to the HC. Thus, the values of $R_{Na_q^{qHC}}^o$ determine the spectral behavior of the HCs. The values of $R_{Na_q^{qHC}}^o$ are also of importance for the dynamic behavior of the HCs. They are, however, less critical than the β_{qHC}^n parameter.

β_{qHC}^n (Table IV) is a measure of the feedback strength of the q HC to the n -cone system. The values of β_{MHC}^R , β_{BHC}^G , and β_{THC}^B are the most critical parameters for the amplitude and phase characteristics. If β_{MHC}^B is too large the THC will depolarize to

670-nm stimuli. $\beta_{\text{BHC}}^{\text{B}}$ must be relatively large to depolarize the THC to green stimuli, and $\beta_{\text{BHC}}^{\text{R}}$ must be relatively large to fit the silent substitution experiments. $\beta_{\text{THC}}^{\text{R}}$ should not be too large because then the MHC will depolarize to blue stimuli.

Finally, it should be realized that the parameters used in the simulations have only relative meaning. We made no attempt to fit the responses exactly by parameter estimation.

Voltage-gated Channels

It has been shown that the HCs isolated from goldfish retina show nonlinear properties which can be attributed to voltage-gated K^+ and Ca^{2+} channels (Tachibana, 1981, 1983). We did not include voltage-gated channels in our model since these channels are normally not seen in an isolated retina. This is presumably due to the extensive coupling between HCs and to strong glutamate input to the HCs acting to shunt the membrane (Winslow, 1989). Of the three voltage-gated K^+ currents, only the anomalous rectifier may be activated within the physiological membrane potential range. If this rectifier had been included in the model, the responses of the HCs would have been enhanced (Byzov et al., 1977), possibly resulting in some quantitative differences to very intense stimuli.

Cone-Cone Coupling

We did not include any cone-cone coupling or coupling of the members of the double cones in the model since no evidence is available for such coupling in carp retina. In other species such evidence exists: in turtle retina (Baylor and Hodgkin, 1973; Detwiler and Hodgkin, 1979) cone-cone coupling exists mainly between cones of equal spectral type and therefore would not be relevant for our analysis; in salamander (Attwell et al., 1983) and in walleye (Kraft and Burkhardt, 1986) it has been shown that the two members of the double cones are completely electrically separate. Marchiafava (1985) showed that in tench the spectral sensitivity of both members of double cones is broader than that of single cones. This indicates that the members of the double cones are coupled. If coupling of double cones, as in tench, were prominent in carp, then the spectral sensitivity of the MHCs would differ from that of the R-cone pigments for all stimulus intensities. This is not the case, since for low stimulus intensities the MHCs have the spectral sensitivity of the R-cone absorption spectrum (Spekreijse et al., 1972).

The Relevance of Our Model for Other Retinas

The model described in this paper is a noncascade model which differs fundamentally from the model of Stell. In our model, the various HC types have similar properties and wiring, whereas in Stell's model the various HC types are wired differently. Our model gives a consistent description of the wiring of the HC layers in carp retina and shows that *all* features of HC responses can be described without the assumption of strict specializations of the HC-cone dendritic contacts.

Our model is based on electrophysiological data obtained from carp retina. Therefore, strictly speaking, it is only valid for carp retina. However, it is unlikely that retinas of other fish species are differently wired since, for instance, HCs in carp

(Norton et al., 1968), goldfish (Kaneko, 1970), and roach (Djamgoz, 1984; Djamgoz et al., 1985, 1988) retina behave similarly.

Furthermore, the conclusion that the connections in the HC layers are specific while HCs have color opponent characteristics may have more general implications for other vertebrate retinas. For instance, it has been reported that neither type of HCs in primate retina makes chromatic specific connections. However, there may be a difference in the ratio of the various cone inputs to those HCs (Boycott, 1987; Boycott et al., 1988). This suggests that the horizontal cells in fish and primates are not a priori functionally different.

The Stell Model

The differences between our model and the model of Stell are at least in part due to the different methods used. The model of Stell was based on morphological data. Cells were classified on the basis of morphology as H1, H2, and H3 cells. The spectral sensitivity of the cells studied was unknown. Stell had to assume that H1 cells were the MHCs, H2 cells were the BHCs, and H3 cells were the THC. Although the morphological differences between H1 and H3 cells are unequivocal, those between the other two pairs are less strict. It is possible that some of the H1 cells in Stell's population were actually BHCs and some of the H2 cells were actually THCs.

It is important to realize that the cone input to HCs determined in electrophysiological experiments reflect the input to the HC layers and not to the individual HCs. Variations in cone inputs to individual cells will be averaged over the entire layer, since the HCs in a layer are coupled strongly and thus there is no reason why each HC of a certain electrophysiological type should have exactly the same morphological connections. Therefore, the data of Stell are not in conflict with our model; on the other hand, Stell's model cannot explain the data from our study and from much of the literature.

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